1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,

3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,

3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propyl-urea,

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,

3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-propyl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea,

1-ethyl-3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,

3-cyclobutyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea,

3-(2-dimethylaminoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropyl-urea,

3-cyclobutyl-1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,

3-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethyl-urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-1-propyl-urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea,
1-ethyl-3-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea,
3-cyclobutyl-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea,

3-(2-dimethylaminoethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-methyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-ethyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-cyclobutyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propylurea,

3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(1-methylpyrazol-4-yl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-methyl-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-methyl-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-ethylurea,

3-cyclobutyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propylurea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

3-cyclopropyl-1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea,

1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-methylurea,

1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-dimethylaminoethyl)urea,

1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-hydroxyethyl)urea,

1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea,

1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-methylurea,

1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(2-hydroxyethyl)urea,

1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea,

1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-methylurea,

3-(2-dimethylaminoethyl)-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea,

1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-hydroxyethyl)urea,

1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea,
3-methyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea,
3-(2-dimethylaminoethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea,
3-(2-hydroxyethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea,
1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea,
3-methyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea,
3-(2-hydroxyethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea,
1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea,
1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-methylurea,
1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(2-hydroxyethyl)urea,
1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea,
3-(2-hydroxyethyl)-1-[5-[4-[1-[4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea,
3-cyclopropyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-ethyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-cyclobutyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

3-(2-cyanoethyl)-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea,

1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-ethyl-1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-cyclopropyl-1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propylurea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-cyclobutyl-1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,

1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propylurea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea,
3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[1-Benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea,

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea,

3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,

1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-1-propylurea,

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,

3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

3-cyclobutyl-1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,

1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,

1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-propylurea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,

3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea

[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-cyclopropyl-1-[4-[4-[4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,

3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-cyclobutyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea,

1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea,

3-(2-dimethylaminoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

N,N-dimethyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide

3-methyl-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea

N-cyclopropyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide

N-cyclopropyl-N-methyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide

3-methyl-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea

1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N,N-dimethylcyclopropane-1-carboxamide

3-cyclopropyl-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea

N-cyclopropyl-1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide

N-cyclopropyl-1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N-methylcyclopropane-1-carboxamide

3-cyclopropyl-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea

1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N,N-dimethylcyclopropane-1-carboxamide

3-(2-hydroxyethyl)-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea

N-cyclopropyl-1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide

N-cyclopropyl-1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N-methylcyclopropane-1-carboxamide,

3-(2-hydroxyethyl)-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2-cyanoethyl)-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2-cyanoethyl)-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea,

3-(2-cyanoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea,

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,

3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

1-ethyl-3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-methylurea,

3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-(1-methylpyrazol-4-yl)urea,

3-(2-hydroxyethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-(1-methylpyrazol-4-yl)-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-methyl-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-ethyl-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-cyclopropyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea,

3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-(5-methylpyrazin-2-yl)urea,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,3-oxazol-2-yl)urea,

3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,
1-ethyl-3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-methylurea,
3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-(1-methylpyrazol-4-yl)urea,
3-(2-hydroxyethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-(1-methylpyrazol-4-yl)-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-methyl-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea,
3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-(5-methylpyrazin-2-yl)urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,3-oxazol-2-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3,3,3-trifluoro-2-hydroxypropyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea,

3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(oxetan-3-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea,
1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-ethyl-3-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-cyclobutyl-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea,
3-(2-hydroxyethyl)-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea,

1-cyclopropyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-methylurea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylcyclopropyl)urea,

3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-tert-butyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-cyano-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-hydroxy-N-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]pyrrolidine-1-carboxamide,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylsulfonylethyl)urea,

3-(1,1-dioxothiolan-3-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

2-[[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]-N,N-dimethylacetamide,

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-

3-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,

1-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-cyclopropylurea,

3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-ethylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-methylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,

3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-

2-[[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]acetic acid,

2-[[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]-N,N-dimethylacetamide,

3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-cyclopropyl-1-methylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-3-yl)urea,

3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-(5-methyl-1,2-oxazol-3-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-oxazol-2-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2,2-trifluoroethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylimidazol-4-yl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

3-(2,2-difluoroethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,

3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,

3-cyclobutyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,

3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,

3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,

3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,

3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea,

1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,

3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylthiourea,

3-(2-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,
3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylthiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)thiourea,
3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylthiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)thiourea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(1H-imidazol-2-ylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(1H-imidazol-2-ylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-(1-methylpyrazol-4-yl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
3-methyl-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-

3-(2-cyanoethyl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-propylurea,

1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propan-2-ylurea,

3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-

1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea,
3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea,
N-[2-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide,
N-[2-[1-[2-[4-(ethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide,
2-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonylacetamide,
2-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonyl-N-methylacetamide,
3-cyclopropyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea,
3-ethyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-

3-cyclopropyl-1-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
N,N-dimethyl-6-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpyridine-3-carboxamide,
6-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-N,N-dimethylpyridine-3-carboxamide,
N,N-dimethyl-3-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpyridine-2-carboxamide,
3-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-N,N-dimethylpyridine-2-carboxamide,
1-[4-[4-[1-(2-methoxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea,
3-ethyl-1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-fluoroethyl)-1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-

1-ethyl-3-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-methyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-ethyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

3-(1-methylpyrazol-4-yl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2-fluoro-4-methylaminophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-cyclopropyl-1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclop,ropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,

1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,

1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-cyclopropyl-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2-fluoroethyl)-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,
1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,
3-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-43-yl)urea,
1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-43-yl)urea
1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-fluoroethyl)-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-43-yl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,
3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
3-cyclopropyl-1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[3-fluoro-4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea,
3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea,
1-[4-[4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3R)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[3-(hydroxymethyl)morpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3R,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,

3-Cyclopropyl-1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,

1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2,2-difluoroethyl)-1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

3-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,

1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,

1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-cyclopropyl-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-ethyl-3-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-cyclopropyl-1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2-fluoroethyl)-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
3-ethyl-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea,
3-cyclopropyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-ethyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea

3-chloro-4-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

3-chloro-4-[1-[2-[4-(ethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

3-chloro-4-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

3-chloro-4-[1-[2-[4-(2-fluoroethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

3-chloro-4-[1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

3-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea

1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea

1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea

1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea

1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea

1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea

3-cyclopropyl-1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,

1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea,

4-[6-[1-(benzenesulfonyl)cyclopropyl]-2-[4-(ethylcarbamoylamino)phenyl]pyrimidin-4-yl]morpholine-3-carboxamide,

4-[6-[1-(benzenesulfonyl)cyclopropyl]-2-[4-(ethylcarbamoylamino)phenyl]pyrimidin-4-yl]-N,N-dimethylmorpholine-3-carboxamide,

3-cyclopropyl-1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-ethylurea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea

3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
3-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea,
1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,
1-[4-[4-[1-(3-chloro-4-methylaminophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-[3-chloro-4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-[3-chloro-4-(2-fluoroethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(3-chloro-4-ethylaminophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea,
3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

3-(2,2-difluoroethyl)-1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyramidin-2-yl]phenyl]-3-ethylurea,

1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea,

3-cyclopropyl-1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea,

3-methyl-1-[4-[4-[1-(2-methylaminoethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,

3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,
3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea,
3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylthiourea,
3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea, and
3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
or a pharmaceutically acceptable salt thereof.

In another aspect of the invention there is provided a compound, or a combination of compounds, selected from any one of
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,
3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,
1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,

3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,

3-cyclopropyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-cyclopropyl-1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea, and

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,

1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,

1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-ethylurea,

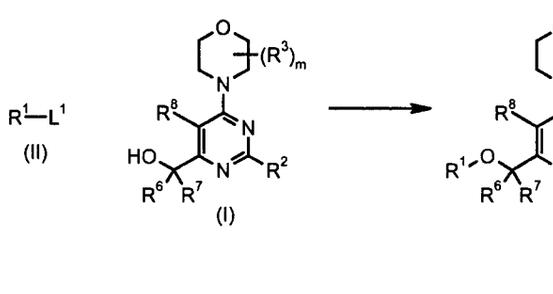
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea, and

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

or a pharmaceutically acceptable salt thereof.

The invention also provides processes for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

A compound of formula (I), wherein X = $-S(O)_2CR^6R^7-$, may be prepared by oxidising a compound of the formula (I), wherein X = SCR^6R^7-, for example by using Oxone® at room temperature in a mixed solvent system of water and ethanol

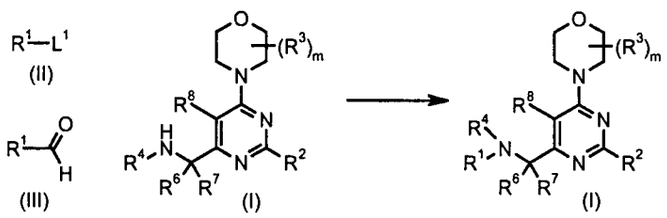


(I) (I)

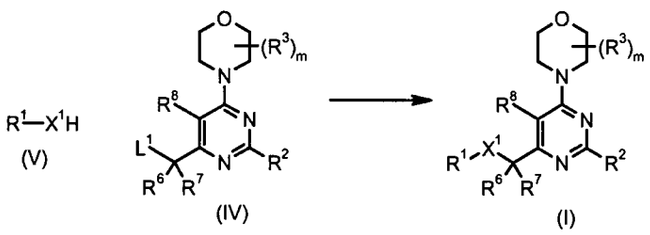
A compound of formula (I), wherein $R^1X = R^1OCR^6R^7-$, may be prepared by the reaction of a compound of formula (I), wherein $R^1X = HOCR^6R^7-$, with a compound of formula (II), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide.

(II) (I) (I)

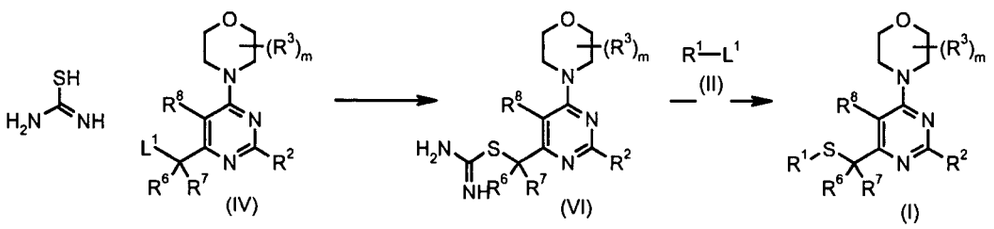
A compound of formula (I), wherein $R^1X = R^1R^4NCR^6R^7$-, may be prepared by the reaction of a compound of formula (I), wherein $R^1X = HR^4NCR^6R^7$-, with a compound of formula (II), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide; or by the reaction of a compound of formula (I), wherein $R^1X = HR^4NCR^6R^7$-, with a compound of formula (III) in the presence of a suitable reducing agent such as $NaCNBH_3$.



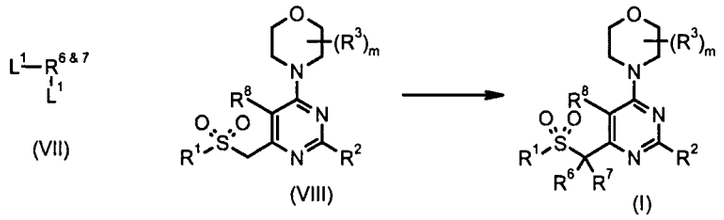
A compound of formula (I), wherein $X^1 = -S(O)_2CR^6R^7$-, $-SCR^6R^7$-, $-OCR^6R^7$-, $-R^4NCR^6R^7$-, $-S(O)CR^6R^7$-, may be prepared by the reaction of a compound of formula (IV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (V) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide.



A compound of formula (I), wherein $X = -SCR^6R^7$-, may be prepared by the reaction of a compound of formula (IV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with thiourea in a suitable solvent such as ethanol to generate a compound of formula (VI) which is then subsequently reacted with a compound of formula (II) in the presence of a suitable base such as sodium hydroxide and a solvent such as *N,N*-dimethylformamide.

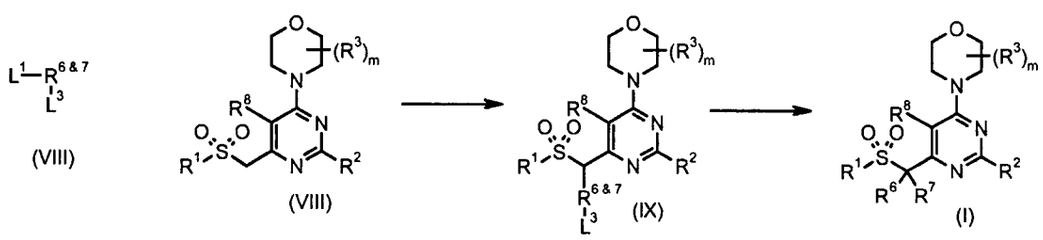


A compound of formula (I), wherein X = $-S(O)_2CR^6R^7-$, may be prepared by the reaction of a compound of formula (VIII) with a compound of formula (VII), wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.



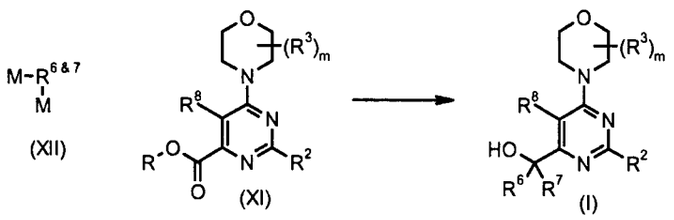
(VII) (VIII) (I)

A compound of formula (I), wherein X = $-S(O)_2CR^6R^7-$, may be prepared by the reaction of a compound of formula (VIII) with a compound of formula (IX), wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), and L^3 is a group which can be transformed to a suitable leaving group (such as halo, tosyl, mesyl) at a later stage, to give a compound of formula (X) in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide, and subsequently converting L^3 to an appropriate leaving group (such as halo, tosyl, mesyl etc.) and then exposing to a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.



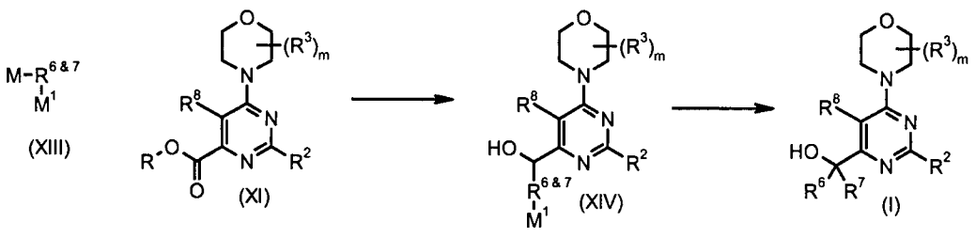
(VIII) (VIII) (IX) (I)

A compound of formula (I), wherein $R^1X = HOCR^6R^7$-, may be prepared by the reaction of a compound of formula (XI), with suitable organometallic reagent of fomula (XII) wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, such as the grignard reagent in a suitable solvent.



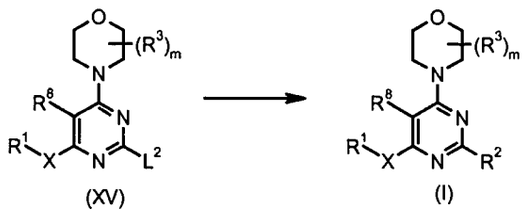
(XII) (XI) (I)

A compound of formula (I), wherein $R^1X = HOCR^6R^7$-, may be prepared by the reaction of a compound of formula (XI), with suitable organometallic reagent of fomula (XIII) wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and M^1 is a group which can be transformed into a suitable organometallic reagent (such as a grignard reagent) at a later date, such as the grignard reagent in a suitable solvent, to give a compound of formula (XIV), and then subsequent conversion of M^1 to a suitable organometallic reagent and subsequent reaction.



(XIII) (XI) (XIV) (I)

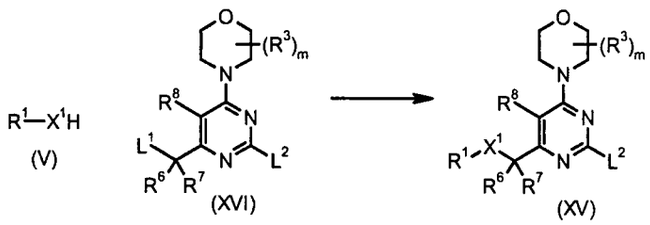
A compound of formula (I) may be prepared from a compound of formula (XV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (I) may be prepared from a compound of formula (XIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



(XV) (I)

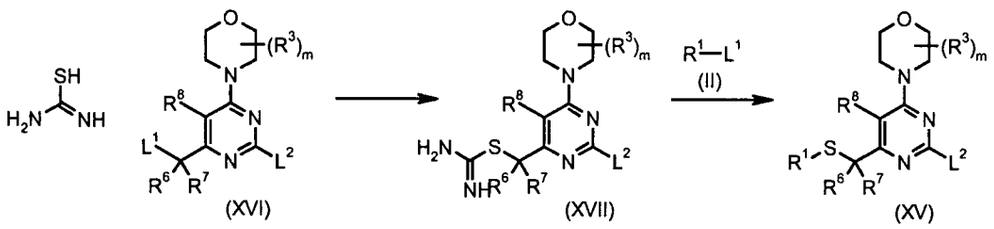
It will be appreciated that a compound of formula (XV) may be transformed into another compound of formula (XV) by techniques such as oxidation, alkylation, reductive amination etc., either listed above or otherwise known in the literature.

A compound of formula (XV), wherein X^1 = $-S(O)_2CR^6R^7-$, $-SCR^6R^7-$, $-OCR^6R^7-$, $-R^4NCR^6R^7-$, $-S(O)CR^6R^7-$, may be prepared by the reaction of a compound of formula (XVI), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (V) optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide.



(V) (XVI) (XV)

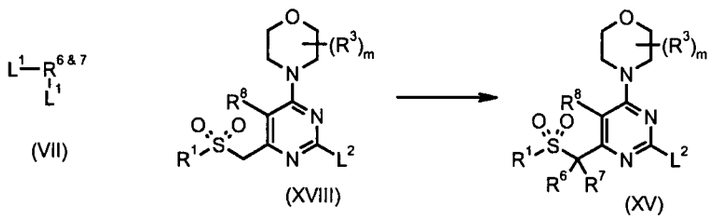
A compound of formula (XV), wherein X = $-SCR^6R^7-$, may be prepared by the reaction of a compound of formula (XVI), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with thiourea in a suitable solvent such as ethanol to generate a compound of formula (XVII) which is then subsequently reacted with a compound of formula (II) in the presence of a suitable base such as sodium hydroxide and a solvent such as *N,N*-dimethylformamide.



(XVI) (XVII) (XV)

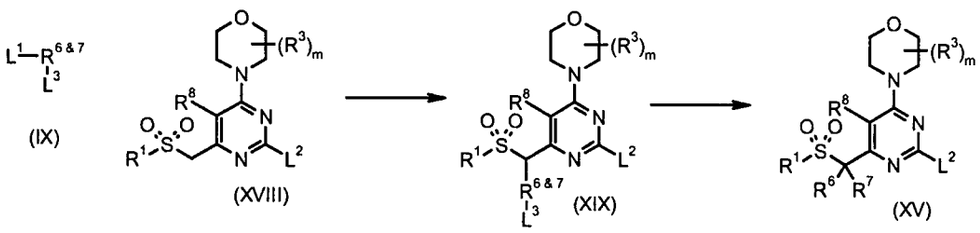
A compound of formula (XV), wherein X = $-S(O)_2CR^6R^7-$, may be prepared by the reaction of a compound of formula (XVIII), wherein X = $-S(O)_2CH_2-$, with a compound of formula (VII), wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), in the presence of a suitable base such as sodium hydride or

potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.



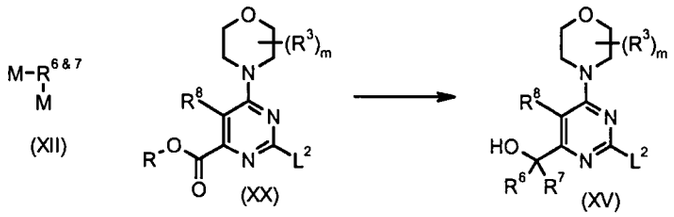
(VII) (XVIII) (XV)

A compound of formula (XV), wherein X = $-S(O)_2CR^6R^7-$, may be prepared by the reaction of a compound of formula (XVIII), wherein X = $-S(O)_2CH_2-$, with a compound of formula (IX), wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), and L^3 is a group which can be transformed to a suitable leaving group (such as halo, tosyl, mesyl) at a later stage, to give a compound of formula (XIX) in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide, and subsequently converting L^3 to an appropriate leaving group (such as halo, tosyl, mesyl etc.) and then exposing to a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.

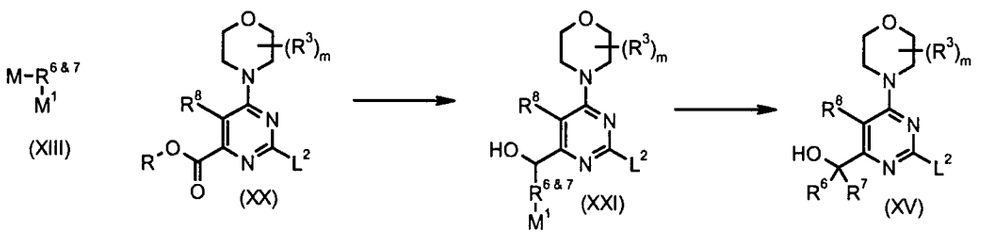


(IX) (XVIII) (XIX) (XV)

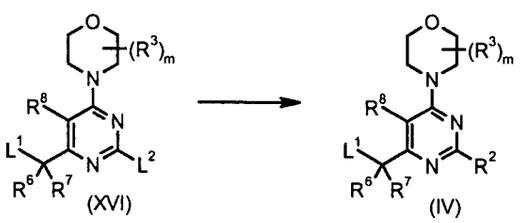
A compound of formula (XV), wherein $R^1X = HOCR^6R^7-$, may be prepared by the reaction of a compound of formula (XX), with suitable organometallic reagent of fomula (XII) wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, such as the grignard reagent in a suitable solvent.



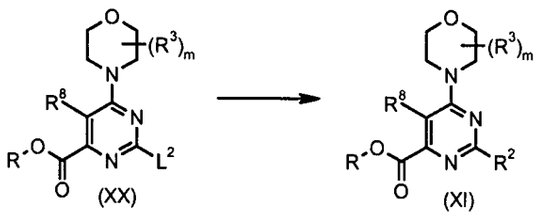
A compound of formula (XV), wherein $R^1X = HOCR^6R^7$-, may be prepared by the reaction of a compound of formula (XX), with suitable organometallic reagent of fomula (XIII) wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and M^1 is a group which can be transformed into a suitable organometallic reagent (such as a grignard reagent) at a later date, such as the grignard reagent in a suitable solvent, to give a compound of formula (XXI), and then subsequent conversion of M^1 to a suitable organometallic reagent and subsequent reaction.



A compound of formula (IV) may be prepared from a compound of formula (XVI), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.) and L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (IV) may be prepared from a compound of formula (XVI), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.

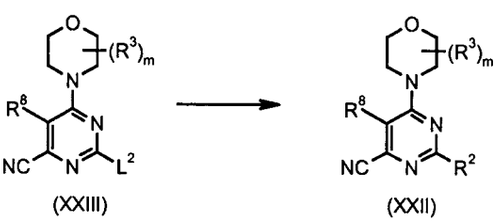


A compound of formula (XI) may be prepared from a compound of formula (XX) wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.) and R is a hydrogen or C_{1-4} alkyl group, with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (XI) may be prepared from a compound of formula (XX), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



(XX) (XI)

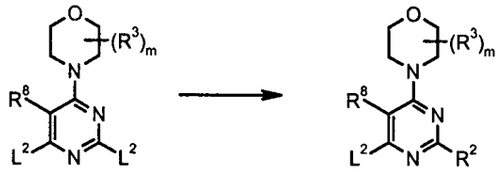
A compound of formula (XXII) may be prepared from a compound of formula (XXIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (XXII) may be prepared from a compound of formula (XXIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



(XXIII) (XXII)

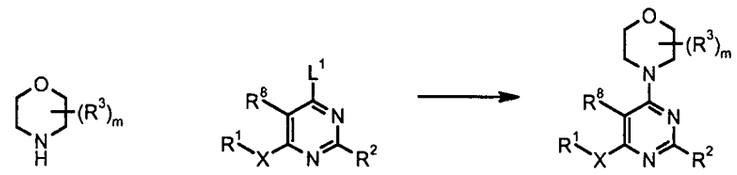
A compound of formula (XXIV) may be prepared from a compound of formula (XXV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), with a suitable organometallic reagent (such as the boronic acid $R^2B(OH)_2$ or the boronic ester $R^2B(OR)_2$ etc.) in the presence of a suitable metal catalyst (such as palladium or copper) in a suitable solvent

such as 1,4-dioxane. Alternatively where R^2 connects to the pyrimidine ring through a nitrogen, oxygen or sulphur atom a compound of formula (XXIV) may be prepared from a compound of formula (XXV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), by reaction with the required amine, alcohol or thiol in the presence of a suitable base such as potassium carbonate in a suitable solvent such as *N,N*-dimethylformamide.



(XXV) (XXIV)

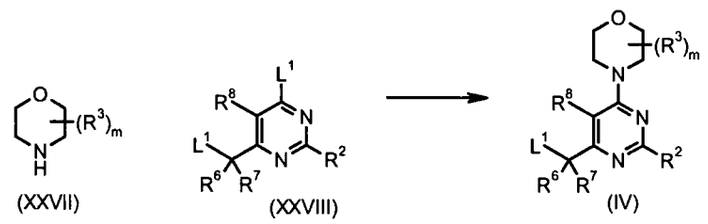
A compound of formula (I), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), may be prepared by the reaction of a compound of formula (XXVI) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



(XXVII) (XXVI) (I)

It will be appreciated that a compound of formula (XXV) may be transformed into another compound of formula (XXV) by techniques such as oxidation, alkylation, reductive amination etc., either listed above or otherwise known in the literature.

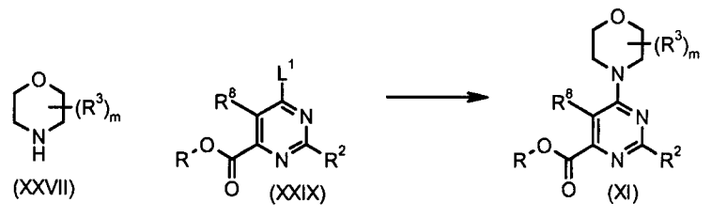
A compound of formula (IV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), may be prepared by the reaction of a compound of formula (XXVIII) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



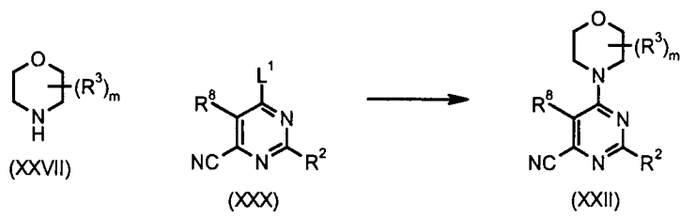
(XXVII) (XXVIII) (IV)

A compound of formula (XI), wherein R is a hydrogen or a C_{1-4} alkyl group, may be prepared by the reaction of a compound of formula (XXIX), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) with a compound of formula (XXVII) optionally in the

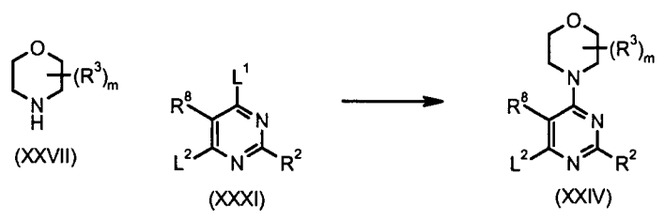
presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



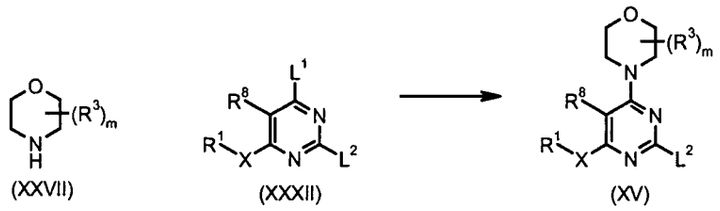
A compound of formula (XXII) may be prepared by the reaction of a compound of formula (XXX), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



A compound of formula (XXIV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXI), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.

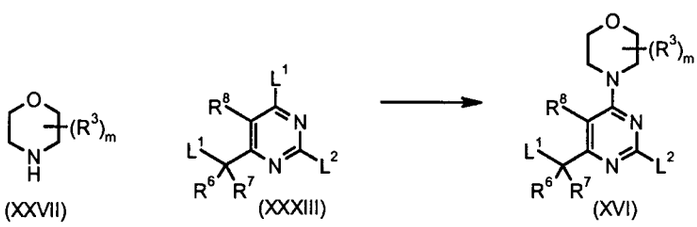


A compound of formula (XV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXII), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.

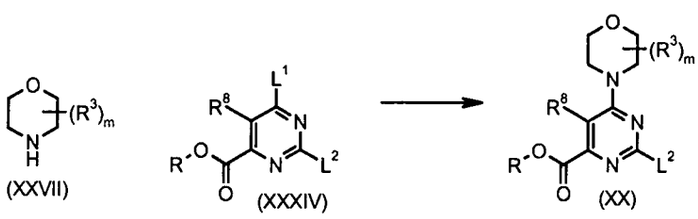


It will be appreciated that a compound of formula (XXXII) may be transformed into another compound of formula (XXXII) by techniques such as oxidation, alkylation, reductive amination etc., either listed above or otherwise known in the literature.

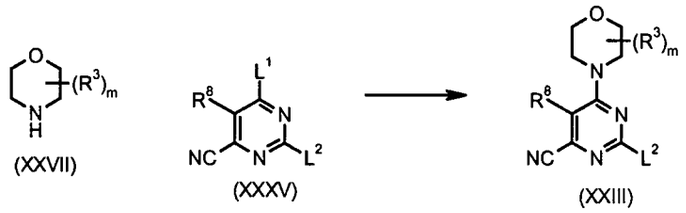
A compound of formula (XVI), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) and L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXIII) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



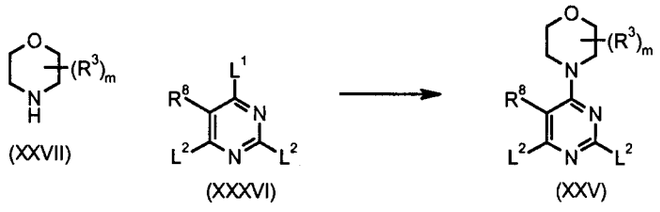
A compound of formula (XX), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.) and R is a hydrogen or a C_{1-4} alkyl group, may be prepared by the reaction of a compound of formula (XXXIV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



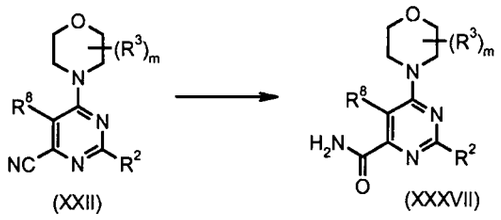
A compound of formula (XXIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXV), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.) with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



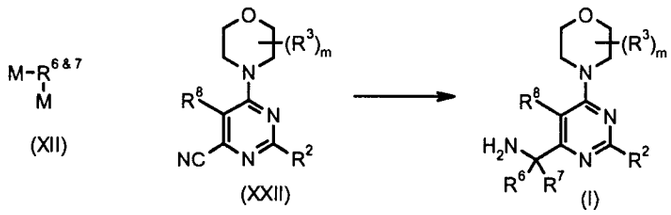
A compound of formula (XXV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XXXVI), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (XXVII) optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



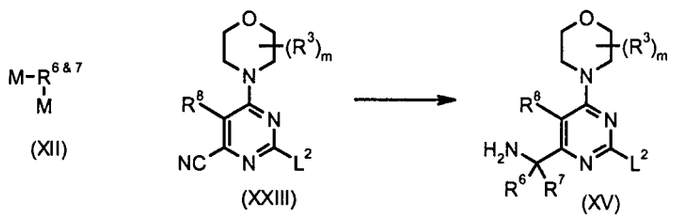
A compound of formula (XXXVII), wherein $R^1X = H_2NC(O)$-, may be prepared from a compound of formula (XXII) by hydrolysis with, for example, sodium hydroxide in a suitable solvent such as a water ethanol mix.



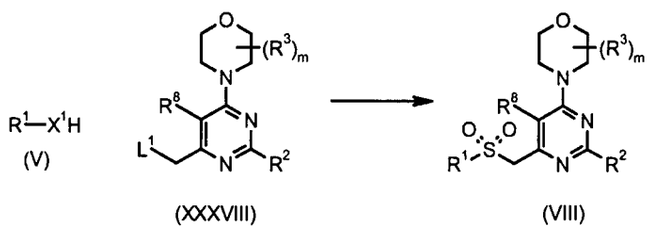
A compound of formula (I), wherein $R^1X = H_2NCR^6R^7$-, may be prepared by the reaction of a compound of formula (XXII), with suitable organometallic reagent of fomula (XII) wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, such as the grignard reagent or alkyl lithium reagent in a suitable solvent.



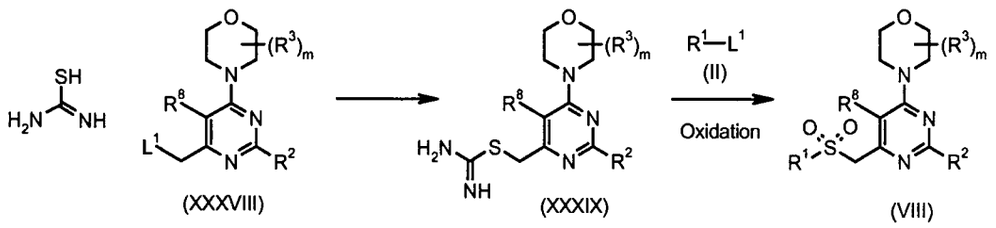
A compound of formula (XV), wherein $R^1X = H_2NCR^6R^7$-, may be prepared by the reaction of a compound of formula (XXIII), with suitable organometallic reagent of fomula (XII) wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which carbon may be optionally replaced with O, N or S, such as the grignard reagent or alkyl lithium reagent in a suitable solvent.



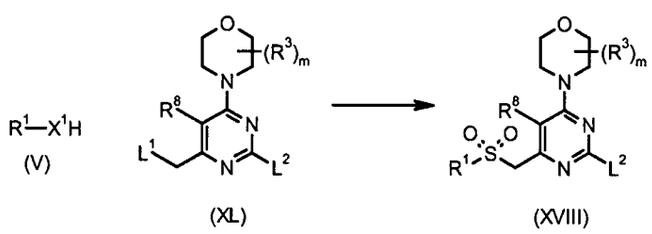
A compound of formula (VIII) may be prepared by the reaction of a compound of formula (XXXVIII), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (V), wherein X^1 = -S-, -SO_2-, optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide. In the case where X^1 = -SH a subsequent oxidation step, for example by using Oxone® at room temperature in a solvent system of water and ethanol, or for example by using 3-chloroperbenzoic acid with dichloromethane as solvent will be required.



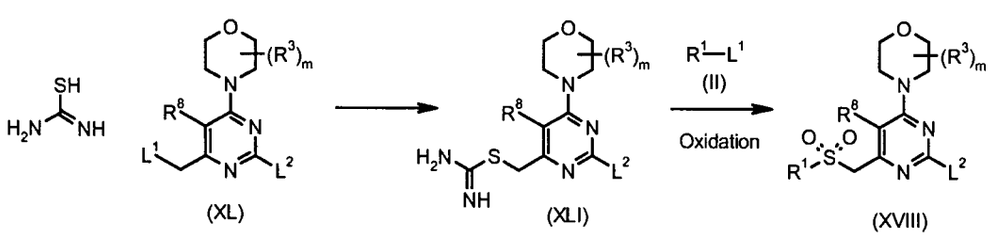
A compound of formula (VIII) may be prepared by the reaction of a compound of formula (XXXVIII), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with thiourea in a suitable solvent such as ethanol to generate a compound of formula (XXXIX) which is then subsequently reacted with a compound of formula (II) in the presence of a suitable base such as sodium hydroxide and a solvent such as *N,N*-dimethylformamide, and subsequently oxidised, for example by using Oxone® at room temperature in a solvent system of water and ethanol, or for example by using 3-chloroperbenzoic acid with dichloromethane as solvent.



A compound of formula (XVIII), wherein L^2 is a leaving group (such as halo, tosyl mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XL), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with a compound of formula (V), wherein X^1 = -S-, $-SO_2-$, optionally in the presence of a suitable base such as triethylamine and a solvent such as tetrahydrofuran or *N,N*-dimethylformamide. In the case where X^1 = -S- a subsequent oxidation step, for example by using Oxone® at room temperature in a solvent system of water and ethanol, or for example by using 3-chloroperbenzoic acid with dichloromethane as solvent will be required.

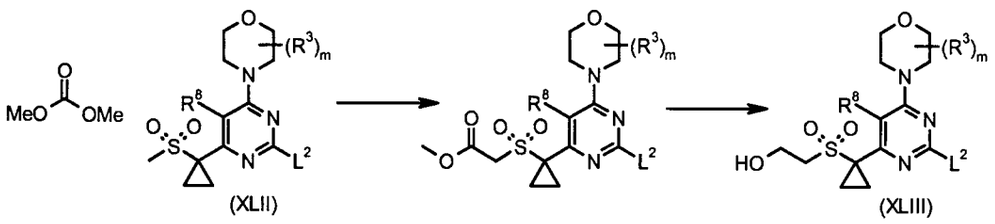


A compound of formula (XVIII), wherein L^2 is a leaving group (such as halo, tosyl mesyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of a compound of formula (XL), wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), with thiourea in a suitable solvent such as ethanol to generate a compound of formula (XLI) which is then subsequently reacted with a compound of formula (II) in the presence of a suitable base such as sodium hydroxide and a solvent such as *N,N*-dimethylformamide, and subsequently oxidised, for example by using Oxone® at room temperature in a solvent system of water and ethanol, or for example by using 3-chloroperbenzoic acid with dichloromethane as solvent.



It will be appreciated that the substituent R^1 present in a compound of formula (I) and formula (XV) can be transformed into another substituent R^1 by a series of chemical

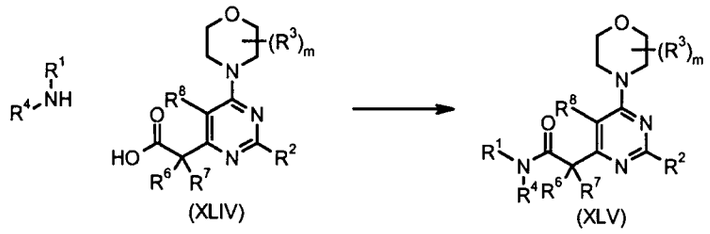
transformations known in the literature, such as oxidation, reduction, nucleophilic or electrophilic reactions, addition and elimination reactions. An example of such a transformation would be the reaction of a compound of formula (XLII), wherein L^2 is a leaving group (such as halo, tosyl mesyl, -SMe, $-S(O)_2Me$ etc.), with an electrophile such as dimethyl carbonate in the presence of a base such as sodium hydride in a suitable solvent such as tetrahydrofuran, followed by a reduction, such as the conversion to a mixed anhydride followed by treatment with a hydride source, to give a compound of formula (XLIII)



It will be appreciated that the R^2 group may be introduced and subsequently converted to another group of the formula R^2 at a subsequent stage in the synthesis using methods known in the literature. For example, but not limited to, an R^2 containing an alkyl or aryl amine (which may be suitably protected as, for example, a nitro or t-butoxycarbamate) may be introduced at any stage and then converted, for instance, to a urea by reaction with a suitable isocyanate (or by activation to a suitable group, such as isocyanate or phenoxycarbamate, and subsequent reaction with an amine); or to a thiourea by reaction with a suitable isothiocyanate (or by activation to a suitable group, such as an isothiocyanate, and subsequent reaction with an amine); or to an amide or sulphonamide by reaction with a suitably activated carboxylic acid or sulphonic acid derivative; or by other methods known in the literature.

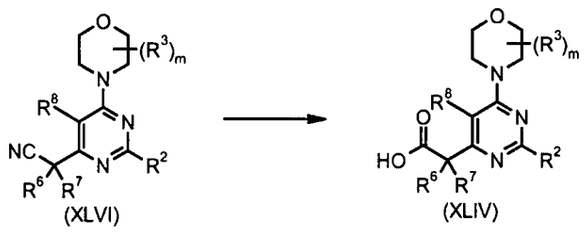
It will be appreciated that where R^6 and R^7, together with the carbon to which they are attached, form a 3-10 membered heterocyclic ring containing a nitrogen atom that the nitrogen atom may be suitably protected (for example a t-butoxycarbamate or benzyl group) and that the protecting group may be removed and if necessary a further reaction performed on the nitrogen (for example an alkylation, reductive amination or amidation) at any stage in the synthesis.

A compound of formula (XLV) may be prepared by the reaction of an amine of formula R^1R^4NH with a compound of formula (XLIV) in the presence of a suitable coupling agent, such as HATU, or following suitable activation of (XLIV), such as the conversion to an acid chloride.



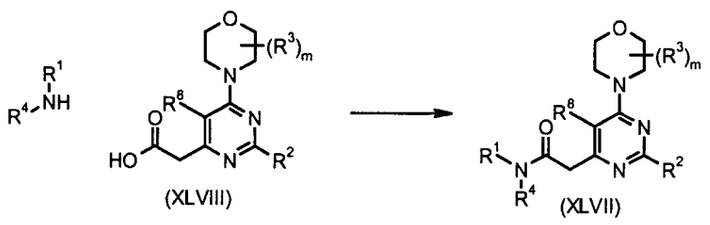
(XLIV) (XLV)

A compound of formula (XLIV) may be prepared from a compound of formula (XLVI) by hydrolysis, for example with sodium hydroxide in a suitable solvent such as an ethanol:water mix.



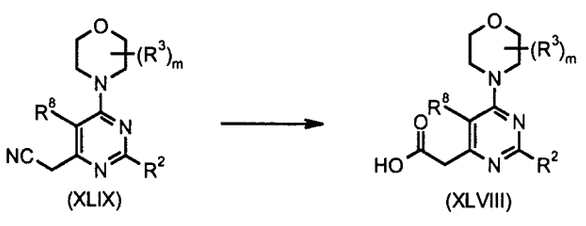
(XLVI) (XLIV)

A compound of formula (XLVII) may be prepared by the reaction of an amine of formula R^1R^4NH with a compound of formula (XLVIII) in the presence of a suitable coupling agent, such as HATU, or following suitable activation of (XLVIII), such as the conversion to an acid chloride.



(XLVIII) (XLVII)

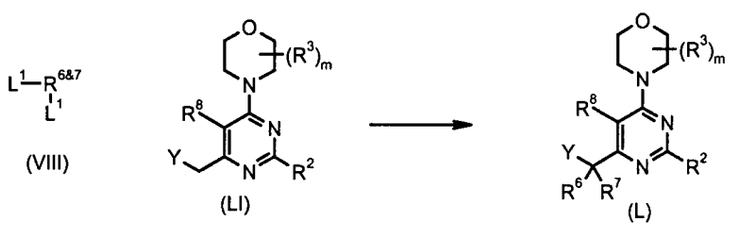
A compound of formula (XLIX) may be prepared from a compound of formula (XLVIII) by hydrolysis, for example with sodium hydroxide in a suitable solvent such as an ethanol:water mix.



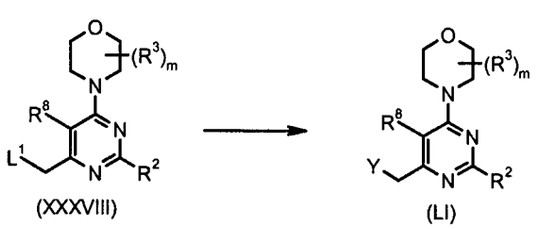
(XLIX) (XLVIII)

A compound of formula (L), wherein Y = $R^1R^4NC(O)$-, ROC(O)-, NC-, may be prepared by the reaction of a compound of formula (VIII) with a compound of formula (LI), wherein $R^{6\ \&\ 7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon

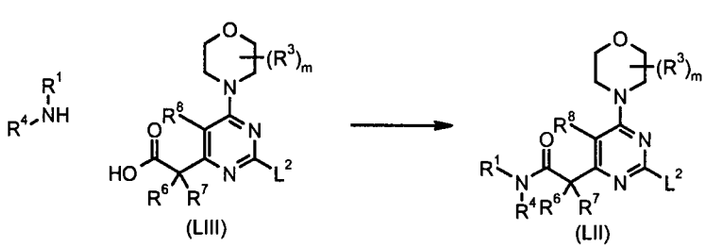
may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.



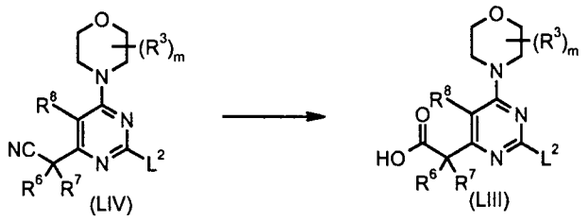
A compound of formula (LI), wherein Y = NC-, HOC(O)-, may be prepared by the reaction of a compound of formula (XXXVIII) with a suitable nucleophile, such as for example sodium cyanide or for example tris(phenylthio)methane anion followed by a suitable hydrolysis.



A compound of formula (LII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.), may be prepared by the reaction of an amine of formula R^1R^4NH with a compound of formula (LIII) in the presence of a suitable coupling agent, such as HATU, or following suitable activation of (LIII), such as the conversion to an acid chloride.

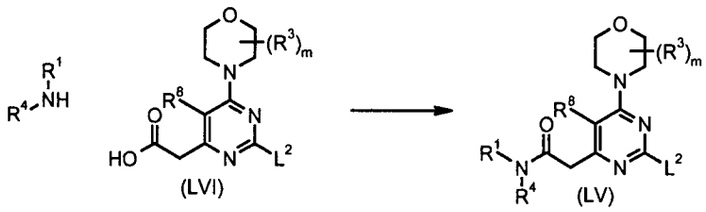


A compound of formula (LIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.), may be prepared from a compound of formula (LIV) by hydrolysis, for example with sodium hydroxide in a suitable solvent such as an ethanol:water mix.



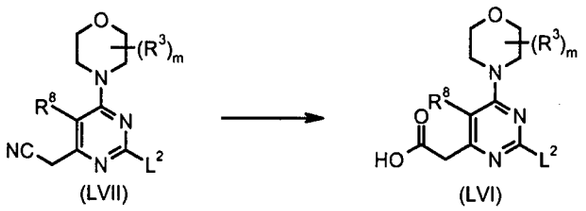
(LIV) (LIII)

A compound of formula (LV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), may be prepared by the reaction of an amine of formula R^1R^4NH with a compound of formula (LVI) in the presence of a suitable coupling agent, such as HATU, or following suitable activation of (LVI), such as the conversion to an acid chloride.



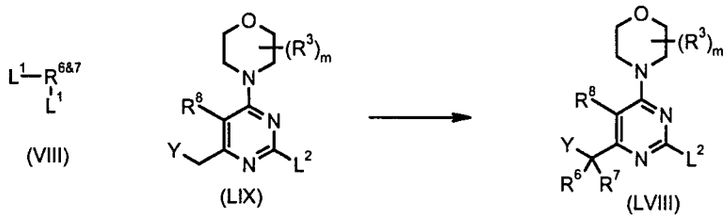
(LVI) (LV)

A compound of formula (LVI), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), may be prepared from a compound of formula (LVII) by hydrolysis, for example with sodium hydroxide in a suitable solvent such as an ethanol:water mix.

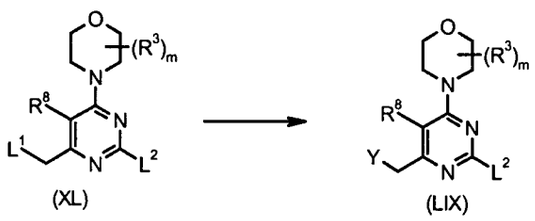


(LVII) (LVI)

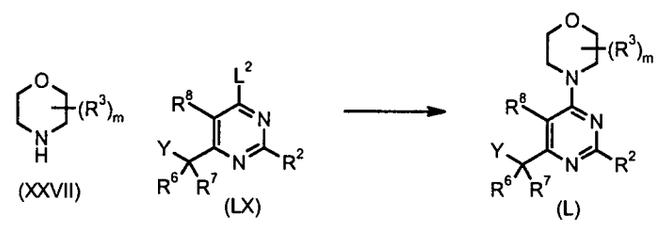
A compound of formula (LVIII), wherein Y = $R^1R^4NC(O)$-, ROC(O)-, NC-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), may be prepared by the reaction of a compound of formula (VIII) with a compound of formula (LIX), wherein $R^{6\&7}$ is a 2 to 9 membered, optionally substituted, alkylene chain in which 1 carbon may be optionally replaced with O, N or S, and wherein L^1 is a leaving group (such as halo, tosyl, mesyl etc.), in the presence of a suitable base such as sodium hydride or potassium *tert*-butoxide in a suitable solvent such as tetrahydrofuran or *N,N*-dimethylformamide, or by using aqueous sodium hydroxide solution and DCM as a solvent with a suitable phase transfer agent such as tetrabutylammonium bromide.



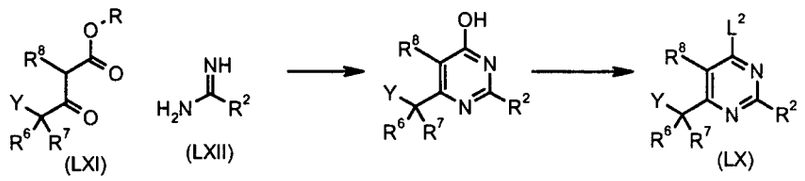
A compound of formula (LIX), wherein Y = NC-, HOC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), may be prepared by the reaction of a compound of formula (XL) with a suitable nucleophile, such as for example sodium cyanide or for example tris(phenylthio)methane anion followed by a suitable hydrolysis.



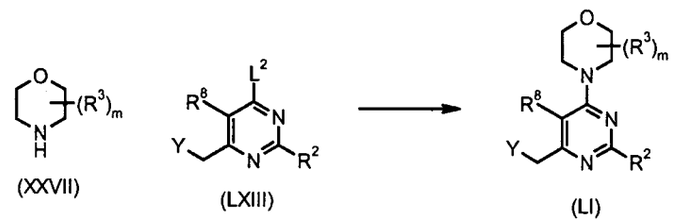
A compound of formula (L), wherein Y = NC-, ROC(O)-, may be prepared by the reaction of a compound of formula (XXVII) with a compound of formula (LX), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.), optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



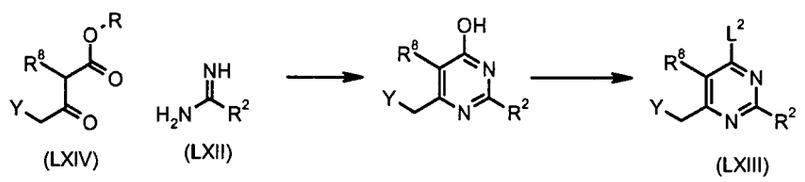
A compound of formula (LX), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, -$S(O)_2$Me etc.) may be prepared by the reaction of a compound of formula (LXI) with a compound of formula (LXII) and subsequent conversion of the OH group to a suitable leaving group, such as by reaction with *N*-phenyltrifluoromethanesulfonimide in the presence of a suitable base such as DBU and a suitable solvent such as dichloromethane.



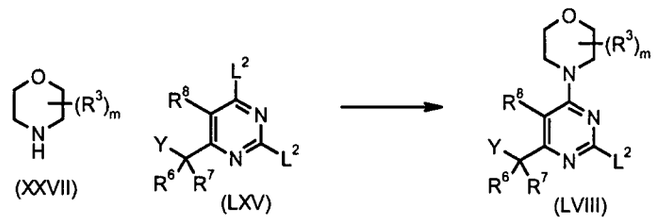
A compound of formula (LI), wherein Y = NC-, ROC(O)-, may be prepared by the reaction of a compound of formula (XXVII) with a compound of formula (LXIII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.), optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



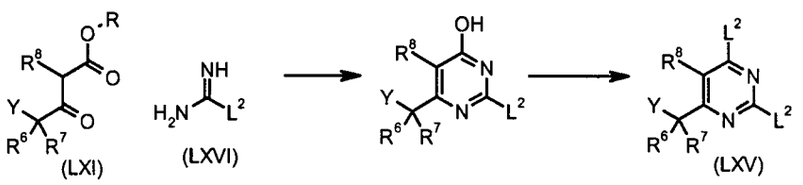
A compound of formula (LXIII), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.) may be prepared by the reaction of a compound of formula (LXIV) with a compound of formula (LXII) and subsequent conversion of the OH group to a suitable leaving group, such as by reaction with *N*-phenyltrifluoromethanesulfonimide in the presence of a suitable base such as DBU and a suitable solvent such as dichloromethane.



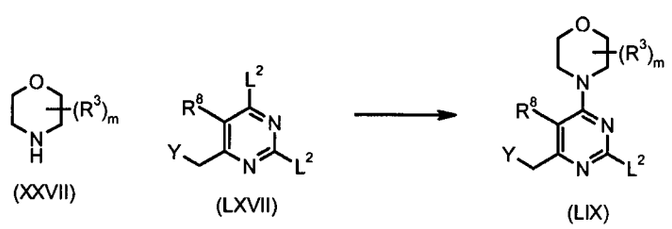
A compound of formula (LVIII), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.) may be prepared by the reaction of a compound of formula (XXVII) with a compound of formula (LXV), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.), optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



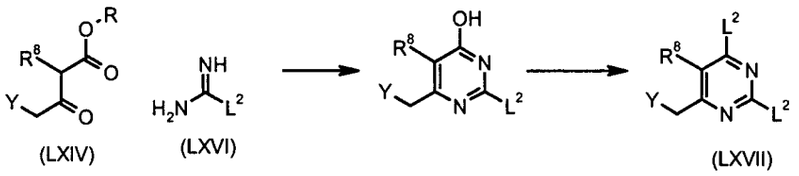
A compound of formula (LXV), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.) may be prepared by the reaction of a compound of formula (LXI) with a compound of formula (LXVI) and subsequent conversion of the OH group to a suitable leaving group, such as by reaction with *N*-phenyltrifluoromethanesulfonimide in the presence of a suitable base such as DBU and a suitable solvent such as dichloromethane.



A compound of formula (LIX), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.) may be prepared by the reaction of a compound of formula (XXVII) with a compound of formula (LXVII), wherein L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.), optionally in the presence of a suitable base such as triethylamine in a suitable solvent such as *N,N*-dimethylformamide.



A compound of formula (LXVII), wherein Y = NC-, ROC(O)-, and L^2 is a leaving group (such as halo, tosyl, mesyl, trifluoromethylsulphonyl, -SMe, $-S(O)_2Me$ etc.) may be prepared by the reaction of a compound of formula (LXIV) with a compound of formula (LXVI) and subsequent conversion of the OH group to a suitable leaving group, such as by reaction with *N*-phenyltrifluoromethanesulfonimide in the presence of a suitable base such as DBU and a suitable solvent such as dichloromethane.



(LXIV) (LXVI) (LXVII)

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. For example compounds of formula (I) may be converted into further compounds of formula (I) by standard aromatic substitution reactions or by conventional functional group modifications. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulfinyl or alkylsulfonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl

group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Many of the intermediates defined herein are novel and these are provided as a further feature of the invention.

Biological Assays

The following assays can be used to measure the effects of the compounds of the present invention as mTOR kinase inhibitors, as PI3 kinase inhibitors, as inhibitors *in vitro* of the activation of PI3 kinase signalling pathways and as inhibitors *in vitro* of the proliferation of MDA-MB-468 human breast adenocarcinoma cells.

(a)(i) *In Vitro* mTOR Kinase Assay

The assay used AlphaScreen technology (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) to determine the ability of test compounds to inhibit phosphorylation by recombinant mTOR.

A C-terminal truncation of mTOR encompassing amino acid residues 1362 to 2549 of mTOR (EMBL Accession No. L34075) was stably expressed as a FLAG-tagged fusion in HEK293 cells as described by Vilella-Bach *et al.*, Journal of Biochemistry, 1999, 274, 4266-4272. The HEK293 FLAG-tagged mTOR (1362-2549) stable cell line was routinely maintained at 37°C with 5% CO_2 up to a confluency of 70-90% in Dulbecco's modified Eagle's growth medium (DMEM; Invitrogen Limited, Paisley, UK Catalogue No. 41966-029) containing 10% heat-inactivated foetal calf serum (FCS; Sigma, Poole, Dorset, UK, Catalogue No. F0392), 1% L-glutamine (Gibco, Catalogue No. 25030-024) and 2 mg/ml Geneticin (G418 sulfate; Invitrogen Limited, UK Catalogue No. 10131-027). Following expression in the mammalian HEK293 cell line, expressed protein was purified using the FLAG epitope tag using standard purification techniques.

Test compounds were prepared as 10 mM stock solutions in DMSO and diluted into water as required to give a range of final assay concentrations. Aliquots (2 µl) of each compound dilution were placed into a well of a Greiner 384-well low volume (LV) white polystyrene plate (Greiner Bio-one). A 30 µl mixture of recombinant purified mTOR enzyme, 1 µM biotinylated peptide substrate (Biotin-Ahx-Lys-Lys-Ala-Asn-Gln-Val-Phe-Leu-Gly-Phe-Thr-Tyr-Val-Ala-Pro-Ser-Val-Leu-Glu-Ser-Val-Lys-Glu-NH_2; Bachem UK Ltd), ATP (20 µM) and a buffer solution [comprising Tris-HCl pH7.4 buffer (50 mM), EGTA (0.1 mM), bovine serum albumin (0.5 mg/mL), DTT (1.25 mM) and manganese chloride (10 mM)] was agitated at room temperature for 90 minutes.

Control wells that produced a maximum signal corresponding to maximum enzyme activity were created by using 5% DMSO instead of test compound. Control wells that produced a minimum signal corresponding to fully inhibited enzyme were created by adding

EDTA (83 mM) instead of test compound. These assay solutions were incubated for 2 hours at room temperature.

Each reaction was stopped by the addition of 10 µl of a mixture of EDTA (50 mM), bovine serum albumin (BSA; 0.5 mg/mL) and Tris-HCl pH7.4 buffer (50 mM) containing p70 S6 Kinase (T389) 1A5 Monoclonal Antibody (Cell Signalling Technology, Catalogue No. 9206B) and AlphaScreen Streptavidin donor and Protein A acceptor beads (200 ng; Perkin Elmer, Catalogue No. 6760002B and 6760137R respectively) were added and the assay plates were left for about 20 hours at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read using a Packard Envision instrument.

Phosphorylated biotinylated peptide is formed *in situ* as a result of mTOR mediated phosphorylation. The phosphorylated biotinylated peptide that is associated with AlphaScreen Streptavidin donor beads forms a complex with the p70 S6 Kinase (T389) 1A5 Monoclonal Antibody that is associated with Alphascreen Protein A acceptor beads. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, the presence of mTOR kinase activity results in an assay signal. In the presence of an mTOR kinase inhibitor, signal strength is reduced.

mTOR enzyme inhibition for a given test compound was expressed as an IC_{50} value.

(a)(ii) *In Vitro* mTOR Kinase Assay (Echo)

The assay used AlphaScreen technology (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) to determine the ability of test compounds to inhibit phosphorylation by recombinant mTOR.

A C-terminal truncation of mTOR encompassing amino acid residues 1362 to 2549 of mTOR (EMBL Accession No. L34075) was stably expressed as a FLAG-tagged fusion in HEK293 cells as described by Vilella-Bach *et al.*, Journal of Biochemistry, 1999, 274, 4266-4272. The HEK293 FLAG-tagged mTOR (1362-2549) stable cell line was routinely maintained at 37°C with 5% CO_2 up to a confluency of 70-90% in Dulbecco's modified Eagle's growth medium (DMEM; Invitrogen Limited, Paisley, UK Catalogue No. 41966-029) containing 10% heat-inactivated foetal calf serum (FCS; Sigma, Poole, Dorset, UK, Catalogue No. F0392), 1% L-glutamine (Gibco, Catalogue No. 25030-024) and 2 mg/ml Geneticin (G418 sulfate; Invitrogen Limited, UK Catalogue No. 10131-027). Following expression in the mammalian HEK293 cell line, expressed protein was purified using the FLAG epitope tag using standard purification techniques.

Test compounds were prepared as 10 mM stock solutions in DMSO and diluted in into waterDMSO as required to give a range of final assay concentrations. Aliquots (120nl2 µl) of each compound dilution were acoustically dispensedplaced using a Labcyte Echo 550 into a well of a Greiner 384-well low volume (LV) white polystyrene plate (Greiner Bio-one). A 1230 µl mixture of recombinant purified mTOR enzyme, 1 µM biotinylated peptide substrate (Biotin-Ahx-Lys-Lys-Ala-Asn-Gln-Val-Phe-Leu-Gly-Phe-Thr-Tyr-Val-Ala-Pro-Ser-Val-Leu-Glu-Ser-Val-Lys-Glu-NH_2; Bachem UK Ltd), ATP (20 µM) and a buffer solution [comprising Tris-HCl pH7.4 buffer (50 mM), EGTA (0.1 mM), bovine serum albumin (0.5 mg/mL), DTT (1.25 mM) and manganese chloride (10 mM)] was incubated at room temperature for 12090 minutes.

Control wells that produced a maximum signal corresponding to maximum enzyme activity were created by using 1005% DMSO instead of test compound. Control wells that produced a minimum signal corresponding to fully inhibited enzyme were created by adding LY294002EDTA (100uM83 mM) compound. These assay solutions were incubated for 2 hours at room temperature.

Each reaction was stopped by the addition of 510 µl of a mixture of EDTA (50 mM), bovine serum albumin (BSA; 0.5 mg/mL) and Tris-HCl pH7.4 buffer (50 mM) containing p70 S6 Kinase (T389) 1A5 Monoclonal Antibody (Cell Signalling Technology, Catalogue No. 9206B) and AlphaScreen Streptavidin donor and Protein A acceptor beads (200 ng; Perkin Elmer, Catalogue No. 6760002B and 6760137R respectively) were added and the assay plates were left overnight at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read using a Packard Envision instrument.

Phosphorylated biotinylated peptide is formed *in situ* as a result of mTOR mediated phosphorylation. The phosphorylated biotinylated peptide that is associated with AlphaScreen Streptavidin donor beads forms a complex with the p70 S6 Kinase (T389) 1A5 Monoclonal Antibody that is associated with Alphascreen Protein A acceptor beads. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, the presence of mTOR kinase activity results in an assay signal. In the presence of an mTOR kinase inhibitor, signal strength is reduced.

mTOR enzyme inhibition for a given test compound was expressed as an IC_{50} value.

(b)(i) *In Vitro* PI3K Enzyme Assay

The assay used AlphaScreen technology (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) to determine the ability of test compounds to inhibit phosphorylation by recombinant Type I PI3K enzymes of the lipid PI(4,5)P2.

DNA fragments encoding human PI3K catalytic and regulatory subunits were isolated from cDNA libraries using standard molecular biology and PCR cloning techniques. The selected DNA fragments were used to generate baculovirus expression vectors. In particular, full length DNA of each of the p110α, p110β and p110δ Type Ia human PI3K p110 isoforms (EMBL Accession Nos. HSU79143, S67334, Y10055 for p110α, p110β and p110δ respectively) were sub-cloned into a pDEST10 vector (Invitrogen Limited, Fountain Drive, Paisley, UK). The vector is a Gateway-adapted version of Fastbac1 containing a 6-His epitope tag. A truncated form of Type Ib human PI3K p110γ isoform corresponding to amino acid residues 144-1102 (EMBL Accession No. X8336A) and the full length human p85α regulatory subunit (EMBL Accession No. HSP13KIN) were also sub-cloned into pFastBac1 vector containing a 6-His epitope tag. The Type Ia p110 constructs were co-expressed with the p85α regulatory subunit. Following expression in the baculovirus system using standard baculovirus expression techniques, expressed proteins were purified using the His epitope tag using standard purification techniques.

DNA corresponding to amino acids 263 to 380 of human general receptor for phosphoinositides (Grp1) PH domain was isolated from a cDNA library using standard molecular biology and PCR cloning techniques. The resultant DNA fragment was sub-cloned into a pGEX 4T1 *E. coli* expression vector containing a GST epitope tag (Amersham Pharmacia Biotech, Rainham, Essex, UK) as described by Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245). The GST-tagged Grp1 PH domain was expressed and purified using standard techniques.

Test compounds were prepared as 10 mM stock solutions in DMSO and diluted into water as required to give a range of final assay concentrations. Aliquots (2 μl) of each compound dilution were placed into a well of a Greiner 384-well low volume (LV) white polystyrene plate (Greiner Bio-one, Brunel Way, Stonehouse, Gloucestershire, UK Catalogue No. 784075). A mixture of each selected recombinant purified PI3K enzyme (15 ng), DiC8-PI(4,5)P2 substrate (40 μM; Cell Signals Inc., Kinnear Road, Columbus, USA, Catalogue No. 901), adenosine triphosphate (ATP; 4 μM) and a buffer solution [comprising Tris-HCl pH7.6

buffer (40 mM, 10 µl), 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS; 0.04%), dithiothreitol (DTT; 2 mM) and magnesium chloride (10 mM)] was agitated at room temperature for 20 minutes.

Control wells that produced a minimum signal corresponding to maximum enzyme activity were created by using 5% DMSO instead of test compound. Control wells that produced a maximum signal corresponding to fully inhibited enzyme were created by adding wortmannin (6 µM; Calbiochem / Merck Bioscience, Padge Road, Beeston, Nottingham, UK, Catalogue No. 681675) instead of test compound. These assay solutions were also agitated for 20 minutes at room temperature.

Each reaction was stopped by the addition of 10 µl of a mixture of EDTA (100 mM), bovine serum albumin (BSA, 0.045 %) and Tris-HCl pH7.6 buffer (40 mM).

Biotinylated-DiC8-PI(3,4,5)P3 (50 nM; Cell Signals Inc., Catalogue No. 107), recombinant purified GST-Grp1 PH protein (2.5 nM) and AlphaScreen Anti-GST donor and acceptor beads (100 ng; Packard Bioscience Limited, Station Road, Pangbourne, Berkshire, UK, Catalogue No. 6760603M) were added and the assay plates were left for about 5 to 20 hours at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read using a Packard AlphaQuest instrument.

PI(3,4,5)P3 is formed *in situ* as a result of PI3K mediated phosphorylation of PI(4,5)P2. The GST-Grp1 PH domain protein that is associated with AlphaScreen Anti-GST donor beads forms a complex with the biotinylated PI(3,4,5)P3 that is associated with Alphascreen Streptavidn acceptor beads. The enymatically-produced PI(3,4,5)P3 competes with biotinylated PI(3,4,5)P3 for binding to the PH domain protein. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, PI3K enzme activity to form PI(3,4,5)P3 and subsequent competition with biotinylated PI(3,4,5)P3 results in a reduced signal. In the presence of a PI3K enzyme inhibitor, signal strength is recovered.

PI3K enzyme inhibition for a given test compound was expressed as an IC_{50} value.

(b)(ii) *In Vitro* PI3K Enzyme Assay (Echo)

The assay used AlphaScreen technology (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) to determine the ability of test compounds to inhibit phosphorylation by recombinant Type I PI3K enzymes of the lipid PI(4,5)P2.

DNA fragments encoding human PI3K catalytic and regulatory subunits were isolated from cDNA libraries using standard molecular biology and PCR cloning techniques. The selected DNA fragments were used to generate baculovirus expression vectors. In particular, full length DNA of each of the p110α, p110β and p110δ Type Ia human PI3K p110 isoforms (EMBL Accession Nos. HSU79143, S67334, Y10055 for p110α, p110β and p110δ respectively) were sub-cloned into a pDEST10 vector (Invitrogen Limited, Fountain Drive, Paisley, UK). The vector is a Gateway-adapted version of Fastbac1 containing a 6-His epitope tag. A truncated form of Type Ib human PI3K p110γ isoform corresponding to amino acid residues 144-1102 (EMBL Accession No. X8336A) and the full length human p85α regulatory subunit (EMBL Accession No. HSP13KIN) were also sub-cloned into pFastBac1 vector containing a 6-His epitope tag. The Type Ia p110 constructs were co-expressed with the p85α regulatory subunit. Following expression in the baculovirus system using standard baculovirus expression techniques, expressed proteins were purified using the His epitope tag using standard purification techniques.

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Test compounds were prepared as 10 mM stock solutions in DMSO and diluted in DMSO to wateras required to give a range of final assay concentrations. Aliquots (120nl2 μl) of each compound dilution were acoustically dispensed using a Labcyte Echo 550 placed into a well of a Greiner 384-well low volume (LV) white polystyrene plate (Greiner Bio-one, Brunel Way, Stonehouse, Gloucestershire, UK Catalogue No. 784075). A mixture of each selected recombinant purified PI3K enzyme (15 ng), DiC8-PI(4,5)P2 substrate (40 μM; Cell Signals Inc., Kinnear Road, Columbus, USA, Catalogue No. 901), adenosine triphosphate (ATP; 4 μM) and a buffer solution [comprising Tris-HCl pH7.6 buffer (40 mM, 10 μl), 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS; 0.04%), dithiothreitol

(DTT; 2 mM) and magnesium chloride (10 mM)] was agitatedincubated at room temperature for 20 minutes.

Control wells that produced a minimum signal corresponding to maximum enzyme activity were created by using 1005% DMSO instead of test compound. Control wells that produced a maximum signal corresponding to fully inhibited enzyme were created by adding Wwortmannin (6 μM; Calbiochem / Merck Bioscience, Padge Road, Beeston, Nottingham, UK, Catalogue No. 681675) instead of test compound. These assay solutions were also incubatedagitated for 20 minutes at room temperature.

Each reaction was stopped by the addition of 10 10μl of a mixture of EDTA (100 mM), bovine serum albumin (BSA, 0.045 %) and Tris-HCl pH7.6 buffer (40 mM).

Biotinylated-DiC8-PI(3,4,5)P3 (50 nM; Cell Signals Inc., Catalogue No. 107), recombinant purified GST-Grp1 PH protein (2.5 nM) and AlphaScreen Anti-GST donor and acceptor beads (100 ng; Packard Bioscience Limited, Station Road, Pangbourne, Berkshire, UK, Catalogue No. 6760603M) were added and the assay plates were left for about 5 to overnight

20 hours at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read using a Packard AlphaQuest instrument.

PI(3,4,5)P3 is formed *in situ* as a result of PI3K mediated phosphorylation of PI(4,5)P2. The GST-Grp1 PH domain protein that is associated with AlphaScreen Anti-GST donor beads forms a complex with the biotinylated PI(3,4,5)P3 that is associated with Alphascreen Streptavidn acceptor beads. The enymatically-produced PI(3,4,5)P3 competes with biotinylated PI(3,4,5)P3 for binding to the PH domain protein. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, PI3K enzme activity to form PI(3,4,5)P3 and subsequent competition with biotinylated PI(3,4,5)P3 results in a reduced signal. In the presence of a PI3K enzyme inhibitor, signal strength is recovered.

PI3K enzyme inhibition for a given test compound was expressed as an IC_{50} value.

(c) *In Vitro* phospho-Ser473 Akt assay

This assay determines the ability of test compounds to inhibit phosphorylation of Serine 473 in Akt as assessed using Acumen Explorer technology (Acumen Bioscience Limited), a plate reader that can be used to rapidly quantitate features of images generated by laser-scanning.

A MDA-MB-468 human breast adenocarcinoma cell line (LGC Promochem, Teddington, Middlesex, UK, Catalogue No. HTB-132) was routinely maintained at 37°C with 5% CO_2 up to a confluency of 70–90% in DMEM containing 10% heat-inactivated FCS and 1% L-glutamine.

For the assay, the cells were detached from the culture flask using 'Accutase' (Innovative Cell Technologies Inc., San Diego, CA, USA; Catalogue No. AT104) using standard tissue culture methods and resuspended in media to give $1.7x10^5$ cells per mL. Aliquots (90 µl) were seeded into each of the inner 60 wells of a black Packard 96 well plate (PerkinElmer, Boston, MA, USA; Catalogue No. 6005182) to give a density of ~15000 cells per well. Aliquots (90 µl) of culture media were placed in the outer wells to prevent edge effects. The cells were incubated overnight at 37°C with 5% CO_2 to allow them to adhere.

On day 2, the cells were treated with test compounds and incubated for 2 hours at 37°C with 5% CO_2. Test compounds were prepared as 10 mM stock solutions in DMSO and serially diluted as required with growth media to give a range of concentrations that were 10-fold the required final test concentrations. Aliquots (10 µl) of each compound dilution were placed in a well (in triplicate) to give the final required concentrations. As a minimum reponse control, each plate contained wells having a final concentration of 100 µM LY294002 (Calbiochem, Beeston, UK, Catalogue No. 440202). As a maximum response control, wells contained 1% DMSO instead of test compound. Following incubation, the contents of the plates were fixed by treatment with a 1.6% aqueous formaldehyde solution (Sigma, Poole, Dorset, UK, Catalogue No. F1635) at room temperature for 1 hour.

All subsequent aspiration and wash steps were carried out using a Tecan 96 well plate washer (aspiration speed 10 mm/sec). The fixing solution was removed and the contents of the plates were washed with phosphate-buffered saline (PBS; 50 µl; Gibco, Catalogue No. 10010015). The contents of the plates were treated for 10 minutes at room temperature with an aliquot (50 µl) of a cell permeabilisation buffer consisting of a mixture of PBS and 0.5% Tween-20. The 'permeabilisation' buffer was removed and non-specific binding sites were blocked by treatment for 1 hour at room temperature of an aliquot (50 µl) of a blocking buffer consisting of 5% dried skimmed milk ['Marvel' (registered trade mark); Premier Beverages, Stafford, GB] in a mixture of PBS and 0.05% Tween-20. The 'blocking' buffer was removed and the cells were incubated for 1 hour at room temperature with rabbit anti phospho-Akt

(Ser473) antibody solution (50 µl per well; Cell Signalling, Hitchin, Herts, U.K., Catalogue No 9277) that had been diluted 1:500 in 'blocking' buffer. Cells were washed three times in a mixture of PBS and 0.05% Tween-20. Subsequently, cells were incubated for 1 hour at room temperature with Alexafluor488 labelled goat anti-rabbit IgG (50 µl per well; Molecular Probes, Invitrogen Limited, Paisley, UK, Catalogue No. A11008) that had been diluted 1:500 in 'blocking' buffer. Cells were washed 3 times with a mixture of PBS and 0.05% Tween-20. An aliquot of PBS (50 µl) was added to each well and the plates were sealed with black plate sealers and the fluorescence signal was detected and analysed.

Fluorescence dose response data obtained with each compound were analysed and the degree of inhibition of Serine 473 in Akt was expressed as an IC_{50} value.

(d) *In Vitro* MDA-MB-468 human breast adenocarcinoma Proliferation Assay

This assay determines the ability of test compounds to inhibit cell proliferation as assessed using Cellomics Arrayscan technology. A MDA-MB-468 human breast adenocarcinoma cell line (LGC Promochem, Catalogue No. HTB-132) was routinely maintained as described in Biological Assay (b) herein.

For the proliferation assay, the cells were detached from the culture flask using Accutase and seeded into the inner 60 wells of a black Packard 96 well plate at a density of 8000 cells per well in 100 µl of complete growth media. The outer wells contained 100 µl of sterile PBS. The cells were incubated overnight at 37°C with 5% CO_2 to allow them to adhere.

On day 2, the cells were treated with test compounds and incubated for 48 hours at 37°C with 5% CO_2. Test compounds were prepared as 10 mM stock solutions in DMSO and serially diluted as required with growth media to give a range of test concentrations. Aliquots (50 µl) of each compound dilution were placed in a well and the cells were incubated for 2 days at 37°C with 5% CO_2. Each plate contained control wells without test compound.

On day 4, BrdU labelling reagent (Sigma, Catalogue No. B9285) at a final dilution of 1:1000 was added and the cells were incubated for 2 hours at 37°C. The medium was removed and the cells in each well were fixed by treatment with 100 µl of a mixture of ethanol and glacial acetic acid (90% ethanol, 5% glacial acetic acid and 5% water) for 30 minutes at room temperature. The cells in each well were washed twice with PBS (100 µl). Aqueous hydrochloric acid (2M, 100 µl) was added to each well. After 20 minutes at room temperature, the cells were washed twice with PBS. Hydrogen peroxide (3%, 50 µl; Sigma, Catalogue No.

H1009) was added to each well. After 10 minutes at room temperature, the wells were washed again with PBS.

BrdU incorporation was detected by incubation for 1 hour at room temperature with mouse anti-BrdU antibody (50 µl; Caltag, Burlingame, CA, US; Catalogue No. MD5200) that was diluted 1:40 in PBS containing 1% BSA and 0.05% Tween-20. Unbound antibody was removed with two washes of PBS. For visualisation of incorporated BrdU, the cells were treated for 1 hour at room temperature with PBS (50 µl) and 0.05% Tween-20 buffer containing a 1:1000 dilution of Alexa fluor 488–labelled goat anti-mouse IgG. For visualisation of the cell nucleus, a 1:1000 dilution of Hoechst stain (Molecular Probes, Catalogue No. H3570) was added. Each plate was washed in turn with PBS. Subsequently, PBS (100 µl) was added to each well and the plates were analysed using a Cellomics array scan to assess total cell number and number of BrdU positive cells.

Fluorescence dose response data obtained with each compound were analysed and the degree of inhibition of MDA-MB-468 cell growth was expressed as an IC_{50} value.

Although the pharmacological properties of the compounds of formula (I) vary with structural change as expected, in general, it is believed that activity possessed by compounds of formula (I) may be demonstrated at the following concentrations or doses in one or more of the above tests (a) to (d) :-

Test (a)(i):- IC_{50} versus mTOR kinase at less than 10 µM, in particular 0.001 - 0.5 µM for many compounds; for example 2b the IC_{50} was measured on three occasions, the values were 0.059, 0.005 and 0.023µM.

Test (b)(i):- IC_{50} versus p110γ Type Ib human PI3K at less than 10 µM, in particular 0.001 - 0.5 µM for many compounds; and IC_{50} versus p110α Type Ia human PI3K at less than 10 µM, in particular 0.001 - 0.5 µM for many compounds;

for example 2b the IC50 was measured, the value was 1.044 µM.

Test (c):- IC_{50} versus Serine 473 in Akt at less than 10 µM, in particular 0.1 - 20 µM for many compounds); for example 2b the IC_{50} was measured on two occasions, the values were 0.052 and 0.025 µM.

Test (d):- IC_{50} at less than 20 µM.

The following examples were tested in enzyme assay Test (a)(ii):

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
1	0.00276	23l	0.00888	52	0.0184
1a	0.00279	23m	0.0577	52a	0.0103
2	0.0015	24	0.00517	52b	0.0307
2a	0.0932	25	0.00155	52c	0.0296
2b	0.000169	25a	0.00224	52d	0.00588
2c	0.00186	25b	0.000817	53	0.00218
2d	0.0239	25c	0.00385	53a	0.00229
2e	0.279	25d	0.00152	53b	0.000669
2f	0.00433	25e	0.000277	53c	0.000688
2g	0.000231	25f	0.0547	53d	0.0031
2h	0.000272	25g	0.00143	53e	0.00198
2i	0.00207	25h	0.000993	53f	0.00634
2j	0.012	25i	0.001	54	0.00217
2k	0.00381	25j	0.00576	54a	0.00918
2l	0.0116	25k	0.00292	54b	0.00317
2m	0.00589	25l	0.000956	54c	0.00453
2n	0.00844	25m	0.00025	54d	0.00882
2o	0.000403	26	0.00605	54e	0.00762
2p	0.0027	26a	0.00672	54f	0.0107
2q	0.000379	26b	0.0039	55	0.00296
2r	0.00103	26c	0.119	55a	0.0213
2s	0.00155	26d	0.0012	55b	0.0161
2t	0.000656	26e	0.00395	55c	0.0189
2u	0.00118	26f	0.00457	55d	0.0351
2v	0.00866	26g	0.00746	55e	0.0204
2w	0.0685	26h	0.004	55f	0.0156
2x	0.00164	27	0.00111	56	0.00231
2y	0.23	27a	0.00388	56a	0.00226
2z	0.0181	27b	0.00425	56b	0.00165

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
2aa	0.0274	27c	0.014	56c	0.00623
2ab	0.0553	27d	0.00307	56d	0.0043
2ac	0.00641	27e	0.000351	57	0.0119
2ad	0.000705	27f	0.000997	57a	0.0104
2ae	0.00072	27g	0.0213	57b	0.00457
2af	0.0462	27h	0.000244	57c	0.00695
2ag	0.0149	27i	0.00302	57d	0.01
3	0.00195	27j	0.00761	57e	0.00728
3a	0.00445	27k	0.00462	57f	0.0106
3b	0.00385	27l	0.00112	57g	0.0585
3c	0.0124	27m	0.00144	58	0.00115
3d	0.0135	28	0.00187	58a	0.00339
3e	0.00166	28a	0.00253	58b	0.002
3f	0.0214	28b	0.00149	58c	0.00327
3g	0.00126	28c	0.00847	58d	0.00293
3h	0.0165	28d	0.00237	58e	0.00256
3i	0.000932	28e	0.000434	58f	0.00267
3j	0.00422	28f	0.0674	58g	0.0102
3k	0.00227	28g	0.00118	59	0.00882
3l	0.00257	28h	0.00093	59a	0.0222
3m	0.000497	28i	0.00153	59b	0.00993
3n	0.0396	28j	0.00557	59c	0.0226
3o	0.00596	28k	0.000954	59d	0.032
3p	0.193	28l	0.000442	59e	0.293
3q	0.00839	29	0.0042	59f	0.0491
3r	0.0488	30	0.025	59g	0.101
3s	0.0263	31	0.00452	60	0.012
3t	0.00479	31a	0.00265	60a	0.0191
3u	0.000604	31b	0.00497	60b	0.00862

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
3w	0.00089	31c	0.00131	60c	0.00695
4	0.000699	31d	0.00955	60d	0.0183
4a	0.00217	31e	0.00107	60e	0.0116
4b	0.00203	31f	0.0016	60f	0.0173
4c	0.0169	31g	0.00323	61	0.0269
4d	0.01	31h	0.000209	61a	0.0326
4e	0.000767	31i	0.00326	61b	0.0136
4f	0.01	31j	0.00103	61c	0.0211
4g	0.0626	31k	0.00191	61d	0.0438
4h	0.00146	31l	0.214	61e	0.0237
4i	0.0115	31m	0.00591	61f	0.0328
4j	0.00379	32	0.00315	62	0.00205
4k	0.00905	32a	0.0425	62a	0.0393
4l	0.00369	32b	0.00829	62b	0.00546
4m	0.00245	32c	0.00288	62c	0.0375
4n	0.0392	32d	0.0131	62d	0.022
5	0.000802	33	0.00929	63	0.0725
5a	0.000289	33a	0.0584	64	0.00785
5b	0.00052	33b	0.012	64a	0.0052
5c	0.00681	33c	0.00258	64b	0.00678
5d	0.00274	33d	0.133	64c	0.00215
5e	0.000864	34	0.00405	64d	0.0067
5f	0.00485	34a	0.0387	64e	0.00537
5g	0.0668	34b	0.0109	64f	0.00521
5h	0.00234	34c	0.00345	64g	0.0342
5i	0.00988	34d	0.0863	64h	0.00148
5j	0.000173	35	0.00531	64i	0.00135
5k	0.00333	35a	0.00552	64j	0.0012
5l	0.000237	35b	0.000577	64k	0.00144

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
5m	0.000604	35c	0.108	64l	0.00111
5n	0.00828	35d	0.00411	64m	0.0408
6	0.001	36a	0.142	64n	0.0161
6a	0.00293	36b	0.00179	64o	0.00345
6b	0.00612	36c	0.114	64p	0.00398
6c	0.00321	36d	0.00317	64q	0.00467
6d	0.000874	36e	0.00667	64r	0.00418
6e	0.0673	36f	0.00278	64s	0.00296
6f	0.000794	36g	0.00841	64t	0.0114
6g	0.00225	36h	0.00314	64u	0.0139
6h	0.000799	36i	0.0518	64v	0.146
6i	0.00462	36j	0.018	64w	0.0161
6j	0.00593	36k	0.0131	64x	0.00761
6k	0.00186	36l	0.0428	64y	0.0125
6l	0.00119	36m	0.0347	64z	0.00866
6m	0.000936	36n	0.0248	64aa	0.00388
7	0.00315	36o	0.00358	64ab	0.0094
7a	0.00231	36p	0.00161	64ac	0.00529
7b	0.0181	36q	0.0889	64ad	0.00298
7c	0.00646	36r	0.00733	64ae	0.00213
7d	0.0038	36s	0.00475	64af	0.00339
7e	0.00212	36t	0.194	64ag	0.00281
7f	0.00915	36u	0.00922	64ah	0.00684
7g	0.211	36v	0.467	64ai	0.00567
7h	0.0116	36w	0.11	64aj	0.00778
7i	0.0182	36x	0.182	64ak	0.00161
7j	0.0105	36y	0.00131	64al	0.00558
7k	0.00482	36z	0.00208	65	0.03
7l	0.00913	36aa	0.0749	65a	0.00688

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
7m	0.00504	36ab	0.011	65b	0.00342
8	0.000959	36ac	0.00441	65c	0.0151
8a	0.00096	36ad	0.0323	65d	0.00448
8b	0.00123	36ae	0.0151	65e	0.0114
8c	0.00185	36af	0.00275	66	0.00303
8d	0.00134	36ag	0.0013	66a	0.00415
8e	0.000342	36ah	0.00247	66b	0.0246
8f	0.00882	36ai	0.00561	67	0.001
8g	0.0784	36aj	0.00255	68	0.00141
8h	0.00176	36ak	0.00245	68a	0.00174
8i	0.0198	36al	0.0161	69	0.00788
8j	0.000751	36am	0.0259	70	0.002
8k	0.0173	36an	0.0104	71	0.0182
8l	0.00813	36ao	0.014	72	0.00432
8m	0.00136	36ap	0.0156	73	0.00744
9	0.0018	36aq	0.0157	74	0.00237
9a	0.0129	36ar	0.00945	74a	0.00398
9b	0.0215	36as	0.00911	74b	0.00244
9c	0.0483	36at	0.00639	74c	0.00314
9d	0.0151	36au	0.0121	74d	0.00279
9e	0.00187	36av	0.00995	74e	0.00506
9f	0.144	36aw	0.0164	74f	0.00399
9g	0.00127	36ax	0.0211	74g	0.00433
9h	0.0057	36ay	0.00117	74h	0.00321
9i	0.0024	36az	0.00105	74i	0.00925
9j	0.046	36ba	0.00167	75	0.029
9k	0.0115	36bb	0.00513	75a	0.0435
9l	0.00395	36bc	0.00285	75b	0.0381
9m	0.00401	36bd	0.00258	75c	0.0339

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
10	0.00448	36be	0.00376	75d	0.0399
10a	0.0395	36bf	0.00457	75e	0.037
10b	0.0266	36bg	0.00189	75f	0.0608
10c	0.147	36bh	0.00137	76	0.00687
10d	0.0432	36bi	0.00231	76a	0.00407
10e	0.00691	36bj	0.00106	76b	0.00719
10f	0.174	36bk	0.00433	76c	0.00319
10g	0.00156	36bl	0.00333	76d	0.00924
10h	0.0268	36bm	0.00193	76e	0.00566
10i	0.00591	36bn	0.00637	76f	0.00678
10j	0.11	36bo	0.0176	77	0.00821
10k	0.0502	36bp	0.00198	77a	0.00524
10l	0.0183	36bq	0.00131	77b	0.0086
10m	0.00497	36br	0.00188	77c	0.00437
11	0.00165	36bs	0.00264	77d	0.0101
11a	0.0059	36bt	0.00188	77e	0.00517
11b	0.00333	36bu	0.00118	77f	0.00919
11c	0.0247	36bv	0.00264	78	0.0418
11d	0.00642	36bw	0.00909	78a	0.0153
11e	0.00197	36bx	0.00269	78b	0.0333
11f	0.00337	36by	0.012	78c	0.0209
11g	0.313	36bz	0.0143	78d	0.0175
11h	0.00913	36ca	0.31	78e	0.0239
11i	0.0294	36cb	0.163	78f	0.0291
11j	0.0122	36cc	0.129	79	0.0186
11k	0.00332	36cd	0.147	79a	0.0222
11l	0.00356	36ce	0.42	79b	0.0109
11m	0.00437	36cf	0.286	79c	0.0299
12	0.00421	36cg	0.136	79d	0.0161

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
12a	0.00167	36ch	0.208	79e	0.0259
12b	0.00271	36ci	0.0386	79f	0.0398
12c	0.00751	36cj	0.00333	80	0.0197
12d	0.00155	36ck	2.62	80a	0.0146
12e	0.00459	36cl	0.0681	80b	0.0103
12f	0.35	36cm	0.00946	80c	0.00921
12g	0.00273	36cn	0.0858	80d	0.00951
12h	0.00392	36co	1.62	80e	0.0143
12i	0.000771	36cp	1.26	81	0.0137
12j	0.00167	36cq	0.114	82	0.00939
12k	0.0043	36cr	0.0435	82a	0.0265
12l	0.00138	36cs	1.17	82b	0.00757
12m	0.0101	36ct	0.00157	82c	0.0185
12n	0.238	36cu	0.0686	82d	0.0243
12o	0.00509	36v	0.259	82e	0.0208
12p	0.0014	36cw	0.0493	82f	0.0273
12q	0.00162	36cx	0.284	83	0.00346
12r	0.000991	36cy	0.0478	83a	0.00483
12s	0.117	36cz	0.0384	83b	0.0114
12t	0.0366	36da	0.0331	83c	0.0124
13	0.00357	36db	0.0209	83d	0.0472
13a	0.00341	36dc	0.00989	84	0.00956
13b	0.0037	36dd	0.00291	84a	0.00909
13c	0.00173	36de	0.00389	84b	0.00385
13d	0.00351	36df	0.00712	84c	0.00829
13e	0.0301	36dg	0.0164	84d	0.00959
13f	0.386	36dh	0.0034	84e	0.00818
13g	0.00479	36di	0.00923	84f	0.0134
13h	0.0106	36dj	0.00891	85	0.00477

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
13i	0.00275	36dk	0.00905	85a	0.00313
13j	0.0178	36dl	0.00399	85b	0.00526
13k	0.0179	36dm	0.0298	85c	0.00509
13l	0.0108	36dn	0.0138	85d	0.00323
13m	0.0532	36do	0.0277	85e	0.0183
13n	0.997	36dp	0.0106	85f	0.0202
13o	0.0287	36dq	0.0245	85g	0.0259
13p	0.00202	36dr	0.294	85h	0.0426
13q	0.00192	36ds	0.000973	85i	0.0153
13r	0.00198	36dt	0.00037	85j	0.0124
13s	0.00846	36du	0.0152	86	0.00247
13t	0.172	36dv	0.0043	86a	0.00522
13u	0.00477	36dw	0.00624	86b	0.00725
14	0.0465	36dx	0.00262	86c	0.00247
14a	0.0136	36dy	0.00636	86d	0.00382
14b	1.39	36dz	0.00277	86e	0.00223
14c	0.0401	36ea	0.00884	86f	0.00345
14d	0.0143	36eb	0.00311	87	0.00487
14e	0.11	36ec	0.00321	87a	0.0887
14f	0.189	36ed	0.00704	87b	0.0177
14g	0.0857	36ee	0.00958	87c	0.00775
14h	0.14	36ef	0.00841	87d	0.0177
14i	0.0339	36eg	0.00877	87e	0.0103
14j	0.0129	37a	0.026	87f	0.00907
14k	0.275	37b	0.0124	88	0.0321
14l	0.0137	37c	0.0033	88a	0.00448
14m	0.0143	37d	0.00439	88b	0.0567
14n	0.0363	37e	0.0049	88c	0.047
14o	0.0217	37f	0.12	88d	0.004

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
14p	0.537	37g	0.0179	88e	0.131
14q	0.0265	37h	0.0198	89	0.485
14r	0.0103	37i	0.00379	90	0.0189
14s	0.122	37j	0.0309	91	0.00498
14t	0.197	37k	0.0161	91a	0.00198
14u	0.123	37l	0.032	91b	0.00521
14v	0.0823	37m	0.0506	91c	0.00368
14w	0.208	37n	0.0393	91d	0.00356
14x	0.63	37o	0.033	92	0.00793
14y	0.152	37p	0.00534	92a	0.00551
14z	0.171	37q	0.00294	92b	0.00746
14aa	0.0186	37r	0.00162	92c	0.0078
15	0.00154	37s	0.00756	92d	0.00807
15a	0.000591	37t	0.00889	92e	0.00599
16	0.00142	37u	0.000395	92f	0.00625
16a	0.0101	37v	0.00549	93	0.00505
16b	0.00577	37w	0.00137	93a	0.00303
16c	0.0016	37x	0.00944	93b	0.0023
16d	0.00364	37y	0.00686	93c	0.0029
16e	0.0214	37z	0.00481	93d	0.000818
16f	0.0212	37aa	0.00567	93e	0.00541
16g	0.0176	37ab	0.00488	94a	0.0136
16h	0.186	37ac	0.0438	94b	0.0122
16i	0.845	37ad	0.00263	94c	0.0118
17	0.00116	37ae	0.00952	94d	0.011
17a	0.000942	37af	0.0233	94e	0.0135
17b	0.000584	37ag	0.0134	94f	0.0151
17c	0.00179	38	0.00131	94g	0.0127
18	0.00135	38a	0.000918	94h	0.0116

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
18a	0.00714	39	0.000351	94i	0.0121
18b	0.0147	39a	0.000502	94j	0.00605
18c	0.032	40	0.00436	94k	0.0106
18d	0.0151	40a	0.00221	95a	0.0139
18e	0.000654	41	0.0308	95b	0.019
18f	0.12	42	0.000705	95c	0.00706
18g	0.00123	42a	0.00261	95d	0.0126
18h	0.00664	42b	0.00535	95e	0.016
18i	0.00555	42c	0.0036	95f	0.0109
18j	0.0303	42d	0.000607	95g	0.0164
18k	0.0113	42e	0.00257	95h	0.013
18l	0.0102	42f	0.00264	95i	0.00479
18m	0.00315	42g	0.00401	95j	0.0131
19	0.00131	42h	0.00412	95k	0.0272
19a	0.00425	43	0.00539	95l	0.00109
19b	0.00119	43a	0.00479	95m	0.00202
19c	0.0214	43b	0.00751	95n	0.000668
19d	0.00318	43c	0.0288	95o	0.00473
19e	0.00135	43d	0.011	95p	0.00543
19f	0.0804	43e	0.188	95q	0.00168
19g	0.000274	43f	0.0392	95r	0.00631
19h	0.00246	43g	0.029	96a	0.0177
19i	0.00152	43h	0.133	96b	0.0268
19j	0.0199	43i	0.102	96c	0.0272
19k	0.00415	43j	0.012	96d	0.0209
19l	0.00152	43k	0.0257	96e	0.00862
19m	0.000944	43l	0.0236	97	0.0882
20	0.0128	43m	0.00531	98a	0.011
20a	0.0163	43n	0.0119	98b	0.00413

Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)	Ex No.	Test (a)(ii) IC_{50} (μM)
20b	0.874	43o	0.0157	98c	0.0267
20c	0.00559	43p	0.0555	98d	0.00441
20d	0.0133	43q	0.028	98e	0.00335
21	0.0253	43r	0.0577	98f	0.00229
21a	0.0378	43s	0.00629	98g	0.0127
21b	0.0133	43t	0.00545	98h	0.00362
21c	0.0234	44	0.0234	98i	0.0285
22	0.503	45	0.00717	98j	0.00374
23	0.00492	46	0.00456	98k	0.00246
23a	0.00459	46a	0.0126	98l	0.00789
23b	0.197	47	0.0155	99a	0.0438
23c	0.000831	47a	0.0054	99b	0.0316
23d	0.00534	47b	0.0149	99c	0.239
23e	0.00876	48	0.00072	99d	0.219
23f	0.0199	48a	0.00116	99e	0.0317
23g	1.21	49	0.00187	99f	0.00589
23h	0.00808	49a	0.00267	99g	0.0152
23i	0.0254	50	0.0104	99h	0.0782
23j	0.0314	50a	0.00794	99i	0.0594
23k	1.14	51	0.00332	99j	0.0124

Compounds may be further selected on the basis of further biological or physical properties which may be measured by techniques known in the art and which may be used in the assessment or selection of compounds for therapeutic or prophylactic application.

The compounds of the present invention are advantageous in that they possess pharmacological activity. In particular, the compounds of the present invention modulate (in particular, inhibit) mTOR kinase and/or phosphatidylinositol-3-kinase (PI3K) enzymes, such as the Class Ia PI3K enzymes (*e.g.* PI3Kalpha, PI3Kbeta and PI3Kdelta) and the Class Ib PI3K enzyme (PI3Kgamma). More particularly compounds of the present invention modulate (in

particular, inhibit) mTOR kinase. More particularly compounds of the present invention modulate (in particular, inhibit) one or more PI3K enzyme. The inhibitory properties of compounds of formula (I) may be demonstrated using the test procedures set out herein and in the experimental section. Accordingly, the compounds of formula (I) may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are mediated by mTOR kinase and/or one or more PI3K enzyme(s), and in particular by mTOR kinase.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in association with a pharmaceutically acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 1 mg to 1 g of active agent (more suitably from 1 to 250 mg, for example from 1 to 100 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of formula I will naturally vary according to the nature and severity of the disease state, the age and sex of the animal or patient and the route of administration, according to well known principles of

medicine.

In using a compound of formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 1 mg/kg to 100 mg/kg body weight is received, given if required in divided doses. In general, lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 1 mg/kg to 25 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 1 mg/kg to 25 mg/kg body weight will be used. Typically, unit dosage forms will contain about 10 mg to 0.5 g of a compound of this invention.

As stated herein, it is known that mTOR kinase and the PI3K enzymes have roles in tumourigenesis as well as numerous other diseases. We have found that the compounds of formula (I) possess potent anti-tumour activity which it is believed is obtained by way of inhibition of mTOR kinase and/or one or more of the PI3K enzymes.

Accordingly, the compounds of the present invention are of value as anti-tumour agents. Particularly, the compounds of the present invention are of value as anti-proliferative, apoptotic and/or anti-invasive agents in the containment and/or treatment of solid and/or liquid tumour disease. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of mTOR and/or one or more of the PI3K enzymes such as the Class Ia PI3K enzymes and the Class Ib PI3K enzyme. Further, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are mediated alone or in part by mTOR and/or one or more of the PI3K enzymes such as the Class Ia PI3K enzymes and the Class Ib PI3K enzyme. The compounds may thus be used to produce an mTOR enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Certain compounds may be used to produce an PI3K enzyme inhibitory effect in a warm-blooded animal in need of such treatment.

As stated herein, inhibitors of mTOR kinase and/or one or more PI3K enzymes should be of therapeutic value for the treatment of proliferative disease such as cancer and in particular solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies and in particular for treatment of, for example, cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate, and of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and

vulva, and of leukaemias [including acute lymphoctic leukaemia (ALL) and chronic myelogenous leukaemia (CML)], multiple myeloma and lymphomas.

Anti-cancer effects which are accordingly useful in the treatment of cancer in a patient include, but are not limited to, anti-tumour effects, the response rate, the time to disease progression and the survival rate. Anti-tumour effects of a method of treatment of the present invention include but are not limited to, inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment, slowing of disease progression. Anti-cancer effects include prophylactic treatment as well as treatment of existing disease.

A mTOR kinase inhibitor, or a pharmaceutically acceptable salt thereof, may also be useful for the treatment patients with cancers, including, but not limited to, haematologic malignancies such as leukaemia, multiple myeloma, lymphomas such as Hodgkin's disease, non-Hodgkin's lymphomas (including mantle cell lymphoma), and myelodysplastic syndromes, and also solid tumours and their metastases such as breast cancer, lung cancer (non-small cell lung cancer (NSCL), small cell lung cancer (SCLC), squamous cell carcinoma), endometrial cancer, tumours of the central nervous system such as gliomas, dysembryoplastic neuroepithelial tumour, glioblastoma multiforme, mixed gliomas, medulloblastoma, retinoblastoma, neuroblastoma, germinoma and teratoma, cancers of the gastrointestinal tract such as gastric cancer, oesophagal cancer, hepatocellular (liver) carcinoma, cholangiocarcinomas, colon and rectal carcinomas, cancers of the small intestine, pancreatic cancers, cancers of the skin such as melanomas (in particular metastatic melanoma), thyroid cancers, cancers of the head and neck and cancers of the salivary glands, prostate, testis, ovary, cervix, uterus, vulva, bladder, kidney (including renal cell carcinoma, clear cell and renal oncocytoma), squamous cell carcinomas, sarcomas such as osteosarcoma, chondrosarcoma, leiomyosarcoma, soft tissue sarcoma, Ewing's sarcoma, gastrointestinal stromal tumour (GIST), Kaposi's sarcoma, and paediatric cancers such as rhabdomyosarcomas and neuroblastomas.

The compounds of the present invention and the methods of treatment comprising the administering or use of a mTOR kinase inhibitor, or a pharmaceutically acceptable salt thereof, are expected to be particularly useful for the treatment of patients with lung cancer, prostate cancer, melanoma, ovarian cancer, breast cancer, endometrial cancer, kidney cancer, gastric

cancer, sarcomas, head and neck cancers, tumours of the central nervous system and their metastases, and also for the treatment of patients with acute myeloid leukaemia.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use as a medicament in a warm-blooded animal such as man.

According to a further aspect of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further aspect of the invention, there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the production of an apoptotic effect in a warm-blooded animal such as man.

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in a warm-blooded animal such as man as an anti-invasive agent in the containment and/or treatment of proliferative disease such as cancer.

According to a further aspect of the invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further aspect of the invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for the production of an apoptotic effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the production of an apoptotic effect in a warm-blooded animal such as man.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the

manufacture of a medicament for use in a warm-blooded animal such as man as an anti-invasive agent in the containment and/or treatment of proliferative disease such as cancer.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the prevention or treatment of proliferative disease such as cancer in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of proliferative disease such as cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the prevention or treatment of those tumours which are sensitive to inhibition of mTOR kinase and/or one or more PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

According to a further feature of this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of mTOR kinase and/or one or more PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) that are involved in the signal transduction

steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of mTOR kinase and/or one or more PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in providing a mTOR kinase inhibitory effect and/or a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect).

According to a further feature of this aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in providing a mTOR kinase inhibitory effect and/or a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect).

According to a further aspect of the invention there is also provided a method for providing a mTOR kinase inhibitory effect and/or a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect) which comprises administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases.

According to a further feature of the invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies.

According to a further feature of the invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of

cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate.

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, endometrium, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

According to a further feature of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein for use in the treatment of lung cancer, prostate cancer, melanoma, ovarian cancer, breast cancer, endometrial cancer, kidney cancer, gastric cancer, sarcomas, head and neck cancers, tumours of the central nervous system and their metastases, and also for the treatment acute myeloid leukaemia.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of of solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the

manufacture of a medicament for use in the treatment of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

According to a further feature of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the treatment of lung cancer, prostate cancer, melanoma, ovarian cancer, breast cancer, endometrial cancer, kidney cancer, gastric cancer, sarcomas, head and neck cancers, tumours of the central nervous system and their metastases, and also for the treatment acute myeloid leukaemia.

According to a further feature of the invention there is provided a method for treating cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a method for treating solid tumours such as carcinoma and sarcomas and the leukaemias and lymphoid malignancies in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a method for treating cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a method for treating cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

According to a further feature of the invention there is provided a method for treating lung cancer, prostate cancer, melanoma, ovarian cancer, breast cancer, endometrial cancer, kidney cancer, gastric cancer, sarcomas, head and neck cancers, tumours of the central nervous system and their metastases, and acute myeloid leukaemia in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined herein.

As stated herein, the *in vivo* effects of a compound of formula (I) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of formula (I).

The invention further relates to combination therapies wherein a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of formula (I) is administered concurrently or sequentially or as a combined preparation with another treatment of use in the control of oncology disease.

In particular, the treatment defined herein may be applied as a sole therapy or may involve, in addition to the compounds of the invention, conventional surgery or radiotherapy or chemotherapy. Accordingly, the compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of cancer.

Suitable agents to be used in combination include :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and gemcitabine); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like paclitaxel and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecins);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin),

progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661), and metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™] and the anti-erbB1 antibody cetuximab [C225]); such inhibitors also include, for example, tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033) and erbB2 tyrosine kinase inhibitors such as lapatinib), inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)) and inhibitors of cell signalling through MEK and/or Akt kinases;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin)];

(vi) vascular damaging agents such as combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense agent;

(viii) gene therapy approaches, including approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapeutic approaches, including *ex-vivo* and *in-vivo* approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

The invention will now be further explained by reference to the following illustrative examples.

Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were of laboratory grade and were used as received.

In the examples ^{1}H NMR spectra were recorded on a Bruker DPX 300 (300 MHz), Bruker DRX 400 (400 MHz) instrument or a Bruker DRX 500 (500 MHz) instrument. The central peaks of chloroform-d (δ_H 7.27 ppm), dimethylsulfoxide-d_6 (δ_H 2.50 ppm) or acetone-d_6 (δ_H 2.05 ppm) were used as internal references. The following abbreviations have been used s, singlet; d, doublet;

t, triplet; q, quartet; m, multiplet; br, broad.

Column chromatography was carried out using silica gel (0.04-0.063 mm, Merck). In general, a Kromasil KR-100-5-C18 reversed-phase column (250 x 20 mm, Akzo Nobel) was used for preparative HPLC with mixtures of acetonitrile and water [containing 0.1% trifluoroacetic acid (TFA)] used as the eluent at a flow rate of 10 mL/min.

The following methods were used for liquid chromatography (LC) / mass spectral (MS) analysis :-

HPLC: Agilent 1100 or Waters Alliance HT (2790 & 2795)

Mass Spectrometer: Waters ZQ ESCi

HPLC Column

The standard HPLC column used is the Phemonenex Gemini C18 5μm, 50 x 2 mm.

Acidic HPLC Methods

The mobile phases used are: Mobile phase A: Water

Mobile Phase B: Acetonitrile

Mobile Phase C: 1% Formic Acid in 50:50 Water:MeCN (v/v)

Each method is followed by a rapid equilibration using a 5 mL flow rate for 0.45 min.

Four generic HPLC methods are available:

5 Minute Monitor Acidic method

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	0	95	5	6	1.1
4.5	0	95	5	6	1.1

Early Acidic method for early eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	57.5	37.5	5	6	1.1
4.5	57.5	37.5	5	6	1.1

Mid Acidic method for middle eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	67.5	27.5	5	6	1.1
4.5	27.5	67.5	5	6	1.1

Late Acidic method for late eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	27.5	67.5	5	6	1.1
4.5	5	95	5	6	1.1

Basic HPLC methods

In some instances the standard acidic methods may be unsuitable for either the compound ionisation or the chromatography separation required. In such cases four comparable Basic HPLC methods are available.

The mobile phases used are: Mobile phase A: Water

Mobile Phase B: Acetonitrile

Mobile Phase D: 0.1% 880 Ammonia in acetonitrile

Each method is followed by a rapid equilibration using a 5 mL flow rate for 0.45 min.

Minute Monitor Basic method

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase D:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	0	95	5	6	1.1
4.5	0	95	5	6	1.1

Early Basic method for early eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase D:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
4	57.5	37.5	5	6	1.1
4.5	57.5	37.5	5	6	1.1

Mid Basic method for middle eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase D:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	67.5	27.5	5	6	1.1
4.5	27.5	67.5	5	6	1.1

Late Basic method for late eluting compounds

Time /min	Mobile Phase A:	Mobile Phase B:	Mobile Phase C:	Curve	Flow Rate /mL/min
0.00	95	0	5	1	1.1
0.01	27.5	67.5	5	6	1.1
4.5	5	95	5	6	1.1

The following method was used for liquid chromatography (LC) / mass spectral (MS) analysis :- Instrument: Agilent 1100; Column: Waters 'Symmetry' 2.1 x 30 mm; Mass Spectral analysis using chemical ionisation (APCI); Flow rate: 0.7 mL/min; Absorption Wavelength: 254 nm; Solvent A: water + 0.1% TFA; Solvent B: acetonitrile + 0.1% TFA ; Solvent Gradient: 15-95% Solvent B for 2.7 minutes followed by 95% Solvent B for 0.3 minutes.

The following methods were used for LC analysis :-

Method A :- Instrument: Agilent 1100; Column: Kromasil C18 reversed-phase silica, 100 x 3 mm, 5μm particle size; Solvent A: 0.1% TFA/water, Solvent B: 0.08% TFA/acetonitrile; Flow Rate: 1 mL/min; Solvent Gradient: 10-100% Solvent B for 20 minutes followed by 100% Solvent B for 1 minute; Absorption Wavelengths: 220, 254 and 280 nm. In general, the retention time of the product was noted.

Method B :- Instrument: Agilent 1100; Column: Waters 'Xterra' C8 reversed-phase silica, 100 x 3 mm, 5μm particle size; Solvent A: 0.015M ammonia in water, Solvent B: acetonitrile; Flow Rate: 1 ml/min, Solvent Gradient: 10-100% Solvent B for 20 minutes followed by 100% Solvent B for 1 minute; Absorption Wavelength: 220, 254 and 280 nm. In general, the retention time of the product was noted.

The following abbreviations are used herein or within the following illustrative examples :-

HPLC	High Performance Liquid Chromatography
HBTU	*O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate;
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate;
HOBT	1-hydroxybenzotriazole;
HOAT	1-hydroxy-7-azabenzotriazole;
NMP	*N*-methylpyrrolidin-2-one;
DMSO	dimethylsulfoxide;
DMF	*N*,*N*-dimethylformamide;
DMA	*N*,*N*-dimethylacetamide;
THF	tetrahydrofuran;
DME	1,2-dimethoxyethane;
DCCI	dicyclohexylcarbodiimide;

MeOH methanol;

MeCN acetonitrile;

DCM dichloromethane;

DIPEA *N,N*-diisopropylethylamine;

DBU 1,8-diazabicyclo[5.4.0]undec-7-ene;

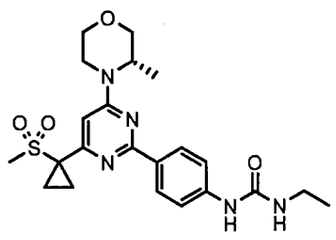
RT room temperature (approximately 17 to 25°C);

tR retention time;

m/z mass/charge ratio.

The chemical names were generated by software which used the Lexichem Toolkit (v. 1.60) from OpenEye Scientific Software (www.eyesopen.com) to generate IUPAC conforming names.

Example 1: 3-Ethyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



To a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine (200 mg, 0.60 mmol) in ethanol was added toluene (1.00 mL), water (1.00 mL), [4-(3-ethylureido)phenyl]boronic acid, pinacol ester (262 mg, 0.90 mmol), tri-potassium orthophosphate (448 mg, 2.11 mmol) and palladiumbis(tri-*tert*-butylphosphine) (18.55 mg, 0.04 mmol). The reaction was degassed then purged with nitrogen and heated at 80°C for 2 hours. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (5 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 0 to 10% (3.5M ammonia in methanol) in DCM, to give the desired material as a white solid (109 mg).

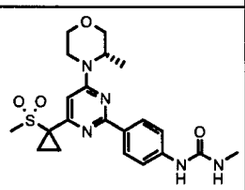
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, m), 1.23 (3H, d), 1.56 (2H, s), 1.67 (2H, s), 3.14 (2H, t), 3.22 (1H, m), 3.30 (3H, s), 3.48 (1H, t), 3.63 (1H, m), 3.76 (1H,

d), 3.97 (1H, d), 4.21 (1H, d), 4.57 (1H, s), 6.16 (1H, t), 6.76 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.66 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 460 ; HPLC tR = 1.83 min

mTOR Kinase Assay (Echo): 0.00276μM

The following compound was made in an analogous fashion from the appropriate boronic ester.

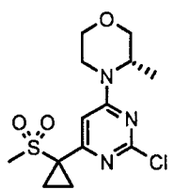
Example	Structure	NAME	LCMS MH+	Retention time (min)
1a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	446	1.68

Example 1a: ^{1}H NMR (400.132 MHz, DMSO) δ 1.23 (3H, d), 1.31 (3H, s), 1.56 (2H, m), 1.67 (2H, m), 2.66 (3H, d), 3.22 (1H, m), 3.48 (1H, m), 3.63 (1H, m), 3.76 (1H, d), 3.97 (1H, m), 4.21 (1H, d), 4.57 (1H, s), 6.07 (1H, m), 6.76 (1H, s), 7.51 (2H, d), 8.19 (2H, d), 8.75 (1H, s)

mTOR Kinase Assay (Echo): 0.00279μM

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine is described below.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine



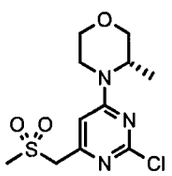
2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (1.2 g, 3.9 mmol) was dissolved in DMF (20 mL) and sodium *tert*-butoxide (755 mg, 7.85 mmol) was added to the reaction, followed by dibromoethane (738 mg, 3.9 mmol). The reaction was stirred at RT for 4 hours then at 60°C overnight. Further sodium *tert*-butoxide (378 mg, 3.9

mmol) was added to the reaction, followed by dibromoethane (369 mg, 1.9 mmol) and the reaction stirred at 60°C a further 24 hours. DCM (20 mL) was added and the reaction washed with 2M aqueous hydrochloric acid (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude solid was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM, to give the desired material (400 mg, 31 %).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (d, 3H), 1.51 (m, 2H), 1.64 (m, 2H), 3.18 (s, 3H), 3.22 (m, 1H), 3.43 (m, 1H), 3.58 (m, 1H), 3.72 (d, 1H), 3.93 (m, 1H), 4.05 (d, 1H), 4.41 (s, 1H), 6.93 (s, 1H)

LCMS Spectrum: m/z (ESI+)(M+H)+ 332, HPLC tR = 1.6 min

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine

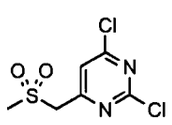


2,4-Dichloro-6-(methylsulfonylmethyl)pyrimidine (30 g, 0.13 mol) was dissolved in dichloromethane and stirred (under nitrogen) at -5°C. Triethylamine (17.4 mL, 0.13 mol) was added to give a clear brown solution. (3*S*)-3-Methylmorpholine was dissolved in dichloromethane and added dropwise keeping the reaction below -5°C. The cooling bath was then removed and the mixture stirred for 1 hour. The reaction mixture was heated at reflux for 2 hours, then the reaction mixture was washed with water, dried then evaporated. The crude material was purified by preparative HPLC to give the desired material as a solid (19.3 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.21 - 1.23 (m, 3H), 3.11 (s, 3H), 3.19 - 3.26 (m, 1H), 3.42 - 3.49 (m, 1H), 3.58 - 3.62 (1H, m), 3.73 (d, 1H), 3.92 - 3.96 (m, 2H), 4.27 - 4.31 (m, 1H), 4.45 (s, 2H), 6.92 (s, 1H)

LCMS Spectrum: MH+ 306, retention time 1.42 min, Method 5 Min Acid

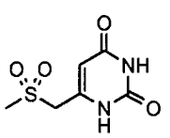
2,4-Dichloro-6-(methylsulfonylmethyl)pyrimidine



6-(Methylsulfonylmethyl)-1*H*-pyrimidine-2,4-dione (132 g, 0.65 mol) was added to phosphorus oxychloride (1.2 L) and the mixture heated to reflux for 16 hours, then cooled to

room temperature. The excess phosphorus oxychloride was removed *in vacuo*, the residue azeotroped with toluene (2 x 500 mL) and dissolved in dichloromethane. This mixture was then poured slowly onto ice (4 L) and stirred for 20 minutes, then extracted with dichloromethane (3 x 1 L) (the insoluble black material was filtered off and discarded) and ethyl acetate (2 x 1 L). The extracts were combined, dried, then evaporated to leave the desired material as a dark brown solid (51 g). The material was used without further purification.
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ3.13 (s, 3H), 4.79 (s, 2H), 7.87 (s, 1H)
LCMS Spectrum: MH+ 239, retention time 1.21 min, Method 5 Min Acid

6-(Methylsulfonylmethyl)-1*H*-pyrimidine-2,4-dione

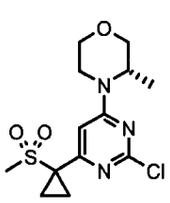


6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (175 g, 1.09 mol) was dissolved in DMF (2 L) and methanesulphinic acid sodium salt (133.5 g, 1.31 mol) was added. The reaction was heated to 125°C for 2 hours then allowed to cool and the suspension filtered and concentrated *in vacuo* to give a yellow solid. The crude material was washed with water, filtered, then triturated with toluene. The solid was filtered then triturated with isohexane to leave the desired compound as a yellow solid (250 g). The material was used without further purification.

6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione is a commercially available material.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine can also be prepared by the method described below.

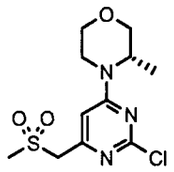
2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine



Sodium hydroxide (50%w/w solution) (115 g, 2877.88 mmol) was addedto 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (16 g, 52.33 mmol), 1,2-

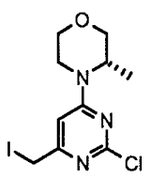
dibromoethane (13.53 ml, 156.98 mmol) and tetrabutylammonium bromide (1.687 g, 5.23 mmol) in toluene (128 mL) and the resulting suspension stirred at RT for 4 hours. Water was added and the mixture was extracted twice with toluene. The toluene was dried over $MgSO_4$, filtered and evaporated. The crude product,15g was purified by flash silicachromatography, elution gradient 0to 20% ethyl acetate in DCM, to give the desired material (13 g) as a white solid which was identical to previous samples.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine



Methanesulfinic acid, sodium salt (11.75 g, 115.11 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (37 g, 104.64 mmol), in acetonitrile (900 mL) and the resulting solution stirred at 85°Cfor 24 hours. The organic layers were combined and washed with water (3 x 100 mL), dried over $MgSO_4$, filtered, and the solvent was removed by evaporation to give the crude product as a dark brown oil, which solidifed (36 g). The crude solidwas purified by flash silicachromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material (22 g) as a cream solid which was identical to previous samples.

2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

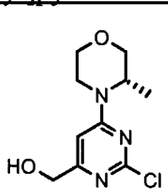


Methanesulfonyl chloride (0.245 mL, 3.14 mmol) was added dropwise over a period of 5 minutes to a solution of triethylamine (0.875 mL, 6.28 mmol) and [2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (510 mg, 2.09 mmol) in DCM (30 mL) at 0°C under nitrogen. The resulting solution was stirred at RT for 45 minutes. The reaction mixture was diluted with water (20 mL). The organic layer was dried ($MgSO_4$) and filtered. Sodium

Iodide (1569 mg, 10.46 mmol) was added and the reaction was heated to 50°C for 20 hours. The reaction mixture was filtered and evaporated to afford the desired material (761 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 1.19 - 1.25 (3H, m), 3.18 - 3.22 (1H, m), 3.40 - 3.47 (1H, m), 3.57 - 3.60 (1H, m), 3.71 (1H, d), 3.90 - 3.94 (1H, m), 3.96 - 3.98 (1H, m), 4.28 - 4.32 (3H, m), 6.94 (1H, s).
LCMS Spectrum: m/z (ESI+) (M+H)+ = 354; HPLC tR = 2.10 min.

2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine can also be prepared by the dropwise addition of methanesulfonyl chloride (91 mL, 1169.52 mmol) to [2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (190 g, 779.68 mmol) and triethylamine (163 mL, 1169.52 mmol) in DCM (2293 mL) at 0°C under air. The resulting solution was allowed to warm up slowly to RT over a period of 4 hours. The reaction mixture was quenched with water, extracted with DCM and the organic layer dried over $MgSO_4$, filtered and evaporated to afford [2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methyl methanesulfonate as a yellow gum (251 g). Sodium iodide (234 g, 1560.07 mmol) was added to this material in acetone (3679 mL) and the resulting suspension stirred at RT for 16 hours. The reaction mixture was evaporated to dryness and redissolved in DCM and washed three times with water then with a saturated aqueous solution of sodium thiosulphate. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude desired product (270 g). This was purified by chromatography to give an off white solid which was further triturated with ether to give the desired material which was identical to previous samples.

[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol



Methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate (3.15 g) was dissolved in dry THF (20 mL) and cooled to 0°C under nitrogen. A solution of lithium borohydride (2.0M in THF, 6.09mL) was added dropwise and the solution allowed to warm to RT and stirred for 1 hour. The reaction was quenched with water (20 mL) then evaporated to dryness, the residue dissolved in ethyl acetate (150 mL) and washed with water (150 mL)

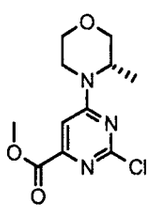
followed by brine (50 mL). The organics were evaporated to dryness to give to the desired material as a white solid (2.44 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 1.20 - 1.21 (3H, m), 3.18 - 3.22 (1H, m), 3.40 - 3.47 (1H, m), 3.56 - 3.60 (1H, m), 3.71 (1H, d), 3.91 - 3.94 (1H, m), 3.98 (1H, d), 4.35 (3H, d), 5.51 (1H, t), 6.74 (1H, s).

Mass Spectrum; M+H$^+$ 244.

[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol can also be prepared by the dropwise addition of lithium borohydride (2M in THF) (454 mL, 908.17 mmol) over a period of 15 minutes to a solution of methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate (235 g, 864.92 mmol) in the THF (4701 mL) at 0°C. The mixture was stirred at RT for 2 hours then water (1500 mL) was added slowly. A white solid formed which was decanted off and the THF was removed under vacuum. To the residue was added more water (500 mL), and extracted with ethyl acetate (3 x 700 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a white solid which was identical to previous samples.

Methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate



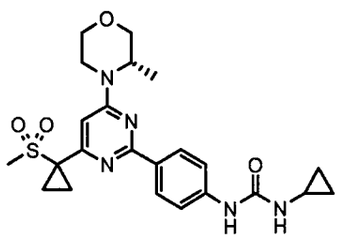
Methyl 2,6-dichloropyrimidine-4-carboxylate (5 g) was dissolved in DCM (120 mL). (3*S*)-3-Methylmorpholine (2.49 g) dissolved in triethylamine (3.70 mL) and DCM (10 mL) was added dropwise to the solution over 10 minute. The reaction was left to stir at room temperature for 1 hour. The reaction was then evaporated to dryness and dissolved in DCM (300 mL). The organics were washed once with water (150 mL) and dried ($MgSO_4$), filtered and evaporated. The crude material was chromatographed on silica, eluting with 2.5% methanol in DCM, to give the desired material as a white solid (3.15 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 1.22 - 1.24 (3H, m), 3.25 (1H, d), 3.41 - 3.48 (1H, m), 3.57 - 3.61 (1H, m), 3.71 (1H, d), 3.87 (3H, s), 3.91 - 3.95 (1H, m), 4.25 (1H, s), 4.45 (1H, s), 7.29 (1H, s).

Mass Spectrum; $M+H^+$ 272.

Methyl 2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine-4-carboxylate can also be prepared by the addition of methyl 2,6-dichloropyrimidine-4-carboxylate (250 g, 1207.65 mmol) to the DCM (2500 mL).Triethylamine (185 mL, 1328.41 mmol) was added and the reaction cooled to 0°C. (3*S*)-3-Methylmorpholine (128 g, 1268.03 mmol) dissolved in DCM (300 mL), was added dropwise over 30 minutes and the mixture stirred at 5° overnight. Water (800 mL) was added, the phases separated and the aquoeus layer extracted with DCM (300 mL). The combined organics were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated to a cream solid. The crude solid was dissolved in hot ethyl acetate (3 volumes) then isohexane (5 volumes) added the mixture left to cool with stirring over the weekend to give the desired material as a solid which was identical to previous samples.

Example 2: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



To a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (200 mg, 0.39 mmol) in DMF (2 mL) was added triethylamine (0.164 mL, 1.18 mmol) followed by cyclopropylamine (0.136 mL, 1.97 mmol) and the reaction heated at 50°C for 2 hours.

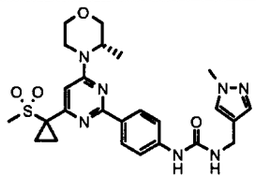
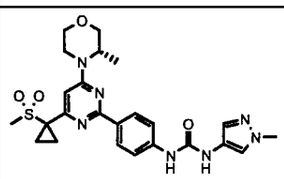
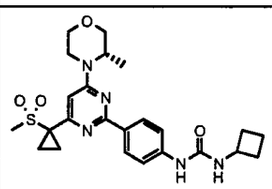
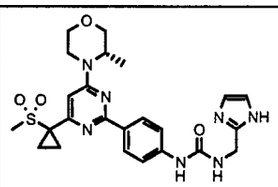
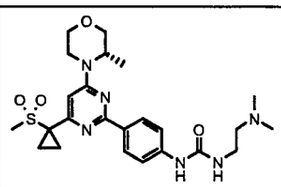
The solvent was removed under reduced pressure to give the crude product which was purified by flash silica chromatography, elution gradient 0 to 10% (3.5M ammonia in methanol) in DCM, to give the desired product as a white solid (168 mg).

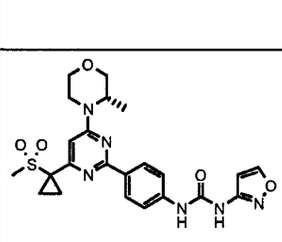
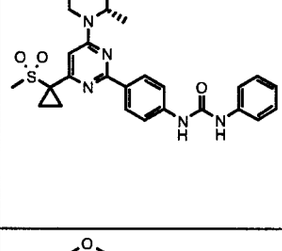
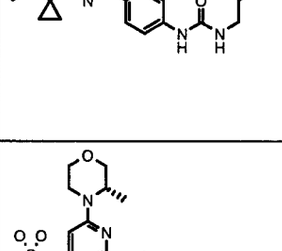
NMR Spectrum: ^1H NMR (400.132 MHz, DMSO-d_6) δ 0.42 (2H, m), 0.65 (2H, m), 1.24 (3H, d), 1.56 (2H, m), 1.67 (2H, m), 2.56 (3H, m), 3.21 (1H, m), 3.48 (1H, m), 3.63 (1H, m), 3.78 (1H, d), 3.97 (1H, m), 4.21 (1H, d), 4.57 (1H, s), 6.43 (1H, d), 6.77 (1H, s), 7.51 (2H, d), 8.20 (2H, d), 8.54 (1H, s)

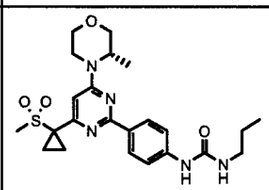
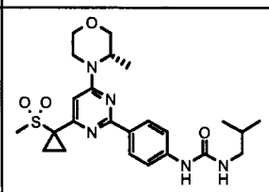
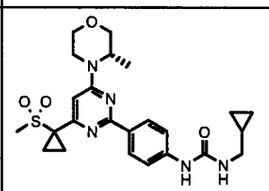
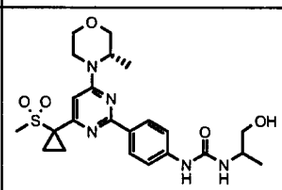
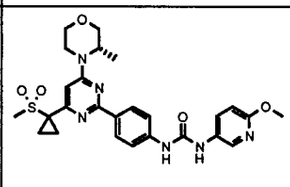
LCMS Spectrum: m/z (ESI+)(M+H)+ = 472; HPLC tR = 1.93 min.

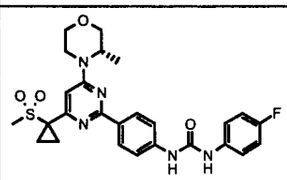
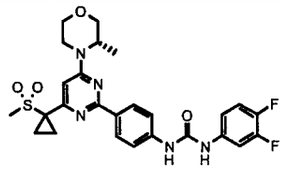
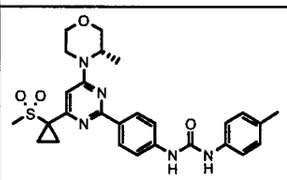
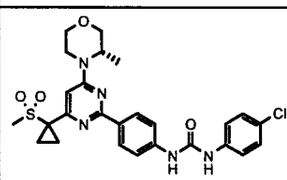
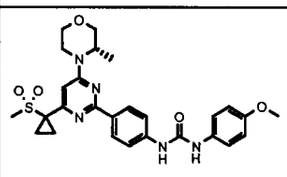
mTOR Kinase Assay (Echo): 0.0015μM

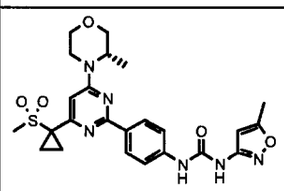
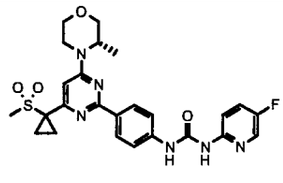
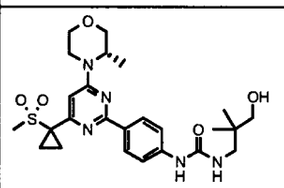
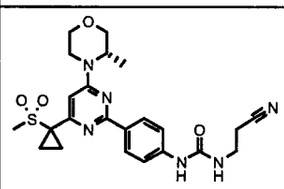
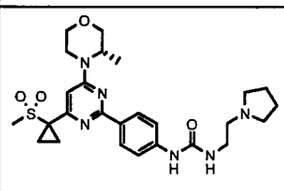
The compounds below were prepared in an analogous fashion using the appropriate amine.

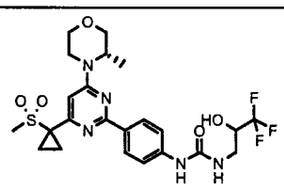
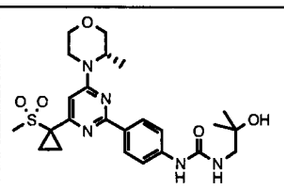
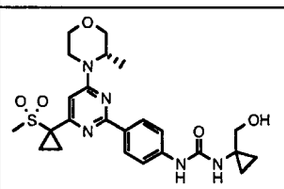
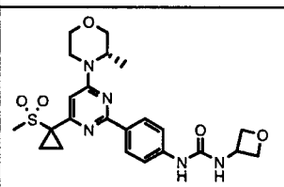
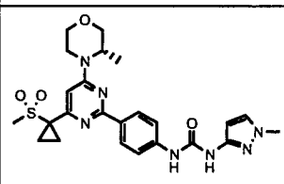
Example	Structure	NAME	LCMS MH+	Retention time (min)
2a		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[(1-methylpyrazol-4-yl)methyl]urea	526	1.73
2b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	512	1.75
2c		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	486	2.21
2d		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	512	1.66
2e		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	502	1.89

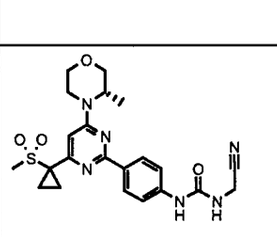
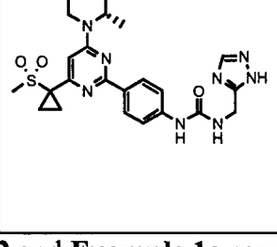
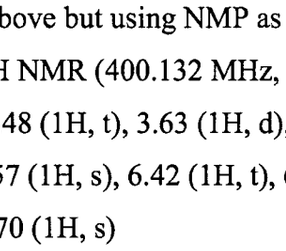
Example	Structure	NAME	LCMS MH+	Retention time (min)
2f		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	503	1.83
2g		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	498	2.03
2h		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-phenyl-urea	507	2.35
2i		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	475	1.54
2j		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	473	2.0

Example	Structure	NAME	LCMS MH+	Retention time (min)
2k		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propyl-urea	473	2.02
2l		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	487	2.18
2m		3-(cyclopropylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	485	2.06
2n		3-(1-hydroxypropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	489	1.63
2o		3-(6-methoxypyridin-3-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	538	2.11

Example	Structure	NAME	LCMS MH+	Retention time (min)
2p		3-(4-fluorophenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	525	2.4
2q		3-(3,4-difluorophenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	543	2.52
2r		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(4-methylphenyl)urea	521	2.49
2s		3-(4-chlorophenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	541	2.59
2t		3-(4-methoxyphenyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	537	2.29

Example	Structure	NAME	LCMS MH+	Retention time (min)
2u		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(5-methyl-1,2-oxazol-3-yl)urea	512	2.16
2v		3-(5-fluoropyridin-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	527	2.35
2w		3-(3-hydroxy-2,2-dimethylpropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	518	2.05
2x		3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	485	1.91
2y		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-pyrrolidin-1-ylethyl)urea	529	2.21

Example	Structure	NAME	LCMS MH+	Retention time (min)
2z		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(3,3,3-trifluoro-2-hydroxypropyl)urea	544	2.11
2aa		3-(2-hydroxy-2-methylpropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	530	1.91
2ab		3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	502	1.81
2ac		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(oxetan-3-yl)urea	488	2.25
2ad		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-3-yl)urea	512	2.11

Example	Structure	NAME	LCMS MH+	Retention time (min)
2ae		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	515	1.43
2af		3-(cyanomethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	471	1.54
2ag		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2H-1,2,4-triazol-3-ylmethyl)urea	513	1.58

Both **Example 2** and **Example 1a** can be prepared in an analogous fashion to that described above but using THF as a solvent. **Example 1a** can also be prepared in an analogous fashion to that described above but using NMP as a solvent.

Example 2a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.56 (2H, s), 1.67 (2H, s), 3.21 (1H, m), 3.48 (1H, t), 3.63 (1H, d), 3.76 (4H, m), 3.80 (3H, s), 3.97 (1H, d), 4.13 (2H, d), 4.20 (1H, s), 4.57 (1H, s), 6.42 (1H, t), 6.77 (1H, s), 7.35 (1H, s), 7.51 (2H, d), 7.59 (1H, s), 8.20 (2H, d), 8.70 (1H, s)

mTOR Kinase Assay (Echo): 0.0932μM

Example 2b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.66 - 1.69 (2H, m), 3.21 (1H, dt), 3.27 - 3.29 (1H, m), 3.29 (3H, s), 3.49 (1H, dt), 3.64 (1H, dd), 3.79 (3H, s), 3.98 (1H, dd), 4.22 (1H, d), 4.58 (1H, s), 6.78 (1H, s), 7.38 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.23 (2H, d), 8.38 (1H, s), 8.84 (1H, s)

mTOR Kinase Assay (Echo): 0.000169μM

Example 2c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.24 (3H, d), 1.54-1.69 (6H, m), 1.81-1.91 (2H, m), 2.18-2.25 (2H, m), 3.17-3.24 (1H, td), 3.29 (3H, s), 3.45-3.52 (1H, td),

3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.10-4.23 (2H, m), 4.57 (1H, bs), 6.45-6.47 (1H, d), 6.77 (1H, s), 7.47-7.50 (2H, d), 8.18-8.21 (2H, d), 8.57 (1H, s).

mTOR Kinase Assay (Echo): 0.00121μM

Example 2d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.66 (2H, q), 1.67-1.69 (2H, q), 3.17-3.25 (1H, td), 3.30 (3H, s), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.32-4.34 (2H, d), 4.57 (1H, bs), 6.61-6.64 (1H, t), 6.77 (1H, s), 6.77 (2H, bs), 7.51-7.54 (2H, d), 8.21-8.22 (2H, d), 8.94 (1H, s), 11.84 (1H, bs).

mTOR Kinase Assay (Echo): 0.0239μM

Example 2e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.24 (3H, d), 1.54-1.58 (2H, q), 1.66-1.69 (2H, q), 2.19 (6H, s), 2.33-2.36 (2H, t), 3.18-3.22 (2H, t), 3.20-3.25 (1H, td), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 6.15-6.18 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.90 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.279μM

Example 2f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25(9H, d), 1.54-1.58 (2H, q), 1.65-1.69 (2H, q), 3.17-3.25 (1H, td), 3.39-3.40 (2H, d), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-4.00 (1H, dd), 4.20-4.23 (1H, d), 4.56 (1H, bs), 4.94-4.97 (1H, t), 6.01 (1H, s), 6.77 (1H, s), 7.45-7.47 (2H, d), 8.18-8.20 (2H, d), 8.74 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.00433μM

Example 2g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.19-3.26 (1H, td), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.81 (1H, s), 6.87-6.88 (1H, d), 7.57-7.59 (2H, d), 8.27-8.29 (2H, d), 8.75-8.76 (1H, d), 9.08 (1H,s), 9.62 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.000137μM

Example 2h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.18-3.26 (1H, td), 3.31 (3H, s), 3.46-3.53 (1H, td), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.59 (1H, bs), 6.79 (1H, s), 6.98-7.01 (1H, t), 7.28-7.32 (2H, t), 7.46-7.48 (2H, d), 7.57-7.59 (2H, d), 8.25-8.27 (2H, d), 8.71 (1H, s), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.000272μM

Example 2i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.24 (3H, d), 1.54-1.58 (2H, q), 1.65-1.70 (2H, q), 3.16-3.25 (1H, td), 3.16-3.21 (2H, q), 3.45-3.52 (1H, td), 3.45-3.49 (2H, q), 3.52-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 4.72-4.74 (1H, t), 6.25-6.27 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.82 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.00207μM

Example 2j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11-1.12 (6H, d), 1.23-1.24 (3H, d), 1.54-1.58 (2H, q), 1.66-1.69 (2H, q), 3.17-3.25 (1H, td), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.74-3.82 (2H, m), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 6.06-6.07 (1H, d), 6.77 (1H, s), 7.48-7.50 (2H, d), 8.19-8.21 (2H, d), 8.54 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.012μM

Example 2k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87-0.91 (3H, t), 1.23-1.25 (3H, d), 1.42-1.51 (2H, m), 1.54-1.58 (2H, q), 1.66-1.69 (2H, q), 3.05-3.09 (2H, q), 3.17-3.25 (1H, td), 3.45-3.52 (1H, td), 3.61-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 6.19-6.22 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.66 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.00406μM

Example 2l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88-0.90 (6H, d), 1.23-1.25 (3H, d), 1.54-1.58 (2H, q), 1.66-1.68 (2H, q), 1.67-1.76 (1H, m), 2.93-2.96 (2H, t), 3.17-3.25 (1H, td), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 6.24-6.27 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.66 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.0116μM

Example 2m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.18-0.22 (2H, m), 0.42-0.46 (2H, m), 0.93-1.00 (1H, m), 1.23-1.25 (3H, d), 1.54-1.58 (2H, q), 1.66-1.69 (2H, q), 2.98-3.01 (2H, t), 3.17-3.25 (1H, td), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 6.25-6.28 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.70 (1H, s). Note:methyl signal obscured by water peak at 3.29.

mTOR Kinase Assay (Echo): 0.00589μM

Example 2n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08-1.10 (3H, d), 1.23-1.25 (3H, d), 1.54-1.57 (2H, q), 1.66-1.69 (2H, q), 2.98-3.01 (2H, t), 3.18-3.25 (1H, td), 3.30 (3H, s), 3.34-3.43 (2H, m), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.69-3.75 (1H, m), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.57 (1H, bs), 4.77-4.80 (1H, t), 6.09-6.11 (1H, d), 6.77 (1H, s), 7.48-7.50 (2H, d), 8.19-8.21 (2H, d), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.00844μM

Example 2o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.18-3.26 (1H, td), 3.30 (3H, s), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.83 (3H, s), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.79(s, 1H), 6.79-6.81 (1H, d), 7.56-7.58 (2H, d), 7.83-7.86 (1H, dd), 8.21-8.22 (1H, d), 8.25-8.27 (2H, d), 8.62 (1H, s), 8.98 (1H, s).

mTOR Kinase Assay (Echo): 0.000851μM

Example 2p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.58 (2H, q), 1.66-1.69 (2H, q), 3.18-3.25 (1H, td), 3.30 (3H, s), 3.46-3.52 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.78 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.79(s, 1H), 7.11-7.16 (2H, t), 7.46-7.50 (2H, m), 7.56-7.58 (2H, d), 8.24-8.27 (2H, d), 8.74 (1H, s), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.0027μM

Example 2q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.18-3.26 (1H, td), 3.30 (3H, s), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.80(s, 1H), 7.14-7.17 (1H, m), 7.32-7.39 (1H, q), 7.56-7.59 (2H, d), 7.65-7.71 (1H, qd), 8.26-8.28 (2H, d), 8.93 (1H, s), 9.00 (1H, s).

mTOR Kinase Assay (Echo): 0.001μM

Example 2r: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 2.26 (3H, s), 3.18-3.26 (1H, td), 3.30 (3H, s), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.79(s, 1H), 7.09-7.12 (2H, d), 7.34-7.36 (2H, d), 7.56-7.58 (2H, d), 8.24-8.27 (2H, d), 8.59 (1H, s), 8.87 (1H, s).

mTOR Kinase Assay (Echo): 0.00066μM

Example 2s: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.18-3.26 (1H, td), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.79(s, 1H), 7.33-7.36 (2H, d), 7.50-7.52

(2H, d), 7.56-7.59 (2H, d), 8.25-8.27 (2H, d), 8.87 (1H, s), 8.97 (1H, s). Note:methyl signal obscured by water peak at 3.29

mTOR Kinase Assay (Echo): 0.00138μM

Example 2t: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.58 (2H, q), 1.67-1.69 (2H, q), 3.18-3.25 (1H, td), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.73 (3H, s), 3.76-3 79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.79(s, 1H), 6.88-6.90 (2H, d), 7.36-7.38 (2H, d), 7.55-7.57 (2H, d), 8.24-8.26 (2H, d), 8.51 (1H, s), 8.84 (1H, s). Note:methyl signal obscured by water peak at 3.29

mTOR Kinase Assay (Echo): 0.00145μM

Example 2u: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 2.38 (3H, s), 3.18-3.26 (1H, td), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.57 (1H, s), 6.80 (s, 1H), 7.56-7.58 (2H, d), 8.27-8.29 (2H, d), 9.06 (1H, s), 9.47 (1H, s). Note:methyl signal obscured by water peak at 3.29

mTOR Kinase Assay (Echo): 0.00118μM

Example 2v: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.19-3.26 (1H, td), 3.31 (3H, s), 3.46-3.53 (1H, td), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H, dd), 4.22-4.25 (1H, d), 4.58 (1H, bs), 6.80 (1H, s), 7.60-7.63 (2H, d), 7.72-7.77 (1H, td), 7.79-7.82 (1H, dd), 8.28-8.30 (3H, m), 9.40 (1H, s), 9.89 (1H, s).

mTOR Kinase Assay (Echo): 0.00866μM

Example 2w: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.82 (6H, s), 1.23 (3H, d), 1.54 - 1.57 (2H, m), 3.00 (2H, d), 3.15 (2H, d), 3.18 - 3.24 (1H, m), 3.29 (3H, s), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.21 (1H, d), 4.55 - 4.62 (2H, m), 6.24 (1H, t), 6.76 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.77 (1H, s).

mTOR Kinase Assay (Echo): 0.0685μM

Example 2x: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 2.70 (2H, t), 3.21 (1H, dt), 3.27 (3H, s), 3.35 - 3.40 (2H, m), 3.48 (1H, dt), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.22 (1H, d), 4.57 (1H, s), 6.53 (1H, t), 6.77 (1H, s), 7.52 (2H, d), 8.21 (2H, d), 8.93 (1H, s).

mTOR Kinase Assay (Echo): 0.00164μM

Example 2y: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.65 - 1.67 (2H, m), 1.70 - 1.73 (4H, m), 2.46 - 2.50 (4H, m), 3.20 - 3.24 (4H, m), 3.27 (3H, s), 3.48

(1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 3.97 (1H, dd), 4.21 (1H, d), 4.56 (1H, s), 6.19 (1H, t), 6.76 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.23μM

Example 2z: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 3.14 - 3.27 (1H, m), 3.29 (3H, s), 3.45 - 3.56 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.05 - 4.11 (1H, m), 4.21 (1H, d), 4.57 (1H, s), 6.39 (1H, t), 6.49 (1H, d), 6.77 (1H, s), 7.51 (2H, d), 8.21 (2H, d), 8.94 (1H, s).

mTOR Kinase Assay (Echo): 0.0181μM

Example 2aa: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, s), 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 3.06 (2H, d), 3.18 (1H, d), 3.22 (1H, dd), 3.29 (3H, s), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.52 (1H, s), 4.57 (1H, s), 6.25 (1H, t), 6.76 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.0274μM

Example 2ab: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63 - 0.67 (2H, m), 0.69 - 0.73 (2H, m), 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 3.18 - 3.24 (1H, m), 3.29 (3H, s), 3.43 - 3.52 (3H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.56 (1H, s), 4.83 (1H, s), 6.57 (1H, s), 6.77 (1H, s), 7.48 (2H, d), 8.20 (2H, d), 8.69 (1H, s).

mTOR Kinase Assay (Echo): 0.0553μM

Example 2ac: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 3.17 - 3.24 (1H, m), 3.29 (3H, s), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.44 (2H, t), 4.56 (1H, s), 4.72 - 4.82 (3H, m), 6.77 (1H, s), 6.95 (1H, d), 7.50 (2H, d), 8.20 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00641μM

Example 2ad: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.66 - 1.69 (2H, m), 3.17 - 3.25 (1H, m), 3.27 (3H, s), 3.49 (1H, dt), 3.64 (1H, dd), 3.74 (3H, s), 3.77 (1H, d), 3.98 (1H, dd), 4.22 (1H, d), 4.57 (1H, s), 6.25 (1H, d), 6.79 (1H, s), 7.54 (1H, t), 7.57 (2H, d), 8.25 (2H, d), 8.92 (1H, s), 9.18 (1H, s).

mTOR Kinase Assay (Echo): 0.000705μM

Example 2ae: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.56 - 1.59 (2H, m), 1.67 - 1.70 (2H, m), 3.17 - 3.23 (1H, m), 3.27 (3H, s), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.24 (1H, d), 4.58 (1H, s), 6.81 (1H, s), 7.64 (2H, d), 8.30 (2H, d), 8.35 (1H, s), 9.46 (1H, s).

mTOR Kinase Assay (Echo): 0.00072μM

Example 2af: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.57 - 1.60 (2H, m), 1.68 - 1.71 (2H, m), 3.18 - 3.24 (1H, m), 3.27 (3H, s), 3.50 (1H, d), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.08 (2H, s), 4.25 (1H, d), 4.61 (1H, s), 6.86 (1H, s), 7.55 (2H, d), 8.14 (1H, s), 8.35 (2H, d), 8.44 (1H, d).

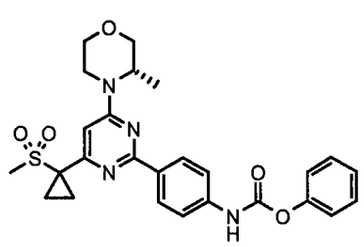
mTOR Kinase Assay (Echo): 0.0462μM

Example 2ag: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.57 (2H, m), 1.66 - 1.68 (2H, m), 3.18 (1H, d), 3.22 (1H, dd), 3.49 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.38 (2H, s), 4.44 (1H, s), 4.57 (1H, s), 6.66 (1H, d), 6.77 (1H, s), 7.52 (2H, d), 8.19 (1H, d), 8.21 (2H, d), 8.95 (1H, s), 13.83 (1H, s), 13.83 (1H, s).

mTOR Kinase Assay (Echo): 0.0149μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate



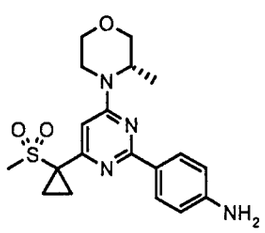
To a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (1.35 g, 3.48 mmol) in 1,4-Dioxane (17.4 mL) was added sodium bicarbonate (0.438 g, 5.21 mmol) and phenyl chloroformate (0.437 mL, 3.48 mmol) and the reaction stirred at RT for 2 hours. The reaction mixture was diluted with DCM (20 mL), and washed with water (20 mL), the organic layer dried (MgSO4), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (1.058 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 1.24 (3H, d), 1.57 (2H, m), 1.68 (2H, m), 3.23 (1H, m), 3.49 (1H, m), 3.58 (3H, s), 3.64 (1H, m), 3.77 (1H, d), 3.97 (1H, m), 4.23 (1H,

d), 4.58 (1H, s), 6.81 (1H, s), 7.25 (2H, d), 7.30 (1H, d), 7.45 (2H, m), 7.64 (2H, d), 8.30 (2H, d), 10.44 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 509; HPLC tR = 2.48 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline

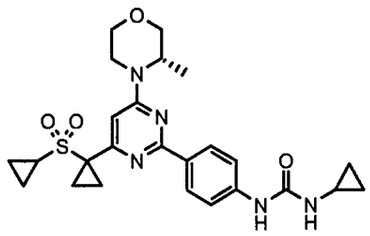


To a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine (1.52 g, 4.58 mmol) in DMF (0.24 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL) was added 4-(*tert*-butoxycarbonylamino)phenylboronic acid (1.629 g, 6.87 mmol), sodium carbonate (5.73 mL, 11.45 mmol), and dichlorobis(triphenylphosphine)palladium(II) (0.161 g, 0.23 mmol) and the suspension heated at 80°C for 2 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was dissolved in DCM (6.67 mL) and trifluoroacetic acid (0.353 mL, 4.58 mmol) added and the reaction was stirred at RT for 16 hours. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% (7.5N ammonia in methanol) in DCM, to give the desired material as a beige solid (1.283 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 1.24 (3H, d), 1.55 (2H, m), 1.67 (2H, m), 3.23 (1H, m), 3.27 (3H, s), 3.47 (1H, m), 3.63 (1H, m), 3.77 (1H, d), 3.97 (1H, m), 4.24 (1H, s), 4.58 (1H, s), 5.75 (1H, s), 6.68 (2H, d), 8.04 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 389; HPLC tR = 1.82 min.

Example 3: 3-Cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



[4-(3-Cyclopropylureido)phenyl]boronic acid, pinacol ester (199 mg, 0.66 mmol), 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (189mg, 0.53 mmol), dichlorobis(triphenylphosphine)palladium(II) (37.1 mg, 0.05 mmol) and sodium carbonate (1.32 mL, 2.64 mmol) were dissolved in a solution of 18% DMF in DME:Water:Ethanol 7:3:2 (4 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 20 minutes in the microwave reactor and cooled to RT. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol and pure fractions were evaporated to dryness to afford a crude product. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the desired material as a colourless gum (69.0 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 0.91 - 0.97 (1H, m), 0.94 (1H, s), 1.02 - 1.04 (2H, m), 1.23 (3H, t), 1.55 - 1.58 (2H, m), 1.64 - 1.66 (2H, m), 2.56 (1H, s), 2.98 - 3.02 (1H, m), 3.18 (1H, d), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.17 - 4.21 (1H, m), 4.53 (1H, s), 6.42 (1H, d), 6.85 (1H, s), 7.49 - 7.51 (2H, m), 8.20 - 8.22 (2H, m), 8.53 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 498; HPLC tR = 1.95 min.

mTOR Kinase Assay (Echo): 0.00195μM

Example 3, 3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea, may also be prepared as described below.

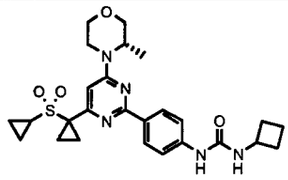
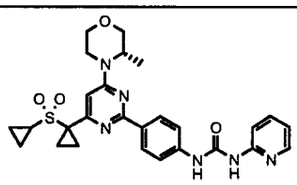
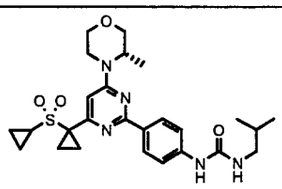
To a solution of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.28 mmol) in DMF (2

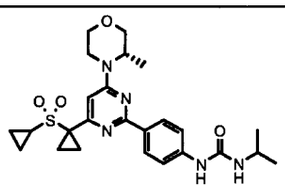
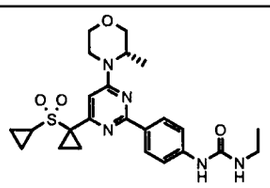
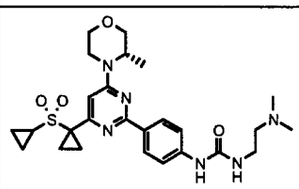
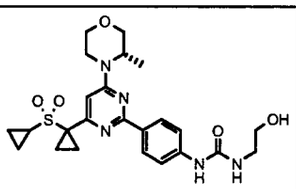
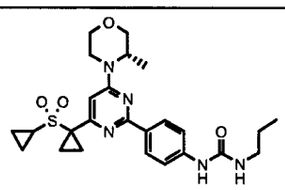
mL) was added triethylamine (0.177 mL, 0.84 mmol) followed by cyclopropylamine (0.097 mL, 1.40mmol) and the reaction heated at 50°C for 2 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (103 mg).

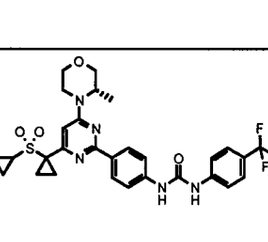
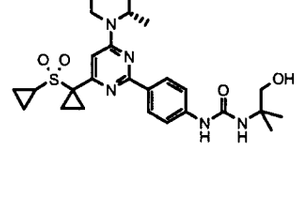
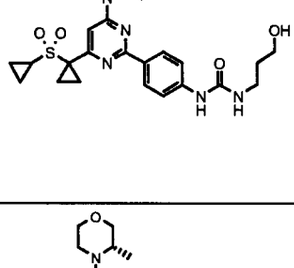
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 0.90 - 0.97 (2H, m), 1.02 - 1.04 (2H, m), 1.24 (3H, d), 1.56 - 1.60 (2H, m), 1.65 (2H, d), 2.60 (1H, t), 2.96 - 3.02 (1H, m), 3.20 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.42 (1H, d), 6.85 (1H, s), 7.50 (2H, d), 8.21 (2H, d), 8.53 (1H, s)

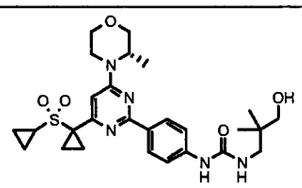
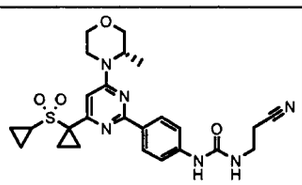
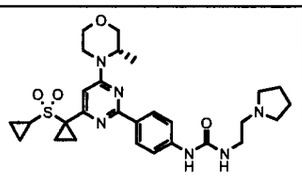
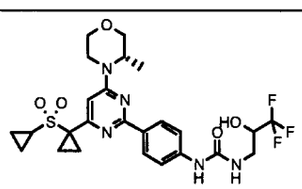
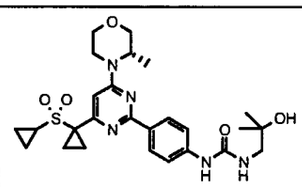
LCMS Spectrum: m/z (ESI+)(M+H)+ = 498; HPLC tR = 2.13 min.

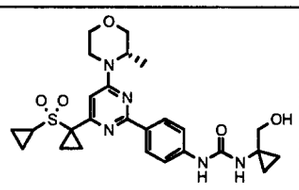
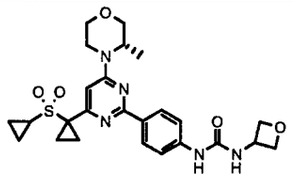
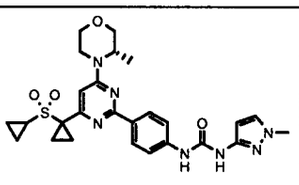
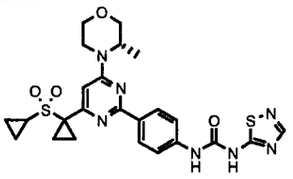
The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
3a		3-cyclobutyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	512	2.38
3b		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	535	2.58
3c		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	514	2.46

Example	Structure	NAME	LCMS MH+	Retention time (min)
3d		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	500	2.28
3e		3-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethyl-urea	486	2.12
3f		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	529	2.04
3g		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	502	1.79
3h		3-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea	500	2.29

Example	Structure	NAME	LCMS MH+	Retention time (min)
3i		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	472	1.96
3j		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	602	3.00
3k		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea	530	2.10
3l		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	516	1.83
3m		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	538	2.00

Example	Structure	NAME	LCMS MH+	Retention time (min)
3n		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxy-2,2-dimethylpropyl)urea	544	2.02
3o		3-(2-cyanoethyl)-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	511	1.92
3p		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-pyrrolidin-1-ylethyl)urea	555	2.17
3q		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3,3,3-trifluoro-2-hydroxypropyl)urea	570	2.01
3r		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxy-2-methylpropyl)urea	530	1.91

Example	Structure	NAME	LCMS MH+	Retention time (min)
3s		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea	528	1.91
3t		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(oxetan-3-yl)urea	514	1.92
3u		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-3-yl)urea	538	2.22
3w		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	542	1.50

Example 3a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.90 - 0.97 (2H, m), 1.02 - 1.04 (2H, m), 1.23 (3H, d), 1.56 - 1.59 (2H, m), 1.63 (2H, d), 1.65 (2H, d), 1.83 (1H, d), 1.86 (1H, t), 2.17 - 2.25 (2H, m), 2.97 - 3.01 (1H, m), 3.17 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.11 - 4.17 (1H, m), 4.20 (1H, s), 4.53 (1H, d), 6.45 (1H, d), 6.84 (1H, s), 7.46 - 7.48 (2H, m), 8.20 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.00445μM

Example 3b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.88 - 0.98 (2H, m), 0.99 - 1.06 (2H, m), 1.25 (3H, d), 1.57 - 1.62 (2H, m), 1.65 - 1.68 (2H, m), 2.99 - 3.05 (1H, m), 3.19 - 3.23 (1H, m), 3.47 - 3.54 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.01 (1H, m), 4.21 (1H, d),

4.54 (1H, d), 6.88 (1H, s), 7.02 - 7.05 (1H, m), 7.56 (1H, d), 7.63 (2H, d), 7.75 - 7.77 (1H, m), 8.29 - 8.31 (3H, m), 9.44 (1H, d), 10.58 (1H, s).

mTOR Kinase Assay (Echo): 0.00385μM

Example 3c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.88 - 0.90 (6H, m), 0.94 (2H, t), 1.00 - 1.06 (2H, m), 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.64 - 1.66 (2H, m), 1.67 - 1.74 (1H, m), 2.94 (2H, t), 2.98 - 3.02 (1H, m), 3.20 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.23 (1H, t), 6.84 (1H, s), 7.47 - 7.50 (2H, m), 8.20 - 8.22 (2H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.0124μM

Example 3d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.97 (2H, m), 1.00 - 1.05 (2H, m), 1.11 (6H, d), 1.23 (3H, d), 1.55 - 1.58 (2H, m), 1.64 - 1.66 (2H, m), 2.97 - 3.03 (1H, m), 3.17 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.76 (2H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.05 (1H, d), 6.84 (1H, s), 7.46 - 7.49 (2H, m), 8.19 - 8.22 (2H, m), 8.52 (1H, s).

mTOR Kinase Assay (Echo): 0.0135μM

Example 3e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.94 (2H, t), 1.02 - 1.04 (2H, m), 1.07 (3H, t), 1.23 (3H, d), 1.58 (2H, d), 1.64 - 1.66 (2H, m), 2.98 - 3.02 (1H, m), 3.17 - 3.18 (1H, m), 3.14 - 3.24 (2H, m), 3.47 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.15 (1H, t), 6.84 (1H, s), 7.47 - 7.51 (2H, m), 8.19 - 8.22 (2H, m), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.00166μM

Example 3f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.97 (2H, m), 0.98 - 1.05 (2H, m), 1.23 (3H, d), 1.55 - 1.58 (2H, m), 1.64 - 1.66 (2H, m), 2.18 (6H, s), 2.34 (2H, t), 2.97 - 3.03 (1H, m), 3.19 (3H, q), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.15 (1H, t), 6.84 (1H, s), 7.47 - 7.50 (2H, m), 8.19 - 8.22 (2H, m), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.0214μM

Example 3g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.97 (2H, m), 1.00 - 1.05 (2H, m), 1.23 (3H, d), 1.55 - 1.58 (2H, m), 1.64 - 1.66 (2H, m), 2.97 - 3.03 (1H, m), 3.16 - 3.21 (3H, m), 3.44 - 3.52 (3H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.17 - 4.21 (1H, m), 4.53 (1H, s), 4.72 (1H, t), 6.25 (1H, t), 6.84 (1H, s), 7.47 - 7.50 (2H, m), 8.20 - 8.22 (2H, m), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.00134μM

Example 3h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (3H, t), 0.91 - 0.95 (2H, m), 1.02 - 1.04 (2H, m), 1.23 (3H, d), 1.41 - 1.50 (2H, m), 1.56 - 1.60 (2H, m), 1.64 - 1.66 (2H, m), 2.98 - 3.02 (1H, m), 3.04 - 3.09 (2H, m), 3.20 - 3.24 (1H, m), 3.47 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.20 (1H, t), 6.84 (1H, s), 7.47 - 7.50 (2H, m), 8.20 - 8.22 (2H, m), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.0165μM

Example 3i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.95 (2H, m), 1.02 - 1.05 (2H, m), 1.23 (3H, d), 1.56 - 1.60 (2H, m), 1.63 - 1.66 (2H, m), 2.66 (3H, d), 2.98 - 3.02 (1H, m), 3.17 - 3.24 (1H, m), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.53 (1H, s), 6.05 (1H, t), 6.84 (1H, s), 7.48 - 7.51 (2H, m), 8.19 - 8.22 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.000932μM

Example 3j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.98 (2H, m), 1.01 - 1.05 (2H, m), 1.25 (3H, d), 1.57 - 1.62 (1H, m), 1.61 (1H, d), 1.65 - 1.68 (2H, m), 2.97 - 3.04 (1H, m), 3.22 - 3.26 (1H, m), 3.47 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.78 (1H, d), 3.97 - 4.00 (1H, m), 4.21 (1H, d), 4.55 (1H, s), 6.87 (1H, s), 7.57 - 7.59 (2H, m), 7.63 - 7.70 (4H, m), 8.29 (2H, d), 9.04 (1H, s), 9.13 (1H, s).

mTOR Kinase Assay (Echo): 0.00422μM

Example 3k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.94 (2H, t), 1.04 (2H, d), 1.23 (6H, d), 1.24 (3H, d), 1.56 - 1.59 (2H, m), 1.64 - 1.66 (2H, m), 2.98 - 3.02 (1H, m), 3.18 (1H, d), 3.39 (2H, d), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.19 (1H, d), 4.52 (1H, s), 4.95 (1H, t), 6.00 (1H, s), 6.84 (1H, s), 7.43 - 7.47 (2H, m), 8.19 - 8.21 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00227μM

Example 3l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.94 (2H, m), 1.01 - 1.05 (2H, m), 1.23 (3H, d), 1.55 - 1.58 (2H, m), 1.60 -1.61 (2H, m), 1.65 (1H, m), 2.98 - 3.02 (1H, m), 3.17 (1H, d), 3.18 - 3.23 (2H, m), 3.45 - 3.49 (3H, m), 3.50 (1H, d), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.17 (1H, s), 4.47 (1H, t), 4.53 (1H, s), 6.20 (1H, t), 6.84 (1H, s), 7.48 - 7.50 (2H, m), 8.21 (2H, d), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00257μM

Example 3m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.95 (2H, m), 1.02 - 1.05 (2H, m), 1.24 (3H, d), 1.57 - 1.60 (2H, m), 1.65 - 1.67 (2H, m), 2.98 - 3.02 (1H, m), 3.18 (1H, t), 3.46 - 3.50 (1H, m), 3.63 - 3.66 (1H, m), 3.76 (1H, s), 3.79 (3H, s), 3.96 - 4.00 (1H, m), 4.18 (1H, s), 4.53 (1H, s), 6.86 (1H, s), 7.38 - 7.38 (1H, m), 7.55 (2H, t), 7.76 (1H, s), 8.25 (2H, d), 8.38 (1H, s), 8.83 (1H, s).

mTOR Kinase Assay (Echo): 0.000497μM

Example 3n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.81 (6H, s), 0.91 - 0.95 (2H, m), 1.01 - 1.05 (2H, m), 1.23 (3H, d), 1.56 - 1.60 (3H, m), 1.63 - 1.66 (2H, m), 2.98 - 3.02 (2H, m), 3.15 (2H, d), 3.21 (1H, dt), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 4.19 (1H, d), 4.53 (1H, s), 4.61 (1H, t), 6.26 (1H, t), 6.84 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.0396μM

Example 3o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.90 - 0.95 (2H, m), 1.00 - 1.06 (2H, m), 1.24 (3H, d), 1.56 - 1.60 (2H, m), 1.63 - 1.66 (2H, m), 2.70 (2H, t), 2.96 - 3.03 (1H, m), 3.17 - 3.25 (1H, m), 3.35 - 3.39 (2H, m), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.53 (1H, s), 6.52 (1H, t), 6.85 (1H, s), 7.51 (2H, d), 8.22 (2H, d), 8.91 (1H, s).

mTOR Kinase Assay (Echo): 0.00596μM

Example 3p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.94 (2H, m), 1.02 - 1.04 (2H, m), 1.23 (3H, d), 1.56 - 1.58 (2H, m), 1.64 - 1.67 (2H, m), 1.72 (8H, m), 2.94 - 3.02 (1H, m), 3.18 - 3.24 (5H, m), 3.49 (1H, t), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.19 (1H, d), 4.53 (1H, s), 6.22 (1H, s), 6.84 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.193μM

Example 3q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.95 (2H, m), 1.00 - 1.06 (2H, m), 1.23 (3H, d), 1.56 - 1.60 (2H, m), 1.63 - 1.66 (2H, m), 2.96 - 3.03 (1H, m), 3.14 - 3.25 (2H, m), 3.46 - 3.55 (2H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.07 - 4.08 (1H, m), 4.19 (1H, d), 4.52 (1H, s), 6.42 (1H, t), 6.49 (1H, s), 6.85 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.95 (1H, s).

mTOR Kinase Assay (Echo): 0.00839μM

Example 3r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.95 (2H, m), 1.00 - 1.06 (2H, m), 1.10 (6H, s), 1.23 (3H, d), 1.56 - 1.60 (2H, m), 1.61 - 1.66 (2H, m), 2.97 - 3.02 (1H, m), 3.06 (2H, d), 3.22 (1H, dd), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.52 (1H, s), 4.54 (1H, s), 6.24 (1H, t), 6.84 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.0488μM

Example 3s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.63 - 0.67 (2H, m), 0.69 - 0.73 (2H, m), 0.91 - 0.95 (2H, m), 1.02 - 1.04 (2H, m), 1.23 (3H, d), 1.56 - 1.60 (2H, m), 1.63 - 1.66 (2H, m), 2.97 - 3.03 (1H, m), 3.17 - 3.25 (2H, m), 3.44 (1H, d), 3.46 - 3.52 (1H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.52 (1H, s), 4.83 (1H, s), 6.56 (1H, s), 6.85 (1H, s), 7.47 (2H, d), 8.21 (2H, d), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.0263μM

Example 3t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.95 (2H, m), 1.00 - 1.07 (2H, m), 1.23 (3H, d), 1.56 - 1.61 (2H, m), 1.63 - 1.66 (2H, m), 2.96 - 3.02 (1H, m), 3.21 (1H, dt), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.45 (2H, t), 4.52 (1H, s), 4.72 - 4.83 (3H, m), 6.85 (1H, s), 6.95 (1H, d), 7.49 (2H, d), 8.22 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00479μM

Example 3u: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.95 (2H, m), 1.00 - 1.07 (2H, m), 1.23 (3H, d), 1.56 - 1.61 (2H, m), 1.63 - 1.66 (2H, m), 2.96 - 3.02 (1H, m), 3.21 (1H, dt), 3.49 (1H, dt), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.45 (2H, t), 4.52 (1H, s), 4.72 - 4.83 (3H, m), 6.85 (1H, s), 6.95 (1H, d), 7.49 (2H, d), 8.22 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.000604μM

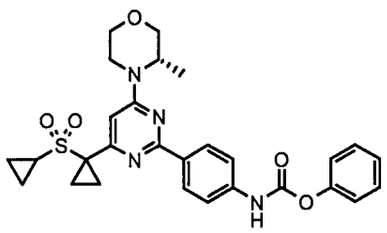
Example 3v: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.94 - 0.96 (2H, m), 1.03 - 1.05 (2H, m), 1.24 (3H, d), 1.57 - 1.59 (2H, m), 1.64 - 1.66 (2H, m), 2.98 - 3.03 (1H, m), 3.19 - 3.25 (1H, m), 3.50 (1H, t), 3.65 (1H, d), 3.74 (3H, s), 3.77 (1H, d), 3.98 (1H, d), 4.21 (1H, d), 4.54 (1H, s), 6.24 (1H, d), 6.86 (1H, s), 7.54 - 7.55 (1H, m), 7.56 (2H, d), 8.26 (2H, d), 8.92 (1H, s), 9.17 (1H, s).

Example 3w: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.96 (2H, m), 1.02 - 1.06 (2H, m), 1.25 (3H, d), 1.58 - 1.60 (2H, m), 1.66 - 1.67 (2H, m), 2.98 - 3.05 (1H, m), 3.20 - 3.23 (1H, m), 3.50 (1H, t), 3.65 (1H, d), 3.78 (1H, d), 3.99 (1H, d), 4.21 (1H, d), 4.55 (1H, s), 6.89 (1H, s), 7.63 (2H, d), 8.31 - 8.36 (3H, m), 9.43 (1H, s).

mTOR Kinase Assay (Echo): 0.00089μM

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

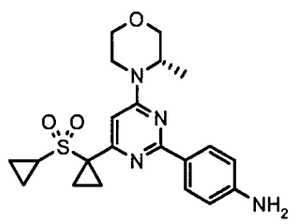


Phenyl chloroformate (0.729 mL, 5.79 mmol) was added dropwise to 4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2.40 g, 5.79 mmol) and sodium bicarbonate (0.730 g, 8.68 mmol) in dioxane (45 mL) under nitrogen. The resulting suspension was stirred at 20°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in ethyl acetate (200 mL) and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a white solid (3.03 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d6) δ 0.92 - 0.95 (2H, m), 1.03 - 1.05 (2H, m), 1.25 (3H, d), 1.57 - 1.61 (1H, m), 1.61 (1H, d), 1.65 - 1.68 (2H, m), 2.99 - 3.03 (1H, m), 3.46 - 3.47 (1H, m), 3.49 - 3.53 (1H, m), 3.63 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.22 (1H, d), 4.56 (1H, s), 6.89 (1H, s), 7.26 (1H, t), 7.24 - 7.30 (2H, m), 7.43 - 7.47 (2H, m), 7.60 - 7.65 (2H, m), 8.29 - 8.32 (2H, m), 10.43 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 535; HPLC tR = 2.84 min.

4-[4-(1-Cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



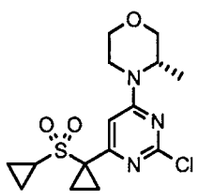
Dichlorobis(triphenylphosphine)palladium(II) (0.524 g, 0.75 mmol) was added to a degassed solution of 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.67 g, 7.46 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.043 g, 9.33 mmol) and sodium carbonate (18.65 mL, 37.31 mmol) in 18% DMF in 7:3:2 DME:Water:Ethanol (20 mL). The resulting solution was stirred at 85°C for 1 hour. The

reaction mixture was concentrated and diluted with DCM (150 mL), and washed with water (100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 2.5% methanol in DCM, to give the desired material as a brown solid (2.40 g).

NMR Spectrum: ^1H NMR (400.13 MHz, DMSO-d6) δ 0.90 - 0.98 (2H, m), 0.98 - 1.05 (2H, m), 1.22 (3H, d), 1.52 - 1.59 (2H, m), 1.62 - 1.64 (2H, m), 2.95 - 3.02 (1H, m), 3.14 - 3.22 (1H, m), 3.45 - 3.51 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.98 (1H, m), 4.14 - 4.17 (1H, m), 4.48 - 4.51 (1H, m), 5.53 (2H, d), 6.60 (2H, d), 6.75 (1H, s), 8.03 - 8.06 (2H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 415; HPLC tR = 2.13 min.

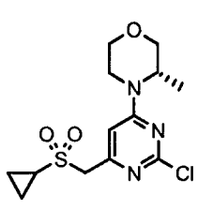
2-Chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



5N Sodium hydroxide solution (1.74 mL, 8.68 mmol) was added to tetrabutylammonium bromide (0.140 g, 0.43 mmol), 1,2-dibromoethane (0.374 mL, 4.34 mmol) and 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.44 g, 4.34 mmol) in DCM (20 mL). The resulting mixture was stirred at 40°C for 2 hours. Additional solid sodium hydroxide (4 g, 0.1 mol) was added directly to the reaction and stirred at 40°C for a further 1 hour. The reaction mixture was diluted with DCM (20 mL) and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material (1.68 g).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 358; HPLC tR = 1.87 min.

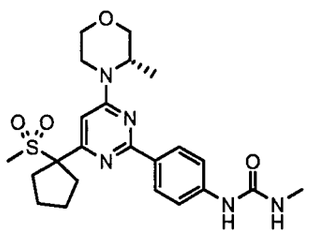
2-Chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Cyclopropanesulfinic acid, sodium salt (381 mg, 2.97 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (700 mg, 1.98 mmol) in acetonitrile (20 mL) at RT. The resulting suspension was stirred at 90°C for 3 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL), and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to gve the desired material as a white solid (458 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO) δ 0.95 - 0.98 (2H, m), 1.02 - 1.06 (2H, m), 1.18 - 1.23 (3H, m), 2.77 - 2.83 (1H, m), 3.19 - 3.25 (1H, m), 3.42 - 3.49 (1H, m), 3.58 - 3.62 (1H, m), 3.73 (1H, d), 3.92 - 3.96 (2H, m), 4.30 (1H, s), 4.48 (2H, s), 6.92 (1H, s).
LCMS Spectrum: m/z (ESI+) (M+H)+ = 332; HPLC tR = 1.68 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 4: 3-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea

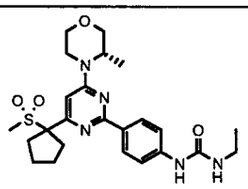
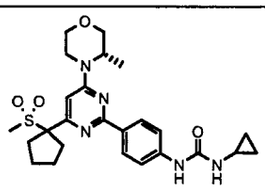
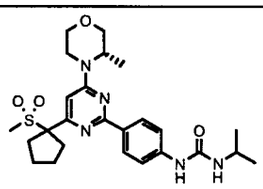
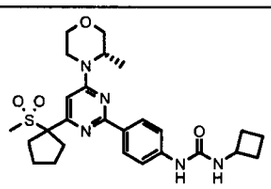
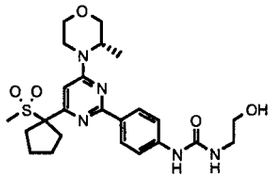


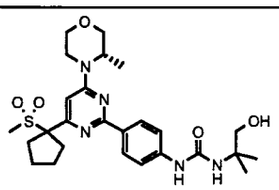
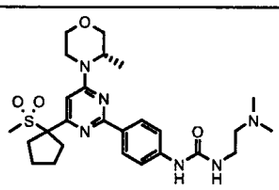
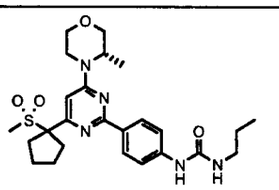
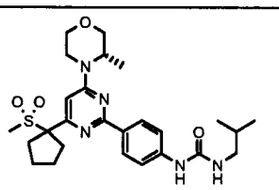
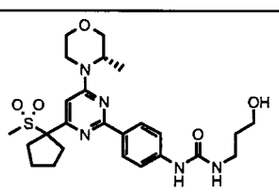
Triethylamine (0.15 mL, 1.1 mmol) was added to a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate (200 mg, 0.37 mmol) and methylamine (2M in THF, 1.48 mmol) in NMP (2 mL). The reaction was heated at 80°C for 2 hours the purified by prep HPLC, using a mixture of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a solid (126 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.52-1.62 (2H, m), 1.75-1.90 (2H, m), 2.38-2.50 (2H, m), 2.65 (3H, d), 2.65-2.78 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.64 (1H, d), 3.75 (1H, d), 3.95 (1H, dd), 4.25 (1H, d), 4.55 (1H, s), 6.05 (1H, q), 6.79 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.72 (1H, s).

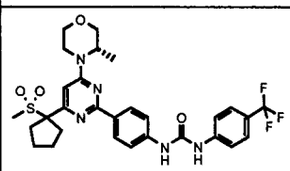
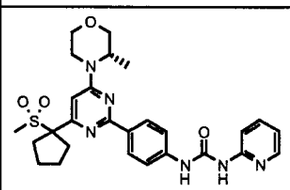
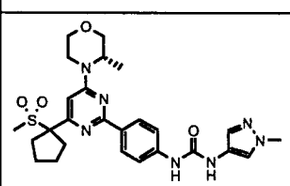
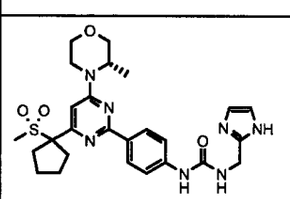
LCMS Spectrum: m/z (ESI+)(M+H)+ = 474; HPLC tR = 1.96 min

mTOR Kinase Assay (Echo): 0.000699μM

The following compounds were prepeared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
4a		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	488	2.13
4b		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	500	2.13
4c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	502	2.29
4d		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	514	2.35
4e		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	504	1.80

Example	Structure	NAME	LCMS MH+	Retention time (min)
4f		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	532	2.09
4g		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	531	2.07
4h		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-propyl-urea	502	2.28
4i		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	517	2.45
4j		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	518	1.84

Example	Structure	NAME	LCMS MH+	Retention time (min)
4k		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	604	2.95
4l		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	537	2.55
4m		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	540	1.99
4n		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	540	1.92

Example 4a: ^{1}H NMR (400.132 MHz, DMSO) δ 1.05 (3H, t), 1.21 (3H, d), 1.50-1.62 (2H, m), 1.78-1.85 (2H, m), 2.35-2.45 (2H, m), 2.65-2.75 (2H, m), 2.89 (3H, s), 3.12 (2H, q), 3.18 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.24 (1H, d), 4.55 (1H, s), 6.15 (1H, t), 6.78 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.00216μM

Example 4b: ^{1}H NMR (400.132 MHz, DMSO) δ 0.41 (2H, q), 0.62 (2H, q), 1.21 (3H, d), 1.51-1.61 (2H, m), 1.75-1.86 (2H, m), 2.35-2.45 (2H, m), 2.55 (1H, m), 2.65-2.85 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.25 (1H, d), 4.55 (1H, s), 6.41 (1H, d), 6.78 (1H, s), 7.50 (2H, d), 8.25 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.00203μM

Example 4c: ^{1}H NMR (400.132 MHz, DMSO) δ 1.11 (6H, d), 1.21 (3H, d), 1.50-1.62 (2H, m), 1.75-1.85 (2H, m), 2.38-2.50 (3H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, dd), 3.99 (1H, dd), 4.23 (1H, d), 4.55 (1H, s), 6.05 (1H, d), 6.79 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.54 (1H, s).

mTOR Kinase Assay (Echo): 0.0169μM

Example 4d: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.65 (4H, m), 1.75-1.90 (4H, m), 2.15-2.20 (2H, m), 2.35-2.50 (2H, m), 2.65-2.80 (2H, m), 2.88 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, dd), 3.95 (1H, dd), 4.15 (1H, q), 4.22 (1H, d), 4.55 (1H, s), 6.42 (1H, d), 6.79 (1H, s), 7.45 (2H, d), 8.22 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.01μM

Example 4e: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.62 (2H, m), 1.78-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.15-3.22 (3H, m), 3.40-3.50 (3H, m), 3.65 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 4.71 (1H, t), 6.22 (1H, t), 6.78 (1H, s), 7.45 (2H, d), 8.22 (2H, d), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00119μM

Example 4f: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.62 (2H, m), 1.75-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.35-3.40 (2H, m), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 4.95 (1H, t), 6.0 (1H, s), 6.78 (1H, s), 7.45 (2H, d), 8.22 (2H, d), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.01μM

Example 4g: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.60 (2H, m), 1.75-1.85 (2H, m), 2.18 (6H, s), 2.31 (2H, t), 2.38-2.50 (2H, m), 2.65-2.75 (2H, m), 2.89 (3H, s), 3.15-3.22 (3H, m), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, dd), 3.96 (1H, dd), 4.22 (1H, dd), 4.55 (1H, s), 6.15 (1H, t), 6.79 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.87 (1H, s).

mTOR Kinase Assay (Echo): 0.0626μM

Example 4h: ^{1}H NMR (400.132 MHz, DMSO) δ 0.88 (3H, t), 1.21 (3H, d), 1.45 (2H, q), 1.50-1.62 (2H, m), 1.75-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.05 (2H, m), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.22 (1H, d), 4.55 (1H, s), 6.20 (1H, t), 6.78 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.00157μM

Example 4i: ^{1}H NMR (400.132 MHz, DMSO) δ 0.88 (6H, d), 1.21 (3H, d), 1.50-1.62 (2H, m), 1.70 (1H, m), 1.75-1.85 (2H, m), 2.35-2.50 (2H, m), 2.65-2.80 (2H, m), 2.90 (3H, s), 2.94 (2H, t), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, dd), 3.97 (1H, dd), 4.24 (1H, d), 4.54 (1H, s), 6.22 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.0115μM

Example 4j: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.62 (4H, m), 1.75-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.10-3.22 (3H, m), 3.45-3.52 (3H, m), 3.65 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.22 (1H, d), 4.45 (1H, t), 4.55 (1H, s), 6.1991H, t), 6.79 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00461μM

Example 4k: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.62 (2H, m), 1.75-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3, 22 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.25 (1H, d), 4.55 (1H, s), 6.80 (1H, s), 7.58 (2H, d), 7.62-7.70 (4H, m), 8.30 (2H, d), 9.04 (1H, s), 9.10 (1H, s).

mTOR Kinase Assay (Echo): 0.00905μM

Example 4l: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.55-1.62 (2H, m), 1.78-1.90 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75 (1H, d), 3.9791H, dd), 4.2591H, d), 4.55 (1H, s), 6.80 (1H, s), 7.02 (1H, dd), 7.58 (1H, d), 7.61 (2H, d), 7.74 (1H, dd), 8.25-8.35 (4H, m), 9.41 (1H, s).

mTOR Kinase Assay (Echo): 0.00369μM

Example 4m: ^{1}H NMR (400.132 MHz, DMSO) δ 1.20 (3H, d), 1.50-1.62 (2H, m), 1.78-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3.65 (1H, dd), 3.75-40 (4H, m), 3.97 (1H, dd), 4.25 (1H, d), 4.55 (1H, s), 6.80 (1H, s), 7.38 (1H, s), 7.55 (2H, d), 7.73 (1H, s), 8.25 (2H, d), 8.35 (1H, s), 8.85 (1H, s).

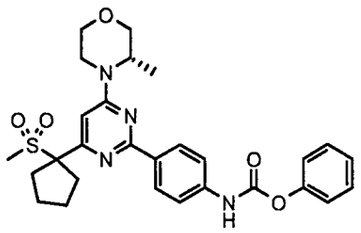
mTOR Kinase Assay (Echo): 0.00245μM

Example 4n: ^{1}H NMR (400.132 MHz, DMSO) δ 1.21 (3H, d), 1.50-1.62 (2H, m), 1.75-1.85 (2H, m), 2.35-2.50 (2H, m), 2.65-2.80 (2H, m), 2.89 (3H, s), 3.20 (1H, dd), 3.50 (1H, dd), 3, 65 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.24 (1H, d), 4.35 (1H, d), 4.55 (1H, s), 6.65 (1H, t), 6.78 (1H, s), 7.04 (2H, s), 7.52 (2H, d), 8.25 (2H, d), 9.0 (1H, s), 12.6 (1H, s).

mTOR Kinase Assay (Echo): 0.0392μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate

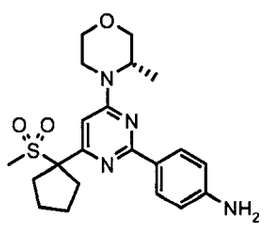


Sodium hydrogen carbonate (1.150 g, 13.68 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]aniline (3.8 g, 9.12 mmol), in dioxane (100 mL) at 21°C under nitrogen. The resulting mixture was cooled to10°C and phenyl chloroformate (1.72 mL, 13.68 mmol) added slowly then the reaction stirred for 3 hours and allowed to warm to RT and left for 16 hours. The reaction mixture was diluted with ethyl acetate (250 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether, iso-hexane and acetone to give the desired material as a white solid (4.50 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.50-1.62 (2h, m), 1.75-1.85 (2H, m), 2.38-2.50 (2H, m), 2.65-2.80 (2H, m), 3.21 (1H, dd), 3.30 (3H, s), 3.50 (1H, dd), 3.63 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.28 (1H, d), 4.57 (1H, s), 6.81 (1H, s), 7.22-7.30 (3Hh, m), 7.43 (2H, dd), 7.61 (1H, d), 8.32 (2H, d), 10.45 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 537 ; HPLC tR = 2.98 min

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]aniline

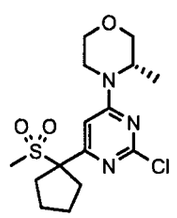


Bis (triphenylphosphine)palladium (II) chloride (0.390 g, 0.56 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine (4.0g, 11.12 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.17 g, 14.45 mmol) and sodium carbonate (20 mL, 40.0 mmol) in a mixture of DMF (20 mL), DME (50 mL), ethanol (20 mL) and water (20 mL) at RT under nitrogen. The resulting mixture was stirred at 95°C for 12 hours. The reaction mixture was diluted with ethyl acetate (400 mL), washed twice with water (200 mL followed by 250 mL), the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was chromatographed on silica, eluting with 5 - 50% ethyl acetate in iso-hexane, to give a yellow solid which was subsequently triturated with a mixture of diethyl ether and iso-hexane to give the desired material as a white solid (4.25 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.50-1.60 (2H, m), 1.75-1.90 (2H, m), 2.34-2.43 (2H, m), 2.62-2.78 (2H, m), 2.88 (3H, s), 3.18 (1H, dd), 3.48 (1H, dd), 3.65 (1H, dd), 3.75 (1H, dd), 3.95 (1H, dd), 4.20 (1H, d), 4.51 (1H, s), 5.55 (2H, s), 6.62 (2H, d), 6.68 (1H, s), 8.09 (1H, d).

Mass Spectrum: m/z (ESI+)(M+H)+ = 417

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine

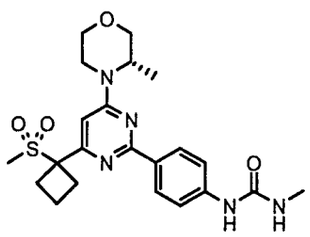


Tetrabutylammonium bromide (0.495 g, 1.54 mmol) was added toa mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6- (methylsulfonylmethyl)pyrimidine (4.7 g, 15.37 mmol), 1, 4-dibromobutane (1.84 mL, 15.37 mmol) and aqueous sodium hydroxide solution (30 mL, 368.9 mmol) in DCM (150 mL) at RT under nitrogen. The resulting mixture was stirred at 40°C for 6 hours. The reaction mixture was diluted with DCM (200 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was chromatographed on silica, eluting with 5 - 50% ethyl acetate in iso-hexane, to give the desired material as a yellow solid (3.90 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.50-1.60 (2H, m), 1.72-1.82 (2H, m), 2.30-2.41 (2H, m,), 2.50-2.60 (2H, m), 2.88 (3H, s), 3.20 (1H, dd), 3.45 (1H, dd), 3.60 (1H, dd), 3.71 (1H, d), 3.94 (1H, dd), 4.0-4.10 (1H, m), 4.42 (1H, s), 6.89 (1H, s).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 360 ; HPLC tR = 2.22 min

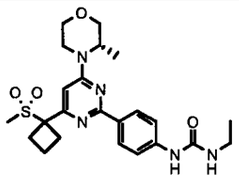
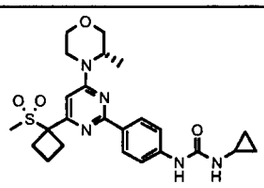
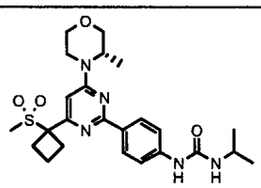
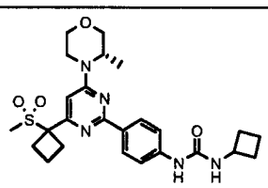
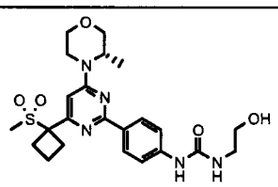
The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine was described earlier.

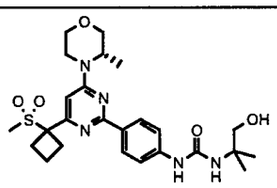
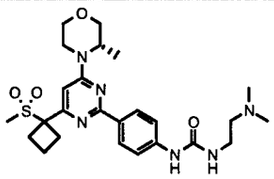
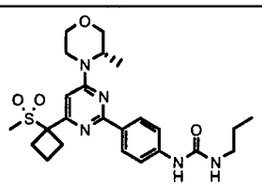
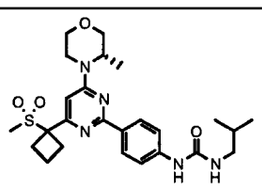
Example 5: 3-Methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea



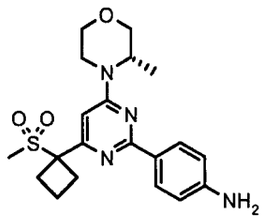
Triethylamine (0.07 mL, 0.48mmol) was added to a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate (86 mg, 0.16 mmol) and methylamine (2M in THF, 0.65 mmol) in NMP (2 mL). The reaction was heated at 80°C for 2 hours the purified by prep HPLC, using a mixture of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a solid (48 mg).
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.91 (2H, m), 2.08 (2H, m), 2.62(3H,d), 2.80 (2H, m), 2.87 (3H, s), 3.21 (1H, td), 3.50 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.24 (1H, d), 4.60 (1H, s), 6.07 (1H, d), 6.71 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.75 (1H, s).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 460; HPLC tR = 1.5 min
mTOR Kinase Assay (Echo): 0.000802μM

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
5a		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	474	1.98
5b		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	486	2.01
5c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	488	2.15
5d		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	500	2.24
5e		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	490	1.69

Example	Structure	NAME	LCMS MH+	Retention time (min)
5f		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	518	1.97
5g		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	517	1.98
5h		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-propyl-urea	488	2.16
5i		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	502	2.33

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]aniline

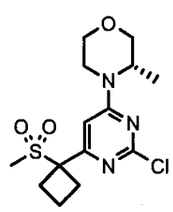


Bis(triphenylphosphine)palladium(II) chloride (0.101 g, 0.14 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidine (1 g, 2.89 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.824 g, 3.76 mmol) and sodium carbonate (5 mL, 10.00 mmol) in a mixture of DMF (5 mL), DME (50 mL), ethanol (20 mL) and water (20 mL) at RT under nitrogen. The resulting mixture was stirred at 95°C for 12 hours. The reaction mixture was diluted with ethyl acetate (400 mL), and washed twice with water (200 mL followed by 250 mL), the organic layer dried (Na_2SO_4), filtered and evaporated. The crude product was chromatographed on silica, eluting with 5 - 60% ethyl acetate in iso-hexane, to give the desired material as a cream solid (0.98 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21(3H,d), 1.85-1.95(2H,m), 2.0-2.10(2H,m), 2.71-2.82(2H,m), 2.82(3H,s), 3.18(1H,dd), 3.50(1H,dd), 3.62(1H,dd), 3.75(1H,d), 3.95(1H,dd), 4.20(1H,d), 4.53(1H,s), 5.55(2H,s), 6.60(3H,d), 8.05(2H,d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 403; HPLC tR = 2.17 min

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidine



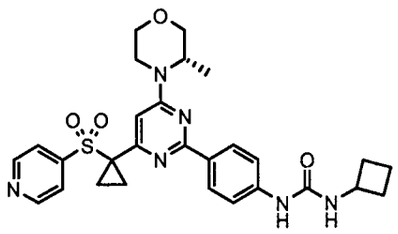
Tetrabutylammonium bromide (0.45 g, 1.40 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (4.27 g, 13.96 mmol), 1,3-dibromopropane (1.42 mL, 13.96 mmol) and aqueous sodium hydroxide solution (30 mL, 368.9 mmol) in DCM (100 mL) at RT under nitrogen. The resulting mixture was stirred at 35°C for 5 hours then diluted with DCM (50 mL), and washed with water (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was

chromatographed on silica, eluting with 5 - 50% ethyl acetate in iso-hexane, to give the desired material (1.0 g).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 346; HPLC tR = 1.92 min

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine was described earlier.

Example 6: 3-Cyclobutyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



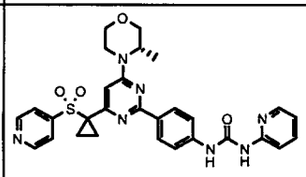
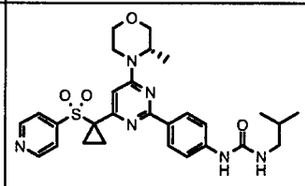
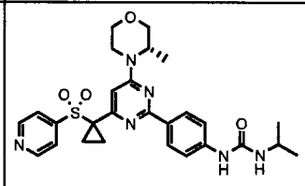
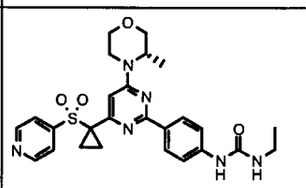
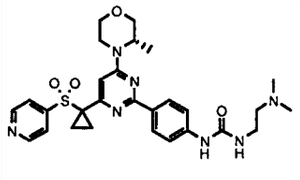
To a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (122 mg, 0.21 mmol) in DMF (2 mL) was added triethylamine (0.088 mL, 0.63 mmol) followed by cyclobutylamine (0.090 mL, 1.05 mmol) and the reaction heated at 50°C overnight. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (90 mg).

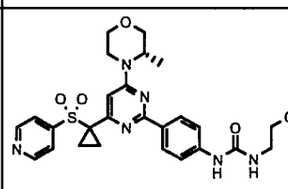
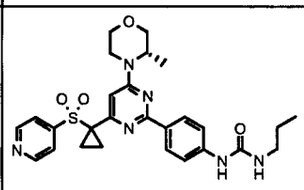
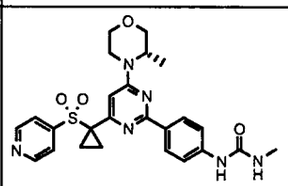
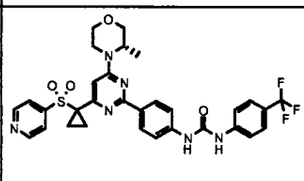
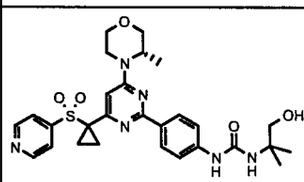
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.57-1.70 (4H, m), 1.82-1.91 (2H, m), 1.95-1.98 (2H, q), 2.18-2.25 (2H, m), 3.12-3.20 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.11-4.17 (2H, m), 4.46 (1H, bs), 6.42-6.44 (1H, d), 6.67 (1H, s), 7.33-7.35 (2H, q), 7.65-7.67 (2H, d), 7.76-7.78 (2H, q), 8.53 (1H, s), 8.85-8.87 (2H, q).

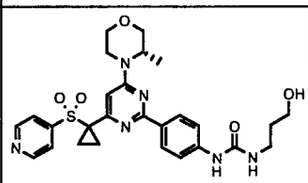
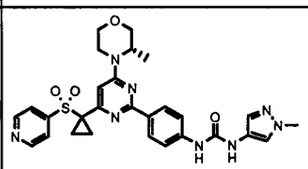
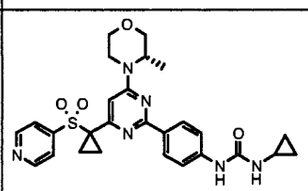
LCMS Spectrum: m/z (ESI+) (M+H)+549 = HPLC tR =2.25 min.

mTOR Kinase Assay (Echo): 0.001μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
6a		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	572	2.44
6b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	551	2.33
6c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	537	2.17
6d		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	523	2.03
6e		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	566	1.32

Example	Structure	NAME	LCMS MH+	Retention time (min)
6f		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	539	1.75
6g		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propyl-urea	537	2.18
6h		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	509	1.89
6i		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	639	2.84
6j		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	567	2.01

Example	Structure	NAME	LCMS MH+	Retention time (min)
6k		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	553	1.80
6l		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	575	1.96
6m		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	535	2.12

Example 6a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21 (3H, d), 1.69-1.72 (2H, q), 1.97-2.00 (2H, q), 3.15-3.22 (1H, td), 3.44-3.51 (1H, td), 3.61-3.64 (1H, dd), 3.74-3.77 (1H, d), 3.95-3.99 (1H, dd), 4.17-4.20 (1H, d), 4.48 (1H, bs), 6.71 (1H, s), 7.02-7.06 (1H, m), 7.49-7.51 (2H, d), 7.56-7.58 (1H, d), 7.74-7.79 (5H, m), 8.30-8.32 (1H, d), 8.88-8.89 (2H, q), 9.43 (1H, s), 10.55 (1H, s).

mTOR Kinase Assay (Echo): 0.00293μM

Example 6b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88-0.90 (6H, d), 1.18-1.20 (3H, d), 1.68-1.74 (3H, m), 1.96-1.98 (2H, q), 2.93-2.96 (2H, t), 3.13-3.20 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.99 (1H, dd), 4.15-4.18 (1H, d), 4.45 (1H, bs), 6.20-6.23 (1H, t), 6.67 (1H, s), 7.34-7.36 (2H, d), 7.65-7.67 (2H, d), 7.77-7.78 (2H, q), 8.62 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.00612μM

Example 6c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11-1.12 (6H, d), 1.18-1.20 (3H, d), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 3.13-3.20 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.82 (2H, m), 3.94-3.98 (1H, dd), 4.14-4.18 (1H, d), 4.46 (1H, bs), 6.02-6.04 (1H, d), 6.67 (1H, s), 7.32-7.36 (2H, q), 7.64-7.67 (2H, q), 7.76-7.78 (2H, q), 8.50 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.00321μM

Example 6d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.05-1.09 (2H, t), 1.18-1.20 (3H, d), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 3.09-3.20 (4H, m), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.15-4.17 (1H, d), 4.46 (1H, bs), 6.12-6.15 (1H, t), 6.67 (1H, s), 7.35-7.37 (2H, q), 7.65-7.67 (2H, d), 7.77-7.78 (2H, q), 8.63 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.000874μM

Example 6e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 2.18 (6H, s), 2.32-2.35 (2H, t), 3.13-3.21 (3H, m), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.15-4.18 (1H, d), 4.47 (1H, bs), 6.12-6.15 (1H, t), 6.67 (1H, s), 7.34-7.37 (2H, q), 7.65-7.67 (2H, d), 7.76-7.78 (2H, q), 8.86-8.87 (3H, m).

mTOR Kinase Assay (Echo): 0.0673μM

Example 6f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 3.13-3.20 (3H, m), 3.43-3.50 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.15-4.18 (1H, d), 4.46 (1H, bs), 4.71-4.74 (1H, t), 6.21-6.24 (1H, t), 6.67 (1H, s), 7.34-7.36 (2H, q), 7.65-7.67 (2H, d), 7.76-7.78 (2H, q), 8.77 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.000794μM

Example 6g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87-0.91 (3H, t), 1.18-1.20 (3H, d), 1.41-1.50 (2H, m), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 3.04-3.09 (2H, q), 3.13-3.19 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, td), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.14-4.18 (1H, d), 4.47 (1H, bs), 6.16-6.19 (1H, t), 6.67 (1H, s), 7.34-7.36 (2H, d), 7.65-7.67 (2H, d0, 7.77-7.78 (2H, q), 8.62 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.00225μM

Example 6h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 2.65-2.67 (3H, d), 3.13-3.20 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H,

dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.15-4.17 (1H, d), 4.46 (1H, bs), 6.02-6.06 (1H, q), 6.67 (1H, s), 7.35-7.38 (2H, q), 7.65-7.67 (2H, d), 7.77-7.78 (2H, q), 8.71 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.000799μM

Example 6i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21 (3H, d), 1.69-1.72 (2H, q), 1.97-2.00 (2H, q), 3.14-3.21 (1H, td), 3.44-3.50 (1H, td), 3.61-3.64 (1H, dd), 3.74-3.77 (1H, d), 3.95-3.98 (1H, dd), 4.16-1.20 (1H, d), 4.48 (1H, bs), 6.70 (1H, s), 7.44-7.46 (2H, d), 7.64-7.70 (4H, q), 7.72-7.75 (2H, q), 7.78-7.79 (2H, q), 8.87-8.89 (2H, q), 9.03 (1H, s), 9.11 (1H, s).

mTOR Kinase Assay (Echo): 0.00462μM

Example 6j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.24 (6H, s), 1.67-1.70 (2H, q), 1.96-1.99 (2H, q), 3.13-3.20 (1H, td), 3.38-3.40 (2H, d), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.15-4.18 (1H, d), 4.46 (1H, bs), 4.94-4.96 (1H, t), 5.97 (1H, s), 6.67 (1H, s), 7.30-7.32 (2H, d), 7.63-7.65 (2H, q), 7.76-7.78 (2H, q), 8.71 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.00593μM

Example 6k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.20 (3H, d), 1.57-1.63 (2H, m), 1.67-1.71 (2H, q), 1.96-1.98 (2H, q), 3.13-3.20 (3H, m), 3.43-3.50 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.14-4.18 (1H, d), 4.46 (1H, bs), 4.46-4.49 (1H, t), 6.16-6.19 (1H, t), 6.67 (1H, s), 7.34-7.36 (2H, q), 7.65-7.67 (2H, d), 7.76-7.78 (2H, q), 8.68 (1H, s), 8.86-8.87 (2H, q).

mTOR Kinase Assay (Echo): 0.00186μM

Example 6l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.20 (3H, d), 1.68-1.71 (2H, q), 1.96-1.99 (2H, q), 3.13-3.21 (1H, td), 3.44-3.50 (1H, td), 3.60-3.63 (1H, dd), 3.74-3.77 (1H, d), 3.79 (3H, s), 3.95-3.98 (1H, dd), 4.16-4.19 (1H, d), 4.47 (1H, bs), 6.68 (1H, s), 7.39-7.42 (3H, m), 7.68-7.70 (2H, d), 7.77-7.79 (3H, m), 8.37 (1H, s), 8.82 (1H, s), 8.86-8.88 (2H, q).

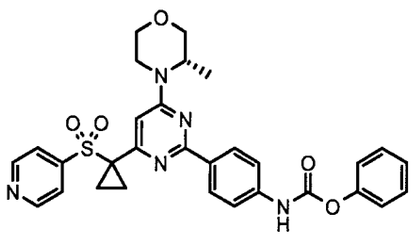
mTOR Kinase Assay (Echo): 0.00119μM

Example 6m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44(2H, m), 0.63-0.67(2H, m), 1.18-1.20(3H, d), 1.68-1.71(2H, q), 1.96-1.99(2H, q), 2.53-2.59(1H, m), 3.13-3.20(1H, td), 3.43-3.63(1H, td), 3.59-3.63(1H, dd), 3.73-3.76(1H, d), 3.94-3.98(1H, dd), 4.15-4.18(1H, d), 4.46(1H, bs), 6.40-6.41(1H, d), 6.67(1H, s), 7.36-7.38(2H, q), 7.65-7.68(2H, q), 7.77-7.78(2H, q), 8.51(1H, s), 8.86-8.87(2H, q).

mTOR Kinase Assay (Echo): 0.000936μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate

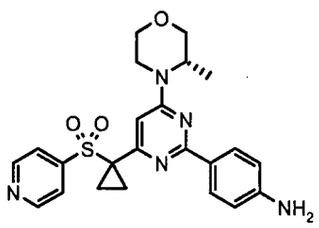


Phenyl chloroformate (0.341 mL, 2.71 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (1.224 g, 2.71 mmol) and sodium bicarbonate (0.342 g, 4.07 mmol) in dioxane (175 mL) at RT under air. The resulting slurry was stirred at RT for 2 hours. Additional portions of phenyl chloroformate (2 x 0.005 mL) were added to the reaction. Water was added to the reaction mixture and the material extracted with DCM. The combined organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, eluting with 0 to 4% methanol in DCM, to give the desired material as a beige solid (1.72 g).

NMR Spectrum: ^1H NMR (400.132 MHz, $CDCl_3$) δ 1.28-1.29 (3H, d), 1.60-1.69 (2H, m), 1.97-2.05 (2H, m), 3.22-3.30 (1H, td), 3.52-3.59 (1H, td), 3.71-3.72 (1H, dd), 3.78-3.81 (1H, d), 3.99-4.03 (1H, dd), 4.09-4.13 (1H, d), 4.38-4.39 (1H, bs), 6.72 (1H, s), 7.13-7.15 (2H, d), 7.19-7.21 (1H, t), 7.32-7.36 (2H, t), 7.46-7.48 (2H, d), 7.61-7.63 (2H, q), 7.97-7.99 (2H, d), 8.74-8.75 (2H, q).

LCMS Spectrum: m/z (ES+) (M+H)+=450; HPLC tR=2.66 min.

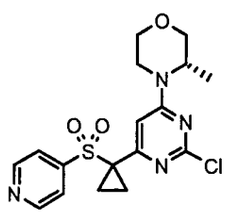
4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline



trans-Dichlorobis(triphenylphosphine)palladium (II) (0.095 g, 0.14 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidine (1.07 g, 2.71 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.89 g, 4.06 mmol) and sodium carbonate (6.77 mL, 13.55 mmol) in 18% DMF in a 7:3:2 mixture of DME:water:ethanol (50 mL) at RT under nitrogen. The resulting solution was stirred at 80°C for 5 hours. The reaction was cooled and diluted with ethyl acetate and water. The reaction mixture was extracted with ethyl acetate, the combined organics dried ($MgSO_4$), filtered and evaporated to afford the desired material (1.224 g).

LCMS Spectrum: m/z (ES+) (M+H)+=452; HPLC tR=2.03 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidine

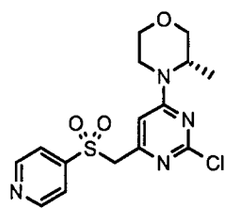


50% v/v Aqueous sodium hydroxide (23 mL, 9.52 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine (3.51 g, 9.52 mmol), 1,2-dibromoethane (0.820 mL, 9.52 mmol) and tetrabutylammonium bromide (0.307 g, 0.95 mmol) in DCM (100 mL) and the reaction warmed to 30°C under air. The resulting slurry was stirred at 30°C for 4 hours then allowed to cool, DCM added and the layers separated. The organic layer was washed with water, dried ($MgSO_4$) and filtered. The resulting solution was evaporated on to silica and purified by flash silica chromatography, eluting with 0 to 60% ethyl acetate in DCM, to give the desired material as a yellow solid (1.07 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15-1.16 (3H, d), 1.61-1.65 (2H, m), 1.90-1.93 (2H, m), 3.11-3.19 (1H, td), 3.37-3.44 (1H, td), 3.53-3.57 (1H, dd), 3.68-3.71 (1H, d), 3.89-3.96 (1H, dd), 3.96 (1H, bs), 4.28 (1H, bs), 6.75 (1H, s), 7.74-7.75 (2H, dd), 8.88-8.90 (2H, dd).

LCMS Spectrum: m/z (ES+) (M+H)+=395; HPLC tR=1.65 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine

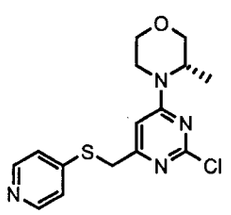


A solution of hydrogen peroxide (1.799 mL, 58.19 mmol) was added dropwise to a stirred solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfanylmethyl)pyrimidine (0.980 g, 2.91 mmol), sodium tungstate dihydrate (0.005 mL, 0.06 mmol) and 2N sulfuric acid (0.075 mL) in dioxane (200 mL) at 55°C, over a period of 5 minutes under air. The resulting solution was stirred at 55 °C for 3 hours. Water (200mL) was added and the reaction was cooled, the solids filtered, washed with water and dried in the vacuum oven at 50°C overnight to give the desired material as a white solid (0.580 g). Additional material was obtained by extracting the aqueous layer with DCM. The extracts were dried ($MgSO_4$), filtered, evaporated and chromatographed on silica, eluting with 0 - 3% methanol in DCM, to give a further portion of the desired material (0.144 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.17-1.19(3H, d), 3.14-3.22(1H, td), 3.40-3.47(1H, td), 3.56-3.60(1H, dd), 3.71-3.74(1H, d), 3.90(1H, bs), 3.91-3.95(1H, dd), 4.20(1H, bs), 4.79(2H, s), 6.79(1H, s), 7.77-7.79(2H, q), 8.92-8.93(2H, q).

LCMS Spectrum: m/z (ES+) (M+H)+=369; HPLC tR=1.40 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfanylmethyl)pyrimidine

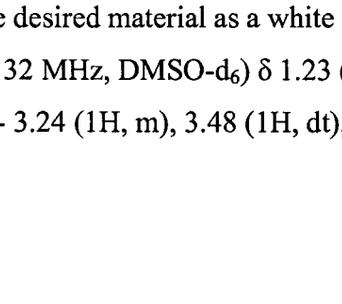


4-Mercaptopyridine (0.752 g, 6.77 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.596 g, 4.51 mmol) in acetonitrile (100 mL) at RT under air. DBU (0.3 mL, 2.01 mmol) was then added and the resulting solution was stirred at RT for 2 minutes. The solvent was removed and DCM was added. The reaction mixture was washed sequentially with water, the organic layer dried ($MgSO_4$), filtered and evaporated. The crude product was chromatographed on silica, eluting with 0 - 2% methanol in DCM. Impure fractions were further chromatographed on silica, eluting with 0 – 4.5% methanol in DCM and combined with the initial pure fractions to give the desired material as a yellow gum (0.980 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.14-1.16(3H, d), 3.11-3.18(1H, td), 3.37-3.44(1H, td), 3.53-3.57(1H, dd), 3.64-3.67(1H, d), 3.86-3.90(2H, dd), 4.01(2H, s), 4.14(1H, bs), 6.43(1H, s), 7.04-7.06(2H, d), 8.29-8.30(2H, d).
LCMS Spectrum: m/z (ES+) (M+H)+=337; HPLC tR=1.62 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier

Example 7: 3-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



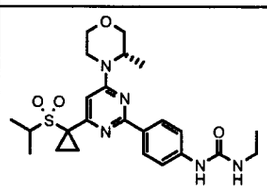
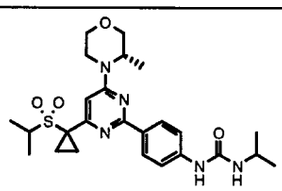
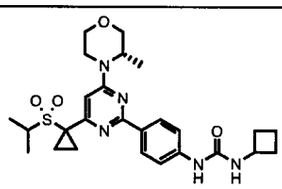
To a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.22 mmol) in DMF (2 mL) was added triethylamine (0.094 mL, 0.67 mmol) followed by methylamine (0.5 mL, 1.1 mmol) and the reaction heated at 50°C for 2 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (71 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.34 (6H, dd), 1.55 - 1.62 (4H, m), 2.66 (3H, d), 3.17 - 3.24 (1H, m), 3.48 (1H, dt), 3.60 - 3.67 (2H, m), 3.76 (1H,

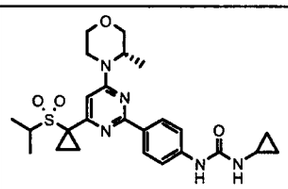
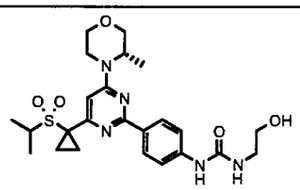
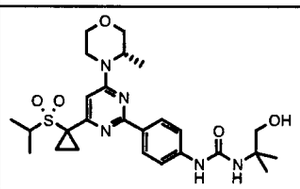
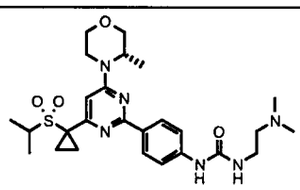
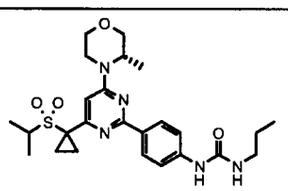
d), 3.98 (1H, dd), 4.19 (1H, d), 4.53 (1H, s), 6.07 (1H, d), 6.79 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.74 (1H, s)

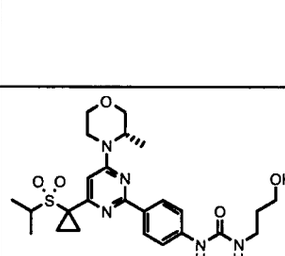
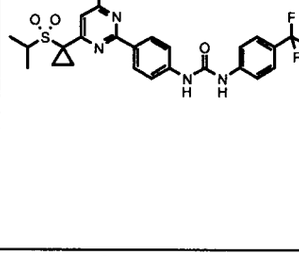
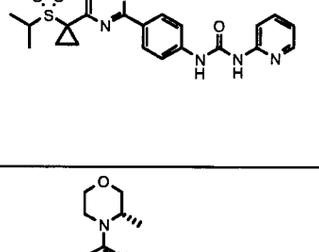
LCMS Spectrum: m/z (ESI+)(M+H)+ = 474; HPLC tR = 1.92 min.

mTOR Kinase Assay (Echo): 0.00315μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
7a		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	488	1.92
7b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	502	2.08
7c		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	514	2.24

Example	Structure	NAME	LCMS MH+	Retention time (min)
7d		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	500	2.34
7e		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	504	2.09
7f		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	532	1.77
7g		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	531	2.06
7h		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-propyl-urea	502	2.00

Example	Structure	NAME	LCMS MH+	Retention time (min)
7i		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	516	2.26
7j		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	518	2.43
7k		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	604	1.81
7l		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	537	2.95
7m		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	540	2.54

Example 7a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.34 (6H, dd), 1.52 - 1.61 (4H, m), 3.09 - 3.16 (2H, m), 3.16 - 3.23 (1H, m), 3.49 (1H, dt), 3.62 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, d), 4.19 (1H, d), 4.53 (1H, s), 6.17 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.66 (1H, s).

mTOR Kinase Assay (Echo): 0.00231μM

Example 7b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.23 (3H, d), 1.34 (6H, dd), 1.52 - 1.61 (4H, m), 3.15 - 3.24 (1H, m), 3.49 (1H, dt), 3.60 - 3.67 (2H, m), 3.73 - 3.82 (2H, m), 3.97 (1H, dd), 4.19 (1H, d), 4.53 (1H, s), 6.07 (1H, d), 6.79 (1H, s), 7.48 (2H, d), 8.18 (2H, d), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.0181μM

Example 7c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.52 - 1.66 (6H, m), 1.81 - 1.91 (2H, m), 2.18 - 2.25 (2H, m), 3.20 (1H, dt), 3.48 (1H, dt), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.09 - 4.21 (2H, m), 4.53 (1H, s), 6.47 (1H, d), 6.79 (1H, s), 7.48 (2H, d), 8.18 (2H, d), 8.56 (1H, s).

mTOR Kinase Assay (Echo): 0.00646μM

Example 7d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.53 - 1.62 (4H, m), 2.54 - 2.58 (1H, m), 3.17 - 3.24 (1H, m), 3.49 (1H, dt), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.20 (1H, d), 4.53 (1H, s), 6.44 (1H, d), 6.80 (1H, s), 7.51 (2H, d), 8.19 (2H, d), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.0038μM

Example 7e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.54 - 1.61 (4H, m), 3.16 - 3.24 (3H, m), 3.44 - 3.52 (3H, m), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.19 (1H, d), 4.52 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00212μM

Example 7f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.24 (6H, s), 1.34 (3H, d), 1.35 (3H, d), 1.55 - 1.62 (4H, m), 3.15 - 3.23 (1H, m), 3.39 (2H, d), 3.49 (1H, dt), 3.62 - 3.68 (2H, m), 3.76 (1H, d), 3.97 (1H, d), 4.20 (1H, d), 4.52 (1H, s), 4.95 (1H, t), 6.01 (1H, s), 6.79 (1H, s), 7.46 (2H, d), 8.18 (2H, d), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00915μM

Example 7g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.52 - 1.61 (4H, m), 2.18 (6H, s), 2.34 (2H, t), 3.17 - 3.24 (3H, m), 3.49 (1H, dt), 3.60 - 3.67

(2H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.19 (1H, d), 4.52 (1H, s), 6.16 (1H, t), 6.79 (1H, s), 7.49 (2H, d), 8.18 (2H, d), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.211μM

Example 7h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.43 - 1.49 (2H, m), 1.53 - 1.62 (4H, m), 3.07 (2H, q), 3.16 - 3.23 (1H, m), 3.49 (1H, dt), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, d), 4.20 (1H, d), 4.54 (1H, s), 6.21 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.0116μM

Example 7i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.55 - 1.62 (4H, m), 1.67 - 1.74 (1H, m), 2.94 (2H, t), 3.18 - 3.23 (1H, m), 3.46 - 3.51 (1H, m), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.20 (1H, d), 4.51 (1H, s), 6.25 (1H, t), 6.79 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.0182μM

Example 7j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.33 (3H, d), 1.35 (3H, d), 1.53 - 1.63 (4H, m), 3.15 - 3.23 (4H, m), 3.45 - 3.51 (4H, m), 3.60 - 3.67 (2H, m), 3.76 (1H, d), 3.97 (1H, d), 4.19 (1H, d), 4.47 (1H, t), 4.53 (1H, s), 6.21 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.0105μM

Example 7k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.34 (3H, d), 1.36 (3H, d), 1.54 - 1.64 (4H, m), 3.19 - 3.25 (1H, m), 3.50 (1H, t), 3.61 - 3.66 (2H, m), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.55 (1H, s), 6.82 (1H, s), 7.59 (2H, d), 7.64 - 7.70 (4H, m), 8.27 (2H, d), 9.04 (1H, s), 9.14 (1H, s).

mTOR Kinase Assay (Echo): 0.00482μM

Example 7l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.35 (3H, d), 1.37 (3H, d), 1.57 - 1.61 (4H, m), 3.18 - 3.27 (1H, m), 3.50 (1H, dt), 3.63 - 3.70 (2H, m), 3.77 (1H, d), 3.98 (1H, dd), 4.21 (1H, d), 4.55 (1H, s), 6.82 (1H, s), 7.02 - 7.05 (1H, m), 7.55 - 7.58 (1H, m), 7.65 (2H, d), 7.77 (1H, t), 8.27 - 8.31 (3H, m), 9.47 (1H, s), 10.62 (1H, s).

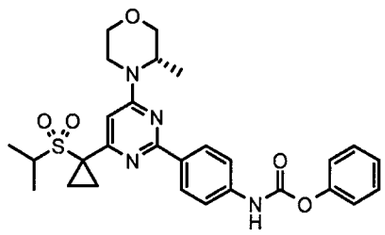
mTOR Kinase Assay (Echo): 0.00913μM

Example 7m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.34 (3H, d), 1.36 (3H, d), 1.53 - 1.63 (4H, m), 3.17 - 3.25 (1H, m), 3.49 (1H, t), 3.61 - 3.68 (2H, m), 3.77 (1H, d), 3.79 (3H, s), 3.97 (1H, d), 4.20 (1H, d), 4.53 (1H, s), 6.81 (1H, s), 7.38 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.22 (2H, d), 8.39 (1H, s), 8.83 (1H, s).

mTOR Kinase Assay (Echo): 0.00504μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate

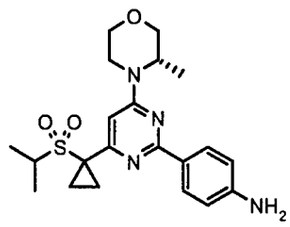


To a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (1.47 g, 3.53 mmol) in 1,4-dioxane (17.65 mL) was added sodium bicarbonate (0.445 g, 5.29 mmol) and phenyl chloroformate (0.474 mL, 3.77 mmol) and the reaction stirred at RT for 2 hours. The reaction mixture was diluted with DCM (20 mL), and washed with water (20 mL), the organic layer dried ($MgSO_4$), filtered and evaporated. The crude solid was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired product as a white solid (1.56 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.27 (3H, d), 1.28 (3H, d), 1.49 - 1.55 (4H, m), 3.14 (1H, dt), 3.39 - 3.44 (1H, m), 3.53 - 3.60 (2H, m), 3.70 (1H, d), 3.90 (1H, dd), 4.14 (1H, d), 4.47 (1H, s), 6.77 (1H, s), 7.17 - 7.23 (3H, m), 7.38 (2H, t), 7.57 (2H, d), 8.22 (2H, d), 10.37 (1H, s)

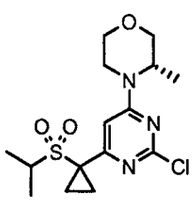
LCMS Spectrum: m/z (ESI+) (M+H)+ = 537; HPLC tR = 2.39 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline



To a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidine (1.6 g, 4.45 mmol) in DMF (0.24 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL) was added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.266 g, 5.78 mmol), sodium carbonate (5 mL, 10.00 mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.156 g, 0.22 mmol) and the suspension heated at 95°C for 2 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired material as a cream solid (1.47 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.32 (3H, d), 1.34 (3H, d), 1.50 - 1.59 (4H, m), 3.17 (1H, dt), 3.44 - 3.51 (1H, m), 3.59 - 3.66 (2H, m), 3.75 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.49 (1H, d), 5.56 (2H, s), 6.61 (2H, d), 6.69 (1H, s), 8.02 (2H, d)
LCMS Spectrum: m/z (ESI+) (M+H)+ = 417; HPLC tR = 2.09 min.

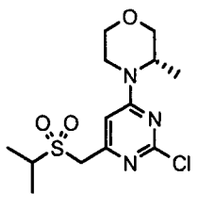
2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-propan-2-ylsulfonylcyclopropyl)pyrimidine



2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidine (2.4 g, 7.19 mmol) was dissolved in DCM (40 mL) and sodium hydroxide concentrate (7.2 mL, 71.89 mmol) was added to the reaction, followed by dibromoethane (0.325 mL, 14.38 mmol). The reaction was stirred at 40°C for 10 hours. The reaction mixture was washed with water (50 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white solid (1.49 g).

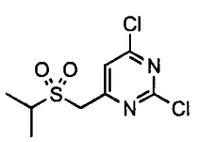
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.27 (6H, d), 1.52 - 1.54 (2H, m), 1.56 - 1.59 (2H, m), 3.21 - 3.24 (1H, m), 3.41 - 3.47 (1H, m), 3.55 - 3.61 (2H, m), 3.72 (1H, d), 3.93 (1H, dd), 4.02 (1H, d), 4.37 (1H, s), 6.94 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ 360, HPLC tR = 1.89 min

2-Chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(propan-2-ylsulfonylmethyl)pyrimidine



2,4-Dichloro-6-[(isopropylsulfonyl)methyl]pyrimidine (2.65 g, 9.85 mmol) was dissolved in DCM (50 mL) and stirred (under nitrogen) at -5°C. Triethylamine (1.5 mL, 10.84 mmol) was added to give a clear brown solution. (3*S*)-3-Methyl morpholine (997 mg, 9.85 mmol) was dissolved in DCM and added dropwise keeping the reaction below -5°C. The cooling bath was then removed and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture was then washed with water (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude material was chromatographed on silica, eluting with 0-50% ethyl acetate in DCM to give the desired material as a white solid (2 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (d, 3H), 1.31 (d, 6H), 3.22 (m, 1H), 3.43 (m, 2H), 3.60 (m, 1H), 3.74 (d, 1H), 3.98 (m, 1H), 4.30 (s, 1H), 4.43 (s, 2H), 6.91 (s, 1H)
LCMS Spectrum: m/z (ESI+)(M+H)+ 332, HPLC tR = 1.70 min

2,4-Dichloro-6-[(isopropylsulfonyl)methyl]pyrimidine



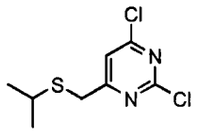
2,4-Dichloro-6-[(isopropylthio)methyl]pyrimidine (6.2 g, 26.16 mmol) was dissolved in DCM (100 mL) and 3,5-dichlorobenzenecarboperoxoic acid (13.5 g, 78.4 mmol) was added portionwise over 10 minutes. The reaction was stirred at room temperature for 4 hours. The reaction mixture was then washed with saturated aqueous sodium bicarbonate (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo* to give a cream solid.

Purification by normal phase chromatography, eluting with 0-50% ethyl acetate in iso-hexane gave the desired material as a cream solid (5.3 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (d, 6H), 3.43 (m, 1H), 4.77 (s, 2H), 7.87 (s, 1H)

LCMS Spectrum: m/z $(M-H)^-$ 267, HPLC tR = 1.64 min

2,4-Dichloro-6-[(isopropylthio)methyl]pyrimidine

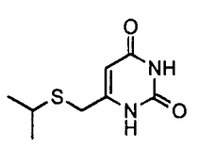


6-[(Isopropylthio)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (8 g, 40 mmol) was added to phosphorus oxychloride (100 mL) and the mixture heated to reflux for 16 hours. The reaction was then cooled to room temperature and the excess phosphorus oxychloride was removed *in vacuo*,. The residue was azeotroped with toluene (2 x 100 mL) and dissolved in DCM. This mixture was then poured slowly onto ice (1 L) and stirred for 20 minutes, then extracted with DCM (3 x 500 mL) The extracts were combined, dried over magnesium sulphate, then concentrated *in vacuo* to give the desired material as a brown oil (6.5 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (d, 6H), 2.96 (m, 1H), 3.85 (s, 2H), 7.82 (s, 1H)

LCMS Spectrum: No mass ion observed, HPLC tR = 2.51 min

6-[(Isopropylthio)methyl]pyrimidine-2,4(1*H*,3*H*)-dione



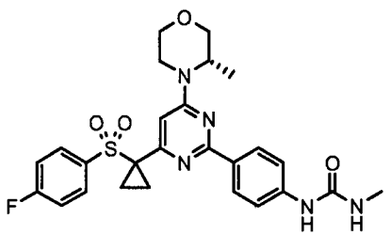
6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (8 g, 50 mmol) was dissolved in acetonitrile (200 mL) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (13 mL, 87.19 mmol) was added and the reaction stirred at room temperature for 15 minutes. Isopropyl mercaptan (8.1 mL, 87.19 mmol) was then added and the reaction stirred at room temperature for a further 2 hours. Solvent removed *in vacuo* and the resulting brown oil was dissolved in DCM and washed

with water. Organic phase dried over magnesium sulphate, filtered and concentrated *in vacuo*. The resulting oil was chromatographed on silica, eluting with 0-10% methanol in DCM to give the desired material as a white solid (8 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (d, 6H), 2.90 (m, 1H), 3.42 (s, 2H), 5.49 (s, 1H), 10.82 (s, 1H), 10.94 (s, 1H)

LCMS Spectrum: m/z $(M-H)^-$ 199, HPLC tR = 0.63 min

Example 8: 1-[4-[4-[1-(4-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea



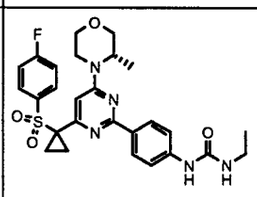
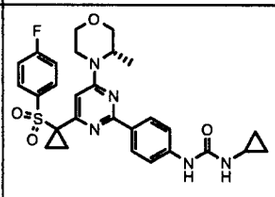
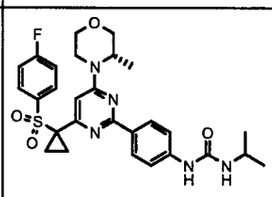
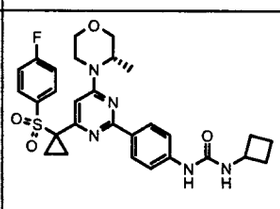
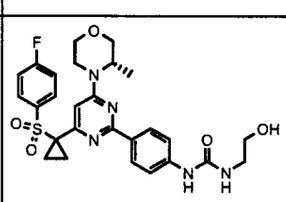
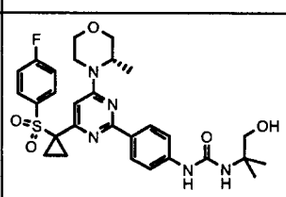
To a solution of phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) in DMF (2 mL) was added triethylamine (0.071 mL, 0.51 mmol) followed by methylamine (0.5 mL, 1.1 mmol) and the reaction heated at 50°C for 2 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (51 mg).

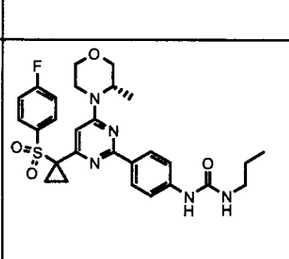
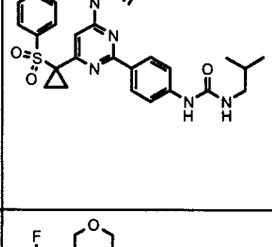
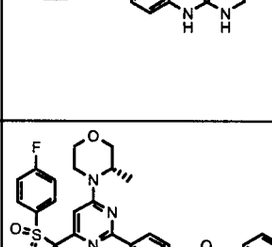
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 2.66 (3H, d), 3.15 (1H, dt), 3.46 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.13 (1H, d), 4.42 (1H, s), 6.03 (1H, d), 6.65 (1H, s), 7.38 - 7.44 (4H, m), 7.79 - 7.86 (4H, m), 8.71 (1H, s)

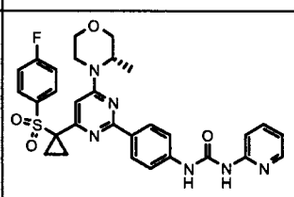
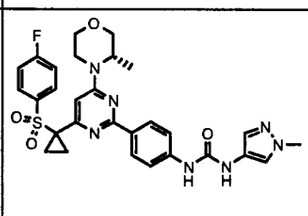
LCMS Spectrum: m/z (ESI+)(M+H)+ = 526; HPLC tR = 2.09 min.

mTOR Kinase Assay (Echo): 0.000576μM

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
8a		1-ethyl-3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	540	2.23
8b		3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	552	2.25
8c		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	554	2.40
8d		3-cyclobutyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	566	2.47
8e		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	556	1.92
8f		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea	584	2.22

Example	Structure	NAME	LCMS MH+	Retention time (min)
8g		3-(2-dimethylaminoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	583	2.17
8h		3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea	554	2.40
8i		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	568	2.55
8j		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	570	1.97
8k		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	656	3.01

Example	Structure	NAME	LCMS MH+	Retention time (min)
8l		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	589	2.63
8m		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	592	2.12

Example 8 can also be prepared in an analogous fashion to that described above but using NMP as the solvent and stirring at 75°C for 30 minutes. The material can then be partitioned between ethyl acetate and water and the organic materials purified by chromatography on silica, eluting with 0-3% methanol in ethyl acetate. The material can then be dissolved in DCM and either evapourated rapidly to give the desired material as a foam or left to stand for approximately 6 weeks upon which time the deired material precipitated from solution.

Example 8a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.18 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 3.09 - 3.18 (3H, m), 3.46 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.13 (1H, d), 4.42 (1H, s), 6.12 (1H, t), 6.65 (1H, s), 7.37 - 7.46 (4H, m), 7.79 - 7.86 (4H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.00096μM

Example 8b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.19 (3H, d), 1.58 - 1.63 (2H, m), 1.89 - 1.91 (2H, m), 2.55 - 2.58 (1H, m), 3.15 (1H, t), 3.46 (1H, t), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.14 (1H, d), 4.42 (1H, s), 6.39 (1H, s), 6.65 (1H, s), 7.39 - 7.44 (4H, m), 7.80 - 7.86 (4H, m), 8.51 (1H, s).

mTOR Kinase Assay (Echo): 0.00123μM

Example 8c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.18 (3H, d), 1.58 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 3.15 (1H, t), 3.46 (1H, t), 3.61 (1H, d), 3.73 - 3.81 (2H, m), 3.96

(1H, d), 4.13 (1H, d), 4.42 (1H, s), 6.02 (1H, d), 6.65 (1H, s), 7.37 (2H, d), 7.42 (2H, t), 7.79 - 7.86 (4H, m), 8.51 (1H, s).

mTOR Kinase Assay (Echo): 0.00185μM

Example 8d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 - 1.66 (4H, m), 1.83 - 1.91 (4H, m), 2.18 - 2.26 (2H, m), 3.12 - 3.19 (1H, m), 3.46 (1H, t), 3.61 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.11 - 4.17 (2H, m), 4.42 (1H, s), 6.42 (1H, d), 6.65 (1H, s), 7.37 (2H, d), 7.42 (2H, t), 7.79 - 7.86 (4H, m), 8.54 (1H, s).

mTOR Kinase Assay (Echo): 0.00134μM

Example 8e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 3.15 - 3.18 (2H, m), 3.40 - 3.48 (2H, m), 3.61 (2H, dd), 3.74 (1H, d), 3.95 (1H, d), 4.05 - 4.16 (2H, m), 4.13 (1H, d), 4.73 (1H, t), 6.22 (1H, t), 6.64 (1H, s), 7.37 - 7.44 (4H, m), 7.79 - 7.86 (4H, m), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.000342μM

Example 8f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.24 (6H, s), 1.57 - 1.63 (2H, m), 1.86 - 1.91 (2H, m), 3.10 - 3.18 (1H, m), 3.38 (2H, d), 3.46 (1H, t), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.14 (1H, d), 4.41 (1H, s), 4.95 (1H, t), 5.97 (1H, s), 6.64 (1H, s), 7.34 (2H, d), 7.42 (2H, t), 7.78 - 7.86 (4H, m), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.00882μM

Example 8g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 2.18 (6H, s), 2.33 (2H, t), 3.15 - 3.21 (3H, m), 3.46 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.13 (1H, d), 4.42 (1H, s), 6.13 (1H, t), 6.65 (1H, s), 7.37 - 7.43 (4H, m), 7.79 - 7.86 (4H, m), 8.86 (1H, s).

mTOR Kinase Assay (Echo): 0.0613μM

Example 8h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.18 (3H, d), 1.45 (2H, sextet), 1.59 - 1.62 (2H, m), 1.88 - 1.90 (2H, m), 3.06 (2H, q), 3.12 - 3.16 (1H, m), 3.40 - 3.49 (1H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.96 (1H, dd), 4.13 (1H, d), 4.42 (1H, s), 6.17 (1H, t), 6.64 (1H, s), 7.37 - 7.44 (4H, m), 7.79 - 7.86 (4H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.00176μM

Example 8i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (6H, d), 1.19 (3H, d), 1.59 - 1.62 (2H, m), 1.67 - 1.74 (1H, m), 1.88 - 1.90 (2H, m), 2.94 (2H, t), 3.12 - 3.19 (1H, m), 3.46 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.42 (1H, s), 6.21 (1H, t), 6.65 (1H, s), 7.37 - 7.43 (4H, m), 7.79 - 7.85 (4H, m), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.0198μM

Example 8j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.56 - 1.63 (4H, m), 1.88 - 1.90 (2H, m), 3.12 - 3.19 (3H, m), 3.47 (2H, q), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.13 (1H, d), 4.43 (1H, s), 4.47 (2H, t), 6.17 (1H, t), 6.65 (1H, s), 7.37 - 7.45 (4H, m), 7.79 - 7.86 (4H, m), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.000751μM

Example 8k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.60 - 1.63 (2H, m), 1.89 - 1.92 (2H, m), 3.13 - 3.21 (1H, m), 3.47 (1H, dt), 3.62 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.15 (1H, d), 4.43 (1H, s), 6.68 (1H, s), 7.41 - 7.49 (4H, m), 7.63 - 7.69 (4H, m), 7.84 - 7.89 (4H, m), 9.02 (1H, s), 9.10 (1H, s).

mTOR Kinase Assay (Echo): 0.0173μM

Example 8l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.61 - 1.63 (2H, m), 1.89 - 1.92 (2H, m), 3.14 - 3.21 (1H, m), 3.47 (1H, t), 3.62 (1H, d), 3.76 (1H, d), 3.96 (1H, d), 4.16 (1H, d), 4.44 (1H, s), 6.68 (1H, s), 7.02 - 7.05 (1H, m), 7.43 (2H, t), 7.53 (2H, d), 7.57 - 7.62 (1H, m), 7.75 - 7.79 (1H, m), 7.83 - 7.91 (4H, m), 8.30 (1H, d), 9.40 (1H, s), 10.50 (1H, s).

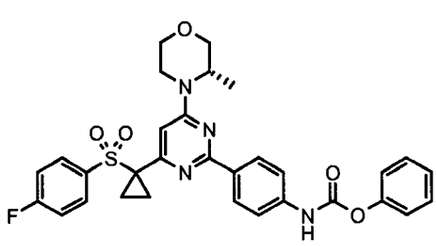
mTOR Kinase Assay (Echo): 0.00813μM

Example 8m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.60 - 1.62 (2H, m), 1.89 - 1.91 (2H, m), 3.12 - 3.20 (1H, m), 3.47 (1H, dt), 3.62 (1H, dd), 3.75 (1H, d), 3.79 (3H, s), 3.96 (1H, dd), 4.14 (1H, d), 4.43 (1H, s), 6.66 (1H, s), 7.38 - 7.45 (5H, m), 7.77 (1H, s), 7.83 - 7.87 (4H, m), 8.35 (1H, s), 8.82 (1H, s).

mTOR Kinase Assay (Echo): 0.00136μM

The preparation of phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

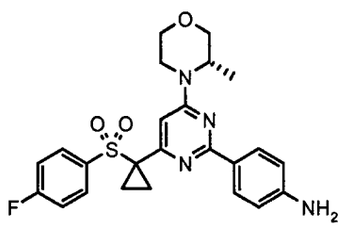


To a solution of 4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.33 g, 2.84 mmol) in 1,4-dioxane (15 mL) was added sodium bicarbonate (0.358 g, 4.26 mmol) and phenyl chloroformate (0.357 mL, 2.84 mmol) and the reaction stirred at RT for 2 hours. The reaction mixture was diluted with DCM (20 mL), and washed with water (20 mL), the organic layer dried ($MgSO_4$), filtered and evaporated. The crude solid was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired product as a white solid (1.46 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.60 - 1.65 (2H, m), 1.89 - 1.92 (2H, m), 3.18 (1H, dt), 3.47 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.17 (1H, d), 4.45 (1H, s), 6.69 (1H, s), 7.25 (3H, d), 7.40 - 7.47 (4H, m), 7.55 (2H, d), 7.83 - 7.87 (2H, m), 7.92 (2H, d), 10.42 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 589; HPLC tR = 2.92 min.

4-[4-[1-(4-Fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



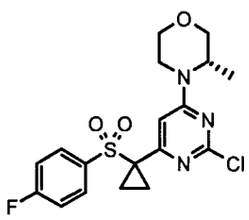
To a solution of 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.5 g, 3.64 mmol) in DMF (0.48 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL) was added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.037 g, 4.73 mmol), sodium carbonate (5 mL, 10.00 mmol) and dichlorobis(triphenylphosphine)palladium(II) (0.128 g, 0.18 mmol) and the suspension heated at 95°C for 2 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired as a cream solid (1.33 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.57 - 1.59 (2H, m), 1.86 - 1.88 (2H, m), 3.12 (1H, dt), 3.45 (1H, dt), 3.60 (1H, dd), 3.73 (1H, d), 3.95 (1H, dd),

4.10 (1H, d), 4.38 (1H, s), 5.52 (2H, s), 6.49 (2H, d), 6.55 (1H, s), 7.41 (2H, t), 7.64 (2H, d), 7.82 - 7.85 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 469; HPLC tR = 2.47 min.

2-Chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



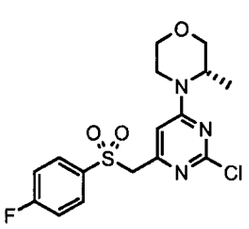
2-Chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.0 g, 7.78 mmol) was dissolved in DCM (40 mL) and sodium hydroxide concentrate (7.8 mL, 77.75 mmol) was added to the reaction, followed by dibromoethane (0.352 mL, 15.55 mmol). The reaction was stirred at 40°C for 16 hours. The reaction mixture was washed with water (50 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated to afford crude product.

The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white solid (1.50 g,).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.53 - 1.56 (2H, m), 1.82 - 1.85 (2H, m), 3.14 (1H, dt), 3.40 (1H, dt), 3.55 (1H, dd), 3.70 (1H, d), 3.91 (2H, dd), 4.25 (1H, s), 6.70 (1H, s), 7.45 (2H, t), 7.79 - 7.84 (2H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ 412, HPLC tR = 2.14 min

2-Chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



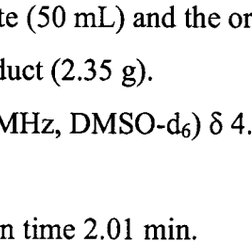
Triethylamine (1.117 ml, 8.01 mmol) was added to 2,4-dichloro-6-[(4-fluorophenyl)sulfonylmethyl]pyrimidine (2.34 g, 7.29 mmol) in DCM (36.4 mL) at 0°C followed by (3*S*)-3-methylmorpholine (0.737 g, 7.29 mmol) in DCM (20 mL) over 15

minutes. The reaction was then stirred at RT for 16 hours. The reaction mixture was washed with water (50 mL), the organic layer dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a beige solid (1.530 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 3.13 - 3.20 (1H, m), 3.27 - 3.28 (1H, m), 3.39 - 3.46 (1H, m), 3.57 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 4.17 (1H, s), 4.65 (2H, s), 6.71 (1H, s), 7.48 (2H, t), 7.83 - 7.87 (2H, m)

LCMS Spectrum: MH+ 386, retention time 1.94 min.

2,4-Dichloro-6-[(4-fluorophenyl)sulfonylmethyl]pyrimidine



3-Chloroperoxybenzoic acid (3.78 g, 21.89 mmol) was added portionwise to 2,4-dichloro-6-[(4-fluorophenyl)sulfanylmethyl]pyrimidine (2.11 g, 7.30 mmol), in DCM (36.5 mL) and the reaction stirred at RT for 2 hours. The reaction mixture was washed with a saturated aqueous solution ofsodium hydrogen carbonate (50 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated to afford desired product (2.35 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 4.99 (2H, s), 7.48 - 7.52 (2H, m), 7.76 (1H, s), 7.85 - 7.88 (2H, m)

LCMS Spectrum: MH+ 319, retention time 2.01 min.

2,4-Dichloro-6-[(4-fluorophenyl)sulfanylmethyl]pyrimidine

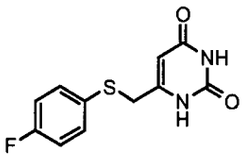
Phosphorus oxychloride (15.2 g, 99.1 mmol) was added to 6-[(4-fluorophenyl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione (2.5 g, 9.91 mmol), and the resulting solution was stirred at reflux for 7 hours. The reaction was allowed to cool and the phosphorus oxychloride removed under reduced pressure to give a brown oil. This was dissolved in DCM and ice water (50 mL) added followed by solid sodium bicarbonate (until

effervescence stops). The aqueous layer was extracted with DCM (2 x 50 mL) and the organics dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in isohexane, to give the desired material as a yellow gum (2.11 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 4.21 (2H, s), 7.09 - 7.14 (2H, m), 7.34 - 7.38 (2H, m), 7.58 (1H, s)

LCMS Spectrum: M-H+ 287, retention time 2.51 min.

6-[(4-Fluorophenyl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione

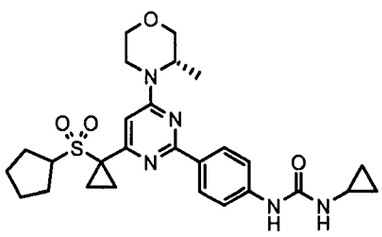


DBU (4.02 mL, 26.91 mmol) was added to 4-fluorobenzenethiol (3.45 g, 26.91 mmol), in DMF (90 mL) at RT. The resulting solution was stirred at 20°C for 15 minutes. 6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (2.88 g, 17.94 mmol) was then added and the reaction stirred for 4 hours. The reaction mixture was concentrated and diluted with DCM (100 mL), and washed with water (100 mL). The aqueous layer was acidified with 2M hydrochloric acid to give a white solid which was filtered and washed with water then dried under vacuum to give desired product (2.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.80 (2H, s), 5.20 (1H, s), 7.18 - 7.23 (2H, m), 7.45 - 7.49 (2H, m), 10.90 (1H, s), 10.93 (1H, s)

LCMS Spectrum: M-H- 251, retention time 0.80 min.

Example 9: 1-[4-[4-(1-Cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropyl-urea



To a solution of phenyl *N*-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (200 mg, 0.36 mmol) and amine

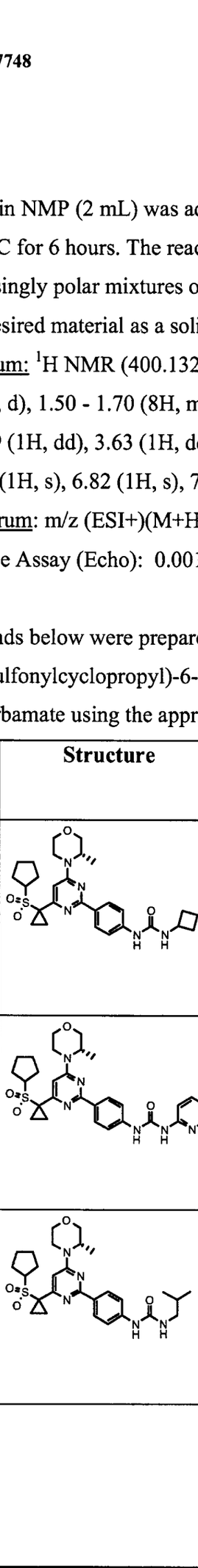
(1.44 mmol) in NMP (2 mL) was added triethylamine (0.198 mL, 1.44 mmol) and mixture heated at 75°C for 6 hours. The reaction was allowed to cool and purified by prep HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a solid (130 mg).

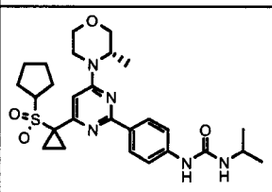
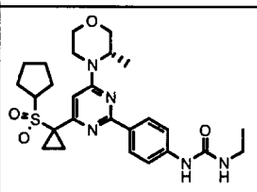
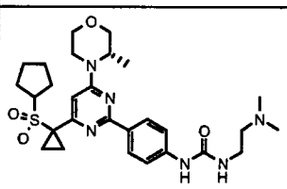
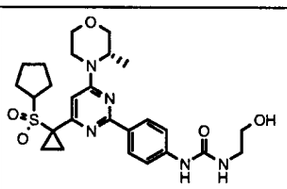
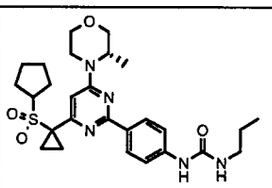
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.23 (3H, d), 1.50 - 1.70 (8H, m), 1.85 - 1.94 (2H, m), 1.99 - 2.07 (2H, m), 3.16 - 3.25 (1H, m), 3.49 (1H, dd), 3.63 (1H, dd), 3.76 (1H, d), 3.89 - 4.00 (2H, m), 4.20 (1H, d), 4.55 (1H, s), 6.46 (1H, s), 6.82 (1H, s), 7.51 (2H, d), 8.20 (2H, d), 8.54 (1H, s)

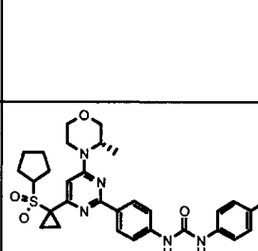
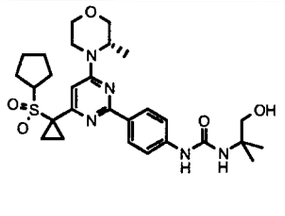
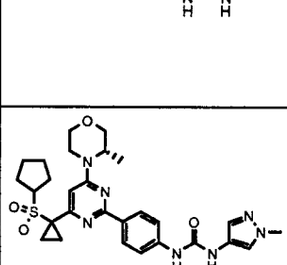
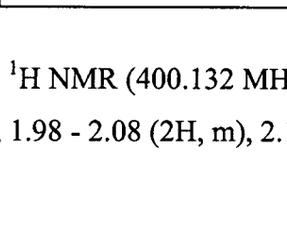
LCMS Spectrum: m/z (ESI+)(M+H)+ = 526; HPLC tR = 2.42 min

mTOR Kinase Assay (Echo): 0.0018μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
9a		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	540	2.67
9b		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	563	2.89
9c		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	542	2.77

Example	Structure	NAME	LCMS MH+	Retention time (min)
9d		3-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethyl-urea	528	2.59
9e		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	514	2.40
9f		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	557	2.33
9g		3-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea	530	2.02
9h		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	528	2.59

Example	Structure	NAME	LCMS MH+	Retention time (min)
9i		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	500	2.25
9j		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea	630	3.25
9k		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	558	2.37
9l		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	544	2.07
9m		1-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	566	2.26

Example 9a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.51 - 1.70 (10H, m), 1.82 - 1.94 (4H, m), 1.98 - 2.08 (2H, m), 2.17 - 2.25 (2H, m), 3.17 - 3.25 (1H, m), 3.49 (1H, td),

3.63 (1H, dd), 3.76 (1H, d), 3.88 - 4.00 (2H, m), 4.10 - 4.22 (2H, m), 4.55 (1H, s), 6.47 (1H, d), 6.81 (1H, s), 7.48 (2H, d), 8.19 (2H, d), 8.56 (1H, s).

mTOR Kinase Assay (Echo): 0.0129μM

Example 9b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.53 - 1.70 (8H, m), 1.86 - 1.96 (2H, m), 2.00 - 2.09 (2H, m), 3.18 - 3.25 (1H, m), 3.46 - 3.54 (1H, m), 3.65 (1H, dd), 3.77 (1H, d), 3.90 - 4.01 (2H, m), 4.22 (1H, d), 4.57 (1H, s), 6.85 (1H, s), 7.04 (1H, t), 7.56 (1H, d), 7.65 (2H, d), 7.77 (1H, t), 8.26 - 8.32 (5H, m), 9.48 (1H, s), 10.63 (3H, s).

mTOR Kinase Assay (Echo): 0.0215μM

Example 9c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.23 (3H, d), 1.51 - 1.75 (8H, m), 1.85 - 1.96 (2H, m), 1.99 - 2.08 (2H, m), 2.94 (2H, t), 3.16 - 3.25 (1H, m), 3.49 (1H, td), 3.63 (1H, dd), 3.76 (1H, d), 3.89 - 4.00 (2H, m), 4.20 (1H, d), 4.55 (1H, s), 6.24 (1H, t), 6.82 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.0483μM

Example 9d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.23 (3H, d), 1.51 - 1.69 (8H, m), 1.85 - 1.94 (2H, m), 1.98 - 2.08 (2H, m), 3.20 (1H, td), 3.49 (1H, td), 3.63 (1H, dd), 3.73 - 3.81 (2H, m), 3.89 - 4.00 (2H, m), 4.19 (1H, d), 4.55 (1H, s), 6.07 (1H, d), 6.83 (1H, s), 7.48 (2H, d), 8.19 (2H, d), 8.54 (1H, s).

mTOR Kinase Assay (Echo): 0.0151μM

Example 9e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.49 - 1.71 (8H, m), 1.86 - 1.96 (2H, m), 1.99 - 2.07 (2H, m), 3.12 (2H, q), 3.17 - 3.25 (1H, m), 3.45 - 3.53 (1H, m), 3.61 - 3.66 (1H, m), 3.89 - 3.99 (2H, m), 4.19 (1H, d), 4.56 (1H, s), 6.17 (1H, t), 6.82 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.00187μM

Example 9f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.50 - 1.70 (8H, m), 1.84 - 1.95 (2H, m), 1.98 - 2.08 (2H, m), 2.20 (6H, s), 2.33 (2H, t), 3.17 - 3.23 (2H, m), 3.49 (1H, td), 3.63 (1H, dd), 3.76 (1H, d), 3.90 - 4.00 (2H, m), 4.20 (1H, d), 4.56 (1H, s), 6.16 (1H, t), 6.82 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.144μM

Example 9g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.50 - 1.71 (8H, m), 1.85 - 1.95 (2H, m), 1.98 - 2.07 (2H, m), 3.14 - 3.24 (3H, m), 3.43 - 3.52 (3H, m), 3.63 (1H, d), 3.76 (1H, d), 3.89 - 4.00 (2H, m), 4.19 (1H, d), 4.55 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.82 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.00127μM

Example 9h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.23 (3H, d), 1.42 - 1.70 (10H, m), 1.84 - 1.94 (2H, m), 1.98 - 2.08 (2H, m), 3.03 - 3.09 (2H, m), 3.16 - 3.25 (1H, m), 3.50 (1H, d), 3.63 (1H, d), 3.76 (1H, d), 3.90 - 4.00 (2H, m), 4.20 (1H, d), 4.55 (1H, s), 6.21 (1H, t), 6.82 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.66 (1H, s).

mTOR Kinase Assay (Echo): 0.0057μM

Example 9i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.49 - 1.71 (8H, m), 1.85 - 1.95 (2H, m), 1.99 - 2.08 (2H, m), 3.16 - 3.24 (1H, m), 3.49 (1H, td), 3.63 (1H, dd), 3.76 (1H, d), 3.87 - 4.01 (2H, m), 4.20 (1H, d), 4.56 (1H, s), 6.09 (1H, q), 6.82 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.0024μM

Example 9j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.52 - 1.70 (8H, m), 1.87 - 1.96 (2H, m), 1.99 - 2.07 (2H, m), 3.17 - 3.27 (1H, m), 3.46 - 3.54 (1H, m), 3.64 (1H, d), 3.77 (1H, d), 3.89 - 4.01 (2H, m), 4.21 (1H, d), 4.57 (1H, s), 6.85 (1H, s), 7.59 (2H, d), 7.67 (4H, q), 8.27 (2H, d), 9.05 (1H, s), 9.15 (1H, s).

mTOR Kinase Assay (Echo): 0.046μM

Example 9k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 - 1.26 (9H, m), 1.51 - 1.71 (8H, m), 1.86 - 1.93 (2H, m), 1.98 - 2.09 (2H, m), 3.16 - 3.24 (1H, m), 3.39 (2H, d), 3.49 (1H, dd), 3.63 (1H, dd), 3.76 (1H, d), 3.90 - 4.01 (2H, m), 4.20 (1H, d), 4.55 (1H, s), 4.95 (1H, t), 6.02 (1H, s), 6.81 (1H, s), 7.45 (2H, d), 8.18 (2H, d), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.0115μM

Example 9l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.50 - 1.70 (8H, m), 1.85 - 1.95 (2H, m), 1.98 - 2.07 (2H, m), 3.12 - 3.25 (3H, m), 3.23 - 3.33 (2H, m), 3.43 - 3.53 (3H, m), 3.63 (1H, d), 3.77 (1H, d), 3.89 - 4.01 (2H, m), 4.20 (1H, d), 4.48 (1H, t), 4.56 (1H, s), 6.21 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.72 (1H, s).

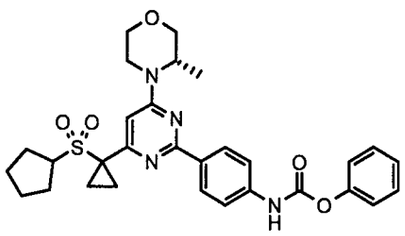
mTOR Kinase Assay (Echo): 0.00395μM

Example 9m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (9H, d), 1.51 - 1.70 (20H, m), 1.86 - 1.95 (6H, m), 1.99 - 2.07 (4H, m), 3.15 - 3.25 (25H, m), 3.50 (1H, d), 3.64 (1H, d), 3.78 (1H, d), 3.90 - 4.01 (2H, m), 4.20 (1H, d), 4.56 (1H, s), 6.86 (1H, s), 7.43 (1H, s), 7.56 (2H, d), 7.81 (1H, s), 8.23 (2H, d), 8.44 (1H, s), 8.87 (1H, s).

mTOR Kinase Assay (Echo): 0.00401μM

The preparation of phenyl *N*-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

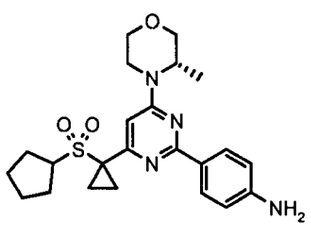


Phenyl chloroformate (1.701 mL, 13.56 mmol) was added to 4-[4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (4 g, 9.04 mmol) and sodium hydrogen carbonate (1.139 g, 13.56 mmol) in dioxane (120 mL) cooled to 5°C under nitrogen. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (125 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude material which was triturated with diethyl ether and isohexane to give the desired material as a white solid (4.77 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.51 - 1.70 (4H, m), 1.85 - 1.95 (2H, m), 1.98 - 2.08 (2H, m), 3.21 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.90 - 4.00 (2H, m), 4.21 (1H, d), 4.58 (1H, s), 6.88 (1H, s), 7.22 - 7.32 (3H, m), 7.41 - 7.49 (2H, m), 7.64 (2H, d), 8.30 (2H, d), 10.45 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 563; HPLC tR = 3.02 min

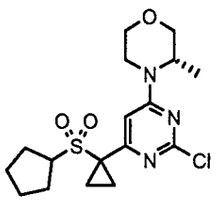
4-[4-(1-Cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Bis(triphenylphosphine)palladium(II) chloride (300 mg, 0.43 mmol) was added to 2-chloro-4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.15 g, 10.75 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.53 g, 16.13 mmol) and sodium carbonate (25 mL, 50.0 mmol) in ethanol (20 mL), DMF (40 mL), water (25 mL) and DME (40 mL) at Rt and the resulting mixture degassed then stirred at 95°C for 18 hours. The reaction mixture was diluted with ethyl acetate (400 mL), and washed with water (2 x 150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 80% ethyl acetate in isohexane, to give the desired material as a cream solid (4.00 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.46 - 1.72 (7H, m), 1.84 - 1.95 (2H, m), 3.13 - 3.22 (1H, m), 3.47 (1H, td), 3.62 (1H, dd), 3.75 (1H, d), 3.89 - 3.99 (2H, m), 4.15 (1H, d), 4.54 (1H, s), 5.58 (2H, s), 6.61 (2H, d), 6.72 (1H, s), 8.02 (2H, d)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 443; HPLC tR = 2.4 min

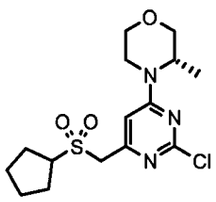
2-Chloro-4-(1-cyclopentylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Sodium hydroxide (62.5 mL, 125.04 mmol) was added to 2-chloro-4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.50 g, 12.50 mmol), 1,2-dibromoethane (4.31 mL, 50.02 mmol) and tetrabutylammonium bromide (0.403 g, 1.25 mmol) in toluene (100 mL) at 30°C under nitrogen. The resulting mixture was stirred at 60°C for 3 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 45% ethyl acetate in isohexane, to give the desired material as a colourless gum (4.47 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.47 - 1.68 (8H, m), 1.80 - 1.89 (2H, m), 1.91 - 1.98 (2H, m), 3.21 (1H, dt), 3.44 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.82 (1H, q), 3.93 (1H, dd), 3.98 - 4.06 (1H, m), 4.41 (1H, s), 6.97 (1H, s)

2-Chloro-4-(cyclopentylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

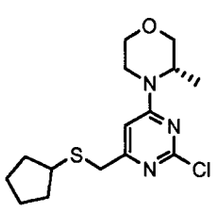


Hydrogen peroxide (19.54 mL, 632 mmol) was added to 2-chloro-4-(cyclopentylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (10.36 g, 31.60 mmol), sodium tungstate dihydrate (0.208 g, 0.63 mmol) (dissolved in minimum quantity of water) and 2M sulphuric acid solution (0.177 mL) in dioxane (100 mL) at 55°C under air. The resulting solution was stirred at 55°C for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water then a 10% aqueous solution of sodium metabisulfite. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 70% ethyl acetate in isohexane, to give the desired material as a colourless gum (9.7 g).

NMR Spectrum: ^1H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.64 (4H, m), 1.95 (4H, m), 3.24 (1H, m), 3.45 (1H, td), 3.60 (1H, dd), 3.71 (1H, m), 3.95 (2H, m), 4.35 (1H, s), 4.40 (2H, s), 6.91 (1H, s)

Mass Spectrum: m/z (ESI+)(M+H)+ = 360

2-Chloro-4-(cyclopentylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



DIPEA (9.62 mL, 55.57 mmol) was added to cyclopentanethiol (5.93 mL, 55.57 mmol), in DMF (80 mL) at RT under nitrogen. The resulting solution was stirred at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (13.1g, 37.05 mmol) was added to the reaction and stirred for 2 hours at RT. The reaction mixture was diluted with ethyl acetate (500 mL), and washed with water (2 x 200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by

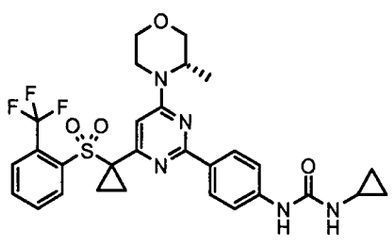
flash silica chromatography, elution gradient 0 to 30% ethyl acetate in isohexane, to give the desired material as a colourless gum (11.13 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.43 (2H, m), 1.53 (2H, m), 1.65 (2H, m), 1.94 (2H, m), 3.16 (2H, m), 3.44 (1H, td), 3.71 (1H, d), 3.95 (2H, m), 4.35 (1H, s), 6.79 (1H, s)

Mass Spectrum: m/z (ESI+)(M+H)+ = 328

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier

Example 10: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea



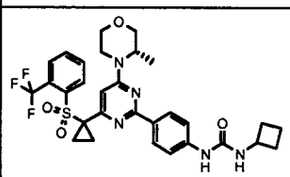
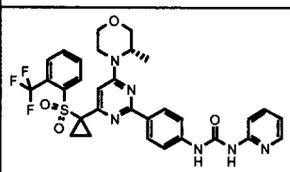
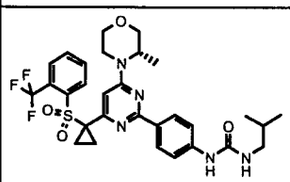
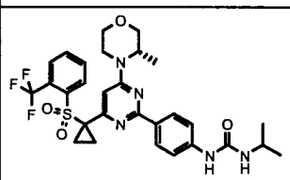
To a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate (200 mg,0.31 mmol) and cyclopropylamine (1.25 mmol) in NMP (2 mL) was added triethylamine (0.175 mL,1.25 mmol). The reaction mixture was heated at 75°C for 6 hours. The reaction mixture was purified by prep HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material (140 mg).

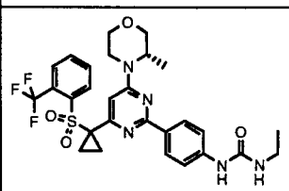
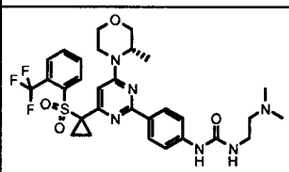
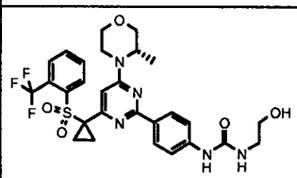
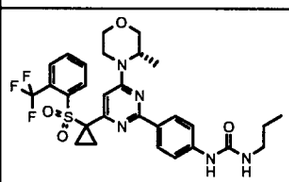
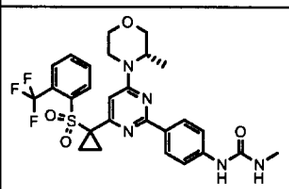
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.14 (3H, d), 1.70 - 1.75 (2H, m), 1.92 - 1.95 (2H, m), 3.11 (1H, td), 3.39 - 3.48 (1H, m), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 6.41 (1H, d), 6.62 (1H, s), 7.37 (2H, d), 7.76 (2H, d), 7.82 - 7.86 (2H, m), 7.91 - 7.95 (1H, m), 8.16 - 8.19 (1H, m), 8.49 (1H, s)

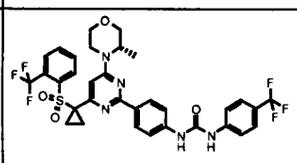
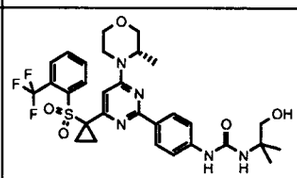
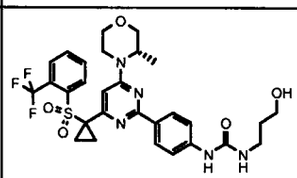
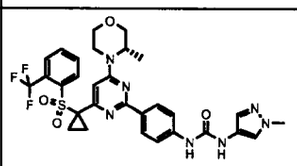
LCMS Spectrum: m/z (ESI+)(M+H)+ = 602; HPLC tR = 2.52 min.

mTOR Kinase Assay (Echo): 0.00448μM

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
10a		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	616	2.73
10b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea		
10c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	618	2.81
10d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	604	2.66

Example	Structure	NAME	LCMS MH+	Retention time (min)
10e		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	590	2.51
10f		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	633	2.46
10g		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	606	2.16
10h		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-1-propyl-urea	604	2.62
10i		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	576	2.34

Example	Structure	NAME	LCMS MH+	Retention time (min)
10j		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	706	3.22
10k		3-(1-hydroxy-2-methyl-propan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	634	2.43
10l		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	620	2.17
10m		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	642	2.35

Example 10a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.56 - 1.75 (4H, m), 1.80 - 1.96 (4H, m), 2.17 - 2.25 (2H, m), 3.11 (1H, td), 3.39 - 3.48 (1H, m), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.04 - 4.18 (2H, m), 4.43 (1H, s), 6.44 (1H, d), 6.61 (1H, s), 7.34 (2H, d), 7.75 (2H, d), 7.82 - 7.86 (2H, m), 7.92 - 7.95 (1H, m), 8.15 - 8.20 (1H, m), 8.52 (1H, s).

mTOR Kinase Assay (Echo): 0.0395μM

Example 10b: mTOR Kinase Assay (Echo): 0.0266μM

Example 10c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (6H, d), 1.14 (3H, d), 1.67 - 1.75 (2H, m), 1.91 - 1.95 (2H, m), 2.94 (2H, t), 3.11 (1H, td), 3.44 (1H, td), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 6.22 (1H, t), 6.61 (1H, s), 7.35 (2H, d), 7.76 (2H, d), 7.81 - 7.87 (2H, m), 7.92 - 7.96 (1H, m), 8.16 - 8.21 (1H, m), 8.60 (1H, s).

mTOR Kinase Assay (Echo): 0.147μM

Example 10d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 - 1.15 (9H, m), 1.68 - 1.77 (2H, m), 1.92 - 1.95 (2H, m), 3.11 (1H, td), 3.44 (1H, td), 3.59 (1H, dd), 3.71 - 3.82 (2H, m), 3.94 (1H, dd), 4.09 (1H, d), 4.42 (1H, s), 6.04 (1H, d), 6.61 (1H, s), 7.34 (2H, d), 7.75 (2H, d), 7.82 - 7.87 (2H, m), 7.91 - 7.95 (1H, m), 8.16 - 8.20 (1H, m), 8.49 (1H, s).

mTOR Kinase Assay (Echo): 0.0432μM

Example 10e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.13 (3H, d), 1.69 - 1.75 (2H, m), 1.91 - 1.95 (2H, m), 3.07 - 3.19 (3H, m), 3.44 (1H, td), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.04 - 4.12 (1H, m), 4.44 (1H, s), 6.14 (1H, t), 6.62 (1H, s), 7.36 (2H, d), 7.75 (2H, d), 7.81 - 7.85 (2H, m), 7.91 - 7.95 (1H, m), 8.16 - 8.20 (1H, m), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.00691μM

Example 10f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.69 - 1.74 (2H, m), 1.91 - 1.95 (2H, m), 2.19 (6H, s), 2.33 (2H, t), 3.11 (1H, td), 3.16 - 3.22 (2H, m), 3.44 (1H, td), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 6.15 (1H, t), 6.62 (1H, s), 7.35 (2H, d), 7.75 (2H, d), 7.82 - 7.87 (2H, m), 7.91 - 7.96 (1H, m), 8.16 - 8.20 (1H, m), 8.86 (1H, s).

mTOR Kinase Assay (Echo): 0.174μM

Example 10g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.68 - 1.76 (2H, m), 1.92 - 1.95 (2H, m), 3.08 - 3.20 (3H, m), 3.39 - 3.48 (3H, m), 3.59 (1H, dd), 3.74 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.62 (1H, s), 7.35 (2H, d), 7.75 (2H, d), 7.82 - 7.85 (2H, m), 7.92 - 7.95 (1H, m), 8.16 - 8.19 (1H, m), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.00156μM

Example 10h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (3H, t), 1.14 (3H, d), 1.45 (2H, q), 1.70 - 1.74 (2H, m), 1.90 - 1.95 (2H, m), 3.03 - 3.15 (3H, m), 3.40 - 3.48 (1H, m), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.41 (1H, s), 6.18 (1H, t), 6.62 (1H, s), 7.36

(2H, d), 7.75 (2H, d), 7.82 - 7.87 (2H, m), 7.92 - 7.95 (1H, m), 8.17 - 8.20 (1H, m), 8.61 (1H, s).

mTOR Kinase Assay (Echo): 0.0268μM

Example 10i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.69 - 1.75 (2H, m), 1.92 - 1.95 (2H, m), 2.66 (3H, d), 3.11 (1H, td), 3.44 (1H, td), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 6.04 (1H, q), 6.61 (1H, s), 7.37 (2H, d), 7.76 (2H, d), 7.82 - 7.85 (2H, m), 7.92 - 7.95 (1H, m), 8.16 - 8.19 (1H, m), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00591μM

Example 10j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.71 - 1.76 (2H, m), 1.91 - 1.96 (2H, m), 3.09 - 3.17 (1H, m), 3.45 (1H, dd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, d), 4.11 (1H, d), 4.44 (1H, s), 6.64 (1H, s), 7.45 (2H, d), 7.63 - 7.70 (4H, m), 7.81 - 7.87 (4H, m), 7.93 - 7.96 (1H, m), 8.17 - 8.21 (1H, m), 9.01 (1H, s), 9.12 (1H, s).

mTOR Kinase Assay (Echo): 0.11μM

Example 10k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.25 (6H, s), 1.69 - 1.75 (2H, m), 1.91 - 1.95 (2H, m), 3.11 (1H, td), 3.37 - 3.48 (3H, m), 3.59 (1H, dd), 3.74 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.42 (1H, s), 4.95 (1H, t), 5.99 (1H, s), 6.62 (1H, s), 7.32 (2H, d), 7.74 (2H, d), 7.82 - 7.87 (2H, m), 7.92 - 7.95 (1H, m), 8.17 - 8.20 (1H, m), 8.69 (1H, s).

mTOR Kinase Assay (Echo): 0.0502μM

Example 10l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.56 - 1.63 (2H, m), 1.69 - 1.74 (2H, m), 1.91 - 1.95 (2H, m), 3.07 - 3.19 (3H, m), 3.40 - 3.50 (3H, m), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.43 (1H, s), 4.47 (1H, t), 6.18 (1H, t), 6.62 (1H, s), 7.36 (2H, d), 7.76 (2H, d), 7.82 - 7.86 (2H, m), 7.91 - 7.96 (1H, m), 8.15 - 8.20 (1H, m), 8.67 (1H, s).

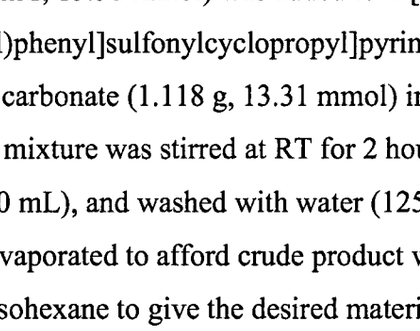
mTOR Kinase Assay (Echo): 0.0183μM

Example 10m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.70 - 1.75 (2H, m), 1.90 - 1.96 (2H, m), 3.12 (1H, td), 3.44 (1H, td), 3.59 (1H, dd), 3.73 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.43 (1H, s), 6.62 (1H, s), 7.37 - 7.44 (3H, m), 7.76 - 7.81 (3H, m), 7.83 - 7.87 (2H, m), 7.92 - 7.95 (1H, m), 8.17 - 8.20 (1H, m), 8.38 (1H, s), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00497μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

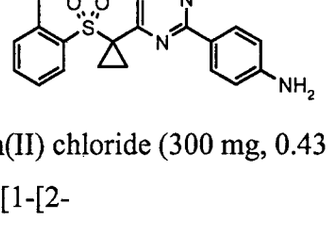
Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (1.669 mL, 13.31 mmol) was added to 4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]aniline (4.6 g, 8.87 mmol) and sodium hydrogen carbonate (1.118 g, 13.31 mmol) in dioxane (20 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 2 hours then the reaction mixture diluted with ethyl acetate (200 mL), and washed with water (125 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material (4.55 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.71 - 1.76 (2H, m), 1.92 - 1.96 (2H, m), 3.12 (1H, td), 3.41 - 3.47 (1H, m), 3.59 (1H, d), 3.73 (1H, d), 3.95 (1H, dd), 4.11 (1H, d), 4.45 (1H, s), 6.65 (1H, s), 7.22 - 7.31 (2H, m), 7.43 - 7.52 (3H,

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidin-2-yl]aniline



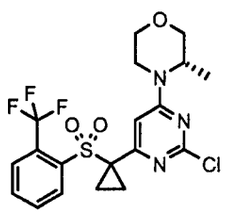
Bis(triphenylphosphine)palladium(II) chloride (300 mg, 0.43 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidine (5 g, 10.83 mmol), 4-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.56 g, 16.24 mmol) and sodium carbonate (20 mL, 40.0 mmol) in a mixture of ethanol (10 mL), DMF (20 mL), water (15 mL) and DME (40 mL) at RT. The resulting mixture was degassed then stirred at 95°C for 18 hours. The reaction was allowed to cool, diluted with ethyl acetate (400 mL), and washed with water (2 x 200 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give the desired material as a cream solid (5.40 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (3H, d), 1.68 - 1.73 (2H, m), 1.90 - 1.93 (2H, m), 3.07 (1H, td), 3.38 - 3.47 (1H, m), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (2H, dd), 4.02 - 4.07 (1H, m), 4.39 (1H, s), 5.50 (2H, s), 6.45 - 6.50 (3H, m), 7.61 (2H, d), 7.81 - 7.85 (2H, m), 7.93 (1H, dd), 8.17 (1H, dd)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 519; HPLC tR = 2.51 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[2-(trifluoromethyl)phenyl]sulfonylcyclopropyl]pyrimidine

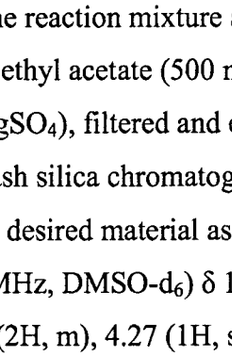


An aqueous solution of sodium hydroxide (30 mL, 247.8 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidine (4.5 g, 10.32 mmol), 1,2-dibromoethane (4.45 mL, 51.62 mmol) and tetrabutylammonium bromide (0.333 g, 1.03 mmol) in toluene (100 mL) at 30°C under nitrogen. The resulting mixture was stirred at 30°C for 3 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired material (4.70 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10 (3H, d), 1.61 - 1.66 (2H, m), 1.86 - 1.91 (2H, m), 3.09 (1H, td), 3.37 (1H, td), 3.52 (1H, dd), 3.68 (1H, d), 3.84 - 3.93 (2H, m), 4.27 (1H, s), 6.69 (1H, s), 7.85 - 7.93 (2H, m), 8.00 (1H, d), 8.07 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 462; HPLC tR = 2.43 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[[2-(trifluoromethyl)phenyl]sulfonylmethyl]pyrimidine

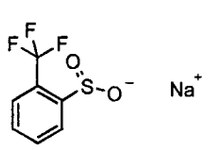


Sodium 2-(trifluoromethyl)benzenesulfinate (10.24 g, 44 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (13 g, 36.77 mmol), in acetonitrile (500 mL) at RT under nitrogen. The resulting mixture was stirred at 80°C for 3 hours. Additional sodium 2-(trifluoromethyl)benzenesulfinate (10.2 g, 44 mmol) was added and reaction heated at 80°C for 1 hour. The reaction mixture allowed to cool and concentrated *in vacuo*. The material was dissolved in ethyl acetate (500 mL), and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in isohexane, to give the desired material as an orange/cream solid (9.48 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 3.17 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (2H, m), 4.27 (1H, s), 4.68 (2H, s), 6.79 (1H, s), 7.94 (3H, m), 8.08 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 436; HPLC tR = 2.35 min.

Sodium 2-(trifluoromethyl)benzenesulfinate



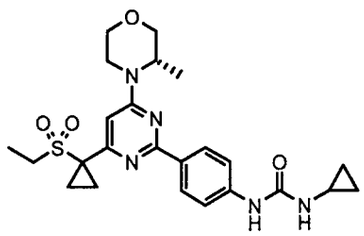
Sodium sulfite (3.92 mL, 81.88 mmol) was dissolved in water and stirred at RT 10 minutes. Sodium bicarbonate (13.74 g, 163.52 mmol) was added and the mixture stirred at 50°C for 1 hour. 2-(Trifluoromethyl)benzene-1-sulfonyl chloride (12.62 mL, 81.76 mmol) was added dropwise to the reaction mixture which was then stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and the residue suspended in methanol (250 mL) and

stirred at RT for 20 minutes. The solid was removed by filtration and the filtrate evaporated to give the desired material (20.00 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.40 (1H, d), 7.51 (1H, d), 7.64 (1H, d), 8.05 (1H, d)

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 11: 3-Cyclopropyl-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



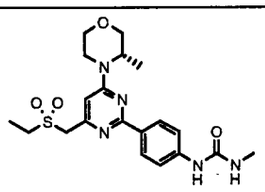
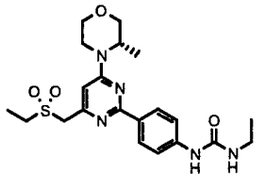
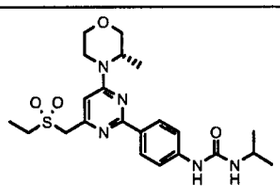
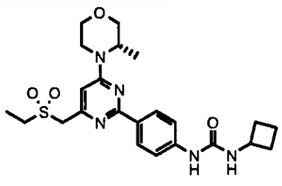
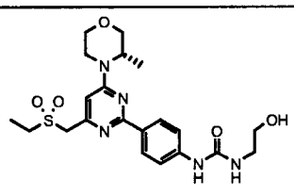
To a solution of phenyl *N*-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.29 mmol) in DMF (2 mL) was added triethylamine (0.120 mL, 0.86 mmol) followed by cyclopropylamine (0.100 mL, 1.44 mmol) and the reaction heated at 50°C for 2 hours. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a white solid (90 mg).

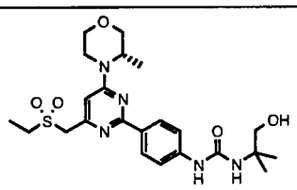
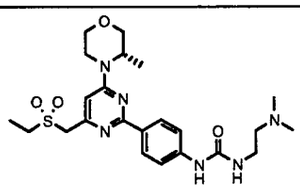
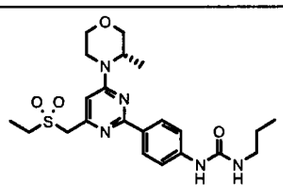
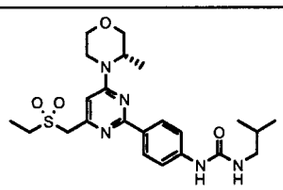
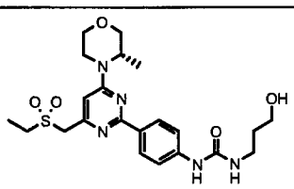
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, t), 1.62 - 1.65 (2H, m), 2.52 - 2.58 (1H, m), 3.17 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.19 - 4.22 (1H, m), 4.56 (1H, s), 6.44 (1H, d), 6.78 (1H, s), 7.50 - 7.52 (2H, m), 8.18 - 8.20 (2H, m), 8.54 (1H, s).

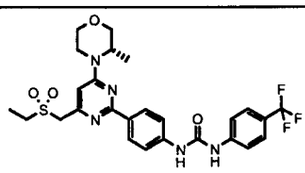
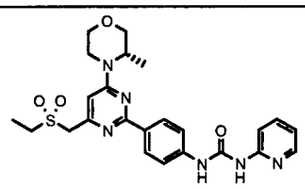
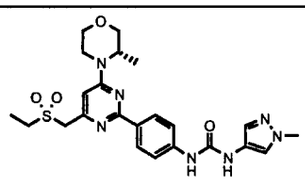
LCMS Spectrum: m/z (ESI+)(M+H)+ = 486; HPLC tR = 1.96 min.

mTOR Kinase Assay (Echo): 0.00165μM

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
11a		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea	460	1.79
11b		1-ethyl-3-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	474	1.93
11c		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-yl-urea	488	2.11
11d		3-cyclobutyl-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	500	2.19
11e		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	490	1.63

Example	Structure	NAME	LCMS MH+	Retention time (min)
11f		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methyl-propan-2-yl)urea	518	1.92
11g		3-(2-dimethylaminoethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	517	1.90
11h		3-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propyl-urea	488	2.11
11i		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	502	2.29
11j		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	504	1.68

Example	Structure	NAME	LCMS MH+	Retention time (min)
11k		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	590	2.80
11l		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-yl-urea	523	2.37
11m		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	526	1.84

Example 11m can also be prepared in an analogous fashion but using DMA as the solvent and stirring at 50°C for 18 hours.

Example 11a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, t), 1.62 - 1.64 (2H, m), 2.67 (3H, t), 3.20 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.19 - 4.22 (1H, m), 4.55 (1H, s), 6.07 (1H, d), 6.77 (1H, s), 7.49 - 7.52 (2H, m), 8.17 - 8.19 (2H, m), 8.74 (1H, s).
mTOR Kinase Assay (Echo): 0.00418μM

Example 11b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, t), 1.62 - 1.65 (2H, m), 3.09 - 3.16 (2H, m), 3.20 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, d), 4.56 (1H, s), 6.16 (1H, t), 6.77 (1H, s), 7.48 - 7.52 (2H, m), 8.17 - 8.19 (2H, m), 8.66 (1H, s).
mTOR Kinase Assay (Echo): 0.00333μM

Example 11c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, t), 1.60 - 1.65 (2H, m), 3.20 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.77 (1H, d), 3.80 (1H, m), 3.95 - 3.99 (1H, m), 4.19 - 4.22 (1H, m), 4.55 (1H, s), 6.07 (1H, d), 6.77 (1H, s), 7.47 - 7.50 (2H, m), 8.17 - 8.19 (2H, m), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.0247μM

Example 11d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.53 - 1.58 (2H, m), 1.62 - 1.64 (2H, m), 1.81 - 1.89 (3H, m), 2.18 - 2.24 (3H, m), 3.20 - 3.24 (1H, m), 3.43 (2H, q), 3.48 - 3.51 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.16 (2H, m), 4.55 (1H, s), 6.46 - 6.48 (1H, m), 6.78 (1H, s), 7.46 - 7.50 (2H, m), 8.18 (2H, d), 8.56 (1H, s).

mTOR Kinase Assay (Echo): 0.00642μM

Example 11e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, t), 1.62 - 1.64 (2H, m), 3.18 (1H, q), 3.20 (2H, d), 3.40 - 3.51 (2H, m), 3.46 (1H, d), 3.42 - 3.52 (2H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, d), 4.56 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.78 (1H, s), 7.48 - 7.50 (2H, m), 8.19 (2H, d), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00135μM

Example 11f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.24 (6H, s), 1.32 (3H, d), 1.53 - 1.58 (2H, m), 1.62 - 1.64 (2H, m), 3.17 - 3.24 (1H, m), 3.39 (2H, d), 3.45 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.19 - 4.22 (1H, m), 4.54 (1H, s), 4.95 (1H, t), 6.01 (1H, s), 6.77 (1H, s), 7.44 - 7.48 (2H, m), 8.18 (2H, d), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.00337μM

Example 11g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.53 - 1.58 (2H, m), 1.62 - 1.64 (2H, m), 2.18 (6H, s), 2.34 (2H, t), 3.17 - 3.23 (3H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.19 (1H, s), 4.56 (1H, s), 6.16 (1H, t), 6.77 (1H, s), 7.48 - 7.51 (2H, m), 8.17 - 8.19 (2H, m), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.313μM

Example 11h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.23 (3H, d), 1.32 (3H, t), 1.41 - 1.50 (2H, m), 1.55 (2H, t), 1.62 - 1.65 (2H, m), 3.04 - 3.09 (2H, m), 3.17 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, d), 4.55 (1H, s), 6.21 (1H, t), 6.77 (1H, s), 7.48 - 7.51 (2H, m), 8.17 - 8.20 (2H, m), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.00913μM

Example 11i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.23 (3H, d), 1.32 - 1.38 (3H, m), 1.55 (2H, t), 1.62 - 1.65 (2H, m), 1.69 - 1.76 (1H, m), 2.94 (2H, t), 3.17 - 3.24 (1H, m), 3.43 (2H, q), 3.45 - 3.52 (1H, m), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, d), 4.56 (1H, s), 6.25 (1H, t), 6.78 (1H, s), 7.48 - 7.51 (2H, m), 8.18 (1H, t), 8.20 (1H, s), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.0294μM

Example 11j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.55 (2H, q), 1.58 (2H, m), 1.62 - 1.64 (2H, m), 3.15 - 3.19 (3H, m), 3.43 (2H, q), 3.46 - 3.47 (2H, m), 3.50 (1H, d), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, d), 4.47 (1H, t), 4.55 (1H, s), 6.21 (1H, t), 6.77 (1H, s), 7.48 - 7.51 (2H, m), 8.17 - 8.20 (2H, m), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.0122μM

Example 11k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.33 (3H, t), 1.56 (2H, t), 1.63 - 1.66 (2H, m), 3.18 - 3.26 (1H, m), 3.44 (2H, q), 3.46 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.22 (1H, d), 4.57 (1H, s), 6.81 (1H, s), 7.58 - 7.60 (2H, m), 7.64 - 7.70 (4H, m), 8.27 (2H, d), 9.05 (1H, s), 9.14 (1H, s).

mTOR Kinase Assay (Echo): 0.00332μM

Example 11l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.34 (3H, t), 1.55 - 1.59 (2H, m), 1.63 - 1.66 (2H, m), 3.18 - 3.23 (1H, m), 3.45 (2H, q), 3.47 - 3.53 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.20 - 4.24 (1H, m), 4.57 (1H, s), 6.81 (1H, s), 7.02 - 7.05 (1H, m), 7.56 (1H, d), 7.65 (2H, d), 7.75 - 7.77 (1H, m), 8.26 - 8.31 (1H, m), 8.27 - 8.31 (2H, m), 9.45 (1H, d), 10.61 (1H, s).

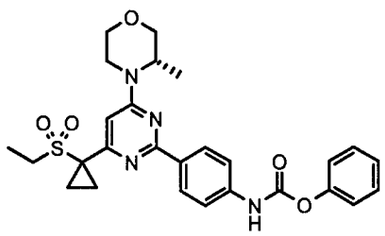
mTOR Kinase Assay (Echo): 0.00356μM

Example 11m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.33 (3H, t), 1.56 (2H, t), 1.63 - 1.65 (2H, m), 3.17 - 3.25 (1H, m), 3.44 (2H, q), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.75 (1H, s), 3.79 (3H, s), 3.96 - 4.00 (1H, m), 4.21 (1H, d), 4.56 (1H, s), 6.79 (1H, s), 7.38 - 7.39 (1H, m), 7.53 - 7.57 (2H, m), 7.76 (1H, s), 8.22 (2H, d), 8.39 (1H, s), 8.84 (1H, s).

mTOR Kinase Assay (Echo): 0.00437μM

The preparation of phenyl *N*-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

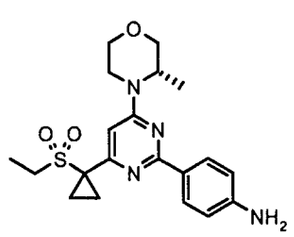


Phenyl chloroformate (0.566 mL, 4.50 mmol) was added dropwise to 4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.81 g, 4.50 mmol) and sodium bicarbonate (0.567 g, 6.75 mmol) in dioxane (30 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in ethyl acetate (200 mL) and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a white solid (2.36 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.33 (3H, t), 1.55 - 1.59 (2H, m), 1.63 - 1.65 (2H, m), 3.21 - 3.25 (1H, m), 3.43 - 3.48 (2H, m), 3.41 - 3.52 (1H, m), 3.62 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.21 (1H, s), 4.57 (1H, s), 6.82 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.64 (2H, d), 8.27 - 8.30 (2H, m), 10.44 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 523; HPLC tR = 2.83 min.

4-[4-(1-Ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



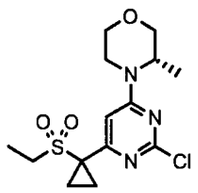
Dichlorobis(triphenylphosphine)palladium(II) (0.317 g, 0.45 mmol) was added to a degassed solution of 2-chloro-4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.56 g, 4.51 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.235 g, 5.64 mmol) and sodium carbonate (11.28 ml, 22.55 mmol) in a mixture of 18% DMF in DME:water:ethanol (7:3:2) (20 mL). The resulting solution was stirred at 85°C for 30 minutes. The reaction mixture was concentrated and partitioned between DCM (100 mL) and

water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 2.5% methanol in DCM, to give the desired material as a brown oil (2.15 g).

NMR Spectrum: ^1H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.31 (3H, t), 1.53 (2H, m), 1.60 - 1.62 (2H, m), 3.17 - 3.21 (1H, m), 3.37 - 3.47 (2H, m), 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.15 - 4.19 (1H, m), 4.51 - 4.53 (1H, m), 5.55 (2H, d), 6.60 - 6.62 (2H, m), 6.67 (1H, s), 8.00 - 8.04 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 403; HPLC tR = 2.14 min.

2-Chloro-4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

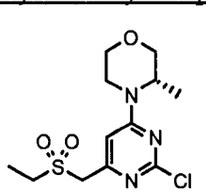


An aqueous sodium hydroxide solution (25.4 mL, 254.1 mmol) was added to tetrabutylammonium bromide (0.328 g, 1.02 mmol), 1,2-dibromoethane (0.876 mL, 10.16 mmol) and 2-chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.25 g, 10.16 mmol) in DCM (75 mL). The resulting mixture was stirred at 40°C for 4 hours. The reaction mixture was diluted with DCM (50 mL) and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (1.56 g).

NMR Spectrum: ^1H NMR (400.13 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.23 (3H, s), 1.49 - 1.52 (2H, m), 1.55 - 1.62 (2H, m), 3.18 - 3.23 (1H, m), 3.35 (2H, t), 3.41 - 3.46 (1H, m), 3.56 - 3.60 (1H, m), 3.72 (1H, d), 3.91 - 3.95 (1H, m), 4.15 - 4.19 (1H, m), 4.40 (1H, s), 6.93 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 346; HPLC 1.97 tR = min.

2-Chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



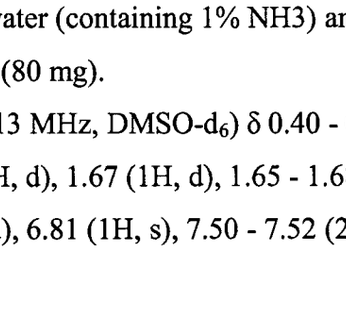
Ethane sulfinic acid sodium salt (3.94 g, 33.94 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (12.0 g, 33.94 mmol) in acetonitrile (250 mL) at RT. The resulting suspension was stirred at 80°C for 16 hours. The reaction mixture was evaporated to dryness and the residue partitioned between DCM (250mL), and water (200mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a yellow solid (5.94 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, m), 1.28 (3H, t), 3.22 (2H, d), 3.32 (1H, s), 3.42 - 3.49 (1H, m), 3.58 - 3.62 (1H, m), 3.73 (1H, d), 3.92 - 3.96 (2H, m), 4.25 - 4.31 (1H, m), 4.43 (2H, s), 6.92 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 320; HPLC tR = 1.46 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 12: 3-Cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea



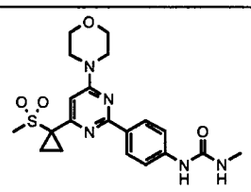
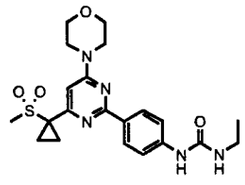
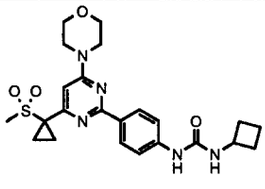
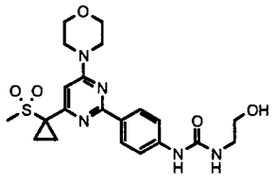
To a solution of phenyl *N*-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate (150 mg, 0.29 mmol) in DMF (2 mL) was added triethylamine (0.127 mL, 0.91 mmol) followed by cyclopropylamine (0.106 mL, 1.52 mmol) and the reaction heated at 50°C for 20 hours. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (80 mg).

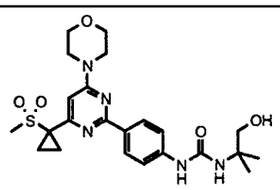
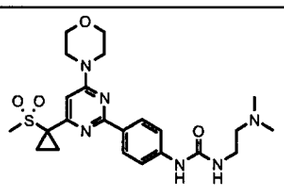
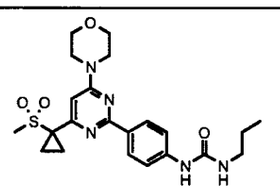
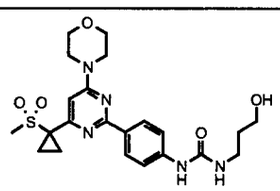
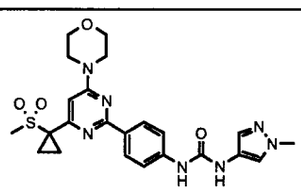
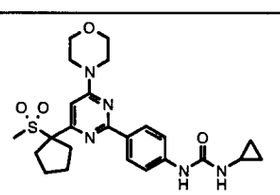
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.64 - 0.66 (2H, m), 1.54 - 1.57 (1H, m), 1.55 (1H, d), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 2.60 (1H, m), 3.30 (3H, s), 3.72 (8H, s), 6.43 (1H, d), 6.81 (1H, s), 7.50 - 7.52 (2H, m), 8.19 - 8.22 (2H, m), 8.55 (1H, s)

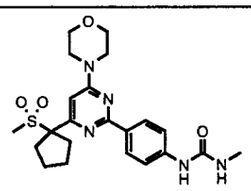
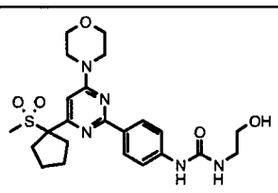
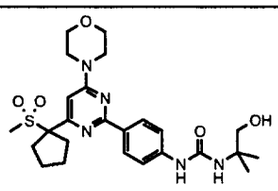
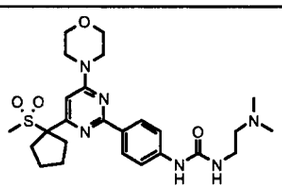
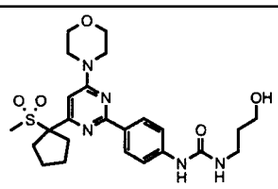
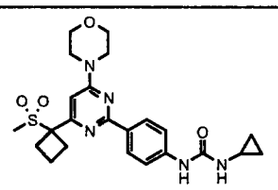
LCMS Spectrum: m/z (ESI+)(M+H)+ = 458; HPLC tR = 1.44 min.

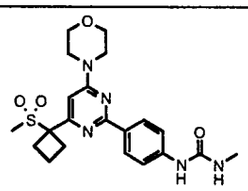
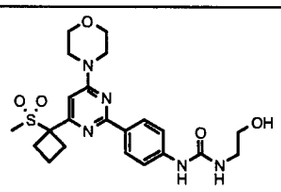
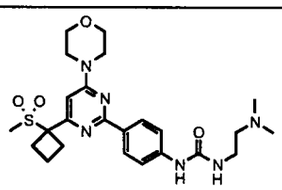
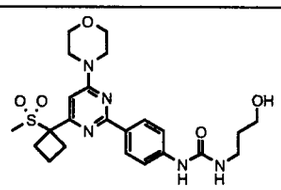
mTOR Kinase Assay (Echo): 0.00421μM

The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate, phenyl *N*-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate and the appropriate amines.

Example	Structure	NAME	LCMS MH+	Retention time (min)
12a		3-methyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	432.5	1.27
12b		3-ethyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	446.5	1.39
12c		3-cyclobutyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	471.5	1.73
12d		3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	462.5	1.15

Example	Structure	NAME	LCMS MH+	Retention time (min)
12e		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	490.5	1.43
12f		3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	489.5	1.05
12g		1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propylurea	460.5	1.6
12h		3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	476.5	1.18
12i		3-(1-methylpyrazol-4-yl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	498.5	1.38
12j*		3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	486	2.04

Example	Structure	NAME	LCMS MH+	Retention time (min)
12k*		3-methyl-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	460	1.88
12l*		3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	490	1.73
12m*		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	518	2.00
12n*		3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	517	1.98
12o*		3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	504	1.77
12p**		3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	472	2.06

Example	Structure	NAME	LCMS MH+	Retention time (min)
12q**		3-methyl-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	446	1.88
12r**		3-(2-hydroxyethyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	476	1.72
12s**		3-(2-dimethylaminoethyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	503	1.92
12t**		3-(3-hydroxypropyl)-1-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	490	1.77

* Reaction stirred at 55°C for 6 hours

** Reaction stirred at 40°C for 6 hours

The crude material for **Example 12** can also be purified either by chromatography on silica, eluting with 50-80% ethyl acetate in isohexane, or by dissolving the material in ethyl acetate and allowing the desired material to precipitate from solution on stirring.

Example 12a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.53 - 1.57 (1H, m), 1.55 - 1.56 (1H, m), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 2.66 (3H, d), 3.30 (3H, s), 3.72 (8H, s), 6.06 (1H, d), 6.81 (1H, s), 7.49 - 7.52 (2H, m), 8.19 - 8.21 (2H, m), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.00167μM

Example 12b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.54 - 1.57 (1H, m), 1.55 (1H, d), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 3.11 - 3.14 (2H, m), 3.30 (3H, s), 3.72 (8H, s), 6.16 (1H, s), 6.81 (1H, s), 7.49 - 7.51 (2H, m), 8.19 - 8.21 (2H, m), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.00271μM

Example 12c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.53 - 1.57 (2H, m), 1.55 (2H, d), 1.59 - 1.67 (2H, m), 1.82 - 1.85 (1H, m), 1.89 (1H, t), 2.18 - 2.25 (2H, m), 3.30 (3H, s), 3.72 (8H, s), 4.14 (1H, d), 6.46 (1H, d), 6.81 (1H, s), 7.47 - 7.49 (2H, m), 8.20 (2H, d), 8.57 (1H, s).

mTOR Kinase Assay (Echo): 0.00152μM

Example 12d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.54 - 1.57 (1H, m), 1.55 - 1.56 (1H, m), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 3.18 (2H, q), 3.30 (3H, s), 3.46 (2H, q), 3.72 (8H, s), 4.73 (1H, t), 6.25 (1H, t), 6.81 (1H, s), 7.48 - 7.50 (2H, m), 8.19 - 8.22 (2H, m), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.00155μM

Example 12e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (6H, s), 1.54 - 1.57 (1H, m), 1.55 (1H, d), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 3.30 (3H, s), 3.39 (2H, d), 3.72 (8H, s), 4.95 (1H, t), 6.00 (1H, s), 6.80 (1H, s), 7.44 - 7.47 (2H, m), 8.18 - 8.20 (2H, m), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.00459μM

Example 12f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.54 - 1.57 (1H, m), 1.55 - 1.56 (1H, m), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 2.18 (6H, s), 2.34 (2H, t), 3.20 (2H, t), 3.30 (3H, s), 3.72 (8H, s), 6.16 (1H, t), 6.80 (1H, s), 7.47 - 7.51 (2H, m), 8.20 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.0605μM

Example 12g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.41 - 1.50 (2H, m), 1.54 - 1.57 (1H, m), 1.55 (1H, d), 1.67 (1H, d), 1.65 - 1.68 (1H, m), 3.04 - 3.09 (2H, m), 3.30 (3H, s), 3.72 (8H, s), 6.20 (1H, t), 6.81 (1H, s), 7.48 - 7.51 (2H, m), 8.18 - 8.22 (2H, m), 8.66 (1H, s).

mTOR Kinase Assay (Echo): 0.00273μM

Example 12h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.53 - 1.58 (2H, m), 1.61 (2H, d), 1.65 - 1.68 (2H, m), 3.17 (2H, d), 3.30 (3H, s), 3.45 - 3.48 (2H, m), 3.72 (8H, s), 4.47 (1H, t), 6.20 (1H, s), 6.81 (1H, s), 7.48 - 7.51 (2H, m), 8.19 - 8.21 (2H, m), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.00392μM

Example 12i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.54 - 1.58 (1H, m), 1.56 - 1.56 (1H, m), 1.67 (2H, t), 3.30 (3H, s), 3.72 (8H, s), 3.79 (3H, s), 6.82 (1H, s), 7.38 - 7.38 (1H, m), 7.54 - 7.56 (2H, m), 7.76 (1H, s), 8.23 - 8.25 (2H, m), 8.38 (1H, s), 8.84 (1H, s).

mTOR Kinase Assay (Echo): 0.000771μM

Example 12j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.58 (2H, t), 1.81 (2H, d), 2.39 - 2.47 (2H, m), 2.57 (1H, t), 2.74 (2H, t), 2.91 (3H, s), 3.73 (8H, s), 6.42 (1H, d), 6.84 (1H, s), 7.49 - 7.53 (2H, m), 8.22 - 8.26 (2H, m), 8.54 (1H, s).

mTOR Kinase Assay (Echo): 0.00167μM

Example 12k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.56 - 1.57 (2H, m), 1.80 - 1.82 (2H, m), 2.42 (2H, d), 2.46 (2H, d), 2.67 (3H, t), 2.91 (3H, s), 3.73 (8H, s), 6.06 (1H, d), 6.84 (1H, s), 7.49 - 7.52 (2H, m), 8.22 - 8.25 (2H, m), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.0043μM

Example 12l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.58 (2H, t), 1.81 (2H, d), 2.41 - 2.44 (2H, m), 2.73 (2H, d), 2.91 (3H, s), 3.18 (2H, q), 3.46 (2H, q), 3.73 (8H, s), 4.72 (1H, t), 6.25 (1H, s), 6.84 (1H, s), 7.48 - 7.50 (2H, m), 8.23 - 8.25 (2H, m), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.00138μM

Example 12m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (6H, s), 1.58 (2H, t), 1.81 (2H, d), 2.41 - 2.44 (2H, m), 2.71 - 2.75 (2H, m), 2.91 (3H, s), 3.39 (2H, d), 3.73 (8H, s), 4.95 (1H, t), 6.00 (1H, s), 6.84 (1H, s), 7.44 - 7.47 (2H, m), 8.22 - 8.24 (2H, m), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.0101μM

Example 12n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.56 - 1.57 (2H, m), 1.81 (2H, d), 2.18 (6H, s), 2.34 (2H, t), 2.39 - 2.46 (2H, m), 2.73 (2H, q), 2.91 (3H, s), 3.19 (2H, q), 3.73 (8H, s), 6.15 (1H, t), 6.84 (1H, s), 7.48 - 7.50 (2H, m), 8.23 - 8.25 (2H, m), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.238μM

Example 12o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.56 - 1.59 (2H, m), 1.57 - 1.63 (2H, m), 1.81 (2H, d), 2.39 - 2.46 (2H, m), 2.72 - 2.74 (2H, t), 2.91 (3H, s), 3.15 - 3.19 (2H, m), 3.45 - 3.50 (2H, m), 3.73 (8H, s), 4.47 (1H, t), 6.20 (1H, t), 6.84 (1H, s), 7.48 - 7.51 (2H, m), 8.22 - 8.25 (2H, m), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.00509μM

Example 12p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 - 0.43 (2H, m), 0.63 - 0.66 (2H, m), 1.90 (1H, m), 2.08 (1H, m), 2.33 (1H, t), 2.68 (1H, t), 2.80 - 2.82 (1H,m), 2.87 (3H, s), 2.90 (2H, m), 3.73 (8H, s), 6.43 - 6.44 (1H, m), 6.77 (1H, s), 7.49 - 7.51 (2H, m), 8.21 - 8.24 (2H, m), 8.56 (1H, s).

mTOR Kinase Assay (Echo): 0.0014μM

Example 12q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.99 - 2.06 (1H, m), 2.09 (1H, m), 2.32 - 2.34 (3H, m), 2.87 (3H, s), 2.90 (2H, s), 2.93 (2H, s), 3.73 (8H, s), 6.06 (1H, d), 6.76 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.00162μM

Example 12r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.89 (1H, t), 2.07 (1H, d), 2.76 - 2.83 (2H, m), 2.87 (3H, s), 2.90 - 2.93 (2H, m), 3.18 (2H, m), 3.46 (2H, m), 3.73 (8H, s), 4.72 (1H, t), 6.25 (1H, t), 6.76 (1H, s), 7.48 - 7.50 (2H, m), 8.21 - 8.23 (2H, m), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.000991μM

Example 12s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.89 (1H, t), 2.07 (1H, t), 2.18 (6H, s), 2.34 (2H, t), 2.80 (2H, d), 2.87 (3H, s), 2.90 (2H, m), 3.19 (2H, t), 3.73 (8H, s), 6.16 (1H, s), 6.76 (1H, s), 7.47 - 7.50 (2H, m), 8.21 - 8.23 (2H, m), 8.90 (1H, s).

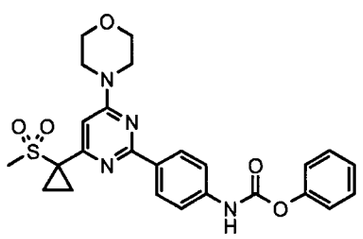
mTOR Kinase Assay (Echo): 0.134μM

Example 12t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.58 (2H, t), 1.87 - 1.92 (1H, m), 2.06 - 2.10 (1H, m), 2.76 - 2.82 (2H, m), 2.87 (3H, s), 2.90 - 2.93 (2H, m), 3.14 - 3.19 (2H, m), 3.45 - 3.49 (2H, m), 3.73 (8H, s), 4.47 (1H, t), 6.20 (1H, t), 6.76 (1H, s), 7.48 - 7.50 (2H, m), 8.21 - 8.23 (2H, m), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.0366μM

The preparation of phenyl *N*-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate



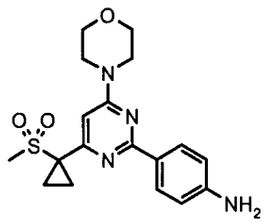
Phenyl chloroformate (0.4 mL, 3.18 mmol) was added dropwise to 4-(4-(1-(methylsulfonyl)cyclopropyl)-6-morpholinopyrimidin-2-yl)aniline (1.19 g, 3.18 mmol) and sodium bicarbonate (0.40 g, 4.77 mmol) in dioxane (30 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and

redissolved in ethyl acetate (100mL) and washed with water (100mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a yellow solid (1.68 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.57 (1H, d), 1.55 - 1.62 (1H, m), 1.68 (1H, d), 1.66 - 1.69 (1H, m), 3.40 (3H, s), 3.73 (8H, s), 6.86 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.63 - 7.65 (2H, m), 8.29 - 8.31 (2H, m), 10.44 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 495; HPLC tR = 2.58 min.

4-[4-(1-Methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline

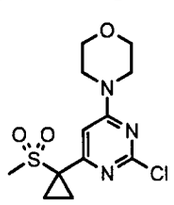


Dichlorobis(triphenylphosphine)palladium(II) (0.636 g, 0.91 mmol) was added to 2-chloro-4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine (2.88 g, 9.06 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.482 g, 11.33 mmol) and sodium carbonate (22.66 mL, 45.31 mmol) in 18% DMF in 7:3:2 DME:Water:Ethanol (40mL). The resulting solution was stirred at 85°C for 1 hour. The reaction mixture was concentrated, diluted with DCM (200 mL), and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 2.5% methanol in DCM, to give the desired material as a yellow solid (1.19 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.51 - 1.53 (2H, m), 1.65 - 1.66 (2H, m), 3.40 (3H, s), 3.70 (8H, s), 5.56 (2H, d), 6.61 (2H, d), 6.70 (1H, s), 8.04 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 375; HPLC tR = 1.65 min.

2-Chloro-4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine

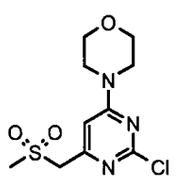


Sodium hydroxide (9.60 mL, 95.97 mmol) was added to 2-chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine (2.80 g, 9.60 mmol), 1,2-dibromoethane (1.654 mL, 19.19 mmol) and tetrabutylammonium bromide (0.619 g, 1.92 mmol) in toluene (120 mL) at RT. The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 2.5% methanol in DCM, to give the desired material as a yellow solid (2.88 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.49 -1.51 (2H, m), 1.62 - 1.65 (2H, m), 3.19 (3H, s), 3.67 (8H, d), 6.96 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 318; HPLC 1.37 tR = min.

2-Chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine

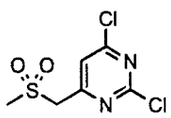


A suspension of 2,4-dichloro-6-(methylsulfonylmethyl)pyrimidine (10.56 g) in DCM (230 mL) was stirred magnetically (under nitrogen) and cooled to -5°C. Triethylamine (6.78 mL) was added followed by the dropwise addition of a solution of morpholine (3.85 mL) in DCM (30 mL) maintaining the reaction temperature below -5°C. The reaction was stirred at room temperature for 1 hour and then the organic mixture washed with water (300 mL). The organic phase was dried (MgSO4), filtered and evaporated to a brown solid which was chromatographed on silica, eluting with 50% ethyl acetate in DCM, to give the desired material (6.81g) as a white solid.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 3.12 (3H, s), 3.63 (4H, s), 3.68 - 3.70 (4H, m), 4.45 (2H, s), 6.96 (1H, s)

Mass Spectrum: MH+ 292.

2,4-Dichloro-6-(methylsulfonylmethyl)pyrimidine

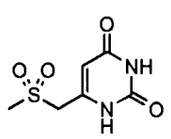


6-(Methylsulfonylmethyl)-1*H*-pyrimidine-2,4-dione (132 g, 0.65 mol) was added to phosphorus oxychloride (1.2 L) and the mixture heated to reflux for 16 hours, then cooled to room temperature. The excess phosphorus oxychloride was removed *in vacuo*, the residue azeotroped with toluene (2 x 500 mL) and dissolved in dichloromethane. This mixture was then poured slowly onto ice (4 L) and stirred for 20 minutes, then extracted with dichloromethane (3 x 1 L) (the insoluble black material was filtered off and discarded) and ethyl acetate (2 x 1 L). The extracts were combined, dried, then evaporated to leave the desired material as a dark brown solid (51 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 3.13 (s, 3H), 4.79 (s, 2H), 7.87 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 239; HPLC 1.21 tR = min.

6-(Methylsulfonylmethyl)-1*H*-pyrimidine-2,4-dione

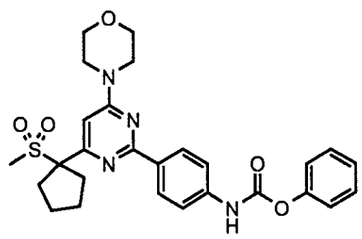


6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (175 g, 1.09 mol) was dissolved in DMF (2 L) and methanesulphinic acid sodium salt (133.5 g, 1.31 mol) was added. The reaction was heated to 125°C for 2 hours then allowed to cool and the suspension filtered and concentrated *in vacuo* to give a yellow solid. The crude material was washed with water, filtered, then triturated with toluene. The solid was filtered then triturated with isohexane to leave the desired compound as a yellow solid (250 g). The material was used without further purification.

6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione is a commercially available material.

The preparation of phenyl *N*-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

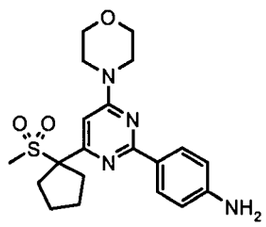
Phenyl *N*-[4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.541 mL, 4.30 mmol) was added dropwise to 4-[4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline (1.73 g, 4.30 mmol) and sodium bicarbonate (0.542 g, 6.45 mmol) in dioxane (50 mL) under nitrogen. The resulting suspension was stirred at RT for 1 hour. The reaction mixture was evaporated to dryness and partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a yellow solid (1.7 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.58 (2H, t), 1.82 (2H, d), 2.40 - 2.47 (2H, m), 2.73 - 2.75 (2H, m), 2.91 (3H, s), 3.74 (8H, s), 6.88 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.64 (2H, d), 8.33 - 8.35 (2H, m), 10.43 (1H, s), LCMS Spectrum: m/z (ESI+) (M+H)+ = 523; HPLC tR = 2.90 min.

4-[4-(1-Methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline



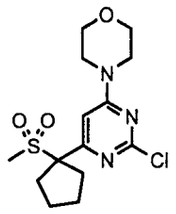
Dichlorobis(triphenylphosphine)palladium (II) (0.224 g, 0.32 mmol) was added to a solution of 2-chloro-4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidine (2.21 g, 6.39 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.75 g, 7.99 mmol) and aqueous sodium carbonate solution (15.98 mL, 31.95 mmol) in a solvent mixture of 18% DMF in 7:3:2 DME:Water:Ethanol (40 mL). The resulting solution was stirred at 85°C for 1 hour. The reaction mixture was concentrated and diluted with DCM (200 mL) and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford

crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 2.5% methanol in DCM, to give the desired material as a yellow solid (1.73 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.57 (2H, t), 1.80 (2H, d), 2.37 - 2.44 (2H, m), 2.69 - 2.74 (2H, m), 2.90 (3H, s), 3.71 (8H, s), 5.55 (2H, d), 6.59 - 6.63 (2H, m), 6.74 (1H, s), 8.05 - 8.09 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 403; HPLC tR = 2.22 min.

2-Chloro-4-(1-methylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidine



10N Sodium hydroxide solution (8.57 mL, 85.69 mmol) was added to 2-chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine (2.50 g, 8.57 mmol), 1,4-dibromobutane (1.014 mL, 8.57 mmol) and tetrabutylammonium bromide (0.552 g, 1.71 mmol) in toluene (120 mL) at RT. The resulting solution was stirred at 60°C for 4 hours. The reaction mixture was evaporated to dryness and the residue partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (2.215 g).

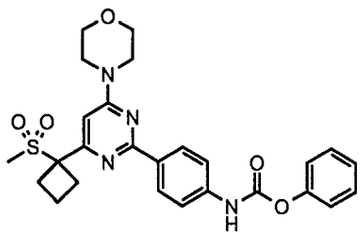
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.51 - 1.58 (2H, m), 1.76 - 1.80 (2H, m), 2.33 - 2.40 (2H, m), 2.52 - 2.59 (2H, m), 2.89 (3H, s), 3.67 (8H, s), 6.96 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 346; HPLC 2.12 tR = min.

The preparation of 2-chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

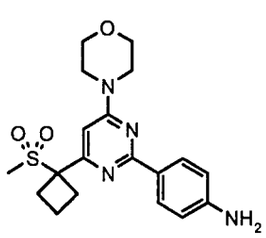


Phenyl chloroformate (0.084 mL, 0.67 mmol) was added dropwise to 4-[4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline (260 mg, 0.67 mmol) and sodium bicarbonate (84 mg, 1.00 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (100 mL) and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a cream solid (380 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.91 (1H, d), 2.06 (1H, t), 2.80 - 2.84 (2H, m), 2.88 (3H, s), 2.93 (2H, d), 3.74 (8H, d), 6.80 (1H, s), 7.24 - 7.26 (2H, m), 7.25 - 7.30 (1H, m), 7.43 - 7.47 (2H, m), 7.63 (2H, d), 8.32 (2H, d), 10.43 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 509; HPLC tR = 2.77 min.

4-[4-(1-Methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline



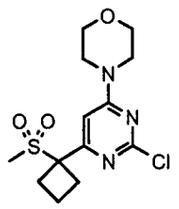
Dichlorobis(triphenylphosphine)palladium(II) (0.167 g, 0.24 mmol) was added to a degassed solution of 2-chloro-4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidine (0.790 g, 2.38 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.652 g, 2.98 mmol) and an aqueous solution of sodium carbonate (5.95 mL, 11.90 mmol) in a solvent mixture of 18% DMF in 7:3:2 DME:Water:Ethanol (40 mL). The resulting solution was stirred at 85°C for 1 hour. The reaction mixture was concentrated, diluted with DCM (200 mL), and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude

product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in isohexane, to give the desired material as a white solid (0.22 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.89 (1H, d), 2.03 - 2.07 (1H, m), 2.74 - 2.81 (2H, m), 2.86 (3H, s), 2.88 - 2.93 (2H, m), 3.71 (8H, s), 5.54 (2H, d), 6.59 - 6.62 (2H, m), 6.66 (1H, s), 8.04 - 8.07 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 389; HPLC tR = 2.05 min.

2-Chloro-4-(1-methylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidine

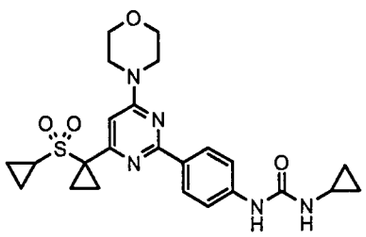


10N Sodium hydroxide solution (9.60 mL, 95.97 mmol) was added to 1,3-dibromopropane (0.979 mL, 9.60 mmol), 2-chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine (2.80 g, 9.60 mmol) and tetrabutylammonium bromide (0.619 g, 1.92 mmol) in toluene (120 mL) at RT. The resulting solution was stirred at 60°C for 18 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine solution (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in isohexane, to give the NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.87 - 1.89 (1H, m), 2.01 (1H, d), 2.66 - 2.73 (2H, m), 2.81 - 2.84 (2H, m), 2.86 (3H, s), 3.67 (8H, s), 6.88 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 332; HPLC 1.44 tR = min.

The preparation of 2-chloro-4-(methylsulfonylmethyl)-6-morpholin-4-yl-pyrimidine was described earlier.

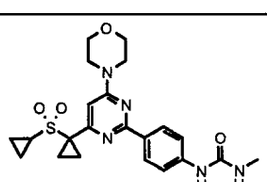
Example 13: 3-Cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea

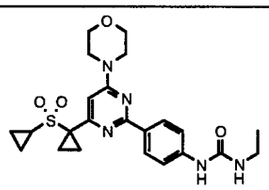
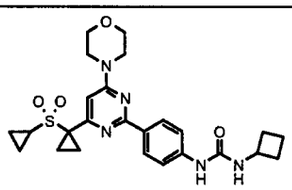
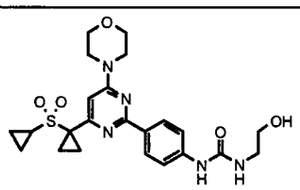
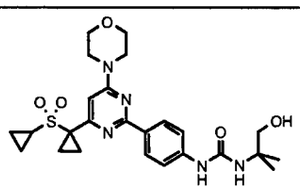
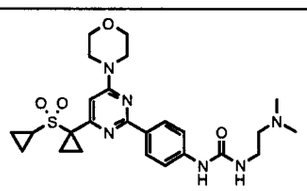
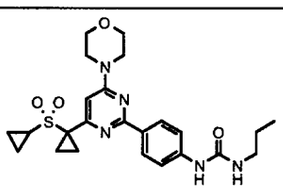


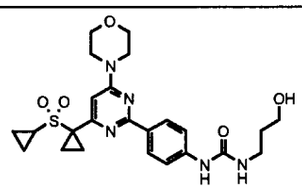
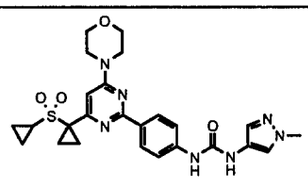
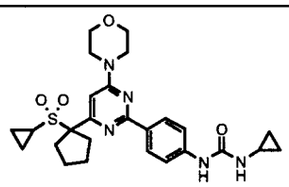
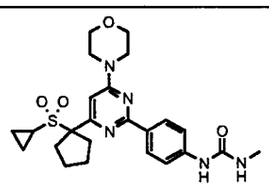
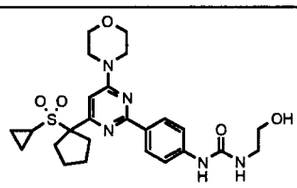
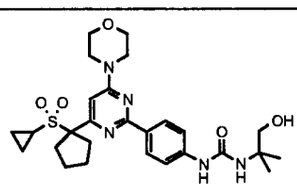
To a solution of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate (100 mg, 0.19 mmol) in DMF (2 mL) was added triethylamine (0.08 mL, 0.58 mmol) followed by cyclopropylamine (55 mg, 0.96 mmol) and the reaction heated at 50°C for 8 hours. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (60 mg).

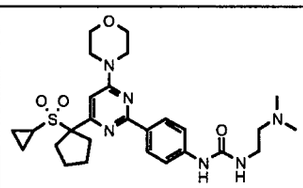
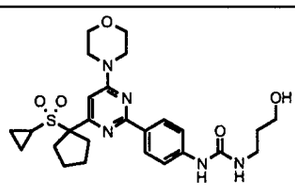
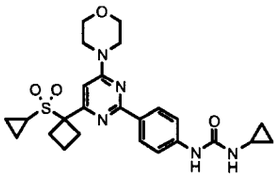
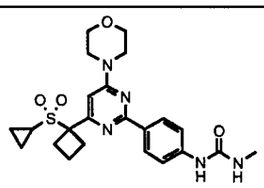
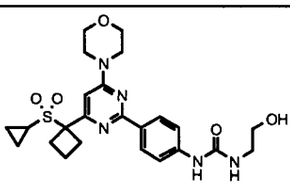
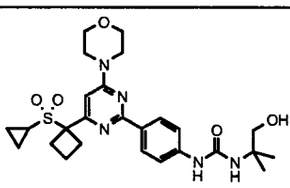
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 - 0.43 (2H, m), 0.64 - 0.66 (2H, m), 0.93 - 0.95 (2H, m), 1.02 - 1.05 (2H, m), 1.57 (2H, d), 1.65 (2H, d), 2.56 (1H, m), 3.02 (1H, s), 3.71 (8H, s), 6.42 (1H, s), 6.88 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.53 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 484; HPLC tR = 1.80 min.
mTOR Kinase Assay (Echo): 0.00357μM

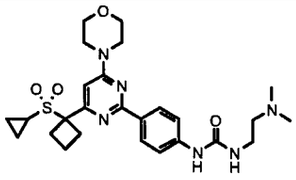
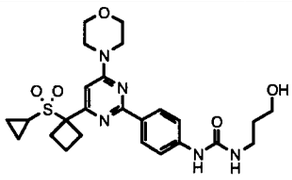
The following compounds were made in an analogous fashion from either phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate, phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
13a		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea	458.3	1.63

Example	Structure	NAME	LCMS MH+	Retention time (min)
13b		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-ethylurea	472.4	1.78
13c		3-cyclobutyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	498.4	2.04
13d		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	488.4	1.5
13e		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	516.4	1.78
13f		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	515.4	1.71
13g		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propylurea	486.4	1.96

Example	Structure	NAME	LCMS MH+	Retention time (min)
13h		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	502.4	1.54
13i		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	524.4	1.71
13j*		3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	512	2.30
13k*		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea	486	2.13
13l*		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	516	1.92
13m*		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	544	2.25

Example	Structure	NAME	LCMS MH+	Retention time (min)
13n*		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	543	2.18
13o*		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	530	1.97
13p*		3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	498	2.05
13q*		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea	498	2.05
13r*		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	502	1.72
13s*		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	530	2.01

Example	Structure	NAME	LCMS MH+	Retention time (min)
13t*		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	529	1.98
13u*		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	516	1.76

* Reaction stirred at 40°C for 6 hours

Example 13a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.95 (2H, m), 1.02 - 1.05 (2H, m), 1.55 - 1.58 (2H, m), 1.63 - 1.66 (2H, m), 2.66 (3H, d), 3.02 (1H, s), 3.71 (8H, s), 6.06 (1H, d), 6.88 (1H, s), 7.48 - 7.51 (2H, m), 8.20 - 8.22 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00341μM

Example 13b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.96 (2H, m), 1.02 (2H, m), 1.06 (3H, q), 1.56 - 1.58 (2H, m), 1.62 - 1.66 (2H, m), 3.00 - 3.04 (1H, m), 3.10 - 3.16 (2H, m), 3.71 (8H, s), 6.15 (1H, t), 6.88 (1H, s), 7.47 - 7.51 (2H, m), 8.20 - 8.23 (2H, m), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.0037μM

Example 13c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 1.00 (2H, m), 1.02 - 1.05 (2H, m), 1.56 (2H, d), 1.56 - 1.60 (2H, m), 1.61 - 1.68 (2H, m), 1.82 - 1.88 (2H, m), 2.17 - 2.24 (2H, m), 3.00 - 3.04 (1H, m), 3.71 (8H, s), 4.14 (1H, d), 6.45 (1H, d), 6.88 (1H, s), 7.46 - 7.48 (2H, m), 8.20 - 8.22 (2H, m), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.0024μM

Example 13d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.95 (2H, m), 1.03 - 1.04 (2H, d), 1.55 - 1.58 (2H, m), 1.63 - 1.66 (2H, m), 3.02 (1H, s), 3.18 (2H, d), 3.45 (2H, t), 3.71 (8H, s), 4.73 (1H, s), 6.25 (1H, s), 6.88 (1H, s), 7.47 - 7.49 (2H, m), 8.22 (2H, d), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00351μM

Example 13e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.95 (2H, m), 1.03 - 1.05 (2H, m), 1.24 (6H, s), 1.56 (2H, d), 1.63 -1.65 (2H, d), 3.02 (1H, m), 3.38 - 3.40 (2H, m), 3.71 (8H, s), 4.95 (1H, s), 5.99 (1H, s), 6.88 (1H, s), 7.45 (2H, d), 8.20 (2H, d), 8.73 (1H, s).
mTOR Kinase Assay (Echo): 0.0301μM

Example 13f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.96 (2H, m), 1.03 - 1.05 (2H, m), 1.55 - 1.58 (2H, m), 1.63 - 1.66 (2H, m), 2.18 (6H, s), 2.34 (2H, t), 3.02 (1H, t), 3.19 (2H, q), 3.71 (8H, s), 6.15 (1H, s), 6.88 (1H, s), 7.47 - 7.49 (2H, m), 8.20 - 8.22 (2H, m), 8.88 (1H, s).
mTOR Kinase Assay (Echo): 0.386μM

Example 13g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (3H, t), 0.93 - 0.96 (2H, m), 1.03 (2H, d), 1.41 - 1.50 (2H, m), 1.56 - 1.58 (2H, t), 1.62 - 1.66 (2H, m), 3.00 - 3.02 (1H, m), 3.06 (2H, s), 3.71 (8H, s), 6.19 (1H, t), 6.88 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.64 (1H, s).
mTOR Kinase Assay (Echo): 0.00479μM

Example 13h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.98 (2H, m), 0.98 - 1.07 (2H, m), 1.55 - 1.56 (2H, m), 1.58 (2H, d), 1.61 - 1.66 (2H, m), 2.99 - 3.05 (1H, m), 3.15 - 3.19 (2H, m), 3.45 - 3.50 (2H, m), 3.71 (8H, s), 4.47 (1H, t), 6.19 (1H, t), 6.88 (1H, s), 7.47 - 7.51 (2H, m), 8.20 - 8.23 (2H, m), 8.70 (1H, s).
mTOR Kinase Assay (Echo): 0.0106μM

Example 13i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.94 (2H, t), 1.03 - 1.06 (2H, m), 1.55 - 1.59 (2H, m), 1.64 - 1.67 (2H, m), 3.02 (1H, s), 3.72 (8H, s), 3.79 (3H, s), 6.89 (1H, s), 7.38 (1H, s), 7.54 (2H, d), 7.76 (1H, s), 8.25 (2H, d), 8.38 (1H, s), 8.84 (1H, s).
mTOR Kinase Assay (Echo): 0.00275μM

Example 13j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 0.71 - 0.73 (2H, m), 0.84 - 0.87 (2H, m), 1.55 (2H, t), 1.81 (2H, d), 2.33 (1H, t), 2.43 - 2.45 (2H, m), 2.57 - 2.61 (1H, m), 2.82 (2H, t), 3.72 (8H, s), 6.45 (1H, d), 6.87 (1H, s), 7.50 (2H, d), 8.25 (2H, d), 8.56 (1H, s).
mTOR Kinase Assay (Echo): 0.0178μM

Example 13k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.73 (2H, m), 0.84 - 0.87 (2H, m), 1.55 (2H, t), 1.79 (1H, d), 1.82 (1H, s), 2.43 (2H, t), 2.57 - 2.61 (1H, m), 2.65 (3H, d), 2.82 (2H, d), 3.72 (8H, s), 6.08 (1H, d), 6.86 (1H, s), 7.49 - 7.51 (2H, m), 8.23 - 8.25 (2H, m), 8.77 (1H, s).
mTOR Kinase Assay (Echo): 0.0179μM

Example 13l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.73 (2H, m), 0.83 - 0.88 (2H, m), 1.55 (2H, t), 1.77 - 1.82 (2H, m), 2.43 - 2.48 (2H, m), 2.55 - 2.62 (1H, m), 2.81 (1H, t), 2.84 (1H, s), 3.15 - 3.18 (2H, m), 3.45 (2H, q), 3.72 (8H, s), 4.77 (1H, t), 6.26 (1H, t), 6.86 (1H, s), 7.47 - 7.50 (2H, m), 8.23 - 8.26 (2H, m), 8.83 (1H, s).

mTOR Kinase Assay (Echo): 0.0108μM

Example 13m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.72 - 0.74 (2H, m), 0.85 - 0.88 (2H, m), 1.24 (6H, s), 1.55 (2H, t), 1.79 (2H, d), 2.42 (1H, s), 2.45 (1H, d), 2.59 (1H, s), 2.80 (2H, s), 3.38 (2H, d), 3.72 (8H, s), 4.99 (1H, t), 6.01 (1H, s), 6.86 (1H, s), 7.44 - 7.46 (2H, m), 8.22 - 8.24 (2H, m), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.0532μM

Example 13n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.73 (2H, m), 0.85 - 0.87 (2H, m), 1.55 (2H, t), 1.79 (2H, d), 2.17 (6H, s), 2.33 (2H, t), 2.42 (1H, s), 2.45 (1H, d), 2.59 (1H, s), 2.81 (2H, s), 3.19 (2H, q), 3.72 (8H, s), 6.17 (1H, s), 6.86 (1H, s), 7.47 - 7.49 (2H, m), 8.23 - 8.25 (2H, m), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.997μM

Example 13o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.73 (2H, m), 0.83 - 0.88 (2H, m), 1.53 - 1.62 (4H, m), 1.79 - 1.82 (1H, m), 1.81 (1H, d), 2.44 (2H, d), 2.57 - 2.61 (1H, m), 2.81 (1H, t), 2.84 (1H, s), 3.14 - 3.18 (2H, m), 3.44 - 3.49 (2H, m), 3.72 (8H, s), 4.52 (1H, t), 6.21 (1H, t), 6.86 (1H, s), 7.48 - 7.50 (2H, m), 8.23 - 8.25 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.0287μM

Example 13p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 0.74 - 0.78 (2H, m), 0.85 - 0.87 (2H, m), 1.88 - 1.91 (1H, m), 2.07 (1H, t), 2.50 (1H, s), 2.53 - 2.58 (1H, m), 2.85 - 2.89 (2H, m), 2.94 - 2.99 (2H, m), 3.73 (8H, s), 6.42 (1H, d), 6.77 (1H, s), 7.48 - 7.52 (2H, m), 8.23 - 8.26 (2H, m), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.00202μM

Example 13q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.74 - 0.78 (2H, m), 0.84 - 0.89 (2H, m), 1.88 - 1.91 (1H, m), 2.07 (1H, t), 2.50 (1H, m), 2.66 (3H, d), 2.85 - 2.89 (2H, m), 2.94 - 2.99 (2H, m), 3.72 (8H, s), 6.06 (1H, q), 6.76 (1H, s), 7.48 - 7.51 (2H, m), 8.22 - 8.26 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00192μM

Example 13r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.76 - 0.78 (2H, m), 0.85 - 0.88 (2H, m), 1.91 (1H, s), 2.07 (1H, t), 2.50 (1H, s), 2.85 - 2.89 (2H, m), 2.94 - 2.97 (2H, m), 3.17 (2H, q),

3.46 (2H, q), 3.72 (8H, s), 4.72 (1H, t), 6.24 (1H, t), 6.76 (1H, s), 7.47 - 7.49 (2H, m), 8.23 - 8.25 (2H, m), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.00198μM

Example 13s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.76 - 0.79 (2H, m), 0.85 - 0.88 (2H, m), 1.24 (6H, s), 1.91 (1H, s), 2.07 (1H, t), 2.50 (1H, s), 2.85 - 2.89 (2H, m), 2.94 (1H, d), 2.96 - 2.97 (1H, m), 3.39 (2H, d), 3.72 (8H, s), 4.95 (1H, t), 6.00 (1H, s), 6.76 (1H, s), 7.44 - 7.46 (2H, m), 8.22 - 8.24 (2H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00846μM

Example 13t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.75 - 0.77 (2H, m), 0.85 - 0.88 (2H, m), 1.88 - 1.91 (1H, m), 2.07 (1H, t), 2.18 (6H, s), 2.32 (1H, s), 2.34 (2H, t), 2.86 (1H, d), 2.88 (1H, s), 2.94 (1H, d), 2.96 (1H, s), 3.20 (2H, t), 3.72 (8H, s), 6.15 (1H, s), 6.76 (1H, s), 7.47 - 7.49 (2H, m), 8.23 - 8.25 (2H, m), 8.88 (1H, s).

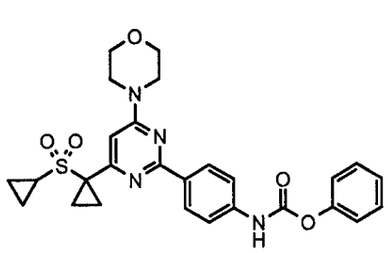
mTOR Kinase Assay (Echo): 0.172μM

Example 13u: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.74 - 0.78 (2H, m), 0.84 - 0.89 (2H, m), 1.57 (1H, d), 1.61 (1H, t), 1.88 - 1.91 (1H, m), 2.06 (1H, d), 2.50 (1H, m), 2.85 - 2.89 (2H, m), 2.94 - 2.99 (2H, m), 3.14 - 3.19 (2H, m), 3.45 - 3.49 (2H, m), 3.72 (8H, s), 4.47 (1H, t), 6.19 (1H, t), 6.76 (1H, s), 7.47 - 7.50 (2H, m), 8.23 - 8.25 (2H, m), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00477μM

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate



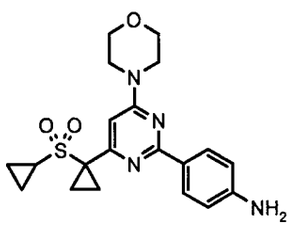
Phenyl chloroformate (0.440 mL, 3.50 mmol) was added dropwise to 4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline (1.40g, 3.50 mmol) and sodium bicarbonate (0.440 g, 5.24 mmol) in dioxane (50 mL) under nitrogen. The

resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (100 mL) and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a yellow solid (1.82 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.93 - 0.95 (2H, m), 1.05 (2H, d), 1.59 (1H, s), 1.60 (1H, t), 1.65 (1H, t), 1.67 (1H, d), 3.01 - 3.05 (1H, m), 3.58 (1H, s), 3.73 (8H, s), 6.94 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.64 (2H, d), 8.31 (2H, d), 10.44 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 521; HPLC tR = 2.68 min.

4-[4-(1-Cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline

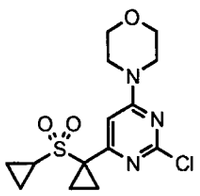


Dichlorobis(triphenylphosphine)palladium(II) (0.376 g, 0.54 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine (1.84 g, 5.35 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.466 g, 6.69 mmol) and sodium carbonate (13.38 mL, 26.76 mmol) in 18% DMF in 7:3:2 DME:Water:Ethanol (40 mL). The resulting solution was stirred at 85°C for 1 hour. The reaction mixture was concentrated and diluted with DCM (200 mL), and washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.40 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.97 (2H, m), 0.98 - 1.06 (2H, m), 1.52 - 1.58 (2H, m), 1.59 - 1.64 (2H, m), 2.97 - 3.04 (1H, m), 3.68 (4H, d), 3.71 - 3.71 (4H, m), 5.54 (2H, d), 6.58 - 6.62 (2H, m), 6.79 (1H, s), 8.03 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 401; HPLC tR = 1.62 min.

2-Chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine

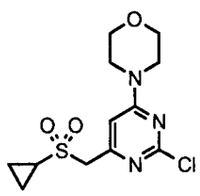


Sodium hydroxide (8.81 mL, 88.11 mmol) was added to 2-chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine (2.80 g, 8.81 mmol), 1,2-dibromoethane (1.519 mL, 17.62 mmol) and tetrabutylammonium bromide (0.568 g, 1.76 mmol) in toluene (120 mL) at RT. The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.84 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 - 0.93 (2H, m), 1.00 - 1.05 (2H, m),), 1.50 (2H, d), 1.62 (2H, d), 2.89 - 2.96 (1H, m), 3.65 (4H, m), 3.66 - 3.67 (4H, m), 7.01 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 344; HPLC 1.48 tR = min.

2-Chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine

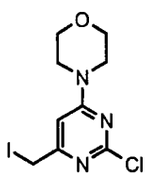


Cyclopropanesulfinic acid sodium salt (5.66 g, 44.17 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine (12.5 g, 36.81 mmol) in acetonitrile (300 mL) at RT. The resulting suspension was stirred at 80 °C for 24 hours. The resulting mixture was evaporated to dryness and the residue was azeotroped with MeCN to afford the desired material (7.12 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.94 - 0.99 (2H, m), 1.01 - 1.07 (2H, m), 2.77 - 2.84 (1H, m), 3.62 (4H, s), 3.67 - 3.69 (4H, s), 4.47 (2H, s), 6.95 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 318; HPLC tR = 1.46 min.

2-Chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine

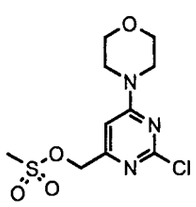


Sodium iodide (27.2 g, 181.31 mmol) was added to (2-chloro-6-morpholin-4-ylpyrimidin-4-yl)methyl methanesulfonate (27.9 g, 90.66 mmol) in acetone (400 mL) at RT under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM (400 mL) and was washed with water (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the desired material as a brown solid (33.9 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 3.59 (4H, s), 3.63 - 3.68 (4H, m), 4.29 (2H, s), 6.97 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+339 = ; HPLC tR = 1.87 min.

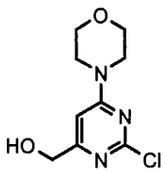
(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)methyl methanesulfonate



Methanesulfonyl chloride (10.57 mL, 136 mmol) was added dropwise to (2-chloro-6-morpholin-4-ylpyrimidin-4-yl)methanol (20.83 g, 90.70 mmol) and DIPEA (23.70 mL, 136 mmol) in DCM (375 mL) at 0°C over a period of 15 minutes, under a nitrogen atmosphere. The resulting solution was stirred at RT for 1 hour. The reaction mixture was diluted with water (100 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated to afford the desired material as a brown oil (27.9 g).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 308; HPLC tR = 1.58 min.

(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)methanol

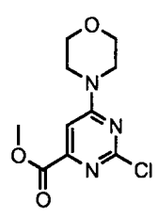


To a suspension of methyl 2-chloro-6-morpholin-4-ylpyrimidine-4-carboxylate (60 g, 232.85 mmol) in THF (1200 mL) at -5°C was added lithium borohydride (2M in THF, 0.122 L, 244.50 mmol) dropwise over 30 minutes. The reaction mixture was warmed to RT and stirred for 1 hour. To this was added water (600 mL), the mixture stirred for 2 hours and then filtered. Further water (600 mL) was added and the solution was extracted three times with ethyl acetate (600 mL). The combined organics were washed with 50% aqueous brine (900 mL), dried ($MgSO_4$) and the solvent was then removed under reduced pressure to give the desired product as a white solid (49.8 g).

NMR Spectrum: ^1H NMR (400.13 MHz, DMSO-d_6) δ 3.59 - 3.68 (8H, m), 4.35 (2H, dd), 5.50 (1H, t), 6.77 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 230; HPLC tR = 1.08 min

Methyl 2-chloro-6-morpholin-4-ylpyrimidine-4-carboxylate



To a solution of 2,6-dichloropyrimidine-4-carboxylate (60 g, 289.84 mmol) in DCM (400 mL) at -5°C was added triethylamine (44.4 mL, 318.82 mmol), washing in with DCM (80 mL). To the resulting solution was added morpholine (26.6 mL, 304.33 mmol) in DCM (120 mL) dropwise over 2 hours, maintaining the temperature below 5°C. The reaction mixture was stirred at 0°C for 2 hours and then warmed to RT. Water (600 mL) was added and the layers were separated. The organic layer was washed twice with water (180 mL) and the combined aqueous fractions extracted twice with DCM (180 mL). The combined organics were washed twice with 75% aqueous brine (180 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to give the crude product. This was purified by

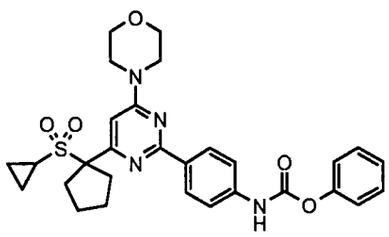
crystallisation from ethyl acetate/isohexane to give the desired product as a white solid (65.4g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.72 - 3.82 (8H, m), 3.99 (3H, s), 7.20 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 258; HPLC tR = 1.38 min

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

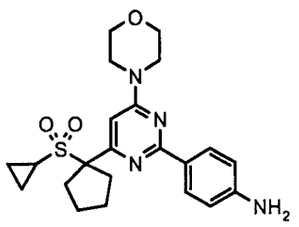


Phenyl chloroformate (0.455 mL, 3.62 mmol) was added dropwise to 4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline (1.55 g, 3.62 mmol) and sodium bicarbonate (0.456 g, 5.43 mmol) in dioxane (50 mL) under nitrogen. The resulting suspension was stirred at RT for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (100 mL) and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a yellow solid (2.31 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.75 (2H, m), 0.84 - 0.89 (2H, m), 1.56 (2H, t), 1.78 - 1.83 (2H, m), 2.45 (1H, t), 2.57 - 2.63 (2H, m), 2.81 - 2.84 (2H, m), 3.73 (8H, s), 6.90 (1H, s), 7.23 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.63 (2H, d), 8.33 - 8.36 (2H, m), 10.42 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 549; HPLC tR = 3.02 min.

4-[4-(1-Cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline

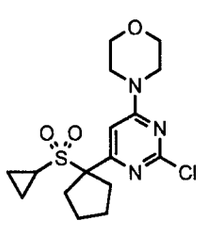


Dichlorobis(triphenylphosphine)palladium(II) (0.170 g, 0.24 mmol) was added to a degassed solution of 2-chloro-4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidine (1.80 g, 4.84 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.326 g, 6.05 mmol) and an aqueous solution of sodium carbonate (12.10 mL, 24.20 mmol) in a solvent mixture of 18% DMF in 7:3:2 DME:Water:Ethanol (40 mL). The resulting solution was stirred at 85°C for 1 hour. The reaction mixture was concentrated, diluted with DCM (100 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 70% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.55 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.73 - 0.75 (2H, m), 0.83 - 0.88 (2H, m), 1.55 (2H, t), 1.78 (1H, s), 1.81 (1H, t), 2.41 (1H, d), 2.45 - 2.47 (1H, m), 2.54 - 2.58 (1H, m), 2.79 (1H, t), 2.82 (1H, s), 3.70 (8H, d), 5.53 (2H, s), 6.59 - 6.62 (2H, m), 6.77 (1H, s), 8.07 - 8.09 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 429; HPLC tR = 2.36 min.

2-Chloro-4-(1-cyclopropylsulfonylcyclopentyl)-6-morpholin-4-ylpyrimidine



10N Sodium hydroxide solution (5.70 mL, 56.96 mmol) was added to 2-chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine (1.81 g, 5.70 mmol), 1,4-dibromobutane (0.674 mL, 5.70 mmol) and tetrabutylammonium bromide (0.367 g, 1.14 mmol) in toluene (100 mL) at RT. The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (75 mL) and washed

with water (75 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (1.8 g).

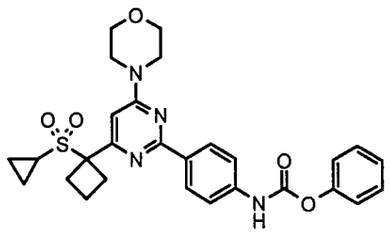
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.71 - 0.75 (2H, m), 0.90 - 0.94 (2H, m), 1.50 - 1.59 (2H, m), 1.77 - 1.80 (2H, m), 2.36 - 2.44 (2H, m), 2.57 - 2.68 (3H, m), 3.67 (8H, s), 6.97 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 372; HPLC tR = 2.26 min.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

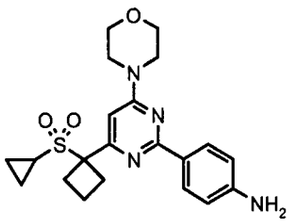


Phenyl chloroformate (0.106 mL, 0.84 mmol) was added dropwise to 4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline (350 mg, 0.84 mmol) and sodium bicarbonate (106 mg, 1.27 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (50 mL) and washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a cream solid (453 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.75 - 0.77 (2H, m), 0.85 - 0.88 (2H, m), 1.90 (1H, d), 2.07 (1H, d), 2.54(1H, m), 2.86 - 2.90 (2H, m), 2.93 - 2.98 (2H, s), 3.73 (8H, s), 6.80 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.63 (2H, d), 8.33 - 8.35 (2H, m), 10.42 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 535; HPLC tR = 2.91 min.

4-[4-(1-Cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidin-2-yl]aniline

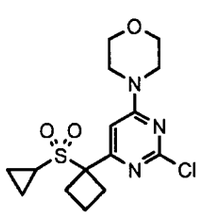


2-Chloro-4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidine (430 mg, 1.20 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (329 mg, 1.50 mmol), dichlorobis(triphenylphosphine)palladium(II) (42.2 mg, 0.06 mmol) and an aqueous solution of sodium carbonate (3.00 mL, 6.01 mmol) were suspended in a solvent mixture of 18% DMF in 7:3:2 DME:Water:Ethanol (8 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 30 minutes in the microwave reactor and cooled to RT. The crude product was purified by ion exchange chromatography using an SCX column, the desired product was eluted from the column using 7M ammonia in methanol. The isolated material was further purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white solid (350 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.74 - 0.78 (2H, m), 0.83 - 0.88 (2H, m), 1.85 - 1.91 (1H, m), 2.03 - 2.07 (1H, m), 2.44 - 2.48 (1H, m), 2.83 - 2.87 (2H, m), 2.90-2.97 (2H, m), 3.70 - 3.71 (8H, m), 5.52 (2H, d), 6.58 - 6.62 (2H, m), 6.67 (1H, s), 8.06 - 8.09 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 415; HPLC tR = 2.19 min.

2-Chloro-4-(1-cyclopropylsulfonylcyclobutyl)-6-morpholin-4-ylpyrimidine



10N Sodium hydroxide solution (9.60 mL, 95.97 mmol) was added to 1,3-dibromopropane (0.979 mL, 9.60 mmol), 2-chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine (2.80 g, 9.60 mmol) and tetrabutylammonium bromide (0.619 g, 1.92 mmol) in toluene (120

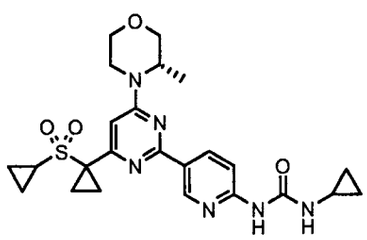
mL) at RT. The resulting solution was stirred at 60°C for 18 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine solution (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (0.795 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.73 - 0.77 (2H, m), 0.89 - 0.94 (2H, m), 1.85 - 1.92 (1H, m), 2.04 - 2.08 (1H, m), 2.53 - 2.57 (1H, m), 2.70 - 2.78 (2H, m), 2.85 - 2.93 (2H, m), 3.66 (8H, d), 6.88 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 358; HPLC 1.95 tR = min.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-morpholin-4-ylpyrimidine was described earlier.

Example 14: 3-Cyclopropyl-1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea



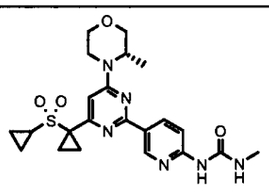
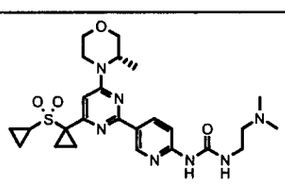
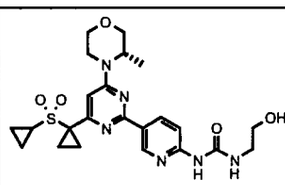
Triethylamine (0.208 mL, 1.5 mmol) was added to a solution of phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate (200 mg, 0.37 mmol) and cyclopropylamine (1.48 mmol) in NMP (2 mL). The reaction was heated at 75°C for 4 hours then purified by prep HPLC, using a mixture of water (containing 1% NH3) and acetonitrile as eluents, to give the desired material as a solid (40 mg).

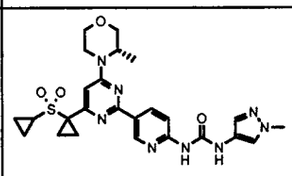
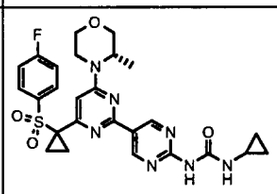
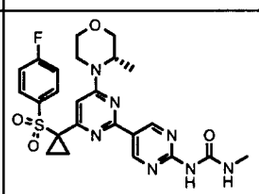
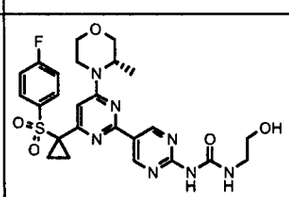
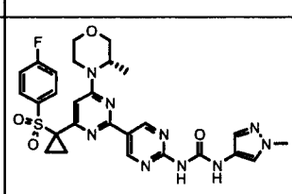
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.44 - 0.50 (2H, m), 0.64 - 0.72 (2H, m), 0.89 - 0.96 (2H, m), 1.00 - 1.06 (2H, m), 1.23 (3H, d), 1.54 - 1.60 (2H, m), 1.59 - 1.68 (2H, m), 2.59 - 2.66 (1H, m), 2.96 - 3.01 (1H, m), 3.16 - 3.25 (1H, m), 3.44 - 3.52 (1H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 (1H, s), 4.54 (1H, s), 6.90 (1H, s), 7.50 (1H, d), 8.18 (1H, s), 8.50 (1H, d), 9.09 (1H, s), 9.37 (1H, s)

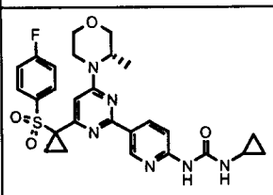
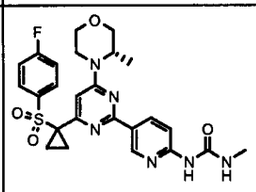
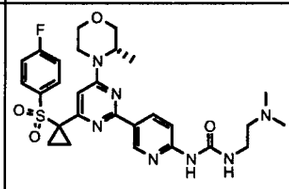
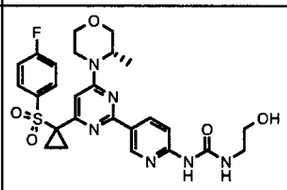
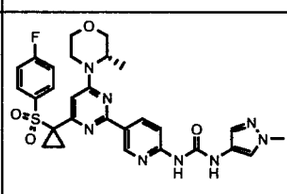
LCMS Spectrum: m/z (ESI+)(M+H)+ = 499; HPLC tR = 2.15 min.

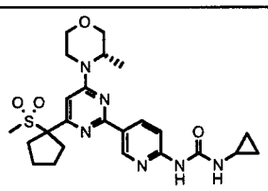
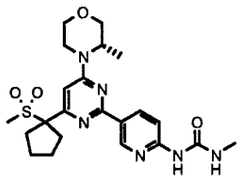
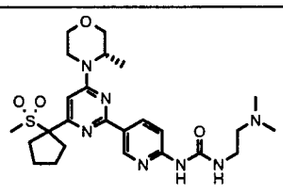
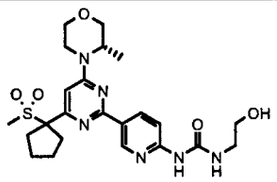
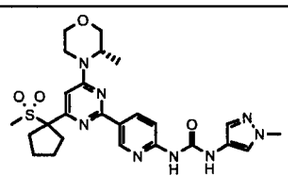
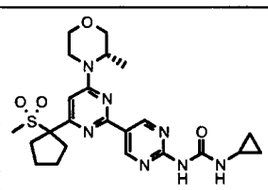
mTOR Kinase Assay (Echo): 0.0465μM

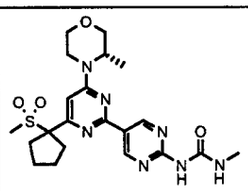
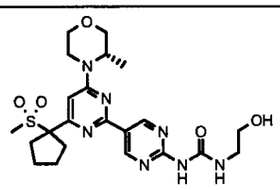
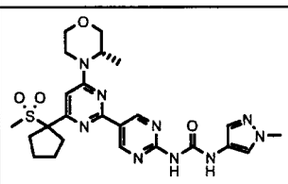
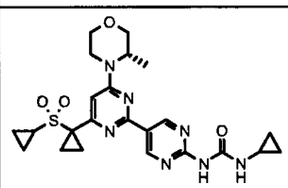
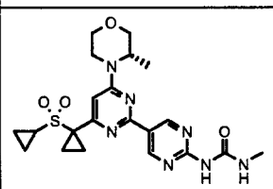
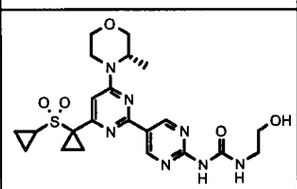
The following compounds were prepared in an analogous fashion from either phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate, phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate, phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate, phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]carbamate, phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]carbamate or phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate using the appropriate amine.

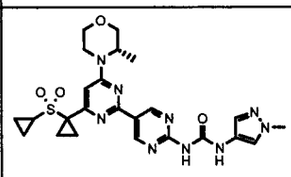
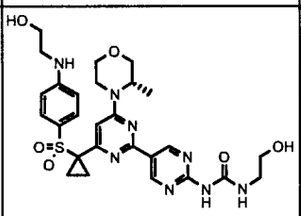
Example	Structure	NAME	LCMS MH+	Retention time (min)
14a		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-methylurea	473	2.03
14b		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-dimethylaminoethyl)urea	530	1.97
14c		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-hydroxyethyl)urea	503	1.73

Example	Structure	NAME	LCMS MH+	Retention time (min)
14d		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea	539	2.01
14e		3-cyclopropyl-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea	554	2.37
14f		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-methylurea	528	2.16
14g		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(2-hydroxyethyl)urea	558	1.91
14h		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea	594	2.19

Example	Structure	NAME	LCMS MH+	Retention time (min)
14i		3-cyclopropyl-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea	553	2.26
14j		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-methylurea	527	2.20
14k		3-(2-dimethylaminoethyl)-1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]urea	584	2.22
14l		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(2-hydroxyethyl)urea	557	1.92
14m		1-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea	593	2.13

Example	Structure	NAME	LCMS MH+	Retention time (min)
14n		3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea	501	2.18
14o		3-methyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea	475	2.01
14p		3-(2-dimethylaminoethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea	532	2.01
14q		3-(2-hydroxyethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]urea	505	1.78
14r		1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]-3-(1-methylpyrazol-4-yl)urea	541	2.01
14s		3-cyclopropyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea	502	2.15

Example	Structure	NAME	LCMS MH+	Retention time (min)
14t		3-methyl-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea	476	1.99
14u		3-(2-hydroxyethyl)-1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]urea	506	1.70
14v		1-[5-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea	542	1.95
14w		3-cyclopropyl-1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea	500	2.0
14x		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-methylurea	474	1.79
14y		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(2-hydroxyethyl)urea	504	1.54

Example	Structure	NAME	LCMS MH+	Retention time (min)
14z		1-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]-3-(1-methylpyrazol-4-yl)urea	540	1.82
14aa*		3-(2-hydroxyethyl)-1-[5-[4-[1-[4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]urea	599	1.63

* Isolated as a by product from the reaction to generate **14g**

Example 14a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.90 - 0.96 (2H, m), 1.01 - 1.06 (2H, m), 1.24 (3H, d), 1.55 - 1.60 (2H, m), 1.62 - 1.68 (2H, m), 2.78 (3H, s), 3.18 - 3.27 (1H, m), 3.44 - 3.54 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.20 (1H, d), 4.56 (1H, s), 6.91 (1H, s), 7.43 (1H, d), 8.15 (1H, s), 8.49 (1H, d), 9.12 (1H, s), 9.48 (1H, s), 9.49 (1H, s).

mTOR Kinase Assay (Echo): 0.0136μM

Example 14b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.91 - 0.95 (2H, m), 1.00 - 1.05 (2H, m), 1.23 (3H, d), 1.56 - 1.60 (2H, m), 1.63 - 1.66 (2H, m), 2.18 (6H, s), 2.36 (2H, t), 2.98 - 3.04 (1H, m), 3.17 - 3.29 (3H, m), 3.48 (1H, td), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.20 (1H, s), 4.54 (1H, s), 6.90 (1H, s), 7.53 (1H, d), 8.05 (1H, s), 8.49 (1H, d), 9.09 (1H, d), 9.48 (1H, s).

mTOR Kinase Assay (Echo): 1.39μM

Example 14c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.90 - 0.94 (2H, m), 1.01 - 1.05 (2H, m), 1.23 (3H, d), 1.55 - 1.60 (2H, m), 1.63 - 1.67 (2H, m), 2.96 - 3.03 (1H, m), 3.16 - 3.28 (3H, m), 3.43 - 3.52 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.20 (1H, s), 4.54 (1H, s), 4.80 (1H, t), 6.90 (1H, s), 7.47 (1H, d), 8.29 (1H, s), 8.50 (1H, d), 9.10 (1H, s), 9.51 (1H, s).

mTOR Kinase Assay (Echo): 0.0401μM

Example 14d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 - 0.96 (2H, m), 1.00 - 1.05 (2H, m), 1.24 (3H, d), 1.58 - 1.61 (2H, m), 1.64 - 1.70 (2H, m), 2.97 - 3.04 (1H, m), 3.22 (1H, td), 3.43 - 3.55 (1H, m), 3.64 (1H, dd), 3.75 - 3.82 (4H, m), 3.98 (1H, dd), 4.23 (1H, s), 4.55 (1H, s), 6.92 (1H, s), 7.49 (1H, d), 7.87 (1H, s), 8.55 (1H, d), 9.18 (1H, s), 9.73 (1H, s), 10.36 (1H, s).

mTOR Kinase Assay (Echo): 0.0143μM

Example 14e: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.53 - 0.55 (2H, m), 0.69 - 0.74 (2H, m), 1.19 (3H, d), 1.60 - 1.63 (2H, m), 1.88 - 1.92 (2H, m), 3.12 - 3.21 (1H, m), 3.44 (1H, d), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.14 - 4.24 (1H, m), 4.40 - 4.54 (1H, m), 6.77 (1H, s), 7.44 (2H, t), 7.85 (2H, dd), 8.88 (2, s), 9.11 (1H, d), 10.11 (1H, s).

mTOR Kinase Assay (Echo): 0.11μM

Example 14f: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 - 1.65 (2H, m), 1.89 - 1.92 (2H, m), 2.79(3H,d), 3.17 (1H, t), 3.46 - 3.63 (2H, m), 3.74 (1H, d), 3.95 (1H, d), 4.18 (1H, s), 4.46 (1H, s), 6.77 (1H, s), 7.43 (2H, t), 7.85 (2H, dd), 8.94 (2H, s), 10.08 (1H, s).

mTOR Kinase Assay (Echo): 0.189μM

Example 14g: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 - 1.66 (2H, m), 1.88 - 1.92 (2H, m), 3.18 (1H, d), 3.30 (2H, q), 3.44 (1H, d), 3.49 - 3.54 (2H, m), 3.60 (1H, d), 3.72 - 3.98 (4H, m), 4.18(1H,s), 4.45(1H,s), 6.77 (1H, s), 7.43 (2H, t), 7.79 - 7.89 (2H, m), 8.91(2H,s), 9.13 - 9.20 (1H, m), 10.08 (1H, s).

mTOR Kinase Assay (Echo): 0.0857μM

Example 14h: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.61 - 1.65 (2H, m), 1.89 - 1.94 (2H, m), 3.19 (1H, d), 3.41 - 3.50 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.82 (3H, s), 3.96 (1H, d), 4.22 (1H, s), 4.48 (1H, s), 6.78 (1H, s), 7.46 (2H, t), 7.54 (1H, s), 7.86 (2H, dd), 7.90 (1H, s), 8.97 (2H, s), 10.47 (1H, s).

mTOR Kinase Assay (Echo): 0.14μM

Example 14i: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.46 - 0.51 (2H, m), 0.65 - 0.70 (2H, m), 1.18 (3H, d), 1.57 - 1.64 (2H, m), 1.86 - 1.92 (2H, m), 2.60 - 2.65 (1H, m), 3.14 - 3.19 (1H, m), 3.45 (1H, dd), 3.60 (1H, dd), 3.74 (1H, d), 3.92 - 3.99 (1H, m), 4.45 (1H, s), 6.73 (1H, s), 7.38 - 7.48 (2H, m), 7.84 (2H, dd), 8.05 - 8.16 (3H, m), 8.62 (1H, s), 9.37 (1H, s).

mTOR Kinase Assay (Echo): 0.0339μM

Example 14j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.57 - 1.64 (2H, m), 1.88 - 1.91 (2H, m), 2.74 (3H, d), 3.11 - 3.21 (1H, m), 3.42 - 3.50 (1H, m), 3.60 (1H, d), 3.74 (1H,

d), 3.93 - 3.98 (1H, m), 4.13 - 4.19 (1H, m), 4.40 - 4.47 (1H, m), 6.71 (1H, s), 7.35 (1H, d), 7.43 (2H, t), 7.84 (2H, dd), 7.98 - 8.07 (2H, m), 8.67 (1H, s), 9.50 (1H, s).

mTOR Kinase Assay (Echo): 0.0129μM

Example 14k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.58 - 1.62 (2H, m), 1.88 - 1.91 (2H, m), 2.19 (6H, s), 2.32 - 2.35 (2H, m), 3.17 (1H, d), 3.24 - 3.29 (2H, m), 3.44 (1H, d), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.13 - 4.21 (1H, m), 4.41 - 4.49 (1H, m), 6.71 (1H, s), 7.39 - 7.46 (3H, m), 7.84 (2H, dd), 7.98 (1H, s), 8.06 (1H, d), 8.65 (1H, s), 9.48 (1H, s).

mTOR Kinase Assay (Echo): 0.275μM

Example 14l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 - 1.65 (2H, m), 1.85 - 1.92 (2H, m), 3.12 - 3.21 (1H, m), 3.22 - 3.27 (2H, m), 3.43 - 3.50 (3H, m), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.17 (1H, s), 4.44 (1H, s), 4.79 (1H, t), 6.71 (1H, s), 7.37 - 7.46 (3H, m), 7.80 - 7.89 (2H, m), 7.84 (3H, dd), 8.04 (1H, d), 8.16 (1H, s), 8.70 (1H, s), 9.49 (1H, s).

mTOR Kinase Assay (Echo): 0.0137μM

Example 14m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.58 - 1.65 (2H, m), 1.88 - 1.92 (2H, m), 3.13 - 3.22 (1H, m), 3.42 - 3.49 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.81 (3H, s), 3.96 (1H, d), 4.14 - 4.24 (1H, m), 4.43 - 4.51 (1H, m), 6.73 (1H, s), 7.42 - 7.50 (3H, m), 7.82 - 7.90 (2H, m), 8.07 - 8.20 (1H, m), 8.71 (1H, s), 9.72 (1H, s), 10.28 (1H, s).

mTOR Kinase Assay (Echo): 0.0143μM

Example 14n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.44 - 0.51 (2H, m), 0.66 - 0.71 (2H, m), 1.22 (3H, d), 1.50 - 1.61 (2H, m), 1.78 - 1.85 (2H, m), 2.40 - 2.47 (2H, m), 2.60 - 2.66 (1H, m), 2.69 - 2.78 (2H, m), 2.90 (3H,s), 3.15 - 3.27 (1H, m), 3.44 - 3.54 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.98 (1H, d), 4.29 (1H, s), 4.58 (1H, s), 6.84 (1H, s), 7.51 (1H, d), 8.20 (1H, s), 8.53 (1H, d), 9.12 (1H, s), 9.37 (1H, s).

mTOR Kinase Assay (Echo): 0.0363μM

Example 14o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.51 - 1.60 (2H, m), 1.75 - 1.86 (2H, m), 2.40 - 2.47 (2H, m), 2.71 - 2.79 (5H, m), 2.90(3H,s), 3.22 (1H, d), 3.48 (1H, d), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.21 - 4.32 (1H, m), 4.58 (1H, s), 6.84 (1H, s), 7.42 (1H, d), 8.18 (1H, s), 8.52 (1H, d), 9.14 (1H, s), 9.52 (1H, s).

mTOR Kinase Assay (Echo): 0.0217μM

Example 14p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.61 (2H, m), 1.78 - 1.84 (2H, m), 2.18 (6H, s), 2.32 - 2.38 (2H, m), 2.38 - 2.47 (2H, m), 2.69 - 2.79 (2H, m), 2.90

(3H,s), 3.14 - 3.29 (3H, m), 3.43 - 3.55 (1H, m), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.26 (1H, s), 4.58 (1H, s), 6.84 (1H, s), 7.54 (1H, d), 8.03 (1H, s), 8.52 (1H, d), 9.12 (1H, s), 9.48 (1H, s).

mTOR Kinase Assay (Echo): 0.537μM

Example 14q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.51 - 1.61 (2H, m), 1.76 - 1.86 (2H, m), 2.37 - 2.46 (2H, m), 2.69 - 2.78 (2H, m), 2.90 (3H, s), 3.17 - 3.29 (3H, m), 3.42 - 3.54 (3H, m), 3.64 (1H, dd), 3.76 (1H, d), 3.92 - 4.01 (1H, m), 4.26 (1H, s), 4.57 (1H, s), 4.80 (1H, t), 6.84 (1H, s), 7.47 (1H, d), 8.31 (1H, s), 8.53 (1H, d), 9.12 (1H, s), 9.50 (1H, s).

mTOR Kinase Assay (Echo): 0.0265μM

Example 14r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.60 (2H, m), 1.79 - 1.85 (2H, m), 2.39 - 2.47 (2H, m), 2.71 - 2.81 (2H, m), 2.90 (3H, s), 3.17 - 3.26 (1H, m), 3.46 - 3.55 (1H, m), 3.65 (2H, d), 3.78 (4H, d), 3.98 (1H, d), 4.28 (1H, s), 4.59 (1H, s), 6.86 (1H, s), 7.50 (2H, d), 7.87 (1H, s), 8.58 (1H, d), 9.20 (1H, s), 9.73 (1H, s), 10.34 (1H, s).

mTOR Kinase Assay (Echo): 0.0103μM

Example 14s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.51 - 0.58 (2H, m), 0.67 - 0.76 (2H, m), 1.23 (3H, d), 1.50 - 1.62 (2H, m), 1.76 - 1.88 (2H, m), 2.31 - 2.49 (2H, m), 2.64 - 2.79 (2H, m), 2.90 (3H, s), 3.15 - 3.26 (1H, m), 3.49 (1H, t), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.29 (1H, s), 4.59 (1H, s), 6.88 (1H, s), 9.15 (1H, s), 9.36 (2H, s), 10.13 (1H, s).

mTOR Kinase Assay (Echo): 0.122μM

Example 14t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.56 (2H,m), 1.77 - 1.87 (2H, m), 2.34 (3H, d), 2.38 - 2.46 (2H, m), 2.68 - 2.76 (2H, m), 2.80 (3H, d), 3.16 - 3.23 (1H, m), 3.46 - 3.51 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.96 (1H, d), 4.22 - 4.35 (1H, m), 4.54 - 4.68 (1H, m), 6.89 (1H, s), 8.97 - 9.07 (1H, m), 9.36 (2H, s), 10.11 (1H, s).

mTOR Kinase Assay (Echo): 0.197μM

Example 14u: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.52 - 1.59 (2H, m), 1.78 - 1.85 (2H, m), 2.38 - 2.52 (4H, m), 2.69 - 2.79 (2H, m), 3.20 (1H, d), 3.32 (3H, s), 3.42 - 3.47 (1H, m), 3.49 - 3.55 (2H, m), 3.61 - 3.67 (1H, m), 3.76 (1H, d), 3.97 (1H, d), 4.30 (1H, s), 4.61 (1H, s), 4.83 (1H, t), 6.89 (1H, s), 9.15 - 9.26 (1H, m), 9.36 (2H, s), 10.11 (1H, s).

mTOR Kinase Assay (Echo): 0.123μM

Example 14v: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.60 (2H, m), 1.79 - 1.86 (2H, m), 2.38 - 2.47 (2H, m), 2.65 - 2.81 (5H, m), 3.11 - 3.27 (1H, m), 3.46 - 3.53 (1H,

m), 3.65 (1H, d), 3.76 (1H, d), 3.81 (3H, s), 3.98 (1H, d), 4.27 - 4.35 (1H, m), 4.57 - 4.65 (1H, m), 6.91 (1H, s), 7.55 (1H, s), 7.92 (1H, s), 9.08 (1H, s), 9.44 (2H, s), 10.49 (1H, s).

mTOR Kinase Assay (Echo): 0.0823μM

Example 14w: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.52 - 0.57 (2H, m), 0.68 - 0.74 (2H, m), 0.91 - 0.95 (2H, m), 0.99 - 1.04 (2H, m), 1.23 (3H, d), 1.56 - 1.61 (2H, m), 1.63 - 1.68 (2H, m), 2.65 - 2.73 (1H, m), 2.95 - 3.03 (1H, m), 3.22 (1H, dd), 3.43 - 3.53 (1H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.23 (1H, s), 4.56 (1H, s), 6.95 (1H, s), 9.15 (1H, s), 9.33 (2H, s), 10.13 (1H, s).

mTOR Kinase Assay (Echo): 0.208μM

Example 14x: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 - 0.96 (2H, m), 1.00 - 1.06 (2H, m), 1.24 (3H, d), 1.56 - 1.61 (2H, m), 1.63 - 1.67 (2H, m), 2.80 (3H, d), 2.98 - 3.05 (1H, m), 3.19 - 3.25 (1H, m), 3.48 (1H, dd), 3.57 - 3.66 (1H, m), 3.70 - 3.80 (1H, m), 3.90 - 4.00 (1H, m), 4.21 (1H, s), 4.56 (1H, s), 6.94 (1H, s), 8.98 (1H, d), 9.33 (2H, s), 10.10 (1H, s).

mTOR Kinase Assay (Echo): 0.63μM

Example 14y: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 - 0.95 (2H, m), 1.00 - 1.05 (2H, m), 1.24 (3H, d), 1.57 - 1.61 (2H, m), 1.64 - 1.69 (2H, m), 2.98 - 3.04 (1H, m), 3.18 - 3.27 (1H, m), 3.29 - 3.34 (2H, m), 3.44 - 3.55 (3H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.23 (1H, s), 4.56 (1H, s), 4.83 (1H, t), 6.95 (1H, s), 9.20 (1H, t), 9.35 (2H, s), 10.11 (1H, s).

mTOR Kinase Assay (Echo): 0.152μM

Example 14z: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.95 (2H, m), 0.98 - 1.07 (2H, m), 1.23 (3H, d), 1.58 - 1.61 (2H, m), 1.62 - 1.68 (2H, m), 2.97 - 3.03 (1H, m), 3.23 (1H, td), 3.49 (1H, td), 3.64 (1H, d), 3.76 - 3.85 (4H, m), 3.98 (1H, dd), 4.24 (1H, s), 4.57 (1H, s), 6.96 (1H, s), 7.56 (1H, s), 7.91 (1H, s), 9.41 (2H, s), 10.49 (1H, s), 11.15 (1H, s).

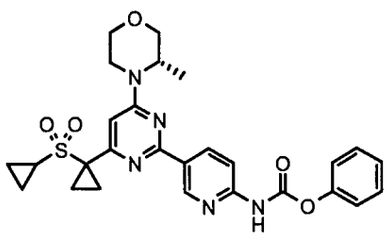
mTOR Kinase Assay (Echo): 0.171μM

Example 14aa: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.53 - 1.61 (2H, m), 1.74 - 1.79 (2H, m), 3.10 - 3.19 (2H, m), 3.28 - 3.36 (4H, m), 3.45 (1H, t), 3.48 - 3.56 (2H, m), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.10 (1H, s), 4.34 (1H, s), 4.75 (1H, t), 4.85 (1H, t), 6.62 (2H, d), 6.65 - 6.70 (2H, m), 7.41 (2H, d), 9.11 (2H, s), 9.20 (1H, t), 10.04 (1H, s).

mTOR Kinase Assay (Echo): 0.0186μM

The preparation of phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate is described below.

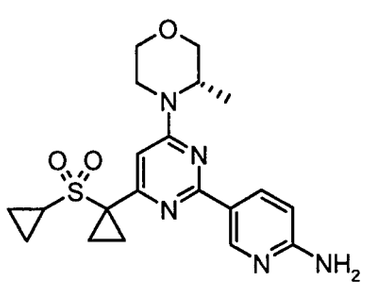
Phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate



Phenyl chloroformate (0.543 mL, 4.33 mmol) was added to a mixture of 5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-amine (1.2 g, 2.89 mmol) and sodium hydrogen carbonate (0.364 g, 4.33 mmol) in dioxane (30 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 1 hour, then at 40°C for 3 hours and again at RT overnight. Additional phenyl chloroformate (1 mL) was added and the mixture heated at 40°C until complete. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was then purified chromatography on silica, eluting with 10 to 80% ethyl acetate in isohexane, to give a mixture of the desired material and material where an additional carbamate group was present (phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]-*N*-phenoxycarbonylcarbamate). This material (1 g) was used in the subsequent step without further attempts to purify.

LCMS Spectrum: m/z (ESI+)(M+H)+ = 536; HPLC tR = 2.65 min.

5-[4-(1-Cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-amine



Bis(triphenylphosphine)palladium(II) chloride (118 mg, 0.17 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (900 mg, 2.51 mmol), 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (830 mg, 3.77 mmol) and sodium carbonate (5.03 mL, 10.06 mmol) in a mixture of DMF (6 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT . The resulting mixture was stirred at 90°C for 18 hours then the reaction mixture diluted with ethyl acetate (200 mL) and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by chromatography on silica, eluting with 0 to 5% methanol in ethyl acetate. The material was further purified by ion exchange chromatography using an SCX column with the desired material eluted using 7M ammonia in methanol, to give the pure desired material as a white solid (1.2 g).

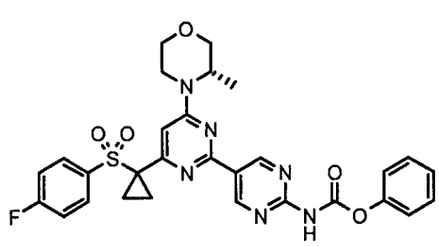
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.92 - 0.95 (2H, m), 1.00 - 1.04 (2H, m), 1.22 (3H, d), 1.53 - 1.59 (2H, m), 1.62 - 1.65 (2H, m), 2.94 - 3.02 (1H, m), 3.19 (1H, td), 3.48 (1H, td), 3.63 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.17 (1H, d), 4.53 (1H, s), 6.39 (2H, s), 6.50 (1H, d), 6.81 (1H, s), 8.23 (1H, d), 8.89 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 416; HPLC tR = 1.81 min.

The preparation of 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate is described below.

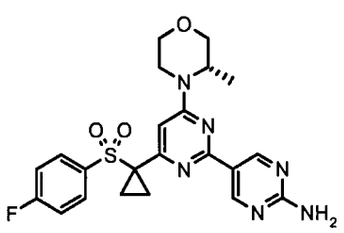
Phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate



Phenyl chloroformate (0.306 mL, 2.44 mmol) was added to a mixture of 5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-

yl]pyrimidin-2-amine (765 mg, 1.63 mmol) and sodium hydrogen carbonate (205 mg, 2.44 mmol) in dioxane (10 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT overnight. Additional phenyl chloroformate (0.2 mL) was added and reaction left to stir overnight. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (2 x 100 mL), and a saturated brine solution (50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford a gum. The crude gum was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired material as a yellow solid (1.0 g). No further purification was performed at this stage.
LCMS Spectrum: m/z (ESI+)(M+H)+ = 591; HPLC tR = 2.61 min.

5-[4-[1-(4-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-amine

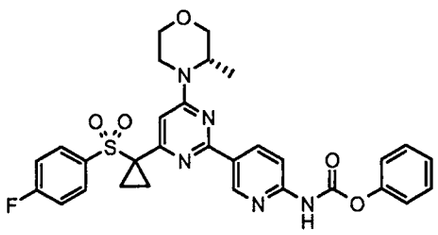


Bis(triphenylphosphine)palladium(II) chloride (0.143 g, 0.20 mmol) was added to 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.25 g, 3.03 mmol), 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.868 g, 3.95 mmol) and sodium carbonate (3 mL, 6.00 mmol) in a mixture of DMF (3 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT and the atmosphere replaced with nitrogen. The mixture was stirred at 90°C for 5 hours the left to stir at RT overnight. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (2 x 100 mL), and the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with DCM to give a solid which was collected by filtration and dried under vacuum to give the desired material as a beige solid (1.1 g).
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.56 - 1.61 (2H, m), 1.86 - 1.90 (2H, m), 3.15 (1H, td), 3.45 (1H, td), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, d), 4.46 (1H, s), 6.69 (1H, s), 7.13 (2H, s), 7.41 (2H, t), 7.80 - 7.85 (2H, m), 8.65 (2H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 471; HPLC tR = 1.94 min.

The preparation of 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

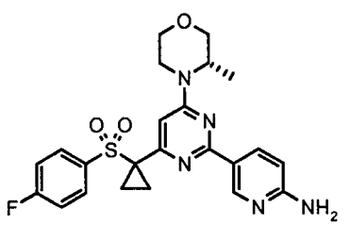
The preparation of phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate is described below.

Phenyl *N*-[5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-yl]carbamate



Phenyl chloroformate (0.962 mL, 7.67 mmol) was added to a mixture of 5-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-amine (900 mg, 1.92 mmol) and sodium hydrogen carbonate (242 mg, 2.88 mmol) in dioxane (50 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 3 days, additional phenyl chloroformate (2 mL) added and the reaction stirred at RT for an additional 16 hours. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (100 mL), and the organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired material as a cream solid (900 mg). LCMS Spectrum: m/z (ESI+)(M+H)+ = 591; HPLC tR = 2.63 min.

5-[4-[1-(4-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyridin-2-amine



Bis(triphenylphosphine)palladium(II) chloride (0.143 g, 0.20 mmol) was added to (2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.25 g, 3.03 mmol), 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.868 g, 3.95 mmol) and sodium carbonate (3 mL, 6.00 mmol) in a mixture of DMF (3 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT under at nitrogen atmosphere. The resulting mixture was stirred at 90°C for 5 hours then at RT for 16 hours. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (2 x 100 mL), and the organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 20 to 80% ethyl acetate in isohexane. The isolated material was further purified by ion exchange chromatography using an SCX column with the desired material eluted from the column using 7M ammonia in methanol. The desired material was isolated as as a white solid (0.94 g).

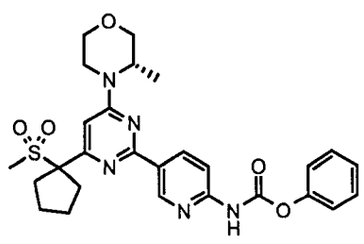
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.57 - 1.61 (2H, m), 1.86 - 1.89 (2H, m), 3.09 - 3.17 (1H, m), 3.41 - 3.49 (1H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.96 (1H, d), 4.11 (1H, d), 4.43 (1H, s), 6.35 - 6.41 (3H, m), 6.63 (1H, s), 7.38 - 7.45 (2H, m), 7.78 - 7.85 (3H, m), 8.51 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 470; HPLC tR = 2.06 min.

The preparation of 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]carbamate is described below.

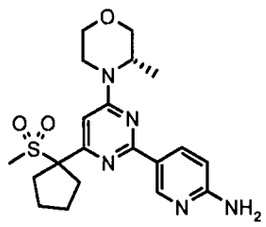
Phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-yl]carbamate



Phenyl chloroformate (1.23 mL, 9.82 mmol) was added to 5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-amine (1.025 g, 2.45 mmol) and sodium hydrogen carbonate (0.309 g, 3.68 mmol) in dioxane (50 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 3 days then additional phenyl chloroformate (2 mL) added and the reaction left to stir at 35°C for 3 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (2 x 100 mL), and the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude liquid was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired material as a cream solid (1.2 g).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 538; HPLC tR = 2.89 min.

5-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyridin-2-amine



Bis(triphenylphosphine)palladium(II) chloride (0.261 g, 0.37 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine (2 g, 5.56 mmol), 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.835 g, 8.34 mmol) and aqueous sodium carbonate solution (11.12 mL, 22.23 mmol) in a mixture of DMF (6 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT under an atmosphere of nitrogen. The resulting mixture was stirred at 90°C for 18 hours. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (2 x 100 mL) and the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 10 to 100% ethyl acetate in isohexane. The isolated material was dissolved in methanol, the solid removed and the filtrate purified by ion exchange chromatography using an SCX column with the desired product eluted from the column using 7M ammonia in methanol. The desired material was isolated as a white solid (2.2 g).

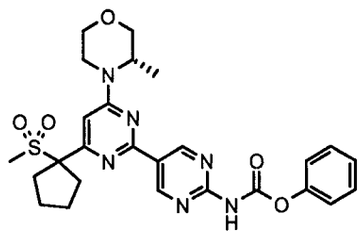
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.60 (2H, m), 1.78 - 1.85 (2H, m), 2.37 - 2.46 (2H, m), 2.65 - 2.78 (2H, m), 2.90 (3H, s), 3.18 (1H, dd), 3.49 (1H, td), 3.64 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.22 (1H, d), 4.56 (1H, s), 6.39 (2H, s), 6.50 (1H, d), 6.75 (1H, s), 8.25 (1H, d), 8.92 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 418; HPLC tR = 2.05 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine was described earlier.

The preparation of phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]carbamate is described below.

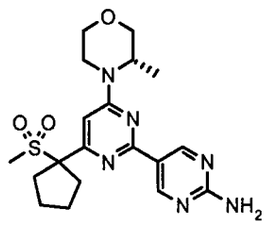
Phenyl *N*-[5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-yl]carbamate



Phenyl chloroformate (0.315 mL, 2.51 mmol) was added to 5-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-amine (700 mg, 1.67 mmol), sodium hydrogen carbonate (211 mg, 2.51 mmol) in dioxane (20 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 48 hours.The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was triturated with diethyl ether to give the desired material as a yellow solid (790 mg).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 539; HPLC tR = 2.52 min.

5-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidin-2-yl]pyrimidin-2-amine



Bis(triphenylphosphine)palladium(II) chloride (0.261 g, 0.37 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine (2 g, 5.56 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyrimidin-2-ylamine (1.843 g, 8.34 mmol) and aqueous sodium carbonate solution (11.12 mL, 22.23 mmol) in a mixture of DMF (6 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT. The resulting mixture was stirred at 90°C for 18 hours under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 3% methanol in ethyl acetate. The isolated material was triturated with a mixture of diethyl ether and isohexane and filtered to give the desired material as a cream solid (2.0 g).

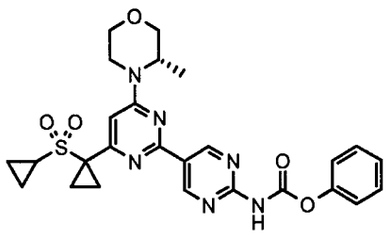
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.53 - 1.60 (2H, m), 1.76 - 1.83 (2H, m), 2.37 - 2.47 (2H, m), 2.64 - 2.76 (2H, m), 2.91 (3H, s), 3.15 - 3.23 (1H, m), 3.49 (1H, td), 3.63 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.24 (1H, d), 4.59 (1H, s), 6.82 (1H, s), 7.14 (2H, s), 9.09 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 419; HPLC tR = 1.83 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopentyl)pyrimidine was described earlier.

The preparation of phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate is described below.

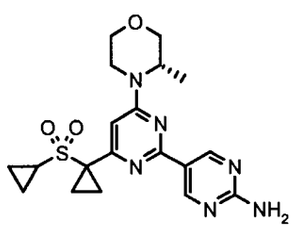
Phenyl *N*-[5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-yl]carbamate



Phenyl chloroformate (0.976 mL, 7.78 mmol) was added dropwise to 5-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-amine (2.16 g, 5.19 mmol), sodium hydrogen carbonate (0.654 g, 7.78 mmol) in dioxane (30 mL) cooled to 10°C under nitrogen. The resulting mixture was stirred at RT for 48 hours. The reaction mixture was diluted with ethyl acetate (150 mL), and washed with water (150 mL followed by 125 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was purified by trituration with diethyl ether to give the desired material as a yellow solid (2.5 g).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 537; HPLC tR = 2.33 min.

5-[4-(1-Cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]pyrimidin-2-amine



Bis(triphenylphosphine)palladium(II) chloride (0.381 g, 0.54 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.9 g, 8.10 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-pyrimidin-2-ylamine (2.69 g, 12.16 mmol) and aqueous sodium carbonate solution (4 mL, 8.00 mmol) in a mixture of DMF (18 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT .The resulting mixture was stirred at 90°C for 18 hours under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was

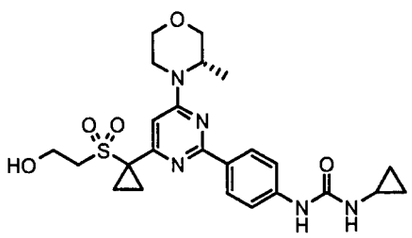
purified by flash silica chromatography, elution gradient 0 to 7% methanol in ethyl acetate. The isolated material was further purified by ion exchange chromatography using an SCX column, eluting with methanol followed by 7M ammonia in methanol, to give the desired material as a white solid (2.16 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.90 - 0.94 (2H, m), 0.99 - 1.04 (2H, m), 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.65 (2H, m), 2.95 - 3.02 (1H, m), 3.16 - 3.23 (1H, m), 3.47 (1H, td), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.18 (1H, s), 4.50 (1H, s), 6.85 (1H, s), 7.16 (2H, s), 9.05 (2H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 417; HPLC tR = 1.70 min.

The preparation of 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 15: 3-Cyclopropyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



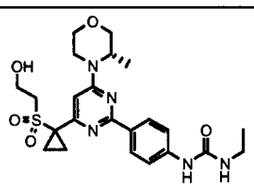
Bis (triphenylphosphine)palladium (II) chloride (6.84 mg, 0.00975 mmol) was added to 2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane (0.101 g, 0.19 mmol), 1-cyclopropyl-3-(4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (0.088 g, 0.29 mmol) and sodium carbonate (0.487 mL, 0.97 mmol) in a solvent mixture (18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol) at RT under nitrogen. The resulting suspension was stirred at 80°C for 17 hours. The solvent was removed and the residue partitioned between DCM and water. The organic layer was dried ($MgSO_4$), filtered and tetrabutylammonium fluoride (0.975 mL, 0.97 mmol) added to the filtrate and stirred for 2 hours. The mixture was washed with water, the organic layer concentrated *in vacuo* and purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (0.057 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.41-0.44 (2H, m), 0.63-0.68 (2H, m), 1.23-1.25 (3H, d), 1.53-1.56 (2H, m), 1.65-1.66 (2H, m), 2.55-2.59 (1H, m), 3.17-3.25 (1H, td), 3.56-3.52 (1H, td), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.88-3.89 (2H, m), 3.96-4.00 (1H, dd), 4.20-4.23 (1H, d), 4.56 (1H, bs), 5.03 (1H, bs), 6.45-6.46 (1H, d), 6.78 (1H, s), 7.50-7.52 (2H, d), 8.20-8.22 (2H, d), 8.56 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+ = 502; HPLC tR = 1.86min.

mTOR Kinase Assay (Echo): 0.00154μM

The compound below was prepared in an analogous fashion using the appropriate boronate.

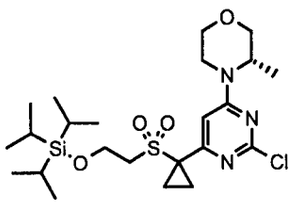
Example	Structure	NAME	LCMS MH+	Retention time (min)
15a		3-ethyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	490	1.82

Example 15a: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.05-1.09 (3H, t), 1.23-1.24 (3H, d), 1.53-1.56 (2H, m), 1.64-1.67 (2H, m), 3.10-3.17 (2H, m), 3.17-3.25 (1H, td), 3.45-3.52 (1H, td), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, t), 3.96-3.99 (1H, dd), 4.19-4.22 (1H, d), 4.55 (1H, bs), 5.03 (1H, bs), 6.17-6.20 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, q), 8.19-8.21 (2H, q), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.000591μM

The preparation of 2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane is described below.

2-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane

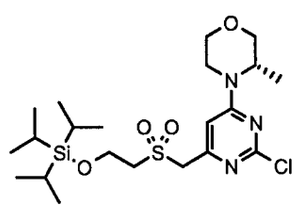


A 50% v/v aqueous sodium hydroxide solution (35 mL, 5.20 mmol) was added to 2-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethoxy-tri(propan-2-yl)silane (2.56 g, 5.20 mmol), 1,2-bibromoethane (1.345 mL, 15.61 mmol) and tetrabutylammonium bromide (0.168 g, 0.52 mmol) in toluene (100 mL) at RT. The resulting slurry was stirred at 60°C for 3 hours then the reaction mixture diluted with water and extracted sequentially with toluene and DCM. The organic layers were combined, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 10% ethyl acetate in DCM, to give the desired material as a colourless oil which solidified on standing (0.304 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.01-1.11 (21H, m), 1.30-1.32 (3H, d), 1.47-1.50 (2H, q), 1.77-1.80 (2H, q), 3.24-3.31 (1H, td), 3.40-3.44 (2H, t), 3.48-3.55 (1H, td), 3.64-3.68 (1H, td), 3.75-3.78 (1H, d), 3.97-4.01 (2H, m), 4.10-4.14 (2H, t), 4.32 (1H, bs), 6.86 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+=518; HPLC tR=3.86min.

2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethoxy-tri(propan-2-yl)silane



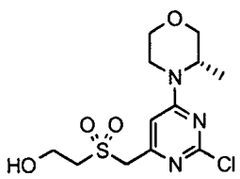
2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethanol (4.21 g, 12.53 mmol) was added to triisopropylsilyl chloride (3.22 mL, 15.03 mmol) and imidazole (2.046 g, 30.06 mmol) in DMF at RT. The resulting solution was stirred at RT overnight under a nitrogen atmosphere. The DMF was removed *in vacuo* and ethyl acetate added. The solids were removed by filtration and the filtrate concentrated *in vacuo* and purified by flash silica chromatography, eluting with 0 to 4% methanol in DCM. The isolated material was

again purified by chromatography on silica, eluting with 0 - 10% ethyl acetate in DCM, to give the desired material to as a clear gum (4.15 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.03-1.15 (21H, m), 1.27-1.29 (3H, d), 3.20-3.28 (1H, td), 3.37-3.40 (2H, m), 3.45-3.52 (1H, td), 3.61-3.65 (1H, dd), 3.71-3.74 (1H, d), 3.93-4.04 (2H, m), 4.15-4.18 (2H, t), 4.28 (3H, s), 6.50 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+ = 492; HPLC tR = 3.72min.

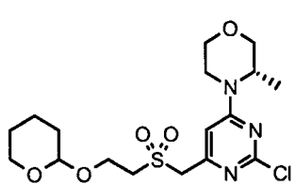
2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethanol



A solution of hydrogen peroxide (30%aqueous solution, 0.225 mL, 7.29 mmol) was added to a stirred solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-(oxan-2-yloxy)ethylsulfonylmethyl]pyrimidine (0.141 g, 0.36 mmol), sodium tungstate dihydrate (2.4 mg, 0.0073 mmol) in water (0.2 mL) and 2N sulfuric acid (0.011 mL) in 1,4-dioxane (1.4 mL) and methanol (1.4 mL) and the reaction stirred at 55°C for 4 hours. Water (50 mL) was added and the reaction cooled. 10% Sodium metabisulfite aqueous solution was added and the mixture extracted with DCM. The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired material as a opaque oil (0.198 g).

LCMS Spectrum: m/z (ES+) (M+H)+=336; HPLC tR=1.18 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[2-(oxan-2-yloxy)ethylsulfonylmethyl]pyrimidine



DIPEA (0.211 g, 1.63 mmol) was added dropwise to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.231 g, 0.65 mmol) and 2-(tetrahydro-2H-pyran-2-yloxy)ethanethiol (0.133 g, 0.82 mmol) in acetonitrile at RT. The resulting solution was stirred at RT for 1 hour. The solvent was removed and the residue partitioned between DCM

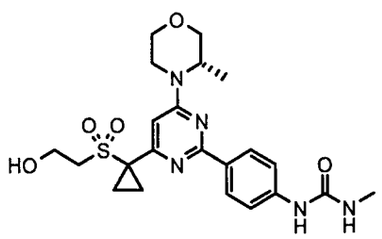
and water. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 2% methanol in DCM, to give the desired material as a colourless oil (0.141 g).

NMR Spectrum: ^{1}H NMR (400MHz, CDCl3) δ 1.24-1.26 (3H, d), 1.40-1.55 (4H, m), 1.60-1.67 (1H, m), 1.69-1.77 (1H, m), 2.68-2.71 (2H, t), 3.17-3.24 (1H, td), 3.41-3.47 (2H, m), 3.50-3.58 (1H, m), 3.59 (2H, s), 3.62-3.63 (1H, d), 3.69-3.72 (1H, d), 3.76-3.86 (2H, m), 3.91-3.95 (1H, dd), 3.97 (1H, bs), 4.25 (1H, bs), 4.52-4.54 (1H, t), 6.44 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+=386; HPLC tR=2.11 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier

Example 16: 1-[4-[4-[1-(2-Hydroxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



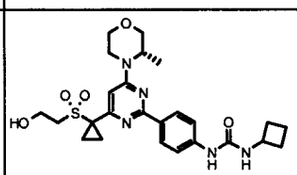
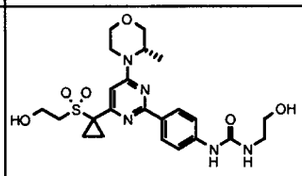
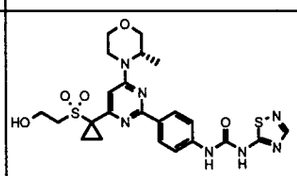
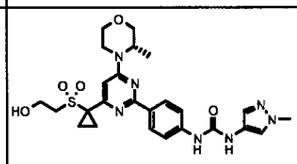
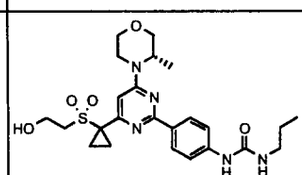
Methylamine (0.542 mL, 1.08 mmol) was added to (S)-phenyl 4- (4- (1- (2-hydroxyethylsulfonyl)cyclopropyl)-6- (3-methylmorpholino)pyrimidin-2-yl)phenylcarbamate (0.117 g, 0.22 mmol) and triethylamine (0.091 mL, 0.65 mmol) in DMF (3 mL) and the solution stirred at RT for 5 minutes. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (0.08 g).

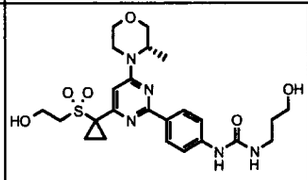
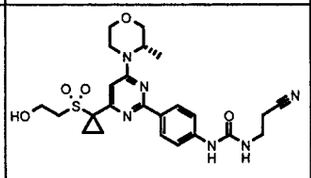
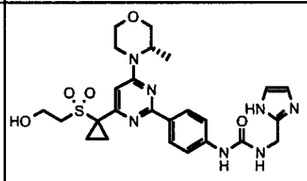
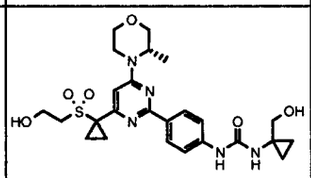
NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.22-1.24 (3H, d), 1.53-1.56 (2H, m), 1.64-1.66 (2H, m), 2.66-2.67 (3H, d), 3.16-3.24 (1H, td), 3.45-3.51 (1H, td), 3.61-3.67 (3H, m), 3.75-3.78 (1H, d), 3.86-3.91 (2H, q), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.56 (1H, bs), 5.06-5.09 (1H, t), 6.08-6.11 (1H, q), 6.77 (1H, s), 7.50-7.52 (2H, d), 8.18-8.21 (2H, d), 8.79 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+=476; HPLC tR=1.69 min.

mTOR Kinase Assay (Echo): 0.00142μM

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
16a		3-cyclobutyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	516	2.11
16b		3-(2-hydroxyethyl)-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	506	1.59
16c		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	546	1.24
16d		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	542	1.79
16e		3-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	504	1.99

Example	Structure	NAME	LCMS MH+	Retention time (min)
16f		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	520	1.61
16g		3-(2-cyanoethyl)-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	515	1.77
16h		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	542	1.64
16i		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea	532	1.66

Example 16a: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.24(3H, d), 1.53-1.69(7H, m), 1.82-1.92(2H, m), 2.18-2.25(2H, m), 3.17-3.24(1H, td), 3.45-3.52(1H, td), 3.63-3.66(3H, m), 3.75-3.78(1H, d), 3.86-3.91(2H, m), 3.96-3.99(1H, dd), 4.20-4.22(1H, d), 4.56(1H, bs), 5.01-5.04(1H, t), 6.46-6.48(1H, d), 6.78(1H, s), 7.47-7.49(2H, d), 8.19-8.21(2H, d), 8.57(1H, s). mTOR Kinase Assay (Echo): 0.0101μM

Example 16b: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.24(3H, d), 1.53-1.56(2H, m), 1.64-1.67(2H, m), 3.16-3.24(3H, m), 3.45-3.52(3H, m), 3.62-3.66(3H, m), 3.75-3.78(1H, d), 3.87-3.91(2H, q), 3.96-3.99(1H, dd), 4.19-4.23(1H, d), 4.56(1H, bs), 4.72-4.75(1H, t), 5.01-5.04(1H, t), 6.25-6.27(1H, t), 6.77(1H, s), 7.48-7.51(2H, d), 8.20-8.22(2H, d), 8.81(1H, s).

mTOR Kinase Assay (Echo): 0.00577μM

Example 16c: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24-1.26(3H, d), 1.55-1.58(2H, m), 1.66-1.68(2H, m), 3.19-3.26(1H, td), 3.47-3.53(1H, td), 3.63-3.67(3H, m), 3.77-3.79(1H, d), 3.88-3.93(2H, m), 3.97-4.01(1H, dd), 4.22-4.24(1H, d), 4.58(1H, bs), 5.02-5.05(1H, t), 6.83(1H, s), 7.62-7.65(2H, d), 8.31-8.33(2H, d), 8.38(1H, s), 9.43(1H, s), 11.37(1H, bs).

mTOR Kinase Assay (Echo): 0.0016μM

Example 16d: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.25(3H, d), 1.54-1.57(2H, m), 1.65-1.67(2H, m), 3.17-3.25(1H, td), 3.46-3.53(1H, td), 3.62-3.67(3H, m), 3.76-3.79(1H, d), 3.79(3H, s), 3.87-3.92(2H, m), 3.97-4.00(1H, dd), 4.20-4.23(1H, d), 4.56(1H, bs), 5.02-5.05(1H, t), 6.79(1H, s), 7.39-7.40(1H, s), 7.54-7.56(2H, d), 7.76(1H, s), 8.23-8.25(2H, d), 8.39(1H, s), 8.84(1H, s).

mTOR Kinase Assay (Echo): 0.00364μM

Example 16e: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87-0.91 (3H, t), 1.23-1.25 (3H, d), 1.42-1.51 (2H, m), 1.53-1.56 (2H, m), 1.64-1.67 (2H, m), 3.05-3.09 (2H, q), 3.17-3.25 (1H, td), 3.46-3.52 (1H, td), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, q), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.56 (1H, bs), 5.01-5.04 (1H, t), 6.19-6.22 (1H, t), 6.78 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.65 (1H, s)

Example 16f: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.53-1.57 (2H, m), 1.59-1.62 (2H, t), 1.64-1.67 (2H, m), 3.15-3.24 (3H, m), 3.46-3.50 (3H, m), 3.63-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, q), 3.96-3.99 (1H, dd), 4.19-4.23 (1H, d), 4.47-4.49 (1H, t), 4.55 (1H, bs), 5.01-5.04 (1H, t), 6.20-6.23 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.72 (1H, s).

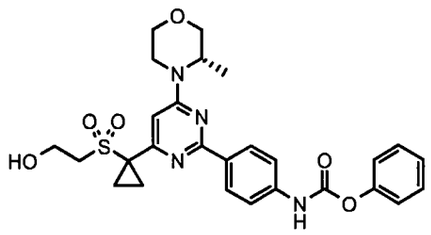
Example 16g: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.54-1.56 (2H, m), 1.65-1.67 (2H, m), 2.69-2.72 (2H, t), 3.17-3.25 (1H, td), 3.35-3.40 (2H, q), 3.46-3.52 (1H, td), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, q), 3.96-4.00 (1H, dd), 4.20-4.23 (1H, d), 4.56 (1H, bs), 5.01-5.04 (1H, t), 6.52-6.55 (1H, t), 6.78 (1H, s), 7.51-7.53 (2H, d), 8.21-8.23 (2H, d), 8.93 (1H, s).

Example 16h: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.54-1.56 (2H, m), 1.64-1.67 (2H, m), 3.17-3.25 (1H, td), 3.46-3.52 (1H, td), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, q), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.32-4.34 (2H, d), 4.56 (1H, bs), 5.01-5.04 (1H, t), 6.62-6.64 (1H, t), 6.78 (1H, s), 6.93-6.96 (2H, bs), 7.51-7.53 (2H, d), 8.21-8.23 (2H, d), 8.94 (1H, s), 11.84 (1H, s).

Example 16i: ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.64-0.67 (2H, m), 0.70-0.73 (2H, m), 1.23-1.24 (3H, d), 1.53-1.56 (2H, m), 1.64-1.67 (2H, m), 3.17-3.25 (1H, td), 3.44-3.52 (3H, m), 3.62-3.66 (3H, m), 3.75-3.78 (1H, d), 3.87-3.91 (2H, q), 3.96-4.00 (1H, dd), 4.19-4.23 (1H, d), 4.55 (1H, bs), 4.84 (1H, bs), 5.01-5.04 (1H, t), 6.58 (1H, s), 6.78 (1H, s), 7.47-7.49 (2H, d), 8.20-8.22 (2H, d), 8.68 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

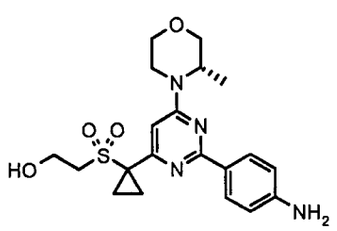
Phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.043 mL, 0.34 mmol) was added to 2-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethanol (0.144 g, 0.34 mmol) and sodium bicarbonate (0.043 g, 0.52 mmol) in dioxane (20 mL) and the resulting slurry stirred at RT overnight. The reaction mixture was partitioned between DCM and water. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash silica chromatography, eluting with 0 to 40% ethyl acetate in DCM, to give the desired material as a beige solid (0.117 g).

LCMS Spectrum: m/z (ES+) (M+H)+=539; HPLC tR=2.50 min.

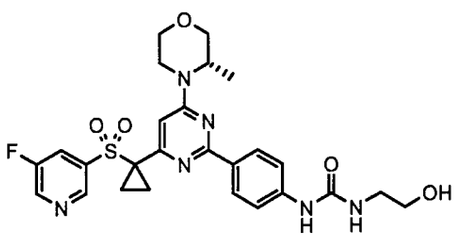
2-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethanol



Bis(triphenylphosphine)palladium (II) chloride (0.012 g, 0.02 mmol) was added to 2-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethoxy-tri(propan-2-yl)silane (0.178 g, 0.34 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.113 g, 0.52 mmol) and an aqueous solution of sodium carbonate (0.859 mL, 1.72 mmol) in a mixture of solvents (18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol). The resulting solution was stirred at 80°C for 4 hours, the solvent removed and the residue partitioned between DCM and water. The organic layer was separated and tetrabutylammonium fluoride (1.718 mL, 1.72 mmol) added. The reaction was allowed to stir for several hours and then additional tetrabutylammonium fluoride (2 mL) was added and the reaction allowed to stir for 2 days. The mixture was washed with a saturated aqueous solution of ammonium chloride, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired material which was used without further purification.

LCMS Spectrum: m/z (ES+) (M+H)+ = 419; HPLC tR = 1.83 min.

Example 17: 1-[4-[4-[1-(5-Fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea



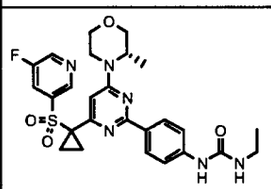
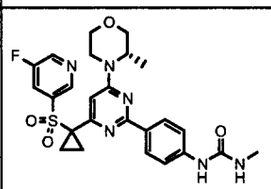
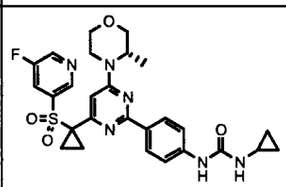
To a solution of phenyl *N*-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (140 mg, 0.24 mmol) in DMF (2 mL) was added triethylamine (0.099 mL, 0.71 mmol) followed by ethanolamine (72mg, 1.19 mmol) and the reaction heated at 50°C for 2 hours. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (55 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.64 - 1.67 (2H, m), 1.99 - 2.02 (2H, m), 3.15 - 3.20 (3H, m), 3.44 - 3.49 (2H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.18 (1H, d), 4.50 (1H, s), 4.73 (1H, t), 6.29 (1H, t), 6.70 (1H, s), 7.38 (2H, d), 7.74 (2H, d), 8.18 - 8.21 (1H, m), 8.81 (2H, d), 8.95 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 557; HPLC tR = 1.82 min.

mTOR Kinase Assay (Echo): 0.00116μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
17a		3-ethyl-1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	541	1.78
17b		1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	527	1.99
17c		3-cyclopropyl-1-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	553	2.13

Example 17a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 1.64 - 1.67 (2H, m), 1.99 - 2.02 (2H, m), 3.09 - 3.21 (3H, m), 3.47 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.18 (1H, d), 4.50 (1H, s), 6.19 (1H, t), 6.70 (1H, s), 7.38 (2H, d), 7.74 (2H, d), 8.18 - 8.19 (1H, m), 8.20 - 8.21 (1H, m), 8.68 (1H, s), 8.81 (1H, s), 8.95 (1H, d).

mTOR Kinase Assay (Echo): 0.000942μM

Example 17b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.64 - 1.67 (2H, m), 1.99 - 2.02 (2H, m), 2.66 (3H, d), 3.14 - 3.21 (1H, m), 3.47 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.18 (1H, d), 4.50 (1H, s), 6.09 - 6.12 (1H, m), 6.70 (1H, s), 7.39 (2H, d), 7.74 (2H, d), 8.18 - 8.22 (1H, m), 8.79 (2H, d), 8.94 (1H, d).

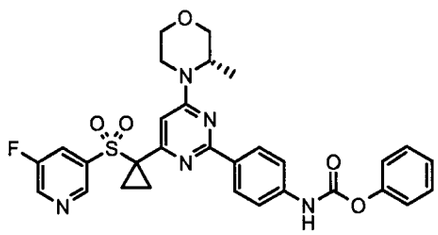
mTOR Kinase Assay (Echo): 0.000584μM

Example 17c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.41 - 0.44 (2H, m), 0.60 - 0.67 (2H, m), 1.20 (3H, d), 1.65 - 1.66 (2H, m), 1.99 - 2.02 (2H, m), 3.15 - 3.21 (2H, m), 3.42 - 3.49 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.18 (1H, d), 4.50 (1H, s), 6.60 (1H, s), 6.70 (1H, s), 7.40 (2H, d), 7.74 (2H, d), 8.18 - 8.22 (1H, m), 8.69 (1H, s), 8.81 (1H, s), 8.95 (1H, d).

mTOR Kinase Assay (Echo): 0.00179μM

The preparation of phenyl *N*-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

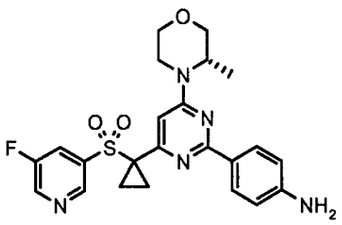


To a solution of 4-[4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (220 mg, 0.47 mmol) in 1,4-dioxane (5 mL) was added sodium bicarbonate (59 mg, 0.70 mmol) and phenyl chloroformate (0.059 mL, 0.47 mmol) and the reaction stirred at RT for 2 hours. The reaction mixture was diluted with DCM (10 mL), and washed with water (10 mL), the organic layer dried ($MgSO_4$), filtered and evaporated. The crude solid was triturated with diethyl ether to give a solid which was collected by filtration and dried under vacuum to give the desired product as a white solid (280 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.65 - 1.69 (2H, m), 2.00 - 2.03 (2H, m), 3.15 - 3.22 (1H, m), 3.44 - 3.52 (1H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.21 (1H, d), 4.51 (1H, s), 6.75 (1H, s), 7.24 - 7.27 (3H, m), 7.45 (2H, t), 7.53 (2H, d), 7.85 (2H, d), 8.20 - 8.23 (1H, m), 8.81 (1H, s), 8.94 (1H, d), 10.40 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 590; HPLC tR = 2.96 min.

4-[4-[1-(5-Fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

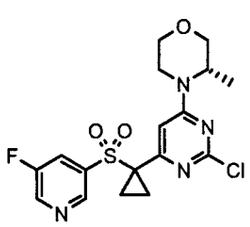


To a solution of 2-chloro-4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (700 mg, 1.70 mmol) in DMF (0.48 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL) was added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (483mg, 2.2 mmol), sodium carbonate (2.5 mL, 5.09 mmol) and dichlorobis(triphenylphosphine)palladium(II) (59.5 mg, 0.08 mmol) and the suspension heated at 95°C for 2 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired material as a cream solid (160 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.61 - 1.65 (2H, m), 1.96 - 2.00 (2H, m), 3.11 - 3.18 (1H, m), 3.42 - 3.49 (1H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, d), 4.46 (1H, s), 5.53 (2H, s), 6.49 (2H, d), 6.60 (1H, s), 7.57 (2H, d), 8.16 - 8.20 (1H, m), 8.80 - 8.80 (1H, m), 8.93 (1H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 470; HPLC tR = 2.30 min.

2-Chloro-4-[1-(5-fluoropyridin-3-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



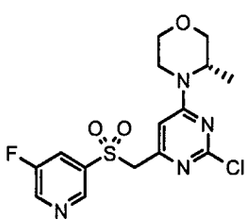
2-Chloro-4-[(5-fluoropyridin-3-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (950 mg, 2.40 mmol) was dissolved in toluene (15 mL) and 10N sodium hydroxide solution (2.45 mL, 24.5 mmol) added, followed by 1,2-dibromoethane (0.42 mL,

4.91 mmol). The reaction was stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine solution (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired product as a white solid (700 mg,).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.61 - 1.63 (2H, m), 1.94 - 1.97 (2H, m), 3.16 (1H, dt), 3.40 (1H, dt), 3.55 (1H, dd), 3.70 (1H, d), 3.91 (1H, dd), 4.00 (1H, s), 4.33 (1H, s), 6.78 (1H, s), 8.21 (1H, dt), 8.79 (1H, t), 8.96 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 413, HPLC tR = 2.14 min

2-Chloro-4-[(5-fluoropyridin-3-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

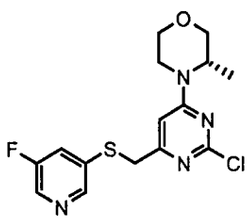


3-Chloroperoxybenzoic acid (2.107 g, 9.16 mmol) was added portion-wise to 2-chloro-4-[(5-fluoropyridin-3-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.3 g, 3.66 mmol), in DCM (18.32 mL) and the reaction stirred at RT for 2 hours. The reaction mixture was washed with a saturated aqueous solution of sodium hydrogen carbonate (50 mL) and the organic layer dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a white solid (0.940 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 3.16 - 3.23 (1H, m), 3.44 (1H, dt), 3.59 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 3.97 (1H, s), 4.22 (1H, s), 4.84 (2H, s), 6.84 (1H, s), 8.21 (1H, dt), 8.80 (1H, t), 8.99 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 387, HPLC tR = 1.86 min

2-Chloro-4-[(5-fluoropyridin-3-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

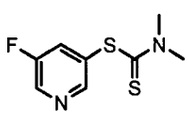


Potassium hydroxide (1.235 g, 22.01 mmol) was added to (5-fluoropyridin-3-yl) dimethylaminomethanedithioate (1.19 g, 5.50 mmol) in ethanol (27.5 mL) at RT. The resulting solution was heated at 65°C for 4 hours The reaction was cooled and 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.72 g, 7.70 mmol) added. The reaction mixture was then stirred at RT for 4 hours. Water (50 mL) was added and the reaction mixture extracted with DCM (2 x 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated to give crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white waxy solid (1.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 3.11 - 3.18 (1H, m), 3.37 - 3.44 (1H, m), 3.56 (1H, dd), 3.70 (1H, d), 3.91 (1H, dd), 3.95 (1H, s), 4.21 (3H, $mult$), 6.81 (1H, s), 7.89 (1H, dt), 8.40 - 8.42 (2H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ 355, HPLC tR = 2.12 min

(5-Fluoropyridin-3-yl) dimethylaminomethanedithioate



3-Bromo-5-fluoropyridine (2.26g, 12.84 mmol) was added portion-wise to isopropylmagnesium chloride - lithium chloride complex (14% in THF, 13.32 mL, 12.84 mmol) at 0°C over a period of 2 minutes under a nitrogen atmosphere. The resulting solution was warmed to RT over a period of 2 hours then cooled to 0°C and tetramethylthiuram disulfide (3.09 g, 12.84 mmol) in DCM (12.84 mL) added. The reaction was warmed to RT and stirred for 3 hours. The reaction was poured into a saturated aqueous solution of ammonium chloroid (50 mL) and the aqueous layer extracted with DCM (2 x 100mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude

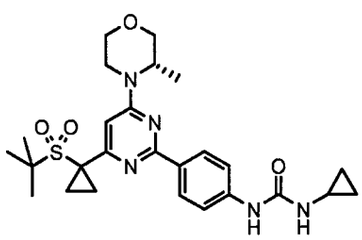
product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a cream waxy solid (1.69 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.48 (3H, s), 3.52 (3H, s), 7.89 (1H, ddd), 8.41 (1H, t), 8.71 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 217, HPLC tR = 1.80 min

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 18: 1-[4-[4-(1-tert-Butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea



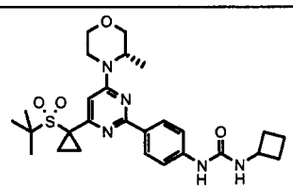
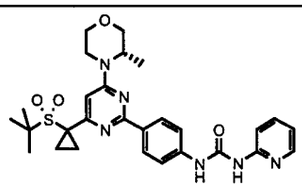
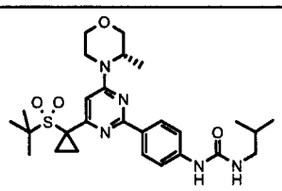
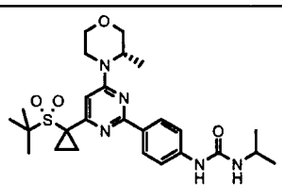
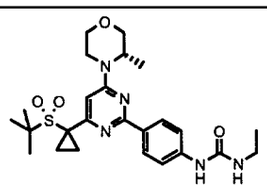
Cyclopropylamine (57 mg, 1.0 mmol) was added to phenyl *N*-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.22 mmol) and triethylamine (0.20 mL, 1.4 mmol) in DMF (1 mL). The reaction mixture was allowed to stand at RT for 4 days. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to afford the desired material as a colourless solid (63 mg).

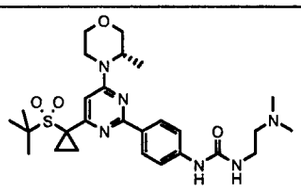
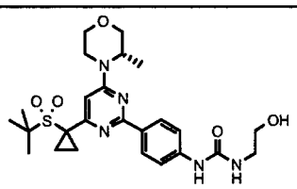
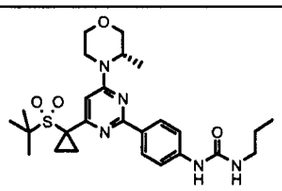
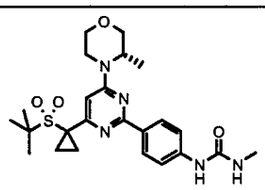
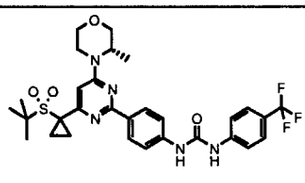
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.21 –1.27 (12H, m), 1.47 - 1.53 (1H, m), 1.62 - 1.69 (3H, m), 2.54 – 2.60 (1H, m), 3.15 – 3.24 (1H, m), 3.46 – 4.54 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.95 - 4.02 (1H, d), 4.18 (1H, d), 4.43 (1H, br, s), 6.44 (1H, d), 6.97 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.56 (1H, s).

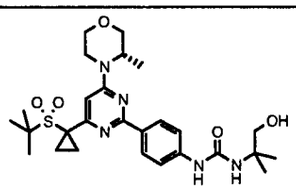
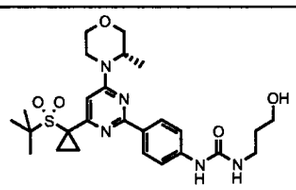
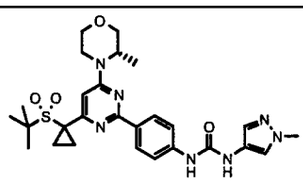
LCMS Spectrum: m/z (ESI+)(M+H)+ = 514; HPLC tR = 2.39 min.

mTOR Kinase Assay (Echo): 0.00135μM

The following compounds were made in an analogous fashion from phenyl *N*-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamateand the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
18a		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea	528	2.62
18b		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	551	2.83
18c		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	530	2.72
18d		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	516	2.54
18e		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	502	2.38

Example	Structure	NAME	LCMS MH+	Retention time (min)
18f		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	545	2.33
18g		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	518	1.98
18h		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propylurea	516	2.56
18i		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	488	2.2
18j		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	618	3.29

Example	Structure	NAME	LCMS MH+	Retention time (min)
18k		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	546	2.32
18l		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	532	2.05
18m		1-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	554	2.22

Example 18a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 – 1.27 (12H, m), 1.47 – 1.53 (1H, m), 1.59 - 1.68 (3H, m), 1.81 – 1.91 (2H, m), 2.17 – 2.26 (2H, m), 3.15 – 3.23 (1H, m), 3.45 – 3.54 (1H, m), 3.62 – 3.68 (1H, m), 3.77 (1H, d), 3.95 – 4.02 (1H, m), 4.10 - 4.24 (2H, m), 4.42 (1H, br, s), 6.47 (1H, d), 6.97 (1H, s), 7.48 (2H, d), 8.22 (2H, d), 8.57 (1H, s).

mTOR Kinase Assay (Echo): 0.00967μM

Example 18b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.25 (12H, m), 1.49 - 1.54 (1H, m), 1.63 - 1.73 (3H, m), 3.16 - 3.25 (1H, m), 3.48 - 3.54 (1H, m), 3.64 - 3.68 (1H, m), 3.78 (1H, d), 3.98 - 4.01 (1H, m), 4.20 (1H, d), 4.43 (1H, br, s), 7.00 (1H, s), 7.03 - 7.06 (1H, m), 7.58 (1H, d), 7.65 (2H, d), 7.78 (1H, t), 8.29 – 8.34 (3H, m), 9.45 (1H, s), 10.57 (1H, s).

mTOR Kinase Assay (Echo): 0.0147μM

Example 18c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.90 (6H, d), 1.22 - 1.25 (12H, m), 1.47 - 1.53 (1H, m), 1.62 - 1.75 (4H, m), 2.95 (2H, t), 3.16 - 3.23 (1H, m), 3.47 - 3.53 (1H, m), 3.63

- 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.18 (1H, d), 4.42 (1H, br, s), 6.25 (1H, t), 6.97 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.66 (1H, s).

mTOR Kinase Assay (Echo): 0.032μM

Example 18d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.12 (6H, d), 1.21 - 1.26 (12H, m), 1.45 – 1.53 (1H, m), 1.62 - 1.71 (3H, m), 3.13 - 3.25 (1H, m), 3.44 - 3.53 (1H, m), 3.62 - 3.67 (1H, m), 3.73 - 3.82 (2H, m), 3.95 - 4.02 (1H, m), 4.18 (1H, d), 4.42 (1H, br, s), 6.07 (1H, d), 6.97 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.0151μM

Example 18e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.25 (9H, s), 1.44 – 1.53 (1H, m), 1.60 – 1.71 (3H, m), 3.08 – 3.25 (3H, m), 3.49 (1H, t), 3.65 (1H, d), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.18 (1H, d), 4.43 (1H, br, s), 6.17 (1H, t), 6.97 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.000654μM

Example 18f: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 - 1.28 (12H, m), 1.47 - 1.54 (1H, m), 1.62 - 1.69 (3H, m), 2.19 (6H, s), 2.34 (2H, t), 3.14 - 3.24 (3H, m), 3.45 - 3.53 (1H, m), 3.62 - 3.67 (1H, m), 3.77 (1H, d), 3.95 - 4.00 (1H, m), 4.18 (1H, d), 4.42 (1H, br, s), 6.17 (1H, t), 6.97 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.91 (1H, s).

mTOR Kinase Assay (Echo): 0.12μM

Example 18g: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.22 - 1.25 (12H, m), 1.48 - 1.52 (1H, m), 1.62 - 1.69 (3H, m), 3.16 - 3.23 (3H, m), 3.45 - 3.53 (3H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.97 - 4.00 (1H, m), 4.18 (1H, d), 4.43 (1H, br, s), 4.74 (1H, t), 6.26 (1H, t), 6.97 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.82 (1H, s).

mTOR Kinase Assay (Echo): 0.00123μM

Example 18h: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.90 (3H, t), 1.19 – 1.28 (12H, m), 1.42 – 1.54 (3H, m), 1.61 - 1.69 (3H, m), 3.07 (2H, q), 3.13 - 3.23 (1H, m), 3.45 - 3.53 (1H, m), 3.61 - 3.68 (1H, m), 3.77 (1H, d), 3.94 – 4.01 (1H, m), 4.18 (1H, d), 4.42 (1H, br, s), 6.21 (1H, t), 6.97 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.00664μM

Example 18i: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.25 (9H, s), 1.45 – 1.55 (1H, m), 1.60 – 1.69 (3H, m), 2.67 (3H, d), 3.14 - 3.23 (1H, m), 3.50 (1H, t), 3.65 (1H, d), 3.77 (1H, d), 3.94 - 3.99 (1H, m), 4.18 (1H, d), 4.43 (1H, br, s), 6.08 (1H, d), 6.97 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.00555μM

Example 18j: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.35 (9H, s), 1.50 – 1.71 (2H, m), 1.81 - 1.91 (2H, m), 3.23 - 3.33 (1H, m), 3.53 - 3.62 (1H, m), 3.68 - 3.74 (1H, m), 3.81 (1H, d), 3.98 - 4.05 (1H, m), 4.17 (1H, d), 4.42 (1H, br, s), 7.03 (1H, s), 7.23 (1H, s), 7.28 (1H, s), 7.48 (2H, d), 7.52 - 7.55 (4H, m), 8.38 (2H, d).

mTOR Kinase Assay (Echo): 0.0303μM

Example 18k: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 – 1.27 (18H, m), 1.48 - 1.52 (1H, m), 1.62 - 1.69 (3H, m), 3.14 - 3.23 (1H, m), 3.40 (2H, d), 3.45 - 3.53 (1H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.18 (1H, d), 4.41 (1H, br, s), 4.96 (1H, t), 6.01 (1H, s), 6.97 (1H, s), 7.46 (2H, d), 8.22 (2H, d), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.0113μM

Example 18l: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.22 - 1.25 (12H, m), 1.48 - 1.52 (1H, m), 1.57 - 1.68 (5H, m), 3.15 - 3.23 (3H, m), 3.43 – 3.54 (3H, m), 3.63 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.18 (1H, d), 4.43 (1H, br, s), 4.49 (1H, t), 6.21 (1H, t), 6.97 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.73 (1H, s).

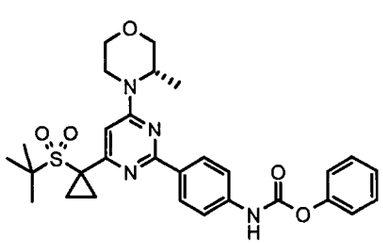
mTOR Kinase Assay (Echo): 0.0102μM

Example 18m: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 – 1.29 (12H, m), 1.48 – 1.55 (1H, m), 1.61 – 1.71 (3H, m), 3.16 - 3.25 (1H, m), 3.49 (1H, t), 3.66 (1H, d), 3.74 – 3.83 (4H, m), 3.99 (1H, d), 4.19 (1H, d), 4.43 (1H, br, s), 6.99 (1H, s), 7.39 (1H, s), 7.55 (2H, d), 7.77 (1H, s), 8.27 (2H, d), 8.39 (1H, s), 8.85 (1H, s).

mTOR Kinase Assay (Echo): 0.00315μM

The preparation of phenyl *N*-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

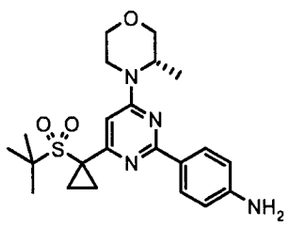


Phenyl chloroformate (0.809 mL, 6.44 mmol) was added to 4-[4-(1-tert-butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2.52g, 5.85 mmol) and sodium hydrogen carbonate (0.738 g, 8.78 mmol) in dioxane (45 mL) at RT. The mixture was stirred at RT for 2 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% – 100% ethyl acetate in isohexane, to give the desired material as a near colourless solid (2.99 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.31 - 1.34 (12H, m), 1.48 - 4.58 (1H, m), 1.62 - 1.70 (1H, m), 1.80 - 1.89 (2H, m), 3.31 (1H, dt), 3.60 (1H, dt), 3.75 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.20 (1H, d), 4.45 (1H, br), 7.06 - 7.11 (2H, m), 7.19 - 7.28 (3H, m), 7.41 (2H, t), 7.54 (2H, d), 8.40 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 551; HPLC tR = 3.06 min.

4-[4-(1-tert-Butylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

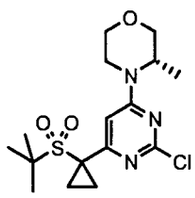


Dichlorobis(triphenylphosphine)-palladium(II) (0.185 g, 0.26 mmol) was added to 4-(1-tert-butylsulfonylcyclopropyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.97 g, 5.27 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.501 g, 6.85 mmol) and 2M aqueous sodium carbonate (9.48 mL, 18.97 mmol) in DMF (11 mL), DME (11 mL), ethanol (11 mL) and water (27.5 mL) at RT under nitrogen. The reaction was purged with nitrogen for 15 minutes and the resulting mixture was stirred at 80°C for 16 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 25% - 100% ethyl acetate in isohexane, to give the desired material as a yellow solid (2.24 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.32 (9H, s), 1.44 - 1.55 (1H, m), 1.60 - 1.68 (1H, m), 1.77 - 1.86 (2H, m), 3.28 (1H, dt), 3.59 (1H, dt), 3.74 (1H, dd), 3.81 (1H, d), 3.90 (2H, s), 4.03 (1H, dd), 4.18 (1H, d), 4.44 (1H, br), 6.71 (2H, d), 6.99 (1H, s), 8.24 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 431; HPLC tR = 2.43 min.

4-(1-tert-Butylsulfonylcyclopropyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

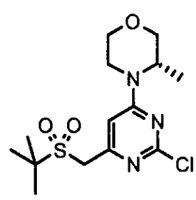


1,2-Dibromoethane (0.349 mL, 15.40 mmol) was added to 4-(tert-butylsulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.68 g, 7.7 mmol) in toluene (40 mL) followed by tetrabutylammonium bromide (0.248 g, 0.77 mmol) and sodium hydroxide concentrate (7.70 mL, 77 mmol). The reaction mixture was vigorously stirred and heated at 60°C for 1 hour. The reaction mixture was cooled and diluted with ethyl acetate and washed with water. The organic solution was concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 0 to 50% ethyl acetate in DCM, to give the desired material as a colourless solid (1.97 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.20 - 1.35 (12H, m), 1.46 - 1.50 (1H, m), 1.52 - 1.61 (1H, m), 1.77 - 1.86 (2H, m), 3.26 (1H, dt), 3.54 (1H, dt), 3.68 (1H, dd), 3.78 (1H, d), 3.98 - 4.08 (2H, m), 4.29 (1H, br, s), 7.14 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 374; HPLC tR = 2.34 min.

4-(tert-Butylsulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



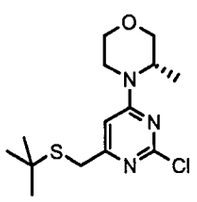
A solution of hydrogen peroxide (35% aqueous solution, 9.48 mL, 107.30 mmol) was added dropwise to a stirred solution of 4-(tert-butylsulfanylmethyl)-2-chloro-6-[(3*S*)-3-

methylmorpholin-4-yl]pyrimidine (9.82 g, 31.1 mmol), sodium tungstate dihydrate (0.205 g, 0.62 mmol) and sulfuric acid (0.6 mL, 1M, 0.6 mmol) in dioxane (80 mL). The mixture was heated at 55°C for 1 hour then diluted with water and cooled. A solution of sodium metabisulfite (10% w/v) was added to destroy remaining peroxide. The solution was extracted with DCM, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired material as a near colourless gum (9.34 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.44 (9H, s), 3.29 (1H, dt), 3.54 (1H, dt), 3.69 (1H, dd), 3.78 (1H, d), 3.97 - 4.13 (2H, m), 4.21 (2H, s), 4.30 (1H, br, s), 6.71 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 348; HPLC tR = 1.82 min.

4-(tert-Butylsulfanylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



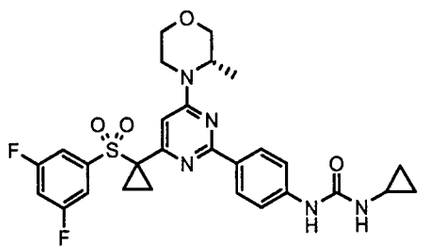
DIPEA (8.61 mL, 49.78 mmol) was added to 2-methyl-2-propanethiol (4.21 mL, 37.33 mmol), in DMF (55 mL) at RT under nitrogen. The resulting solution was stirred at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (11.00 g, 31.11 mmol) was added to the reaction mixture in one portion. The mixture was stirred for 4 hours at RT then at 60°C for 1.5 hours before being partitioned between ethyl acetate and water. The organic layer was washed with additional water and then dried ($MgSO_4$), filtered and evaporated to give the desired material as a yellow gum (10.02 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.34 (9H, s), 3.27 (1H, dt), 3.54 (1H, dt), 3.66 - 3.71 (3H, m), 3.78 (1H, d), 3.97 - 4.07 (2H, m), 4.31 (1H, br, s), 6.56 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 316, 318; HPLC tR = 2.61 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 19: 3-Cyclopropyl-1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



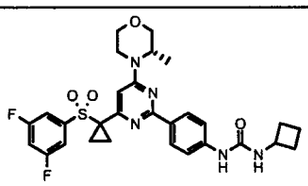
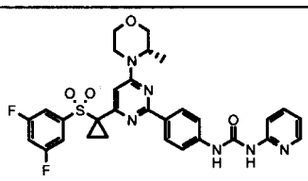
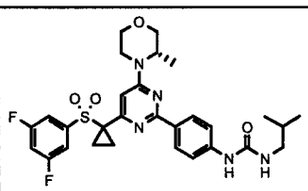
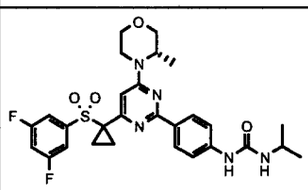
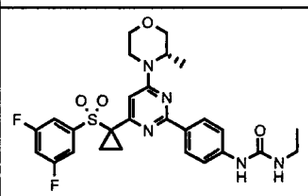
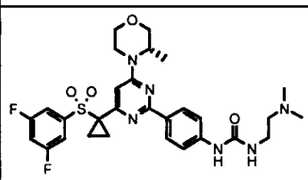
Phenyl *N*-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.22 mmol) was added to a mixture of cyclopropylamine (59 mg, 1.03 mmol) and triethylamine (0.2 mL, 1.49 mmol) in DMF (1 mL) at RT. The reaction mixture was allowed to stand at RT for 65 hours. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a colourless solid (55 mg).

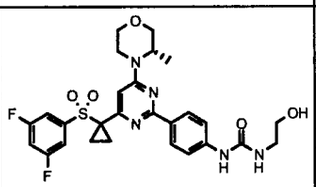
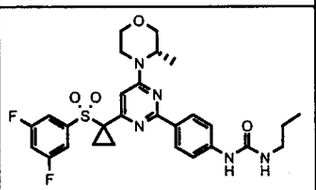
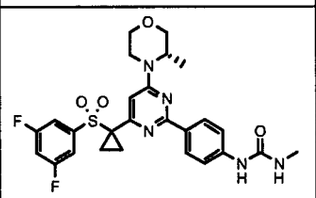
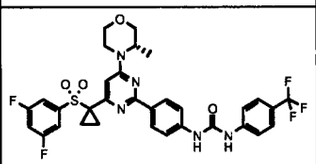
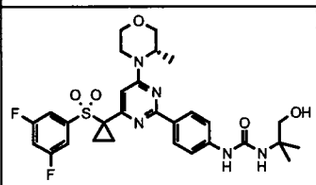
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.41 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.20 (3H, d), 1.62 -1.69 (2H, m), 1.96 - 2.00 (2H, m), 2.53 - 2.59 (1H, m), 3.13 - 3.23 (1H, m), 3.42 - 3.50 (1H, m), 3.59 - 3.63 (1H, m), 3.75 (1H, d), 3.94 - 4.00 (1H, m), 4.18 (1H, d), 4.48 (1H, br, s), 6.42 (1H, d), 6.67 (1H, s), 7.42 (2H, d), 7.54 - 7.59 (2H, m), 7.70 - 7.76 (1H, m), 7.82 (2H, d), 8.53 (1H, s)

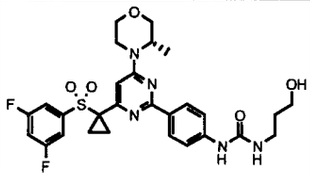
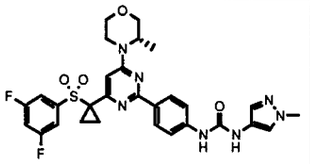
LCMS Spectrum: m/z (ESI+)(M+H)+ = 572; HPLC tR = 2.72 min.

mTOR Kinase Assay (Echo): 0.00131μM

The following compounds were made in an analogous fashion from phenyl *N*-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
19a		3-cyclobutyl-1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	584	2.86
19b		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	607	3.03
19c		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	586	2.94
19d		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	572	2.79
19e		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	558	2.53
19f		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	601	2.5

Example	Structure	NAME	LCMS MH+	Retention time (min)
19g		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	574	2.17
19h		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propylurea	572	2.72
19i		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	544	2.37
19j		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	674	3.27
19k		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	602	2.48

Example	Structure	NAME	LCMS MH+	Retention time (min)
19l		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	588	2.23
19m		1-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	610	2.39

Example 19a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.58 - 1.70 (4H, m), 1.80 - 1.90 (2H, m), 1.95 - 2.02 (2H, m), 2.16 - 2.25 (2H, m), 3.10 - 3.20 (1H, m), 3.40 - 3.48 (1H, m), 3.58 - 3.62 (1H, m), 3.75 (1H, d), 3.92 - 3.98 (1H, m), 4.10 - 4.20 (2H, m), 4.48 (1H, br, s), 6.45 (1H, d), 6.67 (1H, s), 7.39 (2H, d), 7.55 - 7.57 (2H, m), 7.71 - 7.75 (1H, m), 7.82 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.00425μM

Example 19b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.62 - 1.71 (2H, m), 1.96 - 2.03 (2H, m), 3.13 - 3.23 (1H, m), 3.42 - 3.51 (1H, m), 3.60 - 3.65 (1H, m), 3.76 (1H, d), 3.93 - 3.99 (1H, m), 4.19 (1H, d), 4.50 (1H, br, s), 6.71 (1H, s), 7.03 - 7.06 (1H, m), 7.51 - 7.59 (5H, m), 7.70 - 7.80 (2H, m), 7.92 (2H, d), 8.31 (1H, d), 9.44 (1H, s), 10.55 (1H, s).

mTOR Kinase Assay (Echo): 0.00119μM

Example 19c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.89 (3H, s), 0.90 (3H, s), 1.20 (3H, d), 1.63 - 1.75 (3H, m), 1.94 - 2.00 (2H, m), 2.95 (2H, t), 3.11 - 3.21 (1H, m), 3.41 - 3.50 (1H, m), 3.57 - 3.63 (1H, m), 3.75 (1H, d), 3.92 - 3.98 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 6.23 (1H, t), 6.67 (1H, s), 7.40 (2H, d), 7.52 - 7.59 (2H, m), 7.68 - 7.76 (1H, m), 7.83 (2H, d), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.0214μM

Example 19d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.11 (3H, s), 1.13 (3H, s), 1.20 (3H, d), 1.62 - 1.69 (2H, m), 1.95 - 2.00 (2H, m), 3.11 - 3.20 (1H, m), 3.42 - 3.50 (1H, m), 3.57 - 3.63

(1H, m), 3.72 - 3.82 (2H, m), 3.92 - 3.98 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 6.05 (1H, d), 6.67 (1H, s), 7.39 (2H, d), 7.52 - 7.59 (2H, m), 7.69 - 7.76 (1H, m), 7.82 (2H, d), 8.53 (1H, s).
mTOR Kinase Assay (Echo): 0.00318μM

Example 19e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 1.63 - 1.68 (2H, m), 1.95 - 2.00 (2H, m), 3.09 - 3.22 (3H, m), 3.37 (1H, d), 3.42 - 3.49 (1H, m), 3.58 - 3.63 (1H, m), 3.75 (1H, d), 3.93 - 3.98 (1H, m), 4.17 (1H, d), 4.49 (1H, br, s), 6.15 (1H, t), 6.67 (1H, s), 7.40 (2H, d), 7.54 - 7.57 (2H, m), 7.69 - 7.76 (1H, m), 7.82 (2H, d), 8.65 (1H, s).
mTOR Kinase Assay (Echo): 0.00135μM

Example 19f: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.63 - 1.70 (2H, m), 1.95 - 2.00 (2H, m), 2.19 (6H, s), 2.34 (2H, t), 3.11 - 3.23 (3H, m), 3.41 - 3.50 (1H, m), 3.58 - 3.63 (1H, m), 3.75 (1H, d), 3.92 - 3.98 (1H, m), 4.17 (1H, d), 4.49 (1H, br, s), 6.16 (1H, t), 6.67 (1H, s), 7.40 (2H, d), 7.51 - 7.58 (2H, m), 7.68 - 7.76 (1H, m), 7.83 (2H, d), 8.88 (1H, s).
mTOR Kinase Assay (Echo): 0.0804μM

Example 19g: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.66 (2H, s), 1.92 - 2.01 (2H, m), 3.11 - 3.20 (3H, m), 3.40 - 3.51 (3H, m), 3.57 - 3.64 (1H, m), 3.75 (1H, d), 3.92 - 3.99 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 4.74 (1H, t), 6.24 (1H, t), 6.67 (1H, s), 7.40 (2H, d), 7.50 - 7.59 (2H, m), 7.68 - 7.74 (1H, t), 7.83 (2H, d), 8.79 (1H, s).
mTOR Kinase Assay (Echo): 0.000274μM

Example 19h: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.20 (3H, d), 1.41 - 1.51 (2H, m), 1.66 (2H, s), 1.94 - 2.00 (2H, m), 3.07 (2H, q), 3.12 - 3.17 (1H, m), 3.42 - 3.49 (1H, m), 3.58 - 3.64 (1H, m), 3.75 (1H, d), 3.92 - 3.98 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 6.20 (1H, t), 6.67 (1H, s), 7.40 (2H, d), 7.52 - 7.61 (2H, m), 7.68 - 7.76 (1H, m), 7.82 (2H, d), 8.64 (1H, s).
mTOR Kinase Assay (Echo): 0.00246μM

Example 19i: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.61 - 1.70 (2H, m), 1.94 - 2.01 (2H, m), 2.67 (3H, d), 3.10 - 3.20 (1H, m), 3.40 - 3.49 (1H, m), 3.58 - 3.63 (1H, m), 3.75 (1H, d), 3.92 - 3.98 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 6.02 - 6.08 (1H, m), 6.67 (1H, s), 7.41 (2H, d), 7.53 - 7.58 (2H, m), 7.68 - 7.75 (1H, m), 7.82 (2H, d), 8.73 (1H, s).
mTOR Kinase Assay (Echo): 0.00152μM

Example 91j: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.67 (2H, s), 1.94 - 2.03 (2H, m), 3.13 - 3.22 (1H, m), 3.42 - 3.50 (1H, m), 3.59 - 3.64 (1H, m), 3.76 (1H, d), 3.93 - 3.98

(1H, m), 4.19 (1H, d), 4.49 (1H, br, s), 6.70 (1H, s), 7.50 (2H, d), 7.54 - 7.61 (2H, m), 7.62 - 7.78 (5H, m), 7.91 (2H, d), 9.04 (1H, s), 9.12 (1H, s).

mTOR Kinase Assay (Echo): 0.0199μM

Example 19k: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.23 (6H, s), 1.62 – 1.68 (2H, m), 1.94 – 1.98 (2H, m), 3.13 - 3.20 (1H, m), 3.38 (2H, d), 3.42 - 3.50 (1H, m), 3.58 - 3.64 (1H, m), 3.75 (1H, d), 3.93 - 3.98 (1H, m), 4.17 (1H, d), 4.48 (1H, br, s), 4.94 (1H, t), 5.97 (1H, s), 7.35 (2H, d), 7.52 - 7.58 (2H, m), 7.69 - 7.77 (1H, m), 7.81 (2H, d), 8.71 (1H, s).

mTOR Kinase Assay (Echo): 0.00415μM

Example 19l: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.55 – 1.70 (4H, m), 1.95 - 2.01 (2H, m), 3.13 - 3.21 (3H, m), 3.42 - 3.50 (3H, m), 3.58 - 3.65 (1H, m), 3.75 (1H, d), 3.93 - 3.99 (1H, m), 4.18 (1H, d), 4.43 – 4.52 (2H, m), 6.19 (1H, t), 6.67 (1H, s), 7.39 (2H, d), 7.52 - 7.61 (2H, m), 7.69 - 7.78 (1H, m), 7.83 (2H, d), 8.69 (1H, s).

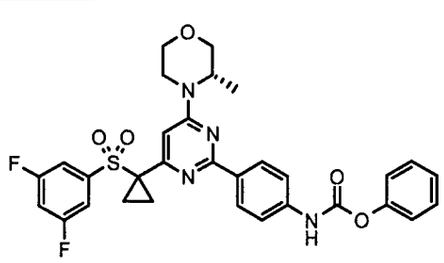
mTOR Kinase Assay (Echo): 0.00152μM

Example 19m: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.60 – 1.69 (2H, m), 1.94 - 2.01 (2H, m), 3.13 - 3.21 (1H, m), 3.42 - 3.50 (3H, m), 3.58 - 3.64 (1H, m), 3.73 – 3.81 (4H, m), 3.93 - 3.98 (1H, m), 4.18 (1H, d), 4.49 (1H, br, s), 6.67 (1H, s), 7.37 (1H, s), 7.43 (2H, d), 7.51 - 7.60 (2H, m), 7.68 - 7.78 (2H, m), 7.76 (2H, d), 8.35 (1H, s), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.000944μM

The preparation of phenyl *N*-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamateis described below.

Phenyl *N*-[4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



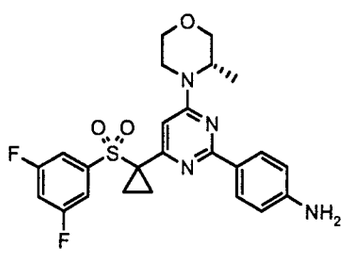
Phenyl chloroformate (0.764 mL, 6.08 mmol) was added to 4-[4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2.69 g, 5.53 mmol) and sodium hydrogen carbonate (0.697 g, 8.29 mmol) in dioxane (40 mL)

at RT. The resulting slurry was stirred at RT for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 25% - 80% ethyl acetate in isohexane, to give the desired material as a yellow dry film (3.07 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.61 - 1.66 (1H, m), 1.68 - 1.73 (1H, m), 1.94 - 2.05 (2H, m), 3.30 (1H, dt), 3.61 (1H, dt), 3.75 (1H, dd), 3.84 (1H, d), 4.05 (1H, dd), 4.16 (1H, d), 4.43 (1H, br, s), 6.79 (1H, s), 6.94 - 7.03 (2H, m), 7.18 - 7.28 (3H, m), 7.30 - 7.35 (2H, m), 7.37 - 7.47 (4H, m), 8.10 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 607; HPLC tR = 3.12 min.

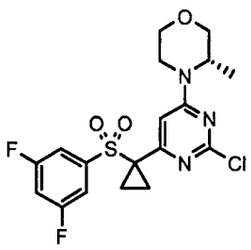
4-[4-[1-(3,5-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



A stream of nitrogen was passed through a mixture of 2-chloro-4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.5 g, 5.82 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.656 g, 7.56 mmol) and 2M aqueous sodium carbonate (10.47 mL, 20.94 mmol) in DMF (11 mL), DME (11 mL), ethanol (11 mL) and water (27.5 mL) at RT for 15 minutes. Dichlorobis(triphenylphosphine)-palladium(II) (0.204 g, 0.29 mmol) was added in one portion and the reaction mixture stirred at 80°C under nitrogen for 1 hour. The reaction mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 25% - 60% ethyl acetate in isohexane, to give the desired material as a near colourless solid (2.76 g).

NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.62 - 1.66 (1H, m), 1.70 - 1.74 (1H, m), 1.93 - 2.03 (2H, m), 3.28 (1H, dt), 3.59 (1H, dt), 3.72 - 3.74 (1H, dd), 3.79 - 3.89 (3H, m), 4.03 (1H, dd), 4.10 - 4.18 (1H, m), 4.37 - 4.45 (1H, m), 6.61 - 6.65 (2H, m), 6.73 (1H, s), 6.98 (1H, tt), 7.31 - 7.36 (2H, m), 7.93 - 7.96 (2H, m) LCMS Spectrum: m/z (ESI+)(M+H)+ = 487; HPLC tR = 2.86 min.

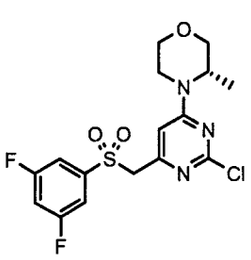
2-Chloro-4-[1-(3,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



1,2-Dibromoethane (1.0 mL, 11.6 mmol) was added to 2-chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.68 g, 9.11 mmol) in toluene (55 mL) followed by tetrabutylammonium bromide (0.294 g, 0.91 mmol) and sodium hydroxide concentrate (9.00 mL, 90 mmol). The reaction mixture was stirred at RT overnight. The mixture was then heated to 80°C and vigorous stirring continued for 3 hours. A further quantity of 1,2-dibromoethane (1 mL, 11.6 mmol) was added and heating was continued for a further 2 hours. The reaction mixture was diluted with ethyl acetate and washed with water. The organic solution was concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10 to 40% ethyl acetate in isohexane, to give the desired material as a colourless solid (3.0 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.56 - 1.60 (1H, m), 1.63 - 1.68 (1H, m), 1.92 - 2.01 (2H, m), 3.28 (1H, dt), 3.55 (1H, dt), 3.70 (1H, dd), 3.80 (1H, d), 4.00 - 4.09 (2H, m), 4.28 (1H, br, s), 6.87 (1H, s), 7.07 (1H, tt), 7.24 - 7.29 (2H, m)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 430, 432; HPLC tR = 2.55 min.

2-Chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



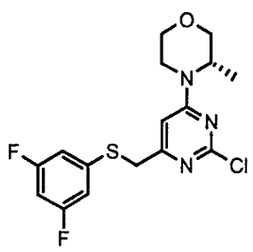
A solution of sodium tungstate dihydrate (199 mg, 0.60 mmol) in water (2 mL) was added to a stirred solution of 2-chloro-4-[(3,5-difluorophenyl)sulfanylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (11.23 g, 30.2 mmol) and sulfuric acid (0.302 mL, 2M,

0.60 mmol) in dioxane (40 mL). Hydrogen peroxide (3.22 mL, 104.19 mmol) was added and the mixture was stirred at RT overnight. A precipitate was collected by filtration and dried *in vacuo*, to give the desired material as a near colourless solid (3.61 g). The filtrate was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 5% - 20% ethyl acetate in DCM, to give the desired material as a near colourless solid (7.66 g).

NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, s), 3.31 (1H, dt), 3.56 (1H, dt), 3.71 (1H, dd), 3.80 (1H, d), 3.98 - 4.10 (2H, m), 4.31 (2H, s), 6.55 (1H, s), 7.12 (1H, tt), 7.30 - 7.36 (2H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 404, 406; HPLC tR = 2.32 min.

2-Chloro-4-[(3,5-difluorophenyl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



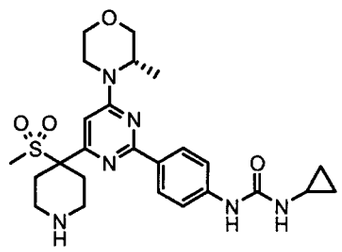
DIPEA (8.07 mL, 46.67 mmol) was added to 3,5-difluorobenzenethiol (5.00 g, 34.22 mmol), in DMF (55 mL) at RT under nitrogen. The resulting solution was stirred at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (11.00 g, 31.11 mmol) was added to the reaction mixture in one portion. The mixture was stirred for 4 hours at RT. The reaction mixture was heated in a water bath at 60°C for 1.5 hours before being partitioned between ethyl acetate and water. The organic solution was washed with further water then was dried ($MgSO_4$), filtered and evaporated to give the desired material as a gum (12.24 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.27 (3H, d), 3.24 (1H, dt), 3.52 (1H, dt), 3.66 (1H, dd), 3.76 (1H, d), 3.96 - 4.04 (4H, m), 4.21 (1H, br, s), 6.41 (1H, s), 6.59 - 6.66 (1H, m), 6.80 - 6.86 (2H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 372, 374; HPLC tR = 2.66 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 20: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea



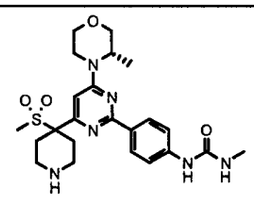
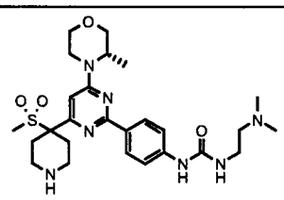
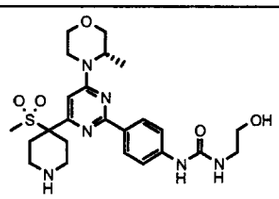
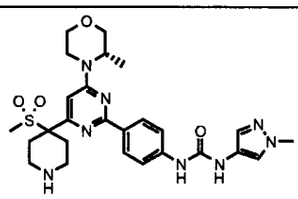
Cyclopropylamine (0.055 mL, 0.76 mmol) was added to tert-butyl 4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate (115 mg, 0.17 mmol) and triethylamine (0.153 mL, 1.10 mmol) in DMF (1 mL) at RT and the reaction was allowed to stand overnight at RT. The mixture was partitioned between ethyl acetate and water. The organic layer was washed twice with water then concentrated under reduced pressure. The residue was dissolved in DCM (1 mL) and treated with TFA (2 mL). The resulting solution was stirred for 30 minutes at RT before being concentrated under reduced pressure. The sample was dissolved in DMF (1.5 mL) and purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a colourless solid (26.7 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.38 - 0.44 (2H, m), 0.61 - 0.68 (2H, m), 1.24 (3H, d), 1.97 - 2.10 (2H, m), 2.30 - 2.45 (2H, m), 2.57 (1H, obscured by DMSO signal), 2.73 - 2.86 (5H, m), 2.90 - 3.00 (2H, m), 3.15 - 3.25 (1H, m), 3.47 - 3.55 (1H, m), 3.63 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.29 (1H, d), 4.56 (1H, br, s), 6.45 (1H, s), 6.79 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.57 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 515; HPLC tR = 1.50 min.

mTOR Kinase Assay (Echo): 0.0128μM

The following compounds were made in an analogous fashion from tert-butyl 4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
20a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea	489.5	1.34
20b		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea	546.5	1.44
20c		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]urea	519.5	1.24
20d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonylpiperidin-4-yl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	555.5	1.41

Example 20a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.97 - 2.09 (2H, m), 2.30 - 2.45 (2H, m), 2.67 (3H, d), 2.70 - 2.85 (5H, m), 2.90 - 3.02 (2H, m), 3.15 - 3.25 (1H, m), 3.45 - 3.55 (1H, m), 3.67 (1H, d), 3.77 (1H, d), 3.99 (1H, d), 4.28 (1H, d), 4.56 (1H, br, s), 6.05 – 6.12 (1H, m), 6.79 (1H, s), 7.51 (2H, d), 8.22 (2H, d), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.0163μM

Example 20b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.98 - 2.09 (2H, m), 2.19 (6H, s), 2.30 – 2.47 (4H, m), 2.72 – 2.83 (5H, m), 2.92 – 3.02 (2H, m), 3.16 – 3.27 (3H, m, obscured by water signal), 3.45 - 3.57 (1H, m), 3.63 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.00 (1H, m), 4.28 (1H, d), 4.57 (1H, br, s), 6.17 (1H, t), 6.79 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.91 (1H, s).

mTOR Kinase Assay (Echo): 0.874μM

Example 20c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.97 – 2.10 (2H, m), 2.32 – 2.46 (2H, m), 2.74 – 2.83 (5H, m), 2.92 – 3.02 (2H, m), 3.14 - 3.26 (3H, m), 3.41 - 3.55 (4H, m), 3.63 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.28 (1H, d), 4.57 (1H, br, s), 4.74 (1H, t), 6.25 (1H, t), 6.79 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.82 (1H, s).

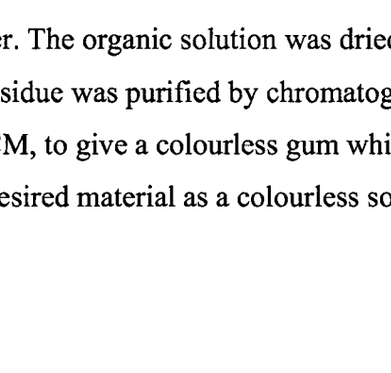
mTOR Kinase Assay (Echo): 0.00559μM

Example 20d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.24 (3H, d), 2.00 – 2.09 (2H, m), 2.32 – 2.47 (2H, m), 2.75 - 2.84 (5H, m), 2.92 – 3.02 (1H, m), 3.17 - 3.26 (1H, m), 3.47 - 3.55 (1H, m), 3.64 - 3.70 (1H, m), 3.75 – 3.82 (4H, m), 3.95 - 4.03 (1H, m), 4.29 (1H, d), 4.57 (1H, br, s), 6.80 (1H, s), 7.38 (1H, d), 7.55 (2H, d), 7.77 (1H, s), 8.26 (2H, d), 8.44 (1H, s), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.0133μM

The preparation of tert-butyl 4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate is described below.

tert-Butyl 4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate

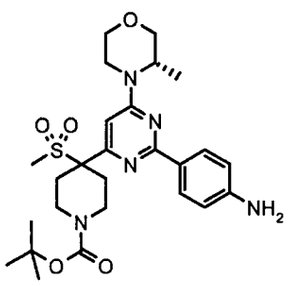


Phenyl chloroformate (0.150 mL, 1.20 mmol) was added to tert-butyl 4-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate (530 mg, 1.00 mmol) and sodium hydrogen carbonate (126 mg, 1.50 mmol) in dioxane (7 mL) at RT. The resulting slurry was stirred at RT for 3 hours. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 60% ethyl acetate in DCM, to give a colourless gum which was subsequently triturated with diethyl ether to give the desired material as a colourless solid (576 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.36 (3H, d), 1.44 (9H, s), 2.29 - 2.41 (2H, m), 2.72 (3H, s), 2.73 - 2.85 (4H, m), 3.33 (1H, dt), 3.61 (1H, dt), 3.76 (1H, dd), 3.84 (1H, d), 4.06 (1H, dd), 4.10 - 4.32 (3H, m), 4.46 (1H, br, s), 6.65 (1H, s), 7.12 (1H, br, s), 7.17 - 7.28 (3H, m), 7.36 - 7.44 (2H, m), 7.54 (2H, d), 8.35 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 652; HPLC tR = 3.11 min.

tert-Butyl 4-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate

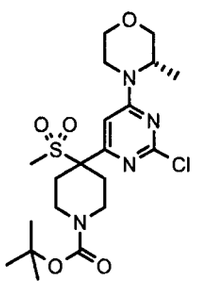


A stream of nitrogen was passed through tert-butyl 4-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate (500 mg, 1.05 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (300 mg, 1.37 mmol) and 2M aqueous sodium carbonate (1.895 mL, 3.79 mmol) in DMF (2 mL), DME (2 mL), ethanol (2 mL) and water (5 mL) at RT for 15 minutes. The reaction mixture was treated with dichlorobis(triphenylphosphine)-palladium(II) (36.9 mg, 0.05 mmol) and the mixture was stirred at 80°C for 30 minutes. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 50% ethyl acetate in DCM. The isolated material was triturated with diethyl ether to give the desired material as a pale orange solid (544 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.44 (9H, s), 2.30 - 2.36 (2H, m), 2.71 (3H, s), 2.69 - 2.85 (4H, m), 3.30 (1H, dt), 3.60 (1H, dt), 3.74 (1H, dd), 3.83 (1H, d), 3.93 (2H, s), 4.04 (1H, dd), 4.09 - 4.29 (3H, m), 4.45 (1H, br, s), 6.58 (1H, s), 6.71 (2H, d), 8.18 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 532; HPLC tR = 2.52 min.

tert-Butyl 4-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-methylsulfonylpiperidine-1-carboxylate

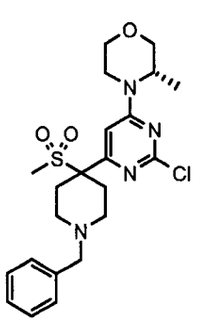


1-Chloroethyl chloroformate (0.315 mL, 2.92 mmol) was added to a solution of 4-(1-benzyl-4-methylsulfonylpiperidin-4-yl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (679 mg, 1.46 mmol) in DCM (10 mL). The solution was heated at reflux for 3 hours. The mixture was cooled, diluted with methanol (10 mL) and allowed to stand overnight. The mixture was treated with di-tert-butyl dicarbonate (0.738 mL, 3.21 mmol) and DIPEA (0.505 mL, 2.92 mmol) and this solution was stirred at RT for 1.5 hours. The solution was partitioned between DCM and water and the organic phase concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 30% ethyl acetate in DCM , to give the desired material as a colourless dry film (519 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.45 (9H, s), 2.23 - 2.34 (2H, m), 2.59 - 2.78 (7H, m), 3.30 (1H, dt), 3.55 (1H, dt), 3.70 (1H, dd), 3.80 (1H, d), 3.98 - 4.40 (5H, m), 6.61 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 475, 477; HPLC tR = 2.53 min.

4-(1-Benzyl-4-methylsulfonylpiperidin-4-yl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



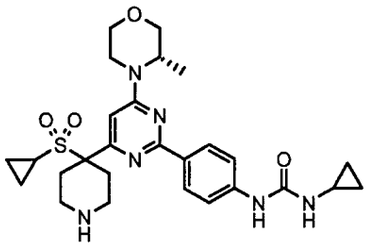
A solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (750 mg, 2.45 mmol) in NMP (8 mL) was treated with sodium hydride (324 mg, 8.10 mmol). The mixture was stirred at RT for 10 minutes before being treated with tetrabutylammonium bromide (979 mg, 3.04 mmol) and *N*-benzyl-2-chloro-*N*-(2-chloroethyl)ethanamine hydrochloride (692 mg, 2.58 mmol). The reaction mixture was stirred for 5 minutes, warmed to 50°C for 1 hour then warmed to 80°C for 2.5 hours. The mixture was allowed to cool and stirred for 65 hours at RT. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution and then extracted with ethyl acetate. The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 50% ethyl acetate in DCM, to give the desired material as a colourless solid (710 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.89 - 1.99 (2H, m), 2.40 - 2.50 (2H, m), 2.57 - 2.64 (2H, m), 2.75 (3H, s), 2.87 - 2.95 (2H, m), 3.29 (1H, dt), 3.41 (2H, s), 3.55 (1H, dt), 3.69 (1H, dd), 3.79 (1H, d), 3.95 - 4.08 (2H, m), 4.29 (1H, br, s), 6.59 (1H, s), 7.21 - 7.32 (5H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 465, 467; HPLC tR = 2.59 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine was described earlier.

Example 21: 3-Cyclopropyl-1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



Cyclopropylamine (0.055 mL, 0.76 mmol) was added to tert-butyl 4-cyclopropylsulfonyl-4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]piperidine-1-carboxylate (120 mg, 0.18 mmol) and triethylamine (0.16 mL, 1.15 mmol) in DMF (1 mL) at RT and the reaction was allowed to stand for overnight at RT. The mixture was partitioned between ethyl acetate and water. The organic layer was washed twice with

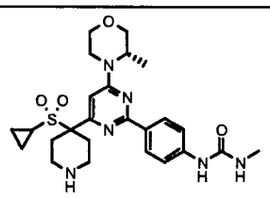
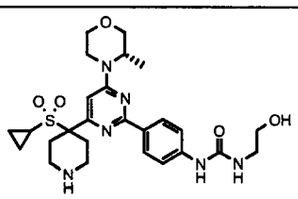
water then concentrated under reduced pressure. The residue was dissolved in DCM (1 mL) and treated with TFA (2 mL). The resulting solution was stirred for 30 minutes at RT before being concentrated under reduced pressure. The sample was dissolved in DMF (1.5 mL). The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% conc. ammonia) and acetonitrile as eluents, to give the desired material as a colourless solid (53 mg).

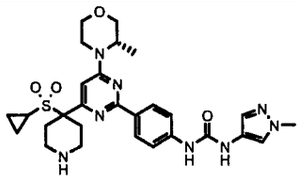
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.38 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 0.70 - 0.74 (2H, m), 0.83 - 0.87 (2H, m), 1.23 (3H, d), 1.98 - 2.12 (2H, m), 2.32 - 2.60 (4H, m), 2.82 – 2.98 (4H, m), 3.15 - 3.24 (1H, m), 3.47 - 3.56 (1H, m), 3.64 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.26 (1H, d), 4.50 – 4.60 (1H, m), 6.44 (1H, s), 6.81 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.54 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 541; HPLC tR = 1.85 min.

mTOR Kinase Assay (Echo): 0.0253μM

The following compounds were made in an analogous fashion from tert-butyl 4-cyclopropylsulfonyl-4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]piperidine-1-carboxylate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
21a		1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	515.6	1.71
21b		1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	545.7	1.56

Example	Structure	NAME	LCMS MH+	Retention time (min)
21c		1-[4-[4-(4-cyclopropylsulfonylpiperidin-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	581.7	1.83

Example 21a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.68 - 0.74 (2H, m), 0.83 - 0.87 (2H, m), 1.23 (3H, d), 1.98 - 2.10 (2H, m), 2.32 - 2.49 (3H, m), 2.67 (3H, d), 2.82 – 2.97 (4H, m), 3.15 - 3.24 (1H, m), 3.47 – 3.57 (1H, m), 3.64 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.26 (1H, d), 4.50 – 4.59 (1H, m), 6.07 (1H, q), 6.81 (1H, s), 7.50 (2H, d), 8.22 (2H, d), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.0378μM

Example 21b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.69 – 0.76 (2H, m), 0.82 - 0.89 (2H, m), 1.23 (3H, d), 1.95 – 2.10 (2H, m), 2.31 - 2.49 (3H, m), 2.83 – 2.97 (4H, m), 3.15 – 3.26 (3H, m), 3.43 - 3.58 (3H, m), 3.64 - 3.69 (1H, m), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.26 (1H, d), 4.50 – 4.59 (1H, m), 4.74 (1H, t), 6.26 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.81 (1H, s).

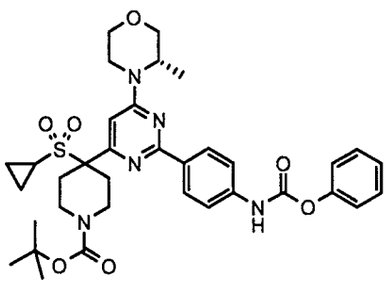
mTOR Kinase Assay (Echo): 0.0133μM

Example 21c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.73 (2H, br, s), 0.87 (2H, d), 1.23 (3H, d), 1.99 – 2.11 (2H, m), 2.33 - 2.48 (3H, m), 2.83 – 2.98 (4H, m), 3.15 – 3.20 (1H, m), 3.45 – 3.56 (1H, m), 3.68 (1H, d), 3.74 – 3.83 (4H, m), 3.99 (1H, d), 4.27 (1H, d), 4.55 (1H, br, s), 6.82 (1H, s), 7.38 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.26 (2H, d), 8.42 (1H, s), 8.86 (1H, s).

mTOR Kinase Assay (Echo): 0.0234μM

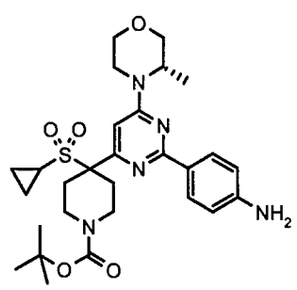
The preparation of tert-butyl 4-cyclopropylsulfonyl-4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]piperidine-1-carboxylateis described below.

tert-Butyl 4-cyclopropylsulfonyl-4-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]piperidine-1-carboxylate



Phenyl chloroformate (0.235 mL, 1.87 mmol) was added to tert-butyl 4-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-cyclopropylsulfonylpiperidine-1-carboxylate (950 mg, 1.70 mmol) and sodium hydrogen carbonate (215 mg, 2.56 mmol) in dioxane (15 mL) at RT. The resulting slurry was stirred at RT for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 25% - 80% ethyl acetate in isohexane. The isolated material was triturated with diethyl ether to give the desired material as a near colourless dry film (1.06 g).
NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.80 - 0.85 (2H, m), 0.94 - 1.06 (2H, m), 1.35 (3H, d), 1.44 (9H, s), 2.14 - 2.22 (1H, m), 2.25 - 2.39 (2H, m), 2.69 - 2.95 (4H, m), 3.33 (1H, dt), 3.62 (1H, dt), 3.76 (1H, dd), 3.84 (1H, d), 4.03 - 4.31 (4H, m), 4.39 - 4.49 (1H, m), 6.68 (1H, s), 7.11 (1H, br, s), 7.19 - 7.28 (3H, m), 7.41 (2H, t), 7.54 (2H, d), 8.37 (2H, d).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 678; HPLC tR = 3.18 min.

tert-Butyl 4-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-cyclopropylsulfonylpiperidine-1-carboxylate

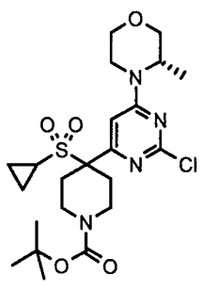


A stream of nitrogen was passed through tert-butyl 4-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-cyclopropylsulfonylpiperidine-1-carboxylate (0.94 g, 1.88 mmol), 4-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.534 g, 2.44 mmol) and 2M aqueous sodium carbonate (3.38 mL, 6.75 mmol) in DMF (3.75 mL), DME (5 mL), ethanol (5 mL) and water (12.5 mL) at RT for 15 minutes. The reaction mixture was treated with dichlorobis(triphenylphosphine)-palladium(II) (0.066 g, 0.09 mmol) and the mixture was stirred at 80°C for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 50% ethyl acetate in DCM. The isolated material was triturated with diethyl ether to give the desired material as a pale brown solid (0.990 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.77 - 0.85 (2H, m), 0.95 - 1.04 (2H, m), 1.32 (3H, d), 1.42 (9H, s), 2.14 - 2.21 (1H, m), 2.24 - 2.37 (2H, m), 2.69 - 2.93 (4H, m), 3.29 (1H, dt), 3.60 (1H, dt), 3.75 (1H, dd), 3.81 (1H, d), 3.90 (2H, s), 4.04 (1H, dd), 4.07 - 4.30 (3H, m), 4.39 - 4.48 (1H, m), 6.61 (1H, s), 6.61 (2H, d), 8.20 (2H, d).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 558; HPLC tR = 2.64 min.

tert-Butyl 4-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]-4-cyclopropylsulfonylpiperidine-1-carboxylate

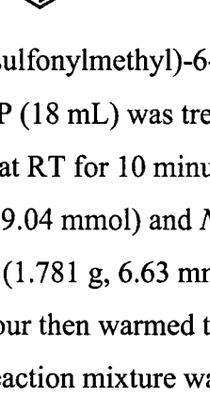


1-Chloroethyl chloroformate (0.971 mL, 9.00 mmol) was added to a solution of 4-(1-benzyl-4-cyclopropylsulfonylpiperidin-4-yl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.21 g, 4.50 mmol) in DCM (15 mL). The solution was heated at reflux for 1.5 hours. The mixture was diluted with methanol (15 mL) and heating was continued for 2 hours. The mixture was treated with di-tert-butyl dicarbonate (2.16 g, 9.90 mmol) and DIPEA (1.6 mL, 9.0 mmol) and this solution was stirred at RT for 1 hour. The solution was partitioned between DCM and water. The organic phase was concentrated under reduced pressure and the residue was purified by chromatography on silica, eluting with 10% - 30% ethyl acetate in DCM, to give the desired material as a colourless solid (1.9 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.93 - 1.00 (4H, m), 1.32 (3H, d), 1.44 (9H, s), 2.19 - 2.30 (3H, m), 2.62 - 2.80 (4H, m), 3.29 (1H, dt), 3.55 (1H, dt), 3.69 (1H, dd), 3.79 (1H, d), 3.95 - 4.37 (5H, m), 6.65 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 501, 503; HPLC tR = 2.70 min.

4-(1-Benzyl-4-cyclopropylsulfonylpiperidin-4-yl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



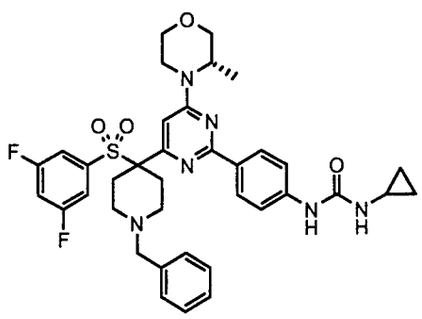
A solution of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2 g, 6.03 mmol) in NMP (18 mL) was treated with sodium hydride (0.796 g, 19.89 mmol). The mixture was stirred at RT for 10 minutes before being treated with tetrabutylammonium bromide (2.91 g, 9.04 mmol) and *N*-benzyl-2-chloro-*N*-(2-chloroethyl)ethanamine hydrochloride (1.781 g, 6.63 mmol). The reaction mixture was stirred for 5 minutes, warmed to 50°C for 1 hour then warmed to 80°C for 1.5 hours. The mixture was then allowed to cool to RT. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution and then extracted with ethyl acetate. The organic solution was washed three times with water then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% - 70% ethyl acetate in DCM, to give the desired material as a colourless foam (2.23 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.92 - 0.96 (2H, m), 0.97 - 1.02 (2H, m), 1.32 (3H, d), 1.92 - 2.00 (2H, m), 2.24 - 2.31 (1H, m), 2.40 - 2.49 (2H, m), 2.68 - 2.74 (2H, m), 2.88 - 2.92 (2H, m), 3.29 (1H, dt), 3.40 (2H, s), 3.55 (1H, dt), 3.70 (1H, dd), 3.79 (1H, d), 3.98 - 4.09 (2H, m), 4.28 (1H,br, s), 6.63 (1H, s), 7.21 - 7.33 (5H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 491, 493; HPLC tR = 2.71 min.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 22: 1-[4-[4-[1-Benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea



A stream of nitrogen was passed through [4-(3-cyclopropylureido)phenylboronic acid, pinacol ester (121 mg, 0.40 mmol), 4-[1-benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (225 mg, 0.40 mmol) and 2M aqueous sodium carbonate (0.719 mL, 1.44 mmol) in DMF (0.8 mL), DME (5 mL), ethanol (5 mL) and water (12.5 mL) at 25°C for 15 minutes. The reaction mixture was treated with dichlorobis(triphenylphosphine)-palladium(II) (14.02 mg, 0.02 mmol) and the mixture was stirred at 80°C for 2 hours. The mixture was partitioned between DCM and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by ion exchange chromatography using an SCX column, eluting with 2M ammonia in methanol. The isolated material was further purified by chromatography on silica, eluting with 10% - 60% ethyl acetate in DCM, to give the desired material as a colourless dry film (125 mg).

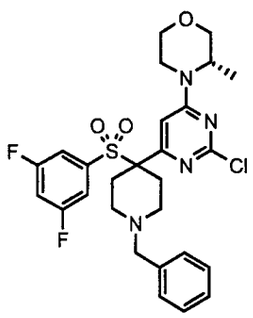
NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.67 - 0.71 (2H, m), 0.85 - 0.90 (2H, m), 1.36 (3H, d), 1.77 - 1.98 (2H, m), 2.47 - 2.67 (3H, m), 2.74 (2H, t), 2.85 - 2.96 (2H, m), 3.30 - 3.38 (3H, m), 3.64 (1H, dt), 3.76 - 3.87 (2H, m), 4.08 (1H, dd), 4.16 (1H, d), 4.40 - 4.51 (1H, m), 4.92 (1H, s), 6.63 (1H, s), 6.80 - 6.86 (1H, m), 6.95 - 7.03 (3H, m), 7.20 - 7.31 (5H, m), 7.39 (2H, d), 7.93 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 703.6; HPLC tR = 2.97 min.

mTOR Kinase Assay (Echo): 0.503μM

The preparation of 4-[1-benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine is described below.

4-[1-Benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



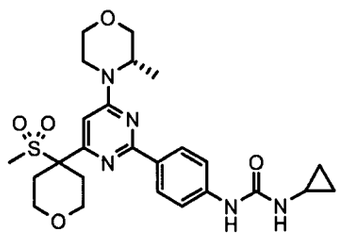
A mixture of 2-chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (874 mg, 2.16 mmol) in NMP (10 mL) was treated with sodium hydride (299 mg, 7.47 mmol) and stirred for 5 minutes at RT. Tetrabutylammonium bromide (698 mg, 2.16 mmol) and *N*-benzyl-2-chloro-*N*-(2-chloroethyl)ethanamine hydrochloride (669 mg, 2.49 mmol) were added and the mixture heated at 80°C for 2 hours. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution and then extracted with ethyl acetate. The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 10% -50% ethyl acetate in isohexane, to give the desired material as a colourless solid (582 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.35 (3H, d), 1.85 - 1.93 (2H, m), 2.41 - 2.49 (2H, m), 2.55 (2H, d), 2.88 - 2.93 (2H, m), 3.32 (1H, dt), 3.38 (2H, s), 3.59 (1H, dt), 3.74 (1H, dd), 3.81 (1H, d), 3.98 - 4.08 (2H, m), 4.31 (1H, br, s), 6.64 (1H, s), 6.97 - 7.11 (3H, m), 7.22 - 7.33 (5H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 563, 565; HPLC tR = 3.18 min.

The preparation of 2-chloro-4-[(3,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 23: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea



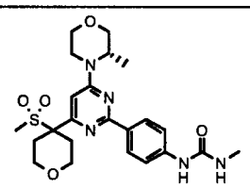
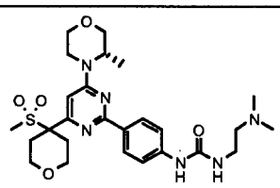
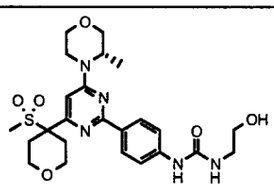
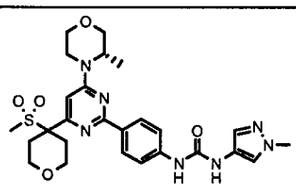
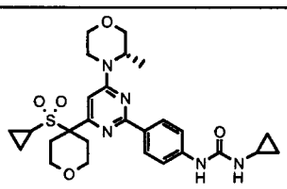
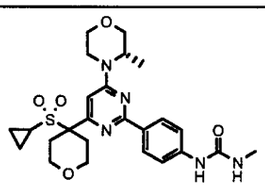
Cyclopropylamine (0.100 mL, 1.45 mmol) was added to phenyl N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.18 mmol) in DMF (2 mL). The resulting solution was stirred at 60°C for 4 hours. The mixture was evaporated to dryness and the residue was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (67 mg).

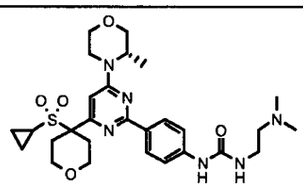
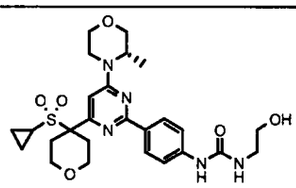
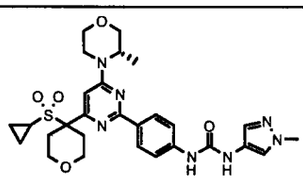
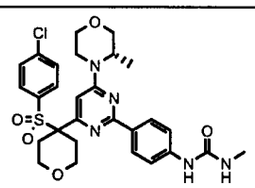
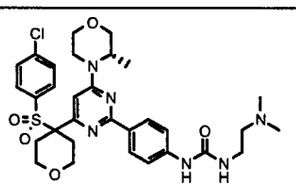
NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.71 (2H, ddd), 0.89 (2H, ddd), 1.35 (3H, d), 2 54 (3H, ddd), 2.64 (1H, m), 2.71 (3H, s), 2.72 (2H, br.d), 3.34 (1H, ddd), 3.42 (1H, ddd), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.05 (3H, m), 4.20 (1H, d), 4.46 (1H, br.d), 4.89 (1H, s), 6.64 (1H, s), 7.00 (1H, s), 7.51 (2H, d), 8.31 (2H, d).

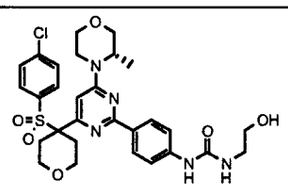
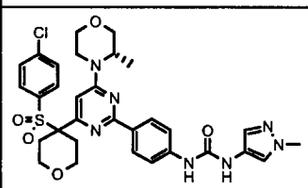
LCMS Spectrum: m/z (ESI+)(M+H)+ = 516; HPLC tR = 1.92 min.

mTOR Kinase Assay (Echo): 0.00492μM

The following compounds were made in an analogous fashion from either phenyl N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]carbamate, phenyl N-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl N-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
23a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea	490	1.77
23b		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea	547	1.84
23c		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]urea	520	1.61
23d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	554 (M-H)-	1.83
23e		3-cyclopropyl-1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	542	2.07
23f		1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	516	1.89

Example	Structure	NAME	LCMS MH+	Retention time (min)
23g		1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	573	1.96
23h		1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	546	1.72
23i		1-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	580 (M-H)-	1.93
23j		1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	586	2.26
23k		1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	643	2.31

Example	Structure	NAME	LCMS MH+	Retention time (min)
23l		1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	616	2.05
23m		1-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	652	2.26

Example 23a: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.54 (2H, ddd), 2.71 (3H, s), 2.72 (2H, d), 2.89 (3H, d), 3.35 (1H, ddd), 3.41 (2H, dd), 3.62 (1H, ddd), 3.76 (1H, dd), 3.84 (1H, d), 4.0-4.1 (3H, m), 4.19 (1H, d), 4.46 (1H, br.d), 4.62 (1H, br.q), 6.32 (1H, s), 6.64 (1H, s), 7.40 (2H, d), 8.31 (2H, d).

mTOR Kinase Assay (Echo): 0.00459μM

Example 23b: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.32 (6H, s), 2.5-2.6 (4H, m), 2.71 (3H, s), 2.72 (2H, d), 3.3-3.4 (3H, m), 3.41 (2H, ddd), 3.62 (1H, ddd), 3.76 (1H, dd), 3.84 (1H, d), 4.0-4.1 (3H, m), 4.19 (1H, d), 4.46 (1H, br.d), 5.22 (1H, br.t), 6.62 (1H, s), 7.44 (2H, d), 8.28 (2H, d).

mTOR Kinase Assay (Echo): 0.197μM

Example 23c: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.5-2.6 (3H, m), 2.71 (3H, s), 2.72 (2H, d), 3.34 (1H, ddd), 3.41 (2H, dd), 3.45 (4H, dt), 3.62 (1H, ddd), 3.76 (1H, dd), 3.78 (2H, m), 3.84 (1H, d), 4.0-4.1 (3H, m), 4.19 (1H, d), 4.45 (1H, br.d), 5.25 (1H, t), 6.64 (1H, s), 6.85 (1H, s), 7.41 (2H, d), 8.30 (2H, d).

mTOR Kinase Assay (Echo): 0.000831μM

Example 23d: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.54 (2H, ddd), 2.72 (3H, s), 2.72 (2H, m), 3.33 (1H, ddd), 3.41 (2H, dd), 3.61 (1H, ddd), 3.75 (1H, dd), 3.83 (1H, d), 3.90 (3H, s), 4.0-4.1 (3H, m), 4.18 (1H, d), 4.45 (1H, br.d), 6.25 (1H, br.s), 6.64 (1H, s), 6.78 (1H, s), 7.41 (1H, s), 7.44 (2H, d), 7.61 (1H, s), 8.29 (2H, d).

mTOR Kinase Assay (Echo): 0.00534μM

Example 23e: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.71 (2H, ddd), 0.83 (2H, m), 0.89 (2H, ddd), 1.02 (2H, m), 1.34 (3H, d), 2.18 (1H, tt), 2.53 (2H, ddd), 2.64 (1H, tt), 2.82 (2H, br.d), 3.34 (2H, ddd), 3.43 (3H, ddd), 3.63 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.02 (2H, m), 4.06 (1H, dd), 4.19 (1H, d), 4.46 (1H, br.d), 4.86 (1H, s), 6.67 (1H, s), 6.97 (1H, s), 7.51 (2H, d), 8.33 (2H, d).

mTOR Kinase Assay (Echo): 0.00876μM

Example 23f: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.83 (2H, m), 1.02 (2H, m), 1.34 (3H, d), 2.18 (1H, tt), 2.52 (2H, m), 2.82 (2H, br.d), 2.86 (3H, d), 3.33 (1H, ddd), 3.42 (2H, ddd), 3.62 (1H, ddd), 3.76 (1H, dd), 3.83 (1H, d), 4.01 (2H, m), 4.05 (1H, dd), 4.18 (1H, d), 4.45 (1H, br.d), 4.83 (1H, q), 6.63 (1H, s), 6.67 (1H, s), 7.40 (2H, d), 8.31 (2H, d).

mTOR Kinase Assay (Echo): 0.0199μM

Example 23g: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.82 (2H, m), 1.01 (2H, m), 1.34 (3H, d), 2.18 (1H, tt), 2.32 (6H, s), 2.52 (4H, m), 2.82 (2H, d), 3.32 (3H, m), 3.43 (2H, ddd), 3.62 (1H, ddd), 3.76 (1H, dd), 3.83 (1H, d), 4.01 (2H, m), 4.05 (2H, dd), 4.18 (1H, d), 4.46 (1H, br.d), 5.30 (1H, br.t), 6.66 (1H, s), 7.44 (2H, d), 8.30 (2H, d).

mTOR Kinase Assay (Echo): 1.21μM

Example 23h: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.83 (2H, m), 1.02 (2H, m), 1.34 (3H, d), 2.18 (1H, tt), 2.53 (3H, m), 2.82 (2H, br.d), 3.33 (1H, ddd), 3.43 (2H, dd), 3.46 (2H, t), 3.62 (1H, ddd), 3.76 (1H, dd), 3.78 (2H, t), 3.83 (1H, d), 4.01 (2H, m), 4.05 (1H, dd), 4.18 (1H, d), 4.45 (1H, br.d), 5.26 (1H, t), 6.67 (1H, s), 6.85 (1H, s), 7.40 (2H, d), 8.32 (2H, d).

mTOR Kinase Assay (Echo): 0.00808μM

Example 23i: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.84 (2H, m), 1.03 (2H, m), 1.34 (3H, d), 2.19 (1H, tt), 2.53 (2H, m), 2.82 (2H, br.d), 3.33 (1H, ddd), 3.42 (2H, ddd), 3.61 (1H, ddd), 3.76 (1H, dd), 3.83 (1H, d), 3.92 (3H, s), 4.02 (2H, m), 4.05 (1H, dd), 4.17 (1H, d), 4.45 (1H, br.d), 6.03 (1H, s), 6.60 (1H, s), 6.67 (1H, s), 7.42 (2H, d), 7.43 (1H, s), 7.60 (1H, s), 8.31 (2H, d).

mTOR Kinase Assay (Echo): 0.0254μM

Example 23j: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.36 (3H, d), 2.55 (2H, td), 2.64 (2H, br.d), 2.87 (2H, d), 3.30 (1H, ddd), 3.34 (1H, ddd), 3.65 (1H, ddd), 3.79 (1H, dd), 3.86 (1H, d), 3.99 (2H, m), 4.08 (1H, dd), 4.16 (1H, d), 4.45 (1H, br.d), 4.64 (1H, br.q), 6.29 (1H, s), 6.62 (1H, s), 7.27 (4H, m), 7.39 (2H, d), 7.83 (2H, d).

mTOR Kinase Assay (Echo): 0.0314μM

Example 23k: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.36 (3H, d), 2.32 (6H, s), 2.52 (2H, t), 2.55 (2H, ddd), 2.63 (2H, d), 3.26 - 3.37 (5H, m), 3.64 (1H, ddd), 3.79 (1H, dd), 3.85 (1H, d), 3.98 (2H, m), 4.07 (1H, dd), 4.17 (1H, d), 4.45 (1H, br.d), 5.18 (1H, br.t), 6.61 (1H, s), 7.27 (2H, d), 7.32 (2H, d), 7.39 (2H, d), 7.80 (2H, d).

mTOR Kinase Assay (Echo): 1.14μM

Example 23l: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.36 (3H, d), 2.37 (1H, t), 2.55 (4H, ddd), 2.64 (2H, br.d), 3.26 - 3.37 (3H, m), 3.46 (2H, dt), 3.64 (1H, ddd), 3.77 - 3.81 (3H, m), 3.86 (1H, d), 3.99 (2H, m), 4.08 (1H, dd), 4.16 (1H, d), 4.45 (1H, br.d), 5.07 (1H, t), 6.49 (1H, s), 6.63 (1H, s), 7.26 (2H, d), 7.28 (2H, d), 7.39 (2H, d), 7.84 (2H, d).

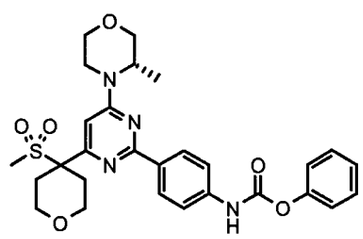
mTOR Kinase Assay (Echo): 0.00888μM

Example 23m: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.53 (3H, ddd), 2.64 (2H, br.d), 3.26 - 3.37 (3H, m), 3.64 (1H, ddd), 3.78 (21H, dd), 3.85 (1H, d), 3.91 (3H, s), 3.99 (2H, m), 4.07 (1H, dd), 4.15 (1H, d), 4.44 (1H, br.d), 6.11 (1H, s), 6.61 (1H, s), 6.63 (1H, s), 7.28 (2H, d), 7.32 (2H, d), 7.41 (2H, d), 7.42 (1H, s), 7.61 (1H, s), 7.84 (2H, d).

mTOR Kinase Assay (Echo): 0.0577μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]phenyl]carbamate



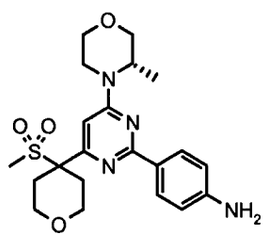
Phenyl chloroformate (0.196 mL, 1.56 mmol) was added dropwise to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]aniline (615 mg, 1.42 mmol) and sodium hydrogen carbonate (179 mg, 2.13 mmol) in dioxane (50 mL) at RT. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was concentrated, diluted with ethyl acetate (100 mL) and washed sequentially with water (2 x 100 mL) and

saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 80% ethyl acetate in *iso*-hexane, to afford the desired material as a white solid (714 mg).

NMR Spectrum: ^1H NMR (399.902 MHz, $CDCl_3$) δ 1.36 (3H, d), 2.55 (2H, m), 2.71 (3H, s), 2.73 (2H, d), 3.35 (1H, ddd), 3.42 (2H, ddd), 3.62 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.02 - 4.08 (3H, m), 4.20 (1H, d), 4.47 (1H, br.d), 6.66 (1H, s), 7.11 (1H, s), 7.21 (2H, d), 7.26 (1H, dd), 7.41 (2H, dd), 7.54 (2H, d), 8.35 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 553; HPLC tR = 2.57 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidin-2-yl]aniline

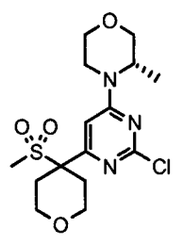


Sodium carbonate (2M in water, 5.75 mL, 11.49 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.839 g, 3.83 mmol) and 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidine (1.200 g, 3.19 mmol) in a mixture of ethylene glycol diethyl ether (10 mL), ethanol (10 mL), DMF (10 mL) and water (20 mL) at RT under nitrogen. The mixture was degassed and purged with nitrogen. Bis(triphenylphosphine)palladium(II) chloride (0.112 g, 0.16 mmol) was added and the mixture was degassed and purged with nitrogen. The resulting suspension was stirred under nitrogen at 80°C for 90 minutes. The reaction mixture was concentrated and diluted with ethyl acetate (150 mL) and washed sequentially with water (2 x 150 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 100% ethyl acetate in *iso*-hexane, to afford the desired material as a white solid (690 mg).

NMR Spectrum: ^1H NMR (399.902 MHz, $CDCl_3$) δ 1.34 (3H, d), 2.53 (2H, ddd), 2.70 (3H, s), 2.72 (2H, br.d), 3.33 (1H, ddd), 3.41 (2H, ddd), 3.61 (1H, ddd), 3.76 (1H, dd), 3.83 (1H, d), 3.93 (2H, s), 4.03 (3H, m), 4.18 (1H, d), 4.45 (1H, br.d), 6.58 (1H, s), 6.71 (2H, d), 8.18 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 433; HPLC tR = 1.98 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(4-methylsulfonyloxan-4-yl)pyrimidine



Sodium *tert*-butoxide (1.38 g, 14.39 mmol) was added portionwise to a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (2.00 g, 6.54 mmol) and bis(2-bromoethyl) ether (2.055 mL, 16.35 mmol) in DMF (75 mL) at 0°C over a period of 10 minutes under nitrogen. The resulting solution was allowed to warm to RT and stirred for 7 hours. Further sodium *tert*-butoxide (629 mg, 6.54 mmol) was added portionwise and the solution was stirred at RT for a further 45 hours. The reaction mixture was concentrated, diluted with ethyl acetate (200 mL) and washed sequentially with water (2 x 200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 100% ethyl acetate in *iso*-hexane. Pure fractions were evaporated to dryness and the residue crystallised from ethyl acetate / *iso*-hexane to afford the desired material as a white crystalline solid (1.42 g).

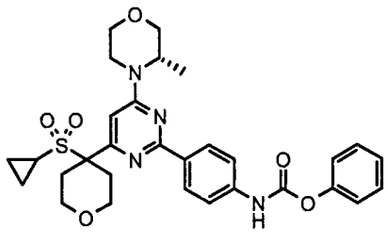
NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.34 (3H, d), 2.50 (2H, m), 2.55 (2H, m), 2.73 (3H, s), 3.33 (3H, m), 3.56 (1H, ddd), 3.71 (1H, dd), 3.80 (1H, d), 4.01 (4H, m), 4.31 (1H, br.s), 6.62 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 376, 378; HPLC tR = 1.85 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

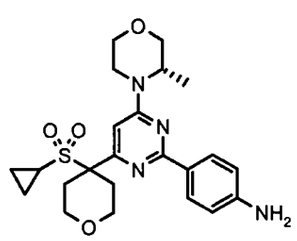
Phenyl *N*-[4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.211 mL, 1.68 mmol) was added to 4-[4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (700 mg, 1.53 mmol) and sodium hydrogen carbonate (192 mg, 2.29 mmol) in 1,4-dioxane (50 mL) at RT. The resulting suspension was stirred at RT for 16 hours. The reaction mixture was concentrated and diluted with ethyl acetate (75 mL) and washed sequentially with water (75 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 70% ethyl acetate in *iso*-hexane, to afford the desired material as a white solid (850 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.83 (2H, m), 1.02 (2H, m), 1.35 (3H, d), 2.18 (1H, tt), 2.54 (2H, m), 2.83 (2H, d), 3.34 (2H, ddd), 3.43 (2H, dd), 3.63 (1H, ddd), 3.77 (1H, dd), 3.84 (1H, d), 4.02 (2H, m), 4.06 (1H, dd), 4.20 (1H, d), 4.47 (1H, br.d), 6.69 (1H, s), 7.08 (1H, s), 7.21 (2H, d), 7.26 (1H, dd), 7.41 (2H, dd), 7.54 (2H, d), 8.37 (2H, d).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 579.5; HPLC tR = 2.72 min.

4-[4-(4-Cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



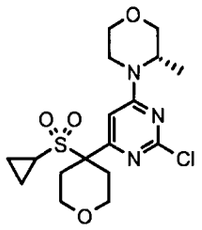
Sodium carbonate (2M in water, 7.48 mL, 14.96 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.092 g, 4.99 mmol) and 2-chloro-4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (1.67 g, 4.16 mmol) in a mixture of ethylene glycol diethyl ether (10 mL), ethanol (10 mL), DMF (10 mL) and water (20 mL) at RT under nitrogen. The mixture was degassed and purged with nitrogen. Bis(triphenylphosphine)palladium(II) chloride (0.146 g, 0.21 mmol) was added and the

mixture was degassed and purged with nitrogen. The resulting suspension was stirred under nitrogen at 80°C for 90 minutes. The reaction mixture was concentrated and diluted with ethyl acetate (150 mL) and washed sequentially with water (2 x 150 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 70% ethyl acetate in *iso*-hexane, to afford the desired material as a white solid (740 mg).

NMR Spectrum: ^1H NMR (399.902 MHz, $CDCl_3$) δ 0.82 (2H, m), 1.01 (2H, m), 1.33 (3H, d), 2.17 (1H, tt), 2.51 (2H, m), 2.82 (2H, br.d), 3.32 (1H, ddd), 3.43 (2H, ddd), 3.62 (1H, ddd), 3.76 (1H, dd), 3.83 (1H, d), 3.91 (2H, s), 3.98 (2H, m), 4.05 (1H, dd), 4.17 (1H, d), 4.45 (1H, br.d), 6.62 (1H, s), 6.71 (2H, d), 8.21 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 459; HPLC tR = 2.05 min.

2-Chloro-4-(4-cyclopropylsulfonyloxan-4-yl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine



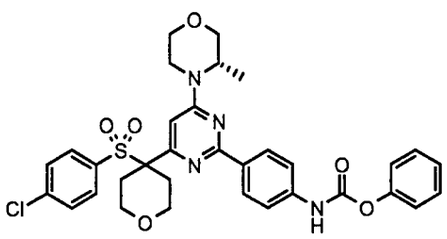
Sodium *tert*-butoxide (1.738 g, 18.08 mmol) was added portionwise to 2-choro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.00 g, 6.03 mmol) and bis(2-bromoethyl) ether (2.273 mL, 18.08 mmol) in DMF (75 mL) at RT over a period of 5 minutes under nitrogen. The resulting solution was stirred at RT for 5 hours. Further bis(2-bromoethyl) ether (0.758 mL, 6.03 mmol), and sodium *tert*-butoxide (0.579 g, 6.03 mmol) were added and the solution was stirred at RT for a further 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (0.5 mL), concentrated, diluted with ethyl acetate (200 mL) and washed sequentially with water (2 x 200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 40 to 60% ethyl acetate in *iso*-hexane, to afford the desired material as a colourless oil which crystallised on standing (1.734 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.01 (2H, m), 1.01 (2H, m), 1.33 (3H, d), 2.22 (1H, tt), 2.47 (2H, ddd), 2.64 (2H, br.d), 3.30 (1H, ddd), 3.36 (2H, dd), 3.56 (1H, ddd), 3.71 (1H, dd), 3.80 (1H, d), 3.97 - 4.04 (4H, m), 4.30 (1H, br.d), 6.66 (1H, s).
LCMS Spectrum: m/z (ESI-)(M-H)- = 400.4; HPLC tR = 2.04 min.

The preparation of 2-choro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

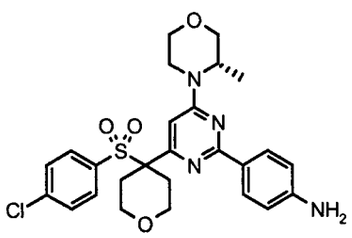
The preparation of phenyl *N*-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.198 mL, 1.58 mmol) was added to 4-[4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (759 mg, 1.43 mmol) and sodium hydrogen carbonate (181 mg, 2.15 mmol) in 1,4-dioxane (50 mL) at RT. The resulting suspension was stirred at RT for 16 hours. The reaction mixture was concentrated and diluted with ethyl acetate (75 mL) and washed sequentially with water (75 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 70% ethyl acetate in *iso*-hexane, to afford the desired material as a white dry film (780 mg).
NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.36 (3H, d), 2.56 (2H, ddd), 2.64 (2H, br.d), 3.31 (2H, ddd), 3.35 (1H, ddd), 3.65 (1H, ddd), 3.80 (1H, dd), 3.86 (1H, d), 4.00 (2H, m), 4.08 (1H, dd), 4.18 (1H, d), 4.45 (1H, br.d), 6.64 (1H, s), 7.04 (1H, s), 7.21 (2H, d), 7.22 (1H, dd), 7.27 (2H, d), 7.39 (2H, d), 7.40 (2H, dd), 7.43 (2H, d), 7.87 (2H, d).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 649, 651; HPLC tR = 3.02 min.

4-[4-[4-(4-Chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

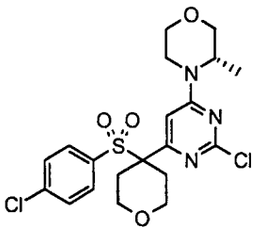


Sodium carbonate (2M in water, 4.02 mL, 8.05 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (490 mg, 2.24 mmol) and 2-chloro-4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (1056 mg, 2.24 mmol) in a mixture of ethanol (10 mL), water (20 mL), DMF (10 mL) and ethylene glycol diethyl ether (10 mL) at RT under nitrogen. The mixture was degassed and purged with nitrogen. Bis(triphenylphosphine)palladium(II) chloride (78 mg, 0.11 mmol) was added and the mixture degassed and purged with nitrogen. The resulting suspension was stirred at 80°C for 2 hours. The reaction mixture was concentrated and diluted with ethyl acetate (100 mL) and water (100 mL). The resulting precipitate was removed by filtration. The organic layer was washed sequentially with water (100 mL) and saturated brine (100 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in *iso*-hexane, to afford the desired material as a white dry film (790 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.54 (2H, ddd), 2.63 (2H, d), 3.27 - 3.35 (3H, m), 3.64 (1H, ddd), 3.79 (1H, dd), 3.85 (1H, d), 3.87 (2H, s), 3.98 (2H, m), 4.06 (1H, dd), 4.16 (1H, d), 4.44 (1H, br.d), 6.56 (1H, s), 6.60 (2H, d), 7.27 (2H, d), 7.39 (2H, d), 7.69 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 529.5, 531.5; HPLC tR = 2.49 min.

2-Chloro-4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine

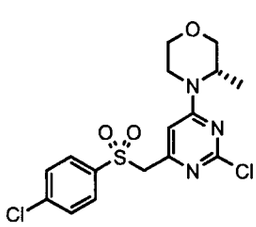


Sodium *tert*-butoxide (1.566 g, 16.30 mmol) was added portionwise to 2-chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.873 g, 4.66 mmol) and bis(2-bromoethyl) ether (1.463 mL, 11.64 mmol) in DMF (75 mL) at RT over a period of 5 minutes under nitrogen. The resulting solution was stirred at RT for 6 hours. Further sodium *tert*-butoxide (0.895 g, 9.31 mmol) was added and the solution was stirred at RT for a further 4 days. The reaction mixture was concentrated and diluted with ethyl acetate (200 mL), and washed sequentially with water (2 x 200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 50% ethyl acetate in *iso*-hexane, to afford the desired material as a white dry film (1.0 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.35 (3H, d), 2.45 - 2.49 (4H, m), 3.22 - 3.35 (3H, m), 3.59 (1H, ddd), 3.73 (1H, dd), 3.82 (1H, d), 3.95 - 4.00 (3H, m), 4.04 (1H, dd), 4.31 (1H, br.s), 6.67 (1H, s), 7.39 (2H, d), 7.45 (2H, d).

LCMS Spectrum: m/z (ESI-)(M-H)- = 470, 472; HPLC tR = 2.62 min.

2-Chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



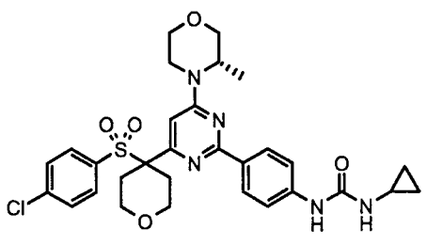
4-Chlorobenzenesulphinic acid sodium salt (5.39 g, 27.15 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (8.00 g, 22.63 mmol) in acetonitrile (400 mL) at RT. The resulting suspension was stirred at 85°C under reflux for 5 hours. The reaction mixture was concentrated and diluted with DCM (400 mL) and washed with water (400 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 25 to 40% ethyl acetate in isohexane, to give the desired material as a white solid (6.90 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, CDCl3) δ 1.33 (3H, d), 3.30 (1H, ddd), 3.55 (1H, ddd), 3.70 (1H, dd), 3.80 (1H, d), 4.02 (2H, m), 4.28 (1H, br.s), 4.29 (2H, s), 6.55 (1H, s), 7.51 (2H, d), 7.70 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 402, 404; HPLC tR = 2.26 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 24: 1-[4-[4-[4-(4-Chlorophenyl)sulfonyloxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea



Sodium carbonate (0.381 mL, 0.76 mmol) was added to 2-chloro-4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (100 mg, 0.21 mmol) and 4-(3-cyclopropylureido)phenylboronic acid (47 mg, 0.21 mmol) in DME (2 mL), ethanol (2 mL), DMF (2 mL) and water (4 mL) at RT under nitrogen. The mixture was degassed and purged with nitrogen then bis(triphenylphosphine)palladium(II) chloride (7.4 mg, 0.011 mmol) added and the mixture stirred at 85°C for 2 hours. The reaction mixture was concentrated, diluted with ethyl acetate (25 mL) and washed sequentially with water (2 x 25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane. The isolated material was further purified trituration with diethyl ether to afford the desired material as a white solid (26 mg).

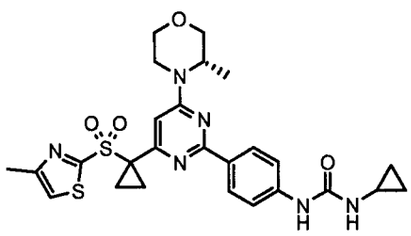
NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.70 (2H, m), 0.88 (2H, m), 1.36 (3H, d), 2.58 (5H, m), 3.31 (2H, m), 3.34 (1H, ddd), 3.65 (1H, ddd), 3.79 (1H, dd), 3.86 (1H, d), 3.99 (2H, m), 4.08 (1H, dd), 4.17 (1H, d), 4.45 (1H, d), 4.88 (1H, s), 6.63 (1H, s), 6.94 (1H, s), 7.27 (2H, d), 7.39 (2H, d), 7.39 (2H, d), 7.84 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 612, 6144; HPLC tR = 2.48 min.

mTOR Kinase Assay (Echo): 0.00517μM

The preparation of 2-chloro-4-[4-(4-chlorophenyl)sulfonyloxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 25: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea



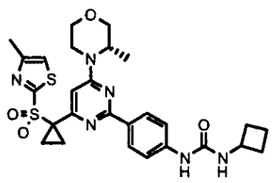
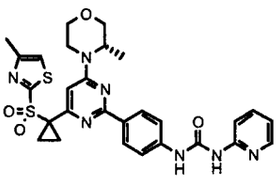
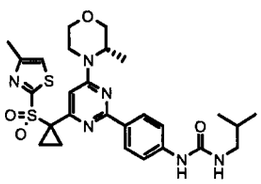
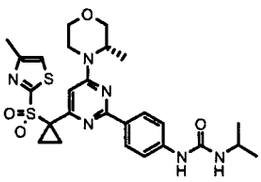
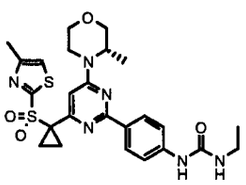
To cyclopropylamine (57 mg, 1 mmol) was added a solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) in DMF (1.5 mL). Triethylamine (0.082 mL, 0.59 mmol) was then added and the resultant mixture was heated to 50°C and stirred overnight (~18 hours). The reaction mixture was cooled then purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) in acetonitrile as eluents, to give the desired material as a white solid (50 mg).

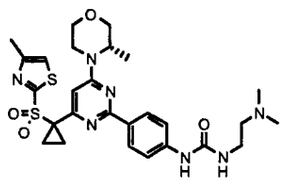
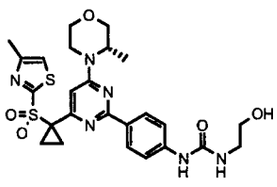
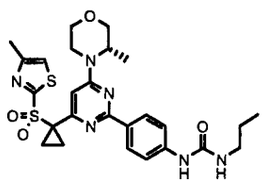
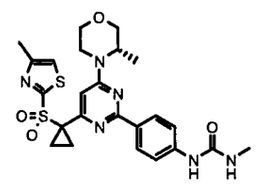
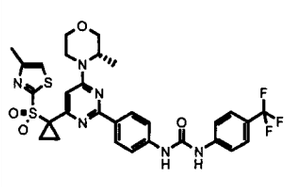
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.21 (3H, d), 1.75 - 1.80 (2H, m), 1.93 - 1.97 (2H, m), 2.47 - 2.49 (3H, m), 2.51 - 2.58 (1H, m), 3.17 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.10 - 4.20 (1H, m), 4.41 - 4.48 (1H, m), 6.41 (1H, d), 6.77 (1H, s), 7.41 - 7.44 (2H, m), 7.83 (1H, d), 7.87 - 7.90 (2H, m), 8.52 (1H, s).

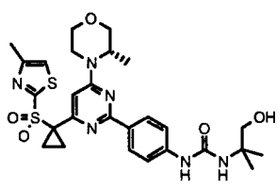
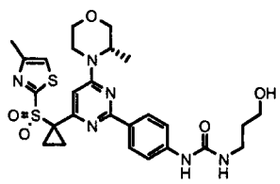
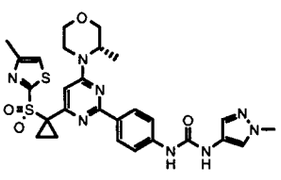
LCMS Spectrum: m/z (ESI+)(M+H)+ = 555; HPLC tR = 2.13 min.

mTOR Kinase Assay (Echo): 0.00155μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
25a		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	569.6	1.90
25b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	592.4	2.51
25c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	571.4	2.42
25d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	557.4	2.26
25e		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	543.4	2.08

Example	Structure	NAME	LCMS MH+	Retention time (min)
25f		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	586.4	1.98
25g		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	559.3	1.78
25h		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-1-propylurea	557.4	2.26
25i		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	529.3	1.94
25j		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	659.3	2.9

Example	Structure	NAME	LCMS MH+	Retention time (min)
25k		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	587.4	2.05
25l		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	573.4	1.82
25m		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	595.4	1.99

Example 25a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.56 - 1.67 (2H, m), 1.75 - 1.79 (2H, m), 1.82 - 1.88 (2H, m), 1.93 - 1.95 (2H, m), 2.16 - 2.24 (2H, m), 2.48 (3H, s), 3.17 (1H, td), 3.46 (1H, td), 3.61 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.08 - 4.20 (2H, m), 4.41 - 4.49 (1H, m), 6.45 (1H, d), 6.77 (1H, s), 7.39 (2H, d), 7.83 - 7.88 (3H, m), 8.57 (1H, s).

mTOR Kinase Assay (Echo): 0.00224μM

Example 25b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.78 - 1.82 (2H, m), 1.95 - 1.99 (2H, m), 2.49 - 2.50 (3H, m), 3.20 (1H, td), 3.48 (1H, td), 3.63 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.13 - 4.21 (1H, m), 4.43 - 4.50 (1H, m), 6.81 (1H, s), 7.02 - 7.05 (1H, m), 7.53 - 7.62 (3H, m), 7.75 - 7.79 (1H, m), 7.85 - 7.87 (1H, m), 7.96 - 7.99 (2H, m), 8.29 - 8.31 (1H, m), 9.42 (1H, s), 10.53 (1H, s).

mTOR Kinase Assay (Echo): 0.000817μM

Example 25c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (6H, d), 1.21 (3H, d), 1.65 - 1.75 (1H, m), 1.75 - 1.80 (2H, m), 1.93 - 1.98 (2H, m), 2.48 - 2.49 (3H, m), 2.94 (2H, t), 3.18 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.20 (1H, m), 4.41 - 4.49 (1H, m), 6.22 (1H, t), 6.77 (1H, s), 7.39 - 7.42 (2H, m), 7.83 - 7.84 (1H, m), 7.87 - 7.90 (2H, m), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.00385μM

Example 25d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.21 (3H, d), 1.76 - 1.80 (2H, m), 1.93 - 1.97 (2H, m), 2.48 - 2.49 (3H, m), 3.18 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.73 - 3.81 (2H, m), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.41 - 4.48 (1H, m), 6.03 (1H, d), 6.77 (1H, s), 7.38 - 7.41 (2H, m), 7.84 - 7.84 (1H, m), 7.87 - 7.90 (2H, m), 8.51 (1H, s).

mTOR Kinase Assay (Echo): 0.00157μM

Example 25e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.21 (3H, d), 1.76 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 - 2.49 (3H, m), 3.09 - 3.21 (3H, m), 3.47 (1H, td), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.41 - 4.49 (1H, m), 6.15 (1H, t), 6.77 (1H, s), 7.39 - 7.43 (2H, m), 7.83 - 7.84 (1H, m), 7.86 - 7.90 (2H, m), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.000277μM

Example 25f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.26 (3H, d), 1.81 - 1.85 (2H, m), 1.99 - 2.02 (2H, m), 2.23 (6H, s), 2.39 (2H, t), 2.53 - 2.54 (3H, m), 3.19 - 3.27 (3H, m), 3.52 (1H, td), 3.67 (1H, dd), 3.81 (1H, d), 4.02 (1H, dd), 4.17 - 4.24 (1H, m), 4.47 - 4.53 (1H, m), 6.20 (1H, t), 6.82 (1H, s), 7.44 - 7.47 (2H, m), 7.88 - 7.90 (1H, m), 7.92 - 7.95 (2H, m), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.0547μM

Example 25g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.76 - 1.80 (2H, m), 1.93 - 1.97 (2H, m), 2.47 - 2.48 (3H, m), 3.13 - 3.21 (3H, m), 3.43 - 3.50 (3H, m), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.41 - 4.49 (1H, m), 4.73 (1H, t), 6.23 (1H, t), 6.77 (1H, s), 7.39 - 7.42 (2H, m), 7.83 - 7.84 (1H, m), 7.87 - 7.90 (2H, m), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00119μM

Example 25h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.21 (3H, d), 1.46 (2H, sextet), 1.76 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 - 2.49 (3H, m), 3.06 (2H, q), 3.14 - 3.21 (1H, m), 3.47 (1H, td), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.41 - 4.49 (1H, m), 6.19 (1H, t), 6.77 (1H, s), 7.39 - 7.43 (2H, m), 7.83 - 7.84 (1H, m), 7.86 - 7.90 (2H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.000993μM

Example 25i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.76 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 – 2.49(3H, m), 2.66 (3H, d), 3.18 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.11 - 4.20 (1H, m), 4.40 - 4.50 (1H, m), 6.05 (1H, q), 6.77 (1H, s), 7.40 - 7.44 (2H, m), 7.83 - 7.84 (1H, m), 7.86 - 7.90 (2H, m), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.001μM

Example 25j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.77 - 1.81 (2H, m), 1.95 - 1.99 (2H, m), 2.48 - 2.49 (3H, m), 3.19 (1H, td), 3.48 (1H, td), 3.63 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.13 - 4.21 (1H, m), 4.42 - 4.51 (1H, m), 6.80 (1H, s), 7.49 - 7.52 (2H, m), 7.63 - 7.70 (4H, m), 7.85 - 7.86 (1H, m), 7.95 - 7.98 (2H, m), 9.03 (1H, s), 9.12 (1H, s).

mTOR Kinase Assay (Echo): 0.00576μM

Example 25k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.24 (6H, s), 1.76 - 1.79 (2H, m), 1.94 - 1.97 (2H, m), 2.48 - 2.49 (3H, m), 3.18 (1H, td), 3.39 (2H, d), 3.47 (1H, td), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.41 - 4.48 (1H, m), 4.95 (1H, t), 5.98 (1H, s), 6.76 (1H, s), 7.34 - 7.39 (2H, m), 7.84 - 7.89 (3H, m), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.00292μM

Example 25l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.60 (2H, quintet), 1.76 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 - 2.49 (3H, m), 3.14 - 3.21 (3H, m), 3.44 - 3.50 (3H, m), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 - 4.19 (1H, m), 4.42 - 4.49 (2H, m), 6.18 (1H, t), 6.77 (1H, s), 7.39 - 7.43 (2H, m), 7.83 - 7.84 (1H, m), 7.86 - 7.90 (2H, m), 8.69 (1H, s).

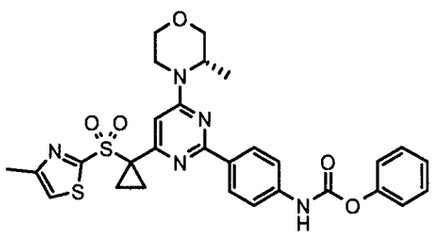
mTOR Kinase Assay (Echo): 0.000956μM

Example 25m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.77 - 1.80 (2H, m), 1.94 - 1.98 (2H, m), 2.48 - 2.49 (3H, m), 3.15 - 3.22 (1H, m), 3.48 (1H, td), 3.62 (1H, dd), 3.75 - 3.79 (4H, m), 3.97 (1H, dd), 4.13 - 4.20 (1H, m), 4.42 - 4.49 (1H, m), 6.79 (1H, s), 7.38 - 7.39 (1H, m), 7.44 - 7.49 (2H, m), 7.77 (1H, s), 7.84 - 7.85 (1H, m), 7.90 - 7.94 (2H, m), 8.38 (1H, s), 8.83 (1H, s).

mTOR Kinase Assay (Echo): 0.00025μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate

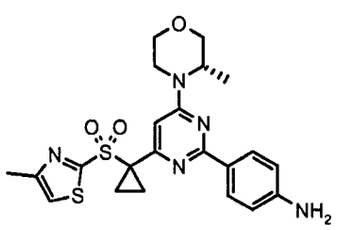


A solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]aniline (1.56 g, 3.31 mmol) in 1,4-dioxane (18 mL) was treated with sodium bicarbonate (0.445 g, 5.29 mmol). Phenyl chloroformate (0.5 mL, 3.99 mmol) was then added dropwise and the resulting suspension was stirred at RT, under nitrogen for 150 minutes. The reaction mixture was evaporated to dryness and the residue partitioned between DCM (100 mL) and water (50 mL). The organic layer washed with brine, dried ($MgSO_4$), filtered and evaporated to an amber gum/foam which was triturated under isohexane / diethyl ether (~1:1 v/v,~100 mL) with sonication and resultant solid collected by suction filtration and dried, under vacuum, at 50°C, to give the desired material as a beige solid (1.72 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.71 - 1.75 (2H, m), 1.87 - 1.91 (2H, m), 2.40 - 2.41 (3H, m), 3.12 (1H, td), 3.40 (1H, td), 3.55 (1H, dd), 3.69 (1H, d), 3.90 (1H, dd), 4.07 - 4.14 (1H, m), 4.35 - 4.44 (1H, m), 6.75 (1H, s), 7.16 - 7.23 (3H, m), 7.35 - 7.40 (2H, m), 7.47 - 7.50 (2H, m), 7.76 - 7.77 (1H, m), 7.90 - 7.93 (2H, m), 10.32 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 592.1; HPLC tR = 2.87 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]aniline

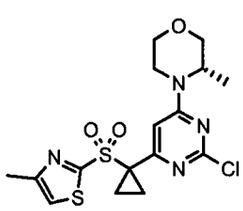


A mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidine (1.9 g, 4.58 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.36 g, 6.21 mmol) and 2M aqueous sodium carbonate solution (5.72 mL, 11.45 mmol) in a mixture of ethanol (5.50 mL), DME (11 mL), water (5.50 mL) and DMF (0.7 mL) was purged with nitrogen for 10 minutes before addition of bis(triphenylphosphine)palladium(II) chloride (0.161 g, 0.23 mmol). The reaction mixture was then heated to 85°C and stirred for 3 hours. The reaction mixture was cooled and partitioned between ethyl acetate (150 mL) and water (250 mL), the organic layer separated and aqueous re-extracted with ethyl acetate (100 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness to afford the crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane. The isolated material was further purified by trituration with hot isohexane and diethyl ether to give the desired material as a beige solid (1.6 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.73 - 1.77 (2H, m), 1.92 - 1.95 (2H, m), 2.48 - 2.49 (3H, m), 3.15 (1H, td), 3.46 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.08 - 4.16 (1H, m), 4.37 - 4.45 (1H, m), 5.52 (2H, s), 6.50 - 6.54 (2H, m), 6.67 (1H, s), 7.70 - 7.74 (2H, m), 7.82 - 7.84 (1H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 472.1; HPLC tR = 2.24 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidine



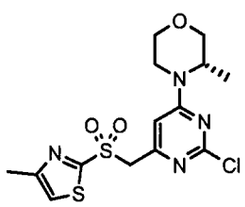
A solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (3.29 g, 8.46 mmol) in toluene (45 mL) was treated with 1,2-dibromoethane (1.4 mL, 16.25 mmol). Tetrabutylammonium bromide (0.273 g, 0.85 mmol) was then added followed by a solution of sodium hydroxide (3.4 g, 85.01 mmol) in water (3.4 mL). The resulting mixture was heated to 65°C, under an atmosphere of nitrogen, for 1 hour then at 75°C for 2.5 hours. The mixture was allowed to cool and partitioned between ethyl acetate (60 mL) and water (30 mL). The organic layer was separated, washed with brine,

dried ($MgSO_4$), filtered and evaporated to a brown gum. The crude product was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired material as a yellow gum (2.76 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.12 (3H, d), 1.63 - 1.66 (2H, m), 1.81 - 1.85 (2H, m), 2.39 - 2.41 (3H, m), 3.11 (1H, td), 3.32 - 3.38 (1H, m), 3.49 (1H, dd), 3.65 (1H, d), 3.82 - 3.92 (2H, m), 4.16 - 4.27 (1H, m), 6.83 (1H, s), 7.81 - 7.84 (1H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 415.10; HPLC tR = 2.12 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine

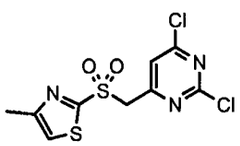


A solution of 2,4-dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (8.35 g, 25.76 mmol) in DCM (100 mL) was cooled to 4°C. Triethylamine (4.3 mL, 30.85 mmol) was then added and mixture stirred for 5 minutes before dropwise addition, over 10 minutes, of a solution of (S)-3-methylmorpholine (2.9 g, 28.67 mmol) in DCM (25 mL). The reaction mixture was then stirred in cooling bath for 45 minutes then at RT overnight. Water (200 mL) was added to reaction mixture and stirred for10 minutes before the organic layer was separated and aqueous layer extracted with DCM (50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated to afford the crude product, which was purified by flash silica chromatography, eluting with 50% ethyl acetate in isohexane, to give the desired material as a yellow gum (5.80 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 2.49 - 2.50 (3H, m), 3.18 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.88 - 3.96 (2H, m), 4.15 - 4.29 (1H, m), 4.82 (2H, s), 6.80 (1H, s), 7.89 - 7.90 (1H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ =389.2; HPLC tR = 1.87min.

2,4-Dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine

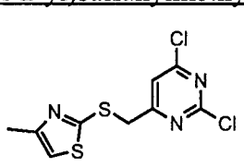


A solution of 2,4-dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfanylmethyl]pyrimidine (7.39 g, 25.29 mmol) in DCM (130 ml) was cooled to 4°C and treated portionwise, over 15 minutes with 3-chloroperoxybenzoic acid (13.60 g, 60.70 mmol). The resulting suspension was stirred in cooling bath for 15 minutes then at RT for 24 hours. A saturated aqueous solution of sodium bicarbonate (200 mL) was added to the reaction mixture and stirred for 30 minutes. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and evaporated to give the desired material as an oil which solidified on standing (8.40 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.47 - 2.49 (3H, m), 5.19 (2H, s), 7.84 (1H, s), 7.93 - 7.95 (1H, m).

LCMS Spectrum: m/z (ESI-) (M-H)- = 322.0; HPLC tR = 1.53 min.

2,4-Dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfanylmethyl]pyrimidine

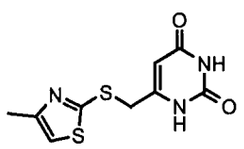


A suspension of 6-[(4-methyl-1,3-thiazol-2-yl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione (14.4 g, 56.40 mmol) in phosphorus oxychloride (60 mL, 643.70 mmol) was warmed to 100°C and stirred for 6 hours. The reaction mixture cooled before evaporating to a brown oil and partitioning between DCM (100 mL) and water (100 mL). With stirring solid sodium hydrogen carbonate was then added carefully to adjust the mixture to pH8, additional aliquots of water (100 mL) and DCM (100 mL) were added during this time. Additional DCM (100 mL) and water (100 mL) were added and the organic layer separated and the aqueous layer re-extracted with DCM (2 x 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to dryness to give the desired material as a tan solid (15.76 g). the material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.30 - 2.32 (3H, m), 4.55 (2H, s), 7.22 - 7.24 (1H, m), 7.84 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 292.1; HPLC tR = 2.36min.

6-[(4-Methyl-1,3-thiazol-2-yl)sulfanylmethyl]-1*H*-pyrimidine-2,4-dione

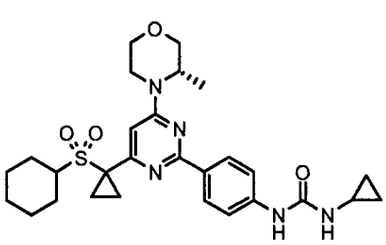


To a solution of 4-methylthiazole-2-thiol (10 g, 76.21 mmol) in DMF (150 mL) at RT was added DBU (14 mL, 93.80 mmol) dropwise over 5 minutes. The resulting solution was stirred at RT for 30 minutes. 6-(Chloromethyl)-1*H*-pyrimidine-2,4-dione (10 g, 62.28 mmol) was then added portionwise over a period of 20 minutes under nitrogen. The resulting solution was stirred at RT for 19 hours then the reaction mixture evaporated to dryness and the residue partitioned between DCM (150 mL) and water (150 mL). The solid precipitate was collected by filtration to give the desired material as a cream solid (11.1 g). Additional desired material (4.3 g) was obtained after the filtrate was acidified with 2M hydrochloric acid and the resultant precipitate collected by filtration.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.34 (3H, s), 4.08 (2H, s), 5.43 (1H, s), 7.27 (1H, s), 10.98 (2H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 256.2; HPLC tR = 0.58 min.

Example 26: 1-[4-[4-(1-Cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea



To cyclopropylamine (56 mg, 0.98 mmol) was added a solution of phenyl *N*-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (79.5 mg, 0.14 mmol) in DMF (2 mL). Triethylamine (0.067 mL, 0.48 mmol) was then added and the resultant mixture was heated to 50°C and stirred for 2 hours.

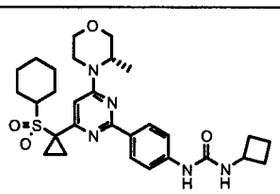
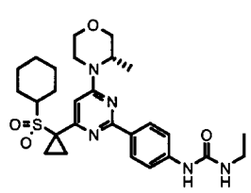
The reaction mixture was cooled and purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% TFA) and acetonitrile as eluants, followed by purification by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) in acetonitrile as eluants, to give the desired material as a white solid (28 mg).

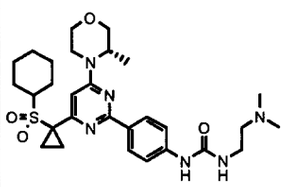
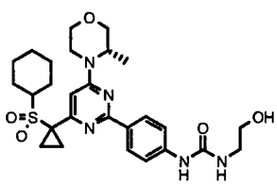
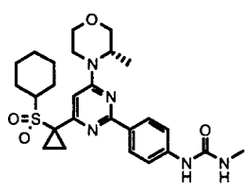
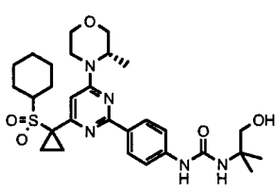
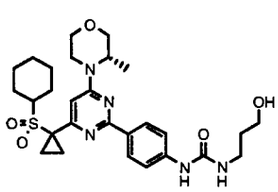
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.13 - 1.29 (6H, m), 1.37 - 1.66 (7H, m), 1.82 - 1.88 (2H, m), 2.26 - 2.34 (2H, m), 2.53 - 2.59 (1H, m), 3.16 - 3.25 (1H, m), 3.44 - 3.53 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.26 (1H, m), 4.49 - 4.59 (1H, m), 6.47 (1H, d), 6.76 (1H, s), 7.50 - 7.54 (2H, m), 8.19 - 8.23 (2H, m), 8.58 (1H, s).

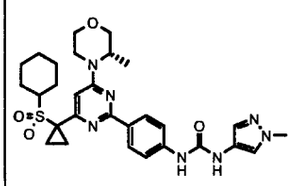
LCMS Spectrum: m/z (ESI+) (M+H)+ = 540; HPLC tR = 2.57 min.

mTOR Kinase Assay (Echo): 0.00605μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
26a		3-cyclobutyl-1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	554	2.81
26b		3-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	528	2.56

Example	Structure	NAME	LCMS MH+	Retention time (min)
26c		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	571	2.53
26d		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	544	2.15
26e		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	514	2.39
26f		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	572	2.27
26g		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	558	2.21

Example	Structure	NAME	LCMS MH+	Retention time (min)
26h		1-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	580	2.40

Example 26a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 - 1.28 (6H, m), 1.37 - 1.69 (9H, m), 1.81 - 1.92 (4H, m), 2.17 - 2.25 (2H, m), 2.26 - 2.34 (2H, m), 3.20 (1H, td), 3.44 - 3.52 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.09 - 4.25 (2H, m), 4.50 - 4.58 (1H, m), 6.49 (1H, d), 6.76 (1H, s), 7.47 - 7.50 (2H, m), 8.19 - 8.22 (2H, m), 8.60 (1H, s).
mTOR Kinase Assay (Echo): 0.00672μM

Example 26b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.13 - 1.29 (6H, m), 1.36 - 1.66 (7H, m), 1.81 - 1.89 (2H, m), 2.26 - 2.35 (2H, m), 3.09 - 3.16 (2H, m), 3.20 (1H, td), 3.45 - 3.53 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.25 (1H, m), 4.50 - 4.58 (1H, m), 6.20 (1H, t), 6.76 (1H, s), 7.48 - 7.52 (2H, m), 8.18 - 8.23 (2H, m), 8.70 (1H, s).
mTOR Kinase Assay (Echo): 0.0039μM

Example 26c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.12 - 1.29 (6H, m), 1.36 - 1.66 (7H, m), 1.82 - 1.88 (2H, m), 2.18 (6H, s), 2.27 - 2.35 (4H, m), 3.16 - 3.24 (3H, m), 3.44 - 3.52 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.25 (1H, m), 4.50 - 4.58 (1H, m), 6.17 (1H, t), 6.76 (1H, s), 7.47 - 7.51 (2H, m), 8.19 - 8.23 (2H, m), 8.90 (1H, s).
mTOR Kinase Assay (Echo): 0.119μM

Example 26d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 - 1.28 (6H, m), 1.38 - 1.65 (7H, m), 1.81 - 1.88 (2H, m), 2.27 - 2.34 (2H, m), 3.16 - 3.24 (3H, m), 3.44 - 3.52 (4H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.25 (1H, m), 4.50 - 4.58 (1H, m), 4.73 (1H, t), 6.27 (1H, t), 6.76 (1H, s), 7.48 - 7.51 (2H, m), 8.19 - 8.23 (2H, m), 8.83 (1H, s).
mTOR Kinase Assay (Echo): 0.0012μM

Example 26e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 - 1.29 (6H, m), 1.37 - 1.66 (7H, m), 1.82 - 1.88 (2H, m), 2.27 - 2.34 (2H, m), 2.66 (3H, d), 3.20 (1H, td), 3.45 - 3.53 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.25 (1H, m), 4.50 - 4.59 (1H, m), 6.09 (1H, q), 6.76 (1H, s), 7.49 - 7.53 (2H, m), 8.19 - 8.22 (2H, m), 8.77 (1H, s).

mTOR Kinase Assay (Echo): 0.00395μM

Example 26f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.12 - 1.29 (12H, m), 1.37 - 1.67 (7H, m), 1.82 - 1.88 (2H, m), 2.27 - 2.34 (2H, m), 3.20 (1H, td), 3.39 (2H, d), 3.45 - 3.53 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.25 (1H, m), 4.49 - 4.59 (1H, m), 4.95 (1H, t), 6.01 (1H, s), 6.75 (1H, s), 7.44 - 7.47 (2H, m), 8.18 - 8.22 (2H, m), 8.77 (1H, s).

mTOR Kinase Assay (Echo): 0.00457μM

Example 26g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 - 1.29 (6H, m), 1.37 - 1.66 (9H, m), 1.81 - 1.88 (2H, m), 2.27 - 2.34 (2H, m), 3.14 - 3.24 (3H, m), 3.44 - 3.52 (4H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.18 - 4.24 (1H, m), 4.47 (1H, t), 4.50 - 4.58 (1H, m), 6.23 (1H, t), 6.76 (1H, s), 7.48 - 7.52 (2H, m), 8.19 - 8.22 (2H, m), 8.74 (1H, s).

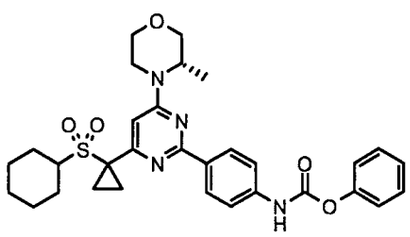
mTOR Kinase Assay (Echo): 0.00746μM

Example 26h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 - 1.30 (6H, m), 1.37 - 1.67 (7H, m), 1.82 - 1.89 (2H, m), 2.28 - 2.34 (2H, m), 3.21 (1H, td), 3.45 - 3.53 (2H, m), 3.64 (1H, dd), 3.74 - 3.79 (4H, m), 3.98 (1H, dd), 4.18 - 4.26 (1H, m), 4.51 - 4.59 (1H, m), 6.77 (1H, s), 7.39 (1H, d), 7.54 - 7.57 (2H, m), 7.77 (1H, s), 8.23 - 8.26 (2H, m), 8.42 (1H, s), 8.87 (1H, s).

mTOR Kinase Assay (Echo): 0.004μM

The preparation of phenyl *N*-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



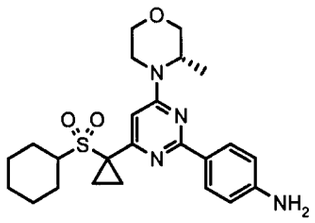
A suspension of 4-[4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (615 mg, 1.35 mmol) in 1,4-dioxane (7 mL) was treated with sodium bicarbonate (182 mg, 2.17 mmol). Phenyl chloroformate (0.20 mL, 1.59 mmol) was then added dropwise and resultant mixture left to stir under nitrogen at RT overnight (~16 hours). The reaction mixture was evaporated to dryness and the residue partitioned between

DCM (10 mL) and water (10 mL). The organic layer was separated and evaporated to an amber gum which was azeotroped with diethyl ether to give the desired material as a beige solid (726 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 - 1.29 (6H, m), 1.37 - 1.48 (2H, m), 1.50 - 1.65 (5H, m), 1.81 - 1.87 (2H, m), 2.26 - 2.34 (2H, m), 3.22 (1H, td), 3.44 - 3.52 (2H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.20 - 4.29 (1H, m), 4.52 - 4.60 (1H, m), 6.83 (1H, s), 7.23 - 7.30 (3H, m), 7.42 - 7.47 (2H, m), 7.63 - 7.67 (2H, m), 8.28 - 8.32 (2H, m), 10.45 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 577.1; HPLC tR = 3.12min.

4-[4-(1-Cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



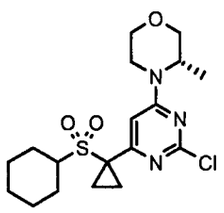
A mixture of 2-chloro-4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.78 g, 4.45 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.474 g, 6.73 mmol) in a mixture of DMF (8 mL), ethanol (8 mL), DME (8 mL) and water (20 mL) was treated with 2M aqueous sodium carbonate solution (11 mL, 22.00 mmol). The resulting mixture was purged with nitrogen for 10 minutes before addition of bis(triphenylphosphine)palladium(II) chloride (0.156 g, 0.22 mmol). The mixture was heated to 85°C and stirred, under nitrogen for 4 hours before being cooled and partitioned between ethyl acetate (100 mL) and water (100 mL). The biphasic mixture was filtered and the organic layer was separated. The aqueous layer was re-extracted with ethyl acetate (2 x 50 mL) and the combined organics were washed with brine, dried ($MgSO_4$) and evaporated to afford the crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired material as a beige solid (0.627 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 - 1.21 (6H, m), 1.31 - 1.49 (6H, m), 1.53 - 1.58 (1H, m), 1.74 - 1.82 (2H, m), 2.19 - 2.26 (2H, m), 3.07 - 3.14 (1H, m), 3.37 -

3.47 (2H, m), 3.55 (1H, dd), 3.68 (1H, d), 3.89 (1H, dd), 4.07 - 4.14 (1H, m), 4.40 - 4.48 (1H, m), 5.50 (2H, s), 6.54 (2H, d), 6.58 (1H, s), 7.98 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 457.3; HPLC tR = 2.55 min.

2-Chloro-4-(1-cyclohexylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

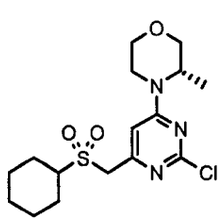


A solution of 2-chloro-4-(cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.8 g, 7.49 mmol) in toluene (40 mL) was treated with 1,2-dibromoethane (1.3 mL, 15.09 mmol). Tetrabutylammonium bromide (0.241 g, 0.75 mmol) was then added followed by a solution of sodium hydroxide (3.00 g, 74.89 mmol) in water (3 mL). The resulting mixture was heated to 64°C and stirred for 90 minutes. The reaction mixture was cooled before addition of ethyl acetate (50 mL) and water (20 mL). The mixture was stirred for 5 minutes then the organic layer separated, washed with brine (30 mL) and evaporated to afford the crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired compound as a pale yellow oil which crystallised on standing (1.785 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10 - 1.41 (8H, m), 1.48 - 1.55 (4H, m), 1.60 - 1.66 (1H, m), 1.77 - 1.84 (2H, m), 2.14 - 2.20 (2H, m), 3.16 - 3.24 (1H, m), 3.32 - 3.47 (2H, m), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 3.99 - 4.07 (1H, m), 4.32 - 4.43 (1H, m), 6.93 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 400.3; HPLC tR = 2.56 min.

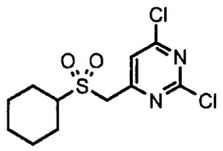
2-Chloro-4-(cyclohexylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



To a solution of 2,4-dichloro-6-(cyclohexylsulfonylmethyl)pyrimidine (1.7g, 5.50 mmol) in DCM (25 ml), cooled with a water / ice bath, was added triethylamine (0.85 mL, 6.10 mmol). The resulting solution was treated, dropwise over 5 minutes, with a solution of (S)-3-methylmorpholine (0.658 g, 6.51 mmol) in DCM (5 mL). The mixture was stirred in cooling bath for 30 minutes then at RT for 3 hours. Water (25 mL) was added to the reaction mixture and stirred for 15 minutes. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to give the crude product, which was purified by flash silica chromatography, elution gradient 25 to 75% ethyl acetate in isohexane, to give the desired material as a yellow oil which crystallised on standing (1.3 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 - 1.45 (8H, m), 1.63 - 1.69 (1H, m), 1.81 - 1.87 (2H, m), 2.11 - 2.17 (2H, m), 3.16 - 3.25 (2H, m), 3.45 (1H, td), 3.60 (1H, dd), 3.73 (1H, d), 3.92 - 4.05 (2H, m), 4.26 - 4.34 (1H, m), 4.40 (2H, s), 6.90 (1H, s).
LCMS Spectrum: m/z (ESI+) (M+H)+ =374.3; HPLC tR = 2.22 min.

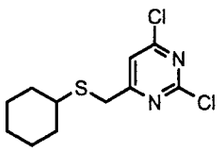
2,4-Dichloro-6-(cyclohexylsulfonylmethyl)pyrimidine



To a solution of 2,4-dichloro-6-(cyclohexylsulfanylmethyl)pyrimidine (4.23 g, 15.26 mmol) in DCM (90 mL), cooled in a water / ice bath, was added 3-chloroperoxybenzoic acid (8.55 g, 38.15 mmol) over a period of 30 minutes under nitrogen, so as to control temperature below 10°C. The resulting suspension was stirred at RT for 3 hours. Saturated aqueous sodium hydrogen carbonate solution (120 mL) was then carefully added portionwise and reaction mixture stirred for 30 minutes before separating the organic layer, drying ($MgSO_4$) and evaporating to give the desired material as an off white solid (4.90 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 - 1.46 (5H, m), 1.62 - 1.68 (1H, m), 1.81 - 1.87 (2H, m), 2.10 - 2.16 (2H, m), 3.22 (1H, tt), 4.74 (2H, s), 7.85 (1H, s).
LCMS Spectrum: m/z (ESI-) (M-H)- = 307.2; HPLC tR = 2.22 min.

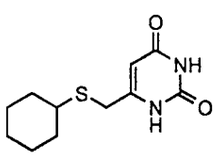
2,4-Dichloro-6-(cyclohexylsulfanylmethyl)pyrimidine



A suspension of 6-(cyclohexylsulfanylmethyl)-1*H*-pyrimidine-2,4-dione (6.4 g, 26.63 mmol) in phosphorus oxychloride (25 mL, 268.2 mmol) was warmed to 100°C, over a period of 15 minutes. The resulting dark orange solution was stirred at 100°C for 7 hours before being cooled and evaporated to a brown oil. The oil was partitioned between DCM (150 mL) and water (150 mL). With stirring solid sodium hydrogen carbonate was then added carefully to adjust the mixture to pH8, aliquots of water (100 mL) and DCM (50 mL) were added during addition. The organic layer was separated, the aqueous layer was re-extracted with more DCM (2 x 75 mL) and the combined organic layers washed with brine (200 mL), dried ($MgSO_4$) and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 15% ethyl acetate in isohexane, to give the desired material as an orange liquid (4.24 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 - 1.31 (5H, m), 1.51 - 1.57 (1H, m), 1.64 - 1.72 (2H, m), 1.86 - 1.92 (2H, m), 2.71 - 2.77 (1H, m), 3.85 (2H, s), 7.82 (1H, s).
LCMS Spectrum: m/z (ESI-) (M-H)- = 275.2 & 277.2 HPLC tR = 3.01 min.

6-(Cyclohexylsulfanylmethyl)-1*H*-pyrimidine-2,4-dione



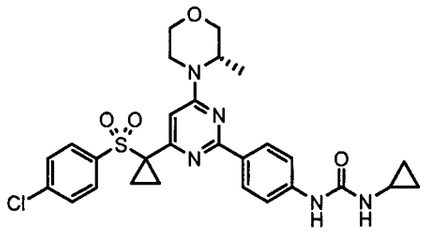
A solution of cyclohexanethiol (10 mL, 81.74 mmol) in DMF (150 mL) at RT was treated with DBU (14 mL, 93.80 mmol). The resulting solution was stirred at RT for 20 minutes then 6-(chloromethyl)-1*H*-pyrimidine-2,4-dione (10 g, 62.28 mmol) added portionwise over a period of 30 minutes, under nitrogen, so as to maintain the internal temperature below 35°C. The resulting solution was stirred at RT overnight. The reaction mixture was evaporated to dryness and the residue was partitioned between DCM (100 mL) and water (150 mL). On mixing a precipitate formed, this was removed by filtration to give the desired material as a

white solid (6.45 g). Additional desired material (3.62 g) was obtained by separating the filtrate, adjusting the aqueous layer to pH2 and collecting the resultant precipitate by filtration.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 - 1.34 (5H, m), 1.51 - 1.58 (1H, m), 1.63 - 1.72 (2H, m), 1.87 - 1.96 (2H, m), 2.65 - 2.72 (1H, m), 3.41 (2H, s), 5.49 (1H, s), 10.75 - 10.96 (2H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 241.3; HPLC tR = 0.99min.

Example 27: 1-[4-[4-[1-(4-Chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea



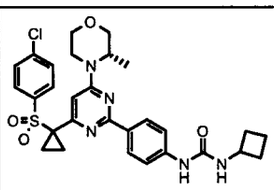
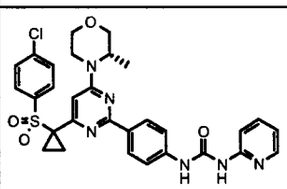
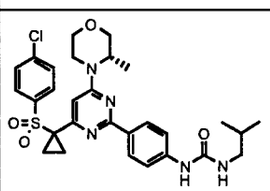
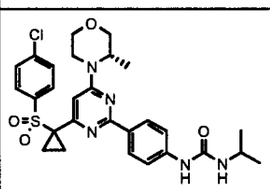
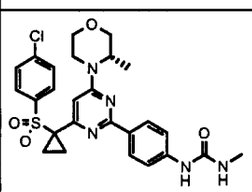
Cyclopropylamine (0.137 mL, 1.98 mmol) was added to phenyl *N*-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.25 mmol) in DMF (2 mL). The resulting solution was stirred at 60°C for 4 hours. The mixture was evaporated to dryness and the residue was partitioned between ethyl acetate (15 mL) and water (15 mL). The organic layer was washed with 1M aqueous citric acid (15 mL) and water (15 mL) and evaporated to dryness. The residue was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to afford the desired material as a white solid (62 mg).

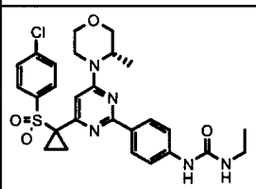
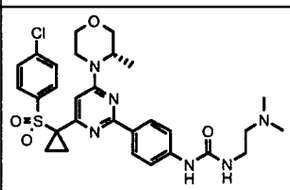
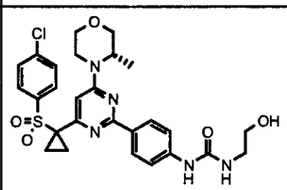
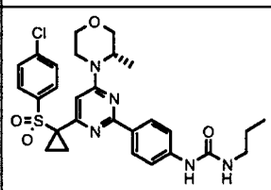
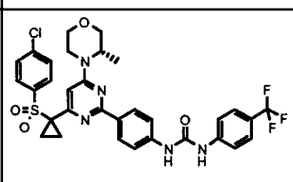
NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.69 (2H, m), 0.87 (2H, m), 1.32 (3H, d), 1.57 (1H, ddd), 1.64 (1H, ddd), 1.98 (2H, m), 2.63 (1H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.04 (1H, dd), 4.14 (1H, d), 4.41 (1H, br.d), 4.87 (1H, s), 6.77 (1H, s), 6.93 (1H, s), 7.40 (2H, d), 7.42 (2H, d), 7.68 (2H, d), 7.99 (2H, d).

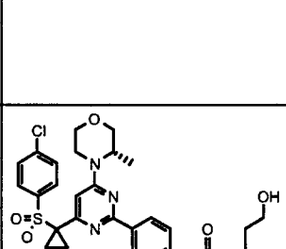
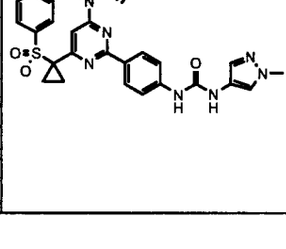
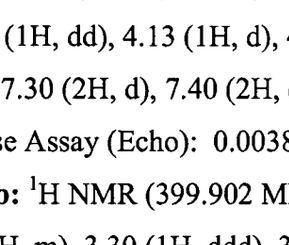
LCMS Spectrum: m/z (ESI+)(M+H)+ = 568, 570; HPLC tR = 2.33 min.

mTOR Kinase Assay (Echo): 0.00144μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
27a		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea	582, 584	2.55
27b		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	605, 607	2.73
27c		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	584, 586	2.63
27d		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	570, 572	2.47
27e		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	542, 544	2.17

Example	Structure	NAME	LCMS MH+	Retention time (min)
27f		3-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	556, 558	2.33
27g		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-dimethylaminoethyl)urea	599, 601	2.23
27h		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	572, 574	2.00
27i		3-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	570, 572	2.48
27j		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	672, 674	3.09

Example	Structure	NAME	LCMS MH+	Retention time (min)
27k		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	600, 602	2.28
27l		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	586, 588	2.04
27m		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	608, 610	2.38

Example 27a: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.59 (2H, m), 1.71 (2H, m), 1.84 (2H, m), 1.98 (2H, m), 2.38 (2H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.30 (1H, tt), 4.41 (1H, br.d), 4.82 (1H, d), 6.26 (1H, s), 6.76 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.00388μM

Example 27b: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.59 (1H, ddd), 1.66 (1H, ddd), 1.99 (2H, m), 3.30 (1H, ddd), 3.61 (1H, ddd), 3.75 (1H, dd), 3.83 (1H, d), 4.05 (1H, dd), 4.15 (1H, d), 4.42 (1H, m), 6.71 (1H, d), 6.78 (1H, s), 6.98 (1H, dd), 7.25 (1H, s), 7.41 (2H, d), 7.60 (2H, d), 7.66 (1H, ddd), 7.69 (2H, d), 8.03 (2H, d), 8.30 (1H, d), 11.92 (1H, s).

mTOR Kinase Assay (Echo): 0.00425μM

Example 27c: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.94 (6H, d), 1.31 (3H, d), 1.56 (1H, ddd), 1.63 (1H, ddd), 1.80 (1H, m), 1.98 (2H, m), 3.10 (2H, dd), 3.29 (1H, ddd), 3.59 (1H, ddd),

3.74 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.41 (1H, br.d), 4.81 (1H, t), 6.41 (1H, s), 6.75 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.014μM

Example 27d: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.19 (6H, d), 1.31 (3H, d), 1.56 (1H, ddd), 1.63 (1H, ddd), 1.98 (2H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 4.03 (2H, m), 4.13 (1H, d), 4.41 (1H, d), 4.54 (1H, br.d), 6.31 (1H, s), 6.75 (1H, s), 7.29 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.97 (2H, d).

mTOR Kinase Assay (Echo): 0.00307μM

Example 27e: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.56 (1H, ddd), 1.62 (1H, ddd), 1.98 (2H, m), 2.87 (3H, d), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.41 (1H, br.d), 4.65 (1H, q), 6.31 (1H, s), 6.76 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.000719μM

Example 27f: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.17 (3H, t), 1.31 (3H, d), 1.56 (1H, ddd), 1.62 (1H, ddd), 1.98 (2H, m), 3.28 (3H, ddd), 3.32 (3H, dq), 3.59 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.41 (1H, br.d), 4.71 (1H, t), 6.38 (1H, s), 6.75 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.000959μM

Example 27g: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.56 (1H, ddd), 1.63 (1H, ddd), 1.97 (2H, m), 2.31 (6H, s), 2.51 (2H, t), 3.28 (3H, ddd), 3.32 (3H, dt), 3.59 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.14 (1H, d), 4.41 (1H, br.d), 5.25 (1H, br.t), 6.74 (1H, s), 7.26 (1H, s), 7.35 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.95 (2H, d).

mTOR Kinase Assay (Echo): 0.0189μM

Example 27h: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.56 (1H, ddd), 1.62 (1H, ddd), 1.98 (2H, m), 2.64 (1H, br.s), 3.28 (1H, ddd), 3.43 (2H, dt), 3.59 (1H, ddd), 3.73 (1H, dd), 3.75 (2H, m), 3.82 (1H, d), 4.04 (1H, dd), 4.12 (1H, d), 4.40 (1H, br.d), 5.27 (1H, t), 6.73 (1H, s), 6.81 (1H, s), 7.31 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.0000856μM

Example 27i: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.94 (3H, t), 1.31 (3H, d), 1.56 (2H, m), 1.56 (1H, ddd), 1.63 (1H, ddd), 1.98 (2H, m), 3.24 (2H, dt), 3.30 (1H, dd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.41 (1H, br.d), 4.74 (1H, t), 6.36 (1H, s), 6.75 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

mTOR Kinase Assay (Echo): 0.00302μM

Example 27j: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.57 (1H, ddd), 1.63 (1H, ddd), 1.99 (2H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.04 (1H, dd), 4.12 (1H, d), 4.40 (1H, br.d), 6.72 (1H, s), 6.77 (1H, s), 6.88 (1H, s), 7.37 (2H, d), 7.41 (2H, d), 7.50 (2H, d), 7.55 (2H, d), 7.69 (2H, d), 8.03 (2H, d).

mTOR Kinase Assay (Echo): 0.00761μM

Example 27k: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.57 (1H, ddd), 1.63 (1H, ddd), 1.98 (2H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.64 (2H, d), 3.73 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.13 (1H, d), 4.40 (1H, br.d), 4.45 (1H, t), 4.88 (1H, s), 6.54 (1H, s), 6.75 (1H, s), 7.27 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.99 (2H, d).

mTOR Kinase Assay (Echo): 0.00462μM

Example 27l: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.56 (1H, ddd), 1.62 (1H, ddd), 1.71 (2H, tt), 1.98 (2H, m), 2.94 (1H, br.s), 3.28 (1H, ddd), 3.44 (2H, dt), 3.59 (1H, ddd), 3.72 (1H, br.s), 3.73 (1H, dd), 3.82 (1H, d), 4.04 (1H, dd), 4.12 (1H, d), 4.40 (1H, br.d), 5.13 (1H, t), 6.62 (1H, s), 6.74 (1H, s), 7.30 (2H, d), 7.40 (2H, d), 7.67 (2H, d), 7.98 (2H, d).

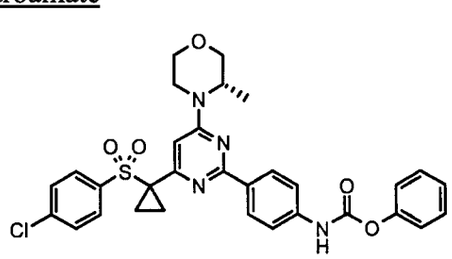
mTOR Kinase Assay (Echo): 0.00112μM

Example 27m: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.57 (1H, ddd), 1.63 (1H, ddd), 1.98 (2H, m), 3.29 (1H, ddd), 3.59 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 3.90 (3H, s), 4.04 (1H, dd), 4.13 (1H, d), 4.40 (1H, br.d), 6.12 (1H, s), 6.63 (1H, s), 6.76 (1H, s), 7.35 (2H, d), 7.40 (2H, d), 7.41 (1H, s), 7.60 (1H, s), 7.67 (2H, d), 7.99 (2H, d).

mTOR Kinase Assay (Echo): 0.00144μM

The preparation of phenyl *N*-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

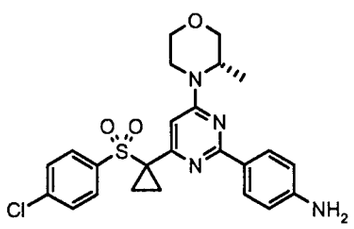


Phenyl chloroformate (0.829 mL, 6.60 mmol) was added dropwise to 4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (3.20 g, 6.60 mmol) and sodium hydrogen carbonate (0.554 g, 6.60 mmol) in 1,4-dioxane (150 mL) at RT. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (400 mL) and washed with water (2 x 400 mL) and saturated brine (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to afford the desired material as a white dry film (3.78 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.57 (1H, ddd), 1.64 (1H, ddd), 1.99 (2H, m), 3.30 (1H, ddd), 3.60 (1H, ddd), 3.74 (1H, dd), 3.83 (1H, d), 4.05 (1H, dd), 4.15 (2H, br.d), 4.42 (1H, br.d), 6.78 (1H, s), 7.04 (1H, s), 7.20 (2H, d), 7.25 (2H, dd), 7.40 (2H, d), 7.40 (2H, dd), 7.45 (2H, d), 7.68 (2H, d), 8.02 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 605, 607; HPLC tR = 3.15 min.

4-[4-[1-(4-Chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

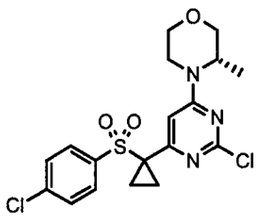


Sodium carbonate (13.45 mL, 26.89 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.637 g, 7.47 mmol), 2-chloro-4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.20 g, 7.47 mmol) in a mixture of DME (20 mL), DMF (20 mL), ethanol (20 mL) and water (40 mL) at RT under nitrogen. The mixture was degassed and purged with nitrogen before bis(triphenylphosphine)palladium(II) chloride (0.262 g, 0.37 mmol) was added and the mixture stirred at 80°C under nitrogen for 90 minutes. The reaction mixture was concentrated and diluted with ethyl acetate (250 mL), and washed sequentially with water (2 x 200 mL) and saturated brine (150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 45% ethyl acetate in isohexane, to afford the desired material as a beige dry film (3.32 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.30 (3H, d), 1.56 (1H, ddd), 1.62 (1H, ddd), 1.96 (2H, m), 3.27 (1H, ddd), 3.59 (1H, ddd), 3.73 (1H, dd), 3.81 (1H, d), 3.86 (2H, s), 4.03 (1H, dd), 4.13 (1H, br.d), 4.41 (1H, br.d), 6.63 (2H, d), 6.70 (1H, s), 7.40 (2H, d), 7.67 (2H, d), 7.85 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 485, 487; HPLC tR = 2.70 min.

2-Chloro-4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



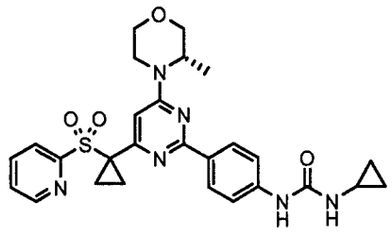
10N Sodium hydroxide solution (7.46 mL, 74.57 mmol) was added to 2-chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.00 g, 7.46 mmol), 1,2-dibromoethane (1.285 mL, 14.91 mmol) and tetrabutylammonium bromide (0.240 g, 0.75 mmol) in toluene (50 mL). The resulting solution was stirred at 60°C for 1 hour. The reaction mixture was concentrated, diluted with ethyl acetate (300 mL), washed with water (2 x 300 mL) and saturated brine (200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to afford the desired material as a white dry film (2.85 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.54 (1H, ddd), 1.60 (1H, ddd), 1.95 (2H, m), 3.27 (1H, ddd), 3.54 (1H, ddd), 3.69 (1H, dd), 3.79 (1H, d), 4.01 (2H, m), 4.27 (1H, br.s), 6.87 (1H, s), 7.46 (2H, d), 7.64 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 428, 430; HPLC tR = 2.51 min.

The preparation of 2-chloro-4-[(4-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 28: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea

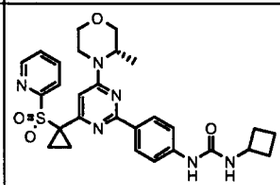


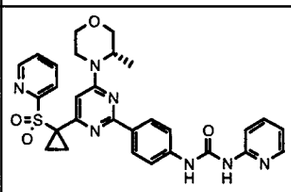
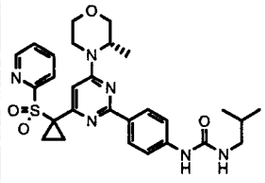
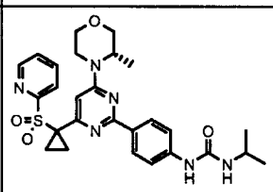
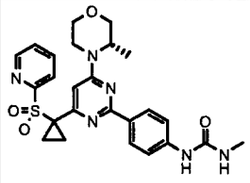
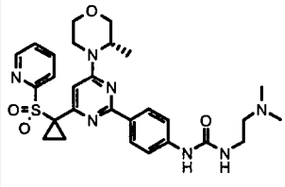
Cyclopropylamine (0.76 mmol) was added in one portion to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (104 mg, 0.19 mmol), in DMF (2 mL) at RT under nitrogen. The resulting solution was stirred at RT for 60 minutes. The reaction mixture was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to afford the desired material as a white solid (49 mg).

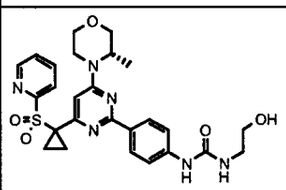
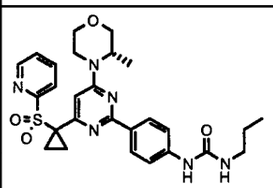
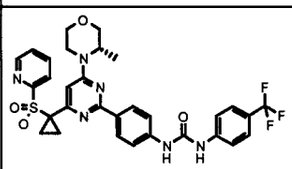
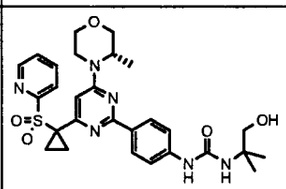
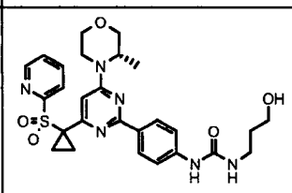
NMR Spectrum: ^{1}H NMR (399.902 DMSO-d_6) δ 0.33 (2H, s), 0.54 - 0.60 (2H, m), 1.06 - 1.10 (3H, m), 1.62 - 1.70 (2H, m), 1.92 (2H, s), 3.01 - 3.11 (1H, m), 3.37 (1H, t), 3.52 (1H, d), 3.66 (1H, d), 3.87 (1H, d), 4.00 - 4.11 (1H, m), 4.32 (1H, s), 6.33 (1H, s), 6.59 (1H, s), 7.29 (2H, d), 7.61 - 7.69 (3H, m), 7.89 - 7.93 (1H, m), 7.98 - 8.03 (1H, m), 8.41 (1H, s), 8.75 (1H, s); LCMS Spectrum: m/z (ESI+)(M+H)+ = 535.4; HPLC tR = 1.91 min.

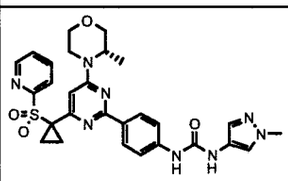
mTOR Kinase Assay (Echo): 0.000816μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
28a		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	549.4	2.13

Example	Structure	NAME	LCMS MH+	Retention time (min)
28b		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	572.4	2.32
28c		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	551.4	2.22
28d		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	537.9	2.06
28e		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	509.4	1.73
28f		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	564.4	1.81

Example	Structure	NAME	LCMS MH+	Retention time (min)
28g		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	539.4	1.6
28h		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-propylurea	537.4	2.07
28i		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	639.4	2.82
28j		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	567.4	1.87
28k		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	553.4	1.63

Example	Structure	NAME	LCMS MH+	Retention time (min)
28l		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	575.4	1.8

Example 28a: ^{1}H NMR (399.902 DMSO-d_6) δ 1.16 (d, 3H), 1.57 - 1.68 (m, 2H), 1.70 - 1.78 (m, 2H), 1.80 - 1.92 (m, 2H), 1.96 - 2.04 (m, 2H), 2.17 - 2.26 (m, 2H), 3.10 - 3.18 (m, 1H), 3.41 - 3.49 (m, 1H), 3.57 - 3.63 (m, 1H), 3.75 (d, 1H), 3.93 - 3.98 (m, 1H), 4.09 - 4.19 (m, 2H), 4.40 (s, 1H), 6.44 (d, 1H), 6.67 (s, 1H), 7.34 (d, 2H), 7.72 (d, 2H), 7.73 - 7.77 (m, 1H), 7.99 (d, 1H), 8.06 - 8.11 (m, 1H), 8.52 (s, 1H), 8.81 - 8.84 (m, 1H).

mTOR Kinase Assay (Echo): 0.00253μM

Example 28b: ^{1}H NMR (399.902 DMSO-d_6) δ 1.18 (d, 3H), 1.71 - 1.82 (m, 2H), 1.98 - 2.05 (m, 2H), 3.11 - 3.21 (m, 1H), 3.42 - 3.51 (m, 1H), 3.59 - 3.64 (m, 1H), 3.76 (d, 1H), 3.94 - 4.00 (m, 1H), 4.15 (d, 1H), 4.42 (s, 1H), 6.71 (s, 1H), 7.02 - 7.07 (m, 1H), 7.50 (d, 2H), 7.56 - 7.60 (m, 1H), 7.75 - 7.80 (m, 2H), 7.81 (d, 2H), 7.99 - 8.02 (m, 1H), 8.08 - 8.13 (m, 1H), 8.29 - 8.32 (m, 1H), 8.83 - 8.85 (m, 1H), 9.42 - 9.44 (m, 1H), 10.53 (s, 1H).

mTOR Kinase Assay (Echo): 0.00149μM

Example 28c: ^{1}H NMR (399.902 DMSO-d_6) δ 0.79 (d, 6H), 1.07 (d, 3H), 1.57 - 1.68 (m, 3H), 1.88 - 1.92 (m, 2H), 2.84 (t, 2H), 3.00 - 3.09 (m, 1H), 3.31 - 3.40 (m, 1H), 3.48 - 3.53 (m, 1H), 3.65 (d, 1H), 3.84 - 3.89 (m, 1H), 4.00 - 4.07 (m, 1H), 4.30 (s, 1H), 6.13 (t, 1H), 6.57 (s, 1H), 7.24 - 7.28 (m, 2H), 7.62 (d, 2H), 7.64 - 7.67 (m, 1H), 7.88 - 7.91 (m, 1H), 7.97 - 8.02 (m, 1H), 8.51 (s, 1H), 8.72 - 8.74 (m, 1H).

mTOR Kinase Assay (Echo): 0.00847μM

Example 28d: ^{1}H NMR (399.902 DMSO-d_6) δ 1.11 (d, 6H), 1.16 (d, 3H), 1.70 - 1.79 (m, 2H), 1.96 - 2.04 (m, 2H), 3.10 - 3.18 (m, 1H), 3.41 - 3.49 (m, 1H), 3.57 - 3.63 (m, 1H), 3.72 - 3.83 (m, 2H), 3.93 - 3.99 (m, 1H), 4.13 (d, 1H), 4.40 (s, 1H), 6.04 (d, 1H), 6.67 (s, 1H), 7.34 (d, 2H), 7.72 (d, 2H), 7.74 - 7.77 (m, 1H), 7.98 - 8.01 (m, 1H), 8.06 - 8.12 (m, 1H), 8.49 (s, 1H), 8.82 - 8.84 (m, 1H).

mTOR Kinase Assay (Echo): 0.00237μM

Example 28e: ^{1}H NMR (399.902 DMSO-d_6) δ 1.16 (d, 3H), 1.70 - 1.80 (m, 2H), 1.96 - 2.03 (m, 2H), 2.66 (d, 3H), 3.10 - 3.18 (m, 1H), 3.41 - 3.49 (m, 1H), 3.58 - 3.63 (m, 1H), 3.75 (d, 1H), 3.93 - 3.98 (m, 1H), 4.13 (d, 1H), 4.41 (s, 1H), 6.05 (q, 1H), 6.67 (s, 1H), 7.37 (d, 2H), 7.72 (d, 2H), 7.73 - 7.77 (m, 1H), 7.99 (d, 1H), 8.07 - 8.12 (m, 1H), 8.70 (s, 1H), 8.82 - 8.84 (m, 1H).

mTOR Kinase Assay (Echo): 0.000434μM

Example 28f: ^{1}H NMR (399.902 DMSO-d_6) δ 1.17 (d, 3H), 1.69 - 1.80 (m, 2H), 1.97 - 2.03 (m, 2H), 2.19 (s, 6H), 2.34 (t, 3H), 3.10 - 3.22 (m, 3H), 3.41 - 3.49 (m, 1H), 3.58 - 3.63 (m, 1H), 3.75 (d, 1H), 3.94 - 3.98 (m, 1H), 4.12 (d, 1H), 4.40 (s, 1H), 6.15 (t, 1H), 6.67 (s, 1H), 7.35 (d, 2H), 7.72 (d, 2H), 7.74 - 7.78 (m, 1H), 8.00 (d, 1H), 8.09 (t, 1H), 8.81 - 8.87 (m, 2H).

mTOR Kinase Assay (Echo): 0.0674μM

Example 28g: ^{1}H NMR (399.902 DMSO-d_6) δ 1.14 - 1.21 (m, 3H), 1.70 - 1.79 (m, 2H), 1.97 - 2.04 (m, 2H), 3.10 - 3.24 (m, 3H), 3.41 - 3.51 (m, 3H), 3.57 - 3.65 (m, 1H), 3.75 (d, 1H), 3.93 - 3.99 (m, 1H), 4.13 (d, 1H), 4.41 (s, 1H), 4.73 (t, 1H), 6.23 (t, 1H), 6.67 (s, 1H), 7.35 (d, 2H), 7.70 - 7.77 (m, 3H), 7.99 (d, 1H), 8.09 (t, 1H), 8.76 (s, 1H), 8.83 (d, 1H).

mTOR Kinase Assay (Echo): 0.0118μM

Example 28h: ^{1}H NMR (399.902 DMSO-d_6) δ 0.87 - 0.94 (m, 3H), 1.15 - 1.21 (m, 3H), 1.42 - 1.52 (m, 2H), 2.01 (s, 2H), 3.03 - 3.20 (m, 3H), 3.47 (t, 1H), 3.62 (d, 1H), 3.76 (d, 1H), 3.97 (d, 1H), 4.15 (d, 1H), 4.42 (s, 1H), 6.20 (s, 1H), 6.69 (s, 1H), 7.37 (d, 2H), 7.70 - 7.79 (m, 3H), 7.98 - 8.03 (m, 1H), 8.07 - 8.14 (m, 1H), 8.63 (s, 1H), 8.84 (s, 1H).

mTOR Kinase Assay (Echo): 0.00093μM

Example 28i: ^{1}H NMR (399.902 DMSO-d_6) δ 1.18 (d, 4H), 1.72 - 1.79 (m, 2H), 2.00 - 2.02 (m, 2H), 3 (d, 1H), 3.11 - 3.20 (m, 1H), 3.43 - 3.50 (m, 2H), 3.59 - 3.64 (m, 1H), 3.75 (d, 1H), 3.94 - 3.99 (m, 2H), 4.14 (d, 1H), 4.42 (s, 1H), 6.70 (s, 1H), 7.45 (d, 2H), 7.67 (q, 4H), 7.74 - 7.82 (m, 3H), 8.08 - 8.13 (m, 1H), 8.82 - 8.85 (m, 1H), 9.01 (s, 1H), 9.11 (s, 1H).

mTOR Kinase Assay (Echo): 0.00153μM

Example 28j: ^{1}H NMR (399.902 DMSO-d_6) δ 1.16 (d, 3H), 1.24 (s, 6H), 1.68 - 1.80 (m, 2H), 1.96 - 2.04 (m, 2H), 3.09 - 3.18 (m, 1H), 3.39 (d, 2H), 3.41 - 3.49 (m, 1H), 3.58 - 3.63 (m, 1H), 3.75 (d, 1H), 3.93 - 3.98 (m, 1H), 4.13 (d, 1H), 4.40 (s, 1H), 4.96 (t, 1H), 5.98 (s, 1H), 6.67 (s, 1H), 7.32 (d, 2H), 7.71 (d, 2H), 7.74 - 7.78 (m, 1H), 7.99 (d, 1H), 8.09 (t, 1H), 8.70 (s, 1H), 8.82 - 8.85 (m, 1H).

mTOR Kinase Assay (Echo): 0.00557μM

Example 28k: ^{1}H NMR (399.902 DMSO-d_6) δ 1.17 (d, 3H), 1.56 - 1.64 (m, 2H), 1.69 - 1.80 (m, 2H), 1.96 - 2.04 (m, 2H), 3.10 - 3.20 (m, 3H), 3.41 - 3.51 (m, 3H), 3.58 - 3.63 (m, 1H), 3.74 (d, 1H), 3.93 - 3.98 (m, 1H), 4.13 (d, 1H), 4.40 (s, 1H), 4.48 (t, 1H), 6.19 (t, 1H), 6.67 (s, 1H), 7.36 (d, 2H), 7.72 (d, 2H), 7.73 - 7.77 (m, 1H), 7.99 (d, 1H), 8.09 (t, 1H), 8.67 (s, 1H), 8.82 - 8.84 (m, 1H).

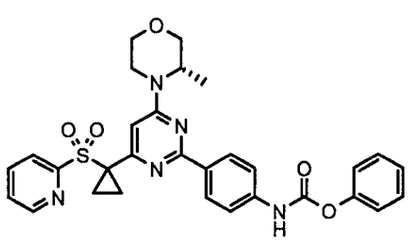
mTOR Kinase Assay (Echo): 0.000954μM

Example 28l: ^{1}H NMR (399.902 DMSO-d_6) δ 1.17 (d, 3H), 1.69 - 1.81 (m, 2H), 1.96 - 2.05 (m, 2H), 3.10 - 3.19 (m, 1H), 3.42 - 3.50 (m, 1H), 3.58 - 3.64 (m, 1H), 3.75 (d, 1H), 3.79 (s, 3H), 3.93 - 3.99 (m, 1H), 4.14 (d, 1H), 4.41 (s, 1H), 6.68 (s, 1H), 7.38 - 7.44 (m, 3H), 7.73 - 7.78 (m, 4H), 8.00 (d, 1H), 8.07 - 8.12 (m, 1H), 8.37 (s, 1H), 8.80 (s, 1H), 8.82 - 8.85 (m, 1H).

mTOR Kinase Assay (Echo): 0.000442μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate

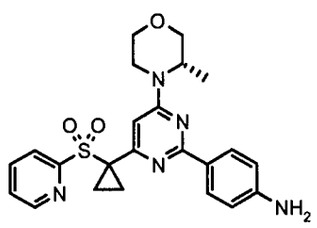


Phenyl chloroformate (0.693 g, 4.43 mmol) was added dropwise to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (2.0 g, 4.43 mmol) and sodium hydrogen carbonate (0.744 g, 8.86 mmol) in dioxane (40 mL) at RT. The resulting slurry was stirred at RT for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica, eluting with 0% - 20% ethyl acetate in DCM, to afford the desired material as a yellow gum (2.07 g).

NMR spectrum: ^{1}H NMR (399.902 $CDCl_3$) δ 1.23 (5H, d), 1.61 - 1.71 (2H, m), 2.06 - 2.15 (2H, m), 3.17 - 3.24 (1H, m), 3.47 - 3.54 (1H, m), 3.75 (1H, d), 4.05 - 4.11 (2H, m), 4.35 (1H, s), 6.82 (1H, s), 6.95 (1H, s), 7.13 (2H, m), 7.16 - 7.21 (1H, m), 7.31 - 7.37 (4H, m), 7.38 - 7.43 (1H, m), 7.73 - 7.77 (1H, m), 7.86 (1H, d), 7.93 - 7.97 (2H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 572.6; HPLC tR = 2.81 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline

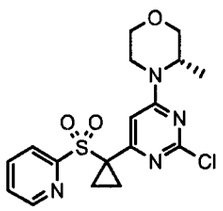


Sodium carbonate (20.51 mL, 41.03 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.498 g, 11.4 mmol) and 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidine (4.5 g, 11.40 mmol) in a mixture of DME (20 mL), ethanol (20 mL), DMF (20 mL) and water (40 mL). The mixture was purged with nitrogen then bis(triphenylphosphine)palladium(II) chloride (0.4 g, 0.57 mmol) was added and the resulting suspension was stirred at 80°C for 90 minutes. The reaction mixture was concentrated, diluted with ethyl acetate (150 mL), and washed sequentially with water (2 x 150 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 45% ethyl acetate in DCM, to afford the desired material as a beige solid (3.64 g).

NMR spectrum: ^{1}H NMR (399.902 $CDCl_3$) δ 1.20 (3H, d), 1.60 - 1.72 (2H, m), 2.04 - 2.12 (2H, m), 3.14 - 3.22 (1H, m), 3.46 - 3.53 (1H, m), 3.71 - 3.78 (3H, m), 3.92 - 3.96 (1H, m), 4.02 - 4.08 (1H, m), 4.33 (1H, s), 6.53 (2H, d), 6.76 (1H, s), 7.37 - 7.41 (1H, m), 7.72 - 7.77 (1H, m), 7.78 - 7.86 (3H, m), 8.64 - 8.66 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 452.6; HPLC tR = 1.40 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidine

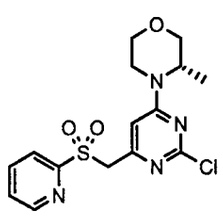


1,2-Dibromoethane (5.61 mL, 65.08 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine (6 g, 16.27 mmol), 10N sodium hydroxide solution (32.5 mL, 325.35 mmol) and tetrabutylammonium bromide (0.524 g, 1.63 mmol) in toluene (400 mL). The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was concentrated and diluted with ethyl acetate (150 mL), then washed with water (2 x 100 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 20% ethyl acetate in DCM, to afford the desired material as a white dry film (3.02 g).

NMR spectrum: ^{1}H NMR (399.902 $CDCl_3$) δ 1.22 (3H, d), 1.56 - 1.67 (2H, m), 1.97 - 2.07 (2H, m), 3.14 - 3.22 (1H, m), 3.41 - 3.49 (1H, m), 3.58 - 3.62 (1H, m), 3.70 (1H, d), 3.89 - 3.99 (2H, m), 4.21 (1H, s), 7.02 (1H, s), 7.44 - 7.48 (1H, m), 7.81 - 7.89 (2H, m), 8.62 - 8.64 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 395.4; HPLC tR = 1.98 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine



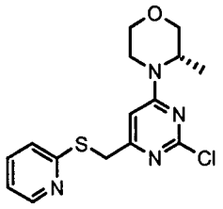
A 35% aqueous solution of hydrogen peroxide (8.26 mL, 93.53 mmol) was added dropwise to a stirred solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfanylmethyl)pyrimidine (10.5g, 31.17 mmol), sodium tungstate dihydrate (0.206 g, 0.62 mmol) and 2N Sulfuric acid (0.6 mL) in dioxane (300 mL) and then the solution warmed to 55°C. The solution was stirred at 55°C for 4 hours. Further hydrogen peroxide (8.26 mL) was added and the mixture stirred at 50°C for 18 hours. 3-Chloroperoxybenzoic acid (5.38 g,

31.17 mmol) was added and the mixture stirred at RT for 2 hours. The solution was diluted with water (500 mL) and cooled to 20°C. A 10% solution of sodium metabisulfite was added to destroy any remaining peroxide and the solution was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and filtered. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a yellow gum (10.5 g,).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.24 (d, 3H), 3.20 (m, 1H), 3.46 (m, 1H), 3.61 (d, 1H), 3.71 (d, 1H), 3.90 - 3.98 (m, 2H), 4.21 (s, 1H), 4.51 (s, 2H), 6.50 (s, 1H), 7.51 - 7.53 (m, 1H), 7.86 - 7.95 (m, 2H), 8.72 - 8.74 (m, 1H)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 369.4; HPLC tR = 1.73 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfanylmethyl)pyrimidine



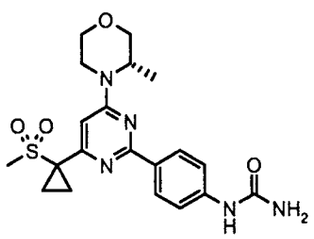
DIPEA (8.77 ml, 50.71 mmol) was added to 2-mercaptopyridine (3.80 g, 34.22 mmol), in DMF (300 mL) at RT in an atmosphere of nitrogen. The resulting solution was stirred at RT for 15 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (11 g, 31.11 mmol) was added portionwise over 5 minutes and the mixture stirred at RT for 3 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (200 mL) and washed sequentially with saturated sodium hydrogen carbonate solution (100 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a tan oil (10.50 g). NMR shows the presence of 0.6 eq. of 3-chlorobenzoic acid. This material was used in the subsequent step without further purification.

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.23 (d, 3H), 3.17 - 3.25 (m, 1H), 3.46 - 3.54 (m, 1H), 3.62 - 3.67 (m, 1H), 3.74 (d, 1H), 3.93 - 4.01 (m, 2H), 4.20 (s, 1H), 4.29 - 4.38 (m, 2H), 6.60 (s, 1H), 6.99 - 7.02 (m, 1H), 7.20 (d, 1H), 7.47 - 7.51 (m, 1H), 8.40 - 8.42 (m, 1H).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 337.5; HPLC tR = 2.19 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 29: [4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



6-Aminopyridin-2(1*H*)-one hydrochloride salt (0.218 g, 1.49 mmol) was added to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (0.151 g, 0.30 mmol) and triethylamine (0.249 mL, 1.78 mmol) in DMF (2 mL) at RT. The resulting solution was stirred at 50°C for 1 day. The solution was cooled and purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (0.094 g).

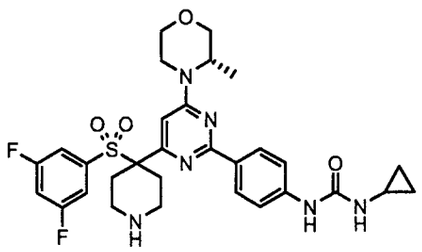
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22-1.25(3H, d), 1.55-1.58(2H, q), 1.66-1.69(2H, q), 3.17-3.26(1H, td), 3.30(3H, s), 3.45-3.52(1H, td), 3.62-3.65(1H, dd), 3.75-3.78(1H, d), 3.96-3.99(1H, dd), 4.20-4.23(1H, d), 4.57(1H, bs), 5.91(2H, s), 6.77(1H, s), 7.50-7.52(2H, q), 8.19-8.21(2H, q), 8.76(1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=432; HPLC tR=1.66 min.

mTOR Kinase Assay (Echo): 0.0042μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 30: 3-Cyclopropyl-1-[4-[4-[4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

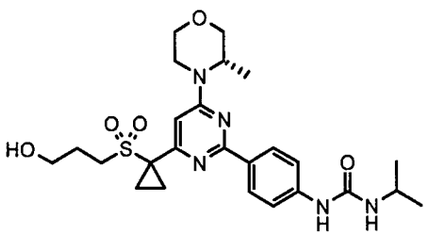


1-Chloroethyl chloroformate (0.015 mL, 0.14 mmol) and 1-[4-[4-[1-benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea (50 mg, 0.07 mmol) were dissolved in DCM (1 mL) and sealed into a microwave tube. The reaction was heated to 110°C for 5 minutes in a microwave reactor and then cooled to RT. Methanol (1 mL) was added and the mixture was heated to 110°C for 5 minutes in a microwave reactor and then cooled to RT. The mixture was purified by ion exchange chromatography using an SCX column, eluting with methanol followed by 2M ammonia in methanol. The isolated material was further purified by chromatography on silica, eluting with 2% methanol in DCM to 20% methanol in DCM containing 1% ammonia. The isolated material was triturated with diethyl ether to give the desired material as a colourless solid (26 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.68 - 0.72 (2H, m), 0.86 - 0.90 (2H, m), 1.36 (3H, d), 2.27 - 2.36 (2H, m), 2.52 - 2.65 (3H, m), 2.70 - 2.79(2H, m), 3.10 - 3.15 (2H, m), 3.34 (1H, dt), 3.64 (1H, dt), 3.77 - 3.87 (2H, m), 4.05 - 4.18 (2H, m), 4.43 - 4.52 (1H, m), 4.91 (1H, s), 6.65 (1H, s), 6.81 - 6.87 (1H, m), 6.95 - 7.02 (3H, m), 7.39 (2H, d), 7.93 (2H, d).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 613.5; HPLC tR = 2.16 min.
mTOR Kinase Assay (Echo): 0.025μM

The preparation of 1-[4-[4-[1-benzyl-4-(3,5-difluorophenyl)sulfonylpiperidin-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea was described earlier.

Example 31: 1-[4-[4-[1-(3-Hydroxypropylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea



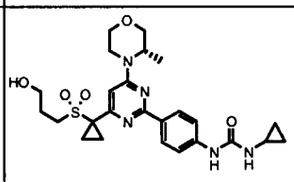
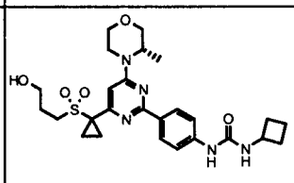
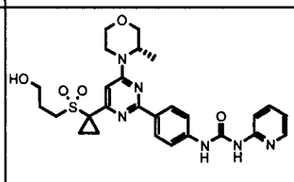
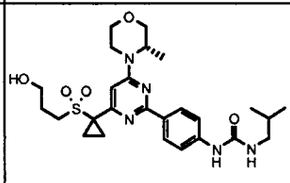
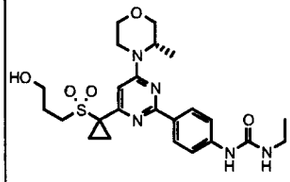
Triethylamine (0.126 mL, 0.90 mmol) was added to phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.18 mmol) and propan-2-amine (0.078 mL, 0.90 mmol) in NMP (2 mL) at RT under air. The resulting solution was stirred at RT for 1 hour. The crude product was purified by preparative, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (65 mg).

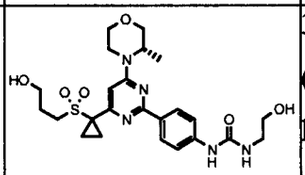
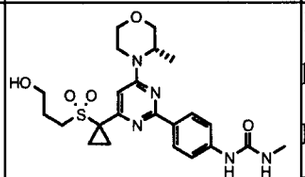
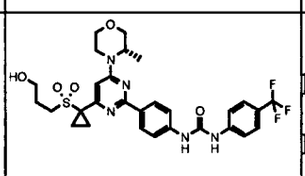
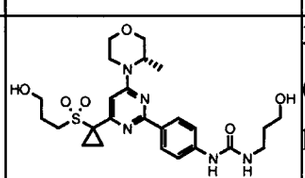
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 3.16 - 3.23 (1H, m), 3.31 - 3.34 (1H, m), 3.44 - 3.55 (4H, m), 3.61 - 3.64 (1H, m), 3.73 - 3.81 (2H, m), 3.95 - 3.99 (1H, m), 4.16 - 4.26 (1H, m), 4.52 - 4.59 (1H, m), 4.73 (1H, t), 6.08 (1H, d), 6.77 (1H, s), 7.47 (2H, d), 8.20 (2H, d), 8.57 (1H, s)

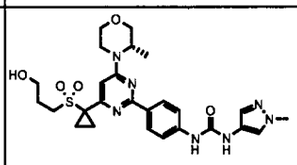
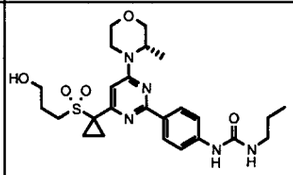
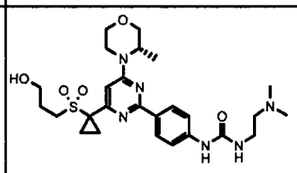
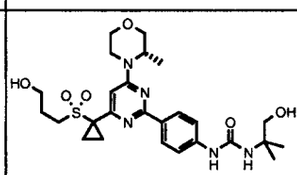
LCMS Spectrum: m/z (ESI+)(M+H)+ = 518; HPLC tR = 2.04min.

mTOR Kinase Assay (Echo): 0.00452μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
31a		3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	516	1.74
31b		3-cyclobutyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	530	1.94
31c		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-pyridin-2-ylurea	553	2.10
31d		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylpropyl)urea	532	2.02
31e		1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	504	1.71

Example	Structure	NAME	LCMS MH+	Retention time (min)
31f		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	520	1.49
31g		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	490	1.59
31h		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[4-(trifluoromethyl)phenyl]urea	620	2.54
31i		3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	534	1.52

Example	Structure	NAME	LCMS MH+	Retention time (min)
31j		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	556	1.66
31k		3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	518	1.86
31l		3-(2-dimethylaminoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	547	1.66
31m		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.72

Example 31a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 2.53 - 2.58 (1H, m), 3.16 - 3.22 (1H, m), 3.44 - 3.55 (5H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 -

3.98 (1H, m), 4.17 - 4.25 (1H, m), 4.53 - 4.59 (1H, m), 4.73 (1H, t), 6.46 (1H, s), 6.77 (1H, s), 7.50 (2H, d), 8.21 (2H, d), 8.58 (1H, s).

mTOR Kinase Assay (Echo): 0.00265μM

Example 31b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.63 (6H, m), 1.81 - 1.97 (4H, m), 2.17 - 2.23 (2H, m), 3.17 - 3.22 (1H, m), 3.45 - 3.54 (5H, m), 3.61 - 3.63 (1H, m), 3.76 (1H, d), 3.96 - 3.98 (1H, m), 4.10 - 4.24 (2H, m), 4.51 - 4.58 (1H, m), 4.73 (1H, t), 6.48 (1H, d), 6.77 (1H, s), 7.47 (2H, d), 8.20 (2H, d), 8.60 (1H, s).

mTOR Kinase Assay (Echo): 0.00497μM

Example 31c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.62 - 1.66 (2H, m), 1.91 - 1.98 (2H, m), 3.18 - 3.25 (1H, m), 3.46 - 3.57 (5H, m), 3.62 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.20 - 4.27 (1H, m), 4.52 - 4.61 (1H, m), 4.75 (1H, t), 6.80 (1H, s), 7.02 - 7.05 (1H, m), 7.55 - 7.58 (1H, m), 7.64 (2H, d), 7.75 - 7.79 (1H, m), 8.29 - 8.31 (1H, m), 8.30 (2H, d), 9.49 (1H, s), 10.63 (1H, s).

mTOR Kinase Assay (Echo): 0.00131μM

Example 31d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (6H, d), 1.22 (3H, d), 1.54 - 1.56 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 2.94 (2H, t), 3.16 - 3.23 (1H, m), 3.45 - 3.55 (6H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.96 - 3.98 (1H, m), 4.16 - 4.26 (1H, m), 4.52 - 4.59 (1H, m), 4.73 (1H, t), 6.26 (1H, t), 6.77 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.00955μM

Example 31e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 3.09 - 3.23 (3H, m), 3.44 - 3.55 (5H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.18 - 4.24 (1H, m), 4.53 - 4.59 (1H, m), 4.73 (1H, t), 6.18 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00107μM

Example 31f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.64 (4H, m), 1.90 - 1.97 (2H, m), 3.15 - 3.19 (2H, m), 3.43 - 3.54 (8H, m), 3.61 - 3.63 (1H, m), 3.76 (1H, d), 3.95 - 3.98 (1H, m), 4.17 - 4.24 (1H, m), 4.51 - 4.59 (1H, m), 4.73 - 4.79 (2H, m), 6.28 (1H, t), 6.76 (1H, s), 7.48 (2H, d), 8.21 (2H, d), 8.84 (1H, s).

mTOR Kinase Assay (Echo): 0.0016μM

Example 31g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 2.66 (3H, d), 3.16 - 3.23 (1H, m), 3.44 - 3.55 (5H, m), 3.61

- 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 - 4.23 (1H, m), 4.52 - 4.59 (1H, m), 4.73 (1H, t), 6.07 - 6.10 (1H, m), 6.77 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00323μM

Example 31h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.59 (2H, m), 1.62 - 1.65 (2H, m), 1.91 - 1.98 (2H, m), 3.17 - 3.25 (1H, m), 3.45 - 3.56 (5H, m), 3.62 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.18 - 4.26 (1H, m), 4.53 - 4.61 (1H, m), 4.75 (1H, t), 6.80 (1H, s), 7.58 (2H, d), 7.64 - 7.70 (4H, m), 8.29 (2H, d), 9.09 (1H, s), 9.17 (1H, s).

mTOR Kinase Assay (Echo): 0.000209μM

Example 31i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.64 (6H, m), 1.90 - 1.97 (2H, m), 3.14 - 3.23 (3H, m), 3.44 - 3.55 (7H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 - 4.25 (1H, m), 4.52 (1H, t), 4.53 - 4.59 (1H, m), 4.73 (1H, t), 6.22 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.00326μM

Example 31j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.58 (2H, m), 1.61 - 1.64 (2H, m), 1.90 - 1.98 (2H, m), 3.16 - 3.24 (1H, m), 3.46 - 3.56 (4H, m), 3.61 - 3.65 (1H, m), 3.79 (3H, s), 3.96 - 3.99 (1H, m), 4.18 - 4.25 (1H, m), 4.53 - 4.58 (1H, m), 4.74 (1H, t), 6.78 (1H, s), 7.39 (1H, s), 7.54 (2H, d), 7.77 (1H, s), 8.24 (2H, d), 8.43 (1H, s), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.00103μM

Example 31k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (3H, t), 1.22 (3H, d), 1.41 - 1.50 (2H, m), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.88 - 1.97 (2H, m), 3.03 - 3.08 (2H, m), 3.16 - 3.23 (1H, m), 3.44 - 3.55 (5H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 - 4.24 (1H, m), 4.51 - 4.59 (1H, m), 4.73 (1H, t), 6.22 (1H, t), 6.77 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.69 (1H, s).

mTOR Kinase Assay (Echo): 0.00191μM

Example 31l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 2.18 (6H, s), 2.33 (2H, t), 3.17 - 3.23 (3H, m), 3.44 - 3.55 (5H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 - 4.25 (1H, m), 4.50 - 4.60 (1H, m), 4.73 (1H, t), 6.17 (1H, t), 6.77 (1H, s), 7.48 (2H, d), 8.20 (2H, d), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.214μM

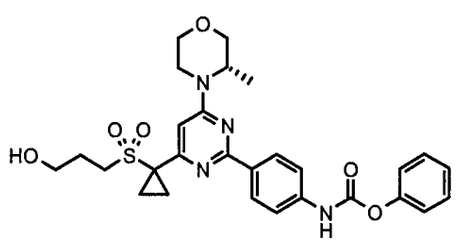
Example 31m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (6H, s), 1.54 - 1.58 (2H, m), 1.60 - 1.64 (2H, m), 1.90 - 1.97 (2H, m), 3.16 - 3.23 (1H, m), 3.38 (2H, d), 3.44 - 3.55 (5H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 - 4.25 (1H, m), 4.51 - 4.59 (1H,

m), 4.74 (1H, t), 4.99 (1H, t), 6.01 (1H, s), 6.76 (1H, s), 7.45 (2H, d), 8.19 (2H, d), 8.77 (1H, s).

mTOR Kinase Assay (Echo): 0.00591μM

The preparation of phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

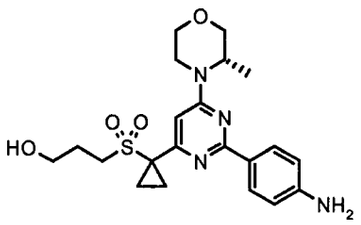


Phenyl chloroformate (0.581 mL, 4.63 mmol) was added to 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol (1.82 g, 4.21 mmol) and sodium bicarbonate (0.530 g, 6.31 mmol) in dioxane (100 mL) at 5°C under a nitrogen atmosphere. The resulting suspension was stirred overnight and allowed to come to RT. The reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford desired product as a gum. The gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (2.32 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.48 - 1.52 (2H, m), 1.55 - 1.61 (2H, m), 1.83 - 1.90 (2H, m), 3.11 - 3.18 (1H, m), 3.38 - 3.46 (4H, m), 3.54 - 3.58 (1H, m), 3.69 (1H, d), 3.75 - 3.94 (2H, m), 3.88 - 3.92 (1H, m), 4.14 - 4.18 (1H, m), 4.47 - 4.53 (1H, m), 6.75 (1H, s), 7.17 - 7.23 (3H, m), 7.36 - 7.39 (2H, m), 7.56 (2H, d), 8.23 (2H, d), 10.37 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 553; HPLC tR = 2.51min.

3-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol

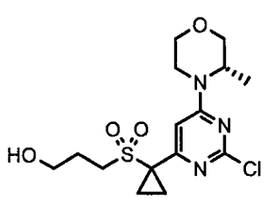


Dichlorobis(triphenylphosphine)palladium (II) (0.218 g, 0.31 mmol) was added to 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol (2.33 g, 6.20 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.766 g, 8.06 mmol) and 2M aqueous sodium carbonate solution (11.16 mL, 22.32 mmol) in DMF (15 mL), water (37.5 mL), ethanol (15 mL) and DME (15 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at 80°C for 17 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product as a brown solid. The crude product was purified by flash silica chromatography, eluting with 0 to 75% ethyl acetate in DCM, to give the desired material as a cream solid (1.82 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.52 - 1.54 (2H, m), 1.60 - 1.62 (2H, m), 1.90 - 1.97 (2H, m), 3.14 - 3.21 (1H, m), 3.44 - 3.52 (5H, m), 3.60 - 3.64 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.16 - 4.19 (1H, m), 4.48 - 4.55 (1H, m), 4.67 (1H, t), 5.56 (2H, s), 6.60 (2H, d), 6.67 (1H, s), 8.04 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 433; HPLC tR = 1.81min.

3-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol



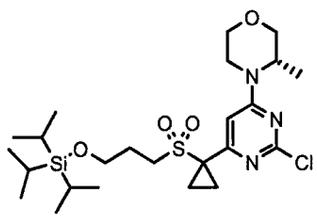
Tetrabutylammonium fluoride (1M in THF, 31 mL, 31 mmol) was added to 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane (3.28 g, 6.16 mmol) in THF (30 mL) at RT. The resulting solution was stirred at RT for 1 hour then concentrated *in vacuo* and diluted with saturated ammonium chloride (10 mL)

and water. The mixture was extracted twice with ethyl acetate, the combined organic extracts washed with brine,dried ($MgSO_4$), filtered and evaporated to give the desired material as a gum (2.33 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.42 - 1.51 (4H, m), 2.07 - 2.14 (2H, m), 2.40 (1H, s), 3.28 - 3.32 (2H, m), 3.37 - 3.42 (3H, m), 3.51 - 3.57 (1H, m), 3.66 - 3.70 (1H, m), 3.77 - 3.80 (2H, m), 3.99 - 4.02 (1H, m), 4.28 - 4.38 (1H, m), 6.84 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 376; HPLC tR = 1.58min.

3-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane

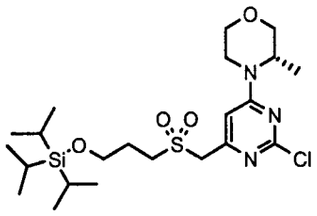


1,2-dibromoethane (1.723 mL, 20 mmol) was added to 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane (5.0 g, 9.88 mmol), 40% sodium hydroxide solution (10 mL, 98.78 mmol) and tetrabutylammonium bromide (0.645 g, 2 mmol) in toluene (50 mL) at RT under air. The resulting mixture was stirred at 60°C for 4 hours. The reaction mixture was evaporated to dryness and redissolved in ethyl acetate (100 mL) and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 0 to 20% ethyl acetate in DCM, to give the desired material as a colourless gum (2.86 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.00 - 1.05 (21H, m), 1.32 (3H, d), 1.49 - 1.52 (2H, m), 1.78 - 1.81 (2H, m), 2.02 - 2.09 (2H, m), 3.21 - 3.32 (3H, m), 3.50 - 3.56 (1H, m), 3.65 - 3.69 (1H, m), 3.77 - 3.80 (3H, m), 3.98 - 4.02 (2H, m), 4.28 - 4.36 (1H, m), 6.90 (1H, s)

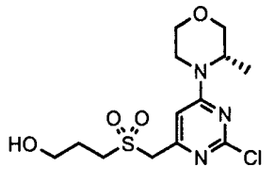
LCMS Spectrum: m/z (ESI+)(M+H)+ = 532; HPLC tR = 3.37min.

3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane



3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propan-1-ol (5.04 g, 14.41 mmol) in DMF (25 mL) was added to chlorotrisopropylsilane (3.70 mL, 17.29 mmol) and imidazole (2.354 g, 34.58 mmol) in DMF (25 mL) at RT over a period of 5 minutes under a nitrogen atmosphere. The resulting solution was stirred at RT for 18 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (200 mL) then washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as an oil (7.29 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.99 - 1.07 (21H, m), 1.33 (3H, d), 2.06 - 2.13 (2H, m), 3.20 - 3.24 (2H, m), 3.26 - 3.34 (1H, m), 3.50 - 3.57 (1H, m), 3.66 - 3.70 (1H, m), 3.77 - 3.83 (3H, m), 3.99 - 4.03 (2H, m), 4.16 (2H, s), 4.25 - 4.37 (1H, m), 6.54 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 506; HPLC tR = 3.42min.

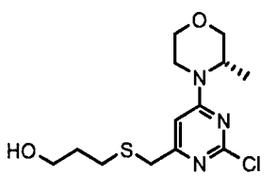
3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propan-1-ol



3-Chlorobenzoperoxoic acid (4.00 g, 23.16 mmol) was added to 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]propan-1-ol (3.68 g, 11.58 mmol) in DCM (100 mL) at RT over a period of 5 minutes. The resulting solution was stirred at RT for 3 hours. A further portion of 3-chlorobenzoperoxoic acid (2.00 g, 11.58 mmol) was added and the resulting solution was stirred at RT for an additional 1 hour. The reaction mixture was washed sequentially with 10% aqueous sodium metabisulphite solution (2 x 100 mL), a saturated aqueous solution of sodium hydrogen carbonate (100 mL), and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a gum (4.05 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.34 (3H, d), 2.12 - 2.18 (2H, m), 3.27 (2H, t), 3.31 - 3.35 (1H, m), 3.51 - 3.57 (1H, m), 3.67 - 3.70 (1H, m), 3.77 - 3.82 (3H, m), 3.99 - 4.03 (1H, m), 4.18 (2H, s), 4.26 - 4.37 (1H, m), 6.51 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 350; HPLC tR = 1.30min.

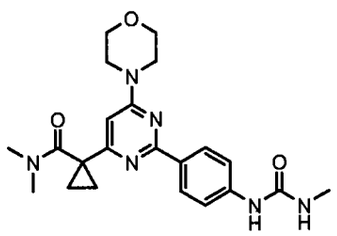
3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]propan-1-ol



A solution of 2-chloro-4-(iodomethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (12.4 g, 35.07 mmol) in DCM (50 mL) was added to a stirred solution of 3-mercapto-1-propanol (3.64 mL, 42.08 mmol) and DIPEA (9.77 mL, 56.11 mmol) in DCM (100 mL) at RT, over a period of 40 minutes under a nitrogen atmosphere. The resulting solution was stirred at RT for 18 hours. The reaction mixture was washed sequentially with a saturated aqueous solution of sodium hydrogen carbonate (2 x 50 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product as a dark brown oil. The crude product was purified by flash silica chromatography, eluting with 0 to 75% ethyl acetate in DCM, to give the desired material as a yellow gum (5.86 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.84 - 1.90 (2H, m), 1.94 (1H, s), 2.69 (2H, t), 3.24 - 3.32 (1H, m), 3.51 - 3.58 (1H, m), 3.61 (2H, s), 3.67 - 3.71 (1H, m), 3.73 - 3.80 (3H, m), 3.98 - 4.04 (2H, m), 4.28 - 4.34 (1H, m), 6.45 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 318; HPLC tR = 1.55min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 32: *N,N*-Dimethyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide



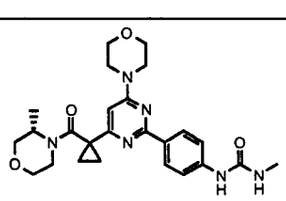
DIPEA (0.127 mL, 0.72 mmol) was added to a suspension of 1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid (96 mg, 0.24 mmol), dimethylamine (2.0M in THF, 0.36 mL, 0.72 mmol) and HBTU (138 mg, 0.36 mmol) in DMF (3 mL). The reactions were stirred at RT for 3 hours. The reaction mixture was passed down a SCX-2 ion exchange column, eluting with methanol followed by 7N ammonia in methanol. The isolated material was further purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (54 mg).

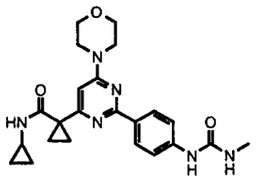
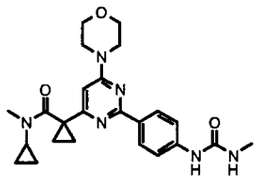
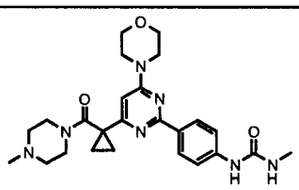
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.28 - 1.31 (2H, m), 1.51 - 1.54 (2H, m), 2.65 (3H, d), 2.87 - 2.89 (3H, s), 2.94 (3H, s), 3.64 (4H, m), 3.69 - 3.71 (4H, m), 6.08 (1H, d), 6.22 (1H, s), 7.46 - 7.49 (2H, m), 8.16 - 8.18 (2H, m), 8.76 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 425; HPLC tR = 1.45 min.

mTOR Kinase Assay (Echo): 0.00315μM

The following compounds were made in an analogous fashion from 1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
32a		3-methyl-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	481.4	1.53

Example	Structure	NAME	LCMS MH+	Retention time (min)
32b		N-cyclopropyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide	437.4	1.5
32c		N-cyclopropyl-N-methyl-1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide	451.4	1.62
32d		3-methyl-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	480.4	1.35

Example 32a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.31 (2H, d), 1.62 (2H, d), 2.65 - 2.66 (3H, m), 3.17 (1H, d), 3.48 (1H, d), 3.50 (1H, m), 3.66 (4H, s), 3.70 (4H, s), 3.70 (1H, s), 3.85 (1H, m), 4.23 (1H, d), 4.47 - 4.49 (1H, m), 6.07 (1H, q), 6.23 (1H, d), 7.48 (2H, d), 8.19 (2H, d), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.0425μM

Example 32b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.42 - 0.46 (2H, m), 0.60 - 0.65 (2H, m), 1.30 - 1.37 (4H, m), 2.66 (3H, d), 2.67 - 2.68 (1H, m), 3.67 (8H, s), 6.08 (1H, d), 6.46 (1H, s), 7.48 - 7.50 (2H, m), 8.14 - 8.17 (2H, m), 8.37 (1H, d), 8.77 (1H, s).

mTOR Kinase Assay (Echo): 0.00829μM

Example 32c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.64 (2H, s), 0.69 (2H, s), 1.32 (2H, s), 1.49 (2H, t), 2.33 (1H, t), 2.65 - 2.66 (3H, m), 2.73 - 2.76 (3H, m), 3.64 (4H, s), 3.69 - 3.71 (4H, m), 6.07 (1H, q), 6.30 (1H, s), 7.46 - 7.49 (2H, m), 8.16 - 8.18 (2H, m), 8.75 (1H, s).

mTOR Kinase Assay (Echo): 0.00288μM

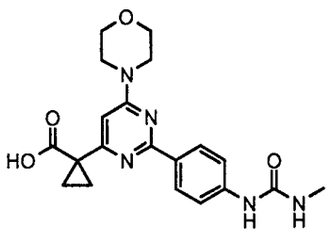
Example 32d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.29 - 1.32 (2H, m), 1.50 - 1.53 (2H, m), 2.11 - 2.11 (3H, m), 2.14 (2H, s), 2.33 (2H, t), 2.65 - 2.66 (3H, m), 3.30 (2H, s), 3.57 (2H, s),

3.67 - 3.70 (8H, m) 6.08 (1H, q), 6.26 (1H, s), 7.46 - 7.50 (2H, m), 8.17 - 8.20 (2H, m), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.0131μM

The preparation of 1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid is described below:

1-[2-[4-(Methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid

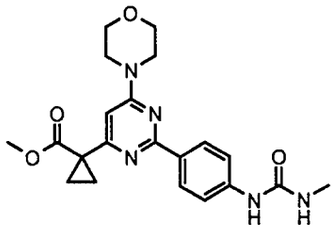


Lithium hydroxide-1-hydrate (59.5 mg, 1.42 mmol) was added in one portion to methyl 1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate (583 mg, 1.42 mmol) in methanol (8 mL) and water (8 mL). The resulting suspension was stirred at 60°C for 5 hours. The reaction mixture was evaporated to dryness, redissolved in water (25 mL), and washed with diethyl ether (25 mL). The aqueous layer was acidified with 2M hydrochloric acid and the precipitate was collected by filtration, washed with diethyl ether and dried under vacuum to give the desired material as a brown solid (486 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.51 - 1.58 (4H, m), 2.65 - 2.66 (3H, m), 3.70 (8H, s), 6.09 (1H, q), 6.73 (1H, s), 7.49 - 7.52 (2H, m), 8.13 - 8.15 (2H, m), 8.80 (1H, s), 14.09 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 398; HPLC tR = 1.21 min.

Methyl 1-[2-[4-(methylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate

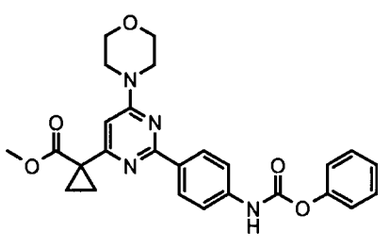


Methylamine (1.97 mL, 3.94 mmol) was added in one portion to methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate (934 mg, 1.97 mmol) in DMF (20 mL) The resulting solution was stirred at RT for 4 hours. The reaction mixture was evaporated to dryness and the residue purified by ion exchange chromatography using an SCX column, eluting with methanol followed by 7M ammonia in methanol, to give the desired material as a yellow solid (713 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.49 - 1.55 (4H, m), 2.66 (3H, d), 3.65 (3H, s), 3.69 (8H, s), 6.05 (1H, t), 6.83 (1H, s), 7.46 - 7.49 (2H, m), 8.16 - 8.19 (2H, m), 8.71 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 412; HPLC tR = 1.93 min.

Methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate

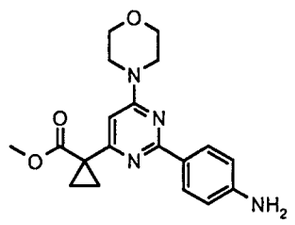


Phenyl chloroformate (0.53 mL, 4.20 mmol) was added dropwise to methyl 1-[2-(4-aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate (1.49 g, 4.20 mmol) and sodium bicarbonate (0.53 g, 6.31 mmol) in dioxane (50 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (60 mL) and washed with water (60 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired material as a yellow solid (2.1 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.52 - 1.54 (4H, m), 3.57 (3H, s), 3.71 (8H, s), 6.89 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.62 (2H, d), 8.27 (2H, d), 10.46 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 475; HPLC tR = 2.83 min.

Methyl 1-[2-(4-aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate

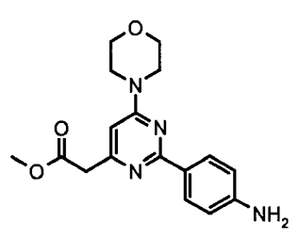


Sodium hydride (434 mg, 10.84 mmol) was added in one portion to methyl 2-[2-(4-aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]acetate (3.56 g, 10.84 mmol) in DMF (75 mL) cooled to 0°C under nitrogen. The resulting solution was stirred at 0°C for 10 minutes then 1,2-dibromoethane (0.981 mL, 11.38 mmol) added and the reaction stirred at 0°C for 5 minutes. Further sodium hydride (434 mg, 10.84 mmol) was added in one portion and the reaction stirred at 0°C for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (10 mL). The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine solution (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was triturated with diethyl ether to give the desired material as a yellow solid (2.23 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.47 - 1.53 (4H, m), 3.64 (8H, t), 3.69 - 3.71 (3H, m), 5.50-5.60 (2H, s), 6.57 - 6.60 (2H, m), 6.73 (1H, s), 7.99 - 8.03 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 355; HPLC tR = 2.06 min.

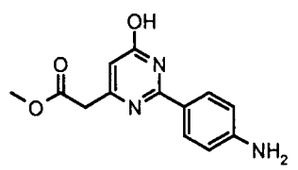
Methyl 2-[2-(4-aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]acetate



DBU (2.2 mL, 14.68 mmol) was added to methyl 2-[2-(4-aminophenyl)-6-hydroxypyrimidin-4-yl]acetate (3.46 g, 13.35 mmol) and *N*-phenyltrifluoromethanesulfonimide (5.24 g, 14.68 mmol) in DCM (120 mL). The resulting solution was stirred at RT for 2 hours. Morpholine (2.91 mL, 33.36 mmol) was added and the reaction stirred at RT for 2 hours. The reaction mixture was diluted with DCM (20 mL) and washed with a saturated aqueous solution of sodium hydrogen carbonate (100 mL). The organic layer was dried (MgSO4) filtered and concentrated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a yellow solid (3.65 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 3.62 (2H, d), 3.66 (8H,m), 3.72 - 3.73 (3H, m), 6.27 (1H, s), 6.61 - 6.64 (2H, m), 7.17 - 7.23 (2H, m), 8.12 - 8.16 (2H, m)
LCMS Spectrum: m/z (ESI+) (M+H)+ = 329; HPLC tR = 1.74 min.

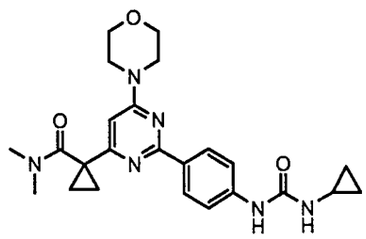
Methyl 2-[2-(4-aminophenyl)-6-hydroxypyrimidin-4-yl]acetate



To a stirred solution of dimethyl 3-oxopentanedioate (15.06g, 86.50 mmol) in methanol (125 mL) was added 4-aminobenzimidamide dihydrochloride (12 g, 57.67 mmol) and potassium carbonate (19.93 g, 144.17 mmol) and the reaction mixture heated at 90°C for 5 hours then allowed to cool to RT. The mixture was concentrated *in vacuo*, redissoved in water (150 mL) and extracted with DCM (150 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The aqueous layer was adjusted to pH5 using acetic acid and the precipitate formed was filtered and dried in a vacuum oven to give the desired material as a yellow solid (3.49g).

LCMS Spectrum: m/z (ES+)(M+H)+=260; HPLC tR=1.06 min.

Example 33: 1-[2-[4-(Cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N,N-dimethylcyclopropane-1-carboxamide



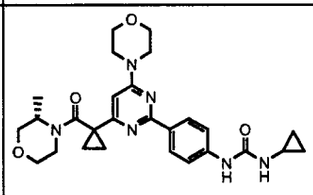
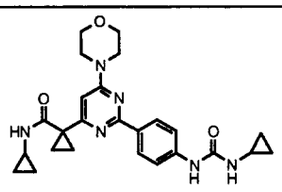
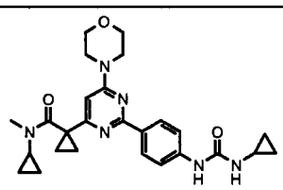
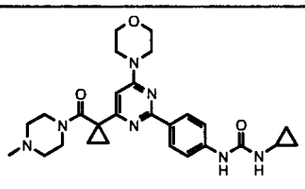
DIPEA (0.142 mL, 0.81 mmol) was added to a suspension of 1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid (115 mg, 0.27 mmol), dimethylamine (2.0M in THF, 0.405 mL, 0.81 mmol) and HBTU (155 mg, 0.36 mmol) in DMF (3 mL). The reactions were stirred at RT for 3 hours then purified on a ion exchange SCX-2 coulmn, eluting with methanol followed by 7N ammonia in methanol. The residue was further purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (20 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.28 - 1.31 (2H, m), 1.51 - 1.54 (2H, m), 2.54 - 2.56 (1H, m), 2.87 (3H, s), 2.94 (3H, s), 3.64 (4H, d), 3.69 - 3.71 (4H, m), 6.22 (1H, s), 6.44 (1H, d), 7.47 - 7.49 (2H, m), 8.16 - 8.19 (2H, m), 8.55 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 451; HPLC tR = 1.83 min.

mTOR Kinase Assay (Echo): 0.00929μM

The following compounds were made in an analogous fashion from 1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
33a		3-cyclopropyl-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	507	1.90
33b		N-cyclopropyl-1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide	463	1.88
33c		N-cyclopropyl-1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N-methylcyclopropane-1-carboxamide	477	2.00
33d		3-cyclopropyl-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	506	1.72

Example 33a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.16 (1H, s), 1.23 (2H, d), 1.32 - 1.36 (2H, m), 1.40 (1H, d), 1.61 - 1.64 (2H, m), 2.52 - 2.57 (1H, m), 3.17 (1H, q), 3.15 - 3.21 (1H, m), 3.46 - 3.49 (1H, m), 3.66 - 3.66 (4H, m), 3.69 (4H, d), 3.71 (1H, s), 4.20 (1H, d), 4.48 (1H, d), 6.24 (1H, s), 6.45 (1H, d), 7.48 (2H, d), 8.19 (2H, d), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.0584μM

Example 33b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 - 0.45 (4H, m), 0.61 - 0.66 (4H, m), 1.31 - 1.35 (4H, m), 2.54 - 2.56 (1H, m), 2.71 (1H, d), 3.67 - 3.72 (8H, m), 6.45 (2H, d), 7.50 (2H, d), 8.15 - 8.17 (2H, m), 8.36 (1H, d), 8.56 (1H, s).

mTOR Kinase Assay (Echo): 0.012μM

Example 33c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.50 (2H, m), 0.63 - 0.65 (2H, m), 0.68 (2H, d), 1.32 -1.40 (2H, m), 1.49 (2H, t), 2.54 - 2.57 (1H, m), 2.75 (3H, d), 2.89 (1H, s), 3.64 (4H, d), 3.69 (4H, d), 6.31 (1H, s), 6.45 (1H, d), 7.48 (2H, d), 8.18 (2H, d), 8.54 (1H, s).

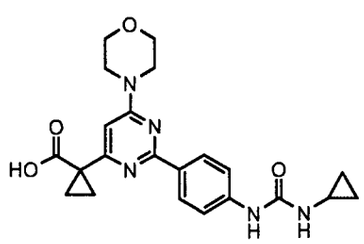
mTOR Kinase Assay (Echo): 0.00258μM

Example 33d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.30 - 1.32 (2H, m), 1.51 (2H, t), 2.12 (4H, s), 2.33 (3H, s), 2.53 - 2.56 (1H, m), 3.58 (4H, s), 3.67 - 3.71 (8H, d), 6.27 (1H, s), 6.45 (1H, d), 7.47 - 7.50 (2H, m), 8.18 - 8.20 (2H, m), 8.55 (1H, s).

mTOR Kinase Assay (Echo): 0.133μM

The preparation of 1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid is described below:

1-[2-[4-(Cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid

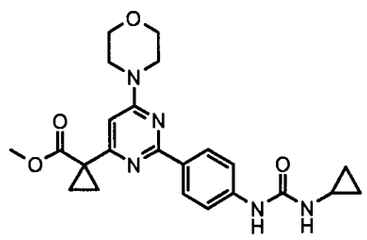


Lithium hydroxide-1-hydrate (67 mg, 1.59 mmol) was added in one portion to methyl 1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate (697 mg, 1.59 mmol) in methanol (8 mL) and water (8 mL) The resulting suspension was stirred at 80°C for 1 hour. The reaction mixture was evaporated to dryness, redissolved in water (25 mL), and washed with diethyl ether (25 mL). The aqueous layer was acidified with 2M hydrochloric acid, the precipitate collected by filtration, washed with diethyl ether and dried under vacuum to give the desired material as a brown solid (580 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.51 - 1.58 (4H, m), 2.53 - 2.57 (1H, m), 3.71 (8H, s), 6.48 (1H, d), 6.75 (1H, s), 7.51 (2H, d), 8.15 (2H, d), 8.63 (1H, s), 14.02 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 424; HPLC tR = 1.09 min.

Methyl 1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate



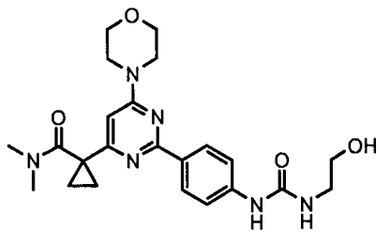
Cyclopropanamine (0.219 mL, 3.15 mmol) was added in one portion to methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate (998 mg, 2.10 mmol) in DMF (20 mL) The resulting solution was stirred at RT for 4 hours and the reaction mixture evaporated to dryness. The crude product was purified by ion exchange chromatography using an SCX column, eluting with methanol followed by 7M ammonia in methanol, to give the desired material as a yellow solid (757 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.50 - 1.53 (4H, m), 2.52 - 2.56 (1H, m), 3.64 (3H, s), 3.69 (8H, d), 6.43 (1H, d), 6.84 (1H, s), 7.47 - 7.49 (2H, m), 8.18 (2H, d), 8.55 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 438; HPLC tR = 2.10 min.

The preparation of methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate was described earlier.

Example 34: 1-[2-[4-(2-Hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N,N-dimethylcyclopropane-1-carboxamide



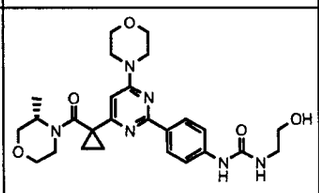
DIPEA (0.106 mL, 0.60 mmol) was added to a suspension of 1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid (86 mg, 0.20 mmol), dimethylamine (2.0M in THF, 0.30 mL, 0.60 mmol) and HBTU (115 mg, 0.30 mmol) in DMF (3 mL). The reactions were stirred at RT for 1 hour then purified by ion exchange using a SCX-2 column, eluting with methanol followed by 7N ammonia in methanol. The isolated material was further purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (56 mg).

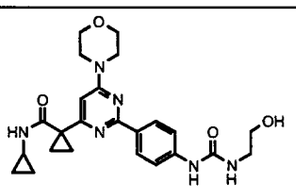
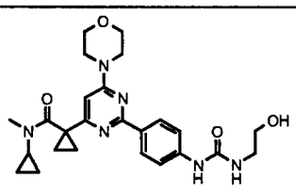
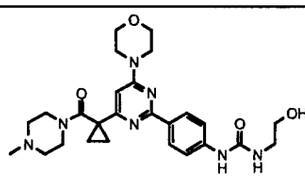
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.30 - 1.31 (2H, m), 1.53 (2H, d), 2.89 (3H, s), 2.94 (3H, s), 3.17 - 3.19 (2H, m), 3.47 (2H, d), 3.65 (4H, d), 3.70 -3.71 (4H, d), 4.74 (1H, s), 6.23 (2H, m), 7.47 (2H, d), 8.18 (2H, d), 8.79 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 455; HPLC tR = 1.52 min.

mTOR Kinase Assay (Echo): 0.00405μM

The following compounds were made in an analogous fashion from 1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
34a		3-(2-hydroxyethyl)-1-[4-[4-[1-[(3S)-3-methylmorpholine-4-carbonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	511	1.59

Example	Structure	NAME	LCMS MH+	Retention time (min)
34b		N-cyclopropyl-1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxamide	467	1.56
34c		N-cyclopropyl-1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]-N-methylcyclopropane-1-carboxamide	481	1.67
34d		3-(2-hydroxyethyl)-1-[4-[4-[1-(4-methylpiperazine-1-carbonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	510	1.44

Example 34a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.22 - 1.25 (3H, m), 1.33 (2H, d), 1.63 (2H, d), 3.16 - 3.20 (1H, m), 3.17 - 3.19 (3H, m), 3.46 (3H, m), 3.67 (4H, s), 3.71 (4H, d), 3.71 (2H, s), 4.20 (1H, d), 4.50(1H, s), 4.74 (1H, t), 6.25 (2H, m), 7.47 (2H, d), 8.20 (2H, d), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.0387μM

Example 34b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.44 - 0.46 (2H, m), 0.62 - 0.65 (2H, m), 1.32 - 1.37 (4H, m), 2.73 (1H, d), 3.18 (2H, d), 3.46 (2H, t), 3.68 (4H, d), 3.71 - 3.71 (4H, d), 4.74 (1H, t), 6.25 (1H, s), 6.46 (1H, s), 7.47 - 7.50 (2H, m), 8.15 - 8.18 (2H, m), 8.35 (1H, s), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.0109μM

Example 34c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.69 (4H, s), 1.50 (4H, m), 2.40 (1H, s), 2.80 (3H, m), 3.16 - 3.19 (2H, m), 3.47 (2H, q), 3.65 (4H, d), 3.70 - 3.72 (4H, m), 4.74 (1H, t), 6.25 (2H, m), 7.46 - 7.48 (2H, m), 8.17 - 8.19 (2H, m), 8.78 (1H, s).

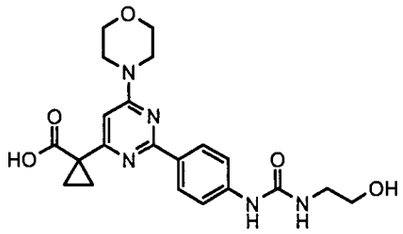
mTOR Kinase Assay (Echo): 0.00345μM

Example 34d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.30 - 1.33 (2H, m), 1.51 - 1.54 (2H, m), 2.10 - 2.15 (5H, m), 2.33 - 2.34 (1H, t), 3.18 - 3.19 (3H, m), 3.36 (1H, d), 3.47 (2H, q), 3.58 (3H, s), 3.66 - 3.71 (4H, m), 3.71 (4H, d), 4.74 (1H, t), 6.25 (1H, t), 6.27 (1H, s), 7.46 - 7.49 (2H, m), 8.18 - 8.21 (2H, m), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.0863μM

The preparation of 1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid is described below:

1-[2-[4-(2-Hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylic acid

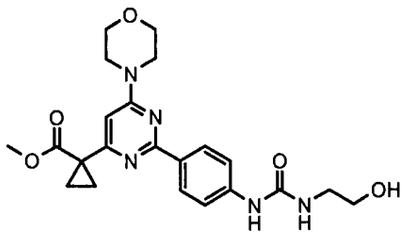


Lithium hydroxide-1-hydrate (67.2 mg, 1.60 mmol) was added in one portion to methyl 1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate (707 mg, 1.60 mmol) in methanol (8 mL) and water (8 mL). The resulting suspension was stirred at 80°C for 1 hour. The reaction mixture was evaporated to dryness, redissolved in water (25 mL), and washed with diethyl ether (25 mL). The aqueous layer was acidified with 2M hydrochloric acid, the precipitate collected by filtration, washed with diethyl ether and dried under vacuum to give the desired material as a beige solid (439 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.51 - 1.58 (4H, m), 3.17 (2H, q), 3.45 (2H, t), 3.70 (8H, s), 4.77 (1H, s), 6.28 (1H, t), 6.74 (1H, s), 7.48 - 7.50 (2H, m), 8.14 - 8.16 (2H, m), 8.86 (1H, s), 14.06 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 428; HPLC tR = 0.92 min.

Methyl 1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropane-1-carboxylate



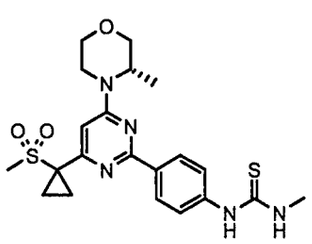
2-Aminoethanol (0.127 mL, 2.10 mmol) was added in one portion to methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate (998 mg, 2.10 mmol) in DMF (20 mL) The resulting solution was stirred at RT for 16 hours. The reaction mixture was evaporated to dryness and the crude product purified by ion exchange chromatography using an SCX column, eluting with methanol followed by 7N ammonia in methanol, to give the desired material as a yellow solid (767 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.50 - 1.52 (4H, m), 3.17 (2H, q), 3.45 (2H, q), 3.64 (3H, s), 3.70 (8H, s), 4.77 (1H, t), 6.25 (1H, t), 6.83 (1H, s), 7.45 - 7.47 (2H, m), 8.16 - 8.19 (2H, m), 8.81 (1H, s)

LCMS Spectrum. m/z (ESI+) (M+H)+ = 442; HPLC tR = 1.71 min.

The preparation of methyl 1-[6-morpholin-4-yl-2-[4-(phenoxycarbonylamino)phenyl]pyrimidin-4-yl]cyclopropane-1-carboxylate was described earlier.

Example 35: 3-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea



To a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (60mg, 0.16 mmol) in DCM (2 mL) and THF (1 mL) was added a solution of di(imidazol-1-yl)methanethione (37 mg, 0.21 mmol) in

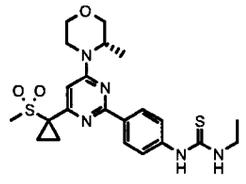
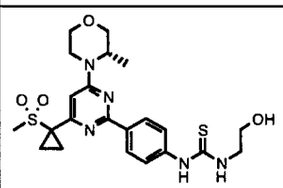
DCM (1 mL) and the resulting solution stirred at RT for 3 hours. Methylamine (2M in THF, 0.4 mL, 0.80 mmol) was added followed by triethylamine (0.022 mL, 0.16mmol) and the solution stirred for 1 hour at RT. The solvent was evaporated and the crude product purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a white solid (19 mg).

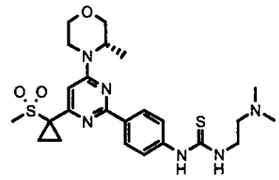
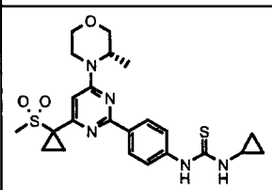
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 – 1.58 (2H, m), 1.66 – 1.69 (2H, m), 2.95 (3H, d), 3.16 (3H, s), 3.21 – 3.26 (1H, m), 3.45 – 3.52 (1H, m), 3.61 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.20 – 4.23 (1H, m), 4.55 – 4.63 (1H, m), 6.80 (1H, s), 7.55 (2H, d), 7.84 (1H, s), 8.26 (2H, d), 9.73 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 462; HPLC tR = 1.86min.

mTOR Kinase Assay (Echo): 0.00531μM

The compounds below were prepared in an analogous fashion from 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
35a		3-ethyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	476	1.94
35b		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	492	1.68

Example	Structure	NAME	LCMS MH+	Retention time (min)
35c		3-(2-dimethylaminoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	519	1.99
35d		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	488	1.89

Example 35a: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.14 (3H, t), 1.24 (3H, d), 1.55 – 1.58 (2H, m), 1.66 – 1.69 (2H, m), 3.17 – 3.25 (1H, m), 3.29 (3H, s), 3.45 – 3.51 (3H, m), 3.61 – 3.65 (1H, m), 3.76 (1H, d), 3.95 – 3.99 (1H, m), 4.20 – 4.23 (1H, m), 4.55 – 4.62 (1H, m), 6.80 (1H, s), 7.57 (2H, d), 7.88 (1H, s), 8.25 (2H, d), 9.63 (1H, s).

mTOR Kinase Assay (Echo): 0.00552μM

Example 35b: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.66 - 1.69 (2H, m), 3.17 - 3.25 (1H, m), 3.29 (3H, s), 3.45 - 3.52 (1H, m), 3.57 (4H, s), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.20 - 4.23 (1H, m), 4.55 - 4.62 (1H, m), 4.77 - 4.85 (1H, m), 6.80 (1H, s), 7.63 (2H, d), 7.86 (1H, s), 8.26 (2H, d), 9.81 (1H, s).

mTOR Kinase Assay (Echo): 0.000577μM

Example 35c: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.66 - 1.69 (2H, m), 2.20 (6H, s), 2.45 (2H, t), 3.18 - 3.25 (1H, m), 3.26 (3H, s), 3.45 - 3.52 (1H, m), 3.56 (2H, s), 3.61 - 3.65 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.21 (1H, d), 4.56 - 4.61 (1H, m), 6.80 (1H, s), 7.65 (2H, d), 7.77 (1H, s), 8.25 (2H, d), 9.90 (1H, s).

mTOR Kinase Assay (Echo): 0.108μM

Example 35d: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.58 - 0.62 (2H, m), 0.74 - 0.79 (2H, m), 1.24 (3H, d), 1.55 - 1.59 (2H, m), 1.67 - 1.69 (2H, m), 2.89 - 2.97 (1H, m), 3.17 - 3.27 (1H, m), 3.30 (3H, s), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.77 (1H, d), 3.96 - 3.99 (1H, m), 4.21 - 4.24 (1H, m), 4.60 (1H, s), 6.81 (1H, s), 7.62 (2H, d), 8.14 (1H, s), 8.25 (2H, d), 9.51 (1H, s).

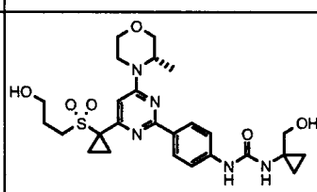
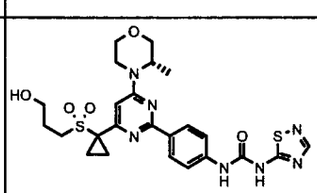
mTOR Kinase Assay (Echo): 0.00411μM

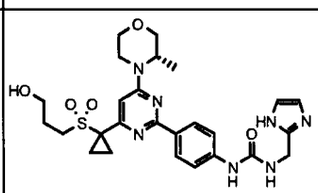
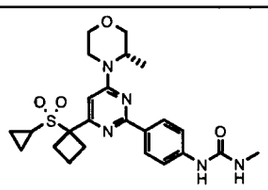
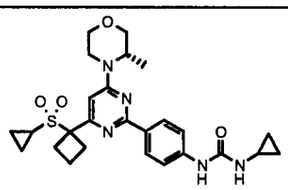
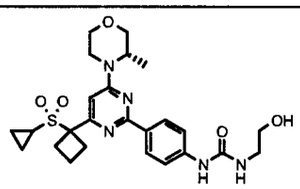
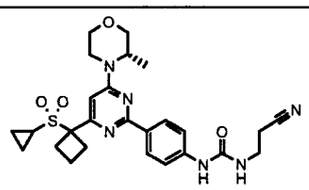
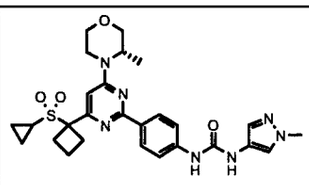
The preparation of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline was described earlier.

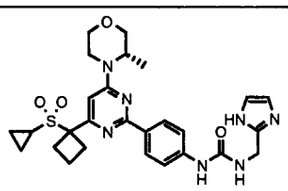
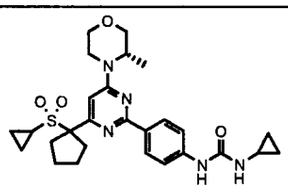
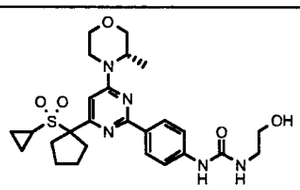
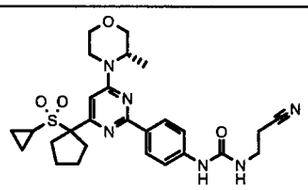
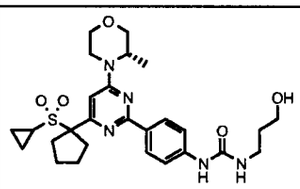
Example 36

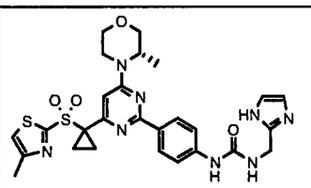
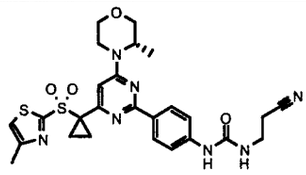
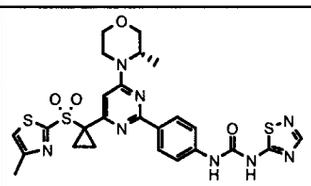
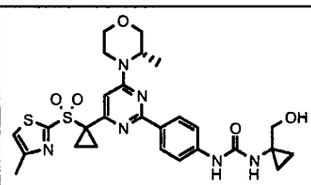
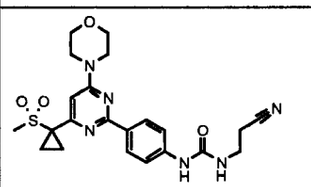
The following compounds were prepared according to the following general procedure:

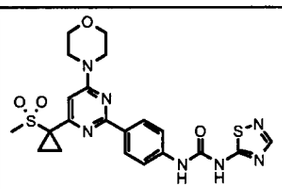
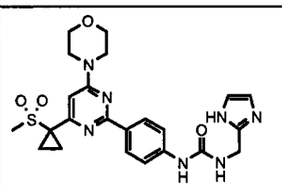
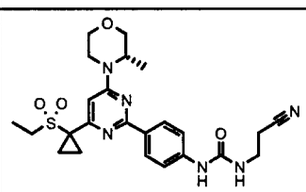
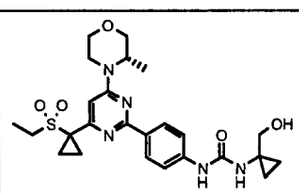
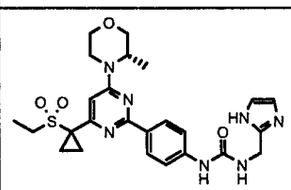
The appropriate phenyl carbamate and an excess of both triethylamine and the appropriate amine were dissolved in either DMF, NMP or DMA and stirred at 50°C – 70°C for between 2 – 18 hours (unless otherwise specified). The materials were purifed by preparative HPLC except where specified.

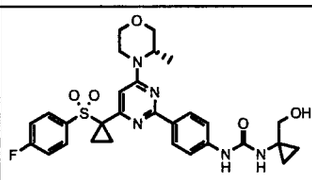
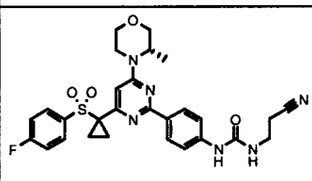
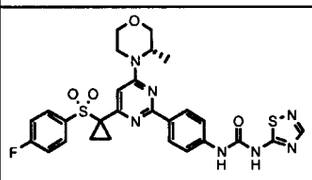
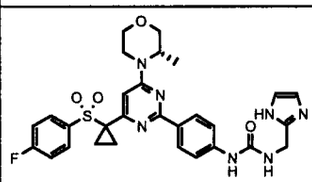
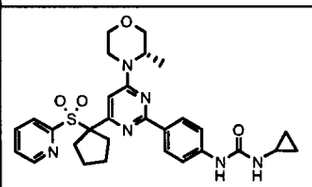
Example	Structure	NAME	LCMS MH+	Retention time (min)
36a		3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	546	1.67
36b		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	560	1.41

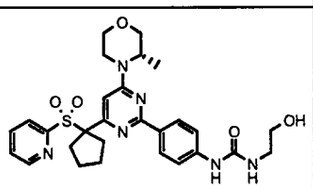
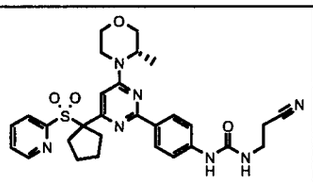
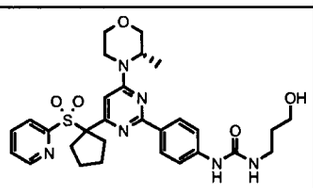
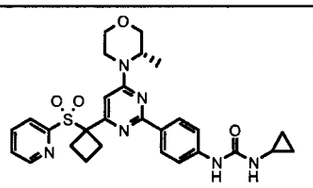
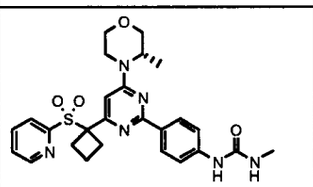
Example	Structure	NAME	LCMS MH+	Retention time (min)
36c		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	556	1.65
36d		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	486	1.92
36e		3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	512	2.16
36f		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	516	1.84
36g		3-(2-cyanoethyl)-1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	525	2.07
36h		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	552	2.04

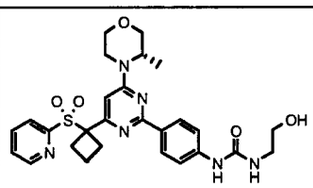
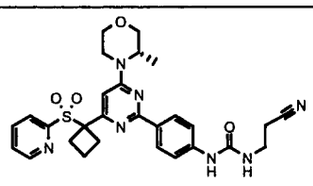
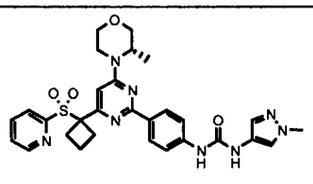
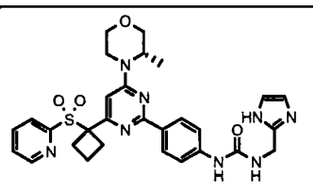
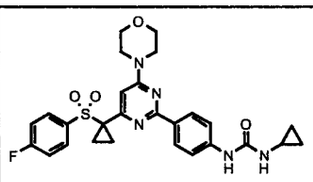
Example	Structure	NAME	LCMS MH+	Retention time (min)
36i		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	552	1.99
36j		3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	526	2.34
36k		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	530	1.97
36l		3-(2-cyanoethyl)-1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	539	2.19
36m		1-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	544	1.99

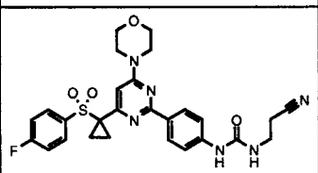
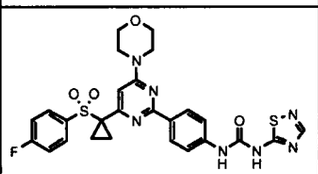
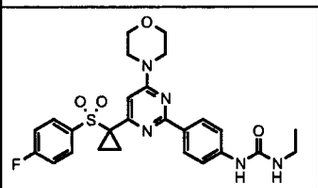
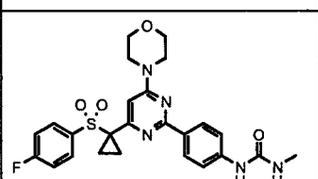
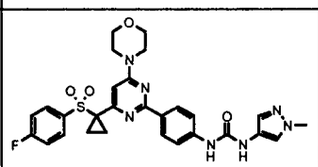
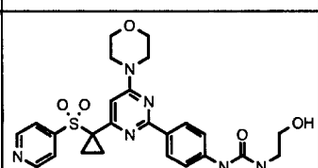
Example	Structure	NAME	LCMS MH+	Retention time (min)
36n		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	595	2.07
36o		3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	568	2.25
36p		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	599	1.81
36q		3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	585	2.09
36r		3-(2-cyanoethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	471.5	1.66

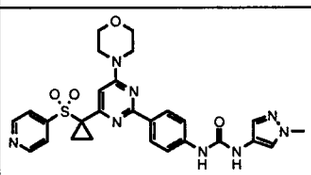
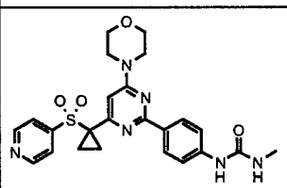
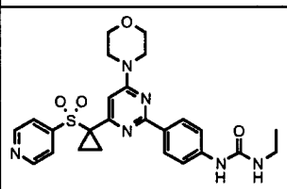
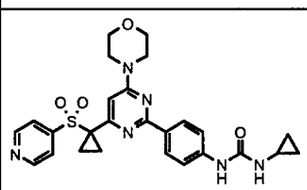
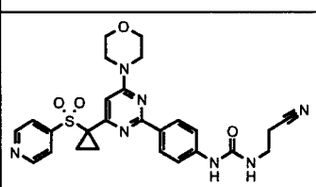
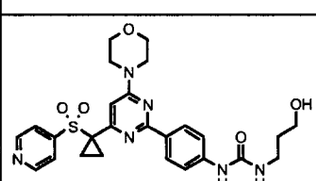
Example	Structure	NAME	LCMS MH+	Retention time (min)
36s*		1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	502	1.61
36t		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	498.6	2.02
36u		3-(2-cyanoethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	499.1	2.10
36v		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea	516.1	1.97
36w		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	526.1	1.94

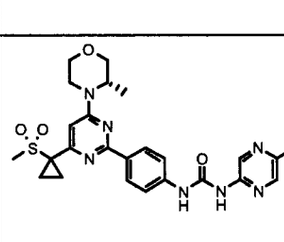
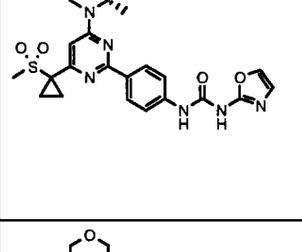
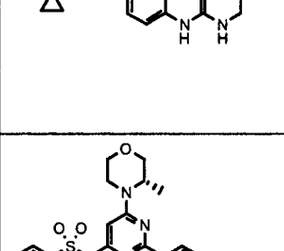
Example	Structure	NAME	LCMS MH+	Retention time (min)
36x		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea	582	2.17
36y		3-(2-cyanoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	565	2.40
36z		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	596	1.49
36aa		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	592	2.07
36ab		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	563	2.38

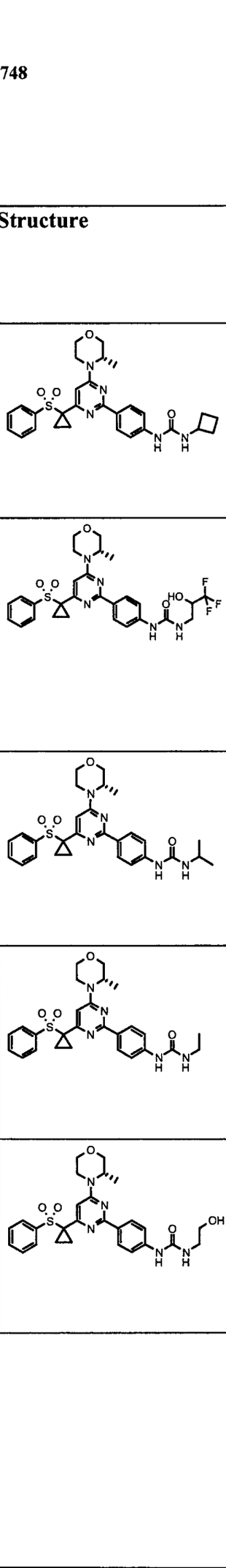
Example	Structure	NAME	LCMS MH+	Retention time (min)
36ac		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	567	2.01
36ad		3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	576	2.28
36ae		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]urea	581	2.05
36af		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	549	2.25
36ag		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	523	2.08

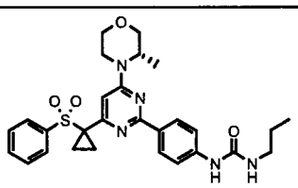
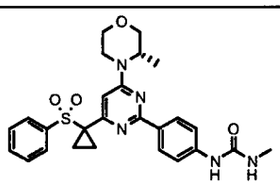
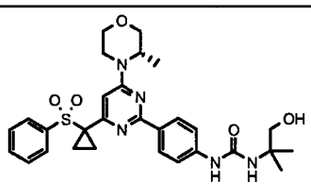
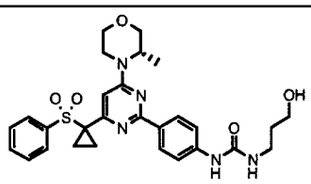
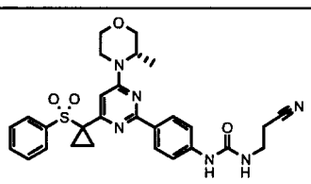
Example	Structure	NAME	LCMS MH+	Retention time (min)
36ah		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	553	1.89
36ai		3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	562	2.15
36aj		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	589	2.11
36ak		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	589	2.34
36al**		3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	538	2.36

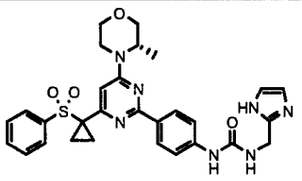
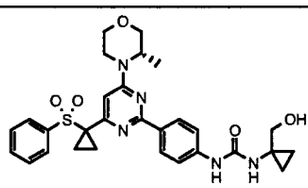
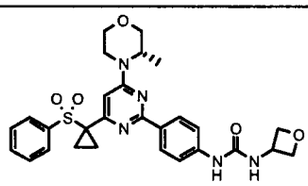
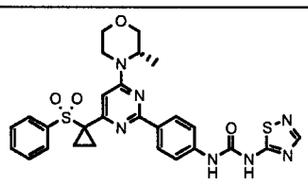
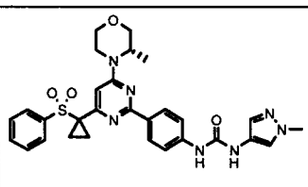
Example	Structure	NAME	LCMS MH+	Retention time (min)
36am**		3-(2-cyanoethyl)-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	551	2.27
36an		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	542	1.41
36ao		1-ethyl-3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	526	2.14
36ap		3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-methylurea	512	1.99
36aq		3-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-(1-methylpyrazol-4-yl)urea	578	2.04
36ar		3-(2-hydroxyethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	525	1.66

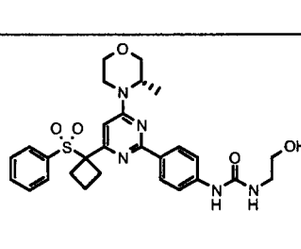
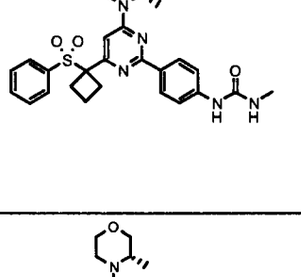
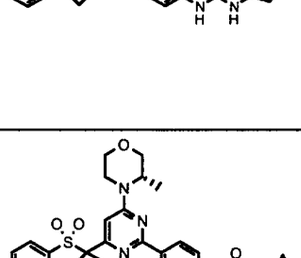
Example	Structure	NAME	LCMS MH+	Retention time (min)
36as		1-(1-methylpyrazol-4-yl)-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	561	1.81
36at		1-methyl-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	495	1.81
36au		1-ethyl-3-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	509	1.99
36av		3-cyclopropyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	521	1.95
36aw		3-(2-cyanoethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	534	1.89
36ax		3-(3-hydroxypropyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	539	1.72

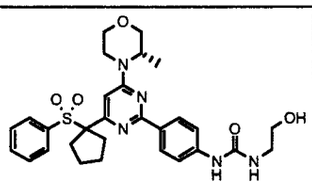
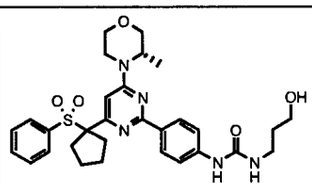
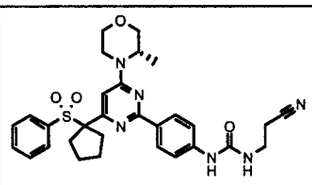
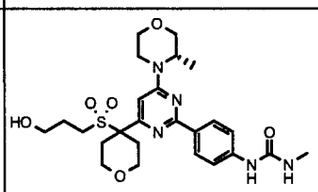
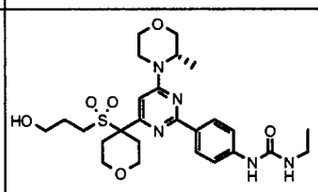
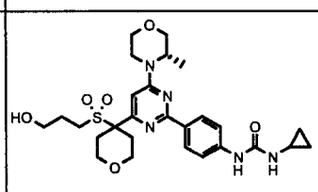
Example	Structure	NAME	LCMS MH+	Retention time (min)
36ay		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea	515	2.19
36az		3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-1-(5-methylpyrazin-2-yl)urea	524	2.35
36ba		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,3-oxazol-2-yl)urea	499	1.99
36bb		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	490	1.75
36bc		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	534	2.39

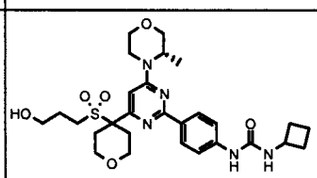
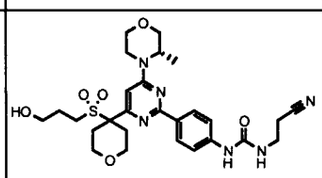
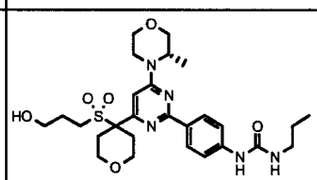
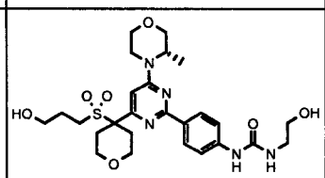
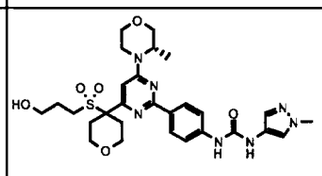
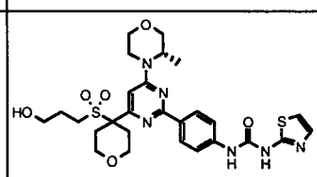
Example	Structure	NAME	LCMS MH+	Retention time (min)
36bd		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclobutylurea	548	2.61
36be		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3,3,3-trifluoro-2-hydroxypropyl)urea	606	2.45
36bf		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-propan-2-ylurea	536	2.51
36bg		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	522	2.32
36bh		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	538	1.98

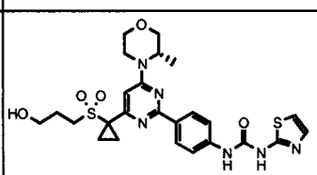
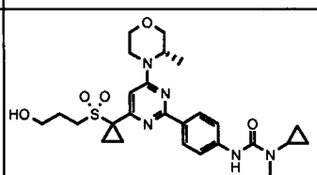
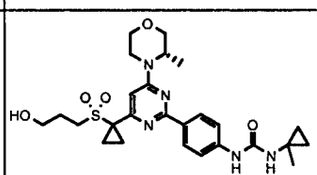
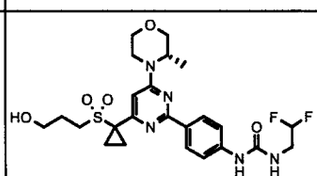
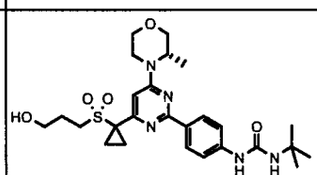
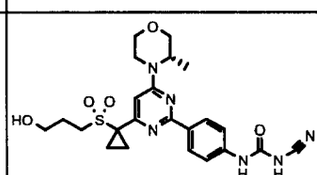
Example	Structure	NAME	LCMS MH+	Retention time (min)
36bi		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	536	2.49
36bj		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	508	2.16
36bk		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	566	2.28
36bl		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	552	2.03
36bm		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea	547	2.24

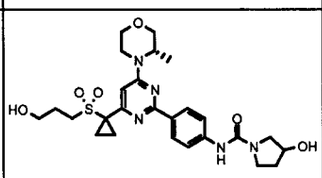
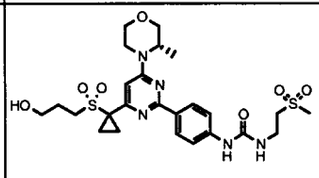
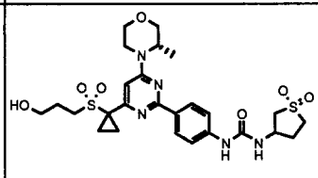
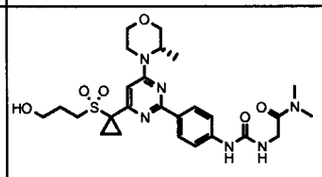
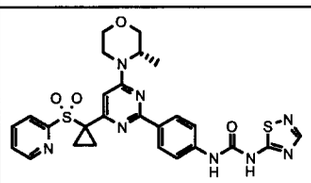
Example	Structure	NAME	LCMS MH+	Retention time (min)
36bn		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	574	2.12
36bo		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[1-(hydroxymethyl)cyclopropyl]urea	564	2.11
36bp		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(oxetan-3-yl)urea	550	2.13
36bq		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	578	1.35
36br		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	574	2.21

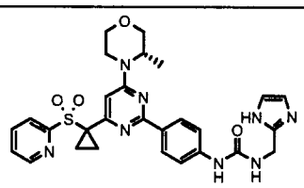
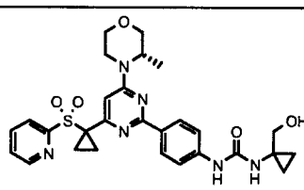
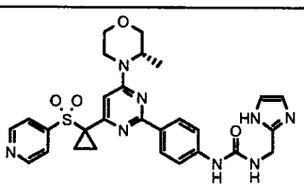
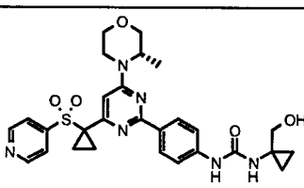
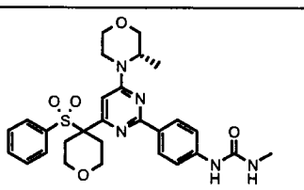
Example	Structure	NAME	LCMS MH+	Retention time (min)
36bs		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	548	2.53
36bt		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	552	2.14
36bu		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	522	2.35
36bv		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	588	2.37
36bw		1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	562	2.75

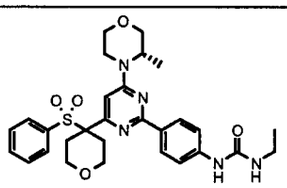
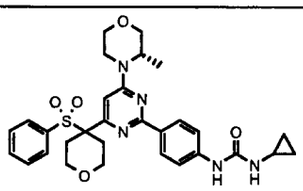
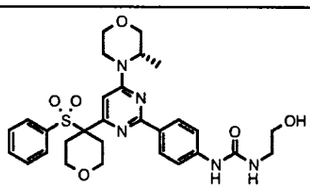
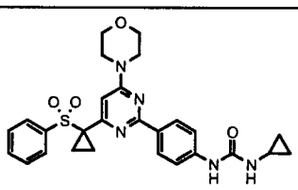
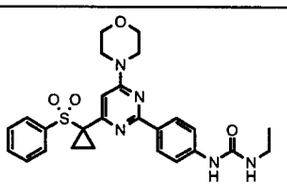
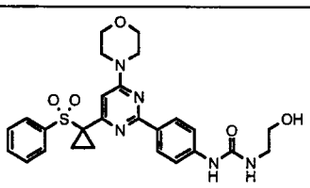
Example	Structure	NAME	LCMS MH+	Retention time (min)
36bx		1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	566	2.30
36by		1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	580	2.31
36bz		1-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea	575	2.55
36ca***		1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	534	1.56
36cb***		1-ethyl-3-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.67
36cc***		3-cyclopropyl-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	560	1.71

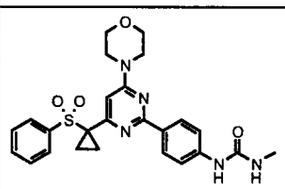
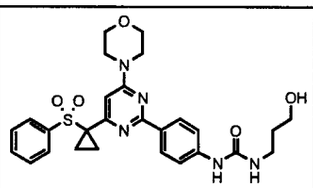
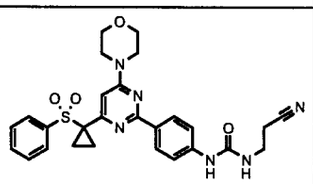
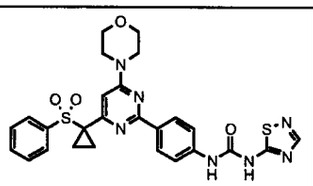
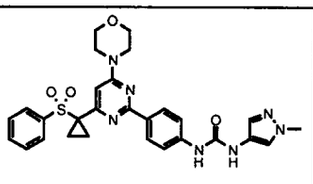
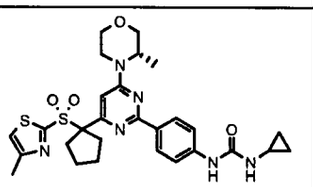
Example	Structure	NAME	LCMS MH+	Retention time (min)
36cd***		3-cyclobutyl-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	574	1.89
36ce***		3-(2-cyanoethyl)-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	573	1.62
36cf***		3-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	562	1.83
36cg***		3-(2-hydroxyethyl)-1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	564	1.46
36ch***		1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	600	1.62
36ci***		1-[4-[4-[4-(3-hydroxypropylsulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea	603	1.87

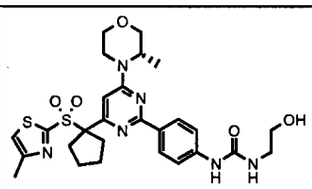
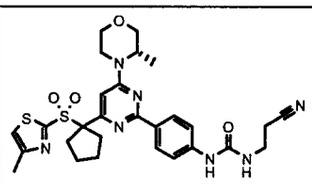
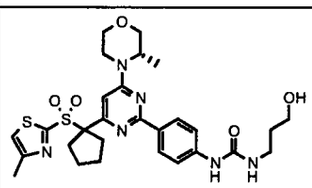
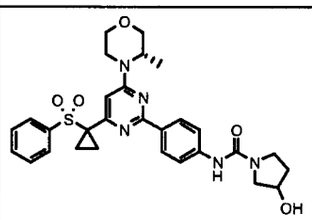
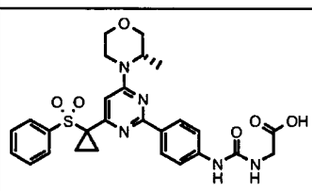
Example	Structure	NAME	LCMS MH+	Retention time (min)
36cj***		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea	559	1.94
36ck***		1-cyclopropyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-methylurea	530	1.96
36cl***		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylcyclopropyl)urea	530	1.88
36cm***		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	540	1.85
36cn***		3-tert-butyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	532	2.10
36co***		3-cyano-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	501	1.12

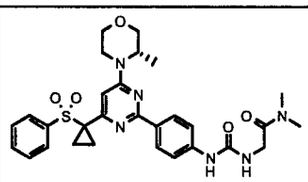
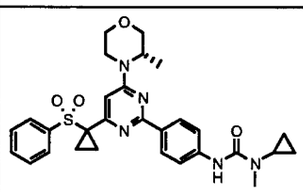
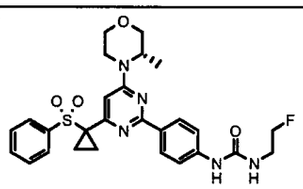
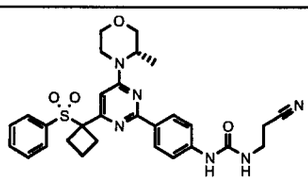
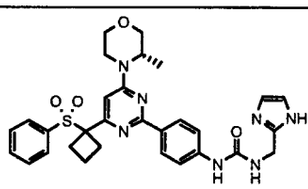
Example	Structure	NAME	LCMS MH+	Retention time (min)
36cp***		3-hydroxy-N-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]pyrrolidine-1-carboxamide	546	1.52
36cq***		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-methylsulfonylethyl)urea	582	1.61
36cr***		3-(1,1-dioxothiolan-3-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	594	1.66
36cs***		2-[[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]-N,N-dimethylacetamide	561	1.59
36ct		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	579	1.37

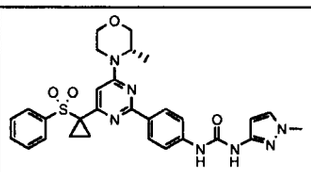
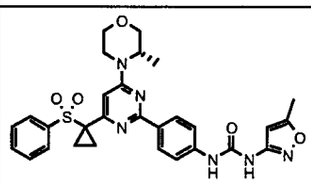
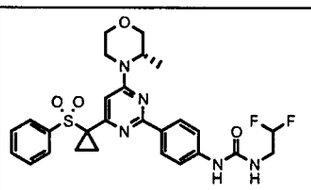
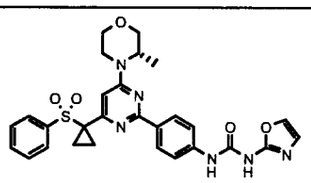
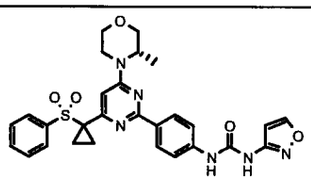
Example	Structure	NAME	LCMS MH+	Retention time (min)
36cu		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	575	1.76
36cv		3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	565	1.77
36cw		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	576	1.77
36cx		3-[1-(hydroxymethyl)cyclopropyl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	566	1.78
36cy		1-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	553	2.14

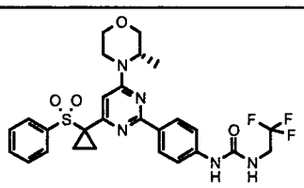
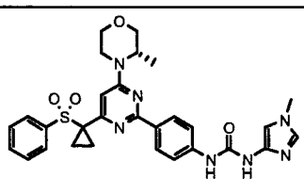
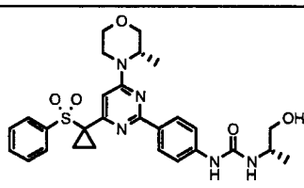
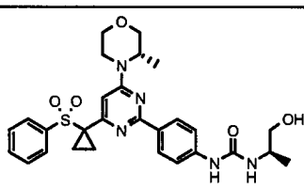
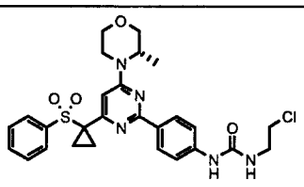
Example	Structure	NAME	LCMS MH+	Retention time (min)
36cz		3-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	567	2.29
36da		1-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	579	2.29
36db		1-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	583	1.93
36dc		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-cyclopropylurea	520	2.24
36dd		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-ethylurea	508	2.24
36de		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	524	1.89

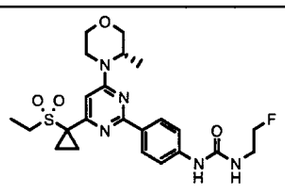
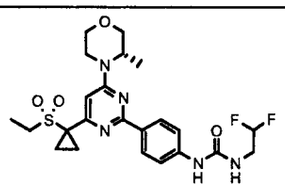
Example	Structure	NAME	LCMS MH+	Retention time (min)
36df		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-methylurea	494	2.08
36dg		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	538	1.95
36dh		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea	533	2.16
36di		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	564	1.41
36dj		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-(1-methylpyrazol-4-yl)urea	560	2.11
36dk****		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea	583	2.62

Example	Structure	NAME	LCMS MH+	Retention time (min)
36dl****		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea	588	2.24
36dm****		3-(2-cyanoethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea	596	2.50
36dn****		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]urea	601	2.28
36do		N-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-hydroxypyrrolidine-1-carboxamide	564	2.02
36dp		2-[[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]acetic acid	552	1.21

Example	Structure	NAME	LCMS MH+	Retention time (min)
36dq		2-[[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamoylamino]-N,N-dimethylacetamide	579	2.11
36dr		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-cyclopropyl-1-methylurea	548	2.61
36ds		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	540	2.33
36dt		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)urea	561	2.41
36du		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	588	2.31

Example	Structure	NAME	LCMS MH+	Retention time (min)
36dv		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-3-yl)urea	574	2.76
36dw		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-(5-methyl-1,2-oxazol-3-yl)urea	575	2.97
36dx		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	558	2.81
36dy		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-oxazol-2-yl)urea	561	2.51
36dz		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	561	2.85

Example	Structure	NAME	LCMS MH+	Retention time (min)
36ea		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2,2-trifluoroethyl)urea	576	2.94
36eb		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylimidazol-4-yl)urea	574	2.61
36ec		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	552	2.47
36ed		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	552	2.47
36ee		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-chloroethyl)urea	590	2.84

Example	Structure	NAME	LCMS MH+	Retention time (min)
36ef****		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	493	2.46
36eg****		3-(2,2-difluoroethyl)-1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	511	2.60

* Following the initial reaction conditions the mixture was placed in a sealed tube and heated at 100°C in a microwave reactor for 10 minutes.

** The material was purified by trituration with diethyl ether

*** Following the initial reaction conditions the mixture was allowed to cool, tetrabutylammonium fluoride (1 equivalent) added and the reaction stirred at RT for 1 hour. The reaction was purified by prep HPLC.

**** The mixture was stirred at RT for 16 hours

Example 36a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63 - 0.68 (2H, m), 0.68 - 0.73 (2H, m), 1.23 (3H, d), 1.53 - 1.58 (2H, m), 1.60 - 1.66 (2H, m), 1.88 - 1.98 (2H, m), 3.16 - 3.25 (1H, m), 3.28 - 3.35 (4H, m), 3.47 - 3.54 (3H, m), 3.63 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.23 (1H, d), 4.56 (1H, s), 4.69 (1H, t), 6.57 (1H, s), 6.77 (1H, s), 7.47 (2H, d), 8.21 (2H, d), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.142μM

Example 36b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.60 (2H, m), 1.62 - 1.68 (2H, m), 1.92 - 1.99 (2H, m), 3.23 - 3.31 (3H, m), 3.47 - 3.58 (3H, m), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.21 (1H, d), 4.57 (1H, s), 4.71 (1H, t), 6.80 (1H, s), 7.64 (2H, d), 8.30 (2H, d), 9.46 (1H, s).

mTOR Kinase Assay (Echo): 0.00179μM

Example 36c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.52 - 1.58 (2H, m), 1.62 - 1.65 (2H, m), 1.89 - 1.97 (2H, m), 3.22 - 3.34 (3H, m), 3.44 - 3.56 (3H, m), 3.63 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.16 - 4.24 (1H, m), 4.35 (2H, d), 4.55 (1H, s), 4.69 (1H, s), 6.67 (1H, t), 6.77 (1H, s), 6.99 (2H, s), 7.52 (2H, d), 8.21 (2H, d), 8.99 (1H, s).

mTOR Kinase Assay (Echo): 0.114μM

Example 36d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 - 0.78 (2H, m), 0.81 - 0.88 (2H, m), 1.23 (3H, d), 1.88 - 1.96 (1H, m), 2.01 - 2.14 (1H, m), 2.67 (3H, d), 2.81 - 2.99 (4H, m), 3.15 - 3.26 (2H, m), 3.50 (1H, dd), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.21 (1H, d), 4.55 (1H, s), 6.06 (1H, t), 6.70 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00317μM

Example 36e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39 - 0.44 (2H, m), 0.61 - 0.68 (2H, m), 0.72 - 0.78 (2H, m), 0.82 - 0.88 (2H, m), 1.23 (3H, d), 1.84 - 1.96 (1H, m), 2.02 - 2.12 (1H, m), 2.50 - 2.59 (2H, m), 2.81 - 3.01 (4H, m), 3.17 - 3.24 (1H, m), 3.50 (1H, dd), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.55 (1H, s), 6.42 (1H, t), 6.71 (1H, s), 7.48 (2H, d), 8.24 (2H, d), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.00667μM

Example 36f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.68 - 0.80 (2H, m), 0.81 - 0.89 (2H, m), 1.23 (3H, d), 1.84 - 1.95 (1H, m), 2.02 - 2.13 (1H, m), 2.76 - 3.00 (4H, m), 3.11 - 3.27 (3H, m), 3.43 - 3.56 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.21 (1H, d), 4.54 (1H, s), 4.72 (1H, t), 6.24 (1H, t), 6.70 (1H, s), 7.48 (2H, d), 8.24 (2H, d), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.00278μM

Example 36g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.69 - 0.79 (2H, m), 0.81 - 0.89 (2H, m), 1.23 (3H, d), 1.84 - 1.96 (1H, m), 2.02 - 2.12 (1H, m), 2.63 - 2.73 (2H, m), 2.83 - 3.03 (4H, m), 3.14 - 3.23 (1H, m), 3.33 - 3.43 (2H, m), 3.51 (1H, dd), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.55 (1H, s), 6.51 (1H, t), 6.71 (1H, s), 7.51 (2H, d), 8.25 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.00841μM

Example 36h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 - 0.80 (2H, m), 0.82 - 0.91 (2H, m), 1.23 (3H, d), 1.86 - 1.97 (1H, m), 2.02 - 2.12 (1H, m), 2.77 - 3.03 (4H, m), 3.15 - 3.29 (5H, m), 3.51 (1H, d), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.55 (1H, s), 6.72 (1H, s), 7.38 (1H, s), 7.54 (2H, d), 7.76 (1H, s), 8.27 (2H, d), 8.37 (1H, s), 8.83 (1H, s).

mTOR Kinase Assay (Echo): 0.00314μM

Example 36i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.74 - 0.84 (2H, m), 0.87 - 0.94 (2H, m), 1.28 (3H, d), 1.91 - 2.01 (1H, m), 2.08 - 2.19 (1H, m), 2.84 - 3.09 (4H, m), 3.25 - 3.32 (2H, m), 3.56 (1H, d), 3.71 (1H, d), 3.82 (1H, d), 4.03 (1H, d), 4.27 (1H, d), 4.38 (2H, d), 4.61 (1H, s), 6.68 (1H, t), 6.76 (1H, s), 7.00 (1H, s), 7.56 (2H, d), 8.31 (2H, d), 8.98 (1H, s).

mTOR Kinase Assay (Echo): 0.0518μM

Example 36j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 0.68 - 0.75 (2H, m), 0.80 - 0.87 (2H, m), 1.22 (3H, d), 1.52 - 1.61 (2H, m), 1.76 - 1.86 (2H, m), 2.50 - 2.61 (4H, m), 2.74 - 2.90 (2H, m), 3.14 - 3.24 (1H, m), 3.50 (2H, dd), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.54 (1H, s), 6.42 (1H, s), 6.81 (1H, s), 7.50 (2H, d), 8.24 (2H, d), 8.53 (1H, s).

mTOR Kinase Assay (Echo): 0.018μM

Example 36k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.66 - 0.77 (2H, m), 0.80 - 0.89 (2H, m), 1.22 (3H, d), 1.52 - 1.61 (2H, m), 1.76 - 1.86 (2H, m), 2.43 - 2.61 (3H, m), 2.75 - 2.89 (2H, m), 3.16 - 3.22 (3H, m), 3.43 - 3.55 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.54 (1H, s), 4.73 (1H, t), 6.25 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.24 (2H, d), 8.79 (1H, s).

mTOR Kinase Assay (Echo): 0.0131μM

Example 36l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.66 - 0.76 (2H, m), 0.82 - 0.87 (2H, m), 1.22 (3H, d), 1.53 - 1.60 (2H, m), 1.74 - 1.85 (2H, m), 2.49 - 2.61 (3H, m), 2.65 - 2.72 (2H, m), 2.74 - 2.88 (2H, m), 3.16 - 3.25 (1H, m), 3.33 - 3.40 (2H, m), 3.50 (1H, d), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.23 (1H, d), 4.55 (1H, s), 6.52 (1H, t), 6.81 (1H, s), 7.51 (2H, d), 8.26 (2H, d), 8.91 (1H, s).

mTOR Kinase Assay (Echo): 0.0428μM

Example 36m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.67 - 0.77 (2H, m), 0.81 - 0.89 (2H, m), 1.22 (3H, d), 1.52 - 1.64 (4H, m), 1.78 - 1.85 (2H, m), 2.41 - 2.56 (3H, m), 2.74 - 2.93 (2H, m), 3.13 - 3.25 (3H, m), 3.42 - 3.56 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.16 - 4.26 (1H, m), 4.47 (1H, t), 4.54 (1H, s), 6.19 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.24 (2H, d), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.0347μM

Example 36n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.76 - 1.80 (2H, m), 1.93 - 1.97 (2H, m), 2.48 (3H, s), 3.14 - 3.21 (1H, m), 3.47 (1H, t), 3.62 (1H, d), 3.76 (1H, d), 3.97

(1H, d), 4.14 - 4.17 (1H, m), 4.32 (2H, d), 4.42 - 4.49 (1H, m), 6.61 (1H, t), 6.78 (1H, s), 6.93 (2H, bs), 7.43 (2H, d), 7.84 (1H, s), 7.90 (2H, d), 8.90 (1H, s), 11.85 (1H, s).

mTOR Kinase Assay (Echo): 0.0248μM

Example 36o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.77 - 1.79 (2H, m), 1.94 - 1.97 (2H, m), 2.48 (3H, s), 2.70 (2H, t), 3.14 - 3.22 (1H, m), 3.35 - 3.39 (2H, m), 3.44 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.15 - 4.18 (1H, m), 4.42 - 4.48 (1H, m), 6.51 (1H, t), 6.78 (1H, s), 7.43 (2H, d), 7.84 (1H, s), 7.90 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.00358μM

Example 36p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.77 - 1.81 (2H, m), 1.95 - 1.99 (2H, m), 2.51 (3H, s), 3.16 - 3.24 (1H, m), 3.45 - 3.51 (1H, m), 3.61 - 3.65 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.16 - 4.20 (1H, m), 4.43 - 4.49 (1H, m), 6.82 (1H, s), 7.55 (2H, d), 7.87 (1H, s), 8.00 (2H, d), 8.37 (1H, s), 9.45 (1H, s), 11.32 (1H, s).

mTOR Kinase Assay (Echo): 0.00161μM

Example 36q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63 - 0.66 (2H, m), 0.69 - 0.73 (2H, m), 1.21 (3H, d), 1.77 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 (3H, s), 3.14 - 3.21 (1H, m), 3.44 (2H, d), 3.47 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.98 (1H, m), 4.14 - 4.17 (1H, m), 4.42 - 4.48 (1H, m), 4.83 (1H, s), 6.54 (1H, s), 6.77 (1H, s), 7.40 (2H, d), 7.84 (1H, s), 7.89 (2H, d), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.0889μM

Example 36r: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.54 - 1.57 (2H, m), 1.65 - 1.68 (2H, m), 2.70 (2H, t), 3.27 (3H, s), 3.35 - 3.40 (2H, m), 3.72 (8H, s), 6.53 (1H, t), 6.81 (1H, s), 7.50 - 7.54 (2H, m), 8.20 - 8.24 (2H, m), 8.93 (1H, s).

mTOR Kinase Assay (Echo): 0.00733μM

Example 36s: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.55 - 1.59 (2H, m), 1.67 - 1.70 (2H, m), 3.27 (3H, s), 3.73 (8H, s), 6.86 (1H, s), 7.61 - 7.65 (2H, m), 8.30 - 8.33 (2H, m), 8.37 (1H, s), 9.44 (1H, s), 11.40 (1H, s).

mTOR Kinase Assay (Echo): 0.00475μM

Example 36t: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.54 - 1.57 (2H, m), 1.65 - 1.68 (2H, m), 3.27 (3H, s), 3.72 (8H, s), 4.32 (2H, d), 6.62 (1H, t), 6.81 - 6.83 (2H, m), 7.03 (1H, s), 7.50 - 7.54 (2H, m), 8.20 - 8.23 (2H, m), 8.94 (1H, s), 11.83 (1H, s).

mTOR Kinase Assay (Echo): 0.194μM

Example 36u: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.53 - 1.56 (2H, m), 1.62 - 1.65 (2H, m), 2.70 (2H, t), 3.17 - 3.24 (1H, m), 3.35 - 3.52 (5H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.24 (1H, m), 4.52 - 4.58 (1H, m), 6.53 (1H, t), 6.78 (1H, s), 7.50 - 7.54 (2H, m), 8.18 - 8.22 (2H, m), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.00922μM

Example 36v: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63 - 0.67 (2H, m), 0.69 - 0.73 (2H, m), 1.23 (3H, d), 1.32 (3H, t), 1.53 - 1.58 (2H, m), 1.60 - 1.65 (2H, m), 3.17 - 3.24 (1H, m), 3.40 - 3.52 (5H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 - 4.24 (1H, m), 4.52 - 4.58 (1H, m), 4.81 - 4.86 (1H, m), 6.57 (1H, s), 6.78 (1H, s), 7.46 - 7.50 (2H, m), 8.17 - 8.21 (2H, m), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.467μM

Example 36w: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.32 (3H, t), 1.53 - 1.56 (2H, m), 1.62 - 1.65 (2H, m), 3.17 - 3.24 (1H, m), 3.40 - 3.52 (3H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.18 - 4.24 (1H, m), 4.32 (2H, d), 4.53 - 4.58 (1H, m), 6.63 (1H, t), 6.78 (1H, s), 6.84 (1H, s), 7.03 (1H, s), 7.50 - 7.54 (2H, m), 8.18 - 8.22 (2H, m), 8.93 (1H, s), 11.84 (1H, s).

mTOR Kinase Assay (Echo): 0.11μM

Example 36x: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63 - 0.66 (2H, m), 1.18 (2H, d), 1.59 - 1.62 (3H, m), 1.88 - 1.90 (2H, m), 2.09 (2H, s), 3.15 (1H, dt), 3.30 (2H, s), 3.44 - 3.49 (1H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.41 (1H, s), 4.83 (1H, s), 6.53 (1H, s), 6.65 (1H, s), 7.36 - 7.44 (4H, m), 7.80 - 7.86 (4H, m), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.182μM

Example 36y: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.91 (2H, m), 2.70 (2H, t), 3.13 - 3.18 (1H, m), 3.33 - 3.39 (2H, m), 3.46 (1H, t), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.14 (1H, d), 4.43 (1H, s), 6.49 (1H, t), 6.65 (1H, s), 7.40 - 7.44 (4H, m), 7.81 - 7.86 (4H, m), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.00131μM

Example 36z: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.62 - 1.64 (2H, m), 1.90 - 1.94 (2H, m), 3.17 - 3.18 (1H, m), 3.42 - 3.51 (1H, m), 3.62 (1H, d), 3.76 (1H, d), 3.94 - 3.98 (1H, m), 4.16 (1H, d), 4.44 (1H, s), 6.69 (1H, s), 7.43 (2H, t), 7.52 (2H, d), 7.83 - 7.87 (2H, m), 7.92 (2H, d), 8.37 (1H, s), 9.39 (1H, s), 11.34 (1H, s).

mTOR Kinase Assay (Echo): 0.00208μM

Example 36aa: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 - 1.62 (2H, m), 1.88 - 1.91 (2H, m), 3.12 - 3.19 (1H, m), 3.43 - 3.49 (1H, m), 3.59 - 3.63 (1H, m), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.32 (2H, d), 4.42 (1H, s), 6.60 (1H, t), 6.65 (1H, s), 6.94 (2H, s), 7.42 (4H, t), 7.81 - 7.86 (4H, m), 8.91 (1H, s), 11.89 (1H, s).

mTOR Kinase Assay (Echo): 0.0749μM

Example 36ab: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.19 (3H, d), 1.51 - 1.60 (2H, m), 1.80 - 1.89 (2H, m), 2.53 - 2.58 (1H, m), 2.70 - 2.80 (4H, m), 3.12 (1H, dt), 3.47 (1H, dt), 3.63 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.10 (1H, d), 4.46 (1H, d), 6.41 (1H, d), 6.59 (1H, s), 7.37 (2H, d), 7.54 - 7.56 (1H, m), 7.57 - 7.59 (1H, m), 7.76 (2H, d), 7.85 (1H, dt), 8.48 (1H, s), 8.73 - 8.75 (1H, m).

mTOR Kinase Assay (Echo): 0.011μM

Example 36ac: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.52 - 1.58 (2H, m), 1.81 - 1.89 (2H, m), 2.68 - 2.80 (4H, m), 3.08 - 3.15 (2H, m), 3.27 (1H, s), 3.44 - 3.50 (3H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.10 (1H, d), 4.47 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.59 (1H, s), 7.36 (2H, d), 7.54 - 7.59 (2H, m), 7.76 (2H, d), 7.85 (1H, dt), 8.73 - 8.75 (2H, m).

mTOR Kinase Assay (Echo): 0.00441μM

Example 36ad: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 8.87 (1H, s), 8.74 (1H, d), 7.85 (1H, td), 7.77 (2H, d), 7.54 - 7.59 (2H, m), 7.38 (2H, d), 6.60 (1H, s), 6.51 (1H, t), 4.48 (1H, s), 4.10 (1H, d), 3.96 (1H, dd), 3.75 (1H, d), 3.63 (1H, dd), 3.47 (1H, td), 3.37 (2H, q), 3.12 (1H, td), 2.72 - 2.81 (4H, m), 2.70 (2H, t), 1.80 - 1.89 (2H, m), 1.55 - 1.58 (2H, m), 1.19 (3H, d).

mTOR Kinase Assay (Echo): 0.0323μM

Example 36ae: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.55 - 1.63 (4H, m), 1.81 - 1.89 (2H, m), 2.68 - 2.80 (4H, m), 3.08 - 3.19 (3H, m), 3.45 - 3.49 (3H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.10 (1H, d), 4.48 (2H, t), 6.18 (1H, t), 6.59 (1H, s), 7.36 (2H, d), 7.53 - 7.59 (2H, m), 7.75 (2H, d), 7.85 (1H, dt), 8.65 (1H, s), 8.74 (1H, d).

mTOR Kinase Assay (Echo): 0.0151μM

Example 36af: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.18 (3H, d), 1.88 - 1.95 (1H, m), 2.11 - 2.17 (1H, m), 2.53 - 2.57 (2H, m), 2.79 - 2.87 (2H, m), 3.12 (1H, dt), 3.23 - 3.28 (3H, m), 3.46 (1H, dt), 3.62 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.09 (1H, d), 4.44 (1H, s), 6.40 (1H, d), 6.48 (1H, s), 7.37 (2H, d), 7.58 - 7.61 (2H, m), 7.87 (1H, ddt), 8.48 (1H, s), 8.74 - 8.75 (1H, m).

mTOR Kinase Assay (Echo): 0.00275μM

Example 36ag: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.86 - 1.97 (1H, m), 2.09 - 2.18 (1H, m), 2.65 (3H, s), 2.79 - 2.87 (2H, m), 3.12 (1H, dt), 3.22 - 3.28 (2H, m), 3.46 (1H, dt), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.08 (1H, d), 4.44 (1H, s), 6.04 - 6.07 (1H, m), 6.48 (1H, s), 7.37 (2H, d), 7.58 - 7.61 (2H, m), 7.74 (2H, d), 7.87 (1H, dt), 8.68 (1H, s), 8.75 (1H, d).

mTOR Kinase Assay (Echo): 0.0013μM

Example 36ah: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.88 - 1.95 (1H, m), 2.10 - 2.17 (1H, m), 2.81 - 2.87 (2H, m), 3.08 - 3.19 (2H, m), 3.22 - 3.27 (3H, m), 3.44 - 3.50 (3H, m), 3.62 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.08 (1H, d), 4.45 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.48 (1H, s), 7.35 (2H, d), 7.60 (2H, t), 7.74 (2H, d), 7.87 (1H, t), 8.75 (2H, s).

mTOR Kinase Assay (Echo): 0.00247μM

Example 36ai: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.88 - 1.95 (1H, m), 2.09 - 2.16 (1H, m), 2.69 (2H, t), 2.78 - 2.87 (2H, m), 3.10 - 3.16 (1H, m), 3.23 - 3.25 (3H, m), 3.35 - 3.39 (2H, m), 3.47 (1H, t), 3.62 (1H, dd), 3.74 (1H, d), 3.95 (1H, d), 4.09 (1H, d), 4.45 (1H, s), 6.49 (1H, s), 7.38 (2H, d), 7.58 - 7.61 (2H, m), 7.76 (2H, d), 7.87 (1H, dt), 8.74 - 8.75 (1H, m), 8.86 (1H, s).

mTOR Kinase Assay (Echo): 0.00561μM

Example 36aj: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.89 - 1.97 (1H, m), 2.11 - 2.18 (1H, m), 2.79 - 2.87 (2H, m), 3.13 (1H, dt), 3.23 - 3.29 (2H, m), 3.47 (1H, dt), 3.62 (1H, dd), 3.75 (1H, d), 3.79 (3H, s), 3.96 (1H, dd), 4.10 (1H, d), 4.45 (1H, s), 6.50 (1H, s), 7.38 (1H, s), 7.41 (2H, d), 7.59 - 7.62 (1H, m), 7.76 (1H, s), 7.77 (2H, d), 7.86 - 7.90 (1H, m), 7.88 (1H, dt), 8.38 (1H, s), 8.75 - 8.76 (1H, m), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00258μM

Example 36ak: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.89 - 1.98 (1H, m), 2.10 - 2.19 (1H, m), 2.79 - 2.87 (2H, m), 3.13 (1H, dt), 3.23 - 3.28 (2H, m), 3.47 (1H, dt), 3.62 (1H, dd), 3.74 (2H, s), 3.75 (1H, d), 3.96 (1H, dd), 4.10 (1H, d), 4.45 (1H, s), 6.25 (1H, d), 6.51 (1H, s), 7.43 (2H, d), 7.54 (1H, d), 7.59 - 7.63 (1H, m), 7.60 (1H, d), 7.79 (2H, d), 7.88 (1H, dt), 8.75 - 8.76 (1H, m), 8.91 (1H, s), 9.11 (1H, s).

mTOR Kinase Assay (Echo): 0.00245μM

Example 36al: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.41 (2H, m), 0.63 - 0.66 (2H, m), 1.59 (2H, m), 1.88 (2H, m), 2.57 - 2.61 (1H, m), 3.66 (4H, s), 3.68 (4H, s), 6.39 (1H, s), 6.71 (1H, s), 7.38 - 7.43 (4H, m), 7.78 (2H, d), 7.85 (2H, t), 8.52 (1H, s).

mTOR Kinase Assay (Echo): 0.0187μM

Example 36am: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58 - 1.61 (2H, m), 1.87 - 1.90 (2H, m), 2.70 (2H, t), 3.37 (2H, q), 3.67 (4H, s), 3.69 (4H, s), 6.49 (1H, t), 6.72 (1H, s), 7.39 - 7.44 (4H, m), 7.79 - 7.86 (4H, m), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.0277μM

Example 36an: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.59 - 1.62 (2H, m), 1.89 - 1.92 (2H, m), 3.68 (4H, s), 3.70 (4H, s), 6.76 (1H, s), 7.43 (2H, t), 7.51 (2H, d), 7.83 - 7.96 (4H, m), 8.37 (1H, s), 9.39 (1H, s), 11.33 (1H, s).

mTOR Kinase Assay (Echo): 0.0104μM

Example 36ao: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.57 - 1.61 (2H, m), 1.87 - 1.90 (2H, m), 3.09 - 3.16 (2H, m), 3.65 - 3.66 (4H, m), 3.69 - 3.70 (4H, m), 6.12 (1H, t), 6.71 (1H, s), 7.37 - 7.44 (4H, m), 7.78 (2H, d), 7.82 - 7.86 (2H, m), 8.64 (1H, s)

Example 36ap: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.57 - 1.61 (2H, m), 1.87 - 1.90 (2H, m), 2.66 (3H, d), 3.66 (4H, s), 3.69 - 3.70 (4H, m), 6.01 - 6.05 (1H, m), 6.71 (1H, s), 7.38 - 7.43 (4H, m), 7.78 (2H, d), 7.82 - 7.86 (2H, m), 8.72 (1H, s)

Example 36aq: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58 - 1.61 (2H, m), 1.88 - 1.91 (2H, m), 3.63 - 3.67 (4H, m), 3.69 - 3.73 (4H, m), 3.79 (3H, s), 6.73 (1H, s), 7.38 - 7.45 (5H, m), 7.77 - 7.86 (5H, m), 8.34 (1H, s), 8.82 (1H, s)

Example 36ar: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.66 - 1.69 (2H, m), 1.95 - 1.98 (2H, m), 3.15 - 3.19 (2H, m), 3.44 - 3.48 (2H, m), 3.69 (8H, s), 4.72 (1H, t), 6.22 (1H, t), 6.73 (1H, s), 7.34 (2H, d), 7.63 (2H, d), 7.77 (2H, d), 8.77 (1H, s), 8.86 (2H, d)

Example 36as: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.66 - 1.70 (2H, m), 1.96 - 1.99 (2H, m), 3.69 (8H, s), 3.79 (3H, s), 6.74 (1H, s), 7.40 (3H, d), 7.66 (2H, d), 7.77 - 7.78 (3H, m), 8.35 (1H, s), 8.80 (1H, s), 8.87 (2H, d).

mTOR Kinase Assay (Echo): 0.00911μM

Example 36at: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.66 - 1.69 (2H, m), 1.95 - 1.99 (2H, m), 2.66 (3H, d), 3.69 (8H, s), 6.02 - 6.04 (1H, m), 6.73 (1H, s), 7.35 (2H, d), 7.63 (2H, d), 7.77 (2H, d), 8.71 (1H, s), 8.86 (2H, d)

Example 36au: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.66 - 1.69 (2H, m), 1.95 - 1.98 (2H, m), 3.09 - 3.16 (2H, m), 3.69 (8H, s), 6.13 (1H, t), 6.73 (1H, s), 7.35 (2H, d), 7.63 (2H, d), 7.77 (2H, d), 8.63 (1H, s), 8.86 (2H, d)

Example 36av: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.66 - 1.69 (2H, m), 1.95 - 1.98 (2H, m), 2.53 - 2.57 (1H, m), 3.69 (8H, s), 6.40 (1H, d), 6.73 (1H, s), 7.36 (2H, d), 7.64 (2H, d), 7.77 (2H, d), 8.50 (1H, s), 8.86 (2H, d).

mTOR Kinase Assay (Echo): 0.00995μM

Example 36aw: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.66 - 1.69 (2H, m), 1.95 - 1.98 (2H, m), 2.70 (2H, t), 3.36 (2H, q), 3.69 (8H, s), 6.49 (1H, t), 6.73 (1H, s), 7.37 (2H, d), 7.64 (2H, d), 7.77 (2H, d), 8.86 (2H, d), 8.89 (1H, s)

Example 36ax: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.56 - 1.63 (2H, m), 1.66 - 1.69 (3H, m), 1.95 - 1.98 (2H, m), 3.16 (2H, q), 3.47 (2H, q), 3.69 (8H, s), 4.47 (1H, t), 6.17 (1H, t), 6.73 (1H, s), 7.34 (2H, d), 7.63 (2H, d), 7.77 (2H, d), 8.86 (2H, d)

Example 36ay: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.19-3.26 (1H, td), 3.30 (3H, s), 3.46-3.53 (1H, td), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H, dd), 4.22-4.25 (1H, bd), 4.58 (1H, bs), 6.81 (1H, s), 7.14 (1H, s), 7.39-7.40 (1H, d), 7.59-7.62 (2H, d), 8.28-8.30 (2H, d), 9.21 (1H, s), 10.50 (1H, s).

mTOR Kinase Assay (Echo): 0.00117μM

Example 36az: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 2.44 (3H, s), 3.19-3.26 (1H, td), 3.31 (3H, s), 3.46-3.52 (1H, td), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.98-4.00 (1H, dd), 4.22-4.25 (1H, bd), 4.59 (1H, bs), 6.81 (1H, s), 7.61-7.63 (2H, d), 8.21-8.22 (1H, d), 8.28-8.30 (2H, d), 8.99-9.00 (1H, d), 9.41 (1H, s), 9.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00149μM

Example 36ba: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.19-3.25 (1H, td), 3.30 (3H, s), 3.47-3.52 (1H, td), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H, dd), 4.22-4.25 (1H, d), 4.59 (1H, bs), 6.81 (1H, s), 7.16 (1H, s), 7.63-7.66 (2H, d), 7.84 (1H, bs), 8.28-8.30 (2H, d), 10.45 (1H, bs), 10.88 (1H, bs).

mTOR Kinase Assay (Echo): 0.00312μM

Example 36bb: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.24 (3H, d), 1.54-1.58 (2H, q), 1.59-1.63 (2H, m), 1.66-1.69 (2H, q), 3.15-3.25 (3H, m), 3.30 (3H, s), 3.45-3.52 (3H, m), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.20-4.23 (1H, d), 4.46-4.49 (1H,

t), 4.58 (1H, bs), 6.19-6.22 (1H, t), 6.77 (1H, s), 7.49-7.51 (2H, d), 8.19-8.21 (2H, d), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.0205μM

Example 36bc: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.16-1.18 (3H, d), 1.60-1.68 (2H, m), 1.89-1.92 (2H, m), 3.10-3.18 (1H, td), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.08-4.12 (1H, d), 4.38 (1H, bs), 5.76 (1H, s), 6.40-6.41 (1H, d), 6.63 (1H, s), 7.38-7.40 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, t), 7.78-7.85 (4H, m), 8.49 (1H, s).

mTOR Kinase Assay (Echo): 0.00205μM

Example 36bd: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.57-1.67 (4H, m), 1.81-1.92 (4H, m), 2.18-2.25 (2H, m), 3.10-3.18 (1H, td), 3.42-3.49 (1H, td), 3.59-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.19 (2H, m), 4.38 (1H, bs), 6.42-6.44 (1H, d), 6.62 (1H, s), 7.35-7.37 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.52 (1H, s).

mTOR Kinase Assay (Echo): 0.00258μM

Example 36be: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.89-1.92 (2H, m), 3.10-3.20 (1H, td), 3.30 (2H, m (under water peak)) 3.42-3.55 (2H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.07-4.11 (1H, d), 4.38 (1H, bs), 6.35-6.38 (1H, t), 6.47-6.49 (1H, d), 6.63 (1H, s), 7.38-7.40 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.81 (2H, d), 7.84-7.86 (2H, d), 8.89 (1H, s).

mTOR Kinase Assay (Echo): 0.00376μM

Example 36bf: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10-1.12 (6H, d), 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.59-1.92 (2H, m), 3.10-3.19 (1H, td), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.81 (2H, m), 3.94-3.97 (1H, dd), 4.09-4.12 (1H, d), 4.38 (1H, bs), 6.02-6.04 (1H, d), 6.62 (1H, s), 7.35-7.38 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.49 (1H, s).

mTOR Kinase Assay (Echo): 0.00457μM

Example 36bg: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.89-1.90 (2H, m), 3.09-3.16 (3H, m), 3.42-3.49 (1H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.95-3.97 (1H, dd), 4.09-4.12 (1H, d), 4.38 (1H, bs), 6.12-6.15 (1H, t), 6.62 (1H, s), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, t), 7.78-7.85 (4H, m), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.000922μM

Example 36bh: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.89-1.92 (2H, m), 3.10-3.15 (1H, td), 3.17-3.19 (2H, m), 3.42-3.49 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.08-4.11 (1H, d), 4.38 (1H, bs), 4.71-4.74 (1H, t), 6.22-6.24 (1H, t), 6.62 (1H, s), 7.36-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.00121μM

Example 36bi: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87-0.91 (3H, t), 1.16-1.18 (3H, d), 1.41-1.50 (2H, m), 1.60-1.67 (2H, m), 1.89-1.92 (2H, m), 3.04-3.09 (2H, q), 3.10-3.17 (1H, td), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.12 (1H, d), 4.39 (1H, bs), 6.16-6.19 (1H, t), 6.62 (1H, s), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.61 (1H, s).

mTOR Kinase Assay (Echo): 0.00231μM

Example 36bj: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.60-1.68 (2H, m), 1.89-1.92 (2H, m), 2.65-2.66 (3H, d), 3.10-3.17 (1H, td), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.09-4.12 (1H, d), 4.38 (1H, bs), 6.03-6.06 (1H, q), 6.62 (1H, s), 7.38-7.40 (2H, d), 7.57-7.61 (2H, t), 7.70-7.73 (1H, tt), 7.74-7.85 (4H, m), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.000621μM

Example 36bk: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.24 (6H, s), 1.60-1.67 (2H, m), 1.88-1.91 (2H, m), 3.10-3.17 (1H, td), 3.38-3.40 (2H, d), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.08-4.12 (1H, d), 4.38 (1H, bs), 4.93-4.96 (1H, t), 5.98 (1H, s), 6.62 (1H, s), 7.33-7.35 (2H, d), 7.58-7.61 (2H, t), 7.70-7.74 (1H, m), 7.78-7.84 (4H, m), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00433μM

Example 36bl: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.56-1.67 (4H, m), 1.89-1.92 (2H, m), 3.10-3.17 (3H, m), 3.42-3.49 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.12 (1H, d), 4.38 (1H, bs), 4.46-4.49 (1H, t), 6.16-6.19 (1H, t), 6.62 (1H, s), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.00208μM

Example 36bm: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.18 (3H, d), 1.60-1.68 (2H, m), 1.89-1.92 (2H, m), 2.68-2.72 (2H, t), 3.11-3.18 (1H, td), 3.34-3.39 (2H, q), 3.43-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.09-4.12 (1H, d), 4.38 (1H, bs), 6.49-6.52 (1H, t), 6.63 (1H, s), 7.39-7.41 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.86 (4H, m), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.00193μM

Example 36bn: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.60-1.68 (2H, m), 1.88-1.93 (2H, m), 3.10-3.17 (1H, td), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.12 (1H, d), 4.31-4.33 (2H, d), 4.38 (1H, bs), 6.59-6.63 (2H, m), 6.94 (2H, bs), 7.39-7.41 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, t), 7.78-7.81 (2H, d), 7.84-7.87 (2H, d), 8.88 (1H, s), 11.84 (1H, bs).

mTOR Kinase Assay (Echo): 0.00637μM

Example 36bo: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.63-0.66 (2H, q), 0.69-0.73 (2H, q), 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.89-1.92 (2H, m), 3.10-3.17 (1H, td), 3.42-3.49 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.09-4.12 (1H, d), 4.38 (1H, bs), 4.83 (1H, bs), 6.54 (1H, s), 6.63 (1H, s), 7.35-7.37 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.74-7.85 (4H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.0176μM

Example 36bp: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.89-1.90 (2H, m), 3.10-3.17 (1H, td), 3.42-3.49 (1H, td), 3.59-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.12 (1H, d), 4.38 (1H, bs), 4.43-4.46 (2H, t), 4.72-4.81 (3H, m), 6.63 (1H, s), 6.91-6.93 (1H, d), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.86 (4H, m), 8.73 (1H, s).

mTOR Kinase Assay (Echo): 0.00198μM

Example 36bq: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18-1.19 (3H, d), 1.61-1.66 (2H, m), 1.91-1.92 (2H, m), 3.12-3.18 (1H, td), 3.44-3.50 (1H, td), 3.61-3.64 (1H, dd), 3.74-3.77 (1H, d), 3.95-3.99 (1H, dd), 4.10-4.14 (1H, d), 4.40 (1H, bs), 6.66 (1H, s), 7.52-7.54 (2H, d), 7.59-7.62 (2H, t), 7.72-7.76 (1H, t), 7.79-7.81 (3H, d), 7.90-7.92 (2H, d), 8.28 (1H, s), 9.39 (1H, s).

mTOR Kinase Assay (Echo): 0.00131μM

Example 36br: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.18 (3H, d), 1.61-1.68 (2H, m), 1.90-1.91 (2H, m), 3.11-3.17 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.74-3.76 (1H, d), 3.79 (3H, s), 3.94-3.98 (1H, dd), 4.09-4.13 (1H, d), 4.39 (1H, bs), 6.64 (1H, s), 7.38 (1H,

s), 7.42-7.44 (2H, d), 7.58-7.62 (2H, t), 7.71-7.73 (1H, t), 7.77-7.81 (3H, m), 7.86-7.88 (2H, d), 8.36 (1H, s), 8.80 (1H, s).

mTOR Kinase Assay (Echo): 0.00188μM

Example 36bs: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39-0.43 (2H, m), 0.62-0.67 (2H, m), 1.19-1.20 (3H, d), 1.82-1.93 (1H, m), 2.03-2.14 (1H, m), 2.54 (1H, m), 2.75-2.82 (2H, m), 3.01-3.09 (2H, m), 3.10-3.17 (1H, td), 3.44-3.51 (1H, td), 3.61-3.65 (1H, dd), 3.74-3.77 (1H, d), 3.94-3.98 (1H, dd), 4.06-4.09 (1H, d), 4.44 (1H, bs), 6.40-6.41 (1H, d), 6.46 (1H, s), 7.36-7.39 (2H, d), 7.43-7.51 (4H, m), 7.58-7.62 (1H, m), 7.78-7.80 (2H, d), 8.48 (1H, s).

mTOR Kinase Assay (Echo): 0.00161μM

Example 36bt: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21 (3H, d), 1.82-1.93 (1H, m), 2.03-2.14 (1H, m), 2.74-2.82 (2H, m), 3.02-3.10 (2H, m), 3.13-3.19 (3H, m), 3.44-3.51 (3H, m), 3.62-3.65 (1H, dd), 3.74-3.77 (1H, d), 3.94-3.98 (1H, dd), 4.07-4.10 (1H, d), 4.45 (1H, bs), 4.71-4.74 (1H, t), 6.22-6.25 (1H, t), 6.47 (1H, s), 7.35-7.37 (2H, d), 7.44-7.51 (4H, m), 7.58-7.62 (1H, m), 7.78-7.81 (2H, d), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.00105μM

Example 36bu: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21 (3H, d), 1.82-1.93 (1H, m), 2.04-2.14 (1H, m), 2.65-2.66 (3H, d), 2.75-2.82 (2H, m), 3.02-3.11 (2H, m), 3.13-3.19 (1H, td), 3.45-3.51 (1H, td), 3.62-3.65 (1H, dd), 3.74-3.77 (1H, d), 3.94-3.98 (1H, dd), 4.06-4.10 (1H, d), 4.45 (1H, bs), 6.03-6.06 (1H, q), 6.46 (1H, s), 7.36-7.38 (2H, d), 7.44-7.51 (4H, m), 7.58-7.62 (1H, m), 7.78-7.80 (2H, d), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.00118μM

Example 36bv: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20-1.21 (3H, d), 1.83-1.94 (1H, m), 2.04-2.15 (1H, m), 2.76-2.83 (2H, m), 3.02-3.10 (2H, m), 3.11-3.18 (1H, td), 3.45-3.52 (1H, td), 3.62-3.66 (1H, dd), 3.75-3.77 (1H, d), 3.79 (3H, s), 3.95-3.98 (1H, dd), 4.07-4.10 (1H, d), 4.46 (1H, bs), 6.48 (1H, s), 7.38-7.51 (7H, m), 7.59-7.76 (1H, m), 7.76 (1H, s), 7.82-7.84 (2H, d), 8.36 (1H, s), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00264μM

Example 36bw: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.20-1.22 (3H, d), 1.49-1.58 (2H, m), 1.80-1.87 (2H, m), 2.53 (2H, m), 2.67-2.73 (2H, m), 3.12-3.18 (1H, td), 3.46-3.53 (1H, td), 3.63-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.95-3.99 (1H, dd), 4.09-4.12 (1H, d), 4.48-4.49 (1H, bs), 6.40-6.41 (1H, d), 6.62 (1H, s), 7.37-7.39 (2H, d), 7.42-7.48 (4H, m), 7.57-7.61 (1H, m), 7.80-7.82 (2H, d), 8.48 (1H, s).

mTOR Kinase Assay (Echo): 0.00909μM

Example 36bx: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20-1.22 (3H, d), 1.50-1.59 (2H, m), 1.80-1.89 (2H, m), 2.52-2.61 (2H, m), 2.66-2.74 (2H, m), 3.11-3.19 (3H, m), 3.44-3.52 (3H, m), 3.63-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.95-3.99 (1H, dd), 4.08-4.12 (1H, d), 4.48 (1H, bs), 4.71-4.74 (1H, t), 6.22-6.25 (1H, t), 6.62 (1H, s), 7.35-7.38 (2H, d), 7.42-7.48 (4H, m), 7.57-7.61 (1H, m), 7.80-7.82 (2H, d), 8.74 (1H, s).

mTOR Kinase Assay (Echo): 0.00269μM

Example 36by: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20-1.22 (3H, d), 1.52-1.56 (2H, m), 1.57-1.63 (2H, m), 1.79-1.88 (2H, m), 2.54-2.61 (2H, m), 2.67-2.72 (2H, m), 3.11-3.17 (3H, m), 3.45-3.52 (3H, m), 3.63-3.66 (1H, dd), 3.75-3.78 (1H, d), 3.95-3.99 (1H, dd), 4.09-4.12 (1H, d), 4.46-4.49 (2H, m), 6.17-6.19 (1H, t), 6.62 (1H, s), 7.35-7.38 (2H, d), 7.42-7.48 (4H, m), 7.57-7.61 (1H, m), 7.79-7.82 (2H, d), 8.65 (1H, s).

mTOR Kinase Assay (Echo): 0.012μM

Example 36bz: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21-1.22 (3H, d), 1.50-1.59 (2H, m), 1.81-1.88 (2H, m), 2.53-2.59 (2H, m), 2.67-2.72 (4H, m), 3.11-3.19 (1H, td), 3.34-3.39 (2H, m), 3.46-3.52 (1H, td), 3.63-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.95-3.99 (1H, dd), 4.09-4.13 (1H, d), 4.49 (1H, bs), 6.49-6.52 (1H, t), 6.63 (1H, s), 7.38-7.40 (2H, d), 7.42-7.48 (4H, m), 7.57-7.61 (1H, m), 7.81-7.83 (2H, d), 8.86 (1H, s).

mTOR Kinase Assay (Echo): 0.0143μM

Example 36ca: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.68-1.74 (2H, m), 2.20-2.27 (2H, td), 2.67-2.68 (3H, d), 2.82-2.87 (2H, t), 3.05-3.09 (2H, m), 3.18-3.22 (1H, m), 3.22-3.25 (2H, t), 3.37-3.40 (2H, t), 3.50-3.58 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96 (2H, m), 3.98-4.01 (1H, dd), 4.39-4.32 (1H, d), 4.57 (1H, s), 6.10-6.13 (1H, q), 6.86 (1H, s), 7.50-7.53 (2H, d), 8.21-8.23 (2H, d), 8.79 (1H, s)

Example 36cb: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.68-1.75 (2H, m), 2.20-2.27 (2H, td), 2.54 (3H, d), 2.82-2.87 (2H, t), 3.06-3.11 (2H, m), 3.12-3.16 (1H, m), 3.18-3.24 (2H, m), 3.37-3.40 (2H, t), 3.50-3.57 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.91-3.95 (2H, m), 4.00-4.02 (1H, dd), 4.29-4.32 (1H, d), 4.58 (1H, s), 6.27-6.29 (1H, t), 6.86 (1H, s), 7.50-7.52v(2H, d), 8.21-8.23 (2H, d), 8.78 (1H, s)

Example 36cc: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (2H, d), 1.68-1.75 (2H, m), 2.20-2.27 (2H, td), 2.538-2.543 (3H, d), 2.82-2.87 (2H, t), 3.06-3.09 (2H, m), 3.16-3.21 (1H, m), 3.22-3.25 (2H, m), 3.37-3.40 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96

(2H, m), 4.00-4.02 (1H, dd), 4.29-4.33 (1H, d), 4.58 (1H, s), 6.49-6.50 (1H, d), 6.86 (1H, s), 7.51-7.53 (2H, d), 8.22-8.24 (2H, d), 8.61 (1H, s)

Example 36cd: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.65 (2H, m), 1.67-1.74 (2H, m), 2.19-2.26 (4H, m), 2.537-2.541 (3H, d), 2.81-2.86 (2H, t), 3.05-3.09 (2H, m), 3.16-3.22 (2H, m), 3.24-3.26 (1H, m), 3.37-3.40 (2H, t), 3.49-3.56 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.79 (1H, d), 3.90-3.96 (2H, m), 3.98-4.01 (1H, dd), 4.11-4.21 (1H, sex), 4.29-4.32 (1H, d), 4.57 (1H, s), 6.52-6.54 (1H, d), 6.86 (1H, s), 7.48-7.50 (2H, d), 7.54-7.67(1H, m), 8.21-8.23 (2H, d), 8.63 (1H, s)

Example 36ce: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.35 (3H, d), 1.67-1.74 (2H, m), 2.20-2.27 (2H, td), 2.538-2.541 (3H, d), 2.70-3.73 (2H, t), 2.82-2.87 (2H, t), 3.05-3.09 (2H, m), 3.18-3.23 (2H, m), 3.25-3.26 (1H, m), 3.18-3.23 (2H, m), 2.25-2.26 (1H, m), 3.36-3.40 (4H, m), 3.50-3.56 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96 (2H, qu), 3.98-4.02 (1H, dd), 4.30-4.33 (1H, d), 4.56-4.58 (1H, m), 6.54-6.57 (1H, t), 6.86 (1H, s), 7.52-7.54 (2H, d), 8.23-8.25 (2H, d), 8.95 (1H, s)

Example 36cf: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.68-1.75 (2H, m), 2.20-2.27 (2H, td), 2.82-2.87 (2H, t), 3.16-3.22 (2H, m), 3.25 (1H, m), 3.37-3.40 (2H, t), 3.50-3.56 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96 (2H, m), 4.00-4.02 (1H, dd), 4.29-4.33 (1H, d), 4.58 (1H, s), 6.23-6.25 (1H, t), 6.86 (1H, t), 7.49-7.52 (2H, d), 8.21-8.23 (2H, d), 8.69 (1H, s)

Example 36cg: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.68-1.75 (2H, m), 2.20-2.27 (2H, td), 2.82-2.87 (2H, t), 3.06-3.09 (2H, m), 3.17-3.23 (4H, m), 3.25-3.26 (1H, m), 3.37-3.40(2H, t), 3.46-3.48 (2H, t), 3.50-3.56 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96 (2H, qu), 3.98-4.02 (1H, dd) 4.29-4.33 (1H, d), 4.57 (1H, s), 6.30-6.33 (1H, t), 6.86 (1H, s), 7.49-7.51 (2H, d), 8.22-8.24 (2H, d), 8.87 (1H, s)

Example 36ch: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.68-1.75 (2H, m), 2.20-2.28 (2H, td), 2.82-2.87 (2H, t), 3.06-3.10 (2H, m), 3.18-3.22 (2H, m), 3.23-3.25 (1H, m), 3.38-3.41 (2H, t), 3.50-3.57 (1H, td), 3.67-3.70 (1H, dd), 3.77 (1H, s), 3.80 (3H, s), 3.91-3.96 (2H, qu), 3.98-4.02 (1H, dd), 4.30-4.33 (1H, d), 4.58 (1H, exchange), 6.87 (1H, s), 7.390-7.392 (1H, d), 7.55-7.57 (2H, d), 7.77 (1H, s), 8.25-8.27 (2H, d), 8.49 (1H, exchange), 8.93 (1H, exchange)

Example 36ci: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.68-1.75 (2H, m), 2.20-2.28 (2H, td), 2.82-2.86 (2H, t), 3.07-3.11 (2H, m), 3.16-3.20 (1H, m), 3.22-3.23 (1H, d),

3.38-3.41 (2H, t), 3.51-3.57 (2H, td), 3.68-3.69 (1H, dd), 3.77-3.80 (1H, d), 3.90-3.96 (2H, t), 3.99-4.01 (1H, d), 4.29-4.33 (1H, d), 4.57-4.58 (1H, exchange), 6.84 (1H, s), 7.23 (1H, s), 7.57-7.59 (1H, m), 7.65-7.67 (2H, d), 8.20-8.22 (2H, d)

Example 36cj: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.63-1.66 (2H, m), 1.93-2.00 (2H, m), 3.15-3.20 (2H, m), 3.217-3.226 (1H, d), 3.47-3.51 (1H, dd), 3.53-3.57 (4H, m), 3.63-3.67 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.01 (1H, dd), 4.22-4.25 (1H, d), 4.57 (1H, exchange), 4.73 (1H, exchange), 6.77 (1H, s), 6.84-6.85 (1H, d), 7.33-7.34 (1H, d), 7.66-7.68 (2H, d), 8.23-8.25 (2H, d)

Example 36ck: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70-0.74 (2H, m), 0.91-0.93 (2H, dd), 1.24-1.26 (3H, d), 1.56-1.58 (2H, m), 1.64-1.66 (2H, m), 1.92-1.99 (2H, m), 2.72-2.77 (1H, sep), 2.89 (2H, s), 3.16-3.20 (2H, t), 3.22-3.23 (1H, d), 3.4703.50 (1H, dd), 3.51-3.56 (4H, m), 3.63-3.67 (1H, dd), 3.77-3.80 (1H, d), 3.97-4.01 (1H, dd), 4.22-4.25 (1H, d), 4.57 (1H, exchange), 6.79 (1H, s), 7.64-7.67 (2H, dd), 8.22-8.24 (2H, s), 8.41 (1H, exchange)

Example 36cl: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.56-0.59 (2H, t), 0.66-0.68 (2H, t), 1.24-1.26 (3H, d), 1.31-1.36 (3H, m), 1.56-1.60 (2H, m), 1.62-1.66 (2H, m), 1.92-2.00 (2H, m), 3.16-3.21 (2H, t), 3.47-3.50 (1H, dd), 2.52-3.55 (4H, m), 3.63-3.67 (1H, dd), 3.52-3.55 (4H, m), 3.63-3.67 (1H, dd), 3.77-3.79 (1H, d), 4.00-4.01 (1H, dd), 4.21-4.24 (1H, d), 4.56 (1H, exchange), 6.78 (1H, s), 7.49-7.51 (2H, d), 8.21-8.23 (2H, d)

Example 36cm: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.58 (2H, m), 1.64-1.67 (2H, m), 1.92-1.99 (2H, m), 3.19-3.26 (1H, dd), 3.51-3.55 (6H, m), 3.63-3.67 (1H, dd), 3.77-3.79 (1H, d), 3.97-4.01 (1H, dd), 4.21-4.24 (1H, d), 4.57 (1H, s), 4.71 (1H, s), 5.94-6.24 (1H, tt), 6.55-6.58 (1H, t), 6.80 (1H, s), 7.51-7.54 (2H, d), 8.23-8.26 (2H, d), 8.96 (1H, s)

Example 36cn: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.32 (9H, s), 1.54-1.60 (2H, m), 1.61-1.67 (2H, m), 1.92-1.99 (2H, m), 3.18-3.26 (1H, m), 3.47-3.50 (1H, dd), 3.52-3.56 (4H, m), 3.63-3.67 (1H, dd), 3.77-3.80 (1H, d), 3.97-4.01 (1H, dd), 4.21-4.24 (1H, d), 4.57 (1H, s), 4.72 (1H, exchange), 6.09 (1H, s), 6.78 (1H, s), 7.45-7.48 (2H, d), 8.20-8.23 (2H, d), 8.52 (1H, s)

Example 36co: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.59 (2H, m), 1.60-1.64 (2H, m), 1.91-1.98 (2H, m), 3.46-3.50 (1H, dd), 3.50-3.54 (4H, m), 3.62-3.66 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.08 (1H, s), 4.19-4.22 (1H, d), 4.55 (exchange), 4.70 (exchange), 6.73 (1H, s), 7.59-7.61 (2H, d), 8.10-8.12 (2H, d), 8.38 (1H, exchange)

Example 36cp: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.55-1.59 (2H, m), 1.62-1.66 (2H, m), 1.77-1.84 (2H, m), 1.91-1.99 (2H, m), 3.16-3.20 (2H, m), 3.21-3.25 (1H, dd), 3.46-3.47 (1H, d), 3.49-3.55 (6H, m), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.21-4.25 (1H, d), 4.31-4.32 (1H, m), 4.56 (exchange), 6.78 (1H, s), 7.64-7.66 (2H, d), 8.20-8.22 (2H, d), 8.34 (exchange)

Example 36cq: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.59 (2H, m), 1.62-1.65 (2H, m), 1.91-1.98 (2H, m), 3.05 (3H, s), 3.16-3.25 (2H, m), 3.33-3.34 (2H, d), 3.46-3.50 (1H, dd), 3.50-3.58 (6H, m), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.20-4.23 (1H, d), 4.56 (exchange), 4.70 (exchange), 6.45-6.48 (1H, t), 6.78 (1H, s), 7.51-7.53 (2H, d), 8.21-8.24 (2H, d), 9.05 (exchange)

Example 36cr: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.56-1.60 (2H, m), 1.62-1.66 (2H, m), 1.92-1.99 (2H, m), 3.00-3.05 (1H, dd), 3.16-3.22 (6H, m), 3.42-3.47 (2H, dd), 3.51-3.55 (4H, m), 3.63-3.67 (1H, dd), 3.76-3.79 (1H, d), 3.97-4.00 (1H, dd), 4.21-4.24 (1H, d), 4.45-4.48 (exchange, t), 4.56 (exchange), 6.79 (1H, s), 7.11 (exchange), 7.52-7.54 (2H, d), 8.22-8.24 (2H, d), 9.21 (exchange)

Example 36cs: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.58 (2H, m), 1.62-1.66 (2H, m), 1.91-1.98 (2H, m), 2.89 (3H, s), 2.98 (3H, s), 3.16-3.22 (2H, m), 3.46-3.50 (1H, dd), 3.50-2.54 (4H, m), 3.63-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-3.97 (1H, d), 3.99-4.00 (2H, d), 4.20-4.24 (1H, d), 4.57 (1H, exchange), 6.43-6.45 (t, exchange), 6.79 (1H, s), 7.50-7.52 (2H, d), 8.22-8.24 (2H, d), 9.19 (exchange)

Example 36ct: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15-1.20 (3H, d), 1.70-1.79 (2H, q), 1.95-2.05 (2H, q), 3.10-3.20 (1H, td), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.10-4.20 (1H, d), 4.45 (1H, bs), 6.70 (1H, s), 7.45-7.52 (2H, d), 7.75-7.80 (1H, dd), 7.80-7.82 (2H, d), 8.00-8.05 (1H, d), 8.10-8.15 (1H, td), 8.40 (1H, s), 8.85 (1H, d), 9.40 (1H, s), 11.40 (1H, br s).

mTOR Kinase Assay (Echo): 0.00157μM

Example 36cu: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10-1.15 (3H, d), 1.70-1.79 (2H, q), 1.95-2.00 (2H, q), 3.10-3.20 (1H, td), 3.45-3.50 (1H, td), 3.60-3.62 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.10-4.20 (1H, d), 4.30 (2H, d), 4.45 (1H, bs), 6.60 (1H, t), 6.70 (1H, s), 6.90-7.00 (2H, br d), 7.40 (2H, d), 7.75-7.80 (3H, m), 8.00-8.05 (1H, d), 8.10-8.15 (1H, td), 8.80 (1H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.0686μM

Example 36cv: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.55-0.65 (2H, q), 0.65-0.75 (2H, q), 1.10-1.15 (3H, d), 1.70-1.79 (2H, q), 1.95-2.00 (2H, q), 3.10-3.20 (1H, td), 3.40-3.50 (2H, m), 3.60-3.62 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.10-4.20 (1H, d), 4.45 (1H, bs), 4.80 (1H, bs), 6.55 (1H, t), 6.65 (1H, s), 7.30 (2H, d), 7.70-7.80 (3H, m), 7.95-8.00 (1H, d), 8.05-8.10 (1H, td), 8.60 (1H, s), 8.80 (1H, d).

mTOR Kinase Assay (Echo): 0.259μM

Example 36cw: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15-1.20 (3H, d), 1.65-1.70 (2H, q), 1.95-2.00 (2H, q), 3.10-3.20 (1H, td), 3.40-3.50 (1H, td), 3.60-3.64 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.10-4.20 (1H, d), 4.35 (2H, d), 4.45 (1H, bs), 6.60 (1H, t), 6.70 (1H, s), 6.80-7.10 (2H, m), 7.40 (2H, d), 7.70 (2H, d), 7.80 (2H, dd), 8.85 (2H, dd), 8.90 (1H, s), 11.85 (1H, s).

Example 36cx: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.55-0.65 (2H, q), 0.65-0.75 (2H, q), 1.15-1.20 (3H, d), 1.70-1.75 (2H, q), 1.95-2.00 (2H, q), 3.10-3.20 (1H, td), 3.45 (2H, d), 3.50 (1H, td), 3.60-3.63 (1H, dd), 3.74-3.78 (1H, d), 3.94-3.99 (1H, dd), 4.10-4.20 (1H, d), 4.45 (1H, bs), 4.80-4.90 (1H, t), 6.55 (1H, s), 6.65 (1H, s), 7.30 (2H, d), 7.65 (2H, d), 7.80 (2H, dd), 8.70 (1H, s), 8.85 (2H, dd)

Example 36cy: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, m), 2.22-2.30 (2H, td), 2.65 (3H, d), 2.75 (2H, t), 3.13 (3H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.75 (1H, d), 3.90-3.95 (2H, d), 3.98 (1H, dd), 4.15 (1H, d), 4.50 (1H, br s), 6.05 (1H, q), 6.68 (1H, s), 7.37 (2H, d), 7.44 (2H, d), 7.46 (2H, d), 7.61 (1H, tt), 7.76 (2H, d), 8.68 (1H, s)

Example 36cz: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.21 (3H, d), 2.26-2.31 (2H, td), 2.74 (2H, t), 3.12 (5H, dt), 3.50 (1H, td), 3.65 (1H, dd), 3.76 (1H, d), 3.90 (2H, d), 3.97 (1H, dd), 4.14 (1H, d), 4.52 (1H, m), 6.14 (1H, t), 6.68 (1H, s), 7.36 (2H, d), 7.44 (4H, q), 7.60 (1H, m), 7.76 (2H, d), 8.60 (1H, s)

Example 36da: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.41 (2H, q), 0.65 (2H, q), 1.21 (3H, d), 2.23-2.32 (2H, td), 2.55 (1H, dd), 2.75 (2H, m), 3.15 (3H, m), 3.50 (1H, td), 3.66 (1H, dd), 3.76 (1H, d), 3.91 (2H, d), 3.97 (1H, dd), 4.14 (1H, d), 4.51 (1H, br s), 6.41 (1H, d), 6.69 (1H, s), 7.37 (2H, d), 7.44 (4H, dd), 7.61 (1H, t), 7.77 (2H, d), 8.48 (1H, s)

Example 36db: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 2.26-2.31 (2H, td), 2.74-2.78 (2H, t), 3.11-3.17 (5H, m), 3.46 (2H, q), 3.56 (1H, dd), 3.66 (1H, dd), 3.76 (1H, d), 3.90 (2H, d), 3.97 (1H, dd), 4.15 (1H, d), 4.50 (1H, br s), 4.72 (1H, t), 6.24 (1H, t), 6.68 (1H, s), 7.36 (2H, d), 7.44 (4H, q), 7.60 (1H, m), 7.77 (2H, d), 8.75 (1H, s)

Example 36dc: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.60-1.64 (2H, q), 1.88-1.91 (2H, q), 2.54-2.57 (1H, m), 3.63-3.64 (4H, m), 3.68-3.70 (4H, m), 6.40-6.41 (1H, d), 6.68 (1H, s), 7.37-7.40 (2H, d), 7.57-7.61 (2H, t), 7.71-7.74 (1H, tt), 7.78-7.83 (4H, t), 8.50 (1H, s)

Example 36dd: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.60-1.64 (2H, q), 1.88-1.91 (2H, q), 3.09-3.16 (2H, m), 3.63-3.64 (4H, m), 3.68-3.70 (4H, m), 6.12-6.15 (1H, t), 6.68 (1H, s), 7.36-7.38 (2H, d), 7.57-7.61 (2H, t), 7.71-7.74 (1H, tt), 7.78-7.82 (4H, m), 8.62 (1H, s).

mTOR Kinase Assay (Echo): 0.00291μM

Example 36de: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.60-1.64 (2H, q), 1.88-1.91 (2H, q), 3.15-3.19 (2H, m), 3.44-3.48 (2H, q), 3.63-3.64 (4H, m), 3.68-3.70 (4H, m), 4.71-4.74 (1H, t), 6.21-6.24 (1H, t), 6.68 (1H, s), 7.36-7.38 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.83 (4H, m), 8.76 (1H, s).

mTOR Kinase Assay (Echo): 0.00389μM

Example 36df: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.60-1.64 (2H, q), 1.88-1.91 (2H, q), 2.65-2.66 (3H, d), 3.63-3.64 (4H, m), 3.68-3.69 (4H, m), 6.02-6.06 (1H, m), 6.68 (1H, s), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.82 (4H, m), 8.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00712μM

Example 36dg: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.56-1.64 (4H, m), 1.88-1.91 (2H, q), 3.14-3.19 (2H, q), 3.45-3.49 (2H, q), 3.63-3.64 (4H, m), 3.68-3.70 (4H, m), 4.46-4.49 (1H, t), 6.16-6.19 (1H, t), 6.68 (1H, s), 7.36-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.82 (4H, m), 8.67 (1H, s).

mTOR Kinase Assay (Echo): 0.0164μM

Example 36dh: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.60-1.64 (2H, q), 1.88-1.91 (2H, q), 2.68-2.72 (2H, t), 3.34-3.39 (2H, q), 3.63-3.64 (4H, m), 3.68-3.69 (4H, m), 6.49-6.52 (1H, m), 6.68 (1H, s), 7.38-7.41 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.84 (4H, m), 8.88 (1H, s).

mTOR Kinase Assay (Echo): 0.0034μM

Example 36di: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.61-1.65 (2H, q), 1.89-1.92 (2H, q), 3.63-3.66 (4H, m), 3.69-3.71 (4H, m), 6.73 (1H, m), 6.95 (1H, s), 7.08 (1H, s), 7.21 (1H, s), 7.49-7.52 (2H, d), 7.59-7.63 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.91 (2H, d), 7.92-7.94 (2H, d), 8.38 (1H, s), 9.40 (1H, s), 11.39 (1H, s). (ammonium salt)

Example 36dj: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.61-1.64 (2H, q), 1.89-1.92 (2H, q), 3.63-3.65 (4H, m), 3.69-3.70 (4H, m), 3.79 (3H, s), 6.69 (1H, s), 7.38-7.39 (1H, d), 7.41-7.44 (2H, d), 7.58-7.62 (2H, t), 7.71-7.75 (1H, tt), 7.77 (1H, s), 7.79-7.81 (2H, dd), 7.83-7.86 (2H, d), 8.36 (1H, s), 8.80 (1H, s)

Example 36dk: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.21 (3H, d), 1.58 - 1.64 (2H, m), 1.86 - 1.88 (2H, m), 2.39 (3H, s), 2.54 - 2.58 (1H, m), 2.75 - 2.78 (4H, m), 3.11 - 3.18 (1H, m), 3.46 - 3.51 (1H, m), 3.62 - 3.66 (1H, m), 3.76 (1H, d), 3.95 - 3.98 (1H, m), 4.13 - 4.16 (1H, m), 4.48 - 4.54 (1H, m), 6.40 (1H, s), 6.66 (1H, s), 7.43 (2H, d), 7.64 (1H, s), 7.89 (2H, d), 8.51 (1H, s).

mTOR Kinase Assay (Echo): 0.00905μM

Example 36dl: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.57 - 1.63 (2H, m), 1.84 - 1.89 (2H, m), 2.39 (3H, s), 2.74 - 2.79 (4H, m), 3.12 - 3.20 (3H, m), 3.44 - 3.51 (3H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.12 - 4.16 (1H, m), 4.48 - 4.53 (1H, m), 4.72 (1H, t), 6.24 (1H, t), 6.66 (1H, s), 7.41 (2H, d), 7.64 (1H, s), 7.89 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00399μM

Example 36dm: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.57 - 1.64 (2H, m), 1.84 - 1.90 (2H, m), 2.39 (3H, s), 2.70 (2H, t), 2.74 - 2.79 (4H, m), 3.12 - 3.18 (1H, m), 3.35 - 3.39 (2H, m), 3.46 - 3.51 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.15 (1H, d), 4.48 - 4.54 (1H, m), 6.51 (1H, t), 6.67 (1H, s), 7.44 (2H, d), 7.64 (1H, s), 7.90 (2H, d), 8.90 (1H, s).

mTOR Kinase Assay (Echo): 0.0298μM

Example 36dn: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.57 - 1.61 (4H, m), 1.85 - 1.90 (2H, m), 2.39 (3H, s), 2.74 - 2.79 (4H, m), 3.12 - 3.19 (3H, m), 3.45 - 3.51 (3H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.14 (1H, d), 4.47 - 4.54 (1H, m), 4.47 (1H, t), 6.18 (1H, t), 6.66 (1H, s), 7.41 (2H, d), 7.64 (1H, s), 7.89 (2H, d), 8.68 (1H, s).

mTOR Kinase Assay (Echo): 0.0138μM

Example 36do: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19(3H, d), 1.61-1.68(2H, m), 1.78-1.86(1H, m), 1.88-1.98(3H, m), 3.10-3.18(1H, td), 3.31-3.33(1H, d), 3.43-3.49(4H, m), 3.59-3.63(1H, dd), 3.73-3.76(1H, d), 3.94-3.98(1H, dd), 4.10-4.13(1H, d), 4.31(1H, bs), 4.38(1H, bs), 4.94-4.95(1H, d), 6.63(1H, s), 7.52-7.55(2H, d), 7.58-7.61(2H, t), 7.70-7.74(1H, tt), 7.79-7.84(4H, m), 8.28(1H, s).

Example 36dp: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.18(3H, d), 1.60-1.68(2H, m), 1.87-1.93(2H, m), 3.10-3.17(1H, td), 3.43-3.49(1H, td), 3.53-3.54(2H, m), 3.59-3.63(1H, dd),

3.73-3.76(1H, d), 3.94-3.97(1H, dd), 4.09-4.12(1H, d), 4.38(1H, bs), 6.47(1H, t), 6.63(1H, s), 7.39-7.41(2H, d), 7.57-7.61(2H, t), 7.70-7.74(1H, tt), 7.78-7.83(4H, m), 9.27(1H, s). (H from OH group barried under water peak).

Example 36dq: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18(3H, d), 1.61-1.68(2H, m), 1.87-1.92(2H, m), 2.88(3H, s), 2.97(3H, s), 3.10-3.18(1H, td), 3.42-3.49(1H, td), 3.59-3.63(1H, dd), 3.73-3.76(1H, d), 3.94-3.98(3H, m), 4.09-4.12(1H, d), 4.39(1H, bs), 6.37-6.40(1H, t), 6.63(1H, s), 7.38-7.40(2H, d), 7.57-7.61(2H, t), 7.69-7.74(1H, tt), 7.78-7.80(2H, dd), 7.84-7.86(2H, d), 9.12(1H, s).

Example 36dr: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.68-0.72(2H, m), 0.88-0.93(2H, m), 1.17-1.19(3H, d), 1.61-1.68(2H, m), 1.89-1.92(2H, m), 2.69-2.75(1H, m), 2.87(3H, s), 3.11-3.18(1H, td), 3.43-3.50(1H, td), 3.59-3.63(1H, dd), 3.74-3.76(1H, d), 3.94-3.98(1H, dd), 4.09-4.14(1H, d), 4.39(1H, bs), 6.64(1H, s), 7.52-7.54(2H, d), 7.58-7.62(2H, t), 7.70-7.74(1H, tt), 7.79-7.85(4H, m), 8.34(1H, s).

Example 36ds: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18(3H, d), 1.60-1.68(2H, m), 1.87-1.93(2H, m), 3.10-3.18(1H, td), 3.36-3.40(1H, q), 3.42-3.49(2H, m), 3.59-3.63(1H, dd), 3.73-3.76(1H, d), 3.94-3.98(1H, dd), 4.09-4.12(1H, d), 4.39(1H, bs), 4.40-4.43(1H, t), 4.52-4.55(1H, t), 6.40-6.43(1H, t), 6.63(1H, s), 7.38-7.40(2H, d), 7.57-7.61(2H, t), 7.70-7.74(1H, tt), 7.78-7.80(2H, dd), 7.84-7.86(2H, d), 8.77(1H, s).

Example 36dt: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21(3H, d), 1.85-1.93(1H, m), 2.04-2.14(1H, m), 2.68-2.72(2H, t), 2.76-2.83(2H, m), 3.02-3.10(2H, m), 3.13-3.19(1H, td), 3.34-3.39(2H, q), 3.45-3.52(1H, td), 3.62-3.65(1H, dd), 3.74-3.77(1H, d), 3.94-3.98(1H, dd), 4.07-4.10(1H, d), 4.45(1H, bs), 6.47(1H, s), 6.49-6.52(1H, t), 7.38-7.40(2H, d), 7.44-7.51(4H, m), 7.58-7.62(1H, tt), 7.80-7.82(2H, d), 8.86(1H, s).

Example 36du: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21(3H, d), 1.82-1.93(1H, m), 2.05-2.13(1H, m), 2.76-2.83(2H, m), 3.02-3.19(4H, m), 3.45-3.51(1H, td), 3.62-3.65(1H, dd), 3.74-3.77(1H, d), 3.94-3.98(1H, dd), 4.06-4.10(1H, d), 4.31-4.33(2H, d), 4.45-4.46(1H, bs), 6.47(1H, s), 6.59-6.62(1H, t), 6.94(2H, bs), 7.38-7.40(2H, d), 7.44-7.51(4H, m), 7.58-7.62(1H, tt), 7.80-7.82(2H, d), 8.87(1H, s).

Example 36dv: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.64 (2H, m), 1.90 (2H, m), 3.15 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.76 (4H, m), 3.95 (1H, m), 4.14 (1H, m), 4.39 (1H, m), 6.26 (1H, m), 6.65 (1H, s), 7.44 (2H, m), 7.59 (3H, m), 7.74 (1H, m), 7.80 (2H, m), 7.88 (2H, m), 8.94 (1H, s), 9.12 (1H, s)

Example 36dw: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.64 (2H, m), 1.91 (2H, m), 3.15 (1H, m), 3.34 (3H, s), 3.46 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.12 (1H, m), 4.40 (1H, m), 6.58 (1H, m), 6.66 (1H, m), 7.45 (2H, m), 7.60 (2H, m), 7.77 (3H, m), 7.90 (2H, m), 9.03 (1H, s), 9.49 (1H, s)

Example 36dx: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.64 (2H, m), 1.90 (2H, m), 3.14 (1H, m), 3.52 (4H, m), 3.75 (1H, m), 3.96 (1H, m), 4.11 (1H, m), 4.38 (1H, m), 6.08 (1H, m), 6.53 (1H, m), 6.63 (1H, s), 7.40 (2H, m), 7.60 (2H, m), 7.72 (1H, m), 7.82 (4H, m), 8.92 (1H, s)

Example 36dy: Spectrum not recorded.

Example 36dz: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.64 (2H, m), 1.90 (2H, m), 3.15 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.13 (1H, m), 4.40 (1H, m), 6.66 (1H, s), 6.88 (1H, m), 7.46 (2H, m), 7.61 (2H, m), 7.77 (3H, m), 7.90 (2H, m), 8.77 (1H, m), 9.05 (1H, s), 9.64 (1H, s)

Example 36ea: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.64 (2H, m), 1.91 (2H, m), 3.14 (1H, m), 3.46 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.94 (3H, m), 4.12 (1H, m), 4.39 (1H, m), 6.64 (1H, s), 6.79 (1H, m), 7.40 (2H, m), 7.59 (2H, m), 7.79 (5H, m), 8.99 (1H, s)

Example 36eb: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.65 (2H, m), 1.91 (2H, m), 3.15 (1H, m), 3.46 (1H, m), 3.61 (4H, m), 3.75 (1H, m), 3.97 (1H, m), 4.12 (1H, m), 4.40 (1H, m), 6.64 (1H, s), 6.97 (1H, s), 7.41 (3H, m), 7.61 (2H, m), 7.80 (5H, m), 8.70 (1H, s), 9.07 (1H, s)

Example 36ec: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.17 (3H, d), 1.64 (2H, m), 1.90 (2H, m), 3.13 (1H, m), 3.40 (3H, m), 3.67 (3H, m), 3.96 (1H, m), 4.10 (1H, m), 4.37 (1H, m), 4.83 (1H, t), 6.10 (1H, m), 6.63 (1H, s), 7.36 (2H, m), 7.60 (2H, m), 7.78 (5H, m), 8.70 (1H, s)

Example 36ed: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.17 (3H, d), 1.64 (2H, m), 1.91 (2H, m), 3.14 (1H, m), 3.42 (3H, m), 3.67 (3H, m), 3.96 (1H, m), 4.11 (1H, m), 4.39 (1H, m), 4.83 (1H, t), 6.10 (1H, m), 6.62 (1H, s), 7.36 (2H, m), 7.59 (2H, m), 7.77 (5H, m), 8.71 (1H, s)

Example 36ee: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.63 (2H, m), 1.90 (2H, m), 3.13 (1H, m), 3.45 (3H, m), 3.67 (4H, m), 3.95 (1H, m), 4.12 (1H, m), 4.39 (1H, m), 6.47 (1H, m), 6.63 (1H, s), 7.39 (2H, m), 7.60 (2H, m), 7.79 (5H, m), 8.91 (1H, s)

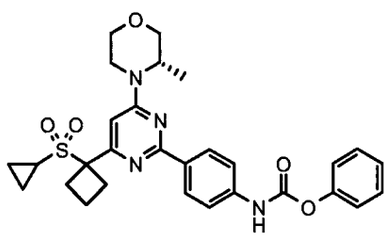
Example 36ef: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.23 (d, 3H), 1.33 (t, 3H), 1.52 - 1.58 (m, 2H), 1.60 - 1.66 (m, 2H), 3.20 (td, 1H), 3.37 - 3.53 (m, 5H), 3.63 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.14 - 4.28 (m, 1H), 4.42 (t, 1H), 4.50 - 4.62 (m, 1H), 4.54 (t, 1H), 6.47 (t, 1H), 6.79 (s, 1H), 7.51 (d, 2H), 8.20 (d, 2H), 8.85 (s, 1H)

Example 36eg: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.23 (d, 3H), 1.33 (t, 3H), 1.53 - 1.58 (m, 2H), 1.60 - 1.66 (m, 2H), 3.20 (td, 1H), 3.44 (q, 2H), 3.48 - 3.65 (m, 4H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.16 - 4.26 (m, 1H), 4.51 - 4.64 (m, 1H), 6.07 (tt, 1H), 6.56 (t, 1H), 6.79 (s, 1H), 7.52 (d, 2H), 8.21 (d, 2H), 8.97 (s, 1H)

The preparation of the phenyl carbamates required for **Examples 36a – 36eg** are either described below or have been described previously.

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



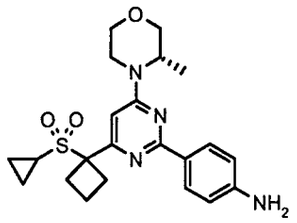
Sodium hydrogen carbonate (259 mg, 3.08 mmol) was added to 4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (880 mg, 2.05 mmol) in dioxane (20 mL) at 5°C under an atmosphere of nitrogen. Phenyl chloroformate (0.387 mL, 3.08 mmol) was then added and the resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with DCM (50 mL), the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid which was collected by filtration and dried under vacuum (1.06 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.69 - 0.80 (2H, m), 0.81 - 0.90 (2H, m), 1.23 (3H, d), 1.86 - 1.98 (1H, m), 2.02 - 2.12 (1H, m), 2.80 - 3.04 (5H, m), 3.15 - 3.28

(1H, m), 3.46 - 3.59 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.23 (1H, d), 4.57 (1H, s), 6.74 (1H, s), 7.22 - 7.31 (3H, m), 7.41 - 7.49 (2H, m), 7.62 (2H, d), 8.33 (2H, d), 10.42 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 549; HPLC tR = 3.05 min.

4-[4-(1-Cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

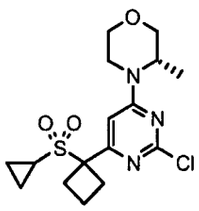


Bis(triphenylphosphine)palladium(II) chloride (0.164 g, 0.23 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.3 g, 3.50 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.149 g, 5.24 mmol) and an aqueous solution of sodium carbonate (1 mL, 2.00 mmol) in a solvent mixture of DMF (5 mL), DME (12 mL), water (1 mL) and ethanol (1 mL) at RT . The resulting mixture was stirred at 90°C for 5 hours under an atmosphere of nitrogen. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, and the crude product further purified by ion exchange chromatography using an SCX column, eluting with 7N ammonia in methanol, to give the desired material as a beige solid (0.88 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 - 0.89 (4H, m), 1.21 (3H, d), 1.84 - 1.93 (1H, m), 2.02 - 2.10 (1H, m), 2.76 - 2.98 (5H, m), 3.10 - 3.24 (1H, m), 3.45 - 3.55 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.18 (1H, d), 4.50 (1H, s), 5.52 (2H, d), 6.60 (2H, d), 8.07 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 429; HPLC tR = 2.41 min.

2-Chloro-4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



1,3-Dibromopropane (2.95 mL, 28.93 mmol) was added to 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.2 g, 9.64 mmol), tetrabutylammonium bromide (0.311 g, 0.96 mmol) and an aqueous solution of sodium hydroxide (2.89 mL, 28.93 mmol) in toluene (24.11 mL). The reaction was stirred at RT for 1 hour then water added and the layers separated. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in isohexane, to give the desired material as a colourless gum (1.3 g).

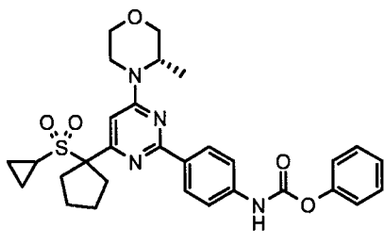
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.69 - 0.78 (2H, m), 0.88 - 0.93 (2H, m), 1.20 (3H, d), 1.83 - 1.95 (1H, m), 2.02 - 2.12 (1H, m), 2.50 - 2.60 (1H, m), 2.67 - 2.80 (2H, m), 2.83 - 2.96 (2H, m), 3.13 - 3.25 (1H, m), 3.40 - 3.49 (1H, m), 3.61 (1H, d), 3.72 (1H, d), 3.93 (1H, d), 4.06 (1H, s), 4.40 (1H, s), 6.82 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 372; HPLC tR = 2.04 min.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

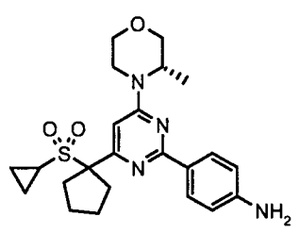


Sodium hydrogen carbonate (228 mg, 2.71 mmol) was added to 4-[4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (800 mg, 1.81 mmol) in dioxane (20 mL) at 5°C under an atmosphere of nitrogen. Phenyl chloroformate (0.341 mL, 2.71 mmol) was then added. The resulting mixture was stirred at RT for 2 hours then diluted with ethyl acetate (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid which was collected by filtration and dried under vacuum (700 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.57 - 0.78 (2H, m), 0.79 - 0.90 (2H, m), 1.23 (3H, d), 1.53 - 1.62 (2H, m), 1.77 - 1.87 (2H, m), 2.41 - 2.50 (2H, m), 2.55 - 2.62 (1H, m), 2.76 - 2.91 (2H, m), 3.16 - 3.26 (1H, m), 3.45 - 3.56 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.55 (1H, s), 6.84 (1H, s), 7.20 - 7.34 (3H, m), 7.41 - 7.51 (2H, m), 7.62 (2H, d), 8.34 (2H, d), 10.42 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 563; HPLC tR = 3.15 min.

4-[4-(1-Cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



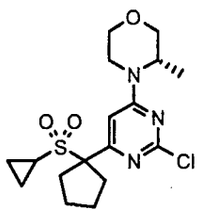
Bis(triphenylphosphine)palladium(II) chloride (0.122 g, 0.17 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1 g, 2.59 mmol), and an aqueous solution of sodium carbonate (1 mL, 2.00 mmol) in a solvent mixture

of DMF (5 mL), DME (12 mL), water (1 mL) and ethanol (1 mL). The resulting mixture was stirred at 90°C for 5 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, followed by ion exchange chromatography using an SCX column, eluting with 7N ammonia in methanol, to give the desired material as a beige solid (0.80 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.67 - 0.79 (2H, m), 0.81 - 0.89 (2H, m), 1.22 (3H, d), 1.50 - 1.59 (2H, m), 1.75 - 1.85 (2H, m), 2.41 - 2.51 (2H, m), 2.72 - 2.90 (3H, m), 3.11 - 3.23 (1H, m), 3.45 - 3.56 (1H, m), 3.58 - 3.66 (1H, m), 3.76 (1H, d), 3.97 (1H, d), 4.18 (1H, d), 4.51 (1H, s), 5.52 (1H, d), 6.61 (2H, d), 6.71 (1H, s), 8.07 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 443; HPLC tR = 2.51 min.

2-Chloro-4-(1-cyclopropylsulfonylcyclopentyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



1,4-Dibromobutane (0.322 mL, 2.71 mmol) was added to 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (900 mg, 2.71 mmol), tetrabutylammonium bromide (87 mg, 0.27 mmol) and an aqueous solution of sodium hydroxide (0.814 mL, 8.14 mmol) in toluene (20 mL). The reaction was stirred at RT for 1 hour then water added and the organic layer separated, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in isohexane, to give the desired material as a yellow gum (1043 mg).

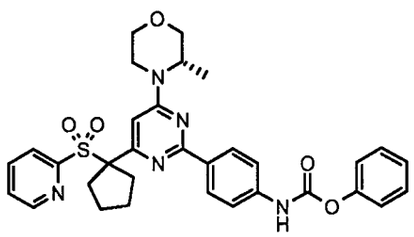
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.66 - 0.75 (2H, m), 0.88 - 0.94 (2H, m), 1.20 (3H, d), 1.50 - 1.57 (2H, m), 1.74 - 1.83 (2H, m), 2.36 - 2.46 (2H, m), 2.54 - 2.69 (3H, m), 3.13 - 3.25 (1H, m), 3.40 - 3.50 (1H, m), 3.59 (1H, d), 3.72 (1H, d), 3.93 (1H, d), 4.04 (1H, d), 4.41 (1H, s), 6.92 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 386; HPLC tR = 2.47 min.

The preparation of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]phenyl]carbamate

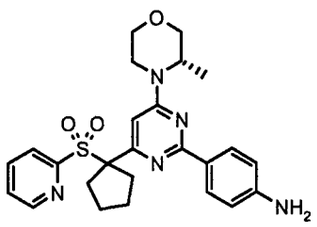


Sodium bicarbonate (139 mg, 1.66 mmol) and phenyl chloroformate (0.14 mL, 1.11 mmol) were added to a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]aniline (530 mg, 1.11 mmol), in 1,4-dioxane (5.6 mL) and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (10 mL), washed with water (10 mL), the organic layer dried ($MgSO_4$), filtered and evaporated. The crude product was triturated with diethyl ether to give the desired material as a cream solid (620 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.51 - 1.62 (2H, m), 1.80 - 1.90 (2H, m), 2.68 - 2.82 (4H, m), 3.10 - 3.17 (1H, m), 3.44 - 3.50 (1H, m), 3.61 - 3.64 (1H, m), 3.75 (1H, d), 3.94 - 3.97 (1H, m), 4.12 (1H, d), 4.49 (1H, s), 6.64 (1H, s), 7.24 - 7.30 (3H, m), 7.45 (2H, t), 7.50 (2H, d), 7.55 - 7.59 (2H, m), 7.84 - 7.86 (3H, m), 8.74 (1H, d), 10.37 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 600; HPLC tR = 3.05 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidin-2-yl]aniline

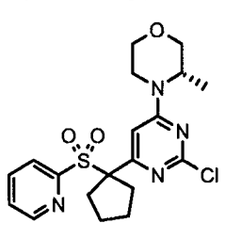


4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (418 mg, 1.91 mmol), an aqueous solution of sodium carbonate (2.2 mL, 4.40 mmol), and dichlorobis(triphenylphosphine)palladium(II) (51.4 mg, 0.07 mmol) were added to a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidine (620 mg, 1.47 mmol) in a solvent mixture of DMF (0.24 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL). The resultant mixture was heated at 90°C for 4 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a cream solid (530 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.51 - 1.58 (2H, m), 1.80 - 1.88 (2H, m), 2.68 - 2.79 (4H, m), 3.09 (1H, dt), 3.46 (1H, dt), 3.61 (1H, dd), 3.74 (1H, d), 3.94 (1H, dd), 4.01 - 4.06 (1H, m), 4.43 (1H, d), 6.46 - 6.49 (3H, m), 7.54 (1H, d), 7.57 - 7.60 (1H, m), 7.60 (2H, d), 7.85 (1H, dt), 8.74 (1H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 480; HPLC tR = 2.37 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopentyl)pyrimidine



1,4-dibromobutane (0.77 mL, 6.51 mmol) was added to 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine (600 mg, 1.63 mmol) in toluene (4 mL) followed by tetrabutylammonium bromide (52.4 mg, 0.16 mmol) and an aqueous solution of sodium hydroxide (0.976 mL, 9.76 mmol). The reaction was stirred at 60°C overnight then

the toluene removed under reduced pressure and the reaction redissolved in DCM and washed with water. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white solid (620 mg).

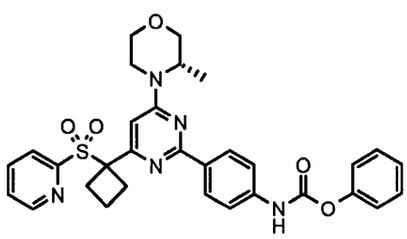
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.50 - 1.58 (2H, m), 1.75 - 1.85 (2H, m), 2.53 - 2.57 (2H, m), 2.63 - 2.71 (3H, m), 3.11 (1H, dt), 3.41 (1H, dt), 3.56 (1H, dd), 3.70 (1H, d), 3.91 (1H, dd), 4.32 (1H, s), 6.67 (1H, s), 7.65 (1H, d), 7.70 - 7.73 (1H, m), 8.03 (1H, dt), 8.74 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 423, HPLC tR = 2.26 min

The preparation of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate



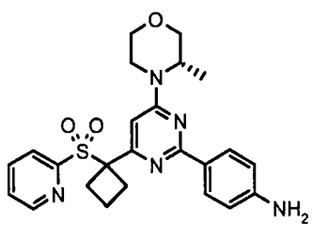
Sodium bicarbonate (154 mg, 1.84 mmol) and phenyl chloroformate (0.154 mL, 1.22 mmol) were added to a solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline (570 mg, 1.22 mmol), in 1,4-dioxane (6.0 mL) and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (10 mL), washed with water (10 mL), the organic layer dried ($MgSO_4$), filtered and evaporated. The crude product was triturated with diethyl ether to give the desired material as a cream solid (600 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.86 - 1.98 (1H, m), 2.07 - 2.19 (1H, m), 2.80 - 2.87 (2H, m), 3.10 - 3.17 (1H, m), 3.23 - 3.30 (2H, m), 3.47 (1H,

dt), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.10 - 4.18 (1H, m), 4.46 (1H, s), 6.52 (1H, s), 6.74 - 6.78 (1H, m), 7.15 (1H, t), 7.23 - 7.30 (3H, m), 7.45 (1H, t), 7.51 (1H, d), 7.60 - 7.62 (2H, m), 7.83 - 7.90 (3H, m), 8.74 (1H, d), 10.39 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 586; HPLC tR = 3.04 min.

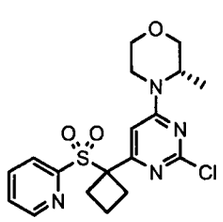
4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline



4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (460 mg, 2.10 mmol), an aqueous solution of sodium carbonate (2.42 mL, 4.84 mmol) and dichlorobis(triphenylphosphine)palladium(II) (56.6 mg, 0.08 mmol) were added to a solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidine (660 mg, 1.61 mmol) in a solvent mixture of DMF (0.24 mL), DME (9.33 mL), water (4.0 mL) and ethanol (2.67 mL) and the suspension heated at 90°C for 4 hours. The reaction mixture was cooled to RT, diluted with ethyl acetate (10 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a cream solid (570 mg).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 466; HPLC tR = 2.27 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclobutyl)pyrimidine



1,3-Dibromopropane (1.565 mLl, 15.35 mmol) was added to 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine (2.83 g, 7.67 mmol), in toluene (20 mL) followed by tetrabutylammonium bromide (0.247 g, 0.77 mmol) and an

aqueous solution of sodium hydroxide (2.3 mL, 23.02 mmol). The reaction was stirred at 60°C overnight. The toluene was removed under reduced pressure and the reaction redissolved in DCM and the organics washed with water then dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a cream solid (0.66 g).

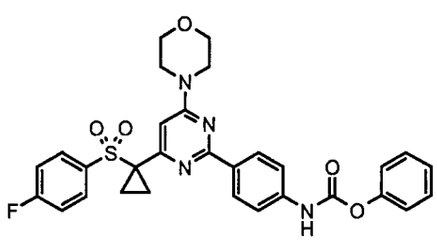
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.86 - 1.95 (1H, m), 2.05 - 2.13 (1H, m), 2.68 - 2.76 (2H, m), 3.07 - 3.18 (3H, m), 3.37 - 3.43 (1H, m), 3.55 (1H, dd), 3.69 (1H, d), 3.90 (2H, dd), 4.28 (1H, s), 6.52 (1H, s), 7.68 - 7.73 (2H, m), 8.03 (1H, dt), 8.74 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 409, HPLC tR = 2.03 min

The preparation of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(pyridin-2-ylsulfonylmethyl)pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate



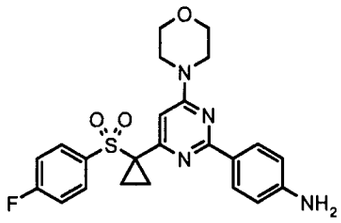
Sodium bicarbonate (0.776 g, 9.24 mmol) was added to 4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline (2.8 g, 6.16 mmol), in 1,4-dioxane (30.8 mL) at RT, followed by the dropwise addition of phenyl chloroformate (0.775 ml, 6.16 mmol) over 2 minutes and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to

afford a solid which was triturated with diethyl ether to give the desired material as a cream solid (3.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.59 - 1.62 (2H, m), 1.88 - 1.91 (2H, m), 3.57 (4H, s), 3.69 (4H, s), 6.75 (1H, s), 7.24 - 7.30 (3H, m), 7.40 - 7.47 (4H, m), 7.53 (2H, d), 7.83 - 7.89 (4H, m), 10.40 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 575; HPLC tR = 3.03 min.

4-[4-[1-(4-Fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline

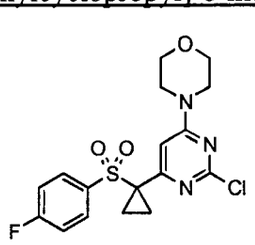


Bis(triphenylphosphine)palladium(II) chloride (0.285 g, 0.41 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.312 g, 10.55 mmol) and 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidine (3.23 g, 8.12 mmol) and an aqueous solution of sodium carbonate (12.18 mL, 24.36 mmol) in a solvent mixture of DME (20 mL), ethanol (10 mL) and water (10 mL) at RT under an atmosphere of nitrogen. The resulting mixture was stirred at 95°C for 4 hours. The reaction mixture was allowed to cool, diluted with ethyl acetate (20 mL), and washed with water (2 x 20mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a cream solid (2.8 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.55 - 1.58 (2H, m), 1.85 - 1.88 (2H, m), 3.62 (4H, d), 3.67 - 3.70 (4H, m), 6.49 (2H, d), 6.61 (1H, s), 7.41 (2H, t), 7.62 (2H, d), 7.82 - 7.85 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 455; HPLC tR = 2.42 min.

2-Chloro-4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-morpholin-4-ylpyrimidine

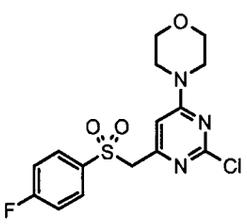


1,2-Dibromoethane (0.695 mL, 8.07 mmol) was added to 2-chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-morpholin-4-ylpyrimidine (3 g, 8.07 mmol), tetrabutylammonium bromide (0.260 g, 0.81 mmol) and an aqueous solution of sodium hydroxide (2.42 mL, 24.21 mmol) in toluene (20.17 mL). The reaction was stirred at RT for 4 hours, the toluene removed under reduced pressure and the residue redissolved in DCM. The organics were washed with water, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was triturated with diethyl ether to give the desired material as a cream solid (3.23 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.52 - 1.55 (2H, m), 1.81 - 1.84 (2H, m), 3.56 (4H, s), 3.63 - 3.65 (4H, m), 6.77 (1H, s), 7.80 - 7.84 (2H, m), 7.82 (2H, t)

LCMS Spectrum: m/z (ESI+)(M+H)+ 398, HPLC tR = 2.26 min

2-Chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-morpholin-4-ylpyrimidine



4-Fluorobenzenesulfinic acid sodium salt (3.30 g, 18.11 mmol) was added to 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine (5.00 g, 14.72 mmol) in acetonitrile (150 mL) at RT under an atmosphere of nitrogen. The resulting solution was stirred at 80°C for 20 hours. The solvent was removed and the residue redissolved in DCM. The organics were washed twice with water, dried ($MgSO_4$) and filtered. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a white solid (3.98 g).

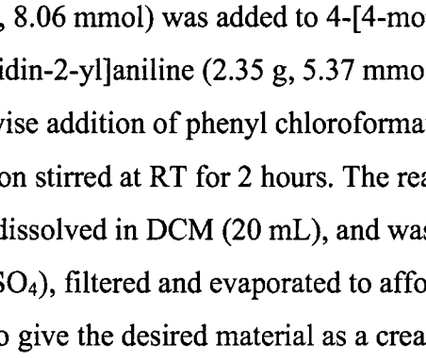
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.55-3.67 (8H, m), 4.65 (2H, s), 6.78 (1H, s), 7.47-7.52 (2H, m), 7.84-7.87 (2H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 372; HPLC tR = 1.99 min.

The preparation of 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate

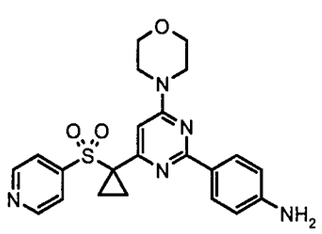


Sodium bicarbonate (0.677 g, 8.06 mmol) was added to 4-[4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (2.35 g, 5.37 mmol), in 1,4-dioxane (26.9 mL) at RT, followed by the dropwise addition of phenyl chloroformate (0.676 mL, 5.37 mmol) over 2 minutes and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as a cream solid (3.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.67 - 1.70 (2H, m), 1.94 - 1.99 (2H, m), 3.57 (4H, s), 3.69 (4H, s), 6.74 - 6.77 (2H, m), 7.24 - 7.26 (2H, m), 7.43 - 7.50 (3H, m), 7.73 (2H, d), 7.78 (2H, d), 8.86 (2H, d), 9.29 (1H, s), 10.39 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 558; HPLC tR = 2.71 min.

4-[4-Morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline



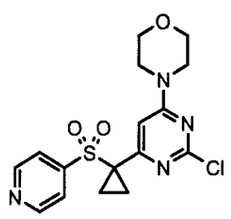
Bis(triphenylphosphine)palladium(II) chloride (0.309 g, 0.44 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.505 g, 11.43 mmol) and 2-chloro-4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidine (3.35 g, 8.80 mmol) and an aqueous

solution of sodium carbonate (13.19 mL, 26.39 mmol) in a solvent mixture of DME (20 mL), ethanol (10 mL) and water (10 mL) at RT under an atmosphere of nitrogen. The resulting mixture was stirred at 95°C for 4 hours. The reaction mixture was diluted with ethyl acetate (20 mL), and washed with water (2 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a brown solid (2.37 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.63 - 1.67 (2H, m), 1.93 - 1.96 (2H, m), 3.64 (4H, d), 3.67 - 3.69 (4H, m), 5.52 (2H, s), 6.45 (2H, d), 6.62 (1H, s), 7.47 (2H, d), 7.76 (2H, dd), 8.85 (2H, dd)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 438; HPLC tR = 1.94 min.

2-Chloro-4-morpholin-4-yl-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidine

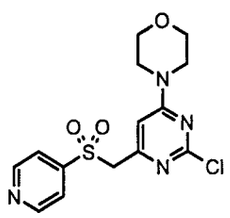


1,2-Dibromoethane (0.510 mL, 22.55 mmol) was added to 2-chloro-4-morpholin-4-yl-6-(pyridin-4-ylsulfonylmethyl)pyrimidine (4 g, 11.27 mmol) in toluene (56.4 mL) followed by tetrabutylammonium bromide (0.363 g, 1.13 mmol) and an aqueous solution of sodium hydroxide (5.64 mL, 56.37 mmol). The reaction was stirred at 60°C for 7 hours then the toluene removed under reduced pressure and the residue redissolved in DCM. The organics were washed with water, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was triturated with diethyl ether to give the desired material as a brown solid (3.35 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.60 - 1.63 (2H, m), 1.89 - 1.92 (2H, m), 3.58 (4H, d), 3.63 - 3.65 (4H, m), 6.81 (1H, s), 7.74 (2H, d), 8.88 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 381, HPLC tR = 1.70 min

2-Chloro-4-morpholin-4-yl-6-(pyridin-4-ylsulfonylmethyl)pyrimidine

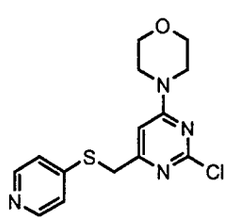


2-Chloro-4-morpholin-4-yl-6-(pyridin-4-ylsulfanylmethyl)pyrimidine (3.28 g, 10.16 mmol) was dissolved in dioxane (45 mL) and 2N sulfuric acid (0.11 mL) was added. The solution was heated to 55°C. A solution of sodium tungstate dihydrate (0.067 g, 0.20 mmol) in water (1.08 mL) was added to the solution and allowed to stir for 10 minutes. Hydrogen peroxide (6.28 mL, 203.2 mmol) was then added dropwise over several minutes. The solution was heated at 55°C for 3 hours. Water was added and the reaction was allowed to cool. The aqueous solution was extracted with DCM and the organics separated, dried ($MgSO_4$), filtered and evaporated. The crude product was triturated with diethyl ether to give the desired material as a cream solid (3.20 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.56 (4H, s), 3.65 - 3.68 (4H, m), 4.77 (2H, s), 6.84 (1H, s), 7.78 (2H, d), 8.92 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 355, HPLC tR = 1.53 min

2-Chloro-4-morpholin-4-yl-6-(pyridin-4-ylsulfanylmethyl)pyrimidine



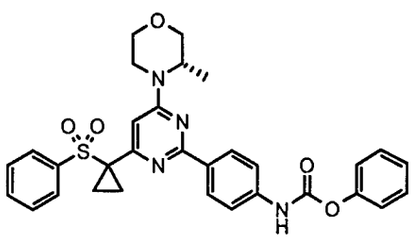
2-Chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine (5 g, 14.72 mmol) was added portionwise to 4-mercaptopyridine (1.8 g, 16.20 mmol) and DBU (2.344 mL, 16.20 mmol) in acetonitrile (73.6 mL) at RT. The resulting suspension was stirred at RT for 30 minutes. The reaction mixture was evaporated to dryness, redissolved in DCM (50 mL) and the organics washed with water (50 mL), dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% ethyl acetate in DCM, to give the desired material as a beige solid (3.3 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.58 (4H, s), 3.64 - 3.67 (4H, m), 4.24 (2H, s), 6.97 (1H, s), 7.35 (2H, d), 8.38 (2H, d)
LCMS Spectrum: m/z (ESI+)(M+H)+ 323, HPLC tR = 1.75 min

The preparation of 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine was described earlier.

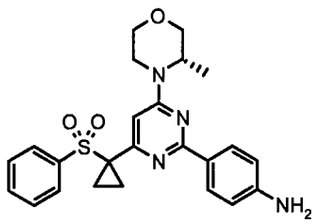
The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.471 mL, 3.75 mmol) was added dropwise to 4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.690 g, 3.75 mmol) and sodium bicarbonate (0.473 g, 5.63 mmol) in dioxane and the resulting mixture stirred at RT for 18 hours. The solvent was removed, DCM added and the organics washed with water dried ($MgSO_4$), filtered and evaporated to give the desired material as a beige solid (2.44 g) which was used without further purification.
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.17-1.19 (3H, d), 1.62-1.69 (2H, m), 1.90-1.93 (2H, m), 3.12-3.19 (1H, td), 3.41-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.10-4.14 (1H, d), 4.39 (1H, bs), 6.66 (1H, s), 7.24-7.30 (3H, m), 7.43-7.47 (2H, t), 7.51-7.53 (2H, d), 7.58-7.61 (2H, t), 7.70-7.74 (1H, t), 7.79-7.81 (2H, d), 7.92-7.94 (2H, d), 10.38 (1H, s).
LCMS Spectrum: m/z (ES+) (M+H)+=571; HPLC tR=3.00 min.

4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

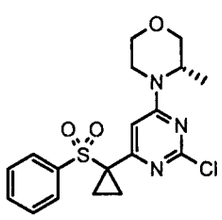


Bis(triphenylphosphine)palladium (II) chloride (0.246 g, 0.35 mmol) was added in one portion to 4-[1-(benzenesulfonyl)cyclopropyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.76 g, 7.01 mmol), 4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.535 g, 7.01 mmol) and an aqueous solution of sodium carbonate (17.52 mL, 35.04 mmol) in a solvent mixture of 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol) and the resulting mixture stirred at 80°C for 3 hours under an atmosphere of nitrogen. The crude product was dissolved in ethyl acetate and washed with water. The organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give the desired material as a yellow solid (3.35 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.15-1.16 (3H, d), 1.58-1.66 (2H, m), 1.85-1.91 (2H, m), 3.07-3.14 (1H, td), 3.41-3.48 (1H, td), 3.58-3.61 (1H, dd), 3.72-3.75 (1H, d), 3.93-3.96 (1H, dd), 4.05-4.08 (1H, d), 4.33 (1H, bs), 5.50 (2H, s), 6.49-6.53 (3H, t), 7.57-7.61 (2H, t), 7.68-7.71 (3H, m), 7.78-7.81 (2H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=451; HPLC tR=2.37 min.

4-[1-(Benzenesulfonyl)cyclopropyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

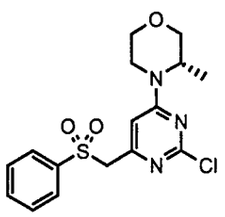


Sodium hydroxide (50% w/w aqueous solution, 299.03 mmol) was added to 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.0 g, 5.44 mmol), 1,2-dibromoethane (1.406 mL, 16.31 mmol) and tetrabutylammonium bromide (0.175 g, 0.54 mmol) in toluene (75 mL) and the resulting mixture stirred at 60°C for 4 hours. Water

was added and the mixture was extracted with toluene. The organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (2.76 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13-1.15 (3H, d), 1.55-1.57 (2H, m), 1.83-1.86 (2H, m), 3.09-3.16 (1H, td), 3.36-3.43 (1H, td), 3.52-3.56 (1H, dd), 3.68-3.71 (1H, d), 3.86-3.93 (2H, m), 4.20 (1H, bs), 6.67 (1H, s), 7.60-7.63 (2H, m), 7.72-7.77 (3H, m).
LCMS Spectrum: m/z (ES+) (M+H)+=394; HPLC tR=2.28 min.

4-(Benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

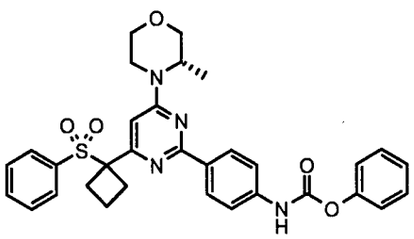


Benzenesulfinic acid, sodium salt (4.22 g, 25.74 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7.0 g, 19.80 mmol) in acetonitrile (200 mL) and the resulting mixture stirred under a nitrogen atmosphere at 80°C for 20 hours. The reaction was cooled and the solvent was removed. DCM was added and the solution was washed with water. The DCM was dried ($MgSO_4$), filtered and the solvent was removed. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a cream solid (6.21 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15-1.16 (3H, d), 3.11-3.18 (1H, td), 3.38-3.45 (1H, td), 3.55-3.58 (1H, dd), 3.70-3.73 (1H, d), 3.85-3.94 (2H, m), 4.15 (1H, bs), 4.64 (2H, s), 6.67 (1H, s), 7.63-7.66 (2H, m), 7.74-7.80 (3H, m).
LCMS Spectrum: m/z (ES+) (M+H)+=368; HPLC tR=2.05 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

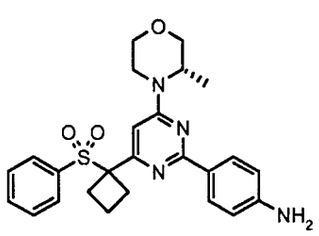


Phenyl chloroformate (0.083 mL, 0.66 mmol) was added to 4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.307 g, 0.66 mmol) and sodium hydrogen carbonate (0.083 g, 0.99 mmol) in dioxane and the resulting mixture was stirred at RT for 2 hours. The solvent was removed and the residue partitioned between DCM and water. The organics were washed with water, dried ($MgSO_4$), filtered and evaporated to give the desired material as a gum (0.386 g) which was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.31-1.33 (3H, d), 1.87-1.99 (1H, m), 2.20-2.31 (1H, m), 2.75-2.83 (2H, m), 3.17-3.32 (3H, m), 3.57-3.63 (1H, td), 3.73-3.77 (1H, dd), 3.80-3.83 (1H, d), 4.01-4.05 (1H, dd), 4.09-4.12 (1H, d), 4.44 (1H, bs), 6.55 (1H, s), 6.78-6.81 (1H, d), 7.16-7.28 (4H, m), 7.36-7.42 (5H, m), 7.49-7.51 (2H, d), 7.56 (1H, s), 7.89-7.92 (2H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=585; HPLC tR=3.30 min.

4-[4-[1-(Benzenesulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



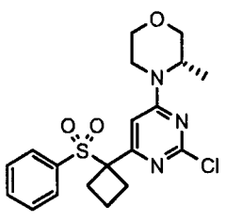
Bis(triphenylphosphine)palladium (II) chloride (0.023 g, 0.03 mmol) was added in one portion to 4-[1-(benzenesulfonyl)cyclobutyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.270 g, 0.66 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.145 g, 0.66 mmol) and an aqueous solution of sodium carbonate (1.653 mL, 3.31 mmol) in

a solvent mixture comprising 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol and the resulting mixture was stirred at 80°C for 3 hours under an atmosphere of nitrogen. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give a sample which was further purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired as a colourless gum (0.395 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.30-1.32 (3H, d), 1.87-1.98 (1H, m), 2.19-2.29 (1H, m), 2.74-2.83 (2H, m), 3.14-3.22 (2H, m), 3.24-3.31 (1H, td), 3.57-3.63 (1H, td), 3.73-3.85 (4H, m), 4.01-4.04 (1H, dd), 4.08-4.12 (1H, d), 4.43-4.45 (1H, m), 6.48 (1H, s), 6.55-6.57 (2H, d), 7.26-7.31 (2H, t), 7.39-7.43 (1H, t), 7.48-7.51 (2H, dd), 7.74-7.76 (2H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=465; HPLC tR=2.49 min.

4-[1-(Benzenesulfonyl)cyclobutyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Sodium hydroxide (50% w/w aqueous solution, 120.21 mmol) was added to 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.804 g, 2.19 mmol), 1,3-dibromopropane (0.666 mL, 6.56 mmol) and tetrabutylammonium bromide (0.070 g, 0.22 mmol) in toluene (50 mL) and the resulting mixture was stirred at 45°C for 1 hour. Water was added, the organics separated, washed with water, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (0.27 g).

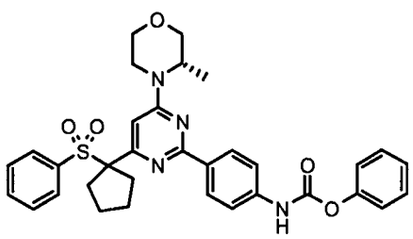
NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.29-1.31 (3H, d), 1.89-1.96 (1H, m), 2.17-2.28 (1H, m), 2.63-2.67 (2H, m), 3.07-3.16 (2H, m), 3.22-3.29 (1H, td), 3.50-3.57 (1H, td), 3.67-3.70 (1H, dd), 3.76-3.79 (1H, d), 3.95-4.01 (2H, m), 4.28 (1H, bs), 6.52 (1H, s), 7.41-7.44 (2H, t), 7.48-7.50 (2H, m), 7.57-7.61 (1H, m).

LCMS Spectrum: m/z (ES+) (M+H)+=408; HPLC tR=2.35 min.

The preparation of 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

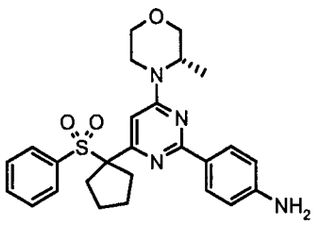


Phenyl chloroformate (0.244 mL, 1.94 mmol) was added to 4-[4-[1-(benzenesulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.930 g, 1.94 mmol) and sodium hydrogen carbonate (0.245 g, 2.91 mmol) in dioxane and the resultant mixture stirred at RT for 2 hours. The solvent was removed and the residue partitioned between DCM and water. The organics were washed with water, dried ($MgSO_4$), filtered and evaporated to give the desired material as a beige solid (1.19 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21-1.23 (3H, d), 1.52-1.56 (2H, m), 1.80-1.88 (2H, m), 2.55-2.60 (2H, m), 2.67-2.69 (2H, m), 3.12-3.19 (1H, td), 3.46-3.52 (1H, td), 3.63-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.95-3.99 (1H, dd), 4.12-4.16 (1H, d), 4.50 (1H, bs), 6.66 (1H, s), 7.23-7.30 (3H, m), 7.42-7.51 (8H, m), 7.56-7.60 (1H, m), 7.88-7.90 (2H, d), 10.37 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+=599; HPLC tR=3.44 min.

4-[4-[1-(Benzenesulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

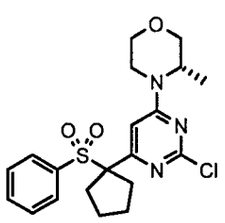


Bis(triphenylphosphine)palladium (II) chloride (0.072 g, 0.10 mmol) was added in one portion to 4-[1-(benzenesulfonyl)cyclopentyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.863 g, 2.05 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.448 g, 2.05 mmol) and an aqueous solution of sodium carbonate (5.11 mL, 10.23 mmol) in a solvent mixture comprising 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol and the resultant mixture stirred at 80°C for 3 hours. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give the desired material as a beige solid (0.93 g).

NMR Spectrum:^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.20 (3H, d), 1.52-1.55 (2H, m), 1.81-1.85 (2H, m), 2.50 (2H, m), 2.67-2.70 (2H, m), 3.07-3.15 (1H, td), 3.45-3.51 (1H, td), 3.62-3.65 (1H, dd), 3.74-3.77 (1H, d), 3.94-3.97 (1H, dd), 4.04-4.08 (1H, d), 4.43-4.45 (1H, bs), 5.47 (2H, s), 6.48-6.51 (3H, m), 7.42-7.48 (4H, m), 7.57-7.62 (1H, m), 7.65-7.67 (2H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=479; HPLC tR=2.67 min.

4-[1-(Benzenesulfonyl)cyclopentyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Sodium hydroxide (50% w/w aqueous solution, 112.53 mmol) was added to 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.753 g, 2.05 mmol), 1,4-dibromobutane (0.733 mL, 6.14 mmol) and tetrabutylammonium bromide (0.066 g, 0.20 mmol) in toluene (50 mL) and the resulting suspension stirred at 60°C for 4 hours. Water was added, the organic layer separated and washed twice with water. The organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica

chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a colourless gum (0.904 g).

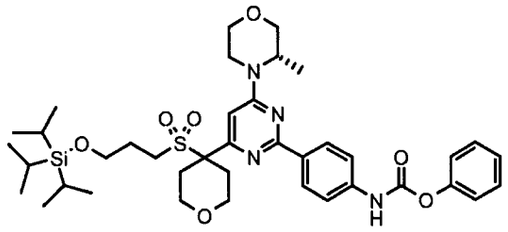
NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.28-1.30 (3H, d), 1.52-1.63 (2H, m), 1.83-1.93 (2H, m), 2.41-2.49 (2H, m), 2.56-2.66 (2H, m), 3.20-3.28 (1H, td), 3.49-3.56 (1H, td), 3.65-3.69 (1H, dd), 3.74-3.77 (1H, d), 3.95-3.99 (2H, m), 4.27 (1H, bs), 6.69 (1H, s), 7.38-7.46 (4H, m), 7.54-7.58 (1H, m).

LCMS Spectrum: m/z (ES+) (M+H)+=422; HPLC tR=2.61 min.

The preparation of 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[4-[3-tri(propan-2-yl)silyloxypropylsulfonyl]oxan-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[4-[3-tri(propan-2-yl)silyloxypropylsulfonyl]oxan-4-yl]pyrimidin-2-yl]phenyl]carbamate



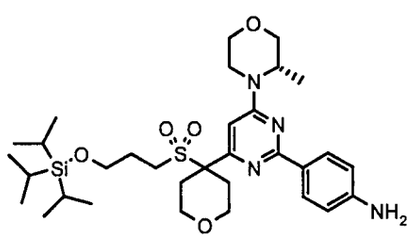
Sodium bicarbonate (0.380 g, 4.53 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[4-[3-tri(propan-2-yl)silyloxypropylsulfonyl]oxan-4-yl]pyrimidin-2-yl]aniline (1.910 g, 3.02 mmol), in 1,4-dioxane (15.09 mL) at RT. Phenyl chloroformate (0.380 mL, 3.02 mmol) was added dropwise over 2 minutes and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (40 mL), and washed with water (40 mL), The organic layer was dried ($MgSO_4$), filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as an amber solid (2.25 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87-0.88 (18H, d), 1.09-1.13 (1H, t), 1.23-1.25 (3H, d), 1.31 (1H, s), 1.74-1.81 (2H, qu), 2.20-2.27 (2H, td), 2.83-2.88 (2H, t), 3.00-3.04 (2H, td), 3.18-3.29 (3H, m), 3.49-3.51 (2H, m), 3.63-3.66 (2H, t), 3.78-3.80 (1H, d), 3.91-3.97 (2H, qu), 3.99-4.03 (1H, dd), 4.30-4.33 (1H, d), 4.58 (1H, exchange), 6.90 (1H, s),

7.25-7.27 (2H, dd), 7.29-7.31 (1H, dd), 7.44-7.47 (2H, d), 7.62-7.64 (2H, d), 8.30-8.32 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 753.4; HPLC tR = 3.97 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[4-[3-tri(propan-2-yl)silyloxypropylsulfonyl]oxan-4-yl]pyrimidin-2-yl]aniline

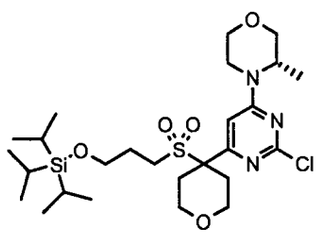


Dichlorobis(triphenylphosphine)palladium (II) (0.118 g, 0.17 mmol) was added to 3-[4-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]oxan-4-yl]sulfonylpropoxy-tri(propan-2-yl)silane (1.94 g, 3.37 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.959 g, 4.38 mmol) and 2M aqueous sodium carbonate (6.06 mL, 12.12 mmol) in water (9.35 mL), ethanol (3.74 mL) and DME (3.74 mL) and the resulting solution stirred at 80°C for 3 hours under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as an amber solid (1.91 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90-0.91 (18H, d), 1.21-1.23 (3H, d), 1.73-1.80 (2H, qu), 2.17-2.25 (2H, td), 2.79-2.84 (2H, t), 2.98-3.02 (2H, td), 3.28 (2H, s), 3.31 (2H, s), 3.47-3.53 (1H, td), 3.63-3.67 (3H, m), 3.76-3.79 (1H, d), 3.90-3.96 (2H, qu), 3.97-4.01 (1H, dd), 4.25-4.29 (1H, d), 4.53-4.54 (1H, m), 5.53-5.55 (1H, d), 6.59-6.61 (2H, d), 6.76 (1H, s), 8.02-8.05 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 633.34; HPLC tR = 3.67 min.

3-[4-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]oxan-4-yl]sulfonylpropoxy-tri(propan-2-yl)silane



Sodium tert-butoxide (1.519 g, 15.80 mmol) was added portionwise to 3-[[2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane (2 g, 3.95 mmol) and bis(2-bromoethyl) ether (1.987 mL, 15.80 mmol) in DMF (19.76 mL) at RT over a period of 5 minutes under a nitrogen atmosphere. The resulting solution was stirred at RT for 16 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (0.5 mL), concentrated and diluted with ethyl acetate (200 mL). The organics were separated, washed sequentially with water (2 x 200 mL) and saturated brine (100 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 40 to 60% ethyl acetate in isohexane, to give the desired material as an off white solid (1.94 g).

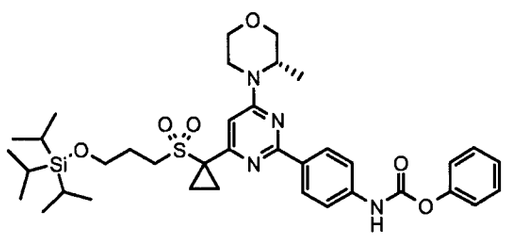
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.98-1.02 (18H, m), 1.20-1.22 (4H, q), 1.78-1.85 (2H, qu), 2.13-2.20 (2H, t), 2.65-2.69 (2H, m), 2.95-3.03 (2H, m), 3.15-3.24 (3H, q), 3.28-3.31 (3H, d), 3.42-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.72-3.76 (2H, q), 3.87-3.92 (2H, qu), 3.94-3.98 (1H, dd), 4.11-4.14 (1H, d), 4.45 (1H, exchange), 6.99 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ 576.31; HPLC tR = 4.06 min

The preparation of 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane was described earlier.

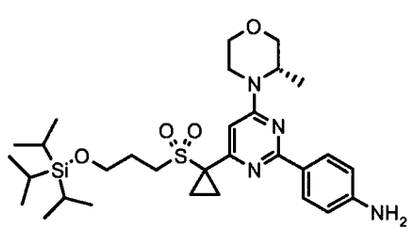
The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate



Sodium bicarbonate (0.749 g, 8.92 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopropyl]pyrimidin-2-yl]aniline (3.5 g, 5.94 mmol), in 1,4-dioxane (29.7 mL) at RT. Phenyl chloroformate (0.748 mL, 5.94 mmol) was added dropwise over 2 minutes and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM (100 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford a solid, which was triturated with diethyl to give the desired material as a light yellow solid (4.13 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.95-0.96 (18H, d), 1.24-1.26 (3H, d), 1.30 (2H, s), 1.58-1.60 (2H, m), 1.54-1.67 (2H, m), 1.95-2.02 (2H, sex), 3.18-3.26 (1H, td), 3.38-3.43 (2H, m), 3.46-3.49 (3H, m), 3.62-3.66 (1H, dd), 3.75-3.78 (2H, t), 3.97-4.01 (1H, dd), 4.21-4.24 (1H, d), 4.57 (1H, exchange), 6.86 (1H, s), 7.25-7.27 (2H, d), 7.29-7.31 (1H, d), 7.44-7.46 (2H, d), 7.63-7.65 (2H, d), 8.27-8.30 (2H, d), 10.45 (1H, exchange)
LCMS Spectrum: m/z (ESI+)(M+H)+ 709.41; HPLC tR = 3.82 min

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopropyl]pyrimidin-2-yl]aniline



Dichlorobis(triphenylphosphine)palladium (II) (0.214 g, 0.31 mmol) was added to 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane (3.25 g, 6.11 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.739 g, 7.94 mmol) and 2M aqueous sodium carbonate (10.99 mL, 21.98 mmol)

in water (16.96 mL), ethanol (6.79 mL) and DME (6.79 mL) and the resulting solution stirred at 80°C for 3 hours under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as an amber gum, which solidified on standing (3.50 g).

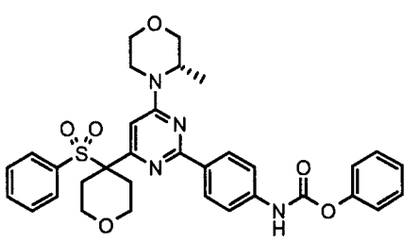
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.98-0.99 (18H, d), 1.53-1.58 (2H, m), 1.60-1.64 (2H, m), 1.96-2.03 (4H, m), 3.14-3.22 (1H, td), 3.29-3.31 (1H, d), 3.45-3.49 (3H, m), 3.61-3.64 (1H, dd), 3.75-3.78 (3H, t), 3.96-4.00 (1H, dd), 4.02-4.08 (1H, q), 4.15-4.19 (1H, d), 4.51 (1H, m), 5.55-5.57 (1H, d), 6.59-6.61 (2H, d), 6.71 (1H, s), 8.02-8.04 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 589.88; HPLC tR = 3.80 min

The preparation of 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane was described earlier.

The preparation of phenyl *N*-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

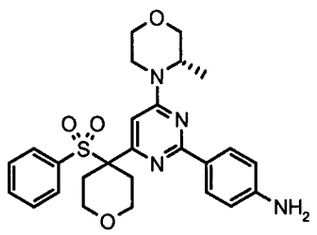


Phenyl chloroformate (0.098 mL, 0.78 mmol) was added dropwise to 4-[4-[4-(benzenesulfonyl)oxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.35 g, 0.71 mmol) and sodium bicarbonate (0.089 g, 1.06 mmol) in dioxane (25 mL) and the resulting suspension stirred at RT for 18 hours. The reaction mixture was diluted with DCM (20 mL), and washed with water (20 mL), the organic layer dried ($MgSO_4$), filtered and evaporated to give the desired material as an orange gum (0.45 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 2.20-2.30 (2H, td), 2.75 (2H, m), 3.23 (3H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.75 (1H, d), 3.85 (2H, dd), 3.97 (1H, dd), 4.20 (1H, d), 4.55 (1H, br s), 6.70-6.80 (3H, m), 7.15 (1H, t), 7.25 (2H, dd), 7.40-7.55 (7H, m), 7.85 (2H, d), 10.40 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 615; HPLC tR = 2.93 min.

4-[4-[4-(Benzenesulfonyl)oxan-4-yl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

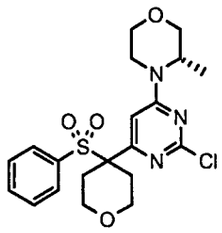


Bis(triphenylphosphine)palladium(II) chloride (0.067 g, 0.09 mmol) was added in one portion to 4-[4-(benzenesulfonyl)oxan-4-yl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.83 g, 1.90 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.498 g, 2.27 mmol) and an aqueous solution of sodium carbonate (4.74 mL, 9.48 mmol) in a DMF (3.60 mL), DME (9.56 mL), water (4.1 mL) and ethanol (2.72 mL) solution mixture. The resulting solution was stirred at 80°C for 3 hours under a nitrogen atmosphere. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (50 mL), and washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a beige solid (0.82 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 2.20-2.30 (2H, td), 2.75 (2H, m), 3.10-3.20 (3H, m), 3.50 (1H, td), 3.65 (1H, dd), 3.75 (1H, d), 3.85 (2H, dd), 3.97 (1H, dd), 4.20 (1H, d), 4.50 (1H, d), 5.47 (2H, s), 6.45 (2H, d), 6.60 (1H, s), 7.40 (4H, m), 7.60 (3H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 495; HPLC tR = 2.37 min.

4-[4-(Benzenesulfonyl)oxan-4-yl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



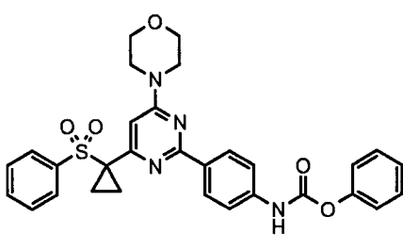
50% v/v aqueous sodium hydroxide (4.49 g, 112.14 mmol) was added to 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (0.75 g, 2.04 mmol), tetrabutylammonium bromide (0.066 g, 0.20 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (1.419 g, 6.12 mmol) in toluene (50 mL). The resulting mixture was stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and washed twice with more water (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a white solid (0.83 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 2.10-2.23 (2H, td), 2.60 (2H, td), 3.10-3.20 (3H, m), 3.25 (1H, d), 3.40 (1H, td), 3.60 (1H, dd), 3.70 (1H, dd), 3.80 (2H, dd), 3.90 (1H, dd), 4.40 (1H, d), 6.70 (1H, s), 7.40 (2H, d), 7.60 (2H, td), 7.75 (1H, td)
LCMS Spectrum: m/z (ESI+) (M+H)+ = 438; HPLC tR = 2.45 min.

The preparation of 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

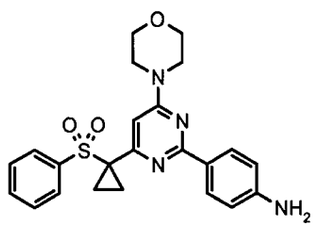


Phenyl chloroformate (0.307 mL, 2.45 mmol) was added to 4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline (1.069 g, 2.45 mmol) and sodium hydrogen carbonate (0.309 g, 3.67 mmol) in dioxane and the resulting suspension stirred at RT overnight. The solids were filtered and washed with dioxane and water and then dried in the vacuum oven at 50°C overnight. The filtrate was concentrated and the solids were filtered, rinsed with water and dried in the vacuum oven overnight. The two crops were combined to give the desired material as a beige solid (1.132 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.62-1.65 (2H, q), 1.89-1.92 (2H, q), 3.66-3.70 (8H, m), 6.71 (1H, s), 7.24-7.31 (3H, m), 7.43-7.47 (2H, t), 7.51-7.54 (2H, d), 7.58-7.62 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.81 (2H, d), 7.90-7.92 (2H, d), 10.40 (1H, bs).

LCMS Spectrum: m/z (ES+) (M+H)+=557; HPLC tR=3.03 min.

4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline

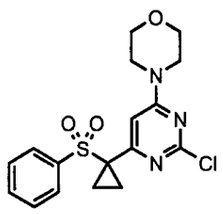


Bis(triphenylphosphine)palladium (II) chloride (0.088 g, 0.13 mmol) was added in one portion to 4-[1-(benzenesulfonyl)cyclopropyl]-2-chloro-6-morpholin-4-ylpyrimidine (0.956 g, 2.52 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.552 g, 2.52 mmol) and an aqueous solution of sodium carbonate (6.29 mL, 12.59 mmol) in a solvent mixture comprising 18% DMF and 82% of a 7:3:2 mixture of DME:water:Ethanol and the solution stirred at 80°C for 3 hours under a nitrogen atmosphere. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol to give a sample that was further purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (1.07 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58-1.62 (2H, q), 1.86-1.89 (2H, q), 3.59-3.60 (4H, m), 3.67-3.69 (4H, m), 5.50 (2H, s), 6.48-6.50 (2H, d), 6.58 (1H, s), 7.57-7.61 (2H, t), 7.66-7.68 (2H, d), 7.69-7.73 (1H, tt), 7.78-7.80 (2H, m).

LCMS Spectrum: m/z (ES+) (M+H)+=437; HPLC tR=2.19 min.

4-[1-(Benzenesulfonyl)cyclopropyl]-2-chloro-6-morpholin-4-ylpyrimidine

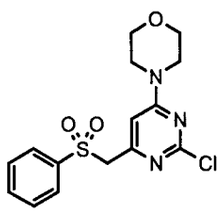


Sodium hydroxide (50% w/w aqueous solution, 248.52 mmol) was added 4-(benzenesulfonylmethyl)-2-chloro-6-morpholin-4-ylpyrimidine (1.599 g, 4.52 mmol), 1,2-dibromoethane (1.168 mL, 13.56 mmol) and tetrabutylammonium bromide (0.146 g, 0.45 mmol) in toluene (75 mL) and the resulting suspension stirred at 60°C for 18 hours. Water was added to the mixture, the organics separated, washed twice with water, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (0.956 g).

NMR Spectrum: ^1H NMR (400.132 MHz, DMSO-d_6) δ 1.53-1.56 (2H, q), 1.82-1.85 (2H, q), 3.53 (4H, bs), 3.63-3.65 (4H, t), 6.72 (1H, s), 7.59-7.63 (2H, m), 7.73-7.77 (3H, m).

LCMS Spectrum: m/z (ES+) (M+H)+=380; HPLC tR=2.02 min.

4-(Benzenesulfonylmethyl)-2-chloro-6-morpholin-4-ylpyrimidine



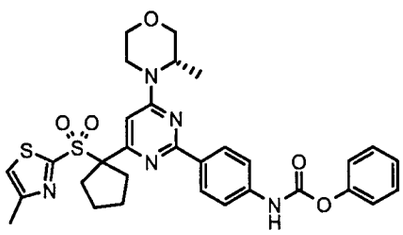
Sodium benzenesulfinate (4.31 g, 26.26 mmol) was added to 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine (6.86 g, 20.20 mmol) in acetonitrile (200 mL) at 22°C under nitrogen. The resulting slurry was stirred at 80 °C for 3 hours. The reaction had gone to completion. The solvent was removed and DCM and water were added. The DCM was washed with water, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM. Pure fractions were evaporated to dryness to afford 4- (2-chloro-6-(phenylsulfonylmethyl)pyrimidin-4-yl)morpholine (4.96 g, 69.4 %) as a cream solid.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.53 (4H, bs), 3.64-3.67 (4H, t), 4.61 (2H, s), 6.71 (1H, s), 7.63-7.67 (2H, m), 7.75-7.81 (3H, m).
LCMS Spectrum: m/z (ES+) (M+H)+=354; HPLC tR=1.79 min.

The preparation of 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine was described earlier.

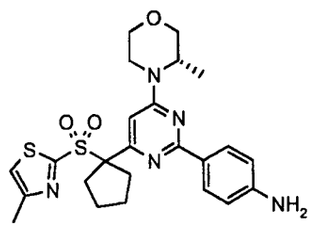
The preparation of phenyl N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]carbamate



Phenylchloroformate (0.232 mL, 1.85 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]aniline (840 mg, 1.68 mmol) and sodium bicarbonate (212 mg, 2.52 mmol) in dioxane (50 mL) at 10°C under a nitrogen atmosphere. The resulting mixture was stirred at 10°C for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford Phenyl N-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]phenyl]carbamate (1.24g) as a yellow dry film.
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.60 - 1.63 (2H, m), 1.83 - 1.92 (2H, m), 2.38 (3H, s), 2.76 - 2.80 (4H, m), 3.12 - 3.19 (1H, m), 3.49 - 3.55 (1H, m), 3.61 - 3.66 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.15 - 4.18 (1H, m), 4.49 - 4.56 (1H, m), 6.70 (1H, s), 7.24 - 7.26 (3H, m), 7.43 - 7.45 (2H, m), 7.56 (2H, d), 7.64 (1H, s), 7.99 (2H, d), 10.39 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 620; HPLC tR = 3.26min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidin-2-yl]aniline

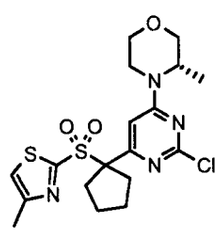


Bis(triphenylphosphine)palladium (II) chloride (0.162 g, 0.23 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidine (2.05g, 4.63 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.318 g, 6.02 mmol) and 2M aqueous sodium carbonate (8.33 mL, 16.66 mmol) in DME (10 mL), ethanol (10 mL) and water (25 mL) and the resulting mixture stirred at 80°C for 18 hours. The cooled reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as a yellow gum (0.84 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.57 - 1.62 (2H, m), 1.83 - 1.89 (2H, m), 2.40 (3H, s), 2.73 - 2.78 (4H, m), 3.08 - 3.15 (1H, m), 3.44 - 3.50 (1H, m), 3.61 - 3.64 (1H, m), 3.75 (1H, d), 3.94 - 3.97 (1H, m), 4.10 (1H, d), 4.43 - 4.49 (1H, m), 5.50 (2H, s), 6.53 (2H, d), 6.54 (1H, s), 7.64 (1H, s), 7.73 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 500; HPLC tR = 2.66min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopentyl]pyrimidine



1,4-Dibromobutane (0.627 mL, 5.30 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (2.06 g, 5.30 mmol), 40% aqueous sodium hydroxide solution (5.30 mL, 53 mmol) and tetrabutylammonium bromide (0.342 g, 1.06 mmol) in toluene (100 mL) and the resulting solution stirred at 60°C for 3 hours. The reaction mixture was concentrated and diluted with ethyl acetate (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as an orange gum (2.55g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ δ 1.18 (3H, d), 1.57 - 1.62 (2H, m), 1.78 - 1.86 (2H, m), 2.45 (3H, s), 2.55 - 2.68 (4H, m), 3.10 - 3.17 (1H, m), 3.39 - 3.46 (1H, m), 3.55 - 3.59 (1H, m), 3.71 (1H, d), 3.90 - 3.99 (2H, m), 4.32 - 4.38 (1H, m), 6.72 (1H, s), 7.87 (1H, s)

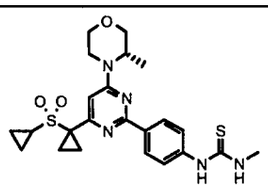
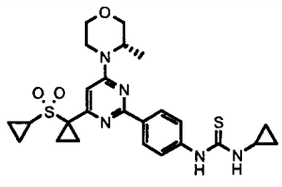
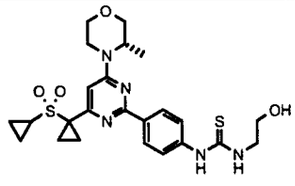
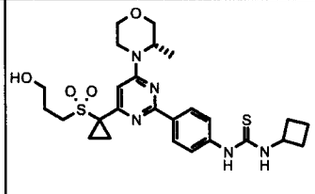
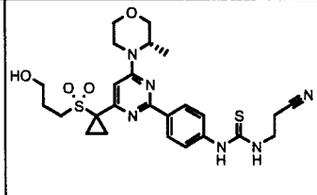
LCMS Spectrum: m/z (ESI+)(M+H)+ = 443; HPLC tR = 2.66min.

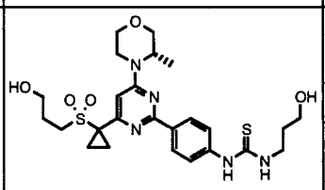
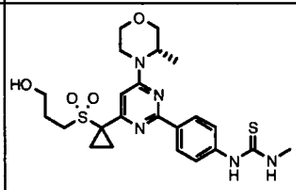
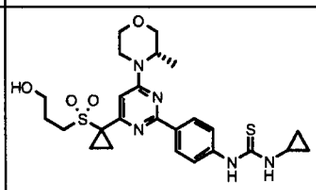
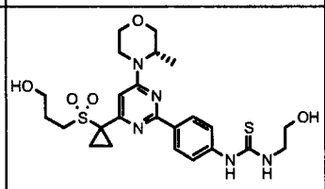
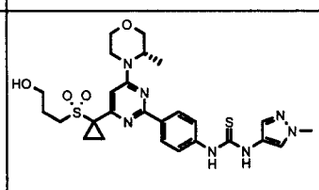
The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine was described earlier.

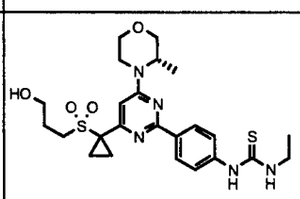
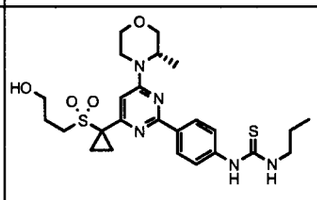
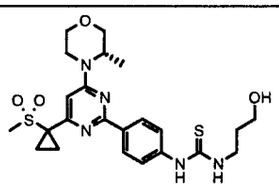
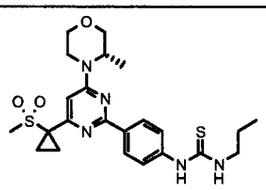
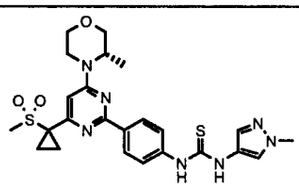
Example 37

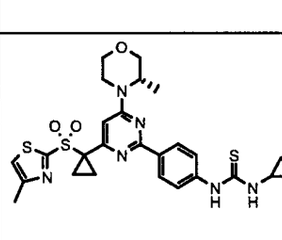
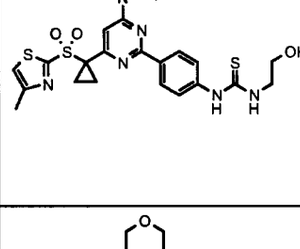
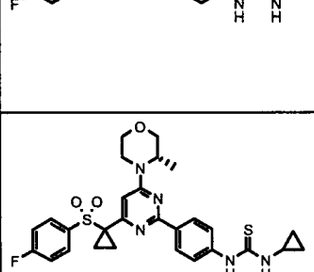
The following compounds were prepared according to the following general procedure.

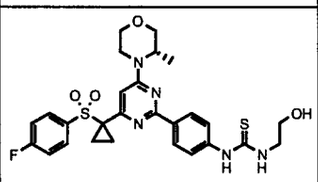
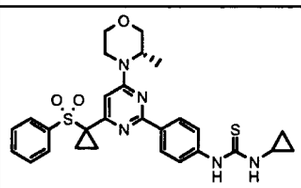
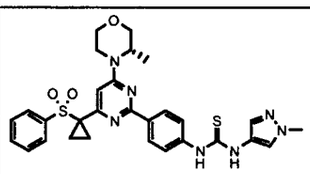
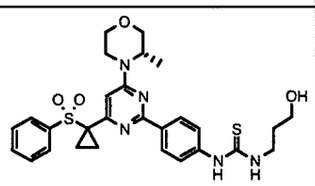
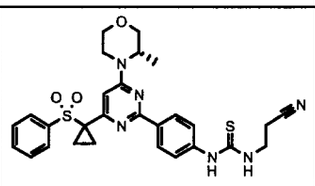
The appropriate aniline was treated with 1,1'-thiocarbonyldiimidazole in a solvent mixture of DCM and THF at RT for 2 - 16 hours. Triethylamine and the appropriate amine were added and the reactions stirred at RT for an additional 1 – 16 hours (unless otherwise stated). The mixtures were purified by prep HPLC.

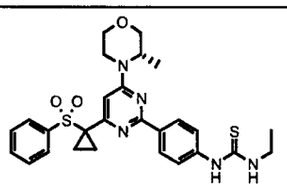
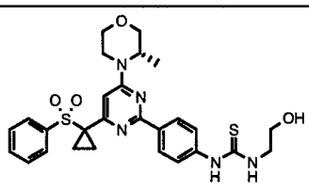
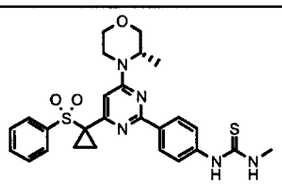
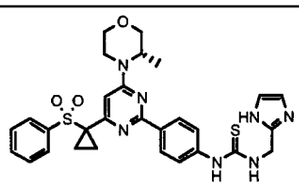
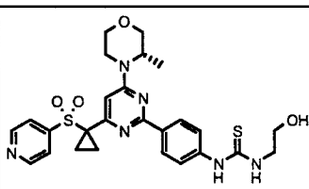
Example	Structure	NAME	LCMS MH+	Retention time (min)
37a		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea	488	2.14
37b		3-cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	514	2.28
37c		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea	518	1.95
37d		3-cyclobutyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	546	2.32
37e		3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	545	2.0

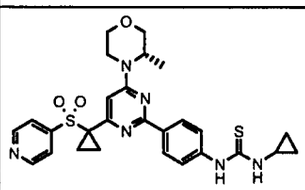
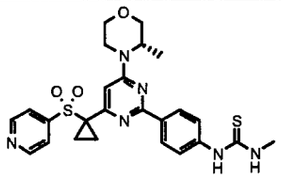
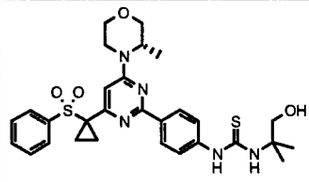
Example	Structure	NAME	LCMS MH+	Retention time (min)
37f		3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	572	1.78
37g		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea	506	1.75
37h		3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	532	1.87
37i		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	536	1.60
37j		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea	572	1.72

Example	Structure	NAME	LCMS MH+	Retention time (min)
37k		1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	520	1.91
37l		3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylthiourea	534	2.07
37m		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	506.5	1.74
37n		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-propylthiourea	490.5	2.24
37o		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea	528.5	1.84

Example	Structure	NAME	LCMS MH+	Retention time (min)
37p		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea	545	2.38
37q		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea	571	2.51
37r		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]thiourea	575	2.13
37s		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea	540	2.52
37t		3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	568	2.65

Example	Structure	NAME	LCMS MH+	Retention time (min)
37u		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea	572	2.27
37v		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylthiourea	550	2.59
37w		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)thiourea	589	2.30
37x		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea	568	2.20
37y		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-cyanoethyl)thiourea	563	2.49

Example	Structure	NAME	LCMS MH+	Retention time (min)
37z		3-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylthiourea	538	2.60
37aa		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea	554	2.18
37ab		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea	524	2.41
37ac		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea	590	2.40
37ad*		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	556	1.92

Example	Structure	NAME	LCMS MH+	Retention time (min)
37ae*		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	552	2.22
37af*		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea	526	2.10
37ag		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)thiourea	582	2.50

* The appropriate aniline was treated with 1,1'-thiocarbonyldiimidazole in a solvent mixture of DCM and THF at RT for 16 hours. Triethylamine and the appropriate amine, dissolved in DMF, were added and the reactions stirred at 50°C for 1 hour. The mixture was purified by prep HPLC.

Example 37a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90 - 0.98 (2H, m), 0.99 - 1.08 (2H, m), 1.24 (3H, d), 1.55 - 1.62 (2H, m), 1.63 - 1.70 (2H, m), 2.91 - 3.05 (4H, m), 3.19 - 3.25 (1H, m), 3.44 - 3.55 (1H, m), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.20 (1H, d), 4.56 (1H, s), 6.88 (1H, s), 7.55 (2H, d), 7.83 (1H, s), 8.27 (2H, d), 9.72 (1H, s).

mTOR Kinase Assay (Echo): 0.026μM

Example 37b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.57 - 0.63 (2H, m), 0.72 - 0.78 (2H, m), 0.90 - 0.96 (2H, m), 0.99 - 1.07 (2H, m), 1.24 (3H, d), 1.55 - 1.62 (2H, m), 1.63 - 1.68

(2H, m), 2.90 - 3.04 (2H, m), 3.17 - 3.27 (1H, m), 3.50 (1H, d), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.18 (1H, d), 4.56 (1H, s), 6.89 (1H, s), 7.62 (2H, d), 8.27 (2H, d), 9.50 (1H, s).
mTOR Kinase Assay (Echo): 0.0124μM

Example 37c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90 - 0.96 (2H, m), 1.00 - 1.07 (2H, m), 1.24 (3H, d), 1.55 - 1.61 (2H, m), 1.64 - 1.69 (2H, m), 2.95 - 3.05 (1H, m), 3.17 - 3.27 (3H, m), 3.44 - 3.56 (3H, m), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.20 (1H, d), 4.55 (1H, s), 4.82 (1H, s), 6.88 (1H, s), 7.57 - 7.68 (2H, m), 7.86 (1H, s), 8.27 (2H, d), 9.81 (1H, s).
mTOR Kinase Assay (Echo): 0.00344μM

Example 37d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.60 (2H, m), 1.62 - 1.71 (3H, m), 1.89 - 1.98 (2H, m), 2.25 - 2.34 (2H, m), 2.42 - 2.52 (2H, m), 3.14 - 3.24 (3H, m), 3.41 - 3.55 (3H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.20 (1H, d), 4.53 - 4.68 (2H, m), 6.81 (1H, s), 7.60 (2H, d), 8.11 (1H, s), 8.26 (2H, d), 9.58 (1H, s).
mTOR Kinase Assay (Echo): 0.00439μM

Example 37e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.60 (2H, m), 1.62 - 1.68 (2H, m), 1.91 - 1.98 (2H, m), 2.84 - 2.92 (2H, m), 3.13 - 3.24 (1H, m), 3.43 - 3.57 (5H, m), 3.64 (1H, d), 3.72 - 3.80 (3H, m), 3.97 (1H, d), 4.20 (1H, d), 4.57 (1H, s), 4.68 (1H, t), 6.83 (1H, s), 7.56 (2H, d), 8.16 (1H, s), 8.29 (2H, d), 9.98 (1H, s).
mTOR Kinase Assay (Echo): 0.0049μM

Example 37f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.59 (2H, m), 1.62 - 1.67 (2H, m), 1.93 - 1.98 (4H, m), 2.28 - 2.36 (2H, m), 2.65 - 2.70 (2H, m), 3.13 - 3.23 (1H, m), 3.44 - 3.56 (5H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.20 (1H, d), 4.58 (1H, s), 4.71 (2H, s), 6.82 (1H, s), 7.00 (2H, s), 7.69 (2H, d), 8.21 (0H, s), 8.29 (2H, s).
mTOR Kinase Assay (Echo): 0.12μM

Example 37g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.59 (2H, m), 1.62 - 1.68 (2H, m), 1.89 - 1.99 (2H, m), 2.96 (3H, s), 3.14 - 3.28 (3H, m), 3.45 - 3.55 (3H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.21 (1H, d), 4.58 (1H, s), 4.68 (1H, t), 6.82 (1H, s), 7.55 (2H, d), 7.84 (1H, s), 8.27 (2H, d), 9.73 (1H, s).
mTOR Kinase Assay (Echo): 0.0179μM

Example 37h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.56 - 0.66 (2H, m), 0.72 - 0.80 (2H, m), 1.24 (3H, d), 1.53 - 1.60 (2H, 1m), 1.62 - 1.68 (2H, m), 1.88 - 2.00 (2H, m), 2.92 (1H, s), 3.16 - 3.27 (1H, m), 3.44 - 3.58 (5H, m), 3.64 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.22 (1H,

d), 4.57 (1H, s), 4.68 (1H, t), 6.82 (1H, s), 7.62 (2H, d), 8.14 (1H, s), 8.26 (2H, d), 9.50 (1H, s).

mTOR Kinase Assay (Echo): 0.0132μM

Example 37i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.59 (2H, m), 1.63 - 1.68 (2H, m), 1.89 - 1.97 (2H, m), 3.14 - 3.29 (5H, m), 3.46 - 3.60 (5H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.21 (1H, d), 4.57 (1H, s), 4.68 (1H, t), 4.81 (1H, s), 6.82 (1H, s), 7.63 (2H, d), 7.96 (1H, s), 8.27 (2H, d), 9.81 (1H, s).

mTOR Kinase Assay (Echo): 0.00306μM

Example 37j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.54 - 1.60 (2H, m), 1.62 - 1.68 (2H, m), 1.89 - 1.99 (2H, m), 3.15 - 3.25 (1H, m), 3.41 - 3.56 (5H, m), 3.64 (1H, d), 3.82 (1H, d), 3.98 (1H, d), 4.22 (1H, d), 4.58 (1H, s), 4.69 (1H, t), 6.82 (1H, s), 7.51 (1H, s), 7.62 (2H, d), 8.05 (1H, s), 8.28 (2H, d), 9.69 (1H, s).

mTOR Kinase Assay (Echo): 0.0309μM

Example 37k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, t), 1.24 (3H, d), 1.53 - 1.60 (2H, m), 1.62 - 1.67 (2H, m), 1.89 - 1.97 (2H, m), 3.14 - 3.28 (3H, m), 3.46 - 3.56 (5H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.21 (1H, d), 4.58 (1H, s), 4.68 (1H, t), 6.82 (1H, s), 7.56 (2H, d), 7.88 (1H, s), 8.27 (2H, d), 9.62 (1H, s).

mTOR Kinase Assay (Echo): 0.0114μM

Example 37l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.91 (3H, t), 1.24 (3H, d), 1.53 - 1.60 (4H, m), 1.62 - 1.67 (2H, m), 1.90 - 1.97 (2H, m), 3.16 - 3.27 (3H, m), 3.42 - 3.53 (5H, m), 3.64 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.21 (1H, d), 4.57 (1H, s), 4.68 (1H, t), 6.82 (1H, s), 7.58 (2H, d), 7.89 (1H, s), 8.26 (2H, d), 9.63 (1H, s).

mTOR Kinase Assay (Echo): 0.032μM

Example 37m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.67 - 1.75 (4H, m), 3.17 - 3.26 (1H, m), 3.28 (3H, s), 3.45 - 3.58 (5H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.18 - 4.25 (1H, m), 4.52 - 4.63 (2H, m), 6.80 (1H, s), 7.57 - 7.60 (2H, m), 7.91 (1H, s), 8.24 - 8.27 (2H, m), 9.71 (1H, s).

mTOR Kinase Assay (Echo): 0.0506μM

Example 37n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.91 (3H, t), 1.24 (3H, d), 1.53 - 1.62 (4H, m), 1.66 - 1.69 (2H, m), 3.22 (1H, td), 3.27 (3H, s), 3.43 - 3.52 (3H, m), 3.64 (1H, dd), 3.77 (1H, d), 3.97 (1H, dd), 4.18 - 4.25 (1H, m), 4.56 - 4.62 (1H, m), 6.80 (1H, s), 7.60 (2H, d), 7.91 (1H, s), 8.24 - 8.28 (2H, m), 9.65 (1H, s).

mTOR Kinase Assay (Echo): 0.0393μM

Example 37o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.56 - 1.59 (2H, m), 1.67 - 1.70 (2H, m), 3.22 (1H, td), 3.27 (3H, s), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.81 (3H, s), 3.98 (1H, dd), 4.19 - 4.25 (1H, m), 4.57 - 4.63 (1H, m), 6.81 (1H, s), 7.51 (1H, s), 7.62 - 7.65 (2H, m), 8.05 (1H, s), 8.25 - 8.29 (2H, m), 9.67 - 9.76 (2H, m).

mTOR Kinase Assay (Echo): 0.033μM

Example 37p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.78 - 1.81 (2H, m), 1.95 - 1.98 (2H, m), 2.48 (3H, s), 2.95 (3H, d), 3.16 - 3.23 (1H, m), 3.44 - 3.51 (1H, m), 3.62 (1H, d), 3.76 (1H, d), 3.96 - 3.99 (1H, m), 4.14 - 4.18 (1H, m), 4.44 - 4.50 (1H, m), 6.82 (1H, s), 7.47 (2H, d), 7.80 (1H, s), 7.84 (1H, s), 7.96 (2H, d), 9.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00534μM

Example 37q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.58 - 0.62 (2H, m), 0.74 - 0.79 (2H, m), 1.22 (3H, d), 1.78 - 1.81 (2H, m), 1.95 - 1.98 (2H, m), 2.49 (3H, s), 2.87 - 2.97 (1H, m), 3.17 - 3.23 (1H, m), 3.44 - 3.51 (1H, m), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.96 - 3.99 (1H, m), 4.15 - 4.18 (1H, m), 4.44 - 4.51 (1H, m), 6.83 (1H, s), 7.54 (2H, d), 7.84 (1H, s), 7.95 (2H, d), 8.15 (1H, s), 9.47 (1H, s).

mTOR Kinase Assay (Echo): 0.00294μM

Example 37r: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.78 - 1.81 (2H, m), 1.94 - 1.98 (2H, m), 2.48 (3H, s), 3.16 - 3.23 (1H, m), 3.44 - 3.50 (1H, m), 3.57 (4H, s), 3.61 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.15 - 4.18 (1H, m), 4.43 - 4.52 (1H, m), 4.82 (1H, s), 6.82 (1H, s), 7.54 (2H, d), 7.84 (2H, s), 7.95 (2H, d), 9.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00162μM

Example 37s: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 - 1.65 (2H, m), 1.89 - 1.91 (2H, m), 2.94 (3H, d), 3.16 (1H, dt), 3.47 (1H, dt), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.44 (1H, s), 6.69 (1H, s), 7.44 (4H, t), 7.80 - 7.90 (5H, m), 9.70 (1H, s).

mTOR Kinase Assay (Echo): 0.00756μM

Example 37t: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.57 - 0.62 (2H, m), 0.74 - 0.79 (2H, m), 1.19 (3H, d), 1.61 - 1.63 (2H, m), 1.89 - 1.91 (2H, m), 2.90 - 2.94 (1H, m), 3.17 (1H, dt), 3.47 (1H, dt), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.45 (1H, s), 6.69 (1H, s), 7.42 (2H, t), 7.52 (2H, d), 7.83 - 7.89 (4H, m), 8.13 (1H, s), 9.47 (1H, s).

mTOR Kinase Assay (Echo): 0.00889μM

Example 37u: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (4H, d), 1.59 - 1.63 (3H, m), 1.89 - 1.91 (2H, m), 3.13 - 3.20 (1H, m), 3.43 - 3.50 (1H, m), 3.56 (4H, m), 3.60 - 3.63 (1H, m), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.44 (1H, s), 4.81 (1H, s), 6.68 (1H, s), 7.42 (2H, t), 7.53 (2H, d), 7.83 - 7.86 (1H, m), 7.88 (2H, d), 9.78 (1H, s).

mTOR Kinase Assay (Echo): 0.000395μM

Example 37v: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.58-0.62 (2H, m), 0.74-0.79 (2H, m), 1.17-1.19 (3H, d), 1.62-1.69 (2H, m), 1.88-1.93 (2H, m), 2.92 (1H, bs), 3.12-3.19 (1H, td), 3.43-3.50 (1H, td), 3.60-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.10-4.13 (1H, d), 4.41 (1H, bs), 6.67 (1H, s), 7.49-7.52 (2H, d), 7.58-7.62 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.81 (2H, d), 7.89-7.91 (2H, d), 8.10 (1H, bs), 9.47 (1H, bs).

mTOR Kinase Assay (Echo): 0.00549μM

Example 37w: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15-1.20 (3H, d), 1.60-1.70 (2H, m), 1.90-1.95 (2H, bs), 3.12-31.7 (1H, m), 3.25-3.30 (1H, m obscured by solvent peak), 3.45-3.50 (1H, m), 3.6 (1H, d), 3.7 (1H, d), 3.8 (3H, s), 4.0 (1H, m), 4.1 (1H, d), 4.40-4.45 (1H, bs), 6.7 (1H, s), 7.49-7.53 (3H, m), 7.68-7.73 (2H, m), 7.7 (1H, t), 7.8 (2H, d), 7.9 (2H, d), 8.0 (1H, bs), 9.7 (1H, bs).

mTOR Kinase Assay (Echo): 0.00137μM

Example 37x: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19 (3H, d), 1.61-1.67 (2H, m), 1.68-1.75 (2H, m), 1.88-1.93 (2H, m), 3.11-3.17 (1H, td), 3.43-3.55 (5H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.09-4.12 (1H, d), 4.40 (1H, bs), 4.53-4.54 (1H, t), 6.66 (1H, s), 7.45-7.47 (2H, d), 7.58-7.62 (2H, t), 7.70-7.75 (1H, tt), 7.79-7.81 (2H, dd), 7.86 (1H, bs), 7.89-7.92 (2H, d), 9.64 (1H, bs).

mTOR Kinase Assay (Echo): 0.00944μM

Example 37y: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19 (3H, d), 1.61-1.68 (2H, m), 1.89-1.92 (2H, m), 2.85-2.88 (2H, t), 3.11-3.19 (1H, td), 3.43-3.49 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.75 (3H, m), 3.94-3.98 (1H, dd), 4.09-4.12 (1H, d), 4.41 (1H, bs), 6.67 (1H, s), 7.42-7.45 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.81 (2H, dd), 7.90-7.93 (2H, d), 8.08-8.11 (1H, t), 9.91 (1H, s).

mTOR Kinase Assay (Echo): 0.00553μM

Example 37z: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.12-1.19 (6H, m), 1.61-1.69 (2H, m), 1.89-1.92 (2H, m), 3.11-3.19 (1H, td), 3.43-3.52 (3H, m), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.09-4.12 (1H, d), 4.40 (1H, bs), 6.66 (1H, s), 7.44-7.46 (2H, d), 7.58-

7.62 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.81 (2H, d), 7.84 (1H, bs), 7.90-7.92 (2H, d), 9.58 (1H, bs).

mTOR Kinase Assay (Echo): 0.00481μM

Example 37aa: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19 (3H, d), 1.61-1.69 (2H, m), 1.88-1.92 (2H, m), 3.11-3.19 (1H, td), 3.43-3.49 (1H, td), 3.51-3.63 (5H, m), 3.72-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.09-4.12 (1H, d), 4.40 (1H, bs), 4.82 (1H, bs), 6.66 (1H, s), 7.51-7.53 (2H, d), 7.58-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.81 (2H, d), 7.89-7.91 (3H, m), 9.83 (1H, bs).

mTOR Kinase Assay (Echo): 0.00567μM

Example 37ab: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19 (3H, d), 1.61-1.68 (2H, m), 1.88-1.92 (2H, m), 2.94-2.95 (3H, d), 3.11-3.17 (1H, td), 3.44-3.49 (1H, td), 3.58-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.08-4.12 (1H, d), 4.41 (1H, bs), 6.67 (1H, s), 7.43-7.45 (2H, d), 7.58-7.62 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.81 (3H, m), 7.90-7.92 (2H, d), 9.70 (1H, bs).

mTOR Kinase Assay (Echo): 0.003μM

Example 37ac: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17-1.19 (3H, d), 1.62-1.69 (2H, m), 1.90-1.93 (2H, m), 3.12-3.18 (1H, td), 3.43-3.50 (1H, td), 3.59-3.63 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.09-4.13 (1H, d), 4.41 (1H, bs), 4.71-4.72 (2H, d), 6.67 (1H, s), 7.00 (2H, bs), 7.56-7.62 (4H, m), 7.70-7.74 (1H, tt), 7.79-7.81 (2H, dd), 7.91-7.93 (2H, d), 8.17 (1H, bs), 9.98 (1H, bs), 11.98 (1H, bs).

mTOR Kinase Assay (Echo): 0.0298μM

Example 37ad: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.70 (2H, q), 1.98 (2H, q), 3.10-3.20 (1H, td), 3.40-3.50 (1H, td), 3.50-3.58 (4H, m), 3.58 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.50 (1H, br s), 4.80 (1H, br s), 6.70 (1H, s), 7.50 (2H, d), 7.74-7.77 (4H, m), 7.82 (1H, s), 8.87 (2H, dd), 9.75 (1H, s)

Example 37ae: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ δ 0.60 (2H, q), 0.77 (2H, q), 1.20 (3H, d), 1.70 (2H, q), 1.98 (2H, q), 2.85-2.95 (1H, m), 3.19 (1H, td), 3.47 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.17 (1H, d), 4.48 (1H, br s), 6.71 (1H, s), 7.49 (2H, d), 7.72 (2H, d), 7.78 (2H, dd), 8.15 (1H, br s), 8.87 (2H, dd), 9.46 (1H, br s)

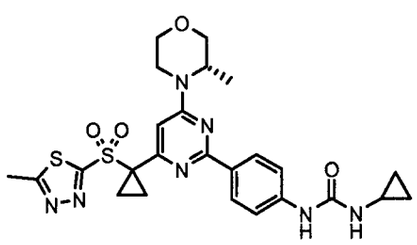
Example 37af: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.70 (2H, q), 1.98 (2H, q), 2.94 (3H, d), 3.17 (1H, td), 3.46 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.10-

4.20 (1H, d), 4.50 (1H, br s), 6.71 (1H, s), 7.43 (2H, d), 7.74-7.76 (2H, d), 7.77-7.79 (2H, dd), 7.82 (1H, m), 8.87 (2H, dd), 9.70 (1H, br s).

Example 37ag: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.45 (6H, s), 1.65 (2H, m), 1.90 (2H, m), 3.14 (1H, m), 3.46 (1H, m), 3.58 (3H, m), 3.75 (1H, m), 3.96 (1H, m), 4.11 (1H, m), 4.41 (1H, m), 6.67 (1H, s), 7.39 (1H, m), 7.50 (2H, m), 7.60 (2H, m), 7.75 (3H, m), 7.88 (2H, m)

The preparations of the anilines required for **Examples 37a – 37ag** have been described earlier.

Example 38: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea



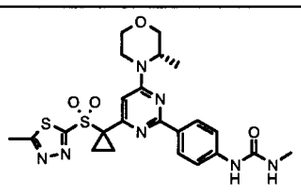
Cyclopropylamine (84 mg, 1.48 mmol) was added to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate (175 mg, 0.30 mmol) and triethylamine (0.205 mL, 1.48 mmol) in NMP (2 mL) at RT and the reaction was allowed to stir for 2 hours. The mixture was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a cream solid (112 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.37 - 0.45 (2H, m), 0.61 - 0.68 (2H, m), 1.21 (3H, d), 1.78 - 1.88 (2H, m), 1.97 - 2.05 (2H, m), 2.83 (3H, s), 3.12 - 3.23 (1H, m), 3.42 - 3.52 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.20 (1H, s), 4.52 (1H, s), 6.46 (1H, t), 6.77 (1H, s), 7.42 (2H, d), 7.74 (2H, d), 8.57 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 556; HPLC tR = 2.25 min.

mTOR Kinase Assay (Echo): 0.00131μM

The following compounds were made in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

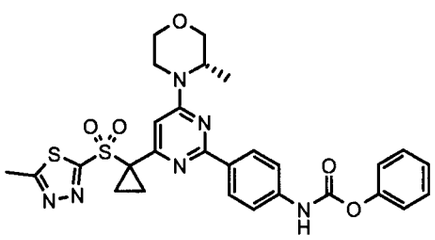
Example	Structure	NAME	LCMS MH+	Retention time (min)
38a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	530	209

Example 38a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.82 - 1.85 (2H, m), 1.98 - 2.04 (2H, m), 2.66 (3H, s), 2.82 (3H, s), 3.13 - 3.25 (1H, m), 3.40 - 3.47 (1H, m), 3.61 (1H, d), 3.76 (1H, d), 3.96 (1H, d), 4.21 (1H, s), 6.08 (1H, t), 6.77 (1H, s), 7.42 (2H, d), 7.74 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.000918μM

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]carbamate



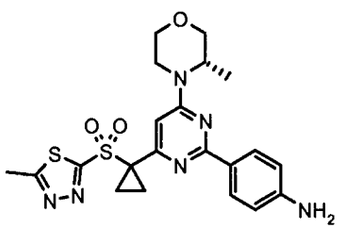
Phenyl chloroformate (0.398 mL, 3.17 mmol) was added slowly to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]aniline (1.25 g, 2.65 mmol) and sodium hydrogen carbonate (0.333 g, 3.97 mmol) in dioxane (30 mL) at 5°C under an atmosphere of nitrogen. The resulting mixture was stirred at

RT for 18 hours then the mixture diluted with ethyl actate (125 mL), and washed sequentially with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The crude material was triturated with diethyl ether and isohexane to give a solid which was collected by filtration and dried under vacuum to give the desired material as a cream solid (1.24 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.82 - 1.88 (2H, m), 2.00 - 2.05 (2H, m), 2.82 (3H, s), 3.20 (1H, dd), 3.42 - 3.50 (1H, m), 3.60 (1H, d), 3.76 (1H, d), 4.00 (1H, d), 4.23 (1H, s), 4.53 (1H, s), 6.81 (1H, s), 7.22 - 7.34 (3H, m), 7.40 - 7.50 (2H, m), 7.55 (2H, d), 7.84 (2H, d), 10.46 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 593; HPLC tR = 2.81 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]aniline



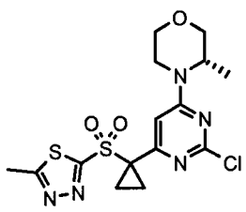
Bis(triphenylphosphine)palladium(II) chloride (0.164 g, 0.23 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidine (1.45 g, 3.49 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.146 g, 5.23 mmol) and aqueous sodium carbonate solution (3 mL, 6.00 mmol) in a solvent mixture of DMF (10 mL), DME (2 mL), water (2 mL) and ethanol (2 mL). The atmosphere was replaced with nitrogen and the reaction stirred at 90°C for 18 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with saturated brine (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 80% ethyl acetate in isohexane, to give the desired material as a beige solid (1.25 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.78 - 1.83 (2H, m), 1.98 - 2.01 (2H, m), 2.83 (3H, s), 3.10 - 3.21 (1H, m), 3.38 - 3.51 (1H, m), 3.60 (1H, d), 3.74

(1H, d), 3.95 (1H, d), 4.16 (1H, s), 4.48 (1H, s), 5.59 (2H, s), 6.51 (2H, d), 6.66 (1H, s), 7.57 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 473; HPLC tR = 2.14 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]cyclopropyl]pyrimidine

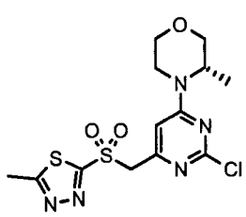


An aqueous solution of sodium hydroxide (20 mL, 532.5 mmol) was added to a stirred mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonylmethyl]pyrimidine (1.8 g, 4.62 mmol), 1,2-dibromoethane (1.99 ml, 23.08 mmol) and tetraethylammonium bromide (0.097 g, 0.46 mmol) in DCM (40 mL) at RT. The resulting mixture was stirred at RT for 24 hours then the mixture diluted with DCM (50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was chromatographed on silica, elution gradient 10 to 60% ethyl acetate in isohexane, to give the desired material as a yellow gum (1.48 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.79 - 1.84 (2H, m), 1.94 - 2.01 (2H, m), 2.87 (3H, s), 3.17 - 3.23 (1H, m), 3.37 - 3.46 (1H, m), 3.55 (1H, dd), 3.71 (1H, d), 3.92 (1H, dd), 4.06 (1H, s), 4.33 (1H, s), 6.87 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 416; HPLC tR = 1.98 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonylmethyl]pyrimidine



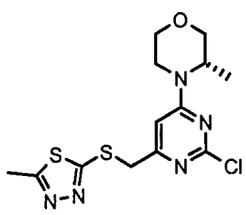
3-Chloroperoxybenzoic acid (4.77 g, 27.66 mmol) was added portionwise to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanylmethyl]pyrimidine (3.3

g, 9.22 mmol), in DCM (70 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 2 hours then diluted with ethyl acetate (250 mL), and washed sequentially with a 10% aqueous solution of sodium metabisulphite (100 mL) and 2M sodium carbonate (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give the desired material as a white solid (2.22 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (4H, d), 2.87 (4H, s), 3.15 - 3.26 (1H, m), 3.44 (1H, td), 3.59 (1H, d), 3.73 (1H, d), 3.94 (2H, m), 4.22 (1H, s), 5.03 (2H, s), 6.92 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 390; HPLC tR = 1.83 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanylmethyl]pyrimidine

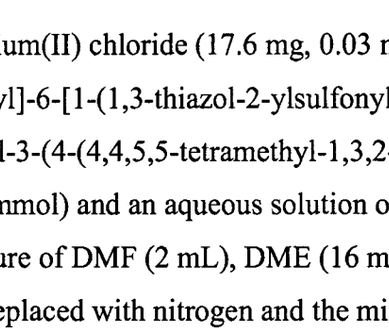


DIPEA (2.94 mL, 16.97 mmol) was added to 5-methyl-1,3,4-thiadiazole-2-thiol (1.645 g, 12.44 mmol), in acetonitrile (40 mL) at RT under an atmosphere of nitrogen. The resulting solution was stirred at RT for 20 minutes then 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4 g, 11.31 mmol) was added. The resulting mixture was stirred at RT for 1 hour then then mixture diluted with ethyl acetate (300 mL), and washed with water (150 mL).The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 0 to 2% methanol in ethyl acetate, to give the desired material as a white solid (3.30 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 6.90 (1H, s), 1.17 (3H, d), 2.68 (3H, s), 3.12 - 3.22 (1H, m), 3.42 (1H, td), 3.57 (1H, dd), 3.71 (1H, d), 3.86 - 4.04 (2H, m), 4.27 (1H, s), 4.42 (2H, s)

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

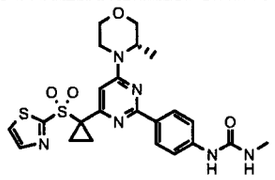
Example 39: 3-Cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea



Bis(triphenylphosphine)palladium(II) chloride (17.6 mg, 0.03 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine (150 mg, 0.37 mmol), 1-cyclopropyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (170 mg, 0.56 mmol) and an aqueous solution of sodium carbonate (5 mL, 10.00 mmol) in a solvent mixture of DMF (2 mL), DME (16 mL), water (2 mL) and ethanol (2 mL). The atmosphere was replaced with nitrogen and the mixture stirred at 90°C for 18 hours. The mixture was allowed to cool and diluted with ethyl acetate (200 mL) and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 0 to 4% methanol in ethyl acetate. The crude material was further purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material (30 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.37 - 0.45 (2H, m), 0.60 - 0.67 (2H, m), 1.19 (3H, d), 1.76 - 1.82 (2H, m), 1.95 - 2.02 (2H, m), 3.12 - 3.21 (1H, m), 3.45 (1H, d), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.18 (1H, s), 4.44 (1H, s), 6.45 (1H, s), 6.73 (1H, s), 7.41 (2H, d), 7.83 (2H, d), 8.24 (1H, s), 8.28 (1H, s), 8.54 (1H, s)

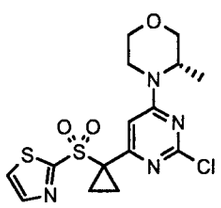
The following compound was made in an analogous fashion from 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
39a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	515	2.05

Example 39a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.76 - 1.81 (2H, m), 1.96 - 2.01 (2H, m), 2.66 (3H, d), 3.11 - 3.22 (1H, m), 3.42 - 3.49 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.17 (1H, s), 4.44 (1H, s), 6.07 (1H, q), 6.73 (1H, s), 7.40 (2H, d), 7.82 (2H, d), 8.24 (1H, d), 8.28 (1H, d), 8.75 (1H, s)

The preparation of 2-chloro-4-[(*3S)*-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine is described below.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine

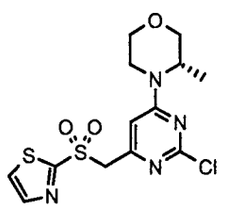


An aqueous solution of sodium hydroxide (0.235 mL, 6.27 mmol) was added to a stirred mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfonylmethyl)pyrimidine (2.35 g, 6.27 mmol), 1,2-dibromoethane (2.70 mL, 31.34 mmol) and tetraethylammonium bromide (0.132 g, 0.63 mmol) in toluene at RT. The resulting mixture was stirred at 70°C for 2 hours then was diluted with ethyl acetate (150 mL), and washed with water (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (2.45 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (4H, d), 1.69 - 1.75 (2H, m), 1.91 - 1.96 (2H, m), 3.12 - 3.21 (1H, m), 3.40 (1H, d), 3.55 (1H, d), 3.70 (1H, d), 3.92 (1H, d), 4.00 (1H, s), 4.27 (1H, s), 6.84 (1H, s), 8.20 (1H, d), 8.33 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 401; HPLC tR = 2.04 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfonylmethyl)pyrimidine

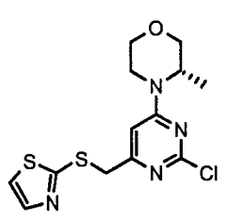


3-Chloroperoxybenzoic acid (6.04 g, 35.00 mmol) was added portionwise to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfanylmethyl)pyrimidine (4 g, 11.67 mmol), in DCM (10 mL) at RT under an atmosphere of nitrogen. The resulting solution was stirred at RT for 3 hours. The reaction mixture was diluted with ethyl acetate (250 mL), and washed with a 10% aqueous solution sodium metabisulphite (100 mL) and a saturated aqueous solution of sodium carbonate (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give the desired material as a white solid (2.85 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 8.33 (1H, d), 1.18 (4H, d), 3.14 - 3.25 (1H, m), 3.43 (1H, dd), 3.58 (1H, d), 3.72 (1H, d), 3.88 - 4.01 (2H, m), 4.20 (1H, s), 4.87 (2H, s), 6.82 (1H, s), 8.24 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 375; HPLC tR = 1.86 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfanylmethyl)pyrimidine



DIPEA (2.94 mL, 16.97 mmol) was added to 2-mercaptothiazole (1.458 g, 12.44 mmol), in acetonitrile (40 mL) at RT under an atmosphere of nitrogen. The resulting solution was stirred

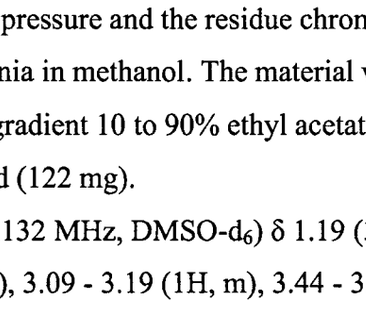
at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4 g, 11.31 mmol) was added and the mixture stirred for 1 hour. The reaction mixture was diluted with ethyl acetate (300 mL), and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 80% ethyl acetate in isohexane, to give the desired material as a colourless gum (3.77 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (5H, d), 3.15 (1H, td), 3.41 (2H, td), 3.56 (1H, dd), 3.70 (1H, d), 3.91 (2H, m), 4.25 (1H, s), 4.36 (2H, s), 6.84 (1H, s), 7.70 (1H, d), 7.76 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 343; HPLC tR = 2.07 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 40: 1-[4-[4-[1-(1*H*-Imidazol-2-ylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



Anisole (0.159 mL, 1.46 mmol) was added to 1-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea (180 mg, 0.29 mmol) in TFA (8 mL) at RT under an atmosphere of nitrogen. The resulting solution was stirred at 60°C for 90 minutes then the solvent removed under reduced pressure and the residue chromatographed on an SCX column, eluting with 7M ammonia in methanol. The material was further purified by flash silica chromatography, elution gradient 10 to 90% ethyl acetate in isohexane, to give the desired material as a cream solid (122 mg).

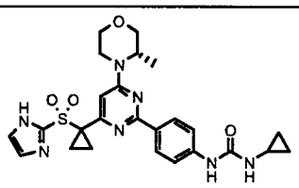
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.68 - 1.74 (2H, m), 1.91 - 1.98 (2H, m), 2.66 (3H, s), 3.09 - 3.19 (1H, m), 3.44 - 3.50 (1H, m), 3.61 (1H, d), 3.76

(1H, d), 3.97 (1H, d), 4.13 (1H, s), 4.40 (1H, s), 6.05 (1H, s), 6.64 (1H, s), 7.35 (2H, s), 7.43 (2H, d), 8.00 (2H, d), 8.71 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 493; HPLC tR = 1.33 min.

mTOR Kinase Assay (Echo): 0.00436μM

The following compound was made in an analogous fashion from 3-cyclopropyl-1-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea.

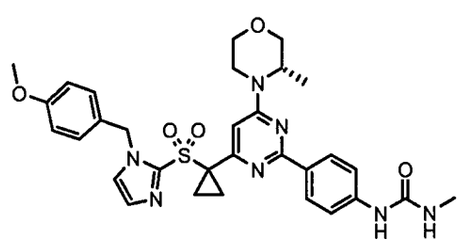
Example	Structure	NAME	LCMS MH+	Retention time (min)
40a		3-cyclopropyl-1-[4-[4-[1-(1H-imidazol-2-ylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	524	1.56

Example 40a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.38 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.19 (3H, d), 1.67 - 1.75 (2H, m), 1.89 - 1.99 (2H, m), 2.51 - 2.57 (1H, m), 3.11 - 3.22 (1H, m), 3.39 - 3.52 (1H, m), 3.61 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.11 (1H, d), 4.39 (1H, s), 6.41 (1H, s), 6.65 (1H, s), 7.36 (2H, s), 7.44 (2H, d), 8.00 (2H, d), 8.50 (1H, s) 13.5(1H,s).

mTOR Kinase Assay (Echo): 0.00649μM

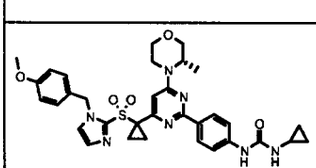
The preparation of 1-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylureais described below.

1-[4-[4-[1-[1-[(4-Methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



Triethylamine (0.246 mL, 1.76 mmol) was added to phenyl *N*-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (240 mg, 0.35 mmol) and methylamine (0.705 mL, 1.41 mmol) in DMF (3 mL) at RT. The resulting solution was stirred at 40°C for 30 minutes then at RT overnight. The mixture was concentrated *in vacuo* and chromatographed on silica, elution gradient 100 % ethyl acetate, to give the desired material as a cream solid (190 mg).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.68 - 1.72 (2H, m), 1.88 - 1.95 (2H, m), 2.67 (3H, d), 3.07 - 3.20 (1H, m), 3.36 - 3.51 (1H, m), 3.57 (1H, d), 3.68 - 3.79 (4H, m), 3.94 (1H, d), 4.06 (1H, s), 4.35 (1H, s), 5.21 (2H, s), 6.05 (1H, t), 6.55 (1H, s), 6.77 (2H, d), 7.05 (2H, d), 7.23 (1H, s), 7.41 - 7.48 (3H, m), 8.02 (2H, d), 8.72 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 618; HPLC tR = 2.17 min

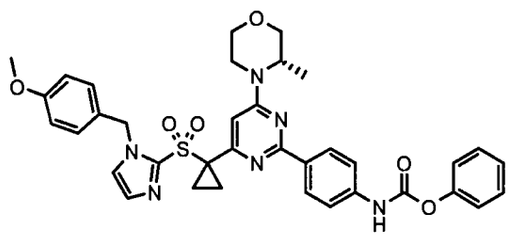
3-Cyclopropyl-1-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]ureawas made in an analogous fashion from phenyl *N*-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Structure	NAME	LCMS MH+	Retention time (min)
	3-cyclopropyl-1-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	644	2.32

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.38 - 0.45 (2H, m), 0.60 - 0.69 (2H, m), 1.14 (3H, d), 1.66 - 1.74 (2H, m), 1.88 - 1.94 (2H, m), 2.53 - 2.62 (1H, m), 3.09 - 3.18 (1H, m), 3.39 - 3.48 (1H, m), 3.57 (1H, d), 3.66 - 3.78 (4H, m), 3.95 (1H, d), 4.11 (1H, s), 4.35 (1H, s), 5.21 (2H, s), 6.43 (1H, s), 6.55 (1H, s), 6.77 (2H, d), 7.06 (2H, d), 7.23 (1H, s), 7.42 - 7.49 (3H, m), 8.02 (2H, d), 8.52 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

Phenyl N-[4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

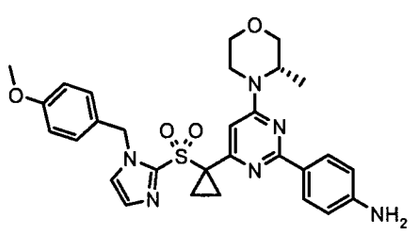


Phenyl chloroformate (0.202 mL, 1.61 mmol) was added to 4-[4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (600 mg, 1.07 mmol) and sodium hydrogen carbonate (135 mg, 1.61 mmol) in dioxane (10 mL) at 5°C under nitrogen. The resulting mixture was stirred at RT for 90 minutes. The reaction mixture was diluted with ethyl acetate (150 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid which was collected by filtration and dried under vacuum (570 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.67 - 1.74 (2H, m), 1.90 - 1.95 (2H, m), 3.03 - 3.21 (1H, m), 3.36 - 3.47 (1H, m), 3.53 - 3.62 (1H, m), 3.64 - 3.76 (4H, m), 3.95 (1H, d), 4.10 (1H, s), 4.37 (1H, s), 5.23 (2H, s), 6.60 (1H, s), 6.77 (2H, d), 7.06 (2H, d), 7.23 - 7.33 (4H, m), 7.42 - 7.50 (3H, m), 7.59 (2H, d), 8.11 (2H, d), 10.41 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 682; HPLC tR = 2.88 min

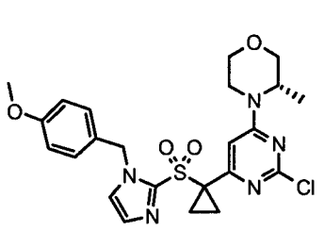
4-[4-[1-[1-[(4-Methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Bis(triphenylphosphine)palladium(II) chloride (42.5 mg, 0.06 mmol) was added to 2-chloro-4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (610 mg, 1.21 mmol), 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (530 mg, 2.42 mmol) and an aqueous solution of sodium carbonate (2 mL, 4.00 mmol) in a solvent mixture of DMF (2 mL), DME (4 mL), water (0.5 mL) and ethanol (0.5 mL) at RT. The atmosphere was replaced with nitrogen and the mixture stirred at 90°C for 5 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give the desired material as a white solid (600 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (3H, d), 1.65 - 1.69 (2H, m), 1.88 - 1.92 (2H, m), 3.04 - 3.15 (1H, m), 3.41 (1H, td), 3.56 (1H, d), 3.67 - 3.75 (4H, m), 3.93 (1H, d), 4.06 (1H, s), 4.31 (1H, s), 5.16 (2H, s), 5.54 (2H, s), 6.44 (1H, s), 6.57 (2H, d), 6.79 (2H, d), 7.06 (2H, d), 7.22 (1H, s), 7.43 (1H, s), 7.87 (2H, d)

2-Chloro-4-[1-[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



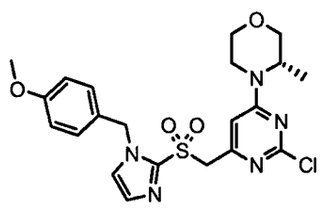
An aqueous solution of sodium hydroxide (10 mL, 186.4 mmol) was added to 2-chloro-4-[[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.1 g, 2.30 mmol), tetraethylammonium bromide (0.097 g, 0.46 mmol), and

1,2-dibromoethane (2.38 mL, 27.62 mmol) in DCM (20 mL) at RT under a nitrogen atmosphere. The reaction was stirred at RT for 4 hours. The reaction mixture was diluted with DCM (50 mL), the phases separated and the organic layer dried (Na_2SO_4), filtered and evaporated. The residue was purified by flash silica chromatography, elution gradient 10 to 75% ethyl acetate in isohexane, to give the desired material as a white solid (0.77 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10 (4H, d), 1.64 (3H, m), 1.85 - 1.89 (2H, m), 3.03 - 3.15 (1H, m), 3.33 - 3.42 (1H, m), 3.50 (1H, d), 3.68 (1H, d), 3.74 (3H, s), 3.87 - 3.93 (2H, m), 4.06 (1H, s), 5.33 (2H, s), 6.57 (1H, s), 6.87 (2H, d), 7.17 (2H, d), 7.22 (1H, s), 7.59 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 504; HPLC tR = 2.35 min

2-Chloro-4-[[1-[(4-methoxyphenyl)methyl]imidazol-2-yl]sulfonylmethyl]-6-[(3I)-3-methylmorpholin-4-yl]pyrimidine

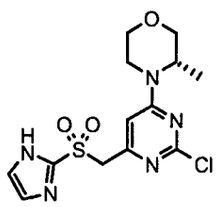


4-Methoxybenzyl chloride (0.470 mL, 3.46 mmol) was added to 2-chloro-4-(1*H*-imidazol-2-ylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.18 g, 3.30 mmol) and potassium carbonate (0.501 g, 3.63 mmol) in DMF (30 mL) at RT under a nitrogen atmosphere. The resulting mixture was stirred at 75°C for 1 hour then allowed to cool and diluted with ethyl acetate (100 mL). The mixture was washed with water (2 x 50 mL), the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give the desired material as a colourless gum (1.27 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 3.10 - 3.19 (1H, m), 3.35 - 3.45 (1H, m), 3.54 (1H, d), 3.70 (1H, d), 3.74 (3H, s), 3.87 - 3.96 (2H, m), 4.14 (1H, s), 4.68 (2H, s), 5.36 (2H, s), 6.55 (1H, s), 6.88 (2H, d), 7.15 - 7.28 (3H, m), 7.57 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 478; HPLC tR = 2.26 min

2-Chloro-4-(1*H*-imidazol-2-ylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

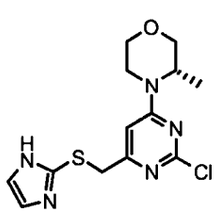


3-Chloroperoxybenzoic acid (2.62 g, 15.19 mmol) was added to 2-chloro-4-(1*H*-imidazol-2-ylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.25 g, 6.91 mmol) in DCM (100 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 2 hours. The reaction mixture was diluted with DCM (100 mL), and washed sequentially with an aqueous 10% solution of sodium metabisulphite (200 mL), and a saturated solution of sodium hydrogen carbonate (200 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid that was collected by filtration and dried under vacuum (1.8 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 3.06 - 3.21 (1H, m), 3.35 - 3.46 (1H, m), 3.55 (1H, d), 3.71 (1H, d), 3.83 - 3.97 (2H, m), 4.16 (1H, s), 4.66 (2H, s), 6.52 (1H, s), 7.35 (2H, s), 13.65(1H,s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 358; HPLC tR = 0.87 min

2-Chloro-4-(1*H*-imidazol-2-ylsulfanylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



DIPEA (2.94 mL, 16.97 mmol) was added to 1*H*-imidazole-2-thiol (1.246 g, 12.44 mmol), in acetonitrile (50 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 20 minutes. 2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4 g, 11.31 mmol) was added and the mixture stirred for 1 hour. The reaction mixture was diluted with ethyl acetate (300 mL), and washed with water (150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was

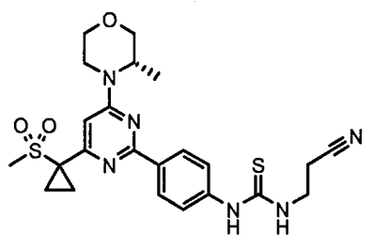
purified by flash silica chromatography, elution gradient 0 to 4% methanol in ethyl acetate, to give the desired material as a white solid (2.80 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 3.11 (1H, dd), 3.34 - 3.45 (1H, m), 3.54 (1H, dd), 3.69 (1H, d), 3.87 - 3.95 (2H, m), 4.06 (2H, s), 4.17 (1H, s), 6.52 (1H, s), 6.96 (1H, s), 7.17 (1H, s), 12.35 (1H,s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 326; HPLC tR = 1.41 min

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 41: 3-(2-Cyanoethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea



A solution of 1,1'-thiocarbonyldiimidazole (50 mg, 0.28 mmol) in DCM (1 mL) was added to a suspension of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (75 mg, 0.19 mmol) in DCM (2 mL) and THF (1 mL). The reaction mixture was stirred at RT for 1 hour before addition of 3-aminopropionitrile (91 mg, 1.30 mmol) and triethylamine (0.026 mL, 0.19 mmol). Stirring was continued at RT overnight. The reaction was incomplete and significant insoluble material was observed so DMF (1 mL) was added and stirring continued for a further 1 hour. The reaction was still incomplete, so the reaction mixture was transferred to a microwave tube, sealed, heated to 100°C in the microwave reactor and held for 10 minutes. The reaction was still incomplete, so further 3-aminopropionitrile (91 mg, 1.30 mmol) was added and the reaction mixture stirred at RT for 2-3 hours. The reaction mixture was evaporated and residue purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents, to give the desired material as a white solid (29 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.58 (2H, m), 1.67 - 1.69 (2H, m), 2.87 (2H, t), 3.19 - 3.26 (1H, m), 3.27 (3H, s), 3.49 (1H, td), 3.64 (1H,

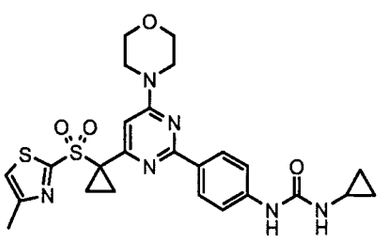
dd), 3.74 - 3.78 (3H, m), 3.98 (1H, dd), 4.18 - 4.25 (1H, m), 4.56 - 4.63 (1H, m), 6.82 (1H, s), 7.57 (2H, d), 8.16 (1H, s), 8.26 - 8.30 (2H, m), 9.98 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 501; HPLC tR = 1.99 min

mTOR Kinase Assay (Echo): 0.0308μM

The preparation of 4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline was described previously.

Example 42: 3-Cyclopropyl-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea



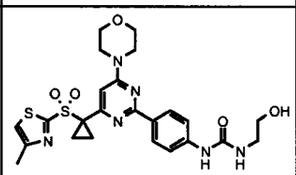
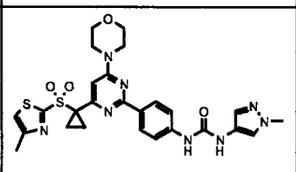
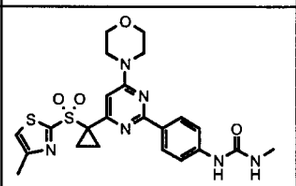
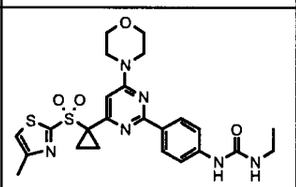
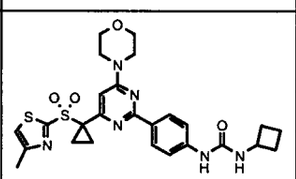
Triethylamine (0.119 mL, 0.85mmol) was added to a solution of phenyl *N*-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) and cyclopropylamine (0.059 mL, 0.85 mmol) in NMP (2 mL) and the resulting solution stirred at ambient temperature for 18 hours. The crude product was purified by preparative HPLC to give the desired material as a white solid (80 mg).

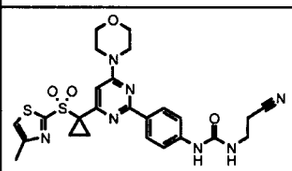
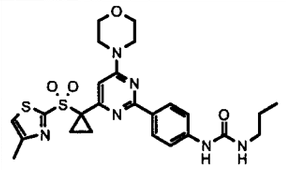
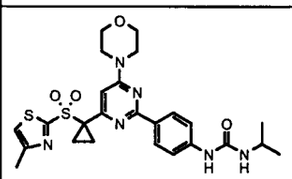
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.49 (3H, s), 2.54 - 2.58 (1H, m), 3.70 (8H, s), 6.40 (1H, s), 6.82 (1H, s), 7.42 (2H, d), 7.84 (1H, s), 7.87 (2H, d), 8.52 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 541; HPLC tR = 2.15min.

mTOR Kinase Assay (Echo): 0.000705μM

The compounds below were prepared in an analogous fashion using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
42a		3-(2-hydroxyethyl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	545	1.79
42b		3-(1-methylpyrazol-4-yl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	581	2.01
42c		3-methyl-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	515	1.96
42d		1-ethyl-3-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	529	2.14
42e		3-cyclobutyl-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	555	1.95

Example	Structure	NAME	LCMS MH+	Retention time (min)
42f		3-(2-cyanoethyl)-1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	554	1.63
42g		3-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-1-propylurea	543	2.13
42h		1-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-propan-2-ylurea	543	2.13

Example 42a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.48 (3H, s), 3.15 - 3.20 (2H, m), 3.44 - 3.48 (2H, m), 3.70 (8H, s), 4.72 (1H, t), 6.23 (1H, t), 6.82 (1H, s), 7.40 (2H, d), 7.84 (1H, s), 7.87 (2H, d), 8.78 (1H, s).

mTOR Kinase Assay (Echo): 0.00261μM

Example 42b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.75 - 1.79 (2H, m), 1.94 - 1.98 (2H, m), 2.50 (3H, s), 3.70 (8H, s), 3.79 (3H, s), 6.83 (1H, s), 7.38 (1H, s), 7.46 (2H, d), 7.77 (1H, s), 7.85 (1H, s), 7.90 (2H, d), 8.36 (1H, s), 8.82 (1H, s).

Example 42c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.49 (3H, s), 2.66 (3H, d), 3.70 (8H, s), 6.04 (1H, q), 6.82 (1H, s), 7.41 (2H, d), 7.84 (1H, s), 7.86 (2H, d), 8.72 (1H, s).

mTOR Kinase Assay (Echo): 0.0036μM

Example 42d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.49 (3H, s), 3.09 - 3.16 (2H, m), 3.70 (8H, s), 6.14 (1H, t), 6.82 (1H, s), 7.41 (2H, d), 7.84 (1H, s), 7.86 (2H, d), 8.64 (1H, s).

mTOR Kinase Assay (Echo): 0.000425μM

Example 42e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.57 - 1.66 (2H, m), 1.75 - 1.78 (2H, m), 1.81 - 1.91 (2H, m), 1.94 - 1.97 (2H, m), 2.18 - 2.25 (2H, m), 2.48 (3H, s), 3.70 (8H, s), 4.09 - 4.19 (1H, m), 6.43 (1H, d), 6.82 (1H, s), 7.39 (2H, d), 7.84 (1H, s), 7.86 (2H, d), 8.54 (1H, s).

mTOR Kinase Assay (Echo): 0.00257μM

Example 42f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.49 (3H, s), 2.70 (2H, t), 3.34 - 3.39 (2H, m), 3.70 (8H, s), 6.52 (1H, t), 6.83 (1H, s), 7.43 (2H, d), 7.84 (1H, s), 7.88 (2H, d), 8.92 (1H, s).

mTOR Kinase Assay (Echo): 0.00264μM

Example 42g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.41 - 1.50 (2H, m), 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.49 (3H, s), 3.04 - 3.09 (2H, m), 3.70 (8H, s), 6.18 (1H, t), 6.82 (1H, s), 7.40 (2H, d), 7.84 (1H, s), 7.86 (2H, d), 8.63 (1H, s).

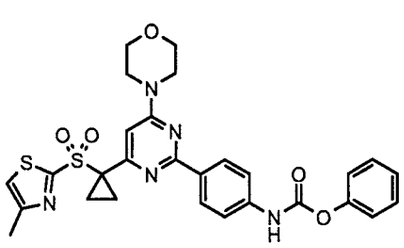
mTOR Kinase Assay (Echo): 0.00401μM

Example 42h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, d), 1.75 - 1.78 (2H, m), 1.94 - 1.97 (2H, m), 2.48 (3H, s), 3.70 (8H, s), 3.73 - 3.81 (1H, m), 6.03 (1H, d), 6.82 (1H, s), 7.39 (2H, d), 7.84 (1H, s), 7.86 (2H, d), 8.51 (1H, s).

mTOR Kinase Assay (Echo): 0.00412μM

The preparation of phenyl *N*-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate



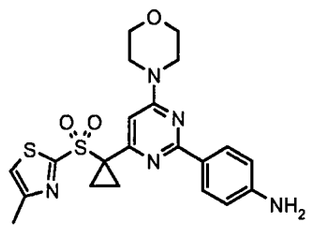
Phenyl chloroformate (0.664 mL, 5.29 mmol) was added to 4-[4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline (2.2 g, 4.81 mmol) and sodium hydrogen carbonate (0.606 g, 7.21 mmol) in dioxane (100 mL) at 10°C under a

nitrogen atmosphere. The resulting mixture was stirred at 10°C for 2 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product as a gum (2.83 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.76 - 1.80 (2H, m), 1.94 - 1.97 (2H, m), 2.48 (3H, s), 3.70 (8H, s), 6.87 (1H, s), 7.24 - 7.30 (3H, m), 7.43 - 7.47 (2H, m), 7.55 (2H, d), 7.85 (1H, s), 7.96 (2H, d), 10.45 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 578; HPLC tR = 2.88 min.

4-[4-[1-[(4-Methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline

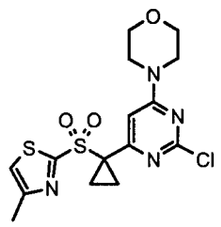


Bis(triphenylphosphine)palladium (II) chloride (0.256 g, 0.37 mmol) was added to 2-chloro-4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidine (2.93 g, 7.31 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.082 g, 9.50 mmol) and 2M aqueous sodium carbonate (13.16 mL, 26.31 mmol) in a solvent mixture of DMF (15 mL), water (37.5 mL), ethanol (15 mL) and DME (15 mL) at RT under an atmosphere of nitrogen. The resulting mixture was stirred at 80°C for 16 hours. The cooled reaction mixture was diluted with ethyl acetate (100 mL) and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as a cream solid (2.2 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.72 - 1.75 (2H, m), 1.91 - 1.94 (2H, m), 2.49 (3H, s), 3.62 - 3.71 (8H, m), 5.57 (2H, s), 6.50 (2H, d), 6.71 (1H, s), 7.68 (2H, d), 7.84 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 458; HPLC tR = 2.21min.

2-Chloro-4-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidine

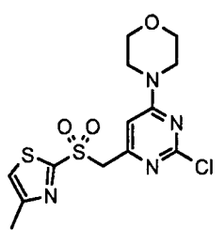


1,2-Dibromoethane (0.230 mL, 2.67 mmol) was added to 2-chloro-4-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]-6-morpholin-4-ylpyrimidine (500 mg, 1.33 mmol), 40% sodium hydroxide solution (1.3 mL,13 mmol) and tetrabutylammonium bromide (86 mg, 0.27 mmol) in toluene (10 mL) at RT. The resulting solution was stirred at 60°C for 3 hours. The cooled reaction mixture was evaporated to dryness and redissolved in ethyl acetate (50 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give the desired material as a pale brown gum (528 mg).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.76 - 1.79 (2H, m), 2.09 - 2.12 (2H, m), 2.52 (3H, s), 3.65 - 3.71 (4H, m), 3.77 - 3.79 (4H, m), 7.29 (1H, s), 7.30 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 401; HPLC tR = 2.04 min.

2-Chloro-4-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]-6-morpholin-4-ylpyrimidine



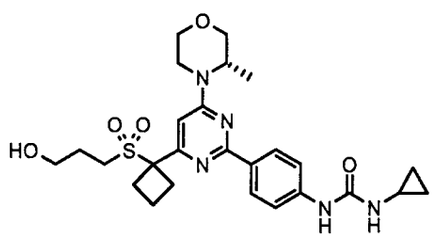
A solution of morpholine (0.994 g, 11.41 mmol) in DCM (25 mL) was added dropwise to a stirred solution of 2,4-dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (3.7 g, 11.41 mmol) and triethylamine (1.155 g, 11.41 mmol) in DCM (50 mL). The resulting solution was stirred at RT for 18 hours. The reaction mixture was washed three times with water and the organic layer dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a yellow solid (2.84 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 2.57 (3H, s), 3.58 - 3.69 (8H, m), 4.56 (2H, s), 6.58 (1H, s), 7.30 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 375; HPLC tR = 2.14 min.

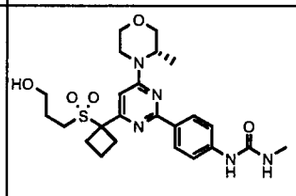
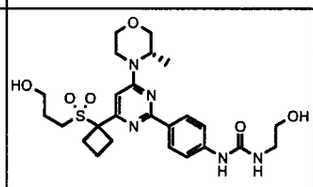
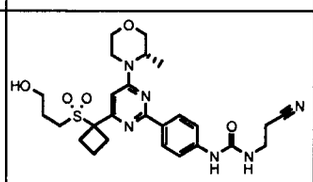
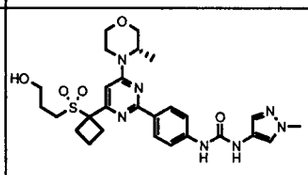
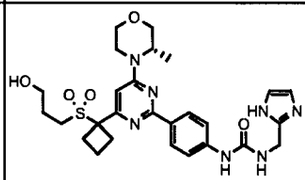
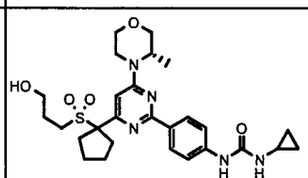
The preparation of 2,4-dichloro-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine was described previously.

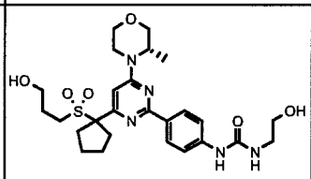
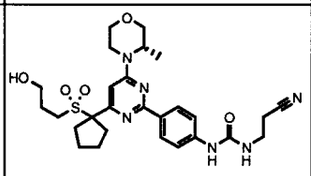
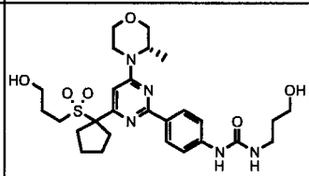
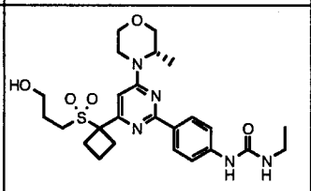
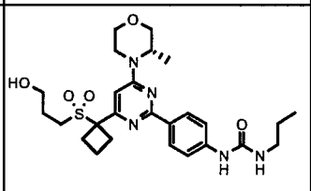
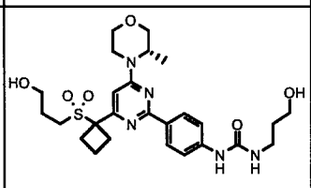
Example 43: 3-Cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

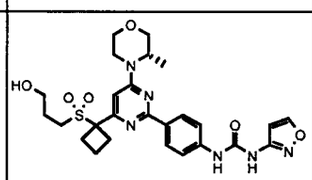
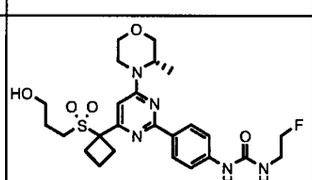
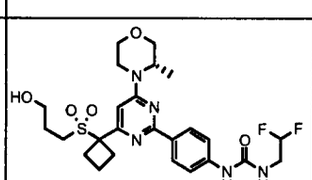
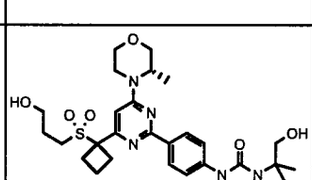
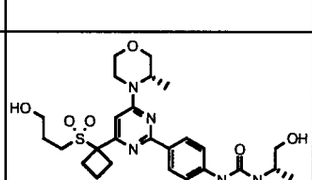
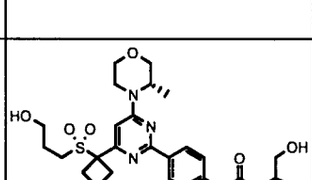


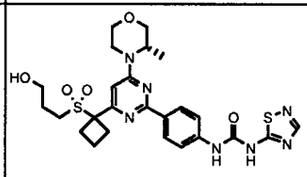
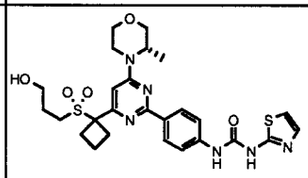
Cyclopropylamine (0.122 mL, 1.76 mmol) was added in one portion to a stirred solution of phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.2 g, 0.35 mmol) and triethylamine (0.148 mL, 1.06 mmol) in DMA (35.3 mL) at RT. The resulting solution was stirred at 50°C for 24 hours. The reaction mixture was then concentrated, and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% methanol in DCM, to give a clear oil which was then triturated with diethyl ether to give the desired material as a white solid (0.126 g).
NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.60 - 0.67 (2H, m), 0.74 - 0.83 (2H, m), 1.33 (3H, d), 1.94 - 2.01 (3H, m), 2.16 - 2.25 (2H, m), 2.57 - 2.63 (1H, m), 2.80 - 2.88 (2H, m), 2.98 - 3.01 (2H, m), 3.09 - 3.16 (2H, m), 3.28 - 3.35 (1H, m), 3.56 - 3.62 (3H, m), 3.71 - 3.75 (1H, m), 3.81 (1H, d), 4.01 - 4.05 (1H, m), 4.16 (1H, d), 4.46 (1H, d), 5.30 (1H, s), 6.55 (1H, s), 7.31 (1H, s), 7.48 (2H, d), 8.32 (2H, d).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 530; HPLC tR = 2.09 min.
mTOR Kinase Assay (Echo): 0.00539μM

The compounds below were prepared in an analogous fashion from either phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
43a		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	504	1.93
43b		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	534	1.83
43c		3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	543	2.00
43d		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	570	1.98
43e		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	570	1.93
43f		3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	544	2.21

Example	Structure	NAME	LCMS MH+	Retention time (min)
43g		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.91
43h		3-(2-cyanoethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	557	2.12
43i		3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	562	1.94
43j*		1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	518	1.89
43k*		3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylurea	532	2.04
43l*		3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.68

Example	Structure	NAME	LCMS MH+	Retention time (min)
43m*		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	557	2.04
43n*		3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	536	1.88
43o*		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	554	2.00
43p*		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	562	1.88
43q*		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.72
43r*		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.71

Example	Structure	NAME	LCMS MH+	Retention time (min)
43s*		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2,4-thiadiazol-5-yl)urea	574	1.28
43t*		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,3-thiazol-2-yl)urea	573	2.05

* The reactions were stirred in NMP at 70°C for 2.5 hours

Example 43a: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.30 (3H, d), 1.94 - 1.99 (3H, m), 2.14 - 2.23 (1H, m), 2.73 (3H, d), 2.79 - 2.90 (3H, m), 2.96 - 3.04 (2H, m), 3.06 - 3.13 (2H, m), 3.24 - 3.32 (1H, m), 3.54 - 3.59 (3H, m), 3.68 - 3.72 (1H, m), 3.78 (1H, d), 3.98 - 4.02 (1H, m), 4.10 - 4.15 (1H, m), 4.43 (1H, s), 5.49 (1H, q), 6.52 (1H, s), 7.41 (2H, d), 7.62 (1H, s), 8.29 (2H, d).

mTOR Kinase Assay (Echo): 0.00479μM

Example 43b: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.28 (3H, d), 1.90 - 2.00 (3H, m), 2.08 - 2.22 (2H, m), 2.79 - 2.88 (2H, m), 2.94 - 3.09 (4H, m), 3.24 - 3.33 (3H, m), 3.45 - 3.56 (6H, m), 3.68 (1H, d), 3.76 (1H, d), 3.98 (1H, d), 4.11 (1H, d), 4.42 (1H, s), 5.84 (1H, t), 6.50 (1H, s), 7.39 (2H, d), 7.89 (1H, s), 8.27 (2H, d).

mTOR Kinase Assay (Echo): 0.00751μM

Example 43c: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.93 - 2.04 (4H, m), 2.16 - 2.25 (1H, m), 2.55 - 2.60 (2H, m), 2.79 - 2.88 (2H, m), 2.97 - 3.06 (2H, m), 3.09 - 3.15 (2H, m), 3.26 - 3.33 (1H, m), 3.43 - 3.49 (2H, m), 3.53 - 3.63 (3H, m), 3.69 - 3.73 (1H, m), 3.79 (1H, d), 3.99 - 4.03 (1H, m), 4.15 (1H, d), 4.44 (1H, s), 5.87 (1H, t), 6.55 (1H, s), 7.42 (2H, d), 7.54 (1H, s), 8.31 (2H, d).

mTOR Kinase Assay (Echo): 0.0288μM

Example 43d: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.30 (3H, d), 1.95 - 2.01 (3H, m), 2.14 - 2.26 (1H, m), 2.78 - 2.91 (2H, m), 3.03 - 3.07 (2H, m), 3.08 - 3.15 (2H, m), 3.25 - 3.32 (1H, m), 3.39 (1H, s), 3.55 - 3.59 (3H, m), 3.67 (3H, s), 3.68 - 3.71 (1H, m), 3.78 (1H, d), 3.98 - 4.02 (1H, m), 4.11 - 4.14 (1H, m), 4.42 (1H, s), 6.53 (1H, s), 7.18 (1H, s), 7.39 (2H, d), 7.44 (1H, s), 7.55 (1H, s), 7.84 (1H, s), 8.29 (2H, d).

mTOR Kinase Assay (Echo): 0.011μM

Example 43e: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.29 (3H, d), 1.92 - 1.99 (3H, m), 2.13 - 2.20 (1H, m), 2.75 - 2.84 (2H, m), 2.96 - 3.01 (2H, m), 3.05 - 3.12 (2H, m), 3.23 - 3.30 (1H, m), 3.48 - 3.55 (4H, m), 3.69 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.11 (1H, d), 4.36 - 4.41 (3H, m), 6.51 (1H, s), 6.91 (2H, s), 7.00 (1H, t), 7.34 (2H, d), 8.23 - 8.25 (2H, m), 8.63 (1H, s).

mTOR Kinase Assay (Echo): 0.188μM

Example 43f: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.53 - 0.56 (2H, m), 0.73 - 0.76 (2H, m), 1.32 (3H, d), 1.63 - 1.66 (2H, m), 1.91 - 1.97 (4H, m), 2.57 - 2.65 (3H, m), 2.73 - 2.80 (3H, m), 3.05 - 3.11 (2H, m), 3.26 - 3.33 (1H, m), 3.55 - 3.62 (3H, m), 3.71 - 3.75 (1H, m), 3.81 (1H, d), 4.00 - 4.04 (1H, m), 4.17 (1H, d), 4.46 (1H, s), 5.81 (1H, s), 6.66 (1H, s), 7.49 (2H, d), 7.82 (1H, s), 8.31 (2H, d).

mTOR Kinase Assay (Echo): 0.0392μM

Example 43g: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.28 (3H, d), 1.58 - 1.64 (2H, m), 1.85 - 1.95 (4H, m), 2.53 - 2.63 (3H, m), 2.67 - 2.78 (3H, m), 3.12 - 3.16 (2H, m), 3.26 - 3.30 (3H, m), 3.52 - 3.58 (5H, m), 3.36 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.12 (1H, d), 4.41 (1H, s), 5.05 (1H, s), 5.90 (1H, t), 6.61 (1H, s), 7.41 (2H, d), 7.96 (1H, s), 8.29 (2H, d).

mTOR Kinase Assay (Echo): 0.029μM

Example 43h: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.31 (3H, d), 1.64 - 1.67 (3H, m), 1.92 - 1.99 (5H, m), 2.47 - 2.64 (4H, m), 2.74 - 2.79 (2H, m), 3.13 - 3.17 (2H, m), 3.26 - 3.33 (1H, m), 3.43 - 3.48 (2H, m), 3.53 - 3.63 (3H, m), 3.69 - 3.73 (1H, m), 3.79 (1H, d), 3.99 - 4.03 (1H, m), 4.15 (1H, d), 4.44 (1H, s), 5.89 (1H, t), 6.66 (1H, s), 7.42 (2H, d), 7.58 (1H, s), 8.32 (2H, d).

mTOR Kinase Assay (Echo): 0.133μM

Example 43i: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.29 (3H, d), 1.54 - 1.62 (4H, m), 1.89 - 1.99 (4H, m), 2.55 - 2.64 (2H, m), 2.70 - 2.80 (2H, d), 3.12 - 3.19 (2H, m), 3.24 - 3.29 (4H, m), 3.52 - 3.59 (5H, m), 3.68 - 3.83 (3H, m), 3.98 (1H, d), 4.11 - 4.14 (1H, m), 4.42 (1H, s), 5.75 (1H, t), 6.62 (1H, s), 7.42 (2H, d), 7.79 (1H, s), 8.29 (2H, d).

mTOR Kinase Assay (Echo): 0.102μM

Example 43j: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.72 - 1.81 (2H, m), 1.88 - 1.96 (1H, m), 1.99 - 2.10 (1H, m), 2.75 - 2.86 (2H, m), 2.90 - 2.96 (2H, m), 2.98 - 3.04 (2H, m), 3.10 - 3.16 (2H, m), 3.19 - 3.25 (1H, m), 3.35 - 3.42 (2H, m), 3.46 - 3.55 (1H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.50 - 4.62 (2H, m), 6.17 (1H, s), 6.72 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.66 (1H, s)

Example 43k: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.24 (3H, d), 1.39 - 1.50 (2H, m), 1.73 - 1.81 (2H, m), 1.86 - 1.96 (1H, m), 2.00 - 2.09 (1H, m), 2.77 - 2.87 (2H, m), 2.90 - 2.97 (2H, m), 2.97 - 3.08 (4H, m), 3.19 - 3.25 (1H, m), 3.35 - 3.41 (2H, m), 3.46 - 3.55 (1H, m), 3.65 (1H, d), 3.77 (1H, d), 3.97 (1H, d), 4.24 (1H, d), 4.53 - 4.60 (2H, m), 6.20 (1H, t), 6.71 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.65 (1H, s)

Example 43l: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 8.21 (2H, d), 1.23 (3H, d), 1.55 - 1.64 (2H, m), 1.74 - 1.80 (2H, m), 1.88 - 1.98 (1H, m), 2.01 - 2.10 (1H, m), 2.77 - 2.87 (2H, m), 2.90 - 2.97 (2H, m), 2.98 - 3.04 (2H, m), 3.13 - 3.24 (3H, m), 3.34 - 3.42 (2H, m), 3.45 - 3.54 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.47 (1H, t), 4.53 - 4.59 (2H, m), 6.20 (1H, t), 6.71 (1H, s), 7.49 (2H, d), 8.71 (1H, s)

Example 43m: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.74 - 1.81 (2H, m), 1.88 - 1.97 (1H, m), 2.01 - 2.11 (1H, m), 2.78 - 2.87 (2H, m), 2.90 - 2.99 (2H, m), 3.00 - 3.06 (2H, m), 3.19 - 3.26 (1H, m), 3.36 - 3.42 (2H, m), 3.47 - 3.56 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.99 (1H, d), 4.26 (1H, d), 4.53 - 4.61 (2H, m), 6.75 (1H, s), 6.87 (1H, s), 7.57 (2H, d), 8.30 (2H, d), 8.76 (1H, s), 9.08 (1H, s), 9.62 (1H, s)

Example 43n: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.73 - 1.81 (2H, m), 1.86 - 1.96 (1H, m), 2.01 - 2.10 (1H, m), 2.78 - 2.86 (2H, m), 2.90 - 2.98 (2H, m), 2.97 - 3.05 (2H, m), 3.13 - 3.26 (1H, m), 3.34 - 3.41 (2H, m), 3.44 - 3.55 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.42 (1H, t), 4.51 - 4.59 (2H, m), 6.43 (1H, t), 6.72 (1H, s), 7.50 (2H, d), 8.23 (2H, d), 8.81 (1H, s)

Example 43o: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.72 - 1.81 (2H, m), 1.88 - 1.96 (1H, m), 2.02 - 2.10 (1H, m), 2.78 - 2.87 (2H, m), 2.91 - 2.98 (2H, m), 2.98 - 3.05 (2H, m), 3.17 - 3.26 (1H, m), 3.35 - 3.43 (2H, m), 3.47 - 3.60 (3H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.53 - 4.60 (2H, m), 5.91 - 6.27 (1H, m), 6.54 (1H, t), 6.73 (1H, s), 7.51 (2H, d), 8.24 (2H, d), 8.93 (1H, s)

Example 43p: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.71 - 1.81 (2H, m), 1.86 - 1.96 (1H, m), 2.02 - 2.11 (1H, m), 2.75 - 2.88 (2H, m), 2.91 - 2.98 (2H, m), 2.99 - 3.05 (2H, m), 3.17 - 3.26 (1H, m), 3.27 - 3.31 (2H, m), 3.35 - 3.42 (2H, m), 3.47 - 3.54 (1H, m), 3.65 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.51 - 4.60 (2H, m), 4.95 (1H, t), 6.00 (1H, s), 6.71 (1H, s), 7.45 (2H, d), 8.20 (2H, d), 8.73 (1H, s)

Example 43q: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.23 (3H, d), 1.72 - 1.82 (2H, m), 1.89 - 1.95 (1H, m), 2.02 - 2.09 (1H, m), 2.75 - 2.85 (2H, m), 2.90 - 2.97 (2H, m), 2.97 - 3.06 (2H, m), 3.17 - 3.25 (1H, m), 3.33 - 3.41 (2H, m), 3.48 - 3.56 (1H, m), 3.63 - 3.79 (4H, m), 3.98 (1H, d), 4.24 (1H, d), 4.51 - 4.59 (2H, m), 4.78 (1H, t), 6.10 (1H, t), 6.72 (1H, s), 7.47 (2H, d), 8.22 (2H, d), 8.71 (1H, s)

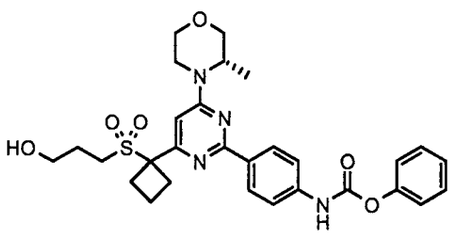
Example 43r: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.29 (3H, d), 1.78 - 1.88 (2H, m), 1.94 - 2.03 (1H, m), 2.07 - 2.16 (1H, m), 2.81 - 2.93 (2H, m), 2.96 - 3.03 (2H, m), 3.03 - 3.10 (2H, m), 3.23 - 3.32 (1H, m), 3.38 - 3.48 (3H, m), 3.53 - 3.61 (1H, m), 3.68 - 3.84 (4H, m), 4.03 (1H, d), 4.30 (1H, d), 4.58 - 4.65 (2H, m), 4.83 (1H, t), 6.15 (1H, t), 6.77 (1H, s), 7.53 (2H, d), 8.27 (2H, d), 8.77 (1H, s)

Example 43s: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.74 - 1.82 (2H, m), 1.89 - 1.98 (1H, m), 2.03 - 2.10 (1H, m), 2.77 - 2.90 (2H, m), 2.92 - 3.00 (2H, m), 3.02 - 3.07 (2H, m), 3.20 - 3.26 (1H, m), 3.36 - 3.44 (2H, m), 3.46 - 3.56 (1H, m), 3.66 (1H, d), 3.78 (1H, d), 3.99 (1H, d), 4.27 (1H, d), 4.51 - 4.63 (2H, m), 6.77 (1H, s), 7.63 (2H, d), 8.28 - 8.39 (3H, m), 9.46 (1H, s)

Example 43t: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.74 - 1.83 (2H, m), 1.88 - 1.96 (1H, m), 2.00 - 2.09 (1H, m), 2.77 - 2.88 (2H, m), 2.91 - 2.98 (2H, m), 3.00 - 3.07 (2H, m), 3.20 - 3.25 (1H, m), 3.37 - 3.43 (2H, m), 3.46 - 3.56 (1H, m), 3.66 (1H, d), 3.78 (1H, d), 3.99 (1H, d), 4.26 (1H, d), 4.53 - 4.62 (2H, m), 6.76 (1H, s), 7.14 (1H, s), 7.40 (1H, s), 7.59 (2H, d), 8.31 (2H, d), 9.20 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

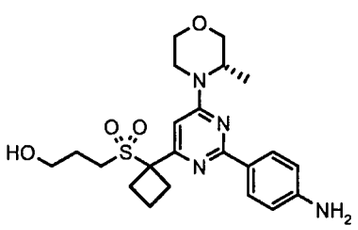
Phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.632 mL, 5.04 mmol) was added dropwise to 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropan-1-ol (1.5 g, 3.36 mmol) and sodium hydrogen carbonate (0.423 g, 5.04 mmol) in dioxane (33.6 mL), cooled to 10°C under a nitrogen atmosphere. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (300 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product as a yellow gum. This material was used directly in the next step without further purification.

LCMS Spectrum: m/z (ESI+) (M+H)+ = 565; HPLC tR = 2.71 min.

3-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropan-1-ol



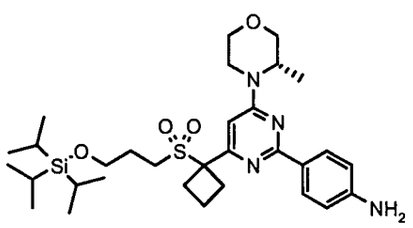
A solution of tetrabutylammonium fluoride (18.25 mL, 18.25 mmol) in THF was added to a stirred solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclobutyl]pyrimidin-2-yl]aniline (2.2 g, 3.65 mmol) in THF (24.33 mL) at RT. The resulting solution was stirred at RT for 2 hours. The reaction mixture was concentrated and diluted with ethyl acetate (150 mL), and washed with water (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% ethyl

acetate in isohexane, to give the desired material as a pale yellow oil which solidified on standing (1.50 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.57 (1H, t), 1.94 - 2.04 (3H, m), 2.18 - 2.25 (1H, m), 2.82 - 2.88 (2H, m), 2.98 (2H, t), 3.09 - 3.16 (2H, m), 3.28 - 3.35 (1H, m), 3.63 (3H, q), 3.73 - 3.76 (1H, m), 3.82 (1H, d), 3.90 (2H, s), 4.01 - 4.05 (1H, m), 4.16 (1H, d), 4.47 (1H, d), 6.51 (1H, s), 6.70 - 6.72 (2H, m), 8.22 - 8.24 (2H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 447; HPLC tR = 2.09 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclobutyl]pyrimidin-2-yl]aniline

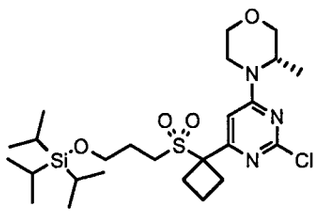


Dichlorobis(triphenylphosphine)palladium(II) (0.132 g, 0.19 mmol) was added in one portion to a carefully degassed solution of 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropoxy-tri(propan-2-yl)silane (2.05 g, 3.75 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.233 g, 5.63 mmol) and 2M aqueous sodium carbonate solution (6.57 mL, 13.14 mmol) in a solvent mixture of DMF (6.82 mL), water (17.06 mL), ethanol (6.82 mL) and DME (6.82 mL). The resulting mixture was stirred at 80°C for 4 hours. The cooled reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in isohexane, to give the desired material as a pale yellow foam which solidified under vacuum (2.2 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.89 - 0.98 (21H, m), 1.32 (3H, s), 1.92 - 1.99 (3H, m), 2.15 - 2.25 (1H, m), 2.84 - 2.87 (2H, m), 2.91 - 2.95 (2H, m), 3.07 - 3.13 (2H, m), 3.26 - 3.34 (1H, m), 3.57 - 3.62 (1H, m), 3.65 (2H, t), 3.74 (1H, dd), 3.81 (1H, d), 3.88 (2H, s), 4.03 (1H, dd), 4.15 (1H, d), 4.47 (1H, s), 6.52 (1H, s), 6.68 - 6.70 (2H, m), 8.21 - 8.23 (2H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 603; HPLC tR = 3.82 min.

3-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropoxy-tri(propan-2-yl)silane



Aqueous sodium hydroxide solution (50% w/w, 48.7 mL) was added to 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane (5.6 g, 11.06 mmol), 1,3-dibromopropane (3.37 mL, 33.19 mmol) and tetrabutylammonium bromide (0.357 g, 1.11 mmol) in toluene (221 mL) at RT. The resulting suspension was stirred at 45°C for 1 hour. Water was added to the solution. The toluene was washed with water twice, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a colourless gum (2.05 g).

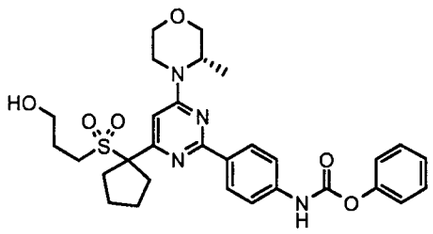
NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.97 - 1.08 (21H, m), 1.32 (3H, d), 1.94 - 2.01 (3H, m), 2.21 - 2.23 (1H, m), 2.70 - 2.76 (2H, m), 2.93 (2H, q), 3.03 - 3.08 (2H, m), 3.28 - 3.32 (1H, m), 3.51 - 3.57 (1H, m), 3.66 - 3.70 (1H, m), 3.76 (3H, t), 3.98 - 4.02 (2H, m), 4.32 (1H, s), 6.55 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 546; HPLC tR = 4.05 min.

The preparation of 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane was described earlier.

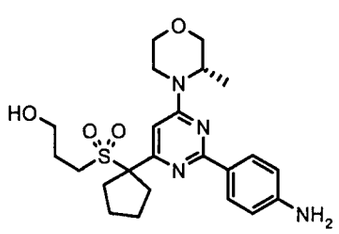
The preparation of phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopentyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (1.512 mL, 12.05 mmol) was added dropwise to 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopentyl]sulfonylpropan-1-ol (3.7 g, 8.03 mmol) and sodium hydrogen carbonate (1.012 g, 12.05 mmol) in dioxane (80 mL) cooled to 10°C under a nitrogen atmosphere. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (300 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a yellow solid which was used without further purification (3.60 g). LCMS Spectrum: m/z (ESI+) (M+H)+ = 581; HPLC tR = 2.83 min.

3-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopentyl]sulfonylpropan-1-ol



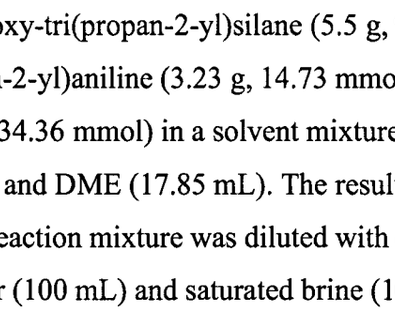
A solution of tetrabutylammonium fluoride (46.2 mL, 46.20 mmol) in THF was added to a stirred solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopentyl]pyrimidin-2-yl]aniline (5.7 g, 9.24 mmol) in THF (61.6 mL) at RT. The resulting solution was stirred at RT for 2 hours. The reaction mixture was concentrated and diluted with ethyl acetate (250 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% ethyl acetate

in isohexane, to give the desired material as a pale yellow oil which solidified on standing (3.70 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.59 (1H, t), 1.61 - 1.70 (2H, m), 1.92 - 1.98 (4H, m), 2.57 - 2.66 (2H, m), 2.74 - 2.83 (2H, m), 3.07 (2H, t), 3.27 - 3.34 (1H, m), 3.57 - 3.65 (3H, m), 3.73 - 3.77 (1H, m), 3.82 (1H, d), 3.90 (2H, s), 4.01 - 4.05 (1H, m), 4.11 - 4.18 (1H, m), 4.46 (1H, d), 6.63 (1H, s), 6.71 (2H, d), 8.23 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 461; HPLC tR = 2.18 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[3-tri(propan-2-yl)silyloxypropylsulfonyl]cyclopentyl]pyrimidin-2-yl]aniline

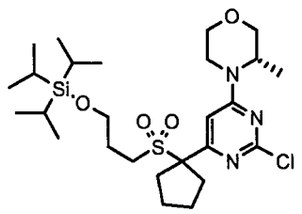


Dichlorobis(triphenylphosphine)palladium(II) (0.345 g, 0.49 mmol) was added in one portion to a carefully degassed solution of 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopentyl]sulfonylpropoxy-tri(propan-2-yl)silane (5.5 g, 9.82 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.23 g, 14.73 mmol) and 2M aqueous sodium carbonate solution (17.18 mL, 34.36 mmol) in a solvent mixture of DMF (17.85 mL), water (44.6 mL), ethanol (17.85 mL) and DME (17.85 mL). The resulting mixture was stirred at 80°C for 4 hours. The cooled reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as a pale yellow foam which solidified under vacuum (5.70 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.90 - 0.98 (21H, m), 1.32 (4H, t), 1.63 - 1.66 (2H, m), 1.89 - 1.96 (4H, m), 2.59 - 2.64 (2H, m), 2.77 - 2.81 (2H, m), 2.98 - 3.02 (2H, m), 3.29 - 3.32 (1H, m), 3.57 - 3.63 (1H, m), 3.66 (2H, t), 3.72 - 3.76 (1H, m), 3.81 (1H, d), 3.88 (2H, s), 4.01 - 4.05 (1H, m), 4.15 (1H, d), 4.45 (1H, s), 6.66 (1H, s), 6.69 (2H, d), 8.22 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 617; HPLC tR = 3.91 min.

3-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopentyl]sulfonylpropoxy-tri(propan-2-yl)silane



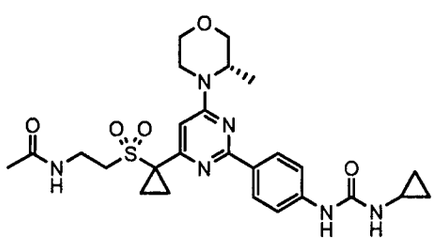
Aqueous sodium hydroxide solution (50% w/w aq, 48.7 mL) was added to 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane (5.6 g, 11.06 mmol), 1,4-dibromobutane (3.93 mL, 33.19 mmol) and tetrabutylammonium bromide (0.357 g, 1.11 mmol) in toluene (221 mL) at RT. The resulting suspension was stirred at 45°C for 1 hour and the toluene washed with water twice, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (5.57 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.98 - 1.08 (21H, m), 1.31 (3H, d), 1.60 - 1.65 (2H, m), 1.88 - 1.99 (4H, m), 2.56 - 2.61 (4H, m), 2.97 - 3.00 (2H, m), 3.28 - 3.32 (1H, m), 3.51 - 3.58 (1H, m), 3.67 - 3.71 (1H, m), 3.76 (3H, t), 3.98 - 4.02 (2H, m), 4.31, (1H, s), 6.71 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 560; HPLC tR = 3.86 min.

The preparation of 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]propoxy-tri(propan-2-yl)silane was described earlier.

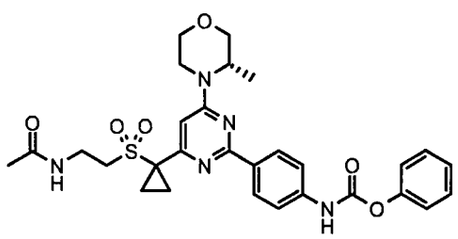
Example 44: *N*-[2-[1-[2-[4-(Cyclopropylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide



Cyclopropylamine (0.120 mL, 1.73 mmol) was added in one portion to a stirred solution of phenyl *N*-[4-[4-[1-(2-acetamidoethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.2 g, 0.35 mmol) in THF (34.5 mL) at RT. The resulting solution was stirred at 40°C for 24 hours. The reaction mixture was then concentrated, and the crude product was purified by flash silica chromatography, elution gradient 0 to 5% methanol in DCM, to give the desired material as a white solid (0.135 g).
NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.66 - 0.70 (2H, m), 0.84 - 0.89 (2H, m), 1.34 (3H, d), 1.49 - 1.58 (2H, m), 1.82 - 1.85 (2H, m), 1.93 (3H, s), 2.61 - 2.66 (1H, m), 3.29 - 3.36 (1H, m), 3.48 - 3.51 (2H, m), 3.56 - 3.63 (1H, m), 3.72 - 3.75 (1H, m), 3.79 - 3.84 (3H, m), 4.03 - 4.06 (1H, m), 4.15 (1H, d), 4.48 (1H, s), 5.05 (1H, s), 6.67 (1H, s), 6.74 (1H, d), 7.13 (1H, s), 7.51 (2H, d), 8.26 (2H, d).
LCMS Spectrum: m/z (ESI+) (M+H)+ = 543; HPLC tR = 1.86 min.
mTOR Kinase Assay (Echo): 0.0234μM

The preparation of phenyl *N*-[4-[4-[1-(2-acetamidoethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(2-acetamidoethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

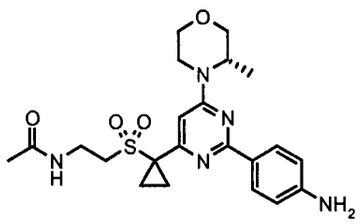


Phenyl chloroformate (0.328 mL, 2.61 mmol) was added dropwise to *N*-[2-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide (800 mg, 1.74 mmol) and sodium hydrogen carbonate (219 mg, 2.61 mmol) in dioxane (174 mL) cooled to 10°C under a nitrogen atmosphere. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (300 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with a mixture

of diethyl ether and isohexane to give the desired material as a yellow solid (741 mg). This material was used directly without further purification.

LCMS Spectrum: m/z (ESI+) (M+H)+ = 580; HPLC tR = 2.44 min.

N-[2-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide

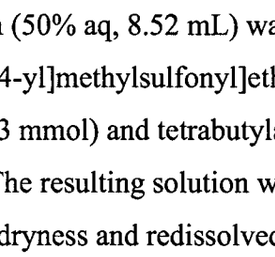


Dichlorobis(triphenylphosphine)palladium(II) (0.174 g, 0.25 mmol) was added in one portion to a carefully degassed solution of *N*-[2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide (2 g, 4.96 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.414 g, 6.45 mmol) and 2M aqueous sodium carbonate solution (8.69 mL, 17.37 mmol) in a solvent mixture of DMF (9.03 mL), water (22.56 mL), ethanol (9.03 mL) and DME (9.03 mL). The resulting mixture was stirred at 80°C for 4 hours. The cooled reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 75% ethyl acetate in DCM, to give the desired material as a pale yellow foam which solidified under vacuum (1.805 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.49 - 1.51 (2H, m), 1.80 - 1.84 (2H, m), 1.93 (3H, s), 3.28 - 3.35 (1H, m), 3.47 - 3.50 (2H, m), 3.55 - 3.62 (1H, m), 3.71 - 3.75 (1H, m), 3.79 - 3.83 (3H, m), 3.92 (2H, s), 4.01 - 4.05 (1H, m), 4.10 - 4.17 (1H, m), 4.47 (1H, s), 6.61 (1H, s), 6.69 - 6.72 (2H, m), 6.81 (1H, s), 8.13 - 8.16 (2H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 460; HPLC tR = 1.79 min.

N-[2-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide

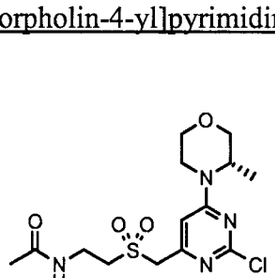


Aqueous sodium hydroxide solution (50% aq, 8.52 mL) was added to *N*-[2-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethyl]acetamide (3.21 g, 8.52 mmol), 1,2-dibromoethane (1.468 mL, 17.03 mmol) and tetrabutylammonium bromide (0.549 g, 1.70 mmol) in toluene (122 mL) at RT. The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness and redissolved in ethyl acetate (200 mL), and washed sequentially with water (200 mL) and saturated brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (2.04 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.44 - 1.47 (2H, m), 1.80 - 1.84 (2H, m), 2.02 (3H, s), 3.27 - 3.34 (1H, m), 3.35 - 3.38 (2H, m), 3.51 - 3.57 (1H, m), 3.66 - 3.70 (1H, m), 3.75 - 3.80 (3H, m), 3.99 - 4.03 (2H, m), 4.34 (1H, s), 6.73 (1H, s), 6.88 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 403; HPLC tR = 1.51 min.

N-[2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]ethyl]acetamide



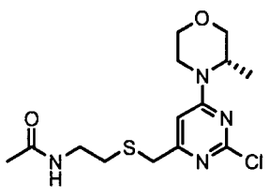
N-[2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide (3.24 g, 9.40 mmol) was dissolved in dioxane (28.2 mL) and 2N sulfuric acid (0.282 mL) was added. The solution was heated to 55°C. Sodium tungstate dihydrate (0.062 g, 0.19 mmol) dissolved in water (2.82 mL) was added to the solution and allowed to stir for 5 minutes. Hydrogen peroxide (5.42 mL, 56.37 mmol) was

then added dropwise over several minutes. The solution was heated at 55°C for 2.5 hours. The heat was removed and water (300 mL) was added. The resulting suspension was stirred for 30 minutes. The solids were filtered, rinsed with water and dried in a vacuum oven at 50°C overnight, to give the desired material as a white solid (3.30 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.82 (3H, s), 3.19 - 3.26 (1H, m), 3.36 - 3.43 (2H, m), 3.45 - 3.51 (3H, m), 3.58 - 3.62 (1H, m), 3.73 (1H, d), 3.92 - 3.96 (2H, m), 4.30 (1H, s), 4.49 (2H, s), 6.92 (1H, s), 8.11 (1H, t).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 377; HPLC tR = 1.37 min.

N-[2-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]ethyl]acetamide



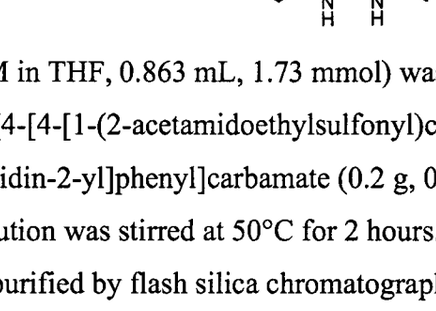
N-Acetylcysteamine (1.804 mL, 16.97 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4 g, 11.31 mmol) and DIPEA (4.93 mL, 28.28 mmol) in acetonitrile (226 mL) at RT. The resulting solution was stirred at RT for 3 hours. The solvent was removed *in vacuo*, and the crude material was then purified by flash silica chromatography, eluting with ethyl acetate, to give the desired material as a white solid (3.24 g).

NMR Spectrum: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.33 (3H, d), 2.01 (3H, s), 2.71 (2H, t), 3.25 - 3.33 (1H, m), 3.48 - 3.58 (3H, m), 3.59 (2H, s), 3.67 - 3.71 (1H, m), 3.79 (1H, d), 3.99 - 4.03 (2H, m), 4.33 (1H, s), 6.40 (1H, s), 6.55 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 345; HPLC tR = 1.54 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 45: *N*-[2-[1-[2-[4-(Ethylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethyl]acetamide



A solution of ethylamine (2M in THF, 0.863 mL, 1.73 mmol) was added in one portion to a stirred solution of phenyl *N*-[4-[4-[1-(2-acetamidoethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.2 g, 0.35 mmol) in THF (34.5 mL) at RT. The resulting solution was stirred at 50°C for 2 hours. The product was concentrated *in vacuo*, then purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give a residue that was triturated with acetonitrile to give the desired material as a white solid (0.147 g).

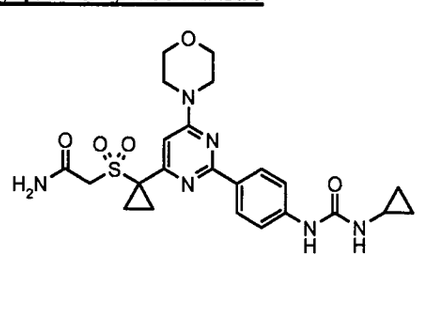
NMR Spectrum: ^{1}H NMR (400.13 MHz, CDCl3) δ 1.16 (3H, t), 1.33 (3H, d), 1.48 - 1.51 (2H, m), 1.81 - 1.84 (2H, m), 1.93 (3H, s), 3.27 - 3.34 (3H, m), 3.49 - 3.52 (2H, m), 3.55 - 3.60 (1H, m), 3.70 - 3.74 (1H, m), 3.78 - 3.83 (3H, m), 4.01 - 4.05 (1H, m), 4.10 - 4.16 (1H, m), 4.46 (1H, s), 5.18 (1H, t), 6.64 (1H, s), 6.89 (1H, t), 7.15 (1H, s), 7.42 (2H, d), 8.23 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 531; HPLC tR = 1.87 min.

mTOR Kinase Assay (Echo): 0.0219μM

The preparation of phenyl *N*-[4-[4-[1-(2-acetamidoethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 46: 2-[1-[2-[4-(Cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonylacetamide



Bis(triphenylphosphine)palladium(II) chloride (19.03 mg, 0.03 mmol) was added to 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetamide (146 mg, 0.40 mmol), 1-cyclopropyl-3-(4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenyl)urea (185 mg, 0.61 mmol) and sodium carbonate (0.809 mL, 1.62 mmol) in a solvent mixture of DMF (3 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT. The resulting mixture was stirred at 90°C for 18 hours under an inert atmosphere.The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (100 mL followed by 75 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of methanol and DCM and the solid removed by filtration. The filtrate was purified by flash silica chromatography, elution gradient 0 to 7% methanol in ethyl acetate, to give a gum which was further purified by ion exchange chromatography on an SCX column, eluting with 7N ammonia in methanol, to give a beige solid which was further purified by prep HPLC to give the desired material (7 mg).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 499; HPLC tR = 1.67 min.

mTOR Kinase Assay (Echo): 0.00456μM

The following compound was prepared in an analogous fashion from 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonyl-*N*-methylacetamide.

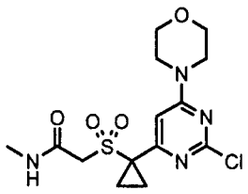
Example	Structure	NAME	LCMS MH+	Retention time (min)
46a		2-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonyl-N-methylacetamide	515	1.74

Example 46a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.61 - 0.67 (2H, m), 1.57 - 1.61 (2H, m), 1.66 - 1.71 (2H, m), 2.63 (3H, d), 3.72 (8H, s), 4.39 (2H, s), 6.46 (1H, s), 6.87 (1H, s), 7.51 (2H, d), 8.20 (2H, d), 8.29 (1H, d), 8.58 (1H, s).

mTOR Kinase Assay (Echo): 0.0126μM

The preparation of 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonyl-*N*-methylacetamide is described below.

2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonyl-*N*-methylacetamide

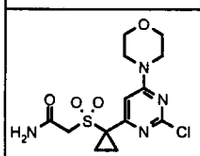


HATU (252 mg, 0.66 mmol) was added to 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetic acid (200 mg, 0.55 mmol) and triethylamine (0.077 mL, 0.55 mmol) in DCM (10 mL) at RT under a nitrogen atmosphere and stirred for 15 minutes. Methylamine (2M in THF, 2 mL) was added and reaction stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with a saturated solution of sodium hydrogen carbonate (100 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 90% ethyl acetate in isohexane, to give the desired material as a yellow gum (156 mg)

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.51 - 1.54 (2H, m), 1.62 - 1.67 (2H, m), 2.62 (3H, d), 3.66 (8H, m), 4.27 (2H, s), 7.06 (1H, s), 8.22 (1H, s)

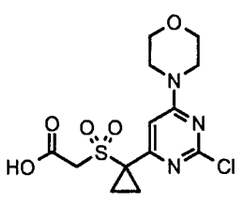
LCMS Spectrum: m/z (ESI+)(M+H)+ = 375; HPLC tR = 1.35 min.

2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetamide was made by an analogous procedure to that above (chromatographed using 0 – 4% methanol in ethyl acetate).

Structure	NAME	LCMS MH+	Retention time (min)
	2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetamide	361	1.31

The preparation of 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetic acid is described below.

2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetic acid

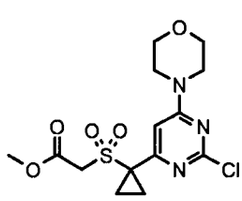


Lithium hydroxide (0.812 g, 33.93 mmol) was added to methyl 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetate (2.55 g, 6.79 mmol), in a mixture of THF (40 mL) and water (8 mL). The resulting mixture was stirred at RT for 2 hours then acidified with 2M hydrochloric acid. The reaction mixture was extracted with ethyl acetate (400 mL) and the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (1.96 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.53 - 1.58 (2H, m), 1.69 - 1.72 (2H, m), 3.66 (8H, s), 4.55 (2H, s), 6.98 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 362; HPLC tR = 0.69 min.

Methyl 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetate



Lithium diisopropylamide (8.92 mL, 16.05 mmol) was added dropwise to 2-chloro-4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine (4.25 g, 13.37 mmol), in THF (80 mL) at -78°C under a nitrogen atmosphere. The resulting mixture was stirred at -78°C for 15 minutes. Dimethyl carbonate (5.63 mL, 66.87 mmol) was added and the resulting mixture stirred at -78 °C for 10 minutes, then left to warm to RT. The mixture was cooled back to -78C and additional lithium diisopropylamide (8.92 mL, 16.05 mmol) added. The mixture was stirred at -78°C for 10 minutes, then dimethyl carbonate (5.63 mL, 66.87 mmol) added and the mixture allowed to come to RT and the pH adjusted to 7 with 2M hydrochloric acid. The

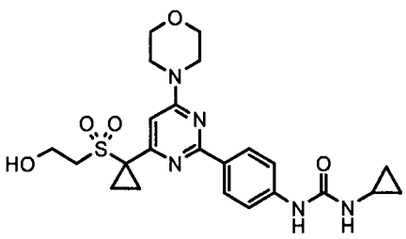
reaction mixture was diluted with ethyl acetate (350 mL), and washed with water (150 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give a yellow solid which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (3.10 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.56 - 1.60 (2H, m), 1.68 - 1.72 (2H, m), 3.63 - 3.70 (11H, m), 4.71 (2H, s), 6.97 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 376; HPLC tR = 1.76 min.

The preparation of 2-chloro-4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidine was described earlier.

Example 47: 3-Cyclopropyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea

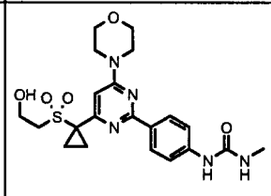
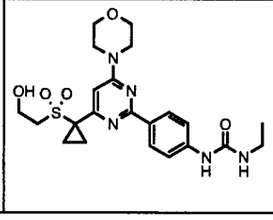


A solution of phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate (50 mg, 0.09 mmol), cyclopropylamine (0.48 mmol) and triethylamine (0.066 mL, 0.048 mmol) in NMP (1 mL) was stirred at RT until the reaction had gone to completion. The crude reaction mixture was purifed by prep HPLC to give the desired material as a solid (31 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.45 (2H, m), 0.61 - 0.67 (2H, m), 1.50 - 1.59 (2H, m), 1.59 - 1.69 (2H, m), 2.54 - 2.61 (1H, m), 3.62 - 3.69 (2H, m), 3.69 - 3.76 (8H, m), 3.86 - 3.92 (2H, m), 5.03 (1H, t), 6.44 (1H, s), 6.81 (1H, s), 7.51 (2H, d), 8.21 (2H, d), 8.54 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 488; HPLC tR = 1.61 min.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

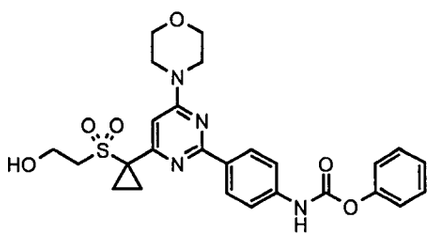
Example	Structure	NAME	LCMS MH+	Retention time (min)
47a		1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]-3-methylurea	462	1.45
47b		3-ethyl-1-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea	476	1.58

Example 47a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.48 - 1.58 (2H, m), 1.62 - 1.69 (2H, m), 2.67 (3H, d), 3.61 - 3.68 (2H, m), 3.69 - 3.76 (8H, m), 3.85 - 3.92 (2H, m), 5.03 (1H, s), 6.09 (1H, t), 6.81 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.76 (1H, s).

Example 47b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.51 - 1.57 (2H, m), 1.62 - 1.68 (2H, m), 3.14 (2H, q), 3.60 - 3.69 (2H, m), 3.69 - 3.77 (8H, m), 3.85 - 3.92 (2H, m), 5.03 (1H, t), 6.16 (1H, t), 6.81 (1H, s), 7.47 (2H, d), 8.20 (2H, d), 8.67 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2-hydroxyethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

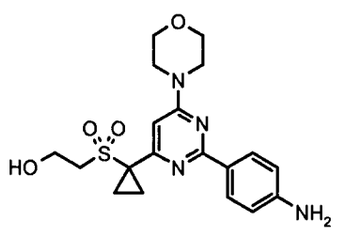


Sodium hydrogen carbonate (65.4 mg, 0.78 mmol) was added to 2-[1-[2-(4-aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonylethanol (210 mg, 0.52 mmol) in dioxane (8 mL) at 5°C under a nitrogen atmosphere. Phenyl chloroformate (0.072 mL, 0.57 mmol) was added and the mixture stirred at RT for 18 hours. The reaction mixture was diluted with ethyl acetate (50 mL), the organic layer dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (170 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.52 - 1.60 (2H, m), 1.61 - 1.70 (2H, m), 3.61 - 3.79 (10H, m), 3.82 - 3.96 (2H, m), 6.85 (1H, s), 7.21 - 7.34 (3H, m), 7.45 (2H, d), 7.64 (2H, d), 8.31 (2H, d), 10.45 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 525; HPLC tR = 2.40 min.

2-[1-[2-(4-Aminophenyl)-6-morpholin-4-ylpyrimidin-4-yl]cyclopropyl]sulfonylethanol



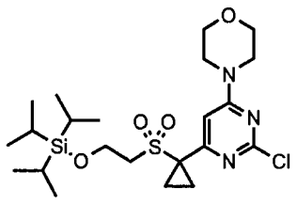
Bis(triphenylphosphine)palladium(II) chloride (48.5 mg, 0.07 mmol) was added to 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane (520 mg, 1.03 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (339 mg, 1.55 mmol) and an aqueous solution of sodium carbonate (1 mL, 2.00 mmol) in a solvent mixture of DMF (5 mL), DME (12 mL), water (1 mL) and ethanol (1 mL) at RT. The atmosphere was replaced with nitrogen and the mixture stirred at 90°C for 18 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL).The organic layer was dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was dissolved in DCM then tetrabutylammonium fluoride (5.16 mL, 5.16 mmol) added and the mixture left to stir for 1 hour. A saturated solution of ammonium chloride was added, the layers separated and the organics dried (Na_2SO_4), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, and the resultant solid further purified by ion exchange chromatography on an

SCX column, eluting with 7N ammonia in methanol. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (210mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.47 - 1.54 (2H, m), 1.59 - 1.67 (2H, m), 3.59 - 3.77 (10H, m), 3.81 - 3.94 (2H, m), 5.02 (1H, t), 5.57 (2H, s), 6.60 (2H, d), 6.71 (1H, s), 8.04 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 405; HPLC tR = 1.65 min.

2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane

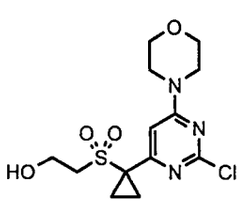


2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethanol (550 mg, 1.58 mmol) was added to triisopropylsilyl chloride (0.406 mL, 1.90 mmol) and imidazole (258 mg, 3.80 mmol) in DMF (10 mL) at RT. The resulting solution was stirred under a nitrogen atmosphere overnight. The DMF was removed *in vacuo* and ethyl acetate added. The solids were removed by filtration and discarded. The filtrate was concentrated *in vacuo* and purified by flash silica chromatography, elution gradient 0 to 4% methanol in DCM, to give material that was further purified by flash silica chromatography, elution gradient 0-10%ethyl acetate in DCM to give the desired material as a clear gum (700 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.02 (18H, d), 1.49 - 1.53 (2H, m), 1.62 - 1.66 (2H, m), 2.00 (2H, s), 3.33 (2H, s), 3.62 - 3.69 (8H, m), 4.03 - 4.09 (3H, m), 6.95 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 504; HPLC tR = 3.63 min.

2-[1-(2-Chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethanol

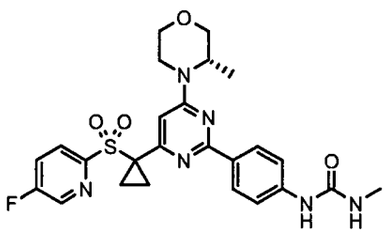


DIPEA (1.052 mL, 6.08 mmol) was added to 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetic acid (1.1 g, 3.04 mmol), in THF (50 mL) at 0°C under a nitrogen atmosphere. The resulting solution was stirred at 0°C for 5 minutes. Ethyl chloroformate (0.349 mL, 3.65 mmol) was added and the reaction stirred at 0°C for 1 hour. The reaction mixture was filtered and filtrate cooled back down to 0°C. Lithium borohydride (13.68 mL, 27.36 mmol) was added and the mixture warmed to allowed to come to RT. The mixture was cooled back to 0°C and additional lithium borohydride (13.68 mL, 27.36 mmol) added and the reaction was allowed to come to RT. The mixture was cooled back to 0°C and additional lithium borohydride (13.68 mL, 27.36 mmol) added and the reaction was allowed to come to RT and stirred for 72 hours. The reaction mixture was adjusted to pH7 with 2M hydrochloric acid and extracted with ethyl acetate (100 mL). The organic layer was washed with water (100 mL), dried (Na_2SO_4), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give the desired material as a white solid (500 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.47 - 1.52 (2H, m), 1.59 - 1.67 (2H, m), 3.49 - 3.57 (2H, m), 3.60 - 3.70 (8H, m), 3.76 - 3.86 (2H, m), 4.99 (1H, t), 6.98 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 348; HPLC tR = 1.38 min.

The preparation of 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylacetic acid was described earlier.

Example 48: 1-[4-[4-[1-(5-Fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



Methylamine (0.509 mL, 1.02 mmol) was added to phenyl *N*-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (200 mg, 0.34 mmol) and triethylamine (0.141 mL, 1.02 mmol) in DMF (1.7 mL) and the

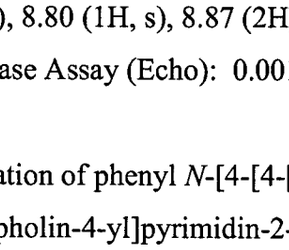
reaction stirred at 50°C for 2 hours. The crude product was purified by prep HPLC to give the desired material as a white solid (70.0 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.69 - 1.72 (2H, m), 1.96 - 1.99 (2H, m), 2.66 (3H, d), 3.12 - 3.18 (1H, m), 3.43 - 3.48 (1H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, d), 4.15 (1H, d), 4.45 (1H, s), 6.02 - 6.04 (1H, m), 6.68 (1H, s), 7.37 (2H, d), 7.68 (2H, d), 7.95 - 8.00 (1H, m), 8.03 - 8.06 (1H, m), 8.72 (1H, s), 8.87 (1H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 527; HPLC tR = 1.61 min.

mTOR Kinase Assay (Echo): 0.00252μM

The following compound was prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

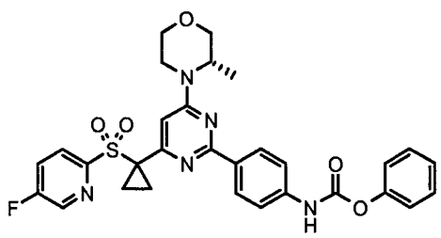
Example	Structure	NAME	LCMS MH+	Retention time (min)
48a		3-cyclopropyl-1-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	553	2.43

Example 48a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.66 - 1.70 (2H, m), 1.96 - 1.99 (2H, m), 3.69 (8H, s), 3.79 (3H, s), 6.74 (1H, s), 7.40 (3H, d), 7.66 (2H, d), 7.77 - 7.78 (3H, m), 8.35 (1H, s), 8.80 (1H, s), 8.87 (2H, d).

mTOR Kinase Assay (Echo): 0.00103μM

The preparation of phenyl *N*-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

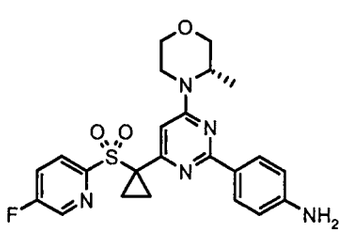


Sodium bicarbonate (0.403 g, 4.79 mmol) was added to 4-[4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.5 g, 3.19 mmol), in 1,4-dioxane (15.97 mL), followed by the dropwise addition of phenyl chloroformate (0.402 mL, 3.19 mmol) over 2 minutes and the reaction stirred at RT for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM (20 mL), the organics washed with water (20 mL), dried ($MgSO_4$), filtered and evaporated to give the desired material (2.0 g) which was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.71 - 1.76 (2H, m), 1.96 - 1.99 (2H, m), 3.14 - 3.22 (1H, m), 3.42 - 3.49 (1H, m), 3.58 - 3.62 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.19 (1H, s), 4.48 (1H, s), 6.74 (1H, s), 7.24 - 7.26 (2H, m), 7.45 (2H, t), 7.54 (2H, d), 7.80 (2H, d), 7.99 (1H, dt), 8.07 (1H, dd), 8.89 (1H, d), 10.48 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 590; HPLC tR = 2.95 min.

4-[4-[1-(5-Fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



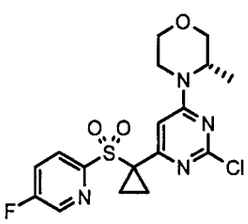
Bis(triphenylphosphine)palladium(II) chloride (0.136 g, 0.19 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.104 g, 5.04 mmol) and 2-chloro-4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.6 g, 3.88 mmol) and an aqueous solution of sodium carbonate (5.81 mL, 11.63 mmol) in a solvent mixture of DMF (0.564 mL), ethanol (4.70 mL) and water (4.70 mL) at RT under an

atmosphere of nitrogen. The resulting mixture was stirred at 85°C for 4 hours. The reaction mixture was diluted with ethyl acetate (20 mL), and the organics washed with water (2 x 20 mL), dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% 3.5N methanolic ammonia in DCM, to give the desired material as a cream solid (1.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.65 - 1.70 (2H, m), 1.94 - 1.97 (2H, m), 3.12 (1H, dt), 3.44 (1H, dt), 3.59 (1H, dd), 3.73 (1H, d), 3.93 (1H, dd), 4.11 - 4.13 (1H, m), 4.41 (1H, s), 6.46 (2H, d), 6.58 (1H, s), 7.49 (2H, d), 7.98 (2H, dt), 8.04 (2H, dd), 8.89 (1H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 470; HPLC tR = 2.30 min.

2-Chloro-4-[1-(5-fluoropyridin-2-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

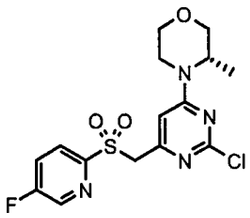


1,2-Dibromoethane (1.025 mL, 11.89 mmol) was added to 2-chloro-4-[(5-fluoropyridin-2-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.3 g, 5.95 mmol), an aqueous solution of sodium hydroxide (2.97 mL, 29.73 mmol) and tetrabutylammonium bromide (0.383 g, 1.19 mmol) in toluene (29.7 mL) and the resulting solution stirred at 60°C for 3 hours. The reaction mixture was evaporated to dryness, redissolved in ethyl acetate (50 mL), and the organics washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 50% ethyl acetate in DCM, to give the desired material as a white solid (1.8 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, d), 1.63 - 1.66 (2H, m), 1.88 - 1.93 (2H, m), 3.11 - 3.17 (1H, m), 3.39 (1H, dt), 3.54 (1H, dd), 3.69 (1H, d), 3.91 (2H, dd), 4.27 (1H, s), 6.81 (1H, s), 8.02 - 8.11 (2H, m), 8.83 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 413, HPLC tR = 2.10 min

2-Chloro-4-[(5-fluoropyridin-2-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

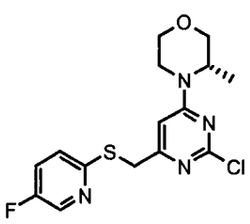


3-Chloroperoxybenzoic acid (5.79 g, 25.15 mmol) was added portionwise to 2-chloro-4-[(5-fluoropyridin-2-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.57 g, 10.06 mmol), in DCM (50.3 mL) and the reaction stirred at RT for 2 hours. The reaction mixture was washed with a saturated solution of sodium hydrogen carbonate (50 mL), the organic layer separated, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a white solid (2.3 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 3.17 (1H, t), 3.42 (1H, dt), 3.57 (1H, dd), 3.71 (1H, d), 3.92 (2H, dd), 4.17 (1H, s), 4.74 (2H, d), 6.82 (1H, s), 8.01 - 8.09 (2H, m), 8.89 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 387, HPLC tR = 1.88 min

2-Chloro-4-[(5-fluoropyridin-2-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



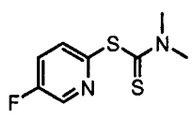
Potassium hydroxide (3.22 g, 57.33 mmol) was added to (5-fluoropyridin-2-yl) dimethylaminomethanedithioate (3.1 g, 14.33 mmol) in ethanol (71.7 mL) and the resulting solution heated at 65°C for 4 hours. The reaction was cooled, 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7.09 g, 20.06 mmol) added and the reaction stirred at RT for 4 hours. Water (50 mL) was added and the reaction extracted with DCM (2 x 100 mL). The organics were dried ($MgSO_4$), filtered and concentrated to give crude product which

was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a beige gum (3.57 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 3.11 - 3.17 (1H, m), 3.41 (1H, dt), 3.54 - 3.57 (1H, m), 3.69 (1H, d), 3.90 (2H, dd), 4.24 - 4.26 (1H, m), 4.29 (2H, d), 6.84 (1H, s), 7.45 (1H, dd), 7.68 (1H, dt), 8.50 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 355, HPLC tR = 2.38 min

(5-Fluoropyridin-2-yl) dimethylaminomethanedithioate



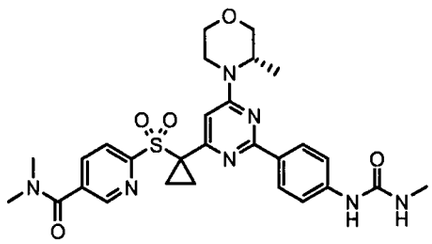
2-Bromo-5-fluoropyridine (4 g, 22.73 mmol) was added portionwise to isopropylmagnesium chloride - lithium chloride complex (14% in THF, 23 mL, 22.73 mmol), at 0°C, over a period of 2 minutes under a nitrogen atmosphere. The resulting solution was warmed to RT over a period of 2 hours then cooled back to 0°C and tetramethylthiuram disulfide (5.46 g, 22.73 mmol) in DCM (22.73 mL) added. The reaction was warmed to RT and stirred for 6 hours. The reaction was poured into a saturated aqueous solution of ammonium chloride (100 mL) and the aqueous layer extracted with DCM (2 x 100 mL). The organics were dried ($MgSO_4$), concentrated *in vacuo* and the crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a brown oil which solidified on standing (3.10 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 3.45 (3H, s), 3.46 (3H, s), 7.70 (1H, dd), 7.86 (1H, dt), 8.65 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ 217, HPLC tR = 1.70 min

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 49: *N,N*-Dimethyl-6-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpyridine-3-carboxamide



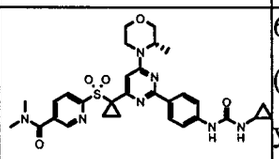
Methylamine (0.250 mL, 0.50 mmol) was added to phenyl *N*-[4-[4-[1-[5-(dimethylcarbamoyl)pyridin-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.064 g, 0.10 mmol) and triethylamine (0.042 mL, 0.30 mmol) in DMF (2 mL) and the resulting solution stirred at 50°C for 18 hours. The reaction was cooled and the mixture purified by preparative HPLC to give the desired material as a white solid (0.03 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ δ 1.16-1.18 (3H, d), 1.73-1.76 (2H, m), 1.99-2.02 (2H, m), 2.65-2.66 (3H, d), 2.88 (3H, s), 3.05 (3H, s), 3.05-3.17 (1H, td), 3.41-3.48 (1H, td), 3.58-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.93-3.97 (1H, dd), 4.15 (1H, bs), 4.44 (1H, bs), 6.07-6.10 (1H, q), 6.65 (1H, s), 7.37-7.39 (2H, d), 7.67-7.69 (2H, d), 8.00-8.01 (1H, d), 8.11-8.13 (1H, dd), 8.72 (1H, s), 8.87-8.88 (1H, dd).

LCMS Spectrum: m/z (ES+) (M+H)+=580; HPLC tR=1.88min.

mTOR Kinase Assay (Echo): 0.00187μM

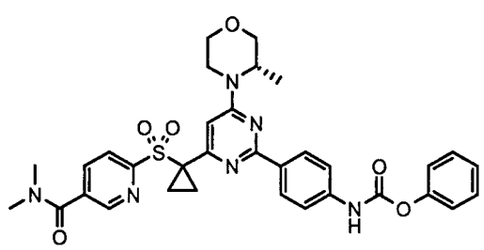
The compound shown in table below was prepared in an analogous manner from phenyl *N*-[4-[4-[1-[5-(dimethylcarbamoyl)pyridin-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
49a		6-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-N,N-dimethylpyridine-3-carboxamide	606	2.00

Example 49a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39-0.43 (2H, m), 0.62-0.67 (2H, m), 1.16-1.18 (3H, d), 1.73-1.76 (2H, m), 2.00-2.02 (2H, m), 2.88 (3H, s), 3.05 (3H, s), 3.11-3.18 (1H, td), 3.42-3.48 (1H, td), 3.58-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.93-3.97 (1H, dd), 4.13 (1H, bs), 4.44 (1H, bs), 6.44-6.45 (1H, d), 6.66 (1H, s), 7.37-7.39 (2H, d), 7.67-7.69 (2H, d), 8.00-8.03 (1H, d), 8.11-8.13 (1H, dd), 8.51 (1H, s), 8.87-8.88 (1H, dd).
mTOR Kinase Assay (Echo): 0.00267μM

The preparation of phenyl *N*-[4-[4-[1-[5-(dimethylcarbamoyl)pyridin-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[5-(dimethylcarbamoyl)pyridin-2-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



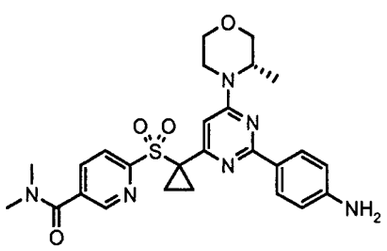
Phenyl chloroformate (0.015 mL, 0.12 mmol) was added dropwise to 6-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-3-carboxamide (0.064 g, 0.12 mmol) and sodium hydrogen carbonate (0.015 g, 0.18 mmol) in dioxane (7.5 mL) and the resulting solution stirred at RT for 1 hour.

The material was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material.

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.29-1.31 (3H, d), 1.66-1.74 (2H, m), 2.17-2.19 (2H, m), 2.88 (3H, s), 3.12 (3H, s), 3.24-3.31 (1H, td), 3.54-3.61 (1H, td), 3.70-3.74 (1H, dd), 3.80-3.83 (1H, d), 4.01-4.05 (1H, dd), 4.16-4.17 (1H, bs), 4.42 (1H, bs), 6.79 (1H, s), .16-7.26 (2H, d), 7.22-7.26 (1H, t), 7.37-7.41 (2H, t), 7.47-7.49 (2H, d), 7.64-7.69 (1H, m), 7.84-7.87 (1H, dd), 7.95-7.97 (3H, m), 8.75-8.76 (1H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=643; HPLC tR=2.62min.

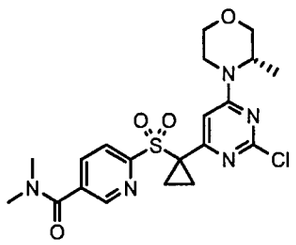
6-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-3-carboxamide



Bis(triphenylphosphine)palladium (II) chloride (0.015 g, 0.02 mmol) was added to 6-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-3-carboxamide (0.203 g, 0.44 mmol), 4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.096 g, 0.44 mmol) and an aqueous solution of sodium carbonate (1.09 mL, 2.18 mmol) in a solvent mixture (2 mL) (the solvent mixture comprised 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol) at RT under a nitrogen atmosphere. The resulting solution was stirred at 80°C for 3 hours. The reaction was cooled, water added and the solids removed by filtration. The filtrate was extracted twice with ethyl acetate and the combined organics dried ($MgSO_4$), filtered and evaporated. The solids from the filtration were combined with those from the extraction to give the desired material which was used without further purification.

LCMS Spectrum: m/z (ES+) (M+H)+=523; HPLC tR=1.98min.

6-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-3-carboxamide

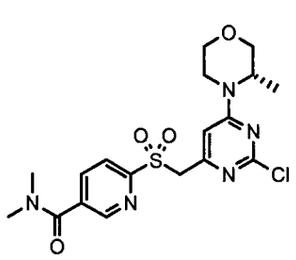


Sodium hydroxide (3.36 g, 83.96 mmol) in water (3.6 mL) was added to 6-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-*N,N*-dimethylpyridine-3-carboxamide (0.666 g, 1.51 mmol), 1,2-dibromoethane (0.652 mL, 7.56 mmol) and tetrabutylammonium bromide (0.049 g, 0.15 mmol) in DCM (20 mL) and the resulting solution stirred at RT for 18 hours. The reaction mixture was diluted with water and extracted with DCM. The organics were washed with saturated brine, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 7% methanol (contaning 0.1% ammonia) in DCM, to give the desired material as a brown gum (0.406 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.27-1.29 (3H, d), 1.61-1.68 (2H, m), 2.07-2.10 (2H, m), 3.00 (3H, s), 3.14 (3H, s), 3.20-3.28 (1H, td), 3.48-3.54 (1H, td), 3.64-3.67 (1H, dd), 3.75-3.78 (1H, d), 3.96-4.02 (2H, m), 4.26 (1H, bs), 6.95 (1H, s), 7.93-7.99 (2H, m), 8.71-8.72 (1H, d).

LCMS Spectrum: m/z (ES+) (M+H)+=466; HPLC tR=1.71min.

6-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-*N,N*-dimethylpyridine-3-carboxamide



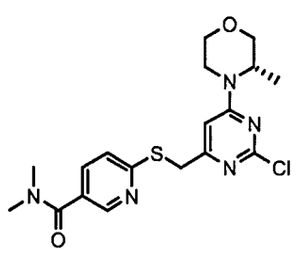
6-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-*N,N*-dimethylpyridine-3-carboxamide (1.47 g, 3.60 mmol) was dissolved in dioxane (45 mL) and 2N sulfuric acid (0.11 mL) added. The solution was heated to 55°C, a solution of sodium

tungstate dihydrate (0.024 g, 0.07 mmol) in water (1.08 mL) added and the solution allowed to stir for 10 minutes. Hydrogen peroxide (2.229 mL, 72.07 mmol) was then added dropwise over several minutes and the solution heated at 55°C for 3 hours. Water was added and the reaction was allowed to cool. The aqueous solution was extracted with DCM, the organics dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a cream solid (1.45 g).

NMR Spectrum: ^1H NMR (400.132 MHz, $CDCl_3$) δ 1.31-1.33 (3H, d), 3.04 (3H, s), 3.17 (3H, s), 3.24-3.32 (1H, td), 3.50-3.57 (1H, td), 3.66-3.70 (1H, dd), 3.78-3.80 (1H, d), 3.99-4.03 (2H, m), 4.26 (1H, bs), 4.58 (2H, s), 6.52 (1H, s), 7.97-8.03 (2H, m), 8.82-8.83 (1H, m).

LCMS Spectrum: m/z (ES+) (M+H)+=440; HPLC tR=1.59min.

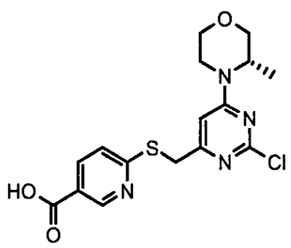
6-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-*N,N*-dimethylpyridine-3-carboxamide



DIPEA (1.043 mL, 5.99 mmol) was added to 6-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]pyridine-3-carboxylic acid (1.369 g, 3.59 mmol) and HATU (1.366 g, 3.59 mmol) in DMA (10 mL) and the resulting solution stirred at RT for 15 minutes. Dimethylamine (1.497 mL, 2.99 mmol) was added and the reaction allowed to stir for 2.5 hours. Water was added to the solution and the solution extracted with ethyl acetate. The ethyl acetate was washed with a saturated aqueous solution of sodium bicarbonate, dried ($MgSO_4$), filtered and evaporated to give the desired material which was used without further purification.

LCMS Spectrum: m/z (ES+) (M+H)+=408; HPLC tR=1.83min.

6-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]pyridine-3-carboxylic acid



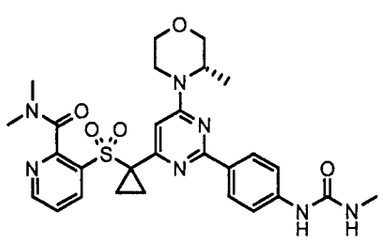
2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.0 g, 5.66 mmol) was added to 6-mercaptonicotinic acid (1.317 g, 8.48 mmol) and DIPEA (2.463 mL, 14.14 mmol) in acetonitrile (100 mL) and the resulting solution stirred at RT for 2 hours. The solvent was removed under vacuum and the residue dissolved in DCM. The organics were washed sequentially with water and saturated brine, dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol (containing 0.1% ammonia) in DCM, to give the desired material as a brown solid (1.79 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.19-1.20 (3H, d), 3.16-3.21 (1H, t), 3.40-3.47 (1H, m), 3.58-3.61 (2H, dd), 3.91-3.94 (2H, d), 4.25 (3H, bs), 6.08 (1H, bs), 6.52 (1H, s), 7.01 (1H, bs), 7.89 (1H, bs), 8.89 (1H, bs).

LCMS Spectrum: m/z (ES+) (M+H)+=381; HPLC tR=0.83min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 50: *N,N*-Dimethyl-3-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpyridine-2-carboxamide



Methylamine (0.441 mL, 0.88 mmol) was added to phenyl *N*-[4-[4-[1-[2-(dimethylcarbamoyl)pyridin-3-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-

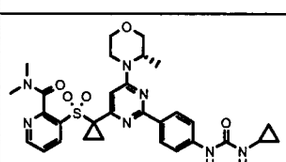
yl]pyrimidin-2-yl]phenyl]carbamate (0.113 g, 0.18 mmol) and triethylamine (0.074 mL, 0.53 mmol) in DMF (2 mL) and the resulting solution stirred at 50°C for 2 hours. The reaction was cooled and purified by preparative HPLC, to give the desired material as a colourless gum (11 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16-1.18 (3H, d), 1.62 (2H, bs), 1.98 (2H, bs), 2.55 (3H, s), 2.66 (3H, s), 2.96 (3H, s), 3.13-3.19 (1H, td), 3.41-3.47 (1H, td), 3.58-3.61 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.98 (1H, dd), 4.16 (1H, bs), 4.47 (1H, bs), 6.12 (1H, bs), 6.73 (1H, s), 7.43-7.46 (2H, d), 7.59-7.62 (1H, q), 7.85-7.87 (2H, d), 8.16-8.18 (1H, d), 8.82 (1H, bs), 8.85-8.86 (1H, dd).

LCMS Spectrum: m/z (ES+) (M+H)+=580; HPLC tR=1.76min.

mTOR Kinase Assay (Echo): 0.0104μM

The following compound was prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[2-(dimethylcarbamoyl)pyridin-3-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

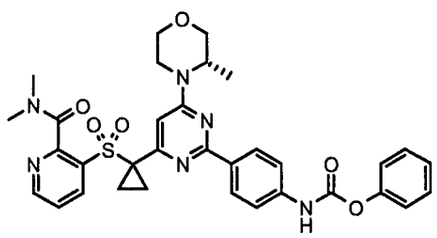
Example	Structure	NAME	LCMS MH+	Retention time (min)
50a		3-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-N,N-dimethylpyridine-2-carboxamide	606	1.92

Example 50a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.16-1.17 (3H, d), 1.60 (2H, bs), 1.96 (2H, bs), 2.55 (3H, s), 2.97 (3H, s), 3.10-3.17 (1H, td), 3.42-3.48 (1H, td), 3.58-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.15 (1H, bs), 4.45 (1H, bs), 6.45-6.46 (1H, d), 6.72 (1H, s), 7.41-7.43 (2H, d), 7.57-7.60 (1H, q), 7.84-7.86 (2H, d), 8.11-8.14 (1H, dd), 8.55 (1H, s), 8.84-8.85 (1H, dd).

mTOR Kinase Assay (Echo): 0.00794μM

The preparation of phenyl *N*-[4-[4-[1-[2-(dimethylcarbamoyl)pyridin-3-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[2-(dimethylcarbamoyl)pyridin-3-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

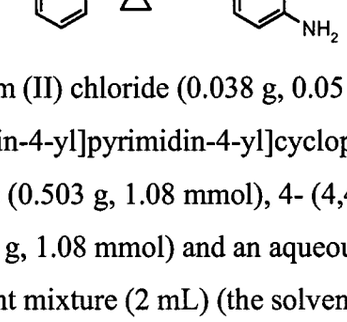


Phenyl chloroformate (0.071 mL, 0.57 mmol) was added dropwise to 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-2-carboxamide (0.296 g, 0.57 mmol) and sodium hydrogen carbonate (0.071 g, 0.85 mmol) in dioxane (18 mL) and the resulting solution stirred at RT for 3 hours. The solids were removed by filtration and the filtrate purified by flash silica chromatography, elution gradient 0 to 100% ethyl acetate in DCM, to give additional desired material as a yellow gum (0.227 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.22-1.24 (3H, d), 1.53-1.60 (2H, m), 2.13-2.17 (2H, m), 2.77 (3H, s), 3.14 (3H, s), 3.18-3.25 (1H, td), 3.50-3.57 (1H, td), 3.66-3.70 (1H, dd), 3.77-3.80 (1H, d), 3.98-3.99 (1H, dd), 4.08 (1H, bs), 4.38 (1H, bs), 6.69 (1H, s), 7.16-7.18 (2H, d), 7.21-7.25 (2H, m), 7.36-7.40 (2H, t), 7.48-7.50 (2H, d), 7.67 (1H, bs), 7.94-7.96 (1H, dd), 8.15-8.17 (2H, d), 8.70-8.72 (1H, dd).

LCMS Spectrum: m/z (ES+) (M+H)+=643; HPLC tR=3.09min.

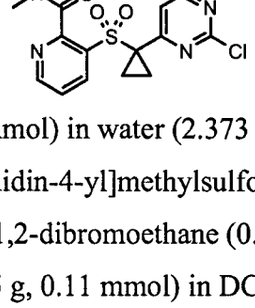
3-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-2-carboxamide



Bis(triphenylphosphine)palladium (II) chloride (0.038 g, 0.05 mmol) was added to 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-2-carboxamide (0.503 g, 1.08 mmol), 4- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.237 g, 1.08 mmol) and an aqueous solution of sodium carbonate (2.70 mL, 5.40 mmol) in a solvent mixture (2 mL) (the solvent mixture comprised 18% DMF, 82% of a 7:3:2 mixture of DME:Water:Ethanol) and the resulting solution stirred at 80°C for 15 hours. The reaction was cooled to RT and water was added. The solids were filtered to give the desired material. The filtrate was extracted with ethyl acetate and the organics dried ($MgSO_4$), filtered and evaporated to dryness to yield an additional sample of the desired material. Both crops of the desired material were combined and used without further purification.

LCMS Spectrum: m/z (ES+) (M+H)+=523; HPLC tR=1.85min.

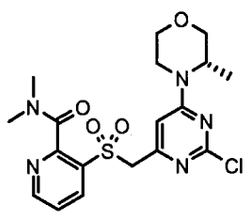
3-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-*N,N*-dimethylpyridine-2-carboxamide



Sodium hydroxide (2.373 g, 59.32 mmol) in water (2.373 mL) was added to 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-*N,N*-dimethylpyridine-2-carboxamide (0.475 g, 1.08 mmol), 1,2-dibromoethane (0.465 mL, 5.39 mmol) and tetrabutylammonium bromide (0.035 g, 0.11 mmol) in DCM and the resulting solution stirred at RT for 18 hours. Water was added and the solution was extracted with DCM. The organic layer was dried ($MgSO_4$) and filtered to give the desired material (0.539 g).

LCMS Spectrum: m/z (ES+) (M+H)+=466; HPLC tR=1.64min.

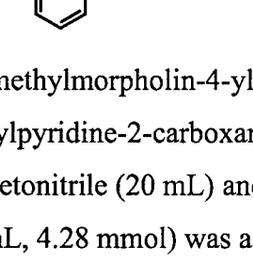
3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-*N,N*-dimethylpyridine-2-carboxamide



3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-*N,N*-dimethylpyridine-2-carboxamide (0.533 g, 1.31 mmol) was dissolved in dioxane (15 mL) and 2N sulfuric acid (0.041 mL) was added. The solution was heated to 55°C and a solution of sodium tungstate dihydrate (8.62 mg, 0.03 mmol) in water (0.4 mL) added and the solution allowed to stir for 10 minutes. Hydrogen peroxide (0.808 mL, 26.13 mmol) was then added dropwise over several minutes. The solution was heated at 55°C for 5.5 hours. The heat was removed and the reaction was allowed to stir at RT overnight. Water was added and the reaction was allowed to cool. The aqueous solution was extracted with DCM. The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 7% methanil (containing 0.1% ammonia) in DCM, to give the desired material as a yellow gum (0.475 g).

LCMS Spectrum: m/z (ES+) (M+H)+=440; HPLC tR=1.62min.

3-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-*N,N*-dimethylpyridine-2-carboxamide

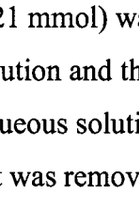


2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.009 g, 2.85 mmol) was added to *N,N*-dimethyl-3-sulfanylpyridine-2-carboxamide (0.520 g, 2.85 mmol) and DIPEA (0.746 mL, 4.28 mmol) in acetonitrile (20 mL) and the resulting solution stirred at RT for 2 hours. Further DIPEA (0.746 mL, 4.28 mmol) was added and the reaction was allowed to stir for several over a weekend. The reaction was heated at 40°C for 7 days. The solvent was removed and the residue dissolved in DCM and washed with water. The organic layer

was dried ($MgSO_4$), filtered and evaporated to afford crude product. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give material which was further purified by flash silica chromatography, elution gradient 0 to 7% methanol in DCM, to give the desired material as a brown gum (0.533 g).

LCMS Spectrum: m/z (ES+) (M+H)+=408; HPLC tR=1.57min.

N,N-Dimethyl-3-sulfanylpyridine-2-carboxamide

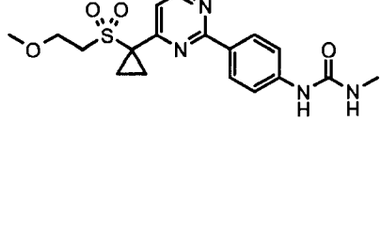


DIPEA (2.164 mL, 12.42 mmol) was added to 3-mercaptopicolinic acid (1.156 g, 7.45 mmol) and HATU (2.83 g, 7.45 mmol) in DMA (30 mL) and the resulting solution stirred at RT for 15 minutes. Dimethylamine (3.11 mL, 6.21 mmol) was added and the reaction was allowed to stir overnight. Water was added to the solution and the solution was extracted with DCM. The organics were washed with a saturated aqueous solution of sodium bicarbonate, dried ($MgSO_4$) and filtered. Most of the solvent was removed and diethyl ether added. The solid was removed by filtration and discarded. Water was added to the filtrate and the product extracted with ethyl acetate. The organics were dried ($MgSO_4$), filtered and evaporated to give the desired material (0.52 g).

LCMS Spectrum: m/z (ES-) (M-H)-=181; HPLC tR=1.17min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 51: 1-[4-[4-[1-(2-Methoxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



Bis(triphenylphosphine)palladium(II) chloride (5.8 mg, 0.827 mmol) was added to 2-chloro-4-[1-(2-methoxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (0.062 g, 0.17 mmol), 1-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (0.046 g, 0.17 mmol) and an aqueous solution of sodium carbonate (0.414 mL, 0.83 mmol) in a solvent mixture (2 mL) (the solvent mixture comprised 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol) at RT under an atmosphere of nitrogen. The resulting suspension was stirred at 80°C for 6 hours. The crude reaction mixture was put down an SCX column, eluting with 7M ammonia in methanol, to give a sample that was concentrated *in vacuo* and redissolved in DMF (2 mL). The mixture was purified by preparative HPLC to give the desired material as a white solid (17 mg).

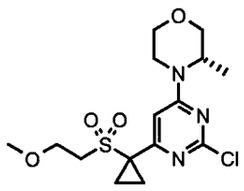
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22-1.23 (3H, d), 1.54-1.57 (2H, m), 1.64-1.66 (2H, m), 2.65-2.66 (3H, d), 3.16-3.23 (1H, td), 3.27 (3H, s), 3.44-3.51 (1H, td), 3.61-3.64 (1H, dd), 3.75-3.78 (1H, d), 3.80-3.81 (4H, t), 3.95-3.99 (1H, dd), 4.21 (1H, bs), 4.57 (1H, bs), 6.07-6.10 (1H, q), 6.76 (1H, s), 7.49-7.51 (2H, d), 8.17-8.19 (2H, d), 8.79 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=490; HPLC tR=1.93min.

mTOR Kinase Assay (Echo): 0.00332μM

The preparation of to 2-chloro-4-[1-(2-methoxyethylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine is described below.

2-Chloro-4-[1-(2-methoxyethylsulfonyl)cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



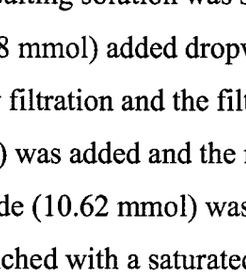
Sodium hydride (0.026 g, 1.07 mmol) was added to (S)-2-(1-(2-chloro-6-(3-methylmorpholino)pyrimidin-4-yl)cyclopropylsulfonyl)ethanol (0.231 g, 0.64 mmol) in THF (20 mL) cooled to 0°C under a nitrogen atmosphere. The resulting solution was stirred at 0°C for 10 minutes. To this solution, methyl iodide (0.040 mL, 0.64 mmol) was added and the reaction was slowly allowed to warm to RT. Water was carefully added and the reaction was

extracted with DCM. The organics were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a colourless dry film (0.062 g).

NMR Spectrum: ^1H NMR (400.132 MHz, $CDCl_3$) δ 1.31-1.32 (3H, d), 1.47-1.50 (2H, q), 1.79-1.82 (2H, q), 3.25-3.32 (1H, td), 3.35 (3H, s), 3.44-3.47 (2H, t), 3.49-3.56 (1H, td), 3.65-3.69 (1H, dd), 3.76-3.79 (1H, d), 3.79-3.85 (2H, m), 3.98-4.03 (2H, m), 4.33 (1H, bs), 6.84 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=376; HPLC tR=1.87min.

2-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylethanol

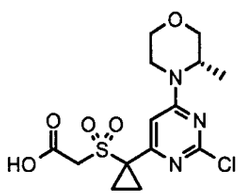


DIPEA (3.70 mL, 21.23 mmol) was added to 2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylacetic acid (3.99 g, 10.62 mmol) in THF cooled to 0°C under a nitrogen atmosphere. The resulting solution was stirred at 0°C for 5 minutes then ethyl chloroformate (1.117 mL, 11.68 mmol) added dropwise. The solution was allowed to stir for 1 hour, the solids removed by filtration and the filtrate cooled back to 0°C. Lithium borohydride (17.52 mL, 35.03 mmol) was added and the reaction was slowly allowed to warm to RT. Additional lithium borohydride (10.62 mmol) was added and the mixture stirred for several hours. The reaction was quenched with a saturated aqueous solution of ammonium chloride and then extracted with DCM. The organic layer was separated, washed with saturated brine, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a white solid (1.96 g).

NMR Spectrum: ^1H NMR (400.132 MHz, DMSO-d_6) δ 1.21-1.22(3H, d), 1.49-1.52(2H, m), 1.62-1.65(2H, m), 3.17-3.25(1H, td), 3.40-3.47(1H, td), 3.52-3.55(2H, t), 3.56-3.60(1H, dd), 3.71-3.74(1H, d), 3.79-3.84(2H, q), 3.92-3.95(1H, dd), 4.04(1H, bs), 4.40(1H, bs), 4.98-5.01(1H, t), 6.95(1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=362; HPLC tR=1.67 min.

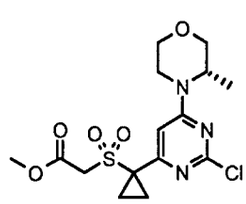
2-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylacetic acid



2 M Sodium hydroxide solution (13.85 mL, 27.70 mmol) was added to methyl 2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylacetate (3.60 g, 9.23 mmol) in THF (100 mL) and the resulting solution stirred at RT for 6 hours. The solution was adjusted to pH7 with 2M hydrochloric acid and salt was added to concentrate the solution. The aqueous solution was extracted with DCM, the organic layer separated, dried ($MgSO_4$), filtered and evaporated to the desired material as a white solid (3.45 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20-1.22(3H, d), 1.55-1.58(2H, q), 1.69-1.72(2H, q), 3.18-3.24(1H, m), 3.40-3.46(1H, td), 3.56-3.59(1H, dd), 3.71-3.74(1H, d), 3.92-3.95(1H, dd), 4.04(1H, bs), 4.41(1H, bs), 4.55(2H, s), 6.95(1H, s), 13.36(1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=376; HPLC tR=0.71 min.

Methyl 2-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylacetate



A solution of lithium diisopropylamide (2M solution in THF/n-heptane, 5.46 mL, 9.84 mmol) in THF (60 mL) was added to a stirred solution of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine (2.720 g, 8.20 mmol), and dimethyl carbonate (6.97 mL, 81.97 mmol) in THF (60 mL), cooled to -78°C, over a period of 5 minutes under an atmosphere of nitrogen. The resulting solution was very slowly allowed to come to RT with stirring over 18 hours. The reaction was cooled back to –78°C and further lithium diisopropylamide (2.73 mL , 4.92 mmol), and dimethyl carbonate (6.97 mL, 81.97 mmol) added. Again the mixture was allowed to warm slowly to RT with stirring over 24 hours. The reaction mixture was diluted with ethyl acetate (150 mL), washed with 1M citric acid (150

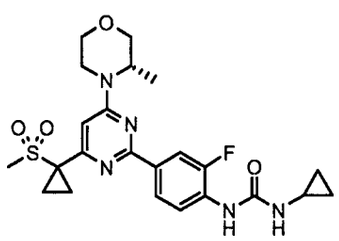
mL) and saturated brine (150 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, to give the desired material as a yellow gum.

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.33 (3H, d), 1.55 (2H, q), 1.91 (2H, q), 3.30 (1H, m), 3.50 (1H, s), 3.68 (1H, q), 3.79 (4H, t), 4.01 (2H, q), 4.28 (2H, s), 4.41 (1H, s), 6.78 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=390; HPLC tR=2.01 min.

The preparation of 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine was described earlier.

Example 52: 3-Cyclopropyl-1-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



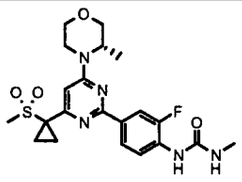
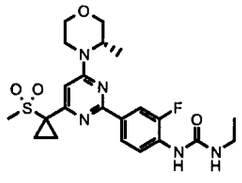
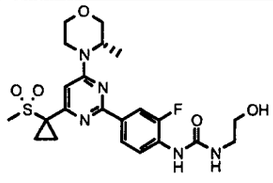
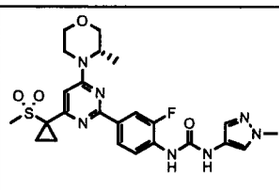
Cyclopropylamine (0.055 mL, 0.80 mmol) followed by triethylamine (0.067 mL, 0.48 mmol) were added to a solution of phenyl *N*-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (85.4mg, 0.16 mmol) in DMF (2 mL) and the reaction heated at 50°C overnight. The crude product was purified by preparative HPLC to give the desired material as a white solid (62 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.64-0.69 (2H, m), 1.23-1.25 (3H, d), 1.55-1.58 (2H, q), 1.66-1.69 (2H, q), 2.55-2.61 (1H, m), 3.18-3.25 (1H, td), 3.28 (3H, s), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 6.81 (1H, s), 6.88-6.89 (1H, d), 8.01-8.04 (1H, dd), 8.06-8.09 (1H, dd), 8.27-8.31 (1H, t), 8.36-8.37 (1H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+490 = HPLC tR =2.28 min.

mTOR Kinase Assay (Echo): 0.0184μM

The compounds below were prepared in an analogous fashion from phenyl *N*-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
52a		1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea	4.64	2.04
52b		3-ethyl-1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	478	2.21
52c		1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	4.94	1.80
52d		1-[2-fluoro-4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	530	2.07

Example 52a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.58 (2H, q), 1.66-1.69 (2H, q), 2.68-2.69 (3H, d), 3.18-3.25 (1H, td), 3.28 (3H, s), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.21-4.24 (1H, d), 4.57 (1H, bs), 6.55-6.58 (1H, q), 6.81 (1H, s), 8.00-8.04 (1H, dd), 8.05-8.08 (1H, dd), 8.26-8.31 (1H, t), 8.54-8.55 (1H, d).

mTOR Kinase Assay (Echo): 0.0103μM

Example 52b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06-1.10 (3H, t), 1.23-1.25 (3H, d), 1.55-1.58 (2H, q), 1.66-1.69 (2H, q), 3.11-3.18 (2H, m), 3.18-3.25 (1H, td), 3.28 (3H, s), 3.45-3.52 (1H, td), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, d), 3.96-3.99 (1H, dd), 4.21-4.24 (1H, d), 4.57 (1H, bs), 6.67-6.69 (1H, t), 6.81 (1H, s), 8.01-8.04 (1H, dd), 8.05-8.08 (1H, dd), 8.27-8.31 (1H, t), 8.47-8.48 (1H, d).

mTOR Kinase Assay (Echo): 0.0307μM

Example 52c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23-1.25 (3H, d), 1.55-1.58 (2H, q), 1.66-1.69 (2H, q), 3.17-3.25 (3H, m), 3.28 (3H, s), 3.45-3.65 (3H, m), 3.62-3.65 (1H, dd), 3.75-3.78 (1H, dd), 3.96-3.99 (1H, dd), 4.21-4.24 (1H, d), 4.58 (1H, bs), 4.73-7.76 (1H, t), 6.81 (1H, s), 6.84-6.87 (1H, t), 8.00-8.04 (1H, dd), 8.05-8.08 (1H, dd), 8.27-8.32 (1H, t), 8.63-8.64 (1H, d).

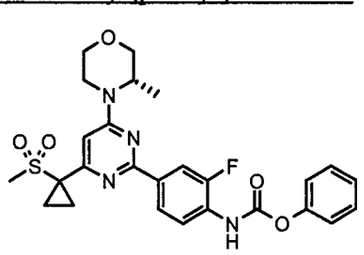
mTOR Kinase Assay (Echo): 0.0296μM

Example 52d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.25 (3H, d), 1.56-1.59 (2H, q), 1.67-1.70 (2H, q), 3.19-3.26 (1H, td), 3.29 (3H, s), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.80 (3H, s), 3.96-3.99 (1H, dd), 4.22-4.25 (1H, d), 4.58 (1H, bs), 6.83 (1H, s), 7.40 (1H, s), 7.79 (1H, s), 8.04-8.08 (1H, dd), 8.09-8.12 (1H, dd), 8.28-8.33 (1H, t), 8.67-8.68 (1H, d), 8.81 (1H, s).

mTOR Kinase Assay (Echo): 0.0107μM

The preparation of phenyl *N*-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate



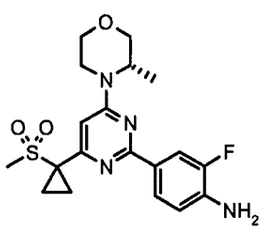
Phenyl chloroformate (0.116 mL, 0.93 mmol) was added to 2-fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (0.376 g, 0.93 mmol) and sodium hydrogen carbonate (0.117 g, 1.39 mmol) in dioxane (10 mL) and the

resulting solution stirred at RT for 2 hours. Water was added and the solution was extracted with DCM. The organics were dried ($MgSO_4$), filtered and evaporated. The residue was triturated with diethyl ether to give the desired material as a white solid (0.427 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24-1.26 (3H, d), 1.27-1.60 (2H, q), 1.68-1.70 (2H, q), 3.19-3.27 (1H, td), 3.28 (3H, s), 3.46-3.53 (1H, td), 3.62-3.66 (1H, dd), 3.76-3.79 (1H, d), 3.96-4.00 (1H, dd), 4.23-4.26 (1H, d), 4.59 (1H, bs), 6.87 (1H, s), 7.24-7.30 (3H, m), 7.43-7.47 (2H, t), 7.87-7.91 (1H, t), 8.08-8.18 (2H, dd), 10.15 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=527; HPLC tR=2.93 min.

2-Fluoro-4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline



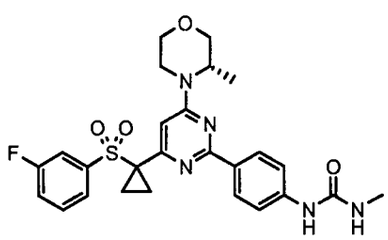
Bis(triphenylphosphine)palladium(II) chloride (0.031 g, 0.04 mmol) was added in one portion to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine (0.297 g, 0.90 mmol), 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.319 g, 1.34 mmol) and an aqueous solution of sodium carbonate (2.24 mL, 4.48 mmol) in a solvent mixture of 18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol. The resulting solution was stirred at 80°C under a nitrogen atmosphere for 30 minutes. The solvent was removed and the residue partitioned between water and ethyl acetate. The organic layer was dried ($MgSO_4$), filtered and purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a brown gum (0.376 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.31-1.33 (3H, d), 1.52-1.55 (2H, q), 1.81-1.84 (2H, q), 3.08 (3H, s), 3.26-3.33 (1H, td), 3.54-3.60 (1H, td), 3.70-3.73 (1H, dd), 3.79-3.80 (1H, d), 4.00-4.03 (3H, m), 4.13 (1H, bs), 4.46-4.47 (1H, bs), 6.72 (1H, s), 6.76-6.80 (1H, t), 7.99-8.02 (2H, m).

LCMS Spectrum: m/z (ES+)(M+H)+=407; HPLC tR=2.29 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine was described earlier.

Example 53: 1-[4-[4-[1-(3-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

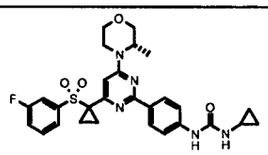
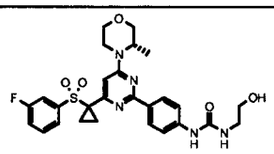
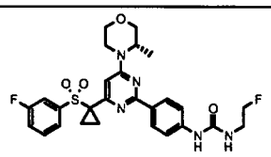
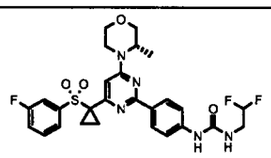


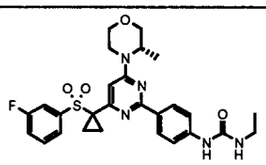
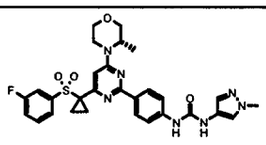
Methylamine (26.4 mg, 0.85 mmol) was added to phenyl *N*-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) in NMP (2 mL). The resulting solution was heated at 50°C for 2 days. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents, to give the desired material as a white solid (41 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.94 (2H, m), 2.67 (4H, m), 3.46 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.14 (1H, m), 4.44 (1H, m), 6.05 (1H, m), 6.65 (1H, s), 7.40 (2H, m), 7.63 (4H, m), 7.82 (2H, m), 8.72 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 526; HPLC tR = 2.07 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
53a		3-cyclopropyl-1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	552	2.28
53b		1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	556	1.97
53c		3-(2-fluoroethyl)-1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	558	2.27
53d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	576	2.39

Example	Structure	NAME	LCMS MH+	Retention time (min)
53e		1-ethyl-3-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	540	2.27
53f		1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	592	2.20

Example 53a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.43 (2H, m), 0.66 (2H, m), 1.19 (3H, d), 1.65 (2H, m), 1.94 (2H, m), 2.56 (1H, m), 3.16 (1H, m), 3.46 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.14 (1H, m), 4.44 (1H, m), 6.41 (1H, m), 6.65 (1H, s), 7.40 (2H, m), 7.62 (4H, m), 7.82 (2H, m), 8.52 (1H, s)

Example 53b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.93 (2H, m), 3.18 (3H, m), 3.46 (3H, m), 3.62 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.15 (1H, m), 4.43 (1H, m), 4.74 (1H, m), 6.23 (1H, m), 6.65 (1H, s), 7.39 (2H, m), 7.63 (4H, m), 7.83 (2H, m), 8.78 (1H, s)

Example 53c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.93 (2H, m), 3.16 (1H, m), 3.43 (3H, m), 3.62 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.43 (2H, m), 4.54 (1H, m), 6.42 (1H, m), 6.66 (1H, s), 7.40 (2H, m), 7.63 (4H, m), 7.83 (2H, m), 8.79 (1H, s)

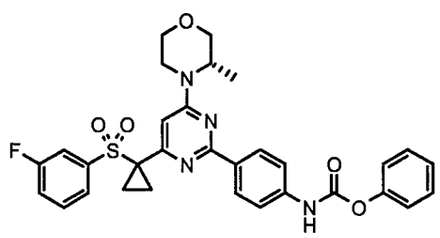
Example 53d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.94 (2H, m), 3.16 (1H, m), 3.53 (4H, m), 3.75 (1H, m), 3.96 (1H, m), 4.15 (1H, m), 4.45 (1H, m), 6.07 (1H, m), 6.53 (1H, m), 6.66 (1H, s), 7.41 (2H, m), 7.63 (4H, m), 7.84 (2H, m), 8.91 (1H, s)

Example 53e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.19 (3H, d), 1.65 (2H, m), 1.94 (2H, m), 3.13 (3H, m), 3.47 (1H, m), 3.62 (1H, m), 3.74 (1H, m), 3.96 (1H, m), 4.13 (1H, m), 4.44 (1H, m), 6.14 (1H, m), 6.65 (1H, s), 7.39 (2H, m), 7.63 (4H, m), 7.82 (2H, m), 8.64 (1H, s)

Example 53f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.65 (2H, m), 1.95 (2H, m), 3.17 (1H, m), 3.47 (1H, m), 3.62 (1H, m), 3.78 (4H, m), 3.97 (1H, m), 4.15 (1H, m), 4.45 (1H, m), 6.66 (1H, s), 7.42 (3H, m), 7.65 (4H, m), 7.77 (1H, s), 7.86 (2H, d), 8.38 (1H, s), 8.81 (1H, s)

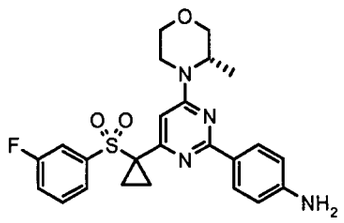
The preparation of phenyl *N*-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamateis described below:

Phenyl *N*-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.206 mL, 1.64 mmol) was added dropwise to 4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (770 mg, 1.64 mmol) and sodium bicarbonate (138 mg, 1.64 mmol) in dioxane (30 mL). The resulting solution was stirred at RT for 3 hours. The reaction mixture was filtered and the precipitate collected and redissolved in DCM (100 mL). This was washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a yellow gum (722 mg).
NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.95 (2H, m), 3.17 (1H, m), 3.46 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 6.70 (1H, s), 7.27 (3H, m), 7.55 (8H, m), 7.92 (2H, m), 10.40 (1H, s)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 589; HPLC tR = 3.02 min.

4-[4-[1-(3-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

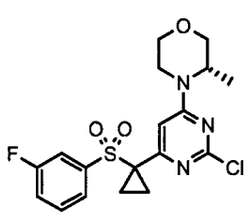


1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.747 g, 1.03 mmol) was added to 2-chloro-4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.25 g, 10.32 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.487 g, 11.35 mmol) in DME (200 mL) and sodium carbonate (5.47 g, 51.59 mmol) in water (25 mL) under nitrogen. The resulting solution was stirred at 80°C for 5 hours. The reaction mixture was diluted with DCM (200 mL), and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to afford crude product as a yellow gum. The crude product was further purified by flash silica chromatography, elution gradient 0 to 5% ethyl acetate in DCM, to give the desired material as a yellow gum (2.86 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.63 (2H, m), 1.92 (2H, m), 3.12 (1H, m), 3.45 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.11 (1H, m), 4.40 (1H, s), 5.52 (2H, s), 6.50 (2H, m), 6.57 (1H, m), 7.63 (6H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 469; HPLC tR = 2.35 min.

2-Chloro-4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



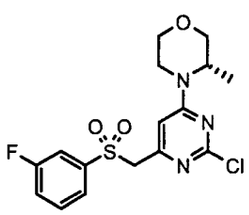
Sodium hydroxide (24.80 g, 620.07 mmol) in water (24.8 mL) was added to 2-chloro-4-[(3-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.35 g, 11.27 mmol), 1,2-dibromoethane (2.91 mL, 33.82 mmol) and tetrabutylammonium bromide (0.363

g, 1.13 mmol) in toluene (200 mL). The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was diluted with DCM (200 mL), and washed twice with water (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a white solid (4.25 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.63 (2H, m), 1.94 (2H, m), 3.18 (1H, m), 3.45 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.97 (2H, m), 4.32 (1H, m), 6.76 (1H, s), 7.69 (4H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 412; HPLC tR = 2.27 min.

2-Chloro-4-[(3-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



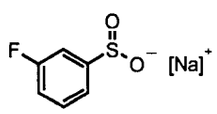
2-Chloro-4-(iodomethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (7 g, 19.80 mmol) was added to sodium 3-fluorobenzenesulfinate (5.41 g, 29.70 mmol) in acetonitrile (100 mL) under nitrogen. The resulting suspension was stirred at 80°C for 3 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (200 mL), and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over MgSO4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% ethyl acetate in DCM, to give the desired material as a white solid (6.38 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 3.16 (1H, m), 3.43 (1H, m), 3.58 (1H, m), 3.73 (1H, m), 3.93 (2H, m), 4.18 (1H, m), 4.71 (2H, s), 6.74 (1H, s), 7.68 (4H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 386; HPLC tR = 2.06 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

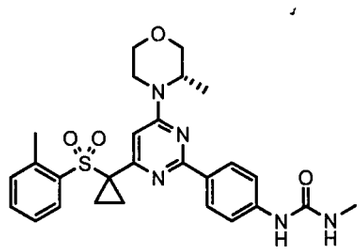
Sodium 3-fluorobenzenesulfinate



A solution of sodium sulphite (7.77 g, 61.66 mmol) in water (60 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (10.36 g, 123.32 mmol) was added and the resulting solution was stirred at 50°C for 1 hour. 3-Fluorobenzene-1-sulfonyl chloride (8.20 mL, 61.66 mmol) was added dropwise and the resulting solution was stirred at 50°C for 20 hours. The reaction mixture was evaporated to dryness and redissolved in MeOH. The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford the desired material (12.60 g) as a white solid, which was air dried overnight under vacuum and used without further purification.

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 7.03 (1H, m), 7.21 (1H, m), 7.29 (1H, m), 7.36 (1H, m)

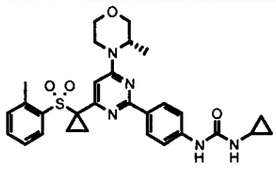
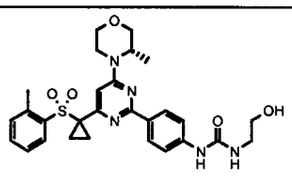
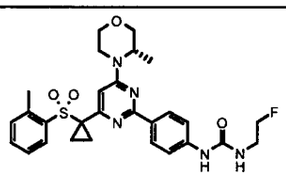
Example 54: 3-Methyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea

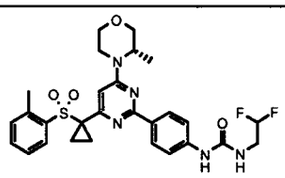
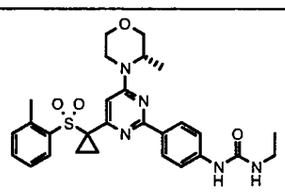
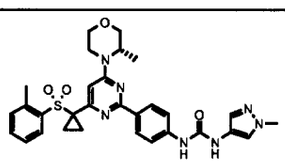


Methylamine (37.27 mg, 1.2 mmol) was added to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate (140 mg, 0.24 mmol) and triethylamine (0.2 mLl, 0.72 mmol) in NMP (2 mL). The resulting solution was heated at 50°C for 2 days. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material (87 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.45 (3H, s), 2.66 (3H, m), 3.12 (1H, m), 3.45 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.94 (1H, m), 4.06 (1H, m), 4.39 (1H, m), 6.05 (1H, m), 6.60 (1H, s), 7.37 (4H, m), 7.51 (1H, m), 7.85 (3H, m), 8.71 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 522; HPLC tR = 2.29 min.The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
54a		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	548	2.47
54b		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	552	2.09
54c		3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	554	2.42

Example	Structure	NAME	LCMS MH+	Retention time (min)
54d		3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	572	2.56
54e		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	536	2.45
54f		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	588	2.31

Example 54a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.42 (2H, m), 0.65 (2H, m), 1.15 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.46 (3H, s), 2.56 (1H, m), 3.13 (1H, m), 3.44 (1H, m), 3.59 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.07 (1H, m), 4.39 (1H, m), 6.42 (1H, m), 6.60 (1H, s), 7.37 (4H, m), 7.51 (1H, m), 7.84 (3H, m), 8.51 (1H, s)

Example 54b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.46 (3H, s), 3.14 (3H, m), 3.45 (3H, m), 3.59 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.07 (1H, m), 4.38 (1H, m), 4.74 (1H, t), 6.24 (1H, m), 6.60 (1H, s), 7.36 (4H, m), 7.51 (1H, m), 7.84 (3H, m), 8.77 (1H, s)

Example 54c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.45 (3H, s), 3.12 (1H, m), 3.43 (3H, m), 3.60 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.07 (1H, m), 4.40 (2H, m), 4.54 (1H, m), 6.42 (1H, m), 6.61 (1H, s), 7.37 (4H, m), 7.51 (1H, m), 7.85 (3H, m), 8.78 (1H, s)

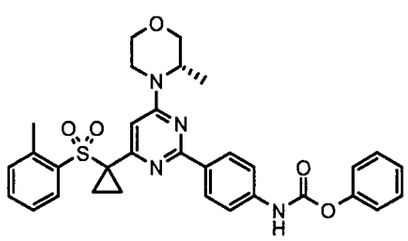
Example 54d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.46 (3H, s), 3.11 (1H, m), 3.51 (4H, m), 3.75 (1H, m), 3.95 (1H, m), 4.07 (1H, m), 4.39 (1H, m), 6.08 (1H, m), 6.52 (1H, m), 6.61 (1H, s), 7.38 (4H, m), 7.51 (1H, m), 7.85 (3H, m), 8.89 (1H, s)

Example 54e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.15 (3H, d), 1.66 (2H, m), 1.85 (2H, m), 2.45 (3H, s), 3.12 (3H, m), 3.44 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.06 (1H, m), 4.39 (1H, m), 6.15 (1H, m), 6.60 (1H, s), 7.37 (4H, m), 7.51 (1H, m), 7.84 (3H, m), 8.63 (1H, s)

Example 54f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.66 (2H, m), 1.86 (2H, m), 2.46 (3H, s), 3.12 (1H, m), 3.45 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.80 (3H, s), 3.95 (1H, m), 4.07 (1H, m), 4.39 (1H, m), 6.61 (1H, s), 7.43 (6H, m), 7.80 (2H, m), 7.90 (2H, m), 8.37 (1H, s), 8.80 (1H, s)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl N-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate



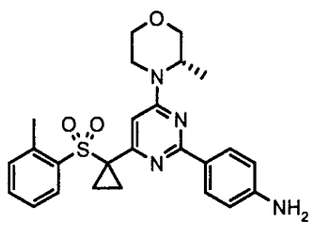
Phenyl chloroformate (0.205 mL, 1.64 mmol) was added dropwise to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]aniline (760 mg, 1.64 mmol) and sodium bicarbonate (151 mg, 1.80 mmol) in dioxane (30 mL). The resulting suspension was stirred at RT for 3 hours. The reaction mixture was filtered and the precipitate was redissolved in DCM (50 mL), and washed sequentially with water (50 mL)

and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a yellow gum (985 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.67 (2H, m), 1.87 (2H, m), 2.47 (3H, s), 3.12 (1H, m), 3.45 (1H, m), 3.61 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.08 (1H, m), 4.40 (1H, m), 6.64 (1H, s), 7.30 (5H, m), 7.49 (5H, m), 7.81 (1H, m), 7.95 (2H, m), 10.39 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 585; HPLC tR = 3.08 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]aniline

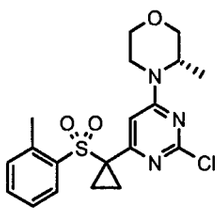


A solution of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidine (2.04 g, 5.00 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.205 g, 5.50 mmol) and sodium carbonate (2.120 g, 20.00 mmol) in DME (60 mL) and water (15.00 mL) was stirred under nitrogen for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (0.351 g, 0.50 mmol) was added and the resulting solution was stirred at 80°C for 2 hours. The reaction mixture was diluted with DCM (200 mL), and washed with water (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a yellow oil which solidified on standing (2.14 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.69 (2H, m), 1.87 (2H, m), 2.51 (3H, s), 3.12 (1H, m), 3.47 (1H, m), 3.63 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.08 (1H, m), 4.39 (1H, m), 5.56 (2H, s), 6.54 (3H, m), 7.39 (2H, m), 7.56 (1H, m), 7.77 (2H, m), 7.87 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 465; HPLC tR = 2.41 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidine

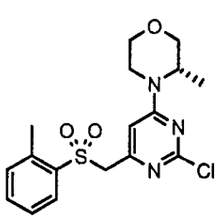


Sodium hydroxide (12.67 g, 317 mmol) in water (12.7 mL) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(2-methylphenyl)sulfonylmethyl]pyrimidine (2.2 g, 5.76 mmol), 1,2-dibromoethane (1.489 mL, 17.28 mmol) and tetrabutylammonium bromide (0.186 g, 0.58 mmol) in toluene (80 mL). The resulting solution was stirred at 60°C for 1 hour. The reaction mixture was diluted with DCM (200 mL), and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a colourless gum which solidified on standing (2.04 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.63 (2H, m), 1.86 (2H, m), 2.48 (3H, s), 3.14 (1H, m), 3.42 (1H, m), 3.58 (1H, m), 3.74 (1H, m), 3.95 (2H, m), 4.25 (1H, m), 6.70 (1H, s), 7.43 (2H, m), 7.63 (1H, m), 7.79 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 408; HPLC tR = 2.44 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(2-methylphenyl)sulfonylmethyl]pyrimidine



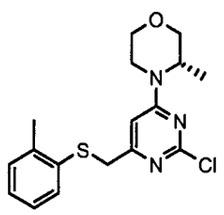
2N sulfuric acid (0.352 mL) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(2-methylphenyl)sulfanylmethyl]pyrimidine (4.37 g, 12.49 mmol) in dioxane (110 mL) and the solution heated to 55°C. Sodium tungstate dihydrate (0.082 g, 0.25 mmol) in water (3.5 mL) was added and the solution was allowed to stir for 5 minutes. Hydrogen peroxide (7.65 mL, 74.94 mmol) was added dropwise to the solution. The resulting solution was stirred at 55°C for 5 hours. The reaction was cooled to RT then water added until precipitation ceased. The

precipitate was collected by filtration, washed with water and dried under vacuum to afford the desired material as a white solid (3.70 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 (3H, d), 2.63 (3H, s), 3.14 (1H, m), 3.42 (1H, m), 3.56 (1H, m), 3.72 (1H, m), 3.93 (2H, m), 4.18 (1H, s), 4.59 (2H, s), 6.67 (1H, s), 7.44 (2H, m), 7.65 (2H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 382; HPLC tR = 2.23 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(2-methylphenyl)sulfanylmethyl]pyrimidine



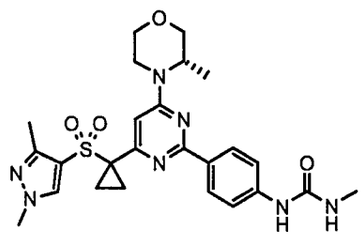
DIPEA (3.70 mL, 21.21 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol) and 2-methylbenzenethiol (2.5 mL, 21.21 mmol) in THF (80 mL). The resulting slurry was stirred at RT for 18 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% ethyl acetate in isohexane, to give the desired material as a yellow gum (4.37 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (3H, d), 2.28 (3H, s), 3.11 (1H, m), 3.40 (1H, m), 3.55 (1H, m), 3.69 (1H, m), 3.90 (2H, m), 4.04 (2H, m), 4.21 (1H, m), 6.65 (1H, s), 7.18 (3H, m), 7.37 (1H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 350; HPLC tR = 2.71 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 55: 1-[4-[4-[1-(1,3-Dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

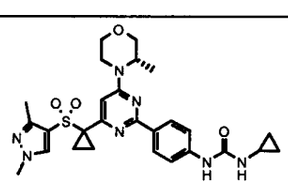


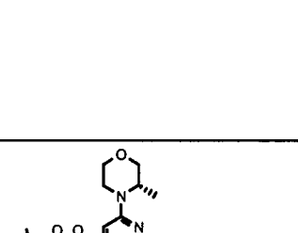
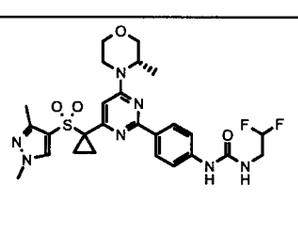
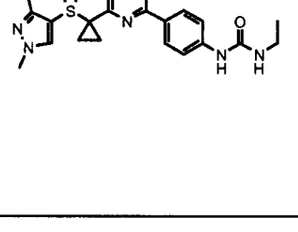
Methylamine (26.4 mg, 0.85 mmol) was added to phenyl *N*-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) and triethylamine (0.2 mL, 0.72 mmol) in NMP (2 mL). The resulting solution was heated at 50°C for 2 days. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material (77 mg).

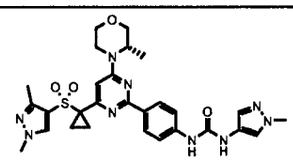
NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.54 (2H, m), 1.74 (2H, m), 2.03 (3H, s), 2.67 (3H, m), 3.20 (1H, m), 3.48 (1H, m), 3.63 (1H, m), 3.77 (4H, m), 3.98 (1H, m), 4.13 (1H, m), 4.46 (1H, m), 6.06 (1H, m), 6.70 (1H, s), 7.45 (2H, d), 7.98 (2H, d), 8.18 (1H, s), 8.72 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 526; HPLC tR = 1.87 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
55a		3-cyclopropyl-1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	552	2.02

Example	Structure	NAME	LCMS MH+	Retention time (min)
55b		1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	556	1.71
55c		1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	558	2.00
55d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	576	2.13
55e		3-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	540	2.00

Example	Structure	NAME	LCMS MH+	Retention time (min)
55f		1-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	592	1.92

Example 55a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.42 (2H, m), 0.65 (2H, m), 1.20 (3H, d), 1.54 (2H, m), 1.74 (2H, m), 2.03 (3H, s), 2.56 (1H, m), 3.18 (1H, m), 3.48 (1H, m), 3.63 (1H, m), 3.76 (4H, m), 3.98 (1H, m), 4.14 (1H, m), 4.45 (1H, m), 6.42 (1H, m), 6.70 (1H, s), 7.46 (2H, m), 7.99 (2H, m), 8.19 (1H, s), 8.53 (1H, s)

Example 55b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.54 (2H, m), 1.73 (2H, m), 2.03 (3H, s), 3.18 (3H, m), 3.47 (3H, m), 3.63 (1H, m), 3.76 (4H, m), 3.98 (1H, m), 4.14 (1H, m), 4.46 (1H, m), 4.74 (1H, t), 6.25 (1H, m), 6.70 (1H, s), 7.44 (2H, d), 7.98 (2H, d), 8.19 (1H, s), 8.79 (1H, s)

Example 55c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.54 (2H, m), 1.74 (2H, m), 2.03 (3H, s), 3.18 (2H, m), 3.39 (1H, m), 3.46 (2H, m), 3.63 (1H, m), 3.76 (4H, m), 3.98 (1H, m), 4.14 (1H, m), 4.49 (2H, m), 6.43 (1H, m), 6.70 (1H, s), 7.46 (2H, d), 7.99 (2H, d), 8.18 (1H, s), 8.80 (1H, s)

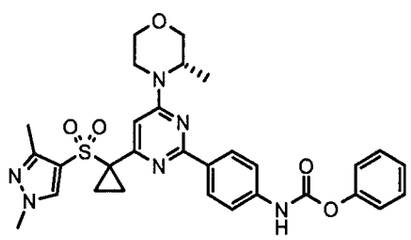
Example 55d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.55 (2H, m), 1.74 (2H, m), 2.02 (3H, s), 3.17 (1H, m), 3.54 (4H, m), 3.76 (4H, m), 3.97 (1H, m), 4.14 (1H, m), 4.47 (1H, m), 6.08 (1H, m), 6.52 (1H, m), 6.71 (1H, s), 7.46 (2H, m), 8.01 (2H, m), 8.19 (1H, s), 8.90 (1H, s)

Example 55e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 1.54 (2H, m), 1.74 (2H, m), 2.03 (3H, s), 3.15 (3H, m), 3.48 (1H, m), 3.63 (1H, m), 3.76 (4H, m), 3.98 (1H, m), 4.13 (1H, m), 4.46 (1H, m), 6.16 (1H, m), 6.70 (1H, s), 7.45 (2H, d), 7.98 (2H, d), 8.19 (1H, s), 8.65 (1H, s)

Example 55f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.54 (2H, m), 1.74 (2H, m), 2.04 (3H, s), 3.18 (1H, m), 3.49 (1H, m), 3.63 (1H, m), 3.77 (7H, m), 3.98 (1H, m), 4.15 (1H, m), 4.47 (1H, m), 6.71 (1H, s), 7.39 (1H, s), 7.50 (2H, d), 7.77 (1H, s), 8.02 (2H, d), 8.19 (1H, s), 8.38 (1H, s), 8.82 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

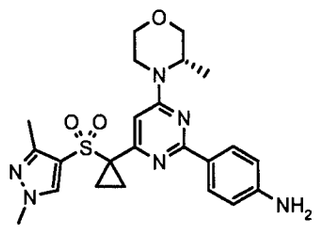


Phenyl chloroformate (0.201 mL, 1.60 mmol) was added dropwise to 4-[4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (750mg, 1.60 mmol) and sodium bicarbonate (148 mg, 1.76 mmol) in dioxane (30 mL). The resulting suspension was stirred at RT for 3 hours. The reaction mixture was filtered and the precipitate was redissolved in DCM (50 mL), and washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as an orange gum which formed a foam solid when heated in desiccator (1.030 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.55 (2H, m), 1.75 (2H, m), 2.04 (3H, s), 3.20 (1H, m), 3.49 (1H, m), 3.63 (1H, m), 3.76 (4H, m), 3.98 (1H, m), 4.16 (1H, m), 4.48 (1H, m), 6.75 (1H, s), 7.28 (3H, m), 7.45 (2H, m), 7.59 (2H, m), 8.07 (2H, m), 8.20 (1H, s), 10.43 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 589; HPLC tR = 2.63 min.

4-[4-[1-(1,3-Dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

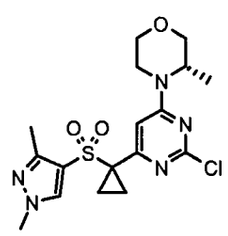


A solution of 2-chloro-4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.44 g, 5.92 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.428 g, 6.52 mmol) and sodium carbonate (2.51 g, 23.69 mmol) in DME (60 mL) and water (15 mL) was stirred under nitrogen for 5 minutes. Dichlorobis(triphenylphosphine)palladium(II) (0.416 g, 0.59 mmol) was added and the resulting solution was stirred at 80°C for 5 hours. The reaction mixture was diluted with DCM (200 mL), and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 1% MeOH in DCM, to give crude product. The crude product was further purified by ion exchange chromatography using an SCX column, eluting with 2M ammonia in methanol, to give the desired material as a orange solid (1.25 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.52 (2H, m), 1.72 (2H, m), 2.04 (3H, s), 3.15 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.75 (4H, m), 3.97 (1H, m), 4.09 (1H, m), 4.42 (1H, m), 5.52 (2H, s), 6.57 (3H, m), 7.82 (2H, m), 8.17 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 469; HPLC tR = 1.87 min.

2-Chloro-4-[1-(1,3-dimethylpyrazol-4-yl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

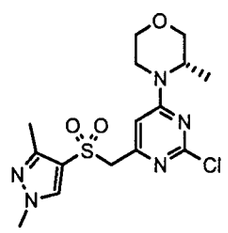


Sodium hydroxide (14.54 g, 363.47 mmol) in water (14.5 mL) was added to a stirred solution of 2-chloro-4-[(1,3-dimethylpyrazol-4-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.55 g, 6.61 mmol), 1,2-dibromoethane (1.708 mL, 19.83 mmol) and tetrabutylammonium bromide (0.213 g, 0.66 mmol) in toluene (100 mL).The resulting solution was stirred at 60°C for 3 hours. The reaction mixture was diluted with DCM (200 mL), and washed sequentially with water (200 mL) and saturated brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a white solid (2.44 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.48 (2H, m), 1.70 (2H, m), 2.05 (3H, s), 3.17 (1H, m), 3.42 (1H, m), 3.57 (1H, m), 3.72 (1H, m), 3.80 (3H, s), 3.93 (2H, m), 4.30 (1H, m), 6.77 (1H, s), 8.20 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 412; HPLC tR = 1.69 min.

2-Chloro-4-[(1,3-dimethylpyrazol-4-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



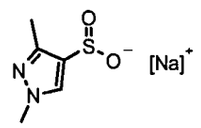
2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol) was added to sodium 1,3-dimethyl-1*H*-pyrazole-4-sulfinate (4.79 g, 26.29 mmol) in DMF (80 mL). The resulting solution was stirred at RT for 18 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a white solid (4.55 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 2.13 (3H, s), 3.18 (1H, m), 3.44 (1H, m), 3.58 (1H, m), 3.73 (1H, m), 3.80 (3H, s), 3.94 (2H, m), 4.22 (1H, s), 4.46 (2H, s), 6.72 (1H, s), 8.14 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 386; HPLC tR = 1.63 min.

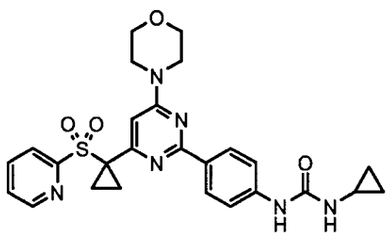
The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Sodium 1,3-dimethyl-1*H*-pyrazole-4-sulfinate



A solution of sodium sulfite (2.82 g, 22.35 mmol) in water (30 mL) was stirred for 10 minutes at RT. Sodium bicarbonate (3.75 g, 44.70 mmol) was added and the solution was stirred for 1 hour at 50°C. 1,3-Dimethyl-1*H*-pyrazole-4-sulfonyl chloride (4.35 g, 22.35 mmol) was added portionwise and the resulting solution was stirred at 50°C for 18 hours. The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford the desired material as a white solid, which was air dried overnight under vacuum and used without further purification (4.79 g).

Example 56: 3-Cyclopropyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea



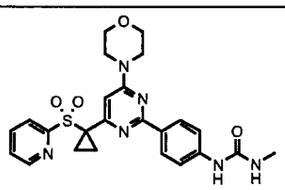
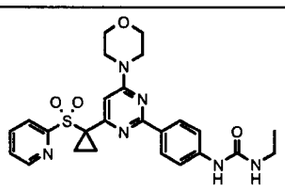
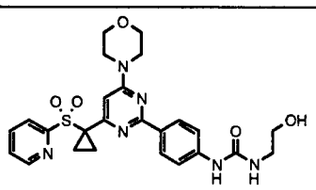
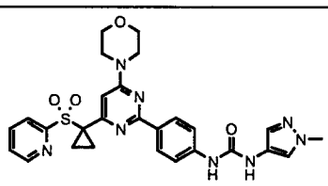
A solution of phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (0.100g, 0.18mmol), cycloprpylamine (0.90 mmol) and triethylamine (0.076 mL, 0.54 mmol) in NMP (2 mL) was heated at 50°C for 16 hours. The crude product was purified by preparative HPLC, using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as a solid (75 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44 (2H, m), 0.63-0.67 (2H, m), 1.71-1.74 (2H, q), 1.98-2.01 (2H, q), 2.54-2.58 (1H, m), 3.63-3.65 (4H, m), 3.68-3.70 (4H,

m), 6.40-6.41 (1H, d), 6.71 (1H, s), 7.35-7.37 (2H, d), 7.68-7.70 (2H, d), 7.73-7.76 (1H, m), 7.96-7.99 (1H, dt), 8.06-8.10 (1H, td), 8.49 (1H, s), 8.82-8.83 (1H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 521; HPLC tR = 1.99min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
56a		3-methyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	495	1.82
56b		3-ethyl-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	509	1.96
56c		3-(2-hydroxyethyl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	525	1.65
56d		3-(1-methylpyrazol-4-yl)-1-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	561	1.88

Example 56a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.70-1.74 (2H, q), 1.98-2.01 (2H, q), 2.65-2.66 (3H, d), 3.63-3.65 (4H, m), 3.68-3.70 (4H, m), 6.02-6.06 (1H, q), 6.71 (1H, s), 7.34-7.37 (2H, d), 7.67-7.70 (2H, d), 7.73-7.76 (1H, m), 7.96-7.98 (1H, dt), 8.06-8.10 (1H, td), 8.69 (1H, s), 8.82-8.84 (1H, m).

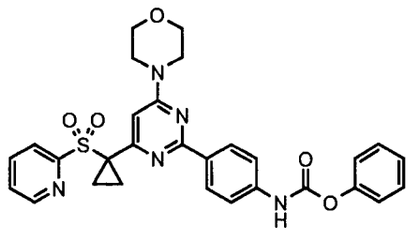
Example 56b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.70-1.73 (2H, q), 1.98-2.01 (2H, q), 3.09-3.16 (2H, m), 3.63-3.64 (4H, m), 3.68-3.69 (4H, m), 6.12-6.15 (1H, t), 6.71 (1H, s), 7.33-7.36 (2H, d), 7.67-7.70 (2H, d), 7.73-7.76 (1H, m), 7.96-7.99 (1H, dt), 8.06-8.10 (1H, td), 8.61 (1H, s), 8.82-8.83 (1H, m).

Example 56c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.70-1.74 (2H, q), 1.98-2.01 (2H, q), 3.15-3.19 (2H, m), 3.44-3.48 (2H, m), 3.63-3.65 (4H, m), 3.68-3.69 (4H, m), 4.71-4.74 (1H, t), 6.23-6.24 (1H, t), 6.71 (1H, s), 7.33-7.35 (2H, d), 7.68-7.70 (2H, d), 7.73-7.76 (1H, m), 7.96-7.99 (1H, dt), 8.06-8.10 (1H, td), 8.76 (1H, s), 8.82-8.84 (1H, m).

Example 56d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.71-1.74 (2H, q), 1.99-2.02 (2H, q), 3.64-3.66 (4H, m), 3.68-3.71 (4H, m), 3.79 (3H, s), 6.73 (1H, s), 7.38-7.41(3H m), 7.71-7.76 (4H, m), 7.97-7.99 (1H, dt), 8.07-8.11 (1H, td), 8.36 (1H, s), 8.79 (1H, s), 8.83-8.84 (1H, m).

The preparation of phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

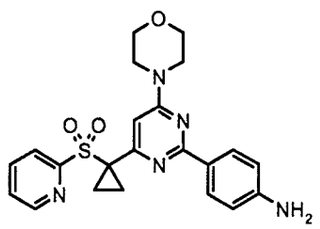
Phenyl *N*-[4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.363 mL, 2.89 mmol) was added to 4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (1.265 g, 2.89 mmol) and sodium hydrogen carbonate (0.364 g, 4.34 mmol) in DCM (50 mL) at RT and the resulting suspension stirred for 2 hours. The mixture was washed with water, dried over $MgSO_4$, filtered and evaporated and the resultant gum dried in the vacuum oven at 50°C overnight to give the desired material as a colorless gum (1.86 g).

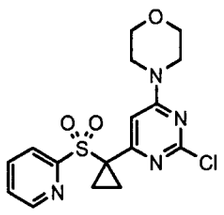
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.73-1.77 (2H, q), 1.99-2.03 (2H, q), 3.68-3.69(8H, m), 6.77 (1H, s), 7.24-7.32 (3H, m), 7.44-7.52 (4H, m), 7.74-7.77 (1H, m), 7.80-7.82 (2H, d), 7.98-8.01 (1H, dt), 8.07-8.11 (1H, td), 8.83-8.85 (1H, dq), 10.4 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=558; HPLC tR=2.75 min.

4-[4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]aniline



Bis(triphenylphosphine)palladium(II) chloride (0.131 g, 0.19 mmol) was added in one portion to 2-chloro-4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidine (1.42 g, 3.73 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.817 g, 3.73 mmol) and 2M aquoeus sodium carbonate solution (9.32 mL, 18.64 mmol) in a DMF solution (18% DMF, 82% of a 7:3:2 mixture of DME:water:Ethanol) at 22°C under nitrogen. The resulting solution was stirred at 80°C for 3 hours. The solvent was removed, ethyl acetate added and the organics washed with water. Precipitate was observed in the aqueous layer and was isolated by filtration to give crude product. This material was dissolved in DCM and insoluble material removed by filtration and discarded. The filtrate was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give material which was further purified by flash silica chromatography, elution gradient 0 to 60% ethyl acetate in DCM, to give the desired material as a white solid (1.265 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.68-1.71 (2H, q), 1.96-2.00 (2H, q), 3.59-3.61 (4H, m), 3.66-3.69 (4H, m), 5.48-5.50 (1H, d (NH2), 6.45-6.47 (2H, d), 6.61 (1H, s), 7.52-7.54 (2H, d), 7.72-7.75 (1H, m), 7.96-7.98 (1H, dt), 8.05-8.10 (1H, td), 8.81-8.83 (1H, dq).
LCMS Spectrum: m/z (ES+)(M+H)+=438; HPLC tR=1.93 min.

2-Chloro-4-morpholin-4-yl-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidine

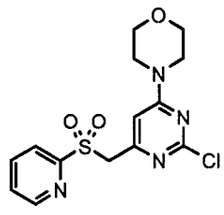


Sodium hydroxide (50%w/w solution) (12.71 g, 317.77 mmol) was added to 2-chloro-4-morpholin-4-yl-6-(pyridin-2-ylsulfonylmethyl)pyrimidine (2.050 g, 5.78 mmol), 1,2-dibromoethane (1.494 mL, 17.33 mmol) and tetrabutylammonium bromide (0.186 g, 0.58 mmol) in toluene (50 mL) at RT. The resulting suspension was stirred at 60°C overnight. Water was added and the layers were separated. The organic layer was washed twice with water, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a white solid (1.42 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.63-1.66 (2H, q), 1.91-1.95 (2H, q), 3.55 (4H, bs), 3.63-3.65 (4H, t), 6.84 (1H, s), 7.73-7.76 (1H, m), 7.98-8.00 (1H, dt), 8.10-8.14 (1H, td), 8.77-8.79 (1H, dt).

LCMS Spectrum: m/z (ES+)(M+H)+=381; HPLC tR=1.71 min.

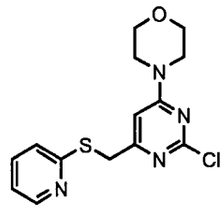
2-Chloro-4-morpholin-4-yl-6-(pyridin-2-ylsulfonylmethyl)pyrimidine



2-Chloro-4-morpholin-4-yl-6-(pyridin-2-ylsulfanylmethyl)pyrimidine (4.96 g, 15.36 mmol) was dissolved in dioxane (70 mL) and 2N sulfuric acid (0.362 mL) was added. The solution was heated to 55°C. Sodium tungstate dihydrate (0.101 g, 0.31 mmol) dissolved in water (3.54 mL) was added to the solution and allowed to stir for 10 minutes. Hydrogen peroxide (9.50 mL, 307.30 mmol) was then added dropwise over several minutes. The solution was heated at 55°C for 4 hours. Water (300mL) was added and the reaction was allowed to cool. The reaction mixture was extracted with DCM, the organic layer dried over $MgSO_4$, filtered and evaporated to afford desired product as a pale yellow solid (5.09g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 3.64 (3H, bs), 3.75-3.77(5H, t), 4.56 (2H, s), 6.60 (1H, s), 7.57-7.61 (1H, m), 7.97-7.97 (2H, m), 8.78-8.80 (1H, dt).
LCMS Spectrum: m/z (ES+)(M+H)+=355; HPLC tR=1.51 min.

2-Chloro-4-morpholin-4-yl-6-(pyridin-2-ylsulfanylmethyl)pyrimidine

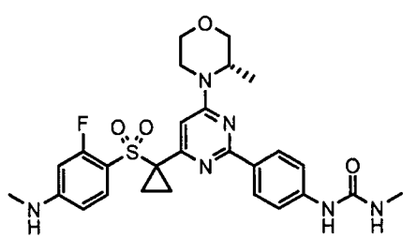


2-Chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine (6.60 g, 19.44 mmol) was added to 2-mercaptopyridine (3.24 g, 29.16 mmol) and DIPEA (5.08 mL, 29.16 mmol) in acetonitrile (140 mL) at RT. The resulting solution was stirred at RT for 2 hours then evaporated to dryness, redissolved in DCM and washed sequentially with water and saturated brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a beige oil which solidified on standing (4.96 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 3.52 (4H, bs), 3.64-3.67 (4H, t), 4.27 (2H, s), 6.58 (1H, s), 6.93-6.96 (1H, q), 7.11-7.13 (1H, dd), 7.41-7.45 (1H, td), 8.34-8.36 (1H, dt).
LCMS Spectrum: m/z (ES+)(M+H)+=323; HPLC tR=1.98 min.

The preparation of 2-chloro-4-(iodomethyl)-6-morpholin-4-ylpyrimidine was described earlier.

Example 57: 1-[4-[4-[1-(2-Fluoro-4-methylaminophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

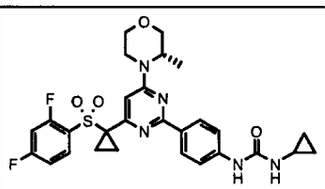
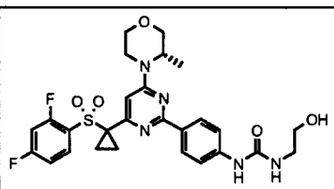


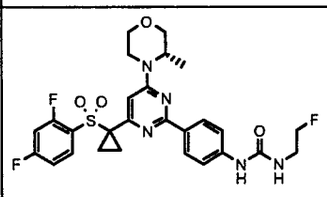
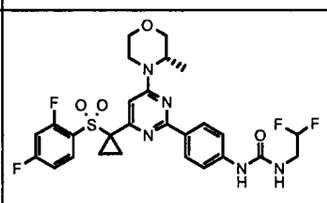
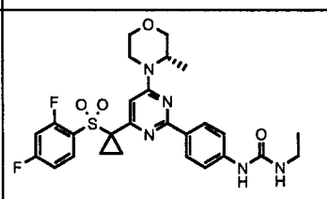
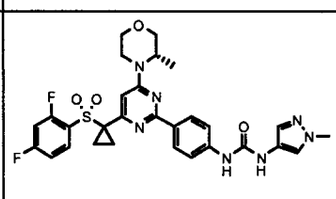
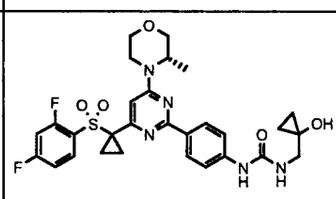
Phenyl *N*-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.15 g, 0.25 mmol), triethylamine (0.103 mL, 0.74 mmol) and methylamine solution (2M in THF, 1.236 mL, 2.47 mmol) were added to dioxane (10 mL) and heated at 50°C over the weekend. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (0.074 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.51 - 1.48 (2H, m), 1.82 - 1.78 (2H, m), 2.66 (3H, d), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.06 (1H, d), 4.43 (1H, s), 6.04 (1H, q), 6.33 - 6.32 (1H, m), 6.38 (1H, dd), 6.43 (1H, ddd), 6.54 (1H, s), 7.47 (3H, m), 7.95 (2H, d), 8.72 (1H, s);

LCMS Spectrum: m/z (ES+)(M+H)+=555; HPLC tR=2.40 min.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
57a		3-cyclopropyl-1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	570	2.51
57b		1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	573	1.96

Example	Structure	NAME	LCMS MH+	Retention time (min)
57c		1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	576	2.47
57d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	595	2.60
57e		3-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	558	2.48
57f		1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	610	2.35
57g		1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea	600	2.31

Example 57a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.43 - 0.40 (2H, m), 0.67 - 0.62 (2H, m), 1.19 (3H, d), 1.67 - 1.64 (2H, m), 1.91 - 1.89 (2H, m), 2.57 - 2.54 (1H, m), 3.16 (1H,

ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.46 (1H, s), 6.39 (1H, s), 6.69 (1H, s), 7.20 (1H, ddd), 7.38 (2H, d), 7.65 - 7.59 (1H, m), 7.77 - 7.72 (3H, m), 8.51 (1H, s).

Example 57b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.67 - 1.63 (2H, m), 1.91 - 1.87 (2H, m), 3.17 (3H, m), 3.48 - 3.42 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, d), 4.15 (1H, d), 4.46 (1H, s), 4.72 (1H, t), 6.22 (1H, t), 6.68 (1H, s), 7.20 (1H, ddd), 7.36 (2H, d), 7.65 - 7.60 (1H, m), 7.77 - 7.72 (3H, m), 8.78 (1H, s).

Example 57c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.67 - 1.64 (2H, m), 1.91 - 1.89 (2H, m), 3.16 (1H, ddd), 3.38 (1H, q), 3.49 - 3.43 (2H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.41 (1H, t), 4.47 (1H, s), 4.53 (1H, t), 6.40 (1H, t), 6.69 (1H, s), 7.20 (1H, ddd), 7.38 (2H, d), 7.65 - 7.60 (1H, m), 7.77 - 7.71 (3H, m), 8.79 (1H, s).

Example 57d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.67 - 1.64 (2H, m), 1.92 - 1.87 (2H, m), 3.16 (1H, ddd), 3.63 - 3.43 (4H, m), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.47 (1H, s), 6.07 (1H, ddt), 6.49 (1H, t), 6.69 (1H, s), 7.20 (1H, t), 7.39 (1H, d), 7.65 - 7.60 (1H, m), 7.76 - 7.71 (4H, m), 8.90 (1H, s).

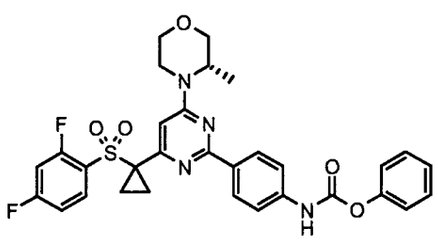
Example 57e: Spectrum not recorded.

Example 57f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.67 - 1.64 (2H, m), 1.92 - 1.90 (2H, m), 3.16 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.75 (1H, d), 3.79 (3H, s), 3.96 (1H, d), 4.16 (1H, d), 4.48 (1H, s), 6.70 (1H, s), 7.20 (1H, ddd), 7.38 (1H, s), 7.42 (2H, d), 7.66 - 7.61 (1H, m), 7.78 - 7.71 (4H, m), 8.34 (1H, s), 8.82 (1H, s).

Example 57g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.51 - 0.48 (2H, m), 0.60 - 0.57 (2H, m), 1.19 (3H, d), 1.67 - 1.62 (2H, m), 1.91 - 1.87 (2H, m), 3.22 (2H, d), 3.29 - 3.27 (1H, m), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.17 - 4.14 (1H, m), 4.47 (1H, s), 6.29 (1H, t), 6.68 (1H, s), 7.20 (1H, t), 7.36 (2H, d), 7.63 (1H, t), 7.73 (3H, d), 8.78 (1H, s).

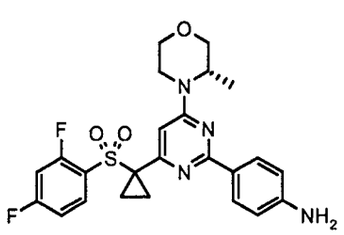
The preparation of phenyl *N*-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



4-[4-[1-(2,4-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2.1 g, 4.32 mmol) and sodium bicarbonate (0.725 g, 8.63 mmol) were added to dioxane (50 mL) and stirred for 10 minutes. Phenyl chloroformate (0.704 mL, 5.61 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with 1.0 N citric acid (50 mL), extracted with ethyl acetate (3 x 75 mL), the organic layer was dried over MgSO4, filtered and evaporated to afford an orange solid. This was dissolved in DCM, the solvent was slowly removed until a solid was observed. Diethyl ether was then added to the solution with rapid stirring to afford the desired material as a white solid (1.65 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.69 - 1.66 (2H, m), 1.92 - 1.89 (2H, m), 3.18 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.36 - 4.10 (1H, m), 4.55 - 4.44 (1H, m), 6.75 (1H, s), 7.30 - 7.18 (4H, m), 7.47 - 7.43 (2H, m), 7.54 (2H, d), 7.64 (1H, t), 7.78 - 7.72 (1H, m), 7.85 (2H, d), 10.43 (1H, s).
LCMS Spectrum: m/z (ESI+) (M+H)+ = 607; HPLC tR = 2.97 min

4-[4-[1-(2,4-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



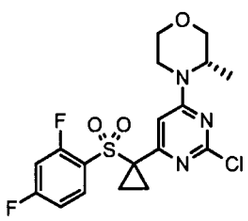
2-Chloro-4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.61 g, 8.40 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.208 g, 10.08 mmol), sodium carbonate (4.45 g, 41.99 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.608 g, 0.84 mmol) were added to

DME (60.0 mL) and water (15 mL) and heated to 90°C over a period of 2 hours under nitrogen. The solvent was evaporated and the residue was quenched water (100 mL), extracted with ethyl acetate (3 x 75 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford a black gum. The crude product was purified by flash silica chromatography, elution gradient 40 to 100% ethyl acetate in isohexane, to give the desired material as a yellow gum (2.2 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.29 (3H, d), 1.58 - 1.55 (1H, m), 1.66 - 1.62 (1H, m), 2.11 - 2.04 (2H, m), 3.26 (1H, ddd), 3.57 (1H, ddd), 3.72 (1H, dd), 3.80 (1H, d), 3.86 (2H, s), 4.02 (1H, dd), 4.11 (1H, m), 4.43 - 4.36 (1H, m), 6.60 (2H, d), 6.65 (1H, s), 6.86 - 6.82 (1H, m), 6.91 (1H, ddd), 7.75 - 7.69 (1H, m), 7.85 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 487; HPLC tR = 2.56 min.

2-Chloro-4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

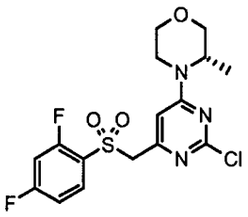


Sodium hydroxide (50%w/w solution) (32.7 g, 817.17 mmol) was added to 2-chloro-4-[(2,4-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (6.0 g, 14.86 mmol), 1,2-dibromoethane (3.84 mL, 44.57 mmol) and tetrabutylammonium bromide (0.479 g, 1.49 mmol) in toluene (75 mL) at RT. The resulting suspension was stirred at 60°C overnight. Water (100 mL) was added and the mixture was extracted with ethyl acetate (3 x 100 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give a crude material which was dissolved in hot diethyl ether and then stirred for 2 hours to afford the desired material as a white solid (3.61 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.30 (3H, d), 1.56 - 1.52 (1H, m), 1.62 - 1.59 (1H, m), 2.10-2.00 (2H, m), 3.26 (1H, ddd), 3.53 (1H, ddd), 3.68 (1H, dd), 3.78 (1H, d), 4.00 (2H, dd), 4.26 (1H, s), 6.81 (1H, s), 6.99 - 6.90 (2H, m), 7.77 - 7.71 (1H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 430; HPLC tR = 2.48 min

2-Chloro-4-[(2,4-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



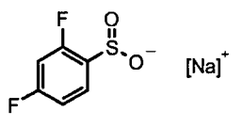
2,4-Difluorobenzenesulfinic acid, sodium salt (3.98 g, 19.80 mmol) and 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7 g, 19.80 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a brown gun, this was quenched with saturated aqueous ammonium chloride solution (50 mL), extracted with diethyl ether (3 x 75 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford a brown solid. The crude material was passed through a plug of silica, eluting with 80% ethyl acetate in isohexane, to give crude material which was triturated with diethyl ether to give the desired material as a white solid (7.04 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.32 (3H, d), 3.28 (1H, ddd), 3.54 (1H, ddd), 3.69 (1H, dd), 3.79 (1H, d), 4.03 - 3.99 (2H, m), 4.28 (1H, s), 4.43 (2H, s), 6.55 (1H, s), 7.03 - 6.98 (2H, m), 7.78 - 7.72 (1H, m).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 404; HPLC tR = 2.30 min;

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

2,4-Difluorobenzenesulfinic acid, sodium salt

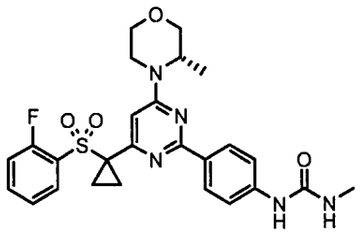


A solution of sodium sulfite (29.6 g, 235.18 mmol) in water (200 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (39.5 g, 470.36 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 2,4-Difluorobenzene-1-sulfonyl chloride (50 g, 235.18 mmol) was added portion wise to the solution and was stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and re-dissolved in methanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered

and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (41.6 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 7.10 - 7.04 (2H, m), 7.74 - 7.68 (1H, m);

Example 58: 1-[4-[4-[1-(2-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

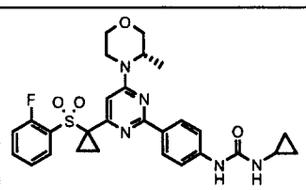
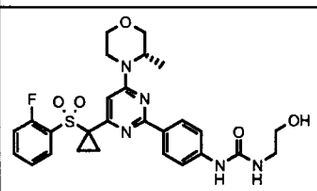
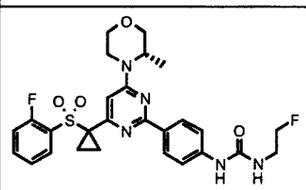
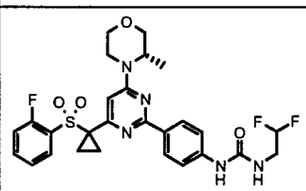
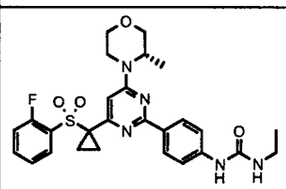
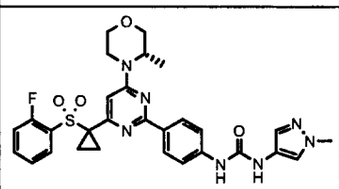


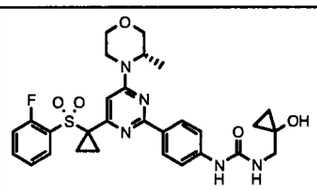
Phenyl *N*-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.2 g, 0.34 mmol) and methylamine solution (2M in THF, 1.699 mL, 3.40 mmol) were added to dioxane (10 mL) and stirred overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (0.119 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.94 - 1.89 (2H, m), 2.66 (3H, d), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.42 (1H, s), 6.04 (1H, q), 6.66 (1H, s), 7.37 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.70 (4H, m), 8.69 (1H, s);

m/z (ESI+) (M+H)+ = 526; HPLC tR = 2.34 min;

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
58a		3-cyclopropyl-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	552	2.45
58b		1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	556	2.09
58c		3-(2-fluoroethyl)-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	558	2.41
58d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	576	2.53
58e		1-ethyl-3-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	540	2.41
58f		1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	591	2.31

Example	Structure	NAME	LCMS MH+	Retention time (min)
58g		1-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea	582	2.26

Example 58a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.43 - 0.40 (2H, m), 0.67 - 0.62 (2H, m), 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.95 - 1.87 (2H, m), 2.58 - 2.51 (1H, m), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.43 (1H, s), 6.40 (1H, d), 6.66 (1H, s), 7.37 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.79 - 7.70 (4H, m), 8.48 (1H, s);

Example 58b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.93 - 1.89 (2H, m), 3.19 - 3.10 (3H, m), 3.48 - 3.42 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.43 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.66 (1H, s), 7.35 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.70 (4H, m), 8.75 (1H, s);

Example 58c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.94 - 1.88 (2H, m), 3.14 (1H, ddd), 3.48 - 3.36 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.46 - 4.40 (2H, m), 4.53 (1H, t), 6.41 (1H, t), 6.66 (1H, s), 7.37 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.69 (4H, m), 8.76 (1H, s);

Example 58d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.71 - 1.67 (2H, m), 1.94 - 1.89 (2H, m), 3.14 (1H, ddd), 3.55 - 3.42 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.13 (1H, d), 4.42 (1H, s), 6.07 (1H, ddt), 6.51 (1H, t), 6.67 (1H, s), 7.38 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.70 (4H, m), 8.87 (1H, s);

Example 58e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.94 - 1.88 (2H, m), 3.17 - 3.09 (3H, m), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, ddd), 4.12 (1H, d), 4.42 (1H, s), 6.13 (1H, t), 6.66 (1H, s), 7.36 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.71 (4H, m), 8.60 (1H, s);

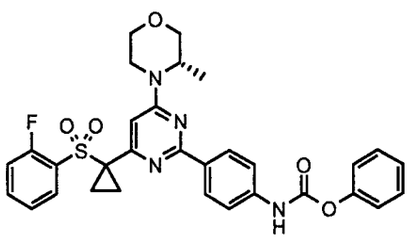
Example 58f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.72 - 1.65 (2H, m), 1.94 - 1.89 (2H, m), 3.15 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.79 (3H, s), 3.95

(1H, dd), 4.13 (1H, d), 4.43 (1H, s), 6.67 (1H, s), 7.34 (1H, t), 7.41 - 7.38 (3H, m), 7.53 - 7.49 (1H, m), 7.79 - 7.70 (5H, m), 8.35 (1H, s), 8.78 (1H, s).

Example 58g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.51 - 0.48 (2H, m), 0.59 - 0.57 (2H, m), 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.94 - 1.90 (2H, m), 3.14 (1H, ddd), 3.22 (2H, d), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.42 (1H, s), 5.36 (1H, s), 6.29 (1H, t), 6.66 (1H, s), 7.35 - 7.31 (3H, m), 7.52 - 7.48 (1H, m), 7.78 - 7.70 (4H, m), 8.76 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



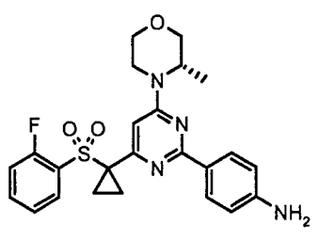
4-[4-[1-(2-Fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (used as the hydrochloride salt) (3.2 g, 6.83 mmol) and sodium bicarbonate (11.47 g, 136.59 mmol) were added to DCM (75 mL) and stirred for 10 minutes. Phenyl chloroformate (1.114 mL, 8.88 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to give the desired material as a yellow foam (3.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.72 - 1.66 (2H, m), 1.97 - 1.88 (2H, m), 3.15 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H,

dd), 4.14 (1H, d), 4.44 (1H, s), 6.70 (1H, s), 7.35 - 7.23 (4H, m), 7.53 - 7.42 (5H, m), 7.77 - 7.71 (2H, m), 7.83 (2H, d), 10.37 (1H, s).

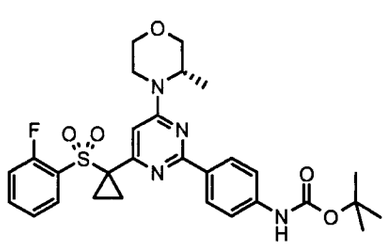
LCMS Spectrum: m/z (ESI+) (M+H)+ = 589; HPLC tR = 3.04 min;

4-[4-[1-(2-Fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



tert-Butyl N-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.6 g, 6.33 mmol) was added to 6N hydrogen chloride in propan-2-ol (60 mL) and stirred at RT for 5 hours. The solvent was removed to 80% of the initial volume then diethyl ether rapidly added to afford the desired material (as a hydrochloride salt) as a yellow solid (3.20 g). This was used in the next step without any further purification.

tert-Butyl *N*-[4-[4-[1-(2-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



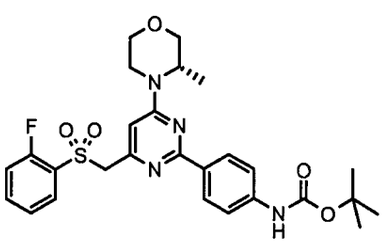
tert-Butyl *N*-[4-[4-[(2-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (5.75 g, 10.60 mmol) was added to sodium hydride (1.526 g, 31.79 mmol) and 1,2-dibromoethane (1.826 mL, 21.19 mmol) in DMF (30 mL) at RT. The resulting suspension was stirred at 45°C for 1 hour. Additional sodium hydride (1.526 g, 31.79 mmol) and 1,2-dibromoethane (1.826 mL, 21.19 mmol) were added and the reaction was stirred at 45°C overnight. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$,

filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a yellow foam (3.60 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.49 (9H, s), 1.71 - 1.65 (2H, m), 1.94 - 1.90 (2H, m), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, ddd), 4.13 (1H, d), 4.42 (1H, s), 6.68 (1H, s), 7.33 (1H, t), 7.42 (2H, d), 7.53 - 7.48 (1H, m), 7.78 - 7.70 (4H, m), 9.48 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 569; HPLC tR = 3.13 min;

tert-Butyl *N*-[4-[4-[(2-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

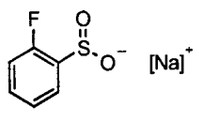


[6-[(3*S*)-3-Methylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate (4.74 g, 9.90 mmol) and lithium iodide (3.98 g, 29.71 mmol) were added to dioxane (70 mL) and heated at 97°C for 30 minutes. To this was added sodium 2-fluorobenzenesulfinate (2.71 g, 14.86 mmol) and DMF (5 mL), the reaction was stirred at 97°C overnight. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange gum. Diethyl ether (100 mL) was added with vigorous stirring to afford the desired material as a white solid (4.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.49 (9H, s), 3.17 (1H, ddd), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.12 (1H, d), 4.39 (1H, s), 4.76 (2H, s), 6.75 (1H, s), 7.34 (1H, t), 7.41 (2H, d), 7.65 - 7.57 (2H, m), 7.71 (2H, d), 7.83 - 7.77 (1H, m), 9.48 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 543; HPLC tR = 2.92 min;

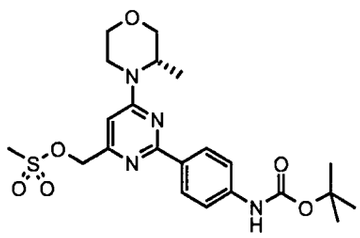
Sodium 2-fluorobenzenesulfinate



A solution of sodium sulfite (32.4 g, 256.92 mmol) in water (200 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (43.2 g, 513.85 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 2-Fluorobenzene-1-sulfonyl chloride (50 g, 256.92 mmol) was added portionwise to the solution and was stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (41.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 6.99 (1H, t), 7.16 (1H, t), 7.28 - 7.22 (1H, m), 7.61 (1H, t).

[6-[(3*S*)-3-Methylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate

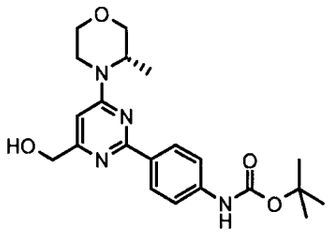


tert-Butyl *N*-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (23 g, 57.43 mmol) and DIPEA (12.04 mL, 68.92 mmol) were added to DCM (80 mL), to this was slowly added methanesulphonyl chloride (4.48 mL, 57.43 mmol) and the reaction was stirred for 30 minutes. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (100 mL), extracted with DCM (2 x 100 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a brown gum (27.0 g). This was used without any further purufucation.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.50 (9H, s), 3.22 (1H, ddd), 3.34 (3H, s), 3.50 (1H, ddd), 3.65 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.19 (1H, d), 4.53 (1H, s), 5.19 (2H, s), 6.71 (1H, s), 7.56 (2H, d), 8.23 (2H, d), 9.55 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 479; HPLC tR = 2.74 min;

tert-Butyl *N*-[4-[4-(hydroxymethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



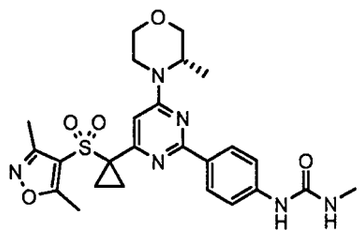
[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (18.00 g, 73.86 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (23.58 g, 73.86 mmol), sodium carbonate (39.1 g, 369.32 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (5.35 g, 7.39 mmol) were added to DME (300 mL) and water (75 mL) and heated to 90°C overnight under nitrogen. The solvent was evaporated and the residue was quenched with water (100 mL), extracted with ethyl acetate (3 x 100 mL), the aqueous layer was dried over $MgSO_4$, filtered and evaporated to afford black gum. The residue was filtered through a plug of silica eluting with ethyl acetate to give a pale orange gum. This was triturated with diethyl ether to give the desired material as a white solid (24.4 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.49 (9H, s), 3.19 (1H, ddd), 3.49 (1H, ddd), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.50 - 4.46 (3H, m), 5.39 (1H, s), 6.67 (1H, s), 7.54 (2H, d), 8.22 (2H, d), 9.50 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 401; HPLC tR = 2.30 min;

The preparation of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol was described earlier.

Example 59: 1-[4-[4-[1-[(3,5-Dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

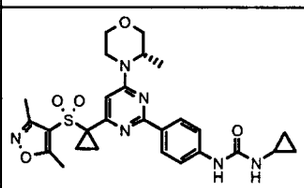


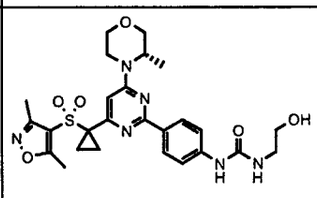
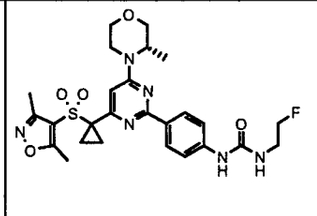
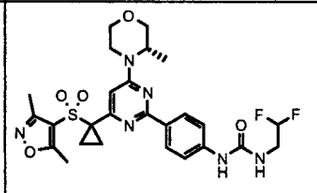
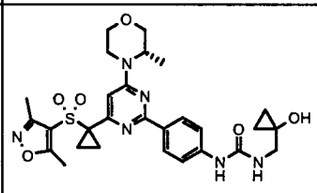
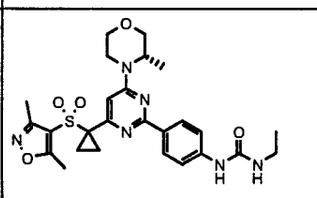
Phenyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.15 g, 0.25 mmol) and methylamine (2M in THF, 1.272 mL, 2.54 mmol) were added to dioxane (10 mL) and stirred overnight at 50°C. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (0.098 g).

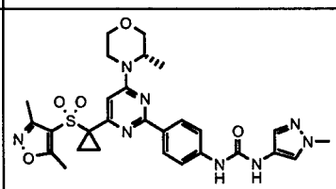
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.59 - 1.52 (2H, m), 1.80 - 1.77 (2H, m), 2.11 (3H, s), 2.33 (3H, s), 2.66 (3H, d), 3.18 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.52 (1H, s), 6.07 (1H, q), 6.75 (1H, s), 7.45 (2H, d), 7.96 (2H, d), 8.72 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 527; HPLC tR = 2.18 min

The following samples were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
59a		3-cyclopropyl-1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	553	2.31

Example	Structure	NAME	LCMS MH+	Retention time (min)
59b		1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	557	2.00
59c		1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	559	2.33
59d		3-(2,2-difluoroethyl)-1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	577	2.44
59e		1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea	583	2.16
59f		3-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	541	2.34

Example	Structure	NAME	LCMS MH+	Retention time (min)
59g		1-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	593	2.21

Example 59a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.44 - 0.40 (2H, m), 0.67 - 0.63 (2H, m), 1.21 (3H, d), 1.59 - 1.52 (2H, m), 1.80 - 1.77 (2H, m), 2.11 (3H, s), 2.32 (3H, s), 2.59 - 2.54 (1H, m), 3.18 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.52 (1H, s), 6.44 (1H, d), 6.76 (1H, s), 7.45 (2H, d), 7.96 (2H, d), 8.52 (1H, s).

Example 59b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.52 (2H, m), 1.80 - 1.75 (2H, m), 2.11 (3H, s), 2.32 (3H, s), 3.22 - 3.14 (3H, m), 3.51 - 3.45 (3H, m), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.52 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.75 (1H, s), 7.43 (2H, d), 7.96 (2H, d), 8.79 (1H, s).

Example 59c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.59 - 1.53 (2H, m), 1.80 - 1.75 (2H, m), 2.11 (3H, s), 2.33 (3H, s), 3.22 - 3.14 (1H, m), 3.39 (1H, q), 3.51 - 3.44 (1H, m), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.42 (1H, t), 4.55 - 4.49 (2H, m), 5.75 (1H, s), 6.44 (1H, t), 6.76 (1H, s), 7.45 (2H, d), 7.97 (2H, d), 8.79 (1H, s);

Example 59d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.60 - 1.52 (2H, m), 1.81 - 1.75 (2H, m), 2.11 (3H, s), 2.33 (3H, s), 3.18 (1H, ddd), 3.64 - 3.44 (4H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.18 (1H, d), 4.52 (1H, s), 6.07 (1H, ddt), 6.54 (1H, t), 6.77 (1H, s), 7.46 (2H, d), 7.98 (2H, d), 8.91 (1H, s).

Example 59e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.53 - 0.49 (2H, m), 0.60 - 0.56 (2H, m), 1.20 (3H, d), 1.59 - 1.52 (2H, m), 1.80 - 1.77 (2H, m), 2.11 (3H, s), 2.32 (3H, s), 3.18 - 3.14 (1H, m), 3.22 (2H, d), 3.47 (1H, ddd), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.52 (1H, s), 5.37 (1H, s), 6.33 (1H, t), 6.76 (1H, s), 7.43 (2H, d), 7.96 (2H, d), 8.80 (1H, s);

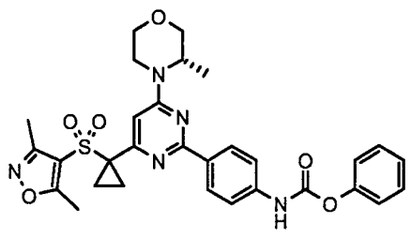
Example 59f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.21 (3H, d), 1.59 - 1.52 (2H, m), 1.80 - 1.77 (2H, m), 2.11 (3H, s), 2.32 (3H, s), 3.22 - 3.09 (3H, m), 3.47 (1H, ddd),

3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.53 (1H, s), 6.17 (1H, t), 6.75 (1H, s), 7.44 (2H, d), 7.95 (2H, d), 8.64 (1H, s);

Example 59g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.59 - 1.53 (2H, m), 1.81 - 1.78 (2H, m), 2.12 (3H, s), 2.33 (3H, s), 3.23 - 3.15 (1H, m), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.79 (3H, s), 3.97 (1H, dd), 4.18 (1H, d), 4.53 (1H, s), 6.77 (1H, s), 7.39 (1H, s), 7.49 (2H, d), 7.77 (1H, s), 7.99 (2H, d), 8.40 (1H, s), 8.82 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

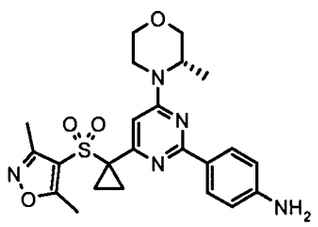


4-[4-[1-[(3,5-Dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (1.94 g, 3.83 mmol) and sodium bicarbonate (1.610 g, 19.17 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.625 mL, 4.98 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. DCM followed by diethyl ether were added and the solvent was slowly removed until a solid was obtained. The solid was collected by filtration and dried under vacuum to give the desired material as as a white solid (1.89 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.60 - 1.52 (2H, m), 1.81 - 1.78 (2H, m), 2.11 (3H, s), 2.33 (3H, s), 3.19 (1H, ddd), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.19 (1H, d), 4.54 (1H, s), 6.80 (1H, s), 7.30 - 7.24 (3H, m), 7.45 (2H, t), 7.57 (2H, d), 8.04 (2H, d), 10.42 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 590; HPLC tR = 2.86 min

4-[4-[1-[(3,5-Dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

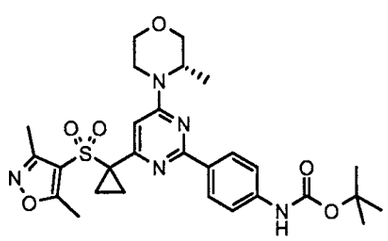


tert-Butyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.6 g, 4.56 mmol) was added to 6N hydrogen chloride in propan-2-ol (40 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a yellow solid (1.96 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.69 - 1.58 (2H, m), 1.84 - 1.82 (2H, m), 2.09 (3H, s), 2.38 (3H, s), 3.30 - 3.24 (1H, m), 3.50 - 3.45 (1H, m), 3.62 (1H, dd), 3.81 - 3.75 (1H, m), 3.99 (1H, dd), 4.28 (1H, s), 4.60 (1H, s), 6.93 (1H, s), 7.23 - 7.13 (2H, m), 8.05 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 470; HPLC tR = 1.88 min

tert-Butyl *N*-[4-[4-[1-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



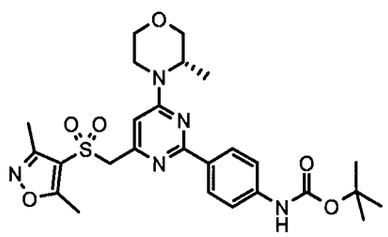
Sodium hydride (2.177 g, 45.36 mmol) and 1,2-dibromoethane (2.61 mL, 30.24 mmol) in DMF (70 mL) were added rapidly to a solution of *tert*-butyl *N*-[4-[4-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (4.11 g, 7.56 mmol) in DMF (70 mL) at RT. The resulting suspension was stirred at RT for 1 hour. Additional sodium hydride (1.1 g, 22.68 mmol) and 1,2-dibromoethane (1.305 mL, 15.12 mmol) were added and the reaction was stirred at RT for 30

minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to afford a yellow foam. This was dissolved in 40% ethyl acetate in isohexane and stirred to give the desired material as a white solid which was collected by filtration (2.60 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.50 (9H, s), 1.59 - 1.53 (2H, m), 1.81 - 1.77 (2H, m), 2.11 (3H, s), 2.32 (3H, s), 3.18 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.18 (1H, d), 4.53 (1H, s), 6.78 (1H, s), 7.51 (2H, d), 7.97 (2H, d), 9.54 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 570; HPLC tR = 2.99 min

tert-Butyl *N*-[4-[4-[(3,5-dimethyl-1,2-oxazol-4-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

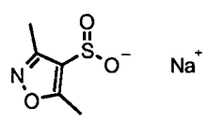


3,5-dimethylisoxazole-4-sulfinic acid, sodium salt (1.443 g, 7.84 mmol) and *tert*-Butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (4 g, 7.84 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid, this was quenched with water (50 mL) and extracted with DCM (2 x 75 mL), dried and solvent evaporated to afford an orange gum, this was rapidly stirred with diethyl ether (100 mL) to afford a solid which was collected by filtration and dried under vacuum to give the desired material as an off white solid (4.11 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.50 (9H, s), 2.19 (3H, s), 2.33 (3H, s), 3.20 (1H, ddd), 3.50 (1H, ddd), 3.65 (1H, dd), 3.78 (1H, d), 3.98 (1H, dd), 4.15 (1H, d), 4.44 (1H, s), 4.69 (2H, s), 6.79 (1H, s), 7.51 (2H, d), 7.97 (2H, d), 9.55 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 544; HPLC tR = 2.76 min

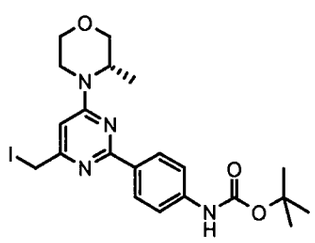
3,5-Dimethylisoxazole-4-sulfinic acid, sodium salt



A solution of sodium sulfite (5.03 g, 39.87 mmol) in water (50 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (6.70 g, 79.74 mmol) was added and the resulting solution was stirred at 50°C for 10 minutes. 3,5-Dimethylisoxazole-4-sulfonyl chloride (7.8 g, 39.87 mmol) was added portion-wise to the solution and was stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and re-dissolved in methanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (7.16 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.24 (3H, s), 2.39 (3H, s).

tert-Butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



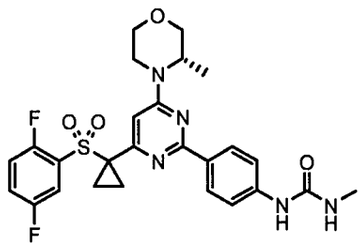
[6-[(3*S*)-3-Methylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate (27 g, 56.42 mmol) and lithium iodide (4.33 mL, 112.84 mmol) were added to dioxane (250 mL) and heated at 60°C for 1 hour and then at RT overnight. The solvent was evaporated to dryness, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (100 mL) and extracted with DCM (3 x 75 mL). The organic extracts were then flushed through a two inch silica plug, eluting with ethyl acetate, to give a brown foam. This was rapidly dissolved in diethyl ether and stirred to afford the desired material as a white solid (25.2 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.50 (9H, s), 3.19 (1H, ddd), 3.49 (1H, ddd), 3.64 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.16 (1H, d), 4.39 (2H, s), 4.48 (1H, s), 6.80 (1H, s), 7.55 (2H, d), 8.22 (2H, d), 9.53 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 511; HPLC tR = 2.85 min

The preparation of [6-[(3*S*)-3-methylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate was described earlier.

Example 60: 1-[4-[4-[1-(2,5-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

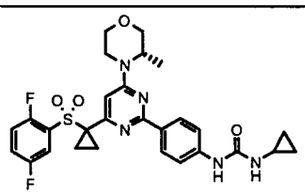
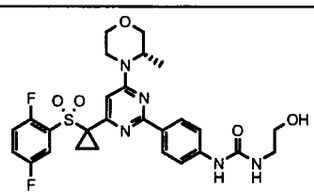
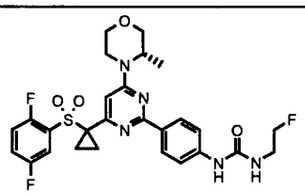
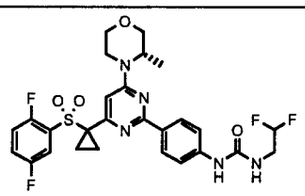
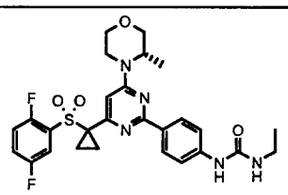


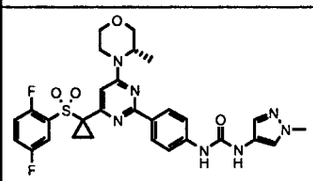
Phenyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.15 g, 0.25 mmol) and methylamine (2M in THF, 1.236 mL, 2.47 mmol) were added to dioxane (10 mL) and stirred overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (0.113 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.72 - 1.70 (2H, m), 1.96 - 1.91 (2H, m), 2.66 (3H, d), 3.16 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.05 (1H, q), 6.68 (1H, s), 7.37 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.73 (2H, d), 8.70 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 544; HPLC tR= 2.30 min

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
60a		3-cyclopropyl-1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	570	2.51
60b		1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	574	2.11
60c		1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	576	2.48
60d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	594	2.61
60e		3-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	558	2.48

Example	Structure	NAME	LCMS MH+	Retention time (min)
60f		1-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	610	2.46

Example 60a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.44 - 0.40 (2H, m), 0.67 - 0.62 (2H, m), 1.19 (3H, d), 1.74 - 1.68 (2H, m), 1.96 - 1.90 (2H, m), 2.58 - 2.53 (1H, m), 3.16 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.41 (1H, s), 6.68 (1H, s), 7.38 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.73 (2H, d), 8.50 (1H, s);

Example 60b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.74 - 1.68 (2H, m), 1.98 - 1.89 (2H, m), 2.09 (3H, s), 3.20 - 3.12 (3H, m), 3.49 - 3.42 (3H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 4.73 (1H, t), 6.24 (1H, t), 6.68 (1H, s), 7.36 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.73 (2H, d), 8.77 (1H, s);

Example 60c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.74 - 1.68 (2H, m), 1.96 - 1.90 (2H, m), 3.16 (1H, ddd), 3.48 - 3.36 (3H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.47 (2H, dt), 4.48 (1H, s), 6.41 (1H, t), 6.68 (1H, s), 7.37 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.74 (2H, d), 8.77 (1H, s);

Example 60d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.74 - 1.68 (2H, m), 1.96 - 1.91 (2H, m), 3.16 (1H, ddd), 3.63 - 3.43 (4H, m), 3.74 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.07 (1H, ddt), 6.51 (1H, t), 6.69 (1H, s), 7.38 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.75 (2H, d), 8.89 (1H, s);

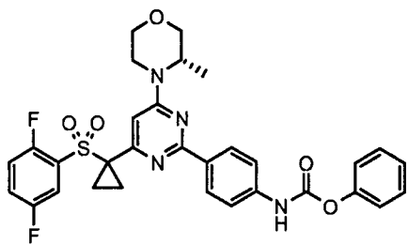
Example 60e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.19 (3H, d), 1.72 - 1.69 (2H, m), 1.95 - 1.91 (2H, m), 3.19 - 3.09 (3H, m), 3.45 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.14 (1H, t), 6.68 (1H, s), 7.36 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.72 (2H, d), 8.62 (1H, s);

Example 60f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.74 - 1.68 (2H, m), 1.96 - 1.92 (2H, m), 3.17 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.75 (1H, d), 3.79 (3H, s), 3.96

(1H, dd), 4.17 (1H, d), 4.48 (1H, s), 6.69 (1H, s), 7.38 (1H, s), 7.42 (2H, d), 7.55 - 7.51 (1H, m), 7.70 - 7.58 (2H, m), 7.78 - 7.75 (3H, m), 8.36 (1H, s), 8.80 (1H, s);

The preparation of phenyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

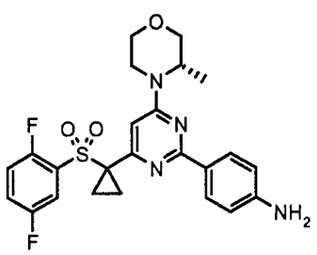


4-[4-[1-(2,5-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (2.54 g, 4.86 mmol) and sodium bicarbonate (2.04 g, 24.28 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.792 mL, 6.31 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The solid was passed through a plug of silica, eluting with ethyl acetate, to give a solid that was further purified by trituration with diethyl ether to give the desired material as a white solid (2.20 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.73 - 1.69 (2H, m), 1.98 - 1.91 (2H, m), 3.17 (1H, ddd), 3.51 - 3.44 (1H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.95 (1H, d), 4.18 (1H, d), 4.49 (1H, s), 6.72 (1H, s), 7.30 - 7.24 (3H, m), 7.45 (2H, t), 7.55 - 7.50 (3H, m), 7.69 - 7.57 (2H, m), 7.83 (2H, d), 10.39 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 607; HPLC tR = 3.15 min

4-[4-[1-(2,5-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

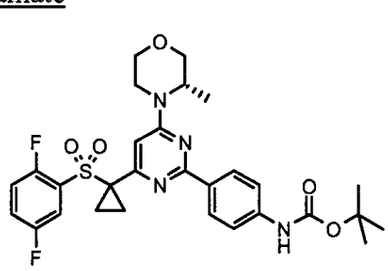


tert-Butyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.85 g, 4.86 mmol) was added to 6N hydrogen chloride in propan-2-ol (30 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as a hydrochloride salt) as a yellow solid (2.4 g, 94 %). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.78 - 1.71 (2H, m), 1.97 - 1.93 (2H, m), 3.23 (1H, ddd), 3.45 (1H, ddd), 3.59 (1H, dd), 3.82 - 3.73 (1H, m), 3.96 (1H, dd), 4.29 - 4.18 (1H, m), 4.59 - 4.47 (1H, m), 6.81 (1H, s), 7.25 (2H, d), 7.63 - 7.54 (2H, m), 7.72 - 7.66 (1H, m), 7.95 (2H, d);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 487; HPLC tR = 2.52 min

tert-Butyl *N*-[4-[4-[1-(2,5-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



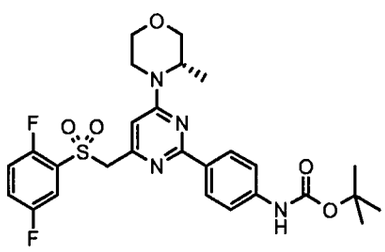
Sodium hydride (1.38 g, 28.56 mmol) was added rapidly to a solution of *tert*-butyl *N*-[4-[4-[(2,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (4.0 g, 7.14 mmol) in DMF (70 mL) and the misture stirred at 40°C for 10 minutes before the slow addition 1,2-dibromoethane (2.459 mL, 28.54 mmol) in DMF (70 mL) at RT. The resulting suspension was stirred at 40°C for 1 hour. Additional sodium hydride (0.69 g, 14.26) and 1,2-dibromoethane (1.23 mL, 14.26 mmol) were added and the reaction was stirred at RT for 30 minutes. The reaction mixture was quenched with water (50

mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give a yellow foam. This was dissolved in 40% ethyl acetate in isohexane and upon stirring the desired material precipitated out as a white solid (2.85 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.49 (9H, s), 1.74 - 1.68 (2H, m), 1.96 - 1.92 (2H, m), 3.16 (1H, ddd), 3.46 (1H, ddd), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.17 (1H, d), 4.48 (1H, s), 6.70 (1H, s), 7.44 (2H, d), 7.54 - 7.50 (1H, m), 7.69 - 7.57 (2H, m), 7.76 (2H, d), 9.50 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 587; HPLC tR = 2.94 min

tert-Butyl *N*-[4-[4-[(2,5-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

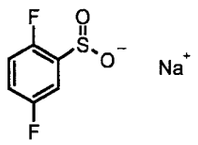


Sodium 2,5-difluorobenzenesulfonate (2.117 g, 9.80 mmol) and *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (5 g, 9.80 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT. The solvent was evaporated and the residue partitioned between water (50 mL) and DCM (75 mL). The layers were separated, the aqueous layer further extracted with DCM (75 mL) and the combined organics passed through a plug of silica, eluting with ethyl acetate, to give a yellow solid. This material was triturated with diethyl ether to give the desired material as a white solid (4.90 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.49 (9H, s), 3.19 (1H, ddd), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.13 (1H, d), 4.41 (1H, s), 4.82 (2H, s), 6.78 (1H, s), 7.44 - 7.42 (3H, m), 7.75 - 7.68 (4H, m), 9.50 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 561; HPLC tR = 2.95 min

2,5-Difluorobenzenesulfinic acid, sodium salt

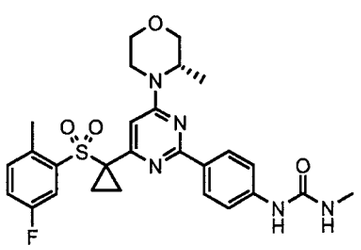


A solution of sodium sulfite (29.6 g, 235.18 mmol) in water (200 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (39.5 g, 470.36 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 2,5-difluorobenzene-1-sulfonyl chloride (50 g, 235 mmol) was added portionwise and the solution stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in ethanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (43.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.09 - 7.05 (2H, m), 7.36 - 7.32 (1H, m).

The preparation of *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 61: 1-[4-[4-[1-(5-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

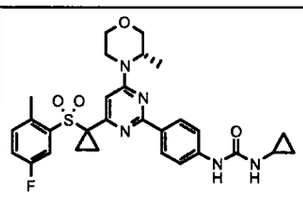
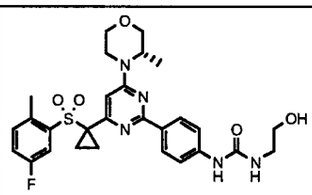
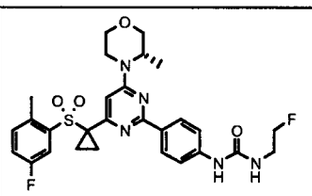


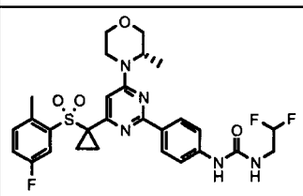
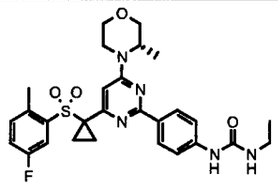
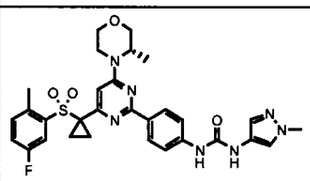
Phenyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.15 g, 0.25 mmol) and methylamine (2M in THF, 1.244 mL, 2.49 mmol) were added to dioxane (10 mL) and stirred overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (0.130 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.70 - 1.64 (2H, m), 1.90 - 1.87 (2H, m), 2.41 (3H, s), 2.66 (3H, d), 3.12 (1H, ddd), 3.44 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.43 (1H, s), 6.05 (1H, q), 6.64 (1H, s), 7.42 - 7.38 (4H, m), 7.62 (1H, d), 7.86 (2H, d), 8.71 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 540; HPLC tR = 2.46 min

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
61a		3-cyclopropyl-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	566	2.65
61b		1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	570	2.28
61c		3-(2-fluoroethyl)-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	572	2.48

Example	Structure	NAME	LCMS MH+	Retention time (min)
61d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	590	2.74
61e		1-ethyl-3-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	554	2.54
61f		1-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	606	2.40

Example 61a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.44 - 0.40 (2H, m), 0.67 - 0.63 (2H, m), 1.16 (3H, d), 1.73 - 1.64 (2H, m), 1.90 - 1.87 (2H, m), 2.41 (3H, s), 2.59 - 2.53 (1H, m), 3.12 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.43 (1H, s), 6.42 (1H, s), 6.64 (1H, s), 7.42 - 7.38 (4H, m), 7.63 - 7.61 (1H, m), 7.86 (2H, d), 8.50 (1H, s).

Example 61b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.70 - 1.64 (2H, m), 1.90 - 1.87 (2H, m), 2.41 (3H, s), 3.20 - 3.09 (3H, m), 3.48 - 3.41 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.43 (1H, s), 4.73 (1H, t), 6.24 (1H, t), 6.64 (1H, s), 7.40 - 7.38 (4H, m), 7.63 - 7.60 (1H, m), 7.86 (2H, d), 8.77 (1H, s);

Example 61c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.70 - 1.64 (2H, m), 1.91 - 1.87 (2H, m), 2.41 (3H, s), 3.13 (1H, ddd), 3.47 - 3.37 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.47 - 4.40 (1H, m), 4.47 (2H, dt), 6.42 (1H, t), 6.64 (1H, s), 7.41 - 7.38 (4H, m), 7.61 (1H, d), 7.87 (2H, d), 8.78 (1H, s).

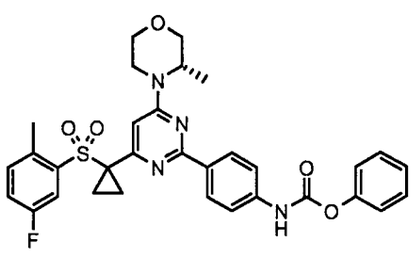
Example 61d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.70 - 1.64 (2H, m), 1.90 - 1.87 (2H, m), 2.41 (3H, s), 3.12 (1H, ddd), 3.62 - 3.41 (4H, m), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.44 (1H, s), 6.08 (1H, ddt), 6.52 (1H, t), 6.65 (1H, s), 7.42 - 7.38 (4H, m), 7.62 - 7.60 (1H, m), 7.88 (2H, d), 8.89 (1H, s).

Example 61e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.16 (3H, d), 1.70 - 1.65 (2H, m), 1.90 - 1.85 (2H, m), 2.4 (S, 3H), 3.15 - 3.09 (3H, m), 3.44 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.43 (1H, s), 6.14 (1H, t), 6.64 (1H, s), 7.39 (4H, d), 7.62 (1H, d), 7.86 (2H, d), 8.63 (1H, s).

Example 61f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.71 - 1.65 (2H, m), 1.90 - 1.88 (2H, m), 2.41 (3H, s), 3.13 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.77 (3H, s), 3.95 (1H, ddd), 4.43 (1H, s), 6.65 (1H, s), 7.41 - 7.39 (4H, m), 7.45 (2H, d), 7.62 (1H, d), 7.77 (1H, s), 7.89 (2H, d), 8.37 (1H, s), 8.80 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

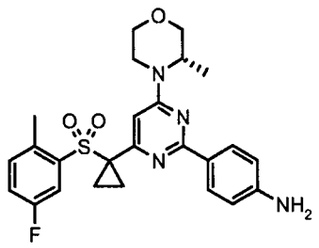


4-[4-[1-(5-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (2.4 g, 4.62 mmol) and sodium bicarbonate (1.942 g, 23.12 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.754 mL, 6.01 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. To this was added DCM and then diethyl ether, the solvent was slowly removed until the desired material precipitated from the mixture as a white solid (2.05 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.72 - 1.66 (2H, m), 1.91 - 1.87 (2H, m), 2.41 (3H, s), 3.14 (1H, ddd), 3.47 - 3.38 (1H, m), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.45 (1H, s), 6.68 (1H, s), 7.30 - 7.24 (3H, m), 7.40 (2H, d), 7.45 (2H, t), 7.54 (2H, d), 7.62 (1H, d), 7.95 (2H, d), 10.39 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 603; HPLC tR = 3.02 min

4-[4-[1-(5-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

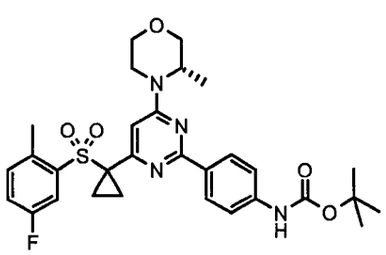


tert-Butyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.7 g, 4.63 mmol) was added to 6N hydrogen chloride in propan-2-ol (30 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a yellow solid (2.40 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.73 - 1.69 (2H, m), 1.93 - 1.90 (2H, m), 2.38 (3H, s), 3.20 (1H, ddd), 3.44 (1H, ddd), 3.58 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.26 - 4.12 (1H, m), 4.51 (1H, s), 6.71 (1H, s), 7.17 - 7.13 (2H, m), 7.45 (2H, d), 7.60 (1H, d), 7.97 (2H, d).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 483; HPLC tR = 2.57 min

tert-Butyl *N*-[4-[4-[1-(5-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

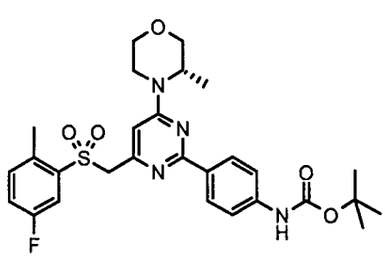


Sodium hydride (1.987 g, 41.39 mmol) was added rapidly to a solution of *tert*-butyl *N*-[4-[4-[(5-fluoro-2-methylphenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.84 g, 6.90 mmol) in DMF (70 mL) and the mixture stirred at RT for 10 minutes before the slow addition 1,2-dibromoethane (2.38 mL, 27.59 mmol) in DMF (70 mL). The resulting suspension was stirred at RT for 30 minutes. Additional sodium hydride (0.95 g, 20.70 mmol) and 1,2 dibromoethane (1.19 g, 20.70 mmol) were added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give a material which was further purified by trituration with 40% ethyl acetate in isohexane to give the desired material as a white solid (2.70 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.49 (9H, s), 1.70 - 1.64 (2H, m), 1.90 - 1.87 (2H, m), 2.41 (3H, s), 3.13 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.11 (1H, d), 4.43 (1H, s), 6.66 (1H, s), 7.41 - 7.38 (2H, m), 7.46 (2H, d), 7.62 - 7.60 (1H, m), 7.88 (2H, d), 9.50 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 583; HPLC tR = 3.19 min

tert-Butyl *N*-[4-[4-[(5-fluoro-2-methylphenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

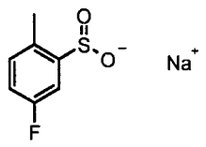


5-Fluoro-2-methylbenzenesulfinic acid, sodium salt (2.079 g, 9.80 mmol) and *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (5 g, 9.80 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT The solvent was evaporated and the residue partitioned between water (50 mL) and DCM (75 mL). The layers were separated, the aqueous layer further extracted with DCM (75 mL) and the combined organics dried and solvent evaporated to afford an orange gum which was further purified by trituration with diethyl ether to give the desired material as an off white solid (4.75 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.50 (9H, s), 2.61 (3H, s), 3.17 (1H, ddd), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.40 (1H, s), 4.75 (2H, s), 6.69 (1H, s), 7.50 - 7.41 (4H, m), 7.56 - 7.53 (1H, m), 7.82 (2H, d), 9.50 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 557; HPLC tR = 2.91 min

5-fluoro-2-methylbenzenesulfinic acid, sodium salt

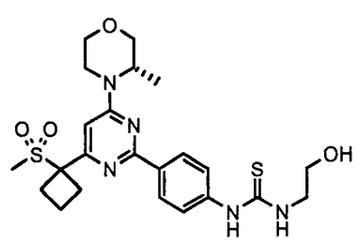


A solution of sodium sulfite (30.2 g, 239.65 mmol) in water (200 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (40.3 g, 479.30 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 5-Fluoro-2-methyl sulfonyl chloride was added portionwise and the solution stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in ethanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (27.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.41 (3H, s), 6.90 (1H, ddd), 7.05 (1H, dd), 7.36 (1H, dd).

The preparation of *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 62: 3-(2-Hydroxyethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea



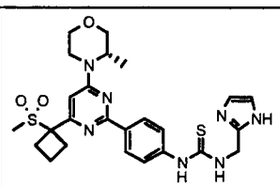
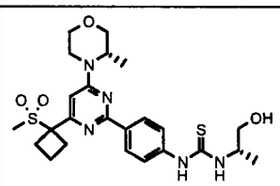
1,1'-Thiocarbonyldiimidazole (57.6 mg, 0.32 mmol) was added to a stirred solution of 4-[4-

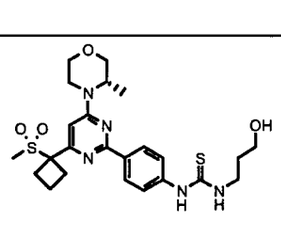
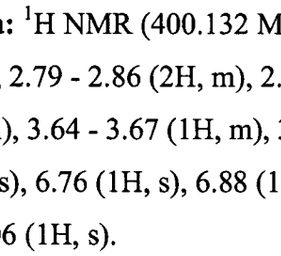
[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]aniline (100 mg, 0.25 mmol) in THF (1.0 mL) and DCM (2.0 mL) at RT. The resulting solution was stirred for 2 hours. Triethylamine (0.035 mL, 0.25 mmol) and ethanolamine (15.18 mg, 0.25 mmol) were added to the reaction mixture and then stirred at RT for a further 1 hour. The reaction mixture was evaporated to dryness and redissolved in acetonitrile (2.0 mL), filtered and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (73 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.92 (1H, d), 2.07 - 2.09 (1H, m), 2.79 - 2.86 (2H, m), 2.88 (3H, s), 2.87 - 2.95 (2H, m), 3.18 - 3.26 (1H, m), 3.47 - 3.54 (1H, m), 3.57 (3H, s), 3.64 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.30 (1H, d), 4.63 (1H, d), 4.85 (1H, s), 6.75 (1H, s), 7.61 - 7.64 (2H, m), 7.90 (1H, s), 8.27 - 8.30 (2H, m), 9.85 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 506.55; HPLC tR = 2.35 min.

The compounds below were prepared in an analogous fashion from 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]aniline using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
62a		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea	542.6	2.41
62b		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea	520.6	2.47

Example	Structure	NAME	LCMS MH+	Retention time (min)
62c		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea	520.6	2.47
62d		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea	520.6	2.39

Example 62a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.90 - 1.93 (1H, m), 2.07 - 2.09 (1H, m), 2.79 - 2.86 (2H, m), 2.88 (3H, s), 2.89 - 2.95 (2H, m), 3.20 - 3.26 (1H, m), 3.47 - 3.54 (1H, m), 3.64 - 3.67 (1H, m), 3.77 (1H, d), 3.97 - 4.00 (1H, m), 4.27 (1H, d), 4.60 (1H, s), 4.71 (2H, s), 6.76 (1H, s), 6.88 (1H, s), 7.09 (1H, s), 7.68 (2H, d), 8.24 (1H, s), 8.28 - 8.32 (2H, m), 10.06 (1H, s).

Example 62b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 - 1.16 (3H, m), 1.24 (3H, s), 1.90 - 1.94 (1H, m), 2.07 - 2.09 (1H, m), 2.79 - 2.84 (2H, m), 2.88 (3H, s), 2.91 - 2.95 (2H, m), 3.20 - 3.26 (1H, m), 3.44 - 3.54 (3H, m), 3.64 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.26 (1H, d), 4.38 (1H, s), 4.60 (1H, s), 4.92 (1H, s), 6.75 (1H, s), 7.63 - 7.66 (2H, m), 7.73 - 7.75 (1H, m), 8.28 (2H, d), 9.75 (1H, s).

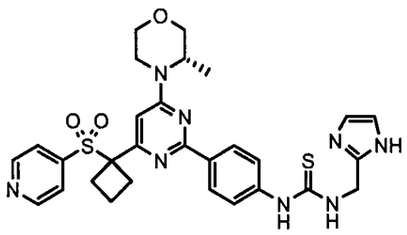
Example 62c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 - 1.16 (3H, m), 1.24 (3H, s), 1.90 - 1.94 (1H, m), 2.07 - 2.09 (1H, m), 2.79 - 2.84 (2H, m), 2.88 (3H, s), 2.91 - 2.95 (2H, m), 3.20 - 3.26 (1H, m), 3.44 - 3.54 (3H, m), 3.64 - 3.67 (1H, m), 3.77 (1H, d), 3.96 - 4.00 (1H, m), 4.26 (1H, d), 4.38 (1H, s), 4.60 (1H, s), 4.92 (1H, s), 6.75 (1H, s), 7.63 - 7.66 (2H, m), 7.73 - 7.75 (1H, m), 8.28 (2H, d), 9.75 (1H, s).

Example 62d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 - 1.25 (3H, m), 1.68 - 1.75 (2H, m), 1.90 - 1.93 (1H, m), 2.07 - 2.09 (1H, m), 2.79 - 2.86 (2H, m), 2.88 (3H, s), 2.89 - 2.95 (2H, m), 3.18 - 3.25 (1H, m), 3.47 - 3.54 (5H, m), 3.64 - 3.67 (1H, m), 3.77 (1H, d), 3.96 -

4.00 (1H, m), 4.26 (1H, d), 4.58 (2H, s), 6.75 (1H, s), 7.55 - 7.59 (2H, m), 7.93 (1H, s), 8.27 - 8.30 (2H, m), 9.74 (1H, s).

The preparation of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclobutyl)pyrimidin-2-yl]aniline was described earlier.

Example 63: 3-(1*H*-Imidazol-2-ylmethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]thiourea



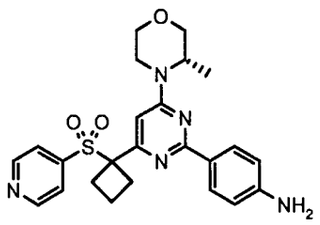
1,1'-Thiocarbonyldiimidazole (49.8 mg, 0.28 mmol) was added to a stirred solution of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline (100 mg, 0.21 mmol) in THF (1.0 mL) and DCM (2.0 mL) at RT. The resulting solution was stirred for 2 hours. Triethylamine (0.030 mL, 0.21 mmol) and (1H-imidazol-2-yl)methanamine (20.86 mg, 0.21 mmol) were then added to the reaction mixture and stirred at RT for 1 hour. The reaction mixture was evaporated to dryness and redissolved in acetonitrile (2.0 mL), filtered and then purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to afford desired material as a white solid (85mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 - 1.23 (3H, d), 1.94 (1H, m), 2.15 (1H, m), 2.82 (2H, m), 3.14 (2H, m), 3.51 (1H, t), 3.63 (1H, d), 3.68 (1H, d), 3.77 (1H, d), 3.97 (1H, dd), 4.17 (1H, d), 4.55 (1H, s), 4.73 (2H, s), 6.57 (1H, s), 6.89 (1H, s), 7.08 (1H, s), 7.48 (2H, d), 7.56 (2H, d), 7.79 (2H, d), 8.20 (1H, s), 8.73 (2H, d), 10.00 (1H, s), 11.94 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 605.51; HPLC tR = 2.03 min.

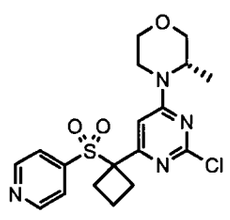
The preparation of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline is described below:

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline



Bis(triphenylphosphine)palladium(II) chloride (79 mg, 0.11 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidine (920 mg, 2.25 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (641 mg, 2.92 mmol) and 2M aqueous sodium carbonate solution (5 mL, 10.0 mmol) in DMF (10 mL), DME (40 mL), ethanol (10 mL) and water (10 mL) at RT under a nitrogen atmosphere. The resulting mixture was stirred at 80°C for 2 hours. The reaction mixture was then diluted with ethyl acetate (400 mL) and washed sequentially with water (200 mL) and then brine (250 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, with an elution gradient of 0% to 50% ethyl acetate in DCM, to afford the desired material as a creamy white solid (1.01 g).
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.19 - 1.21 (3H, m), 1.88 - 1.95 (1H, m), 2.10 - 2.15 (1H, m), 2.76 - 2.83 (2H, m), 3.05 - 3.18 (3H, m), 3.45 - 3.52 (1H, m), 3.62 - 3.65 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.13 (1H, d), 4.47 (1H, d), 5.50 (2H, d), 6.45 - 6.48 (2H, m), 6.52 (1H, s), 7.44 - 7.46 (2H, m), 7.52 - 7.66 (2H, d), 8.70 - 8.72 (2H, m)
LCMS Spectrum: m/z (ESI+) (M+H)+ = 466.20; HPLC tR = 2.06 min

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidine



Sodium hydroxide (50%w/w solution) (24.39 g, 609.89 mmol) was added to a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine (4.09 g, 11.09 mmol), 1,3-dibromopropane (3.38 mL, 33.27 mmol) and tetrabutylammonium bromide (0.357 g, 1.11 mmol) in toluene (200 mL) at RT under air. The resulting mixture was warmed

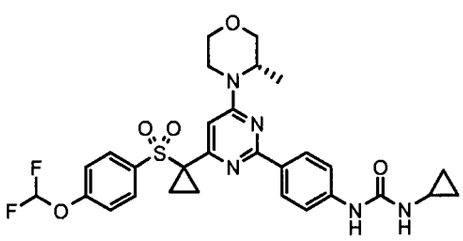
to 45°C for 3 hours. Water (100 mL) was added to the solution and the toluene layer was washed with further water, brine and then dried over $MgSO_4$. The mixture was filtered and the filtrate was evaporated to dryness. The crude product was purified by flash silica chromatography, eluting with a gradient of 30 to 50% ethyl acetate in DCM, to afford desired material as a solid (936 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.17 - 1.19 (3H, m), 1.89 - 1.94 (1H, m), 2.07 - 2.13 (1H, m), 2.68 - 2.75 (2H, m), 2.96 - 3.06 (2H, m), 3.11 - 3.19 (1H, m), 3.39 - 3.46 (1H, m), 3.56 - 3.59 (1H, m), 3.71 (1H, d), 3.91 - 3.94 (2H, m), 4.34 (1H, s), 6.65 (1H, s), 7.47 - 7.49 (2H, m), 8.83 - 8.85 (2H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 409; HPLC tR = 2.04 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(pyridin-4-ylsulfonylmethyl)pyrimidine was described earlier.

Example 64: 3-Cyclopropyl-1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

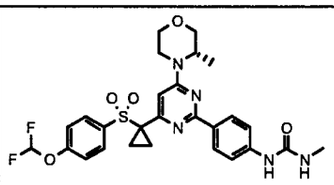
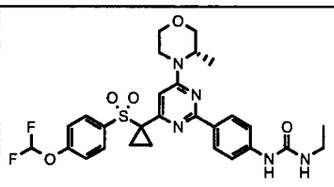
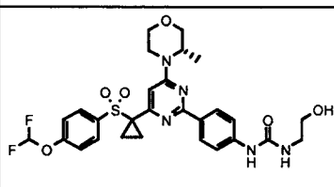
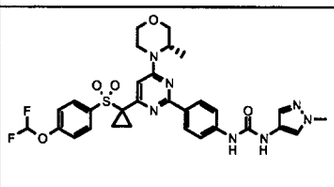


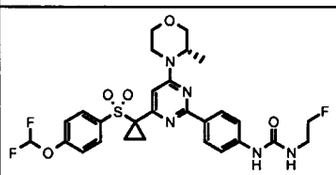
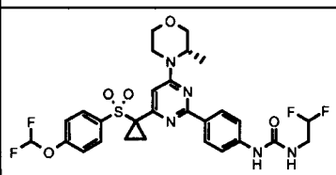
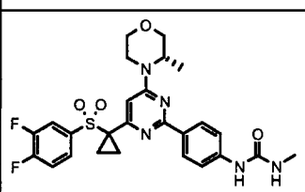
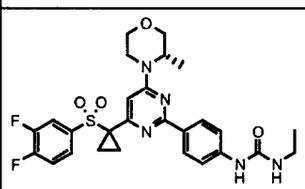
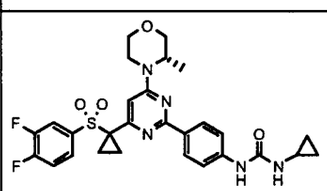
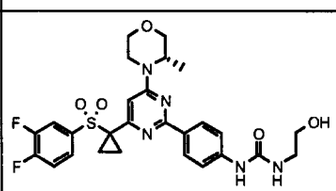
Cyclopropylamine (0.136 mL, 0.80 mmol) was added to a solution of phenyl *N*-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.16 mmol) and triethylamine (0.066 mL, 0.48 mmol) in DMA (1 mL). The reaction was stirred at RT for 18 hours. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile to afford the desired product as a solid (66 mg).

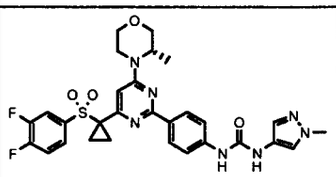
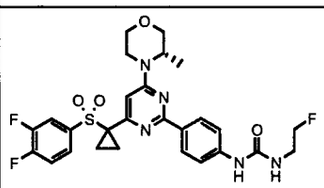
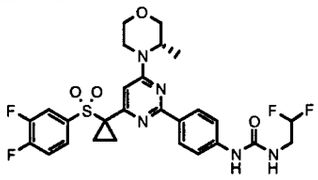
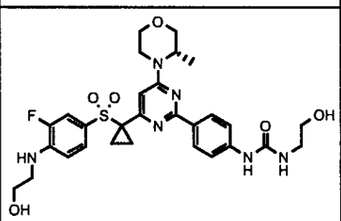
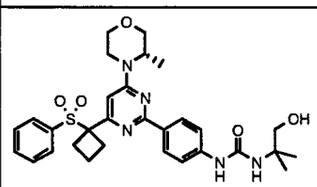
NMR Spectrum: ^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.41 (2H, m), 0.64 (2H, m), 1.18 (3H, d), 1.61 (2H, m), 1.87 (2H, m), 2.55 (1H, dd), 3.14 (1H, m), 3.46 (1H, td), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, s), 4.40 (1H, s), 6.40 (1H, d), 6.63 (1H, s), 7.37 – 7.58 (5H, m), 7.84 (4H, m), 8.50 (1H, s)

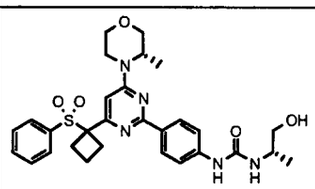
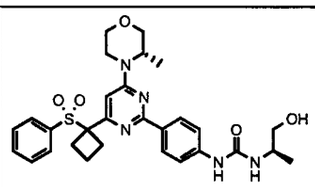
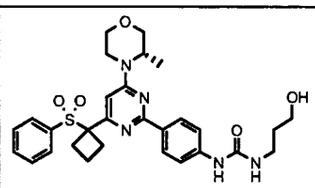
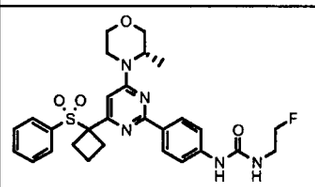
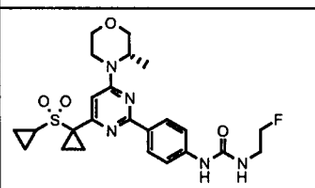
LCMS Spectrum: m/z (ESI+)(M+H)+ = 600; HPLC tR = 2.36 min.

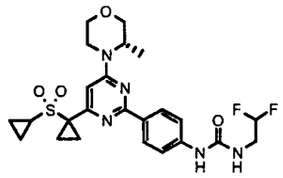
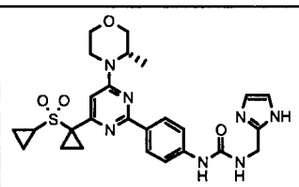
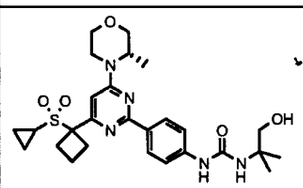
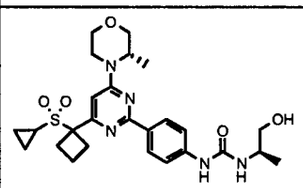
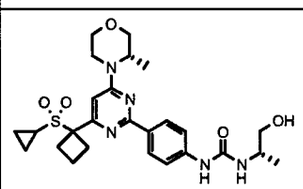
The compounds below were prepared in an analogous fashion using the appropriate carbamate and the appropriate amine.

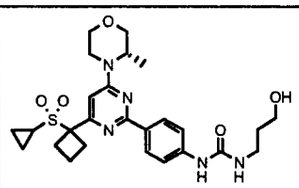
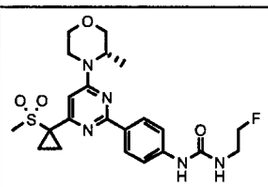
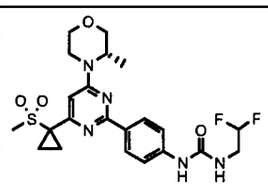
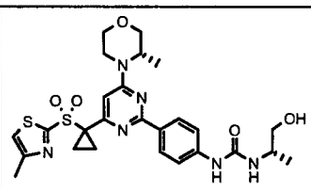
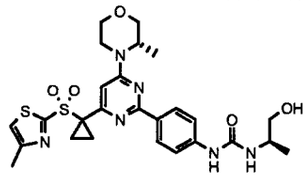
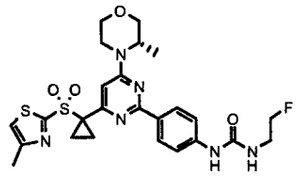
Example	Structure	NAME	LCMS MH+	Retention time (min)
64a*		1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	574	2.21
64b*		3-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	588	2.35
64c*		1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	604	2.05
64d**		1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	640	2.22

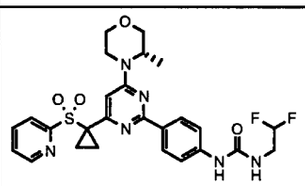
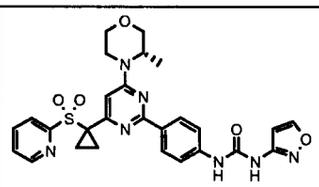
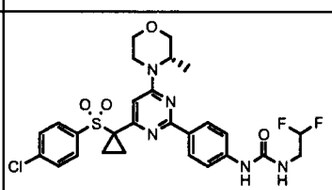
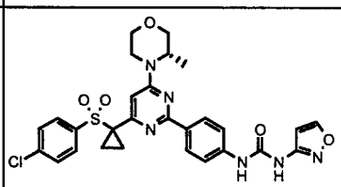
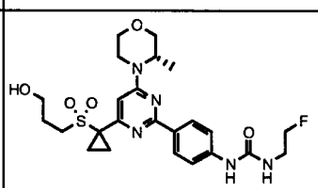
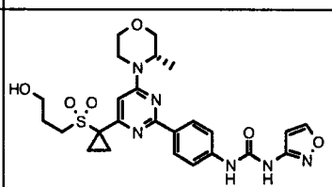
Example	Structure	NAME	LCMS MH+	Retention time (min)
64e**		1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	606	2.33
64f**		3-(2,2-difluoroethyl)-1-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	624	2.45
64g*		1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	544	2.21
64h*		3-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	558	2.40
64i		3-cyclopropyl-1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	570	2.47
64j		1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	574	2.06

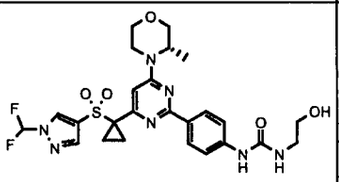
Example	Structure	NAME	LCMS MH+	Retention time (min)
64k**		1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	610	2.22
64l**		1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	576	2.34
64m**		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	594	2.45
64n***		1-[4-[4-[1-[3-fluoro-4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	615	1.72
64o		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	580	2.30

Example	Structure	NAME	LCMS MH+	Retention time (min)
64p		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	566	2.11
64q		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	566	2.11
64r		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	566	2.05
64s**		1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	554	2.32
64t**		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	504	1.95

Example	Structure	NAME	LCMS MH+	Retention time (min)
64u**		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	522	2.10
64v		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	538	1.77
64w		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	544	2.11
64x		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	530	1.91
64y		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	530	1.91

Example	Structure	NAME	LCMS MH+	Retention time (min)
64z		1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	530	1.86
64aa**		3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	478	1.84
64ab**		3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	496	2.03
64ac		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	573	1.92
64ad		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	573	1.92
64ae**		3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea	561	2.14

Example	Structure	NAME	LCMS MH+	Retention time (min)
64af**		3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	559	2.07
64ag		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	562	2.12
64ah**		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	592	2.48
64ai		1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	595	2.51
64aj**		3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	522	1.72
64ak		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1,2-oxazol-3-yl)urea	543	1.77

Example	Structure	NAME	LCMS MH+	Retention time (min)
64al*		1-[4-[4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	578	2.00

* 1.2 Equivalents of amine used

** Reaction heated at 50°C for 3 hours

*** By product formed and isolated when preparing **Example 64j**

Example 64a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.60 (2H, m), 1.89 (2H, m), 2.66 (3H, d), 3.14 (1H, td), 3.46 (1H, td), 3.62 (1H, dd), 3.74 (1H, d), 3.94 (1H, dd), 4.15 (1H, d), 4.40 (1H, s), 6.04 (1H, q), 6.63 (1H, s), 7.36 – 7.61 (5H, m), 7.84 (4H, m), 8.70 (1H, s)

Example 64b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.18 (3H, d), 1.61 (2H, m), 1.88 (2H, m), 3.13 (3H, m), 3.46 (1H, td), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.40 (1H, s), 6.13 (1H, t), 6.63 (1H, s), 7.37 – 7.59 (5H, m), 7.84 (4H, m), 8.62 (1H, s)

Example 64c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.60 (2H, m), 1.87 (2H, m), 3.16 - 3.18 (3H, m), 3.46 (3H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.40 (1H, s), 4.72 (1H, t), 6.24 (1H, t), 6.63 (1H, s), 7.37 – 7.60 (5H, m), 7.84 (4H, m), 8.76 (1H, s)

Example 64d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.61 (2H, m), 1.89 (2H, m), 3.17 (1H, td), 3.46 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.79 (3H, s), 3.96 (1H, dd), 4.15 (1H, d), 4.40 (1H, s), 6.65 (1H, s), 7.36 – 7.60 (6H, m), 7.76 (1H, s), 7.84 - 7.86 (4H, dd), 8.35 (1H, s), 8.80 (1H, s)

Example 64e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.61 (2H, m), 1.89 (2H, m), 3.16 (1H, td), 3.38 (1H, m), 3.45 (2H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.15

(1H, d), 4.41 (2H, t), 4.53 (1H, t), 6.41 (1H, t), 6.64 (1H, s), 7.37-7.60 (5H, m), 7.84 (4H, m), 8.77 (1H, s)

Example 64f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.60 (2H, m), 1.89 (2H, m), 3.16 (1H, td), 3.48 -3.54 (3H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.40 (1H, s), 5.90 - 6.40 (1H, m), 6.50 (1H, t), 6.64 (1H, s), 7.38 - 7.60 (5H, m), 7.85 (4H, m), 8.88 (1H, s)

Example 64g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, m), 1.61 (2H, dd), 1.93 (2H, dd), 2.67 (3H, t), 3.17 (1H, m), 3.46 (1H, td), 3.62 (1H, dd), 3.75 (1H, m), 3.92 (1H, dd), 4.20 (1H, d), 4.45 (1H br s), 6.04 (1H, q), 6.67 (1H, s), 7.40 (2H, m), 7.67 (2H, m), 7.79 (2H, m), 7.91 (1H, m), 8.73 (1H, s)

Example 64h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.19 (3H, d), 1.61 (2H, dd), 1.93 (2H, dd), 3.12 (2H, m), 3.16 (1H, m), 3.45 (1H, td), 3.62 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.45 (1H, br s), 6.13 (1H, t), 6.67 (1H, s), 7.39 (2H, m), 7.65 (1H, d), 7.67 (1H, t), 7.79 (2H, m), 7.91 (1H, m), 8.65 (1H, s)

Example 64i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.42 (2H, dt), 0.65 (2H, td), 1.19 (3H, d), 1.61 (2H, dd), 1.93 (2H, dd), 2.56 (1H, m), 3.18 (1H, td), 3.46 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.47 (1H, br s), 6.30 (1H, s), 6.67 (1H, s), 7.40 (2H, m), 7.66 (2H, m), 7.80 (2H, m), 7.90 (1H, td), 8.53 (1H, s)

Example 64j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.61 (2H, dd), 1.93 (2H, m), 3.17 (3H, q), 3.45 (3H, m), 3.61 (1H, dd), 3.73 (1H, d), 3.91 (1H, dd), 4.15 (1H, d), 4.50 (1H, br s), 4.72 (1H, t), 6.22 (1H, s), 6.67 (1H, s), 7.38 (2H, m), 7.66 (1H, t), 7.67 (1H, s), 7.79 (2H, m), 7.90 (1H, m), 8.79 (1H, s)

Example 64k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.62 (2H, dd), 1.94 (2H, dd), 3.17 (1H, td), 3.47 (1H, td), 3.62 (1H, dd), 3.74 (1H, d), 3.79 (3H, s), 3.96 (1H, dd), 4.17 (1H, d), 4.47 (1H, br s), 6.68 (1H, s), 7.38 (1H, d), 7.45 (2H, m), 7.67 (2H, m), 7.77 (1H, d), 7.83 (2H, d), 7.91 (1H, t), 8.35 (1H, s), 8.84 (1H, s)

Example 64l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, m), 1.61 (2H, dd), 1.93 (2H, dd), 3.17 (1H, td), 3.39 (1H, t), 3.45 (2H, q), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.42 (1H, t), 4.50 (1H, br s), 4.53 (1H, t), 6.40 (1H, t), 6.67 (1H, s), 7.40 (2H, m), 7.66 (1H, d), 7.67 (1H, t), 7.80 (2H, d), 7.90 (1H, m), 8.80 (1H, s)

Example 64m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.61 (2H, dd), 1.94 (2H, dd), 3.17 (1H, td), 3.45 (1H, td), 3.54 (2H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.17

(1H, d), 4.47 (1H, br s), 5.90-6.20 (1H, tt), 6.50 (1H, t), 6.68 (1H, s), 7.41 (2H, m), 7.67 (2H, m), 7.82 (2H, m), 7.90 (1H, m), 8.92 (1H, s)

Example 64n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.56 (2H, m), 1.81 (2H, m), 3.15 (1H, m), 3.17 (2H, m), 3.46 (3H, q), 3.57 (2H, q), 3.62 (1H, m), 3.75 (1H, d), 3.96 (1H, dd), 4.06 (1H, m), 4.37 (1H, br s), 4.73 (2H, q), 6.25 (1H, t), 6.36 (1H, m), 6.58 (1H, s), 6.82 (1H, t), 7.33 (1H, m), 7.41 (3H, m), 7.96 (2H, m), 8.76 (1H, s)

Example 64o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.22 (6H, s), 1.87 (1H, m), 2.08 (1H, m), 2.78 (2H, m), 3.04-3.20 (3H, m), 3.38 (2H, d), 3.48 (1H, td), 3.63 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.08 (1H, d), 4.44 (1H, br s), 4.95 (1H, t), 5.97 (1H, s), 6.46 (1H, s), 7.32 (2H, m), 7.47 (4H, m), 7.60 (1H, m), 7.78 (2H, d), 8.67 (1H, s)

Example 64p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.20 (3H, d), 1.87 (1H, m), 2.08 (1H, m), 2.79 (2H, m), 3.04-3.20 (3H, m), 3.36 (2H, m), 3.48 (1H, td), 3.63 (1H, dd), 3.71 (2H, m), 3.96 (1H, dd), 4.07 (1H, d), 4.45 (1H, br s), 4.78 (1H, t), 6.07 (1H, m), 6.46 (1H, s), 7.35 (2H, m), 7.47 (4H, m), 7.60 (1H, m), 7.79 (2H, d), 8.65 (1H, s)

Example 64q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.20 (3H, d), 1.87 (1H, m), 2.08 (1H, m), 2.79 (2H, m), 3.04 -3.20 (3H, m), 3.36 (2H, m), 3.48 (1H, td), 3.63 (1H, dd), 3.71 (1H, m), 3.73 (1H, m), 3.96 (1H, dd), 4.07 (1H, d), 4.45 (1H, br s), 4.78 (1H, t), 6.07 (1H, d), 6.46 (1H, s), 7.35 (2H, d), 7.47 (4H, m), 7.59 (1H, td), 7.79 (2H, m), 8.65 (1H, s)

Example 64r: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 (2H, m), 1.87 (1H, m), 2.08 (1H, m), 2.79 (2H, m), 3.04 (2H, m), 3.12 (1H, m), 3.25 (2H, d), 3.46 (3H, m), 3.63 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.07 (1H, m), 4.47 (2H, m), 6.18 (1H, t), 6.46 (1H, s), 7.36 (2H, m), 7.48 (4H, m), 7.59 (1H, m), 7.79 (2H, d), 8.65 (1H, s)

Example 64s: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.87 (1H, m), 2.12 (1H, m), 2.75 (2H, m), 3.00-3.20 (3H, m), 3.40 (1H, t), 3.45 (2H, m), 3.61 (1H, dd), 3.74 (1H, d), 3.92 (1H, dd), 4.15 (1H, d), 4.41 (2H, m), 4.53 (1H, t), 6.41 (1H, t), 6.47 (1H, s), 7.37 (2H, m), 7.48 (4H, m), 7.60 (1H, t), 7.80 (2H, m), 8.75 (1H, s)

Example 64t: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.94 (2H, m), 1.03 (2H, m), 1.24 (3H, d), 1.58 (2H, m), 1.65 (2H, m), 3.00 (1H, m), 3.15 (1H, td), 3.36 (1H, m), 3.46 (2H, m), 3.61 (1H, dd), 3.77 (1H, d), 3.94 (1H, dd), 4.20 (1H, d), 4.42 (1H, t), 4.53 (2H, t), 6.43 (1H, t), 6.85 (1H, s), 7.50 (2H, m), 8.22 (2H, m), 8.80 (1H, s)

Example 64u: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.94 (2H, m), 1.03 (2H, m), 1.24 (3H, d), 1.59 (2H, m), 1.65 (2H, m), 3.00 (1H, m), 3.21 (1H, td), 3.54 (3H, m), 3.64 (1H, dd), 3.77

(1H, d), 3.98 (1H, dd), 4.20 (1H, d), 4.54 (1H, br s), 5.90-6.20 (1H, tt), 6.53 (1H, t), 6.85 (1H, s), 7.51 (2H, m), 8.23 (2H, m), 8.91 (1H, s)

Example 64v: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.94 (2H, m), 1.03 (2H, m), 1.24 (3H, d), 1.59 (2H, m), 1.65 (2H, m), 3.00 (1H, m), 3.19 (1H, td), 3.49 (1H, td), 3.64 (1H, dd), 3.77 (1H, d), 3.96 (1H, dd), 4.20 (1H, d), 4.32 (2H, d), 4.54 (1H, br s), 6.62 (1H, t), 6.85 (1H, s), 6.95 (1H, br s), 7.51 (2H, m), 8.22 (2H, m), 8.92 (1H, s)

Example 64w: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.76 (2H, m), 0.85 (2H, m), 1.24 (9H, m), 1.90 (1H, m), 2.10 (1H, m), 2.45 (1H, m), 2.80 – 3.30 (4H, m), 3.20 (1H, td), 3.39 (2H, d), 3.50 (1H, td), 3.65 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.20 (1H, d), 4.50 (1H, br s), 4.95 (1H, t), 6.00 (1H, s), 6.70 (1H, s), 7.45 (2H, m), 8.22 (2H, m), 8.72 (1H, s)

Example 64x: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 (2H, m), 0.85 (2H, m), 1.10 (3H, d), 1.25 (3H, d), 1.90 (1H, m), 2.10 (1H, m), 2.45 (1H, m), 2.80 -3.00 (4H, m), 3.15 (1H, td), 3.35 (2H, m), 3.50 (1H, td), 3.60-3.80 (3H, m), 3.95 (1H, dd), 4.20 (1H, d), 4.55 (1H, br s), 4.75 (1H, t), 6.10 (1H, d), 6.70 (1H, s), 7.45 (2H, m), 8.20 (2H, m), 8.70 (1H, s)

Example 64y: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 (2H, m), 0.84 (2H, m), 1.08 (3H, d), 1.23 (3H, d), 1.89 (1H, m), 2.10 (1H, m), 2.46 (1H, m), 2.84-3.00 (4H, m), 3.15 (1H, td), 3.36 (2H, m), 3.51 (1H, td), 3.67 (1H, td), 3.77 (2H, m), 3.95 (1H, dd), 4.20 (1H, d), 4.55 (1H, br s), 4.78 (1H, t), 6.09 (1H, d), 6.70 (1H, s), 7.47 (2H, m), 8.23 (2H, m), 8.70 (1H, s)

Example 64z: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.70 (2H, m), 0.84 (2H, m), 1.20 (3H, d), 1.57 (2H, m), 1.89 (1H, m), 2.10 (1H, m), 2.46 (1H, m), 2.80-3.00 (4H, m), 3.15 (4H, m), 3.45 (2H, m), 3.55 (1H, td), 3.65 (1H, dd), 3.77 (1H, d), 3.95 (1H, dd), 4.20 (1H, d), 4.45 (1H, t), 4.55 (1H, br s), 6.20 (1H, t), 6.70 (1H, s), 7.47 (2H, m), 8.25 (2H, m), 8.70 (1H, s)

Example 64aa: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, m), 1.58 (2H, m), 1.67 (2H, m), 2.47 (3H, s), 3.20 (1H, td), 3.39 (1H, q), 3.46 (2H, m), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.42 (1H, t), 4.54 (1H, br s), 4.55 (1H, t), 6.43 (1H, t), 6.77 (1H, s), 7.51 (2H, m), 8.21 (2H, m), 8.82 (1H, s)

Example 64ab: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.56 (2H, m), 1.67 (2H, m), 2.46 (3H, s), 3.15 (1H, td), 3.47 -3.63 (4H, m), 3.76 (1H, d), 3.97 (1H, dd), 4.21 (1H, d), 4.57 (1H, br s), 5.90 – 6.20 (1H, m), 6.53 (1H, t), 6.78 (1H, s), 7.52 (2H, m), 8.22 (2H, m), 8.93 (1H, s

Example 64ac: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.21 (3H, d), 1.77 (2H, m), 1.94 (2H, m), 2.48 (3H, d), 3.18 (1H, td), 3.36 (2H, m), 3.40 (1H, td), 3.63 (1H, dd), 3.71

(1H, m), 3.76 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.45 (1H, br s), 4.78 (1H, t), 6.07 (1H, m), 6.77 (1H, s), 7.39 (2H, m), 7.84-7.90 (3H, m), 8.69 (1H, s)

Example 64ad: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.21 (3H, d), 1.77 (2H, m), 1.94 (2H, m), 2.48 (3H, d), 3.18 (1H, td), 3.36 (2H, m), 3.40 (1H, td), 3.63 (1H, dd), 3.71 (1H, m), 3.76 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.45 (1H, br s), 4.78 (1H, t), 6.07 (1H, m), 6.77 (1H, s), 7.39 (2H, m), 7.84-7.90 (3H, m), 8.70 (1H, s)

Example 64ae: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.77 (2H, m), 1.96 (2H, m), 2.48 (3H, d), 3.18 (1H, td), 3.38 (1H, m), 3.45 (2H, m), 3.62 (1H, dd), 3.76 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.41 (1H, t), 4.45 (1H, br s), 4.53 (1H, t), 6.41 (1H, t), 6.78 (1H, s), 7.42 (2H, m), 7.84 (1H, s), 7.90 (2H, m), 8.79 (1H, s)

Example 64af: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.74 (2H, m), 1.97 (2H, m), 3.15 (1H, td), 3.40(1H, td), 3.50 -3.60 (3H, m), 3.74 (1H, d), 3.95 (1H, dd), 4.13 (1H, d), 4.40 (1H, br s), 5.90-6.20 (1H, m), 6.50 (1H, t), 6.70 (1H, s), 7.35 (2H, m), 7.76 (3H, m), 7.95 (1H, m), 8.09 (1H, td), 8.75 (1H, d), 8.83 (1H, s)

Example 64ag: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.74 (2H, m), 2.00 (2H, m), 3.15 (1H, td), 3.52 (1H, td), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.13 (1H, d), 4.40 (1H, br s), 6.70 (1H, s), 6.87 (1H, s), 7.43 (2H, m), 7.76-7.81 (3H, m), 7.99 (1H, m), 8.09 (1H, td), 8.75 (1H, s), 8.83 (1H, m), 9.02 (1H, s), 9.60 (1H, s)

Example 64ah: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.61 (2H, dd), 1.90 (2H, dd), 3.17 (1H, m), 3.40 - 3.64 (4H, m), 3.75 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.45 (1H, br s), 5.90 - 6.20(1H, t), 6.49 (1H, t), 6.64 (1H, s), 7.41 (2H, d), 7.66 (2H, m), 7.78 (4H, m), 8.90 (1H, s)

Example 64ai: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, m), 1.62 (2H, m), 1.91 (2H, m), 3.15 (1H, td), 3,45 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.45 (1H, br s), 6.66 (1H, s), 6.87 (1H, s), 7.47 (2H, d), 7.67 (2H, d), 7.79 (2H, d), 7.84 (2H, m), 8.75 (1H, s), 9.10 (1H, s), 9.60 (1H, s)

Example 64aj: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.56 (2H, m), 1.64 (2H, m), 1.94 (2H, m), 3.15-3.25 (2H, m), 3.39 (1H, m), 3.40 - 3.52 (5H, m), 3.65 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.20 (1H, br s, 4.42 (1H, t), 4.54 (2H, m), 4.69 (1H, t), 6.43 (1H, t), 6.77 (1H, s), 7.50 (2H, m), 8.22 (2H, m), 8.81 (1H, s)

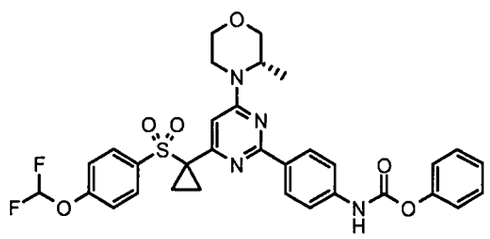
Example 64ak: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.57 (2H, m), 1.64 (2H, m), 1.94 (2H, m), 3.25 (1H, m), 3.51 (1H, m), 3.53 (4H, m), 3.76 (1H, dd), 3.86 (1H, d), 4.10

(1H, dd), 4.30 (1H, d), 4.65 (1H, br s), 4.70 (1H, t), 6.80 (1H, s), 6.87 (1H, s), 7.57 (2H, m), 8.29 (2H, m), 8.76 (1H, s), 9.07 (1H, s), 9.62 (1H, s)

Example 64al: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.60 (2H, m), 1.85 (2H, m), 2.78 (1H, s), 2.95 (1H, s), 3.15 (2H, m), 3.42 (2H, m), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.15 (1H, d), 4.45 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.70 (1H, s), 7.40 (2H, m), 7.70 -8.00 (3H, m), 8.20 (1H, s), 8.80 (1H, s), 8.91 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

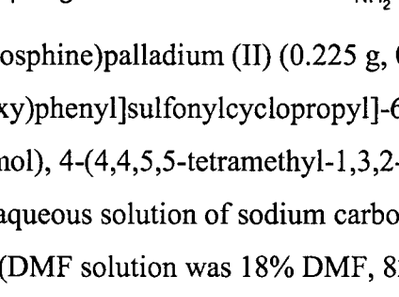


Phenyl chloroformate (0.170 mL, 1.36 mmol) was added dropwise to 4-[4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.700 g, 1.36 mmol) and sodium hydrogen carbonate (0.114 g, 1.36 mmol) in dioxane and the resulting suspension stirred at RT for 6 hours. The reaction mixture was concentrated and diluted with DCM (50 mL), and washed sequentially with water (10 mL), water (10 mL), and saturated brine(10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether:isohexane (20:80) to give the desired material as a white solid (0.710 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, m), 1.62 (2H, dd), 1.90 (2H, dd), 3.16 (1H, td), 3.46 (1H, td), 3.60 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.42 (1H, s), 6.67 (1H, s), 7.24 -7.27 (3H, m), 7.37 (3H, m), 7.45 (2H, m), 7.53 (2H, m), 7.84 (2H, m), 7.93 (2H, m), 10.40 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=637; HPLC tR=3.04 min.

4-[4-[1-[4-(Difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

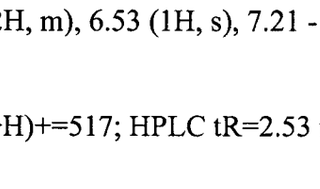


Trans-Dichlorobis(triphenylphosphine)palladium (II) (0.225 g, 0.32 mmol) was added to 2-chloro-4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.95 g, 6.41 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.476 g, 6.74 mmol) and 2M aqueous solution of sodium carbonate (16.04 mL, 32.07 mmol) in the DMF solution (150mL) (DMF solution was 18% DMF, 82% of a 7:3:2 mixture of DME:H_2O:Ethanol) at RT under nitrogen. The resulting solution was stirred at 80°C for 5 hours. The reaction was cooled and the reaction mixture diluted with ethyl acetate and water. The reaction mixture was extracted with ethyl acetate and the combined organics dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% ethyl acetate in DCM, to give the desired material as a beige solid (1.35 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 (2H, dd), 1.87 (2H, dd), 3.26 (1H, td), 3.50 (1H, td), 3.61 (1H, dd), 3.73 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.40 (1H, br s), 5.51 (2H, br s), 6.50 (2H, m), 6.53 (1H, s), 7.21 - 7.60 (1H, m), 7.35 (2H, m), 7.68 (2H, m), 7.83 (2H, m).

LCMS Spectrum: m/z (ES+)(M+H)+=517; HPLC tR=2.53 min.

2-Chloro-4-[1-[4-(difluoromethoxy)phenyl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



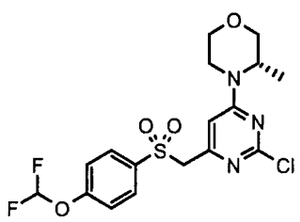
A solution of 50% w/v sodium hydroxide (14.2 mL, 354.96 mmol) was added portionwise to a stirred solution of 2-chloro-4-[[4-(difluoromethoxy)phenyl]sulfonylmethyl]-6-[(3*S*)-3-

methylmorpholin-4-yl]pyrimidine (2.8 g, 6.45 mmol), tetrabutylammonium bromide (0.208 g, 0.65 mmol) and 1,2-dibromoethane (1.668 mL, 19.36 mmol) in toluene (150 mL) and the resulting suspension stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and the washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% ethyl acetate in DCM, to give the desired material as a colourless oil which solidified on standing (2.95 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, dd), 1.55 (2H, dd), 1.83 (2H, dd), 3.13 (1H, td), 3.40 (1H, td), 3.54 (1H, dd), 3.69 (1H, d), 3.90 (2H, dd), 4.23 (1H, br s), 6.68 (1H, s), 7.23-7.60 (1H, t), 7.37 (2H, d), 7.82 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=459; HPLC tR=2.49 min.

2-Chloro-4-[[4-(difluoromethoxy)phenyl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

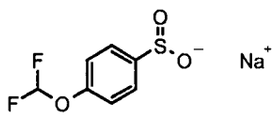


Sodium 4-(difluoromethoxy)benzenesulfinate (2.54 g, 11.03 mmol) was added portionwise to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.25 g, 9.19 mmol) in acetonitrile (125 mL) and the resulting suspension stirred at 80°C for 6 hours. Additional sodium 4-(difluoromethoxy)benzenesulfinate (680mg, 3.39 mmol) was added in one portion and the suspension was stirred at 80°C for a further 2 hours. The reaction mixture was concentrated and diluted with DCM (200 mL) and washed sequentially with 10% aqueous sodium thiosulfate solution (50 mL), water (50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude gum was triturated with diethyl ether to give the desired material as a beige solid (2.94 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 3.15 (1H, td), 3.42 (1H, m), 3.57 (1H, dd), 3.71 (1H, d), 3.91 (1H, br s), 3.92 (1H, dd), 4.17 (1H, br s), 4.64 (2H, s), 6.68 (1H, s), 7.25-7.60 (1H, t), 7.41 (2H, m), 7.84 (2H, m).

LCMS Spectrum: m/z (ES+)(M+H)+=434; HPLC tR=2.29 min.

Sodium 4-(difluoromethoxy)benzenesulfinate

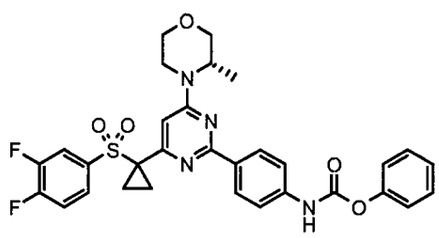


A solution of sodium sulfite (1.470 g, 11.66 mmol) in water (15 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (1.960 g, 23.33 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 1 hour. 4-(Difluoromethoxy)benzene-1-sulfonyl chloride (2.83 g, 11.66 mmol) was added dropwise with caution to the solution and was stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (15 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate was evaporated to give a crude product that was triturated with isohexane to give the desired material as a cream solid (2.85 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.10 (2H, dd), 7.50 (2H, dd).

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl N-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



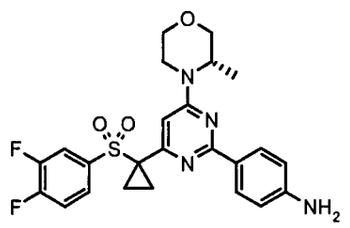
Phenyl chloroformate (0.206 mL, 1.64 mmol) was added dropwise to 4-[4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (800 mg, 1.64 mmol) and sodium hydrogen carbonate (138 mg, 1.64 mmol) in dioxane and

the resulting suspension was stirred at RT for 6 hours. The reaction mixture was concentrated and diluted with DCM (50 mL), and washed sequentially with water (2 x 10 mL), and saturated brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude solid was triturated with acetonitrile to give the desired material as a white solid (1.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.63 (2H, dd), 1.94 (2H, dd), 3.17 (1H, td), 3.47 (1H, td), 3.61 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.18 (1H, d), 4.50 (1H, br s), 6.71 (1H, s), 7.25 (2H, dt), 7.29 (1H, m), 7.45 (2H, dd), 7.54 (2H, d), 7.67 (2H, m), 7.91 (3H, dd), 10.40 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=607; HPLC tR=3.05 min.

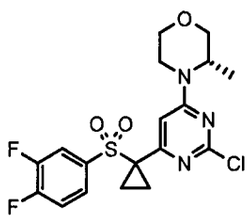
4-[4-[1-(3,4-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Trans-Dichlorobis(triphenylphosphine)palladium (II) (0.252 g, 0.36 mmol) was added to 2-chloro-4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.09 g, 7.19 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.575 g, 7.19 mmol)and a 2M aqueous solution of sodium carbonate (17.97 mL, 35.94 mmol) in the DMF solution (DMF solution was 18% DMF, 82% of a 7:3:2 mixture of DME:H_2O:Ethanol) (150mL) at RT under nitrogen. The resulting solution was stirred at 80°C for 5 hours. The reaction was cooled and the mixture diluted with ethyl acetate and water. The reaction mixture was extracted with ethyl acetate and the combined organics dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0to 5% ethyl acetate in DCM, to give a material which was further purified by ion exchange chromatography using an SCXcolumn, eluting with 7M ammonia in methanol, to give the desired material as a tan solid (1.94 g).

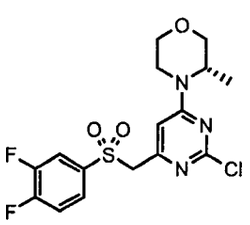
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 (2H, dd), 1.91 (2H, dd), 3.10 (1H, td), 3.45 (1H, td), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.13 (1H, m), 4.43 (1H, br s), 5.53 (2H, d), 6.50 (2H, m), 6.57 (1H, s), 7.64 (1H, m), 7.65 (3H, m), 7.89 (1H, m).
LCMS Spectrum: m/z (ES+)(M+H)+=487; HPLC tR=2.55 min.

2-Chloro-4-[1-(3,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



A solution of 50% w/v sodium hydroxide (17.32 mL, 433.10 mmol) was added portionwise to a stirred solution of 2-chloro-4-[(3,4-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.18 g, 7.87 mmol), tetrabutylammonium bromide (0.254 g, 0.79 mmol) and 1,2-dibromoethane (2.036 mL, 23.62 mmol) in toluene (200 mL) and the resulting suspension stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a white solid (3.09 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.56 (2H, dd), 1.88 (2H, dd), 3.15 (1H, td), 3.40 (1H, td), 3.54 (1H, dd), 3.69 (1H, d), 3.91 (1H, dd), 3.97 (1H, d), 4.29 (1H, br s), 6.73 (1H, s), 7.65 (1H, m), 7.66 (1H, m), 7.92 (1H, ddd).
LCMS Spectrum: m/z (ES+)(M+H)+=430; HPLC tR=2.41 min.

2-Chloro-4-[(3,4-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

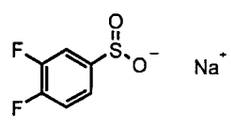


Sodium 3,4-difluorobenzenesulfinate (3.40 g, 16.97 mmol) was added portionwise to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (6 g, 16.97 mmol) in acetonitrile (200 mL) and the resulting suspension stirred at 80°C for 6 hours. Additional sodium 3,4-difluorobenzenesulfinate (680mg, 3.39mmol) was added in one portion and the suspension was stirred at 80°C for a further 2 hours. The reaction mixture was concentrated and diluted with DCM (200 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% ethyl acetate in DCM, to give the desired material as a yellow solid (4.58 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, m), 3.10-3.20 (1H, td), 3.40-3.45 (1H, td), 3.55-3.60 (1H, dd), 3.70 (1H, d), 3.90-4.00 (2H, dd), 4.20 (1H, br s), 4.70 (2H, s), 6.77 (1H, s), 7.66 (1H, m), 7.74 (1H, dt), 7.95 (1H, ddd).

LCMS Spectrum: m/z (ES+)(M+H)+=404; HPLC tR=2.24 min.

Sodium 3,4-difluorobenzenesulfinate



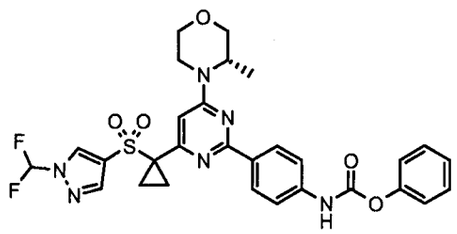
A solution of sodium sulfite (2.96 g, 23.52 mmol) in water (25 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (3.95 g, 47.04 mmol) was added to the stirred solution. The resulting solutionwas stirred at 50°C for 1 hour. 3,4-Difluorobenzene-1-sulfonyl chloride (5 g, 23.52 mmol) was added portionwise to the solution and was stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (15 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate was evaporated to afford the desired material as a white solid (5.30 g), which was dried overnight under vacuum and used without further purification.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.28 (1H, ddd), 7.37 (2H, m).

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier

The preparation of phenyl *N*-[4-[4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

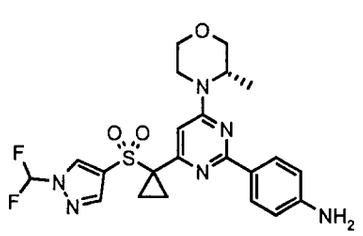


Phenyl chloroformate (0.018 mL, 0.14 mmol) was added dropwise to 4-[4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (70 mg, 0.14 mmol) and sodium hydrogen carbonate (11.99 mg, 0.14 mmol) in dioxane and the resulting suspension stirred at RT for 6 hours. The reaction mixture was concentrated and diluted with DCM (50 mL), and washed sequentially with water (2 x 10 mL), and saturated brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude solid was triturated with diethyl ether:isohexane (20:80) to give the desired material as a white solid (80 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 (2H, m), 1.89 (2H, m), 3.15 (1H, td), 3.45 (1H, td), 3.63 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.50 (1H, br s), 6.75 (1H, m), 7.26 (3H, m), 7.45 (2H, m), 7.56 (2H, m), 7.70-8.00 (1H, t),8.00 (2H, m), 8.17 (1H, s), 8.93 (1H, s), 10.40 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=611; HPLC tR=2.83 min.

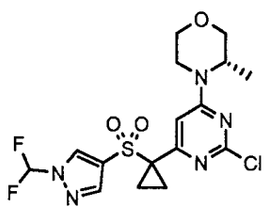
4-[4-[1-[1-(Difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



Trans-Dichlorobis(triphenylphosphine)palladium (II) (0.197 g, 0.28 mmol) was added to 2-chloro-4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.44 g, 5.62 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.232 g, 5.62 mmol) and a 2M aqueous solution of sodium carbonate (14.06 mL, 28.12 mmol) in the DMF solution (DMF solution was 18% DMF, 82% of a 7:3:2 mixture of DME:H_2O:Ethanol) (150mL) and the resulting solution stirred at 80°C for 5 hours. The reaction mixture was partitioned between ethyl acetate and water, the layers separated and the aqueous layer extracted with ethyl acetate. The combined organics were dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% ethyl acetate in DCM, to give the desired material as a tan solid (0.070 g).

LCMS Spectrum: m/z (ES+)(M+H)+=491; HPLC tR=2.23 min.

2-Chloro-4-[1-[1-(difluoromethyl)pyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



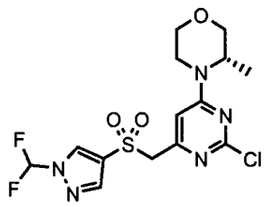
A solution of 50% w/v sodium hydroxide (16.18 mL, 404.59 mmol) was added portionwise to a stirred solution of 2-chloro-4-[[1-(difluoromethyl)pyrazol-4-yl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3 g, 7.36 mmol), tetrabutylammonium bromide (0.237 g, 0.74 mmol) and 1,2-dibromoethane (1.902 mL, 22.07 mmol) in toluene (200 mL) and the resulting suspension stirred at RT for 6 hours. The reaction mixture was diluted with water (50 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% ethyl acetate in DCM, to give the desired material as a yellow oil (2.44 g) which solidified on standing.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.57 (2H, dd), 1.82 (2H, dd), 3.16 (1H, td), 3.40 (1H, td), 3.56 (1H, dd), 3.70 (1H, d), 3.92 (1H, dd), 4.04 (1H, d), 4.30

(1H, br s), 6.78 (1H, s), 7.70-8.00 (1H, t), 8.19 (1H, s), 8.93 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=434; HPLC tR=2.15 min.

2-Chloro-4-[[1-(difluoromethyl)pyrazol-4-yl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

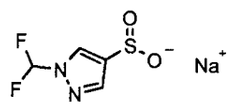


Sodium 1-(difluoromethyl)-1H-pyrazole-4-sulfinate (3.28 g, 16.09 mmol) was added portionwise to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.74 g, 13.41 mmol) in acetonitrile (150 mL) and the resulting suspension stirred at 80°C for 6 hours. Additional sodium 1-(difluoromethyl)-1H-pyrazole-4-sulfinate (680 mg, 3.39mmol) was added in one portion and the suspension was stirred at 80°C for a further 2 hours. The reaction mixture was concentrated and diluted with DCM (200 mL), and washed sequentially with 10% aqueous sodium thiosulfate solution (50 mL), water (50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude residue was triturated with diethyl ether to give the desired material as a beige solid (4.50 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 3.18 (1H, td), 3.43 (1H, td), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (2H, dd), 4.21 (1H, br s), 4.67 (2H, s), 6.77 (1H, s), 7.70-8.05 (1H, t), 8.13 (1H, s), 8.87 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=408; HPLC tR=1.91 min.

Sodium 1-(difluoromethyl)-1H-pyrazole-4-sulfinate



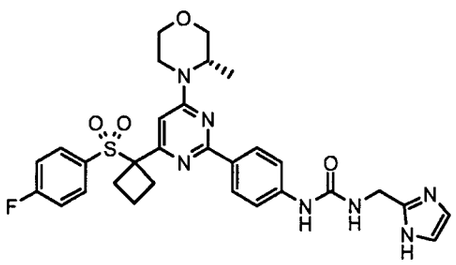
A solution of sodium sulfite (2.87 g, 22.81 mmol) in water (25 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (3.83 g, 45.62 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 1hour. 1-(Difluoromethyl)-1H-pyrazole-4-sulfonyl chloride (4.94 g, 22.81 mmol) was added dropwise with caution to the solution and was

stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (15 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to give a solid which was triturated with isohexane to give the desired material as a white solid (5.85 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.60 (1H, m), 7.74 (1H, s), 7.90 (1H, m).

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier

Example 65: 1-[4-[4-[1-(4-Fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea

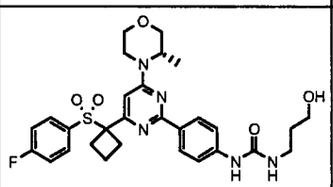
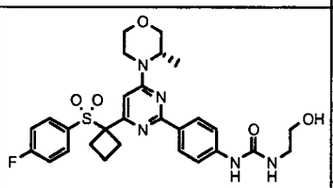
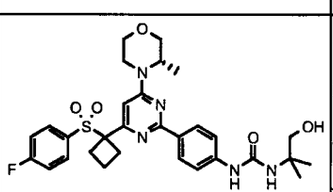
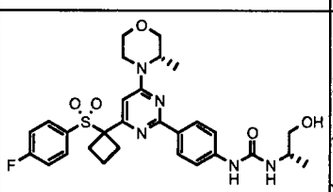


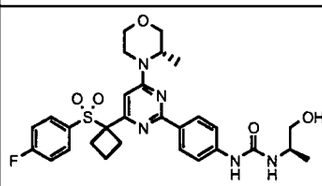
C-(1*H*-Imidazol-2-yl)-methylamine (17.73 mg, 0.18 mmol) was added in one portion to phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) and triethylamine (0.069 mL, 0.50 mmol) in NMP (2 mL) at RT and stirred for a period of 16 hours under air. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a cream solid (42 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.83 - 1.93 (m, 1H), 2.04 - 2.15 (m, 1H), 2.75 - 2.82 (m, 2H), 3.02 - 3.11 (m, 2H), 3.16 (td, 1H), 3.49 (td, 1H), 3.64 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.15 (d, 1H), 4.32 (d, 2H), 4.44 - 4.54 (m, 1H), 6.55 (s, 1H), 6.60 (t, 1H), 6.80 - 6.90 (m, 1H), 7.00 - 7.08 (m, 1H), 7.29 (dd, 2H), 7.40 (dt, 2H), 7.55 (ddd, 2H), 7.80 (d, 2H), 8.90 (s, 1H), 11.85 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 606.55; HPLC tR = 2.09 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
65a		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	584.5	2.15
65b		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	570.5	2.05
65c		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	598.6	2.33
65d		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	584.5	2.15

Example	Structure	NAME	LCMS MH+	Retention time (min)
65e		1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	584.5	2.13

Example 65a : ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.57 - 1.63 (m, 2H), 1.83 - 1.94 (m, 1H), 2.05 - 2.15 (m, 1H), 2.75 - 2.82 (m, 2H), 3.01 - 3.09 (m, 2H), 3.17 (dd, 3H), 3.48 (dd, 3H), 3.64 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.10 - 4.19 (m, 1H), 4.48 (t, 2H), 6.18 (t, 1H), 6.54 (s, 1H), 7.29 (t, 2H), 7.38 (d, 2H), 7.55 (ddd, 2H), 7.78 (d, 2H), 8.68 (s, 1H)

Example 65b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.83 - 1.94 (m, 1H), 2.04 - 2.15 (m, 1H), 2.75 - 2.82 (m, 2H), 3.01 - 3.09 (m, 2H), 3.16 - 3.20 (m, 3H), 3.44 - 3.50 (m, 3H), 3.64 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.09 - 4.19 (m, 1H), 4.43 - 4.53 (m, 1H), 4.73 (t, 1H), 6.23 (t, 1H), 6.54 (s, 1H), 7.29 (t, 2H), 7.37 (d, 2H), 7.55 (ddd, 2H), 7.78 (d, 2H), 8.77 (s, 1H)

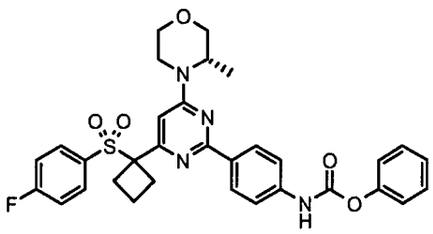
Example 65c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.25 (s, 6H), 1.83 - 1.94 (m, 1H), 2.05 - 2.15 (m, 1H), 2.73 - 2.83 (m, 2H), 3.01 - 3.09 (m, 2H), 3.12 - 3.20 (m, 1H), 3.39 (d, 2H), 3.49 (td, 1H), 3.64 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.10 - 4.18 (m, 1H), 4.43 - 4.53 (m, 1H), 4.96 (t, 1H), 5.98 (s, 1H), 6.54 (s, 1H), 7.27 - 7.35 (m, 4H), 7.53 - 7.57 (m, 2H), 7.77 (d, 2H), 8.70 (s, 1H)

Example 65d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.09 (d, 3H), 1.21 (d, 3H), 1.82 - 1.93 (m, 1H), 2.02 - 2.15 (m, 1H), 2.75 - 2.82 (m, 2H), 3.01 - 3.11 (m, 2H), 3.16 (td, 1H), 3.33 - 3.43 (m, 2H), 3.49 (td, 1H), 3.64 (dd, 1H), 3.69 - 3.73 (m, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.11 - 4.19 (m, 1H), 4.44 - 4.53 (m, 1H), 4.79 (t, 1H), 6.08 (d, 1H), 6.54 (s, 1H), 7.29 (ddd, 2H), 7.36 (d, 2H), 7.55 (ddd, 2H), 7.78 (d, 2H), 8.68 (s, 1H)

Example 65e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.09 (d, 3H), 1.21 (d, 3H), 1.83 - 1.94 (m, 1H), 2.05 - 2.15 (m, 1H), 2.75 - 2.82 (m, 2H), 3.01 - 3.09 (m, 2H), 3.16 (td, 1H), 3.33 - 3.43 (m, 2H), 3.49 (td, 1H), 3.64 (dd, 1H), 3.69 - 3.73 (m, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.10 - 4.18 (m, 1H), 4.44 - 4.53 (m, 1H), 4.79 (t, 1H), 6.08 (d, 1H), 6.54 (s, 1H), 7.29 (ddd, 2H), 7.36 (d, 2H), 7.55 (ddd, 2H), 7.78 (d, 2H), 8.68 (s, 1H)

The preparation of phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

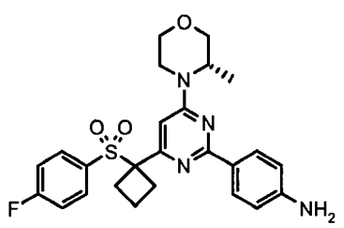


Phenyl chloroformate (0.285 mL, 2.27 mmol) was added dropwise to 4-[4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (1.095 g, 2.27 mmol) and sodium hydrogencarbonate (0.191 g, 2.27 mmol) in dioxane (20 mL) and the resulting suspension was stirred at RT for 3 hours. The reaction mixture was evaporated and DCM (50 mL) added and washed sequentially with water (2 x 20 mL), and saturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford desired material as a dry film (1.4 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.22 (d, 3H), 1.84 - 1.95 (m, 1H), 2.05 - 2.16 (m, 1H), 2.74 - 2.86 (m, 2H), 3.02 - 3.12 (m, 2H), 3.17 (td, 1H), 3.45 - 3.55 (m, 1H), 3.61 - 3.69 (m, 1H), 3.71 - 3.85 (m, 1H), 3.93 - 4.03 (m, 1H), 4.11 - 4.24 (m, 1H), 4.45 - 4.58 (m, 1H), 7.22 - 7.35 (m, 5H), 7.42 - 7.49 (m, 2H), 7.50 - 7.60 (m, 4H), 7.88 (d, 2H), 10.40 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 603.17; HPLC tR = 3.15 min.

4-[4-[1-(4-Fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

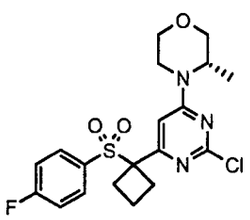


Bis(triphenylphosphine)palladium(II) chloride (0.086 g, 0.12 mmol) was added in one portion to 2-chloro-4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.046 g, 2.46 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.538 g, 2.46 mmol) and sodium carbonate (6.14 mL, 12.28 mmol) in a DMF:DME :water:ethanol solution and the reaction mixture thoroughly degassed and stirred at 80°C for 3 hours under a nitrogen atmosphere. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL), and washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 100% ethyl acetate in isohexane, to afford desired material as a colourless dry film (1.1 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (d, 3H), 1.82 - 1.95 (m, 1H), 2.03 - 2.14 (m, 1H), 2.71 - 2.82 (m, 2H), 2.98 - 3.08 (m, 2H), 3.13 (td, 1H), 3.48 (td, 1H), 3.63 (dd, 1H), 3.75 (d, 1H), 3.93 - 3.99 (m, 1H), 4.07 - 4.15 (m, 1H), 4.41 - 4.49 (m, 1H), 5.49 (d, 1H), 6.44 (s, 1H), 6.49 (d, 2H), 7.28 (ddd, 2H), 7.54 (ddd, 2H), 7.62 (d, 2H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 483.27; HPLC tR = 2.39 min.

2-Chloro-4-[1-(4-fluorophenyl)sulfonylcyclobutyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



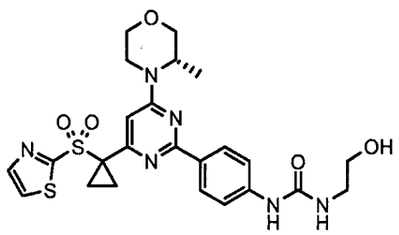
Sodium hydroxide (50%w/w solution) (16.91 g, 422.79 mmol) was added to 2-chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.966 g, 7.69 mmol), 1,3-dibromopropane (2.341 mL, 23.06 mmol) and tetrabutylammonium bromide (0.248 g, 0.77 mmol) in toluene (150 mL) and the resulting suspension stirred at 45°C for 1 hour. The organics were washed with water twice, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 10 to 30% ethyl acetate in DCM, to afford desired material as a colourless dry film (1.055 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (d, 3H), 1.81 - 1.92 (m, 1H), 2.01 - 2.12 (m, 1H), 2.65 - 2.72 (m, 2H), 2.91 - 3.01 (m, 2H), 3.14 (td, 1H), 3.42 (td, 1H), 3.57 (dd, 1H), 3.71 (d, 1H), 3.88 - 4.00 (m, 2H), 4.23 - 4.40 (m, 1H), 6.56 (s, 1H), 7.38 - 7.44 (m, 2H), 7.54 - 7.60 (m, 2H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 426.06; HPLC tR = 2.52 min.

The preparation of 2-chloro-4-[(4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 66: 3-(2-Hydroxyethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea

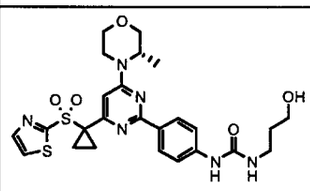
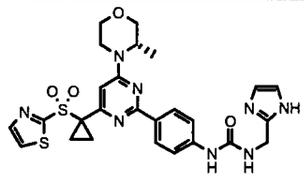


Ethanolamine (0.052 mL, 0.87 mmol) was added in one portion to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) and triethylamine (0.072 mL, 0.52 mmol) in NMP (2 mL) and warmed to 55°C over a period of 16 hours under air. The crude reaction mixture was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to afford the desired material as a colourless dry film. (84 mg)

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.77 - 1.82 (m, 2H), 1.98 - 2.02 (m, 2H), 3.14 - 3.21 (m, 3H), 3.44 - 3.50 (m, 3H), 3.62 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.10 - 4.21 (m, 1H), 4.40 - 4.51 (m, 1H), 4.74 (t, 1H), 6.25 (t, 1H), 6.74 (s, 1H), 7.40 (d, 2H), 7.85 (d, 2H), 8.24 (d, 1H), 8.29 (d, 1H), 8.78 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 545.75; HPLC tR = 1.79 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

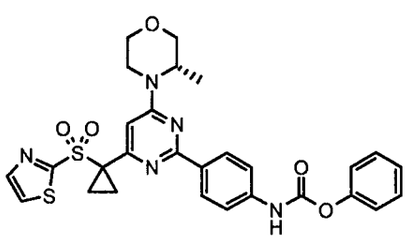
Example	Structure	NAME	LCMS MH+	Retention time (min)
66a		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	559.8	1.84
66b		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	581.8	1.30

Example 66a : ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21, 1.60, 1.77 - 1.82, 1.97 - 2.03, 3.14 - 3.21, 3.44 - 3.50, 3.62, 3.76, 3.97, 4.12 - 4.20, 4.40 - 4.52, 4.49, 6.19, 6.74, 7.40, 7.85, 8.23, 8.28, 8.68

Example 66b : ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (d, 3H), 1.77 - 1.82 (m, 2H), 1.97 - 2.03 (m, 2H), 3.14 - 3.21 (m, 1H), 3.47 (td, 1H), 3.62 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.11 - 4.21 (m, 1H), 4.32 (d, 2H), 4.39 - 4.54 (m, 1H), 6.62 (t, 1H), 6.74 (s, 1H), 6.88 - 7.01 (m, 2H), 7.43 (d, 2H), 7.87 (d, 2H), 8.23 (d, 1H), 8.28 (d, 1H), 8.90 (s, 1H), 11.85 (s, 1H)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate

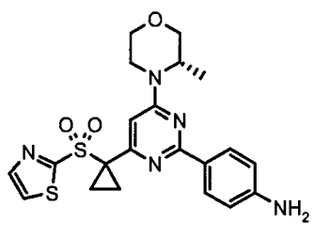


Phenyl chloroformate (0.123 mL, 0.98 mmol) was added dropwise to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline (450 mg, 0.98 mmol) and sodium hydrogencarbonate (83 mg, 0.98 mmol) in dioxane and the resulting suspension stirred at RT for 3 hours. The reaction mixture was evaporated and DCM (50 mL) added and washed sequentially with water (2 x 20 mL), and saturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford desired product as a dry film (522 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.22 (d, 3H), 1.78 - 1.84 (m, 2H), 1.98 - 2.04 (m, 2H), 3.19 (td, 1H), 3.48 (td, 1H), 3.63 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.12 - 4.24 (m, 1H), 4.40 - 4.52 (m, 1H), 6.79 (s, 1H), 7.23 - 7.32 (m, 3H), 7.46 (t, 2H), 7.55 (d, 2H), 7.95 (d, 2H), 8.24 (d, 1H), 8.29 (d, 1H), 10.41 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 578.04; HPLC tR = 2.83 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline



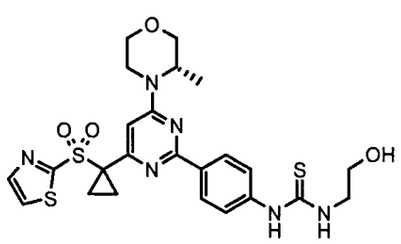
Bis(triphenylphosphine)palladium(II) chloride (0.139 g, 0.20 mmol) was added in one portion to 2-chloro-4-[(*3S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine (1.59 g, 3.97 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.869 g, 3.97 mmol) and sodium carbonate (9.92 mL, 19.83 mmol) in a DMF, DME, water and ethanol solution at RT under nitrogen. The reaction mixture was thoroughly degassed and was stirred at 80°C for 3 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL), and washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 100 % ethyl acetate in isohexane, to afford desired material as a beige dry film (1.430 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 - 1.21 (m, 3H), 1.75 - 1.79 (m, 2H), 1.96 - 2.01 (m, 2H), 3.14 (td, 1H), 3.46 (td, 1H), 3.61 (dd, 1H), 3.75 (d, 1H), 3.96 (dd, 1H), 4.07 - 4.17 (m, 1H), 4.35 - 4.48 (m, 1H), 5.50 - 5.55 (m, 1H), 6.52 (d, 2H), 6.63 (s, 1H), 7.69 (d, 2H), 8.22 (d, 1H), 8.27 (d, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 458.16; HPLC tR = 1.68 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidine was described earlier.

Example 67: 3-(2-Hydroxyethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]thiourea



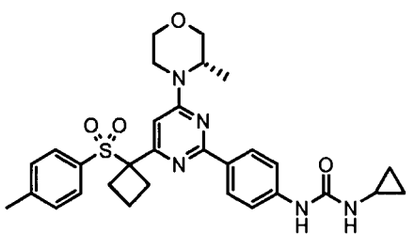
A solution of 1,1'-thiocarbonyldiimidazole (50.6 mg, 0.28 mmol) in DCM (2 mL) was added to a stirred solution 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline (100 mg, 0.22 mmol) in THF (1 mL) and DCM (2 mL) at RT, over a period of 2 minutes under nitrogen. The resulting solution was stirred at RT for 2 hours. Triethylamine (0.030 mL, 0.22 mmol) and ethanolamine (0.066 mL, 1.09 mmol) were added to the reaction mixture. The resulting solution was stirred at RT for 60 hours. The reaction mixture was evaporated to dryness and redissolved in acetonitrile (2 mL), filtered and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to afford desired material as a beige solid (88 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.22 (d, 3H), 1.78 - 1.84 (m, 2H), 1.98 - 2.03 (m, 2H), 3.19 (td, 1H), 3.48 (td, 1H), 3.54 - 3.60 (m, 3H), 3.63 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 1H), 4.16 (d, 1H), 4.41 - 4.53 (m, 1H), 4.78 - 4.88 (m, 1H), 6.79 (s, 1H), 7.54 (d, 2H), 7.82 - 7.89 (m, 1H), 7.92 (dt, 2H), 8.24 (d, 1H), 8.28 (d, 1H), 9.78 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 561.82; HPLC tR = 2.12 min.

The preparation of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline was described earlier.

Example 68: 3-Cyclopropyl-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]urea

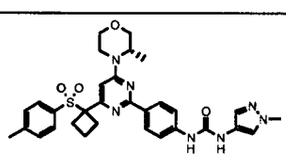


Triethylamine (0.057 mL, 0.41 mmol) was added to phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]carbamate (82 mg, 0.14 mmol) and cyclopropylamine (0.047 mL, 0.68 mmol) in NMP (2 mL) and the resulting solution stirred at 50°C overnight. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (43 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40-0.44(2H, m), 0.63-0.67(2H, m), 1.19-1.20(3H, d), 1.81-1.92(1H, m), 2.02-2.13(1H, m), 2.27(3H, s), 2.54-2.59(1H, m), 2.73-2.79(2H, m), 2.99-3.07(2H, m), 3.09-3.17(1H, td), 3.45-3.51(1H, td), 3.62-3.65(1H, dd), 3.74-3.77(1H, d), 3.95-3.98(1H, dd), 4.07-4.10(1H, d), 4.44(1H, bs), 6.40-6.41(1H, d), 6.45(1H, s), 7.24-7.26(2H, d), 7.35-7.40(4H, m), 7.76-7.78(2H, d), 8.49(1H, s).

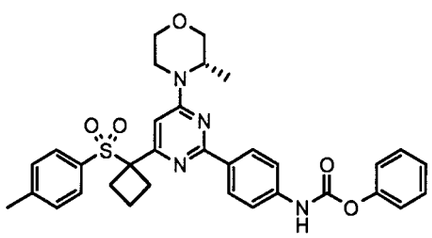
LCMS Spectrum: m/z (ESI+)(M+H)+562 = HPLC tR =2.60 min.

The following compound was made in an analogous fashion using the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
68a		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	601	2.44

Example 68a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19-1.21(3H, d), 1.83-1.90(1H, m), 2.04-2.12(1H, m), 2.28(3H, s), 2.73-2.80(2H, m), 3.00-3.07(2H, m), 3.10-3.15(1H, td), 3.45-3.52(1H, td), 3.62-3.66(1H, dd), 3.75-3.78(1H, d), 3.79(3H, s), 3.95-3.99(1H, dd), 4.08-4.11(1H, d), 4.45(1H, bs), 6.46(1H, s), 7.24-7.26(2H, d), 7.35-7.38(3H, m), 7.42-7.44(2H, d), 7.77(1H, s), 7.79-7.81(2H, d), 8.35(1H, s), 8.79(1H, s).

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]phenyl]carbamate

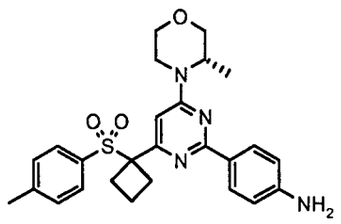


Phenyl chloroformate (0.034 mL, 0.27 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]aniline (129 mg, 0.27 mmol)and sodium hydrogen carbonate (34.0 mg, 0.40 mmol) in dioxane (10 mL). The resulting suspension was stirred at RT for 5 hours. The reaction mixture was evaporated to dryness and redissolved in ethyl acetate(125 mL), and washed sequentially with water (125 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material (182 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, CDCl3) δ 1.34 (3H, d), 1.87 - 1.98 (1H, m), 2.19 - 2.30 (4H, m), 2.72 - 2.81 (2H, m), 3.15 - 3.25 (2H, m), 3.30 (1H, td), 3.63 (1H, td), 3.70 (1H, s), 3.72 - 3.82 (3H, m), 4.03 - 4.16 (3H, m), 4.46 (1H, q), 6.56 (1H, s), 7.01 (21H, s), 7.07 (2H, d), 7.19 - 7.27 (3H, m, obscured by CDCL3 peak), 7.35 - 7.42 (6H, m), 7.91 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=599; HPLC tR=3.25 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidin-2-yl]aniline

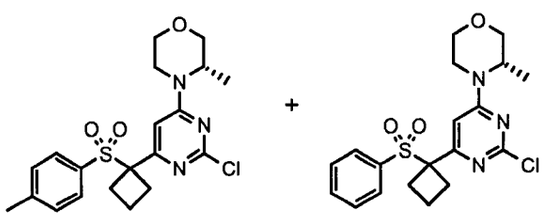


Bis(triphenylphosphine)palladium(II) chloride (0.131 g, 0.19 mmol) was added in one portion to a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidine and 4-[1-(benzenesulfonyl)cyclobutyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.522 g), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.817 g, 3.73 mmol) and a solution of sodium carbonate (9.33 mL, 18.66 mmol) in DMF (18 mL), DME (47.8 mL), water (20.5 mL)and ethanol (13.5 mL) and the resulting solution stirred at 80°C for 2 hours. The reaction mixture was concentrated *in vacuo* to remove the ethanol then the reaction mixture was acidified with 2M hydrochloric acid. The resulting suspension was purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, followed by preparative HPLC, to give the desired material as an off white solid (0.136 g).

NMR Spectrum:^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.85 - 1.97 (1H, m), 2.17 - 2.29 (4H, m), 2.71 - 2.81 (2H, m), 3.11 - 3.33 (3H, m), 3.61 (1H, t), 3.74 - 3.90 (4H, m), 4.03 (1H, d), 4.09 - 4.15 (1H, m), 4.44 (1H, q), 6.48 (1H, s), 6.57 (2H, d), 7.07 (2H, d), 7.36 (2H, d), 7.75 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=479; HPLC tR=2.23 min.

Mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidine and 4-[1-(benzenesulfonyl)cyclobutyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

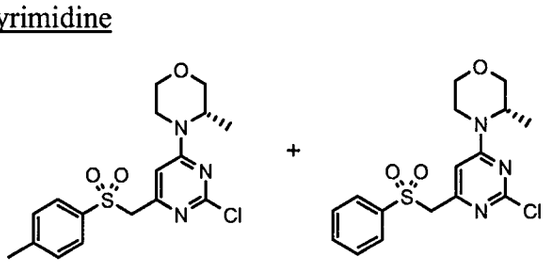


Sodium hydroxide (50%w/w solution) (52.4 g, 654.89 mmol) was added to a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine and 4-(benzenesulfonylmethyl)-2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (4.38 g), 1,3-dibromopropane (3.63 mL, 35.72 mmol) and tetrabutylammonium bromide (0.384 g, 1.19 mmol) in toluene (270 mL). The resulting suspension was stirred at 45°C for 1 hour. The reaction mixture was diluted with water (300 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give a white solid (1.522 g) which appeared to be a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclobutyl]pyrimidine (12%) and 4-[1-(benzenesulfonyl)cyclobutyl]-2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (83%). The mixture was taken through into the next step with no further purification.

LCMS Spectrum: m/z (ES+)(M+H)+=422; HPLC tR=2.59 min.

LCMS Spectrum: m/z (ES+)(M+H)+=408; HPLC tR=2.45 min.

Mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine and 4-(benzenesulfonylmethyl)-2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine



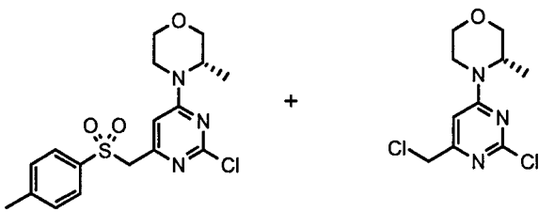
Benzenesulfinic acid, sodium salt (3.66 g, 22.32 mmol) was added to a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine and 2-chloro-4-(chloromethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (5.85 g) in acetonitrile (200 mL) under argon. The resulting suspension was stirred at reflux for 18 hours. Additional benzenesulfinic acid, sodium salt (1.2 g, 7.31 mmol) and sodium iodide (0.335 g, 2.23 mmol) were added and the suspension was stirred at reflux for a further 24 hours. The reaction mixture was evaporated to dryness, redissolved in DCM (500 mL) and washed with water (250 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude material was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate

in DCM, to give a white solid (4.38 g) which appeared to be a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine (7%) and 4-(benzenesulfonylmethyl)-2-chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (93%). The mixture was taken through into the next step with no further purification.

LCMS Spectrum: m/z (ES+)(M+H)+=382; HPLC tR=2.23 min.

LCMS Spectrum: m/z (ES+)(M+H)+=368; HPLC tR=2.06 min.

Mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine and 2-chloro-4-(chloromethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine



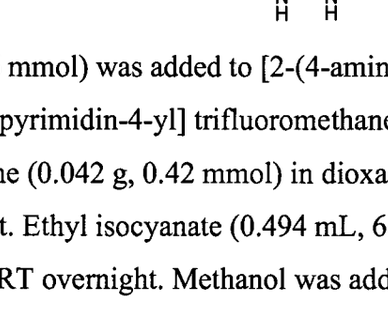
A solution of p-toluenesulfonyl chloride (23.47 g, 123.11 mmol) in DCM (50 mL) was added dropwise to a stirred solution of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol (20 g, 82.07 mmol) and DIPEA (21.44 mL, 123.11 mmol) in DCM (200 mL) cooled to 5°C, over a period of 1 hour under nitrogen. The resulting solution was stirred at 5°C for 72 hours and then at reflux for 24 hours. The reaction mixture was washed with water and the organic layer was dried over $MgSO_4$, filtered and evaporated to afford a brown gum which appeared to be a mixture of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine (11%) and 2-chloro-4-(chloromethyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (87%). The mixture was taken through into the next step with no further purification.

LCMS Spectrum: m/z (ES+)(M+H)+=398; HPLC tR=2.52 min.

LCMS Spectrum: m/z (ES+)(M+H)+=262; HPLC tR=1.97 min.

The preparation of [2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methanol was described earlier.

Example 69: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*R*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea

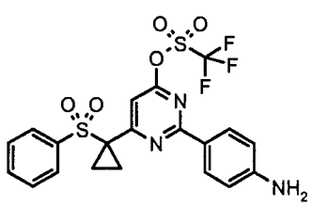


Triethylamine (0.064 mL, 0.46 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.104 g, 0.21 mmol), (*R*)-3-methylmorpholine (0.042 g, 0.42 mmol) in dioxane (5 mL) and the resulting solution stirred at RT overnight. Ethyl isocyanate (0.494 mL, 6.25 mmol) was added and the solution was allowed to stir at RT overnight. Methanol was added carefully and then all of the solvent was removed. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a tan solid (0.052 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) 1.05-1.08 (3H, t), 1.16-1.18 (3H, d), 1.60-1.67 (2H, m), 1.88-1.92 (2H, m), 3.09-3.19 (3H, m), 3.42-3.49 (1H, td), 3.59-3.62 (1H, dd), 3.73-3.76 (1H, d), 3.94-3.97 (1H, dd), 4.08-4.12 (1H, d), 4.37(1H, bs), 6.13-6.16 (1H, t), 6.62 (1H, s), 7.37-7.39 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.78-7.85 (4H, m), 8.63 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=522; HPLC tR=2.32min.

[2-(4-Aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate



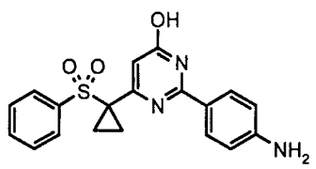
2-(4-Aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-ol (4.0 g, 10.89 mmol), 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide (4.28 g, 11.98 mmol)were dissolved in DCM (75 mL), to this was added DBU (1.791 mL, 11.98 mmol) and the reaction was stirred at RT overnight. The solvent was evaporated to dryness and the gum

was quenched with 1.0N citric acid (100 mL) and extracted with diethyl ether (3 x 100 mL). The combined organics were dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The solid was passed through a silica plug, eluting with diethyl ether, to give a yellow solid. This solid was dissolved in a minimum amount hot diethyl ether, to which iso-hexane was added and the system was stirred to afford the desired material as a yellow solid (1.5 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) 1.79 (2H, q), 2.02 (2H, q), 5.43 (2H, s), 6.62 (2H, d), 7.43 (1H, s), 7.59 (2H, t), 7.68 (2H, d), 7.72 (1H, t), 7.80 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=500; HPLC tR=2.96min

2-(4-Aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-ol

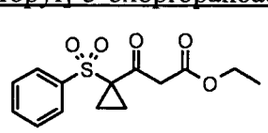


Ethyl 3-[1-(benzenesulfonyl)cyclopropyl]-3-oxopropanoate (5.4 g, 15.12 mmol), 4-aminobenzamidine dihydrochloride (3.78 g, 18.15 mmol) and potassium carbonate (3.83 mL, 63.52 mmol) were added to methanol (150 mL) and heated at reflux overnight. The solvent was evaporated to dryness and the remaining solid was acidified with 1.0N citric acid. The solid was filtered and then triturated with hot acetonitrile to give the desired material as a yellow solid (4.0 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) 1.58 (2H, q), 1.86 (2H, q), 5.86 (2H, s), 6.21 (1H, s), 6.50 (2H, d), 7.51 (2H, d), 7.60 (2H, t), 7.72 (1H, t), 7.82 (2H, d), 12.11 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=368; HPLC tR=1.23min

Ethyl 3-[1-(benzenesulfonyl)cyclopropyl]-3-oxopropanoate

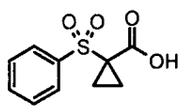


Triethylamine (20.70 mL, 148.51 mmol) and magnesium chloride (9.28 g, 97.46 mmol) were added to a stirred solution of potassium 3-ethoxy-3-oxopropanoate (15.80 g, 92.82 mmol) in acetonitrile (150 mL). The reaction was stirred for 2 hours. 1-(Benzenesulfonyl)cyclopropane-1-carboxylic acid (10.5 g, 46.41 mmol) and 1,1'-carbonyldiimidazole (9.03 g, 55.69 mmol) were dissolved in acetonitrile (30 mL) and stirred for 2 hours. This was then added to the

initial reaction and the system was stirred over the weekend at RT. 2M hydrochloric acid (150 mL) was added and the mixture extracted with diethyl ether (3 x 50 mL), the organics separated and evaporated to afford an orange oil. This oil was washed with a saturated solution of sodium hydrogen carbonate (100 mL) and extracted with diethyl ether (3 x 100 mL). The organics were dried over $MgSO_4$, filtered and evaporated to afford a yellow gum. This was passed through a plug of silica, eluting with DCM, to afford a colourless gum. The crude product was further purified by flash silica chromatography, eluting with DCM, to give the desired material as a colourless gum (5.6 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.23 (3H, t), 1.74 (2H, q), 1.99 (2H, q), 3.77 (2H, s), 4.12 (2H, q), 7.57 (2H, t), 7.67 (1H, t), 7.92 (2H, d).

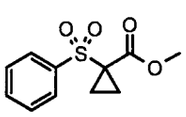
1-(Benzenesulfonyl)cyclopropane-1-carboxylic acid



Methyl 1-(benzenesulfonyl)cyclopropane-1-carboxylate (11 g, 45.78 mmol) was added to ethanol (50 mL) and water (50 mL), to this was added sodium hydroxide (1.904 mL, 48.07 mmol) and the reaction was stirred for 1 hour. The ethanol was carefully evaporated and the reaction mixture was extracted with diethyl ether (1 x 100 mL). The aqueous layer was quenched with 2M hydrochloric acid (50 mL), extracted with diethyl ether (3 x 100 mL) and the combined organics dried over MgSO4, filtered and evaporated to afford a white solid. The crude solid was triturated with ethyl acetate to give the desired material as a white solid (10.5 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.63 (2H, q), 1.85 (2H, q), 7.63 (2H, t), 7.73 (1H, t), 7.97 (2H, d).

Methyl 1-(benzenesulfonyl)cyclopropane-1-carboxylate



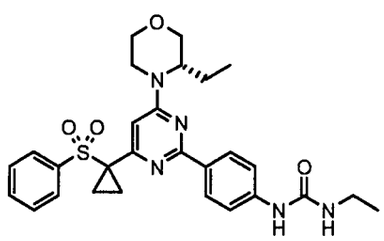
Methyl 2-(phenylsulfonyl)acetate (15 g, 70.02 mmol), benzyltriethylammonium chloride (4.77 g, 21.00 mmol), Potassium carbonate (29.0 g, 210.05 mmol) and 1,2-dibromoethane (12.07 mL, 140.03 mmol) were added to toluene (200 mL) and heated at 100°C over the

weekend. The reaction was filtered and solvent evaporated to afford a viscous gum. This reaction mixture was quenched with water (100 mL) and extracted with diethyl ether (3 x 100 mL). The organics were dried over $MgSO_4$, filtered and evaporated to afford an orange liquid. This liquid was passed through a plug of silica, eluting with diethyl ether, to afford an orange gum. The crude gum was triturated with ethanol to give the desired material as a white solid (11.0 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 11.70 (2H, q), 2.00 (2H, q), 3.63 (3H, s), 7.55 (2H, t), 7.64 (1H, t), 8.00 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=241; HPLC tR=1.84min

Example 70: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea



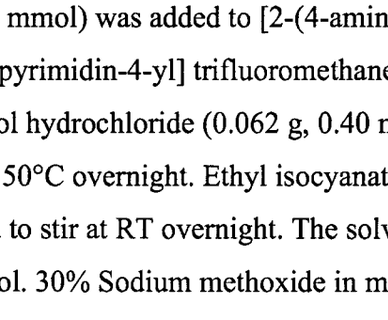
Triethylamine (0.062 mL, 0.45 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.102 g, 0.20 mmol), (*S*)-3-ethylmorpholine (0.047 g, 0.41 mmol) in dioxane (5 mL) and the resulting solution stirred at 50°C overnight. Ethyl isocyanate (0.564 mL, 7.12 mmol) was added and the solution allowed to stir at RT overnight. Methanol was added and then the solvent was removed. The crude product was purified by preparative HPLC, to give the desired material as a white solid (0.042 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.83-0.86(3H, t), 1.05-1.08(3H, t), 1.56-1.67(4H, m), 1.71-1.80(1H, m), 1.88-1.91(2H, m), 3.09-3.16(3H, m), 3.40-3.47(1H, td), 3.50-3.54(1H, dd), 3.84-3.87(1H, d), 3.90-3.94(1H, dd), 4.18(1H, bs), 6.12-6.15(1H, t), 6.61(1H, s), 7.37-7.40(2H, d), 7.57-7.61(2H, t), 7.69-7.74(1H, tt), 7.77-7.80(2H, dd), 7.84-7.86(2H, d), 8.61(1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=536; HPLC tR=2.43min.

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier.

Example 71: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[3-(hydroxymethyl)morpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea

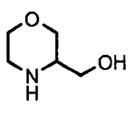


Triethylamine (0.112 mL, 0.80 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.100 g, 0.20 mmol), morpholin-3-ylmethanol hydrochloride (0.062 g, 0.40 mmol) in dioxane (5 mL) and the resulting solution stirred at 50°C overnight. Ethyl isocyanate (0.555 mL, 7.01 mmol) was added and the solution allowed to stir at RT overnight. The solvent was removed and the sludge was taken up in methanol. 30% Sodium methoxide in methanol solution was added and the reaction was allowed to stir overnight. Additional 30% sodium methoxide in methanol solution was added and the reaction refluxed overnight. Approximately 80% of the methanol was removed and the solution was quenched with saturated ammonium chloride solution. The mixture was extracted with DCM, the organics dried over $MgSO_4$, filtered and evaporated. The crude product was purified by preparative HPLC, to give the desired material as a cream solid (0.019 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.58-1.66 (2H, m), 1.86-1.92 (2H, m), 3.07-3.16 (3H, m), 3.42-3.53 (3H, m), 3.69-3.73 (1H, m), 3.92-3.95 1H, dd), 4.05-4.08 (1H, d), 4.18 (1H, bs), 4.93 (1H, bs), 6.14-6.17 (1H, t), 6.68 (1H, s), 7.36 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.84 (4H, m), 8.64 (1H, s) (1 peak under water or solvent peak).

LCMS Spectrum: m/z (ES+)(M+H)+=538; HPLC tR=1.95min.

Morpholin-3-ylmethanol

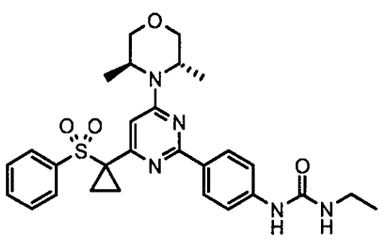


(4-Benzylmorpholin-3-yl)methanol (0.473 g, 2.28 mmol) and palladium (5% on carbon, 50%wet) (0.094 g, 0.02 mmol) in ethanol (50 mL) were stirred under an atmosphere of hydrogen at 5 bar and 25°C for 18 hours. The mixture was filtered and then hydrochloric acid (0.628 mL, 2.51 mmol) added. The reaction was stirred overnight at RT and then the solvent removed to give the desired material (as a hydrochloride salt) as an orangey brown gum (257 mg).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.43-1.46(1H, t), 3.14-3.67(3H, m), 3.81-4.18(4H, m), 4.62(1H, bs), 9.32(bs), 9.60(bs), 10.43(bs).

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier.

Example 72: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea



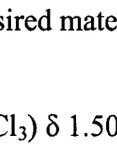
DIPEA (0.141 mL, 0.81 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.101 g, 0.20 mmol) and (3*S*,5*S*)-3,5-dimethylmorpholine (hydrochloride salt) (0.061 g, 0.40 mmol) in dioxane (5 mL) under nitrogen. The resulting solution was stirred at 70°C overnight then at 90°C for several hours. Additional (3*S*,5*S*)-3,5-dimethylmorpholine (hydrochloride salt) was added and the reaction was allowed to stir at 90°C overnight. Ethyl isocyanate (0.320 mL, 4.05 mmol) was added and the reaction allowed to stir at RT over the weekend. Methanol was added and then the solvent was removed. The crude product was purified by preparative HPLC, to give the desired material as a cream solid (0.029 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.27-1.29(6H, d), 1.61-1.71 (2H, m), 1.88-1.95 (2H, m), 3.09-3.16 (2H, m), 3.67-3.70 (2H, m), 4.10-4.16 (4H, m), 6.14-6.16 (1H, t), 6.60 (1H, s), 7.39-7.41 (2H, d), 7.57-7.61 (2H, t), 7.69-7.73 (1H, tt), 7.78-7.81 (2H, dd), 7.86-7.89 (2H, d), 8.62 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=536; HPLC tR=2.41min.

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier.

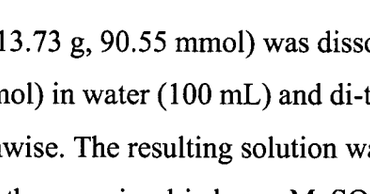
(3*S*,5*S*)-3,5-Dimethylmorpholine



Hydrogen chloride (4M solution in dioxane, 30.1 mL, 120.25 mmol) was added to *tert*-butyl (3*S*,5*S*)-3,5-dimethylmorpholine-4-carboxylate (5.23 g, 24.29 mmol) in dioxane (50 mL) and the resulting solution stirred at RT overnight. The solvent was removed and the solid was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a white solid (3.22 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.50-1.51(6H, d), 3.56-3.67 (4H, m), 3.97-4.00 (2H, dd), 9.96 (2H, bs).

tert-Butyl (3*S*,5*S*)-3,5-dimethylmorpholine-4-carboxylate and *tert*-butyl (3*S*,5*R*)-3,5-dimethylmorpholine-4-carboxylate



(3*S*)-3,5-Dimethylmorpholine (13.73 g, 90.55 mmol) was dissolved in a solution of sodium hydroxide (3.91 mL, 208.26 mmol) in water (100 mL) and di-tert-butyl dicarbonate (22.88 mL, 99.60 mmol) added portionwise. The resulting solution was stirred at RT overnight then extracted with diethyl ether and the organics dried over $MgSO_4$, filtered and evaporated to give a clear liquid. The crude material was purified and the diastereomers separated using silica chromatography, eluting with 0-10% ethyl acetate in isohexane, to give *tert*-butyl (3*S*,5*S*)-3,5-dimethylmorpholine-4-carboxylate (first product to elut) as a colourless liquid (5.93 g) and *tert*-butyl (3*S*,5*R*)-3,5-dimethylmorpholine-4-carboxylate (second product to elut) as a colourless liquid (5.03 g).

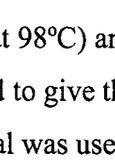
tert-butyl (3*S*,5*S*)-3,5-dimethylmorpholine-4-carboxylate:

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.28-1.29(6H, d), 1.47(9H, s), 3.43-3.48 (2H, m), 3.77-3.84 (4H, m).

tert-butyl (3*S*,5*R*)-3,5-dimethylmorpholine-4-carboxylate

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.30-1.31(6H, d), 1.47(9H, s), 3.52-3.56(2H, dd), 3.68-3.71(2H, d), 3.90-3.96(2H, m).

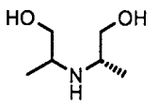
(3*S*)-3,5-Dimethylmorpholine



2-[[(2*S*)-1-Hydroxypropan-2-yl]amino]propan-1-ol (14.79 g, 111.01 mmol) was cooled to 0°C with stirring and concentrated sulfuric acid (19.85 g, 202.39 mmol) added. The mixture was heated to 180°C for 5 hours. Potassium hydroxide (23.95 g, 426.87 mmol) in water (120 mL) was added slowly then the mixture filtered to leave a dark black aqueous solution. This solution was distilled (distillate came off at 98°C) and the distillate acidified with 2M hydrochloric acid. The water was removed to give the desired material (as the hydrochloride salt) as a white solid (13.73g). The material was used in the following step without further purification.

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.44-1.46 (3H, d), 1.48-1.50 (3H, d), 3.31-3.34 (1H, m), 3.56-3.59 (1H, m), 3.62-3.72 (2H, m), 3.84-3.88 (1H, m), 3.96-3.99 (1H, dd), 9.69-10.12 (2H, bt).

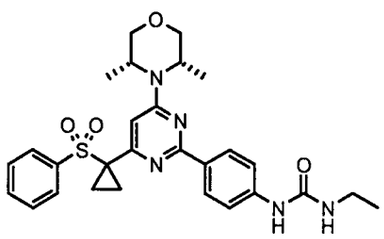
2-[[(2*S*)-1-Hydroxypropan-2-yl]amino]propan-1-ol



(*S*)-2-Aminopropan-1-ol (9 g, 119.82 mmol), platinum(IV) oxide (0.052 g, 0.23 mmol) and 1-hydroxypropan-2-one (11.54 g, 155.77 mmol) in methanol (100 mL) were stirred for 1 hour and then placed under an atmosphere of hydrogen at 1 bar and 25°C for 3 hours. The solution was filtered and evaporated to give a crude product that was purified by distillation at (0.55 mBar, 92°C) to give the desired material as a yellow oil (10.71 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.01-1.03 (3H, d), 1.07-1.09 (3H, d), 2.56 (1H, bs), 2.83-2.94 (2H, m), 3.27-3.32 (2H, m), 3.55-3.61 (2H, m).

Example 73: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*R*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea

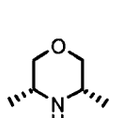


DIPEA (0.140 mL, 0.81 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.101 g, 0.20 mmol), (3*S*,5*R*)-3,5-dimethylmorpholine (as the hydrochloride salt) (0.052 g, 0.34 mmol) in dioxane (5 mL) under nitrogen. The reaction was heated to 90°C overnight. The reaction cooled and the solvent was removed. The residue was taken up in dioxane and ethyl isocyanate (0.319 mL, 4.03 mmol) added. The reaction was allowed to stir over the weekend. Methanol was added and the solvent was removed. The crude product was purified by preparative HPLC, to give the desired material as a white solid (9.00 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.05-1.09 (3H, t), 1.17-1.20(6H, m), 1.62-1.68 (2H, m), 1.89-1.92 (2H, m), 3.09-3.14 (2H, m), 3.43-3.48 (2H, m), 3.86-3.90 (1H, dd), 3.94-4.16 (1H, dd), 4.12-4.16 (1H, m), 4.29-4.31 (1H, m), 6.12-6.15 (1H, t), 6.60 (1H, s), 7.37-7.40 (2H, d), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.86 (4H, m), 8.61 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=536; HPLC tR=2.38min.

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier.

(3*S*,5*R*)-3,5-Dimethylmorpholine



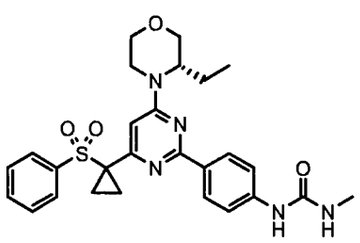
Hydrogen chloride (4M solution in dioxane, 9.98 mL, 39.92 mmol) was added to *tert*-butyl (3*S*,5*R*)-3,5-dimethylmorpholine-4-carboxylate (1.910 g, 8.87 mmol) in dioxane (15 mL) and

the resulting solution stirred at RT overnight. The solvent was removed and the solid was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a white solid (0.960 g).

NMR Spectrum:^{1}H NMR (400MHz, $CDCl_3$) δ 1.47-1.48(6H, d), 3.31-3.40 (2H, m), 3.68-3.74 (2H, t), 3.86-3.90 (2H, dd), 9.77 (1H, bs), 10.22 (1H, bs).

The preparation of *tert*-butyl (3*S*,5*R*)-3,5-dimethylmorpholine-4-carboxylate was described earlier.

Example 74: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

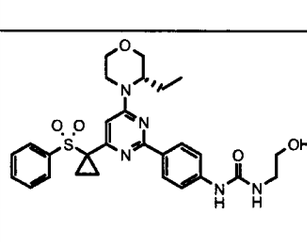
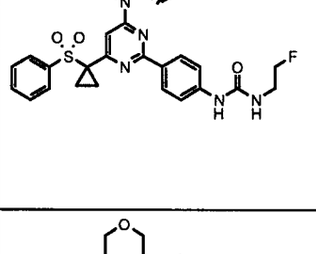
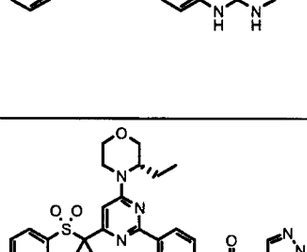


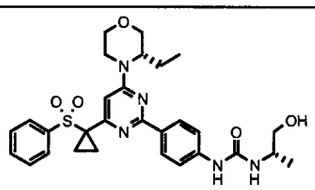
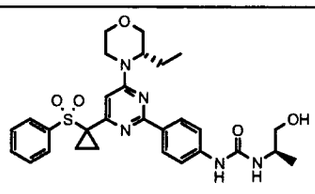
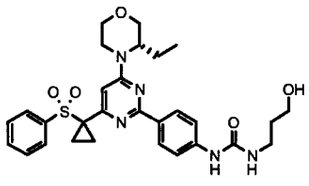
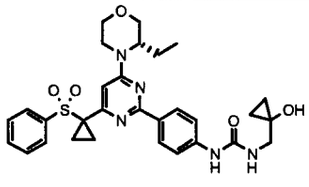
Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.1 g, 0.17 mmol), triethylamine (0.072 mL, 0.51 mmol) and methylamine (0.51 mmol) were dissolved in dioxane (10 mL) and heated at 50°C overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.65 - 1.56 (3H, m), 1.80 - 1.71 (1H, m), 1.91 - 1.87 (2H, m), 2.66 (3H, d), 3.12 (1H, ddd), 3.43 (1H, ddd), 3.51 (1H, dd), 3.85 (1H, d), 3.91 (1H, dd), 4.24 - 4.12 (2H, m), 6.04 (1H, q), 6.61 (1H, s), 7.39 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.84 (2H, d), 8.69 (1H, s).

LCMS Spectrum: m/z (ES+) (M+H)+ = 522; HPLC tR= 2.31 min;

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
74a		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	548	2.46
74b		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	552	2.11
74c		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	554	1.95
74d		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	572	2.45
74e		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	588	2.33

Example	Structure	NAME	LCMS MH+	Retention time (min)
74f		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	566	2.21
74g		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	566	2.21
74h		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	578	2.28
74i		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea	578	2.29

Example 74a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.43 - 0.39 (2H, m), 0.67 - 0.62 (2H, m), 0.84 (3H, t), 1.64 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.92 - 1.85 (2H, m), 2.57 - 2.52 (1H, m), 3.12 (1H, ddd), 3.43 (1H, ddd), 3.51 (1H, dd), 3.85 (1H, d), 3.91 (1H, dd), 4.28 - 4.09 (2H, m), 6.40 (1H, s), 6.61 (1H, s), 7.39 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.49 (1H, s);

Example 74b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.64 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.91 - 1.86 (2H, m), 3.19 - 3.09 (3H, m), 3.48 - 3.40 (3H, m), 3.51 (1H, dd),

3.85 (1H, d), 3.91 (1H, dd), 4.26 - 4.08 (2H, m), 4.72 (1H, t), 6.23 (1H, t), 6.61 (1H, s), 7.38 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.75 (1H, s);

Example 74c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.64 - 1.58 (3H, m), 1.80 - 1.71 (1H, m), 1.91 - 1.87 (2H, m), 3.12 (1H, ddd), 3.47 - 3.36 (3H, m), 3.51 (1H, dd), 3.85 (1H, d), 3.91 (1H, dd), 4.28 - 4.09 (2H, m), 4.47 (2H, dt), 6.42 (1H, t), 6.62 (1H, s), 7.39 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.86 (2H, d), 8.77 (1H, s);

Example 74d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.65 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.91 - 1.87 (2H, m), 3.12 (1H, ddd), 3.43 (1H, ddd), 3.59 - 3.50 (3H, m), 3.85 (1H, d), 3.92 (1H, dd), 4.27 - 4.12 (2H, m), 6.07 (1H, tt), 6.51 (1H, t), 6.62 (1H, s), 7.40 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.87 (2H, d), 8.87 (1H, s);

Example 74e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.85 (3H, t), 1.68 - 1.59 (3H, m), 1.80 - 1.73 (1H, m), 1.92 - 1.87 (2H, m), 3.12 (1H, ddd), 3.43 (1H, ddd), 3.52 (1H, dd), 3.79 (3H, s), 3.86 (1H, d), 3.92 (1H, dd), 4.30 - 4.18 (2H, m), 6.62 (1H, s), 7.38 (1H, s), 7.43 (2H, d), 7.59 (2H, t), 7.72 (1H, t), 7.76 (1H, s), 7.78 (2H, d), 7.88 (2H, d), 8.36 (1H, s), 8.78 (1H, s);

Example 74f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.08 (3H, d), 1.65 - 1.58 (3H, m), 1.82 - 1.73 (1H, m), 1.90 - 1.88 (2H, m), 3.12 (1H, ddd), 3.39 - 3.33 (2H, m), 3.43 (1H, ddd), 3.51 (1H, dd), 3.73 - 3.67 (1H, m), 3.85 (1H, d), 3.91 (1H, dd), 4.25 - 4.13 (2H, m), 4.78 (1H, t), 6.07 (1H, d), 6.61 (1H, s), 7.36 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.66 (1H, s);

Example 74g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.08 (3H, d), 1.67 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.90 - 1.88 (2H, m), 3.12 (1H, ddd), 3.40 - 3.32 (2H, m), 3.44 (1H, ddd), 3.51 (1H, dd), 3.73 - 3.67 (1H, m), 3.85 (1H, d), 3.91 (1H, dd), 4.27 - 4.08 (2H, m), 4.78 (1H, t), 6.07 (1H, d), 6.61 (1H, s), 7.36 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.66 (1H, s);

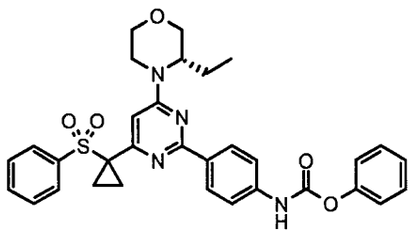
Example 74h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.64 - 1.56 (5H, m), 1.82 - 1.69 (1H, m), 1.91 - 1.87 (2H, m), 3.19 - 3.08 (3H, m), 3.53 - 3.40 (4H, m), 3.85 (1H, d), 3.91 (1H, dd), 4.26 - 4.08 (2H, m), 4.47 (1H, t), 6.18 (1H, t), 6.61 (1H, s), 7.38 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.66 (1H, s);

Example 74i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.53 - 0.48 (2H, m), 0.59 - 0.56 (2H, m), 0.84 (3H, t), 1.64 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.92 - 1.88 (2H, m), 3.12 (1H, ddd), 3.21 (2H, d), 3.46 - 3.38 (1H, m), 3.51 (1H, dd), 3.85 (1H, d), 3.91 (1H, dd), 4.27 - 4.05 (2H,

m), 6.30 (1H, t), 6.61 (1H, s), 7.38 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.85 (2H, d), 8.76 (1H, s), hydroxy missing

The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

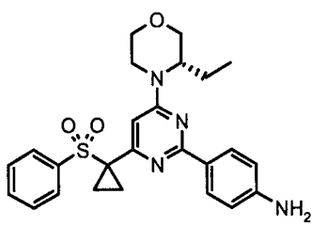


4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (1.418 g, 2.83 mmol) and sodium bicarbonate (2.377 g, 28.30 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.462 mL, 3.68 mmol) was added slowly and the reaction stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.22 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.68 - 1.59 (3H, m), 1.80 - 1.73 (1H, m), 1.92 - 1.89 (2H, m), 3.13 (1H, ddd), 3.43 (1H, ddd), 3.52 (1H, dd), 3.85 (1H, d), 3.92 (1H, dd), 4.18 (2H, s), 6.66 (1H, s), 7.29 - 7.24 (3H, m), 7.45 (2H, t), 7.54 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.79 (2H, d), 7.95 (2H, d), 10.39 (1H, s);

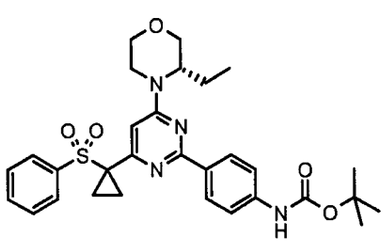
LCMS Spectrum: m/z (ES+) (M+H)+ = 585; HPLC tR= 3.12 min;

4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]aniline



tert-Butyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (1.6 g, 2.83 mmol) was added to 6.0 N hydrogen chloride in propan-2-ol (20 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a yellow solid (1.40 g). NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.81 - 0.71 (3H, m), 1.78 - 1.60 (5H, m), 1.96 - 1.87 (2H, m), 3.20 (1H, ddd), 3.41 (1H, ddd), 3.50 (1H, dd), 3.84 (1H, d), 3.93 (1H, dd), 6.56 (1H, s), 7.01 (2H, s), 7.61 (2H, t), 7.79 - 7.75 (4H, m), 7.95 (2H, d);
LCMS Spectrum: m/z (ES+) (M+H)+ = 465; HPLC tR= 2.54 min;

tert-Butyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



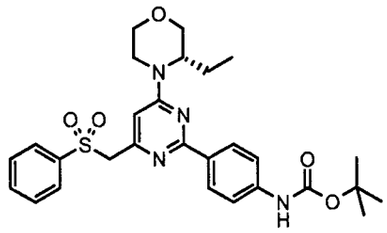
Sodium hydride (0.724 g, 15.07 mmol) was added rapidly to *tert*-butyl *N*-[4-[4-(benzenesulfonylmethyl)-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.03 g, 3.77 mmol) in DMF (30 mL) and the mixture stirred at RT for 10 minutes before the slow addition 1,2-dibromoethane (1.299 mL, 15.07 mmol) in DMF (30 mL). The resulting suspension was stirred at RT for 1 hour. Additional sodium hydride (0.36 g, 7.53 mmol) and 1,2 dibromoethane (0.65 mL, 7.53 mmol) were rapidly added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to afford yellow foam. This was dissolved in

40% ethyl acetate in isohexane and stirred resulting in the desired material precipitating out as a white solid (1.65 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.49 (9H, s), 1.65 - 1.58 (3H, m), 1.80 - 1.73 (1H, m), 1.90 - 1.87 (2H, m), 3.12 (1H, ddd), 3.43 (1H, ddd), 3.51 (1H, dd), 3.85 (1H, d), 3.91 (1H, dd), 4.18 (2H, s), 6.63 (1H, s), 7.45 (2H, d), 7.58 (2H, t), 7.71 (1H, t), 7.78 (2H, d), 7.87 (2H, d), 9.49 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 565; HPLC tR= 3.23 min;

tert-Butyl *N*-[4-[4-(benzenesulfonylmethyl)-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

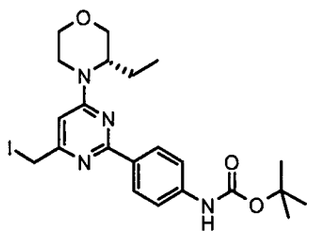


Sodium benzenesulfinate (0.626 g, 3.81 mmol) and *tert*-butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(iodomethyl)pyrimidin-2-yl]phenyl]carbamate (2.0 g, 3.81 mmol) were dissolved in DMF (25 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid which was partitioned between aqueous sodium thiosulphate solution (50 mL) and DCM (75 mL). The organics were purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane., to give the desired material as a white foam (1.99 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.86 (3H, t), 1.49 (9H, s), 1.66 - 1.57 (1H, m), 1.82 - 1.74 (1H, m), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.53 (1H, dd), 3.87 (1H, d), 3.93 (1H, dd), 4.16 (2H, s), 4.69 (2H, s), 6.61 (1H, s), 7.45 (2H, d), 7.61 (2H, t), 7.74 (1H, t), 7.85 - 7.80 (4H, m), 9.49 (1H, s);

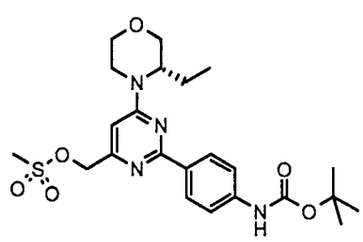
LCMS Spectrum: m/z (ES+) (M+H)+ = 539; HPLC tR= 3.00 min;

tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(iodomethyl)pyrimidin-2-yl]phenyl]carbamate



[6-[(3*S*)-3-Ethylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate (10.34 g, 20.99 mmol) and lithium iodide (1.208 mL, 31.49 mmol) were added to dioxane (250 mL) and heated at 60°C for 1 hour and then at RT overnight. The solvent was evaporated and the reaction mixture quenched with saturated ammonium chloride solution (100 mL) then extracted with DCM (3 x 75 mL). The organic extracts were flushed through a 2 inch silica plug, eluting with ethyl acetate, to give a brown foam. This was dissolved in diethyl ether and isohexane carefully added until a cloudy solution was observed. Upon cooling to 0°C, the desired material precipitated out as a white solid and was isolated by filtration (9.80 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (3H, t), 1.50 (9H, s), 1.72 - 1.63 (1H, m), 1.83 - 1.76 (1H, m), 3.17 (1H, ddd), 3.47 (1H, ddd), 3.55 (1H, dd), 3.87 (1H, d), 3.93 (1H, dd), 4.29 (2H, s), 4.38 (2H, s), 6.81 (1H, s), 7.56 (2H, d), 8.22 (2H, d), 9.53 (1H, s);
LCMS Spectrum: m/z (ES+) (M+H)+ = 525; HPLC tR= 3.17 min;

[6-[(3*S*)-3-Ethylmorpholin-4-yl]-2-[4-[(2-methylpropan-2-yl)oxycarbonylamino]phenyl]pyrimidin-4-yl]methyl methanesulfonate

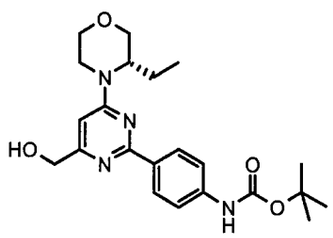


tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(hydroxymethyl)pyrimidin-2-yl]phenyl]carbamate (8.7 g, 20.99 mmol) and DIPEA (4.40 mL, 25.19 mmol) were added to DCM (80 mL), to this was slowly added methane sulphonyl chloride(1.636 mL, 20.99 mmol) and the reaction was stirred for 30 minutes. The reaction mixture was quenched with saturated

ammonium chloride solution (100 mL), extracted with DCM (2 x 100 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a brown gum (10.2 g). This was used without any further purification.

LCMS Spectrum: m/z (ES+) (M+H)+ = 493; HPLC tR= 2.90 min;

tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(hydroxymethyl)pyrimidin-2-yl]phenyl]carbamate

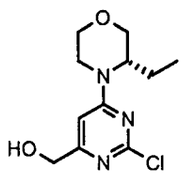


[2-Chloro-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-4-yl]methanol (12 g, 46.56 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylcarbamate (14.86 g, 46.56 mmol), sodium carbonate (24.68 g, 232.81 mmol) and 1,1'-bis(diphenyl phosphino)ferrocenedichloropalladium(II) (3.37 g, 4.66 mmol) were added to DME (150 mL) and water (37.5 mL) and heated to 90°C overnight under nitrogen. The solvent was evaporated and the residue was quenched with water (100 mL), extracted with ethyl acetate (3 x 100 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford black gum. The residue was filtered through a plug of silica, eluting with ethyl acetate, to give a very dark gum. This was purified by flash silica chromatography, elution gradient 40 to 100% ethyl acetate in isohexane, to give an orange gum. The gum was dissolved in diethyl ether and isohexane carefully added until a cloudy solution was observed, further stirring gave the desired material as a white solid precipitate which was isolated by filtration (8.7 g).

NMR Spectrum: ^1H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.49 (9H, s), 1.73 - 1.64 (1H, m), 1.84 - 1.77 (1H, m), 3.19 (1H, ddd), 3.47 (1H, ddd), 3.55 (1H, dd), 3.88 (1H, d), 3.94 (1H, dd), 4.33 - 4.23 (2H, m), 4.45 (2H, d), 5.38 (1H, t), 6.67 (1H, s), 7.53 (2H, d), 8.21 (2H, d), 9.50 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 415; HPLC tR= 2.49 min;

[2-Chloro-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidin-4-yl]methanol

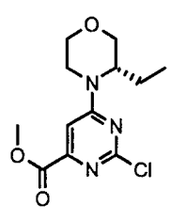


Lithium borohydride, 2M in THF (17.63 mL, 35.26 mmol) was added dropwise to methyl 2-chloro-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidine-4-carboxylate te (15.5 g, 54.25 mmol) in THF (100 mL) at 0°C over a period of 30 minutes under nitrogen. The resulting solution was stirred at 0°C for 30 minutes then allowed to warm to RT. Water (250 mL) was added and the THF evaporated. The aqueous residues were extracted with ethyl acetate (2 x 500 mL) and the combined organics were washed with water (2 x 300 mL). The organic layer was dried over $MgSO_4$ then evaporated to dryness to afford a viscous oil, this was triturated with hot diethyl ether to give the desired material as a white solid (13.4 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.84 (3H, t), 1.80 - 1.66 (2H, m), 3.19 - 3.14 (1H, m), 3.42 (1H, ddd), 3.51 (1H, dd), 3.82 (1H, d), 3.89 (1H, dd), 4.15 - 4.06 (2H, m), 4.34 (2H, d), 5.50 (1H, t), 6.74 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 258; HPLC tR= 1.45 min;

Methyl 2-chloro-6-[(3*S*)-3-ethylmorpholin-4-yl]pyrimidine-4-carboxylate



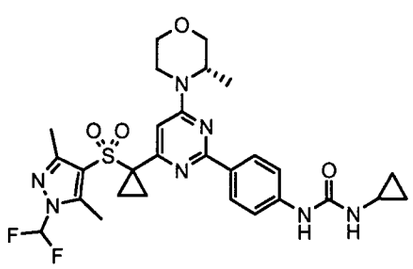
A solution of (S)-3-ethylmorpholine (10 g, 86.83 mmol) in DCM (75 mL) was added dropwise to a stirred solution of methyl 2,6-dichloropyrimidine-4-carboxylate (19.77 g, 95.51 mmol) and triethylamine (24.20 ml, 173.65 mmol) in DCM (200 mL) at RT, over a period of 2 hours under air. The resulting solution was stirred at RT overnight. The reaction mixture was quenched with water (250 mL), extracted with DCM (300 mL) and the solvent was removed to 30% the initial volume. The dark solution was passed through a 2 inch plug of silica, eluting with ethyl acetate, to give an orange gum which was dissolved in ethyl acetate (40 mL). To this was added diethyl ether (120 mL) and then isohexane until a cloudy solution was observed. The reaction was seeded with 15 mg of methyl 2-chloro-6-[(3*S*)-3-

methylmorpholin-4-yl]pyrimidine-4-carboxylate and stirred for 15 minutes to afford the desired material as a white solid (15.8 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.83 (3H, t), 1.75 (2H, septet), 3.22 (1H, s), 3.44 (1H, ddd), 3.53 (1H, dd), 3.82 (1H, d), 3.91 - 3.87 (4H, m), 4.22 (2H, m), 7.32 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 286; HPLC tR= 1.81 min;

Example 75: 3-Cyclopropyl-1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

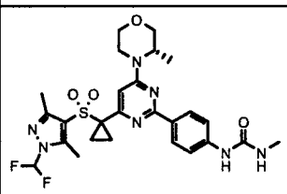
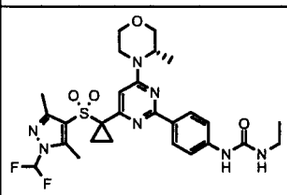
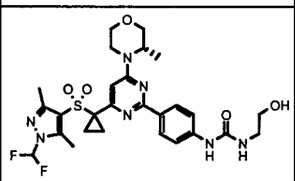
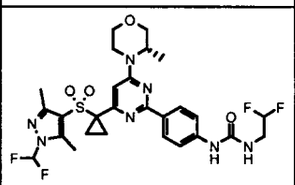
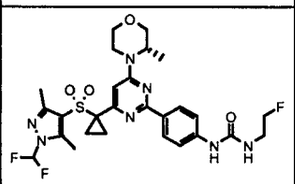


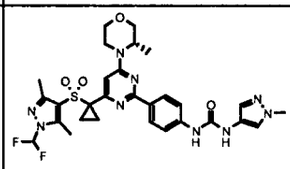
Cyclopropylamine (0.038 mL, 0.54 mmol) was added to a solution of phenyl *N*-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.115g, 0.18mmol) in NMP (2 mL) followed by triethylamine (0.076 mL, 0.54 mmol) and the reaction was heated at 50°C overnight. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as an off white solid (88 mg).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.19 - 1.21 (3H, d), 1.46 - 1.54 (2H, m), 1.75 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 2.53 - 2.58 (1H, m), 3.12 - 3.20 (1H, m), 3.44 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.13 (1H, d), 4.51 (1H, s), 6.42 (1H, d), 6.69 (1H, s), 7.42 - 7.45 (2H, m), 7.64 - 7.93 (1H, t), 7.91 - 7.94 (2H, m), 8.53 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 602; HPLC tR = 2.20 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
75a		1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	576	2.05
75b		3-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	590	2.19
75c		1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	606	1.89
75d		3-(2,2-difluoroethyl)-1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	626	2.31
75e		1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	608	2.18

Example	Structure	NAME	LCMS MH+	Retention time (min)
75f*		1-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	642	2.08

* In addition to the reaction conditions described above this reaction was subsequently subjected to the addition of DIPEA (3 equivalents) and heating at 95°C for 90 minutes.

Example 75a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.46 - 1.54 (2H, m), 1.75 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 2.68 (3H, d), 3.12 - 3.17 (1H, m), 3.44 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.13 (1H, d), 4.51 (1H, s), 6.05 (1H, q), 6.69 (1H, s), 7.42 - 7.44 (2H, m), 7.64 - 7.92 (1H, t), 7.90 - 7.93 (2H, m), 8.73 (1H, s).

Example 75b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 1.49 - 1.51 (2H, m), 1.75 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 3.10 - 3.20 (3H, m), 3.44 - 3.50 (1H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.11 - 4.15 (1H, m), 4.51 (1H, s), 6.14 (1H, t), 6.69 (1H, s), 7.41 - 7.44 (2H, m), 7.64 - 7.92 (1H, t), 7.91 - 7.93 (2H, d), 8.65 (1H, s).

Example 75c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, s), 1.46 - 1.54 (2H, m), 1.75 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 3.12 - 3.20 (3H, m), 3.45 - 3.50 (3H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.13 (1H, d), 4.51 (1H, s), 4.74 (1H, t), 6.24 (1H, t), 6.69 (1H, s), 7.42 (2H, d), 7.64 - 7.92 (1H, t), 7.92 (2H, d), 8.79 (1H, s).

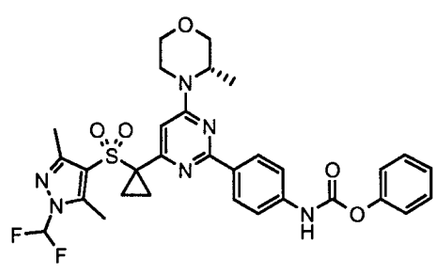
Example 75d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.46 - 1.54 (2H, m), 1.75 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 3.16 - 3.19 (1H, m), 3.44 - 3.64 (4H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.12 - 4.15 (1H, m), 4.51 (1H, s), 5.93 - 6.23 (1H, m), 6.52 (1H, t), 6.70 (1H, s), 7.44 (2H, d), 7.64 - 7.92 (1H, t), 7.95 (2H, d), 8.92 (1H, s).

Example 75e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.46 - 1.54 (2H, m), 1.73 - 1.78 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 3.14 - 3.20 (1H, m), 3.36 - 3.50 (3H, m), 3.60 - 3.64 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.13 (1H, d), 4.42 (1H, t), 4.54 (2H, t), 6.42 (1H, t), 6.70 (1H, s), 7.43 (2H, d), 7.64 - 7.93 (1H, t), 7.93 (2H, d), 8.80 (1H, s).

Example 75f: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 - 1.21 (3H, m), 1.47 - 1.54 (2H, m), 1.74 - 1.79 (2H, m), 2.07 (3H, s), 2.35 (3H, s), 3.13 - 3.21 (1H, m), 3.44 - 3.51 (1H, m), 3.61 - 3.64 (1H, m), 3.75 - 3.78 (1H, m), 3.80 (3H, s), 3.95 - 3.99 (1H, m), 4.14 (1H, d), 4.52 (1H, s), 6.70 (1H, s), 7.39 - 7.39 (1H, m), 7.46 - 7.49 (2H, m), 7.78 (1H, s), 7.65 - 7.94 (1H, t), 7.96 (2H, d), 8.37 (1H, s), 8.84 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

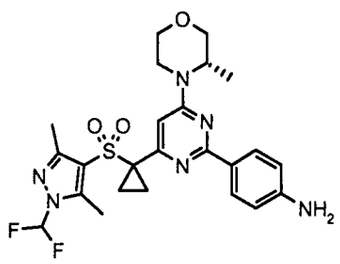


Phenyl chloroformate (0.176 mL, 1.40 mmol) was added dropwise to a mixture of 4-[4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.726 g, 1.4 mmol) and sodium hydrogen carbonate (0.176 g, 2.10 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The precipitate was collected by filtration, washed with a mixture of isohexane (4 mL) and diethyl ether (2 mL), then suspended in water (20 mL) and stirred for 20 minutes. The precipitate was collected by filtration, washed with water (5 mL) then with a mixture of isohexane (10 mL) and diethyl ether (5 mL) and dried under vacuum to afford the desired material as a white solid (0.826 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.48 - 1.55 (2H, m), 1.74 - 1.79 (2H, m), 2.07 (3H, s), 2.35 (3H, s), 3.14 - 3.17 (1H, m), 3.39 - 3.50 (1H, m), 3.61 - 3.64 (1H, m), 3.77 (1H, m), 3.95 - 3.99 (1H, m), 4.16 (1H, d), 4.53 (1H, s), 6.75 (1H, s), 7.24 - 7.31 (3H, m), 7.44 - 7.48 (2H, m), 7.57 (2H, d), 7.64 - 7.93 (1H, t), 8.00 - 8.03 (2H, m), 10.42 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 639; HPLC tR = 2.92 min.

4-[4-[1-[1-(Difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

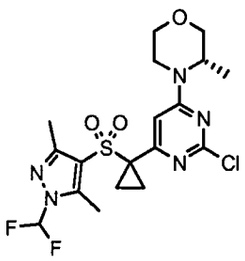


Dichlorobis(triphenylphosphine)palladium(II) (0.412 g, 0.59 mmol) was added in one portion to a mixture of sodium carbonate (1.867 g, 17.61 mmol), 2-chloro-4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.712 g, 5.87 mmol) and (4-aminophenyl)boronic acid pinacol ester (1.351 g, 6.16 mmol) in DME (50 mL)and water (12.5 mL) under nitrogen. The mixture was stirred at 80°C for 2 hours, cooled to RT then diluted with DCM (100 mL) and water (50 mL). The organic layer was washed with saturated brine (50 mL) then dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give a residue which was further purified by trituration with isohexane (25 mL) and diethyl ether (25 mL), to give the desired material as a yellow solid (2.84 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.18 (3H, m), 1.43 - 1.51 (2H, m), 1.73 - 1.76 (2H, m), 2.07 (3H, s), 2.34 (3H, s), 3.09 - 3.17 (1H, m), 3.42 - 3.49 (1H, m), 3.59 - 3.63 (1H, m), 3.75 (1H, d), 3.94 - 3.97 (1H, m), 4.48 (1H, s), 5.52 (2H, m), 6.52 - 6.55 (2H, m), 6.58 (1H, s), 7.75 - 7.78 (2H, m), 7.64 - 7.93 (1H, t).

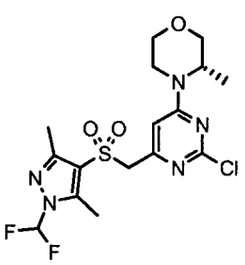
LCMS Spectrum: m/z (ESI+)(M+H)+ = 519; HPLC tR = 1.91 min.

2-Chloro-4-[1-[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Sodium hydroxide (33.0 mL, 412.50 mmol) was added to 2-chloro-4-[[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.27 g, 7.5 mmol), 1,2-dibromoethane (1.939 mL, 22.50 mmol) and tetrabutylammonium bromide (0.242 g, 0.75 mmol) in toluene (132 mL). The resulting solution was stirred at 60°C for 1 hour. The reaction mixture was diluted with DCM (200 mL), and washed twice with water (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a white solid (2.77 g).
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.45 - 1.52 (2H, m), 1.69 - 1.76 (2H, m), 2.13 (3H, s), 2.37 (3H, s), 3.12 - 3.19 (1H, m), 3.37 - 3.44 (1H, m), 3.53 - 3.57 (1H, m), 3.71 (1H, d), 3.90 - 3.94 (2H, m), 4.35 (1H, s), 6.80 (1H, s), 7.71 - 8.00 (1H, t).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 462; HPLC tR = 2.26 min.

2-Chloro-4-[[1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl]sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



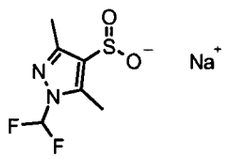
Sodium 1-(difluoromethyl)-3,5-dimethylpyrazole-4-sulfinate (3.44 g, 14.83 mmol) was added to a solution of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.37 g, 12.36 mmol) in DMF (20 mL). The resulting mixture was stirred at RT for 1 hour. The reaction mixture was evaporated to dryness, redissolved in DCM (150 mL), and washed

sequentially with water (100 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 60% ethyl acetate in isohexane, to give the desired material as a white solid (5.22 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.19 (3H, d), 2.21 (3H, s), 2.42 (3H, s), 3.15 - 3.22 (1H, m), 3.40 - 3.47 (1H, m), 3.57 - 3.60 (1H, m), 3.73 (1H, d), 3.92 - 3.96 (2H, m), 4.25 (1H, s), 4.57 (2H, s), 6.82 (1H, s), 7.73 - 8.02 (1H, t).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 436; HPLC tR = 2.13 min.

Sodium 1-(difluoromethyl)-3,5-dimethylpyrazole-4-sulfinate

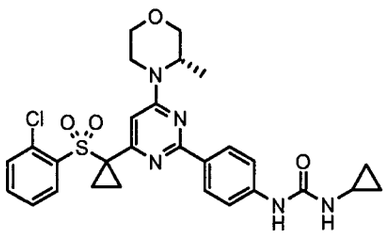


Sodium hydrogen carbonate (3.43 g, 40.88 mmol) was added to a solution of sodium sulfite (2.58 g, 20.44 mmol) in water (25 mL) and the resulting solution was stirred at 50°C for 1 hour. 1-(Difluoromethyl)-3,5-dimethyl-1H-pyrazole-4-sulfonyl chloride (5 g, 20.44 mmol) was added portionwise and the solution was stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and methanol (75 mL) was added. The suspension was allowed to stir at RT for 20 minutes, filtered and the filtrate was evaporated. The residue was dissolved in ethanol (50 mL) at 50°C, filtered and evaporated to afford the desired material as a white solid (4.59 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 2.24 (3H, s), 2.46 (3H, s), 7.44 - 7.74 (1H, t).

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 76: 1-[4-[4-[1-(2-Chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea

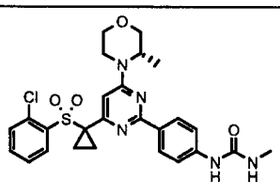


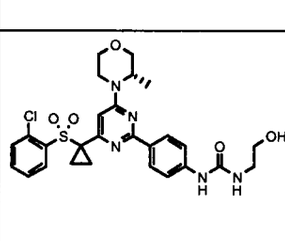
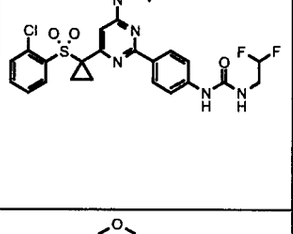
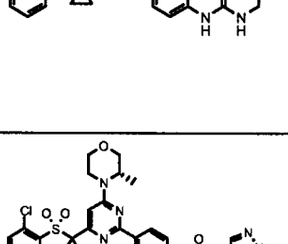
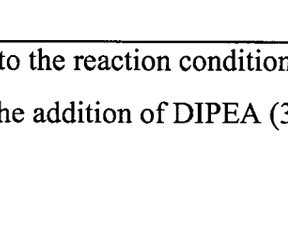
Cyclopropylamine (0.037 mL, 0.51 mmol) was added to a solution of phenyl *N*-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.103g, 0.17mmol) in NMP (2 mL) followed by triethylamine (0.072 mL, 0.51 mmol) and the reaction was heated at 50°C overnight. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents, to give the desired material as an off- white solid (82mg, 80%).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.68 (2H, m), 1.16 (3H, d), 1.71 - 1.75 (2H, m), 1.97 - 2.01 (2H, m), 2.53 - 2.57 (1H, m), 3.12 - 3.16 (1H, m), 3.41 - 3.48 (1H, m), 3.58 - 3.61 (1H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.10 (1H, d), 4.41 (1H, s), 6.42 (1H, d), 6.63 (1H, s), 7.37 - 7.40 (2H, m), 7.43 - 7.46 (1H, m), 7.60 - 7.64 (1H, m), 7.67 - 7.69 (1H, m), 7.78 - 7.82 (2H, m), 7.90 - 7.92 (1H, m), 8.50 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 568; HPLC tR = 2.30 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
76a		1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	542	2.16

Example	Structure	NAME	LCMS MH+	Retention time (min)
76b		3-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	556	2.30
76c		1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	572	1.99
76d		1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	592	2.40
76e		1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	574	2.27
76f*		1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	608	2.12

* In addition to the reaction conditions described above this reaction was subsequently subjected to the addition of DIPEA (3 equivalents) and heating at 95°C for 90 minutes.

Example 76a: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.15 - 1.16 (3H, m), 1.73 2H, m), 1.97 - 2.01 (2H, m), 2.66 (3H, d), 3.12 (1H, d), 3.40 – 3.48 (1H, m), 3.58 - 3.61 (1H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.08 (1H, m), 4.41 (1H, s), 6.06 (1H, d), 6.62 (1H, s), 7.38 (2H, d), 7.46 (1H, m), 7.60 - 7.62 (1H, m), 7.67 - 7.69 (1H, m), 7.79 (2H, d), 7.90 - 7.92 (1H, d), 8.70 (1H, s).

Example 76b: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.16 (3H, d), 1.72 - 1.75 (2H, m), 1.97 - 2.01 (2H, m), 3.10 - 3.16 (3H, m), 3.42 - 3.45 (1H, m), 3.58 - 3.61 (1H, m), 3.73 - 3.75 (1H, m), 3.93 – 3.98 (1H, m), 4.10 (1H, d), 4.41 (1H, s), 6.15 (1H, t), 6.63 (1H, s), 7.35 - 7.39 (2H, m), 7.43 - 7.47 (1H, m), 7.60 - 7.64 (1H, m), 7.67 - 7.70 (1H, m), 7.78 - 7.81 (2H, d), 7.90 - 7.92 (1H, m), 8.62 (1H, s).

Example 76c: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.15 - 1.16 (3H, m), 1.73 (2H, m), 1.97 - 2.01 (2H, m), 3.16 (1H, m), 3.17 - 3.19 (2H, m), 3.46 (3H, m), 3.58 - 3.61 (1H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.10 (1H, m), 4.42 (1H, s), 4.74 (1H, t), 6.24 (1H, t), 6.63 (1H, s), 7.36 (2H, d), 7.42 - 7.47 (1H, m), 7.60 - 7.62 (1H, m), 7.67 - 7.70 (1H, m), 7.80 (2H, d), 7.90 - 7.92 (1H, m), 8.76 (1H, s).

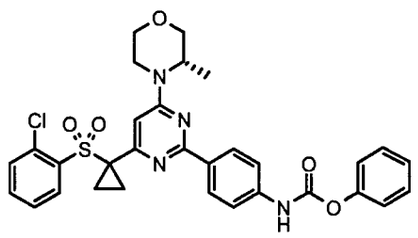
Example 76d: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.70 - 1.77 (2H, m), 1.96 - 2.03 (2H, m), 3.09 - 3.16 (1H, m), 3.41 - 3.48 (1H, m), 3.49 - 3.62 (3H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.08 - 4.12 (1H, d), 4.41 (1H, s), 5.92 - 6.22 (1H, m), 6.52 (1H, t), 6.64 (1H, s), 7.37 - 7.41 (2H, d), 7.44 - 7.47 (1H, m), 7.60 - 7.62 (1H, m), 7.67 - 7.70 (1H, m), 7.82 (2H, d), 7.90 - 7.92 (1H, m), 8.88 (1H, s).

Example 76e: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.69 - 1.77 (2H, m), 1.95 - 2.03 (2H, m), 3.09 - 3.16 (1H, m), 3.36 - 3.48 (3H, m), 3.58 - 3.62 (1H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.10 (1H, d), 4.42 (2H, m), 4.54 (1H, t), 6.42 (1H, t), 6.63 (1H, s), 7.36 - 7.40 (2H, m), 7.43 - 7.47 (1H, m), 7.60 - 7.66 (1H, m), 7.67 - 7.70 (1H, m), 7.80 - 7.82 (2H, m), 7.90 - 7.92 (1H, m), 8.77 (1H, s).

Example 76f: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.10 - 1.17 (3H, d), 1.72 - 1.75 (2H, m), 1.98 - 2.01 (2H, m), 3.13 - 3.16 (1H, m), 3.42 - 3.48 (1H, m), 3.58 - 3.62 (1H, m), 3.75 (1H, d), 3.80 (3H, s), 3.94 - 3.97 (1H, m), 4.12 (1H, m), 4.42 (1H, s), 6.64 (1H, s), 7.40 - 7.47 (4H, m), 7.61 - 7.63 (1H, m), 7.68 - 7.71 (1H, m), 7.77 (1H, s), 7.83 (2H, d), 7.90 - 7.93 (1H, m), 8.38 (1H, s), 8.80 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

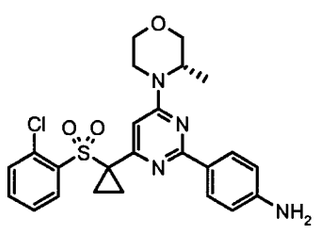


Phenyl chloroformate (0.189 mL, 1.50 mmol) was added dropwise to a mixture of 4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.727 g, 1.5 mmol) and sodium hydrogen carbonate (0.189 g, 2.25 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The precipitate was collected by filtration, washed with diethyl ether (10 mL), suspended in water (20 mL), stirred for 20 minutes, collected by filtration, washed with water (10 mL) then ether (2 mL) and dried under vacuum to afford the desired material as a white solid (0.735 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.72 - 1.77 (2H, m), 1.98 - 2.01 (2H, m), 3.10 - 3.18 (1H, m), 3.44 - 3.62 (2H, m), 3.74 (1H, d), 3.93 - 3.97 (1H, m), 4.12 (1H, d), 4.43 (1H, s), 6.67 (1H, s), 7.24 - 7.31 (3H, m), 7.43 - 7.48 (3H, m), 7.51 - 7.53 (2H, m), 7.60 - 7.63 (1H, m), 7.67 - 7.70 (1H, m), 7.88 - 7.92 (3H, m), 10.40 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 605; HPLC tR = 3.02 min.

4-[4-[1-(2-Chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

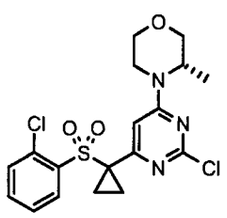


Dichlorobis(triphenylphosphine)palladium(II) (0.519 g, 0.74 mmol) was added in one portion to a mixture of sodium carbonate (2.352 g, 22.20 mmol), 2-chloro-4-[1-(2-

chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.169 g, 7.40 mmol) and (4-aminophenyl)boronic acid pinacol ester (1.702 g, 7.77 mmol) in DME (56 mL)and water (14 mL) under nitrogen. The mixture was stirred at 80°C for 2 hours, cooled to RT then diluted with DCM (100 mL) and water (50 mL). The organic layer was washed with saturated brine (50 mL) then dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give a residue which was further purified by trituration with isohexane (25 mL) and diethyl ether (25 mL), to give the desired material as a yellow solid (3.21 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.08 - 1.19 (3H, m), 1.67 - 1.75 (2H, m), 1.97 - 2.00 (2H, m), 3.05 - 3.13 (1H, m), 3.39 - 3.43 (1H, m), 3.56 - 3.60 (1H, m), 3.73 (1H, d), 3.91 - 3.96 (1H, m), 4.04 (1H, q), 4.37 (1H, s), 5.49 (2H, m), 6.47 - 6.49 (2H, m), 6.52 (1H, s), 7.43 - 7.47 (1H, m), 7.59 - 7.68 (4H, m), 7.90 - 7.93 (1H, m).
LCMS Spectrum: m/z (ESI+)(M+H)+ = 485; HPLC tR = 1.94 min.

2-Chloro-4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

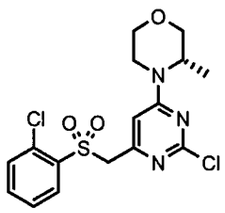


Sodium hydroxide (50%w/w solution) (35.2 mL, 440.00 mmol) was added to 2-chloro-4-[(2-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.22 g, 8mmol), 1,2-dibromoethane (2.068 mL, 24.00 mmol) and tetrabutylammonium bromide (0.258 g, 0.80 mmol) in toluene (141 mL). The resulting solution was stirred at 60°C for 18 hours. The reaction mixture was diluted with DCM (150 mL), and washed twice with water (150 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% ethyl acetate in DCM, to give the desired material as a colourless dry film (3.23 g).
NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.64 - 1.67 (2H, m), 1.92 - 1.95 (2H, m), 3.07 - 3.15 (1H, m), 3.35 - 3.41 (1H, m), 3.51 - 3.55 (1H, m), 3.69 (1H, d), 3.88

- 3.92 (2H, m), 4.24 (1H, s), 6.72 (1H, s), 7.52 - 7.56 (1H, m), 7.66 - 7.73 (2H, m), 7.88 - 7.91 (1H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 428; HPLC tR = 2.42 min.

2-Chloro-4-[(2-chlorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



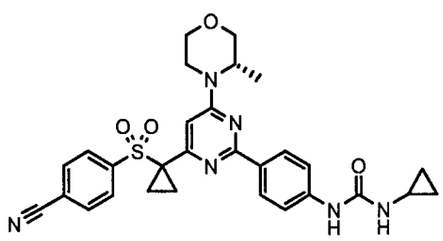
Sodium 2-chlorobenzenesulfinate (3.19 g, 16.07 mmol) was added to a solution of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.37 g, 12.36 mmol) in DMF (20 mL). The resulting mixture was stirred at RT for 1 hour. The reaction mixture was evaporated to dryness and redissolved in DCM (150 mL) and washed sequentially with water (100 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 60% ethyl acetate in isohexane, to give the desired material as a white solid (4.34 g).

NMR Spectrum: ^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.16 - 1.18 (3H, d), 3.13 - 3.20 (1H, m), 3.39 - 3.46 (1H, m), 3.56 - 3.59 (1H, m), 3.72 (1H, d), 3.91 - 3.95 (2H, m), 4.22 (1H, s), 4.78 (2H, s), 6.79 (1H, s), 7.56 - 7.59 (1H, m), 7.74 - 7.79 (2H, m), 7.82 - 7.84 (1H, m).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 402; HPLC tR = 2.26 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 77: 1-[4-[4-[1-(4-Cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea

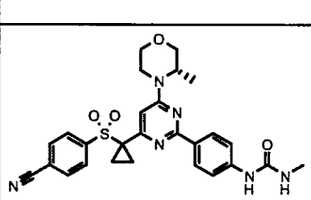


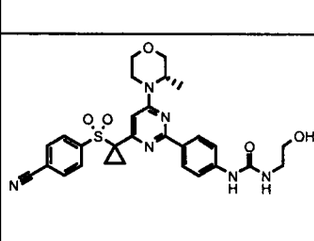
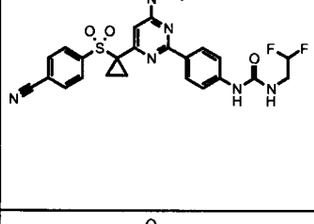
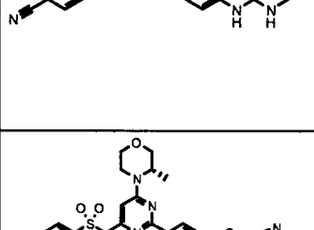
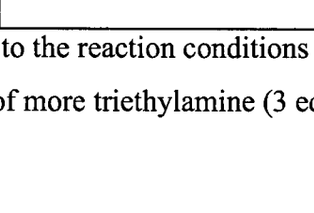
Cyclopropylamine (32 mg, 0.564 mmol) was added to phenyl *N*-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (112 mg, 0.188 mmol) and triethylamine (0.080 mL, 0.564 mmol) in NMP (2 mL). The resulting solution was stirred at 50°C for 16 hours then cooled to RT and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a solid (81 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.42 (2H, m), 0.65 (2H, m), 1.19 (3H, d), 1.65 (2H, m), 1.96 (2H, m), 2.56 (1H, m), 3.17 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 6.41 (1H, d), 6.67 (1H, s), 7.39 (2H, d), 7.68 (2H, d), 7.98 (2H, d), 8.08 (2H, d), 8.53 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 559; HPLC tR = 2.36 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
77a		1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	533	2.20

Example	Structure	NAME	LCMS MH+	Retention time (min)
77b		3-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	547	2.34
77c		1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	563	2.00
77d		1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	583	2.46
77e		1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	565	2.34
77f		1-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	599	2.22

* In addition to the reaction conditions described above this sample was further subjected to the addition of more triethylamine (3 equivalents) and stirred for an additional 7 hours at 80°C.

Example 77a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.65 (2H, m), 1.95 (2H, m), 2.66 (3H, d), 3.16 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 6.06 (1H, q), 6.66 (1H, s), 7.39 (2H, d), 7.68 (2H, d), 7.98 (2H, d), 8.08 (2H, d), 8.73 (1H, s).

Example 77b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.19 (3H, d), 1.65 (2H, m), 1.95 (2H, m), 3.09 - 3.20 (3H, m), 3.47 (1H, m), 3.62 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 6.15 (1H, t), 6.66 (1H, s), 7.38 (2H, d), 7.67 (2H, d), 7.98 (2H, d), 8.08 (2H, d), 8.65 (1H, s).

Example 77c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.65 (2H, m), 1.96 (2H, m), 3.18 (3H, m), 3.47 (3H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 4.74 (1H, t), 6.25 (1H, t), 6.66 (1H, s), 7.37 (2H, d), 7.67 (2H, d), 7.98 (2H, d), 8.09 (2H, d), 8.79 (1H, s).

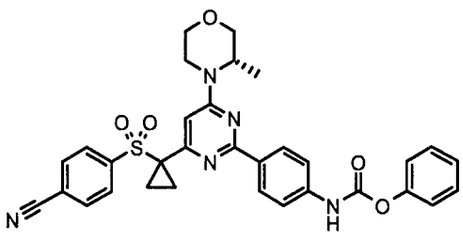
Example 77d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.65 (2H, m), 1.96 (2H, m), 3.17 (1H, m), 3.43 - 3.63 (4H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.46 (1H, m), 5.92 - 6.22 (1H, m), 6.52 (1H, t), 6.67 (1H, s), 7.39 (2H, d), 7.70 (2H, d), 7.98 (2H, d), 8.08 (2H, d), 8.91 (1H, s).

Example 77e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.65 (2H, m), 1.96 (2H, m), 3.16 (1H, m), 3.39 (1H, m), 3.47 (2H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.16 (1H, m), 4.41 - 4.55 (3H, m), 6.43 (1H, t), 6.67 (1H, s), 7.39 (2H, d), 7.69 (2H, d), 7.98 (2H, d), 8.09 (2H, d), 8.80 (1H, s).

Example 77f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (4H, d), 1.65 (2H, m), 1.96 (3H, m), 3.17 (2H, m), 3.47 (1H, m), 3.62 (1H, m), 3.74 - 3.80 (4H, m), 3.97 (1H, m), 4.17 (1H, m), 4.47 (1H, m), 6.68 (1H, s), 7.38 (2H, s), 7.43 (3H, d), 7.71 (3H, d), 7.77 (2H, s), 7.98 (2H, d), 8.09 (2H, d), 8.38 (1H, s), 8.83 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

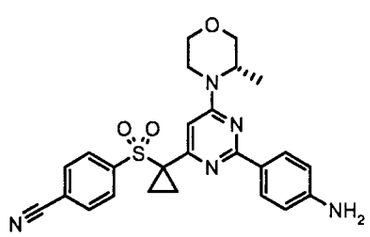


Phenyl chloroformate (0.185 mL, 1.47 mmol) was added dropwise to 4-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile (700 mg, 1.47 mmol) and sodium bicarbonate (185 mg, 2.21 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The precipitate was collected by filtration, washed with diethyl ether (2 mL) and suspended in water (20 mL) and stirred for 20 minutes. The precipitate was collected by filtration, washed with water (5 mL) then diethyl ether (5 mL) and dried under vacuum to afford the desired material as a white solid (786 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.67 (2H, m), 1.97 (2H, m), 3.18 (1H, m), 3.45 (1H, m), 3.62 (1H, m), 3.76 (1H, m), 3.97 (1H, m), 4.18 (1H, m), 4.47 (1H, m), 6.71 (1H, s), 7.27 (3H, m), 7.46 (2H, m), 7.53 (2H, d), 7.78 (2H, d), 7.98 (2H, d), 8.09 (2H, d), 10.44 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 596; HPLC tR = 3.01 min.

4-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile



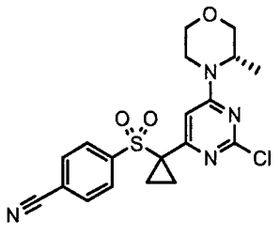
Sodium carbonate (1.693 g, 15.97 mmol) was added to 4-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile (2.23 g, 5.32 mmol) and (4-aminophenyl)boronic acid pinacol ester (1.225 g, 5.59 mmol) in a mixture of DME (40 mL) and water (10.00 mL). The mixture was bubbled with nitrogen for 10 minutes then

dichlorobis(triphenylphosphine)palladium(II) (0.374 g, 0.53 mmol) was added and the mixture stirred at 80°C for 2 hours. The reaction mixture was cooled to RT then diluted with DCM (100 mL) and water (50 mL). The organic layer was washed with saturated brine (50 mL) then dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 40% ethyl acetate in isohexane followed by 40% ethyl acetate in isohexane, to give the desired material as an orange solid (2.31 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.62 (2H, m), 1.93 (2H, m), 3.14 (1H, m), 3.45 (1H, m), 3.60 (1H, m), 3.74 (1H, m), 3.95 (1H, m), 4.12 (1H, m), 4.42 (1H, m), 5.55 (2H, s), 6.48 (2H, d), 6.56 (1H, s), 7.50 (2H, d), 7.97 (2H, d), 8.08 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 476; HPLC tR = 2.37 min.

4-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile



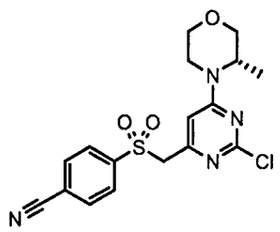
Sodium hydride, 60% dispersion in mineral oil (0.316 g, 7.91 mmol) was added in one portion to 4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]benzonitrile (2.96 g, 7.53 mmol) in DMF (20 mL) at 0°C under nitrogen. The resulting suspension was stirred for 10 minutes then 1,2-dibromoethane (0.682 mL, 7.91 mmol) was added. The mixture was warmed to 10°C for 10 minutes then cooled back to 0°C and a further portion of sodium hydride, 60% dispersion in mineral oil (0.316 g, 7.91 mmol) added. The mixture was warmed to 50°C and stirred at 50°C for 2 hours. A further portion of sodium hydride, 60% dispersion in mineral oil (0.158 g, 3.95 mmol) and 1,2-dibromoethane (0.341 ml, 3.95 mmol) was added and stirred for a further 2 hours. The reaction mixture was cooled to RT, quenched with saturated aqueous ammonium chloride (2 mL) and the solvents evaporated. The residues were stirred in water (50 mL) for 15 minutes then the resulting solid collected by filtration. The solid was dissolved in DCM (50 mL), washed with water (20 mL), then saturated brine (20 mL), dried over $MgSO_4$, filtered and evaporated to give the crude

product. The crude product was purified by flash silica chromatography, elution gradient 20 to 40% ethyl acetate in isohexane, to give the desired material as a white solid (2.33 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.60 (2H, m), 1.90 (2H, m), 3.15 (1H, m), 3.40 (1H, m), 3.55 (1H, m), 3.70 (1H, m), 3.90 - 3.99 (2H, m), 4.27 (1H, m), 6.72 (1H, s), 7.96 (2H, d), 8.11 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 419; HPLC tR = 2.19 min.

4-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]benzonitrile

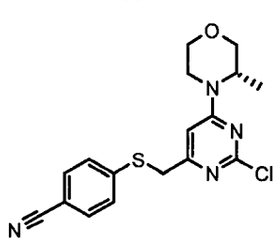


2N Sulfuric acid (0.4 mL) was added to a stirred solution of 4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]benzonitrile (5.18 g, 14.35 mmol) in dioxane (125 mL) and the solution heated to 55°C. Sodium tungstate dihydrate (0.095 g, 0.29 mmol) in water (3.5 mL) was added and the solution was allowed to stir for 5 minutes. Hydrogen peroxide, 30% by wt solution in water (8.80 mL, 86.13 mmol) was added dropwise and the solution stirred at 55°C for 3 hours. The reaction was cooled to RT then water added until precipitation ceased. The precipitate was collected by filtration, washed with water and dried under vacuum to afford the desired material as a white solid (5.0 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 3.18 (1H, m), 3.43 (1H, m), 3.58 (1H, m), 3.73 (1H, m), 3.91 (2H, m), 4.18 (1H, m), 4.77 (2H, s), 6.76 (1H, s), 7.99 (2H, d), 8.15 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 393; HPLC tR = 1.99 min.

4-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]benzonitrile



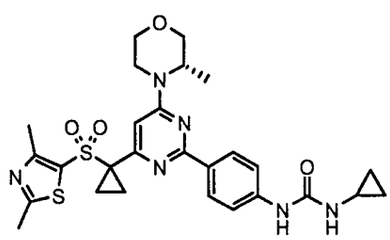
4-Mercaptobenzonitrile (3.48 g, 25.74 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7 g, 19.80 mmol) and DIPEA (5.32 mL, 29.70 mmol) in THF (50 mL). The resulting slurry was stirred at RT for 16 hours then the temperature was increased to 70°C for a further 16 hours. The reaction mixture was cooled to RT then diluted with DCM (200 mL), and washed sequentially with water (200 mL) then saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 30% ethyl acetate in isohexane, to give the desired material as a yellow solid (5.18 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (3H, d), 3.16 (1H, m), 3.42 (1H, m), 3.57 (1H, m), 3.71 (1H, m), 3.90 - 3.99 (2H, m), 4.26 (3H, m), 6.88 (1H, s), 7.55 (2H, d), 7.75 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 361; HPLC tR = 2.33 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 78: 3-Cyclopropyl-1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea



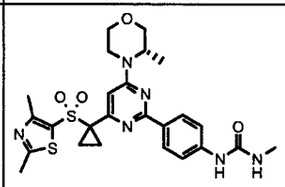
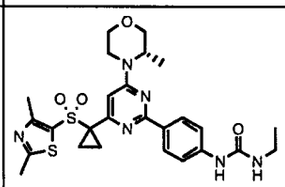
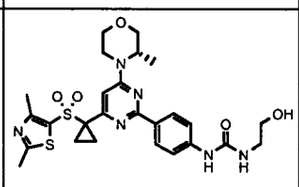
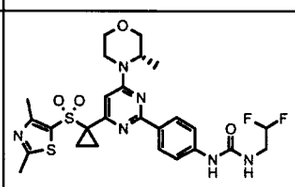
Cyclopropylamine (26 mg, 0.450 mmol) was added to phenyl *N*-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (91 mg, 0.150 mmol) and triethylamine (0.063 mL, 0.450 mmol) in NMP (2 mL). The resulting solution was stirred at 50°C for 16 hours then cooled to RT and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (64 mg).

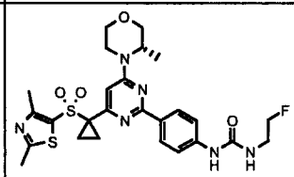
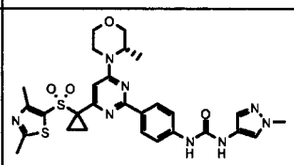
NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.42 (2H, m), 0.66 (2H, m), 1.21 (3H, d), 1.62 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.56 (1H, m), 2.62 (3H, s), 3.18 (1H, m), 3.48

(1H, m), 3.63 (1H, m), 3.76 (1H, m), 3.97 (1H, m), 4.16 (1H, m), 4.49 (1H, m), 6.43 (1H, d), 6.73 (1H, s), 7.45 (2H, d), 7.93 (2H, d), 8.53 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 569; HPLC tR = 2.27 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
78a		1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	543	2.08
78b		3-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	557	2.25
78c		1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	573	1.91
78d		3-(2,2-difluoroethyl)-1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	593	2.38

Example	Structure	NAME	LCMS MH+	Retention time (min)
78e		1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	575	2.24
78f*		1-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	609	2.13

* Stirred for an additional 4 hours at 80°C

Example 78a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.61 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 2.67 (3H, d), 3.18 (1H, m), 3.48 (1H, m), 3.63 (1H, m), 3.76 (1H, m), 3.97 (1H, m), 4.16 (1H, m), 4.49 (1H, m), 6.06 (1H, q), 6.72 (1H, s), 7.44 (2H, d), 7.92 (2H, d), 8.74 (1H, s).

Example 78b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.21 (3H, d), 1.62 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 3.10 - 3.22 (3H, m), 3.48 (1H, m), 3.63 (1H, m), 3.76 (1H, m), 3.98 (1H, m), 4.16 (1H, m), 4.49 (1H, m), 6.15 (1H, t), 6.72 (1H, s), 7.43 (2H, d), 7.92 (2H, d), 8.66 (1H, s).

Example 78c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.62 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 3.14 - 3.22 (3H, m), 3.44 - 3.51 (3H, m), 3.63 (1H, m), 3.76 (1H, m), 3.97 (1H, m), 4.16 (1H, m), 4.49 (1H, m), 4.74 (1H, t), 6.24 (1H, t), 6.73 (1H, s), 7.43 (2H, d), 7.93 (2H, d), 8.80 (1H, s).

Example 78d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.62 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 3.18 (1H, m), 3.45 - 3.65 (4H, m), 3.76 (1H, m), 3.97 (1H, m), 4.16 (1H, m), 4.49 (1H, m), 5.93 - 6.23 (1H, m), 6.53 (1H, t), 6.74 (1H, s), 7.45 (2H, d), 7.95 (2H, d), 8.92 (1H, s).

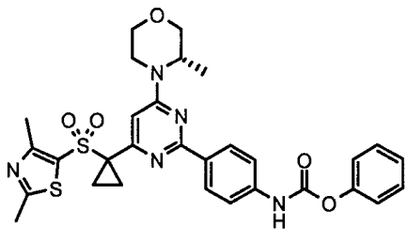
Example 78e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.62 (2H, m), 1.79 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 3.18 (1H, m), 3.37 - 3.51 (3H, m), 3.63 (1H, m), 3.77 (1H, m),

3.98 (1H, m), 4.16 (1H, m), 4.41 - 4.55 (3H, m), 6.43 (1H, t), 6.73 (1H, s), 7.44 (2H, d), 7.93 (2H, d), 8.81 (1H, s).

Example 78f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.62 (2H, m), 1.80 (2H, m), 2.23 (3H, s), 2.63 (3H, s), 3.19 (1H, m), 3.48 (1H, m), 3.64 (1H, m), 3.77 (1H, m), 3.80 (3H, s), 3.98 (1H, m), 4.17 (1H, m), 4.49 (1H, m), 6.74 (1H, s), 7.39 (1H, s), 7.49 (2H, d), 7.78 (1H, s), 7.96 (2H, d), 8.38 (1H, s), 8.83 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

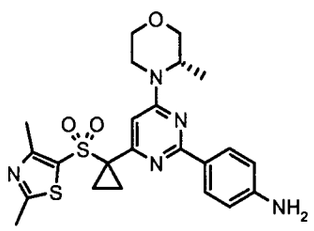


Phenyl chloroformate (0.181 mL, 1.44 mmol) was added dropwise to 4-[4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (700 mg, 1.44 mmol) and sodium bicarbonate (182 mg, 2.16 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The precipitate was collected by filtration, washed with diethyl ether (2 mL) and suspended in water (20 mL) and stirred for 20 minutes. The precipitate was collected by filtration, washed with water (5 mL) then diethyl ether (5 mL) and dried under vacuum to afford the desired material as a beige solid (637 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.63 (2H, m), 1.81 (2H, m), 2.24 (3H, s), 2.61 (3H, s), 3.20 (1H, m), 3.49 (1H, m), 3.63 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.17 (1H, m), 4.51 (1H, m), 6.78 (1H, s), 7.28 (3H, m), 7.46 (2H, m), 7.58 (2H, d), 8.02 (2H, d), 10.43 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 606; HPLC tR = 2.91 min.

4-[4-[1-[(2,4-Dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

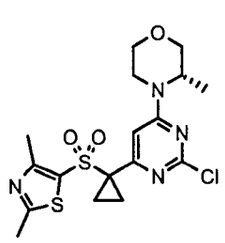


Sodium carbonate (2.105 g, 19.86 mmol) was added to 2-chloro-4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.84 g, 6.62 mmol) and (4-aminophenyl)boronic acid pinacol ester (1.523 g, 6.95 mmol) in a mixture of DME (40 mL) and water (10 mL). The mixture was bubbled with nitrogen for 10 minutes then dichlorobis(triphenylphosphine)palladium(II) (0.465 g, 0.66 mmol) was added and the mixture stirred at 80°C for 2 hours. Further dichlorobis(triphenylphosphine)palladium(II) (0.232 g, 0.33 mmol) was added and the mixture was stirred at 80°C for a further 4 hours. The reaction mixture was cooled to RT then diluted with DCM (250 mL) and water (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 40 to 50% ethyl acetate in isohexane followed by 50% ethyl acetate in isohexane, to give a material which was further purified by ion exchange chromatography using an SCX column, eluting with 2M ammonia in methanol, to give the desired material as an orange solid (2.59 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.59 (2H, m), 1.77 (2H, m), 2.22 (3H, s), 2.62 (3H, s), 3.15 (1H, m), 3.47 (1H, m), 3.61 (1H, m), 3.75 (1H, m), 3.96 (1H, m), 4.12 (1H, m), 4.45 (1H, m), 5.54 (2H, s), 6.54 (2H, d), 6.62 (1H, s), 7.76 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 486; HPLC tR = 2.17 min.

2-Chloro-4-[1-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

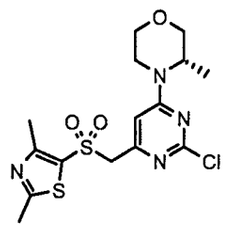


Sodium hydroxide (15.94 g, 398.59 mmol) in water (16 mL) was added to a stirred solution of 2-chloro-4-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.92 g, 7.25 mmol), 1,2-dibromoethane (1.874 mL, 21.74 mmol) and tetrabutylammonium bromide (0.234 g, 0.72 mmol) in toluene (100 mL). The resulting solution was stirred at RT for 90 minutes then at 60°C for 1 hour. The reaction mixture was diluted with water (300 mL), the organic layer separated and washed with saturated brine (100 mL) then dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to give the desired material as a white solid (2.84 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.59 (2H, m), 1.76 (2H, m), 2.29 (3H, s), 2.68 (3H, s), 3.17 (1H, m), 3.42 (1H, m), 3.56 (1H, m), 3.72 (1H, m), 3.91 - 4.00 (2H, m), 4.33 (1H, m), 6.82 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 429; HPLC tR = 2.09 min.

2-Chloro-4-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

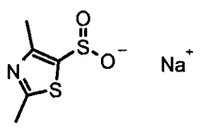


Sodium 2,4-dimethylthiazole-5-sulfinate (5.2 g, 26.10 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.01 g, 11.35 mmol) in DMF (50 mL). The resulting mixture was stirred at RT for 1 hour. The reaction mixture was evaporated to dryness and redissolved in DCM (250 mL), and washed sequentially with water (150 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane followed by 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (4.77 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 (3H, d), 2.40 (3H, s), 2.67 (3H, s), 3.19 (1H, m), 3.44 (1H, m), 3.59 (1H, m), 3.73 (1H, m), 3.93 (2H, m), 4.23 (1H, m), 4.69 (2H, s), 6.83 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 403; HPLC tR = 1.82 min.

Sodium 2,4-dimethylthiazole-5-sulfinate

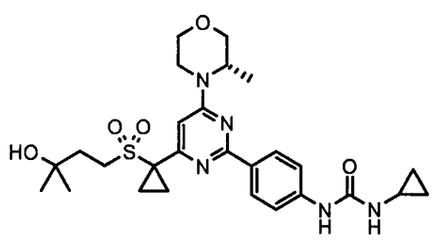


A solution of sodium sulfite (2.98 g, 23.62 mmol) in water (25 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (3.97 g, 47.24 mmol) was added and the resulting solution was stirred at 50°C for 1 hour. 2,4-Dimethylthiazole-5-sulfonyl chloride (5 g, 23.62 mmol) was added portion wise to the solution and stirring was continued at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (75 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford the desired material as a yellow solid (5.21 g), which was dried under vacuum and used without further purification.

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 2.28 (3H, s).

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 79: 3-Cyclopropyl-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

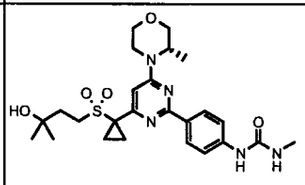
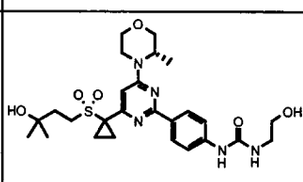
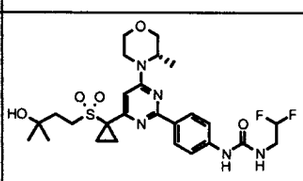
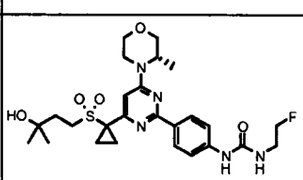


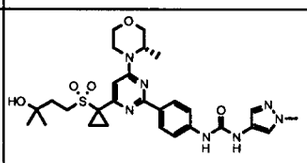
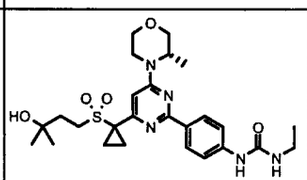
Cyclopropylamine (33 mg, 0.573 mmol) was added to phenyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (111 mg, 0.191 mmol) and triethylamine (0.080 mL, 0.573 mmol) in NMP (2 mL). The resulting solution was stirred at 50°C for 16 hours then cooled to RT and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (83 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.43 (2H, m), 0.65 (2H, m), 1.12 (6H, s), 1.24 (3H, d), 1.56 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 2.56 (1H, m), 3.21 (1H, m), 3.49 (1H, m), 3.56 (2H, m), 3.63 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.22 (1H, m), 4.49 (1H, s), 4.56 (1H, m), 6.44 (1H, d), 6.76 (1H, s), 7.50 (2H, d), 8.24 (2H, d), 8.57 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 544; HPLC tR = 2.10 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
79a		1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	518	1.93
79b		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	548	1.78
79c		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	568	2.18
79d		3-(2-fluoroethyl)-1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	550	2.06

Example	Structure	NAME	LCMS MH+	Retention time (min)
79e*		1-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	584	1.98
79f		1-ethyl-3-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	532	2.07

* 6 Equivalents of triethylamine were used.

Example 79a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.23 (3H, d), 1.55 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 2.67 (3H, d), 3.21 (1H, m), 3.45 - 3.58 (3H, m), 3.63 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.22 (1H, m), 4.49 (1H, s), 4.57 (1H, m), 6.07 (1H, m), 6.75 (1H, s), 7.49 (2H, d), 8.23 (2H, d), 8.77 (1H, s).

Example 79b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.24 (3H, d), 1.55 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 3.16 - 3.24 (3H, m), 3.45 - 3.49 (3H, m), 3.56 (2H, m), 3.63 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.22 (1H, m), 4.49 (1H, s), 4.56 (1H, m), 4.74 (1H, t), 6.25 (1H, t), 6.76 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.82 (1H, s).

Example 79c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.24 (3H, d), 1.56 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 3.21 (1H, m), 3.45 - 3.65 (6H, m), 3.77 (1H, m), 3.98 (1H, m), 4.23 (1H, m), 4.49 (1H, s), 4.57 (1H, m), 5.93 - 6.23 (1H, m), 6.53 (1H, t), 6.77 (1H, s), 7.50 (2H, d), 8.26 (2H, d), 8.95 (1H, s).

Example 79d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.12 (6H, s), 1.24 (3H, d), 1.55 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 3.21 (1H, m), 3.36 - 3.58 (5H, m), 3.64 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.22 (1H, m), 4.41 - 4.58 (4H, m), 6.43 (1H, t), 6.76 (1H, s), 7.49 (2H, d), 8.25 (2H, d), 8.83 (1H, s).

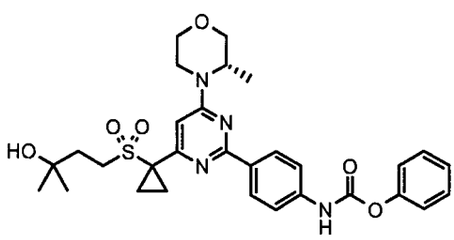
Example 79e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.24 (3H, d), 1.56 (2H, m), 1.66 (2H, m), 1.86 (2H, m), 3.22 (1H, m), 3.49 (1H, m), 3.57 (2H, m), 3.64 (1H, m), 3.78

(4H, m), 3.98 (1H, m), 4.23 (1H, m), 4.50 (1H, s), 4.57 (1H, m), 6.77 (1H, s), 7.39 (1H, s), 7.54 (2H, d), 7.78 (1H, s), 8.27 (2H, d), 8.38 (1H, s), 8.86 (1H, s)

Example 79f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.12 (6H, s), 1.23 (3H, d), 1.59 (4H, m), 1.84 (2H, m), 3.17 (3H, m), 3.54 (4H, m), 3.76 (1H, m), 3.98 (1H, m), 4.23 (1H, m), 4.56 (2H, m), 6.17 (1H, m), 6.75 (1H, s), 7.48 (2H, d), 8.23 (2H, d), 8.72 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

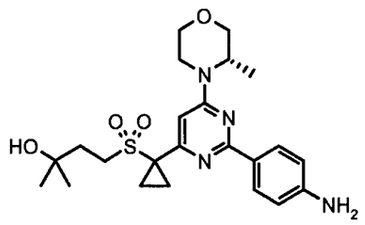


Phenyl chloroformate (0.191 mL, 1.52 mmol) was added dropwise to 4-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-2-methylbutan-2-ol (700 mg, 1.52 mmol) and sodium bicarbonate (192 mg, 2.28 mmol) in dioxane (20 mL) under nitrogen. The resulting suspension was stirred at RT for 2 hours. The precipitate was collected by filtration then washed with diethyl ether (2 mL). The precipitate was suspended in water (20 mL) then extracted into DCM (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a yellow solid (774 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.12 (6H, s), 1.24 (3H, d), 1.57 (2H, m), 1.66 (2H, m), 1.85 (2H, m), 3.22 (1H, m), 3.46 - 3.57 (3H, m), 3.64 (1H, m), 3.77 (1H, m), 3.98 (1H, m), 4.24 (1H, m), 4.58 (1H, m), 6.80 (1H, s), 7.28 (3H, m), 7.46 (2H, m), 7.62 (2H, d), 8.33 (2H, d), 10.43 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 581; HPLC tR = 2.63 min.

4-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-2-methylbutan-2-ol

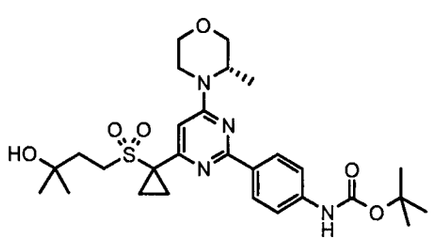


TFA (5 mL) was added to *tert*-butyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.08 g, 3.71 mmol) in DCM (5 mL). The resulting solution was stirred at RT for 1 hour then added to an SCX column. The crude product was eluted from the column using 2M ammonia in methanol the further purified by flash silica chromatography, elution gradient 40 to 50% ethyl acetate in isohexane, to give the desired material as a white solid (1.15 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.22 (3H, d), 1.52 (2H, m), 1.63 (2H, m), 1.85 (2H, m), 3.18 (1H, m), 3.48 (1H, m), 3.55 (2H, m), 3.62 (1H, m), 3.76 (1H, m), 3.97 (1H, m), 4.19 (1H, m), 4.48 (1H, s), 4.53 (1H, m), 5.57 (2H, s), 6.59 (2H, d), 6.65 (1H, s), 8.07 (2H, d).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 461; HPLC tR = 1.96 min.

tert-Butyl *N*-[4-[4-[1-(3-hydroxy-3-methylbutyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

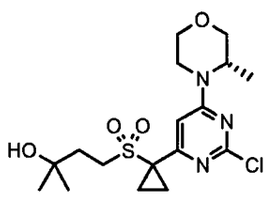


Sodium carbonate (1.299 g, 12.25 mmol) was added to 4-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-2-methylbutan-2-ol (1.65 g, 4.08 mmol) and (4-boc-aminophenyl)boronic acid pinacol ester (1.369 g, 4.29 mmol) in a mixture of DME (40 mL) and water (10 mL). The mixture was bubbled with nitrogen for 10 minutes then 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.296 g, 0.41 mmol) was

added and the mixture stirred at 80°C for 8 hours. The reaction mixture was cooled to RT then diluted with DCM (150 mL), and washed with water (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to give the desired material as a yellow gum (2.08 g).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 561; HPLC tR = 2.69 min.

4-[1-[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-2-methylbutan-2-ol

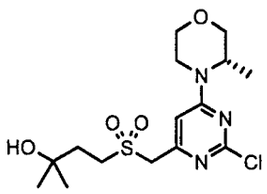


Sodium hydroxide (11.93 g, 298.37 mmol) in water (12 mL) was added to a stirred solution of 4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-2-methylbutan-2-ol (2.05 g, 5.42 mmol), 1,2-dibromoethane (1.402 mL, 16.27 mmol) and tetrabutylammonium bromide (0.175 g, 0.54 mmol) in toluene (75 mL). The resulting solution was stirred at RT for 5 hours then at 45°C for 3 hours. The reaction mixture was diluted with water (100 mL), the organic layer separated and dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in isohexane, to give the desired material as a yellow dry film (1.75 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 (6H, s), 1.22 (3H, d), 1.52 (2H, m), 1.61 (2H, m), 1.80 (2H, m), 3.21 (1H, m), 3.36 - 3.47 (3H, m), 3.58 (1H, m), 3.72 (1H, m), 3.93 (1H, m), 4.05 (1H, m), 4.40 (1H, m), 4.46 (1H, s), 6.94 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 404; HPLC tR = 1.83 min.

4-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]-2-methylbutan-2-ol

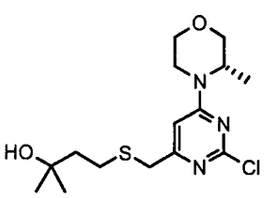


2N Sulfuric Acid (0.307 mL) was added to a stirred solution of 4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-2-methylbutan-2-ol (3.78 g, 10.93 mmol) in dioxane (100 mL) and the solution heated to 55°C. Sodium tungstate dihydrate (0.072 g, 0.22 mmol) in water (3 mL) was added and the solution was allowed to stir for 5 minutes. Hydrogen peroxide, 30% by wt solution in water (6.7 mL, 65.57 mmol) was added dropwise and the solution stirred at 55°C for 2.5 hours. The reaction mixture was cooled to RT and diluted with water (100 mL), and extracted with DCM (2 x 200 mL). The organic layer was washed with brine (50 mL) then dried over $MgSO_4$, filtered and evaporated to afford the desired material as a cream solid (4.39 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (6H, s), 1.23 (3H, d), 1.82 (2H, m), 3.19 - 3.30 (3H, m), 3.46 (1H, m), 3.61 (1H, m), 3.74 (1H, m), 3.93 - 4.02 (2H, m), 4.31 (1H, m), 4.46 (2H, s), 4.48 (1H, s), 6.95 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 378; HPLC tR = 1.64 min.

4-[[2-Chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]-2-methylbutan-2-ol



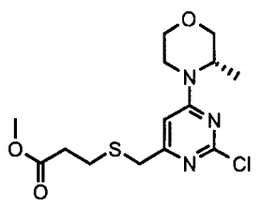
Methylmagnesium bromide, 3M in diethyl ether (13.17 mL, 39.50 mmol) was added dropwise to methyl 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]propanoate (4.14 g, 11.97 mmol) in THF (50 mL) at 0°C over a period of 10 minutes under nitrogen. The resulting solution was stirred at 0°C for 30 minutes then at RT for 90 minutes. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (1 mL), diluted with water (100 mL) then extracted with DCM (3 x 100

mL), the organic layer was washed with brine (100 mL) then dried over $MgSO_4$, filtered and evaporated to afford the desired material as a yellow gum (3.96 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.08 (6H, s), 1.21 (3H, d), 1.61 (2H, m), 2.54 (2H, m), 3.18 (1H, m), 3.44 (1H, m), 3.57 (2H, s), 3.61 (1H, m), 3.72 (1H, m), 3.91 - 4.01 (2H, m), 4.23 (1H, s), 4.32 (1H, m), 6.78 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 346; HPLC tR = 1.79 min.

Methyl 3-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfanyl]propanoate



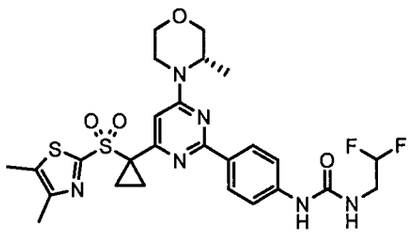
Methyl 3-mercaptopropionate (2.55 g, 21.21 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol) and DIPEA (3.80 mL, 21.21 mmol) in THF (50 mL). The resulting slurry was stirred at RT for 16 hours. The reaction mixture was diluted with DCM (150 mL), and washed sequentially with water (100 mL) then saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 30% ethyl acetate in isohexane, to give the desired material as a colourless liquid (4.6 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.21 (3H, d), 2.65 (2H, t), 2.76 (2H, t), 3.19 (1H, m), 3.45 (1H, m), 3.56 - 3.64 (6H, m), 3.72 (1H, m), 3.91 - 4.00 (2H, m), 4.33 (1H, m), 6.81 (1H, s).

LCMS Spectrum: m/z (ESI+)(M+H)+ = 346; HPLC tR = 2.05 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 80: 3-(2,2-Difluoroethyl)-1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

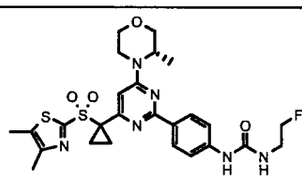


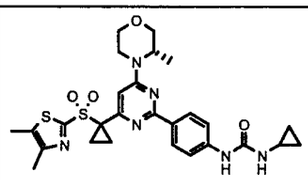
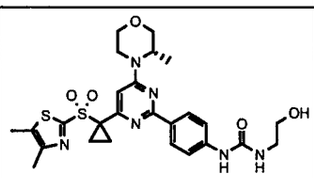
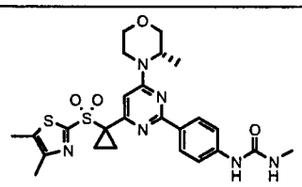
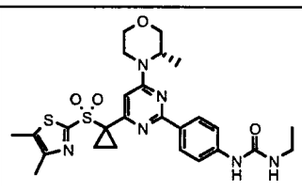
Phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.25 mmol), triethylamine (0.104 mL, 0.74 mmol) and 2,2-difluoroethanamine (60.2 mg, 0.74 mmol) were added to dioxane (10 mL) and heated at 50°C for 72 hours. The reaction mixture was evaporated under reduced pressure to a gum which was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (83 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.77 - 1.72 (2H, m), 1.95 - 1.88 (2H, m), 2.37 (3H, s), 2.40 (3H, s), 3.23 - 3.13 (1H, m), 3.66 - 3.41 (4H, m), 3.80 - 3.73 (1H, m), 3.97 (1H, d), 4.17 (1H, d), 4.51 - 4.41 (1H, m), 6.23 - 5.91 (1H, m), 6.51 (1H, t), 6.79 (1H, s), 7.44 (2H, d), 7.90 (2H, d), 8.91 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 493; HPLC tR = 2.42 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
80a		1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	576	2.25

Example	Structure	NAME	LCMS MH+	Retention time (min)
80b		3-cyclopropyl-1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	569	2.23
80c		1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	573	1.90
80d*		1-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	543	2.06
80e*		3-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	557	2.21

* Stirred at RT for 16 hours

Example 80a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.78 - 1.71 (2H, m), 1.94 - 1.89 (2H, m), 2.37 (3H, s), 2.40 (3H, s), 3.24 - 3.13 (1H, m), 3.51 - 3.35 (4H, m), 3.65 - 3.59 (1H, m), 3.79 - 3.74 (1H, m), 4.01 - 3.94 (1H, m), 4.17 (1H, d), 4.56 - 4.38 (3H, m), 6.41 (1H, t), 7.43 (2H, d), 7.89 (2H, d), 8.80 (1H, s)

Example 80b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.45 - 0.38 (2H, m), 0.69 - 0.61 (2H, m), 1.21 (3H, d), 1.76 - 1.72 (2H, m), 1.94 - 1.89 (2H, m), 2.37 (3H, s), 2.41 (3H, s), 2.59 - 2.53 (1H, m), 3.24 - 3.13 (1H, m), 3.47 (1H, t), 3.64 - 3.59 (1H, m), 3.80 - 3.72 (1H, m), 3.98

(1H, d), 4.17 (1H, d), 4.50 - 4.41 (1H, m), 6.41 (1H, d), 6.78 (1H, s), 7.43 (2H, d), 7.88 (2H, d), 8.53 (1H, s)

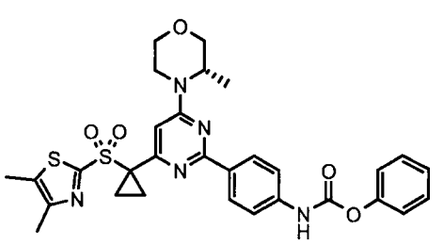
Example 80c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.77 - 1.72 (2H, m), 1.94 - 1.89 (2H, m), 2.37 (3H, s), 2.40 (4H, s), 3.51 - 3.42 (3H, m), 3.65 - 3.59 (1H, m), 3.79 - 3.74 (1H, m), 3.97 (1H, d), 4.06 (2H, q), 4.17 (1H, d), 4.50 - 4.41 (1H, m), 4.72 (1H, t), 6.23 (1H, t), 6.78 (1H, s), 7.41 (2H, d), 7.88 (2H, d), 8.79 (1H, s)

Example 80d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.78 - 1.72 (2H, m), 1.94 - 1.89 (2H, m), 2.37 (3H, s), 2.40 (3H, s), 2.66 (3H, d), 3.23 - 3.13 (1H, m), 3.52 - 3.42 (1H, m), 3.65 - 3.59 (1H, m), 3.79 - 3.74 (1H, m), 3.97 (1H, d), 4.20 - 4.13 (1H, m), 4.49 - 4.41 (1H, m), 6.07 - 6.03 (1H, m), 6.78 (1H, s), 7.43 (2H, d), 7.87 (2H, d), 8.73 (1H, s)

Example 80e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.21 (3H, d), 1.77 - 1.71 (2H, m), 1.95 - 1.88 (2H, m), 2.37 (3H, s), 2.41 (3H, s), 3.23 - 3.07 (3H, m), 3.47 (1H, t), 3.65 - 3.59 (1H, m), 3.79 - 3.73 (1H, m), 3.98 (1H, d), 4.16 (1H, d), 4.51 - 4.40 (1H, m), 6.14 (1H, t), 6.78 (1H, s), 7.42 (2H, d), 7.88 (2H, d), 8.65 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

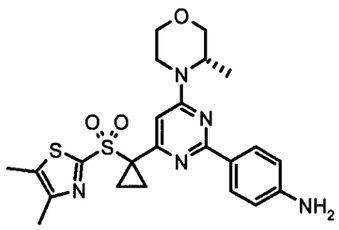


Phenyl chloroformate (0.866 mL, 6.91 mmol) was added dropwise to 4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2.58 g, 5.31 mmol) and sodium hydrogencarbonate (8.93 g, 106.26 mmol) in DCM (52.3 mL) at RT under nitrogen. The resulting suspension was stirred at RT for 90 minutes, saturated ammonium chloride solution added followed by DCM (40 mL). The organics were separated, washed with water (50 mL) and saturated brine (50 mL), dried over $MgSO_4$ and evaporated to give the desired material (2.91 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.87 - 1.77 (2H, m), 2.14 - 2.10 (2H, m), 2.34 (3H, s), 2.36 (3H, s), 3.32 (1H, t), 3.60 (1H, t), 3.77 - 3.72 (1H, m), 3.85 - 3.81 (1H, m), 4.04 (1H, d), 4.20 (1H, d), 4.53 - 4.44 (1H, m), 7.04 (1H, s), 7.10 (1H, s), 7.28 - 7.17 (3H, m), 7.40 (2H, t), 7.46 (2H, d), 8.16 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 606; HPLC tR = 2.90 min.

4-[4-[1-[(4,5-Dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

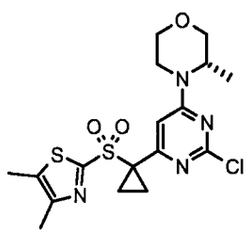


Dichlorobis(triphenylphosphine)palladium(II) (0.219 g, 0.31 mmol) was added in one portion to 2-chloro-4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.68 g, 6.25 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.369 g, 6.25 mmol) and sodium bicarbonate (15.62 mL, 31.24 mmol) in a mix of solvents (18% DMF, 82% of a 7:3:2 mixture of DME:water:ethanol) (75 mL) and the resulting mixture stirred at 80°C for 16 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (2 x 150 mL) and saturated brine (3 x 100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a yellow foam (2.85 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.32 (3H, d), 1.88 - 1.75 (2H, m), 2.16 - 2.06 (2H, m), 2.34 (3H, s), 2.36 (3H, s), 3.33 - 3.24 (1H, m), 3.63 - 3.55 (1H, m), 3.88 - 3.71 (4H, m), 4.03 (1H, d), 4.18 (1H, d), 4.51 - 4.43 (1H, m), 6.64 (2H, d), 7.04 (1H, s), 8.01 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 486; HPLC tR = 1.65 min.

2-Chloro-4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine

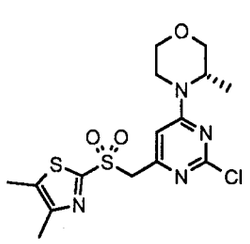


Sodium hydroxide (50% w/w) (45.9 g, 573.32 mmol) was added in one portion to 2-chloro-4-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (4.2 g, 10.42 mmol), tetrabutylammonium bromide (0.336 g, 1.04 mmol) and 1,2-dibromoethane (2.69 mL, 31.27 mmol) in toluene (52.1 mL) and the resulting mixture stirred at 60°C for 5 hours. The reaction mixture was diluted with toluene (50 mL) and water (100 mL) and washed sequentially with water (2 x 100 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% ethyl acetate in DCM, to give the desired material as a white foam (3.42 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.34 (3H, d), 1.83 - 1.72 (2H, m), 2.11 - 2.02 (2H, m), 2.37 (3H, s), 2.44 (3H, s), 3.29 (1H, t), 3.54 (1H, t), 3.72 - 3.66 (1H, m), 3.82 - 3.76 (1H, m), 4.13 - 3.97 (2H, m), 4.35 (1H, s), 7.29 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 429; HPLC tR = 2.35 min.

2-Chloro-4-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



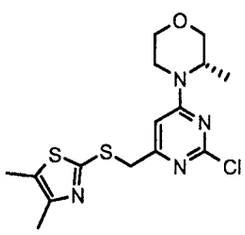
3-Chloroperoxybenzoic acid (11.18 g, 49.88 mmol) was added portionwise to (2-chloro-4-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7.4 g, 19.95 mmol) in DCM (100 mL) at 5°C over a period of 15 minutes under nitrogen. The resulting suspension was stirred at 5°C for 1 hour then allowed to warm to RT and stirred for

3 hours. A saturated solution of sodium hydrogen carbonate (100 mL) was added and the organics separated and washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in DCM, to give the desired material as a white solid (4.2 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.32 (3H, d), 2.42 (3H, s), 2.46 (3H, s), 3.28 (1H, t), 3.54 (1H, t), 3.71 - 3.66 (1H, m), 3.81 - 3.76 (1H, m), 4.09 - 3.96 (2H, m), 4.35 - 4.23 (1H, m), 4.51 (2H, s), 6.59 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 403; HPLC tR = 2.02 min.

2-Chloro-4-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfanylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



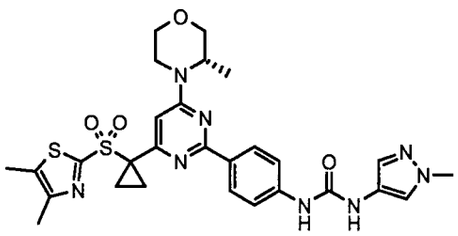
2-Chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7 g, 19.80 mmol) was added to 4,5-dimethylthiazole-2-thiol (3.16 g, 21.78 mmol) and DIPEA (5.17 mL, 29.70 mmol) in THF (10 mL) and the slurry stirred at RT for 7 hours. The solvent was removed under reduced pressure and the residue diluted with DCM and washed sequentially with water and saturated brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a yellow gum (7.95 g).

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 - 1.19 (3H, m), 2.23 (3H, d), 2.29 (3H, d), 3.16 - 3.20 (1H, td), 3.39 - 3.46 (1H, td), 3.55 - 3.59 (1H, dd), 3.71 (1H, d), 3.91 - 3.94 (2H, dd), 4.21 - 4.29 (3H, m), 6.80 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 371; HPLC tR = 2.31 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 81: 1-[4-[4-[1-[(4,5-Dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea



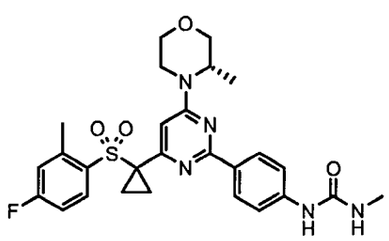
Phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.25 mmol), 1-methyl-1H-pyrazol-4-amine dihydrochloride (126 mg, 0.74 mmol) and DIPEA (0.428 mL, 2.48 mmol) were dissolved in dioxane (10 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 150 minutes in the microwave reactor and cooled to RT. The solvent was evaporated under reduced pressure, and the crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (70 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.77 - 1.72 (2H, m), 1.95 - 1.89 (2H, m), 2.37 (3H, s), 2.41 (3H, s), 3.24 - 3.14 (1H, m), 3.52 - 3.43 (1H, m), 3.65 - 3.59 (1H, m), 3.81 - 3.75 (4H, m), 4.00 - 3.95 (1H, m), 4.22 - 4.11 (1H, m), 4.51 - 4.41 (1H, m), 6.79 (1H, s), 7.38 (1H, s), 7.47 (2H, d), 7.77 (1H, s), 7.92 (2H, d), 8.36 (1H, s), 8.83 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 609; HPLC tR = 2.09 min.

The preparation of phenyl *N*-[4-[4-[1-[(4,5-dimethyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 82: 1-[4-[4-[1-(4-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea

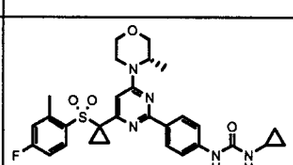
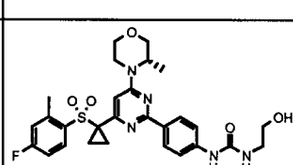
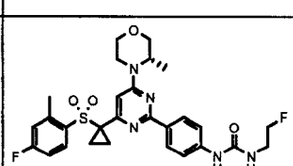


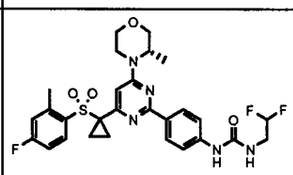
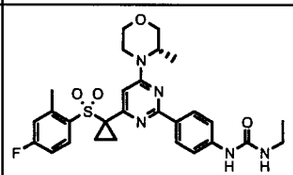
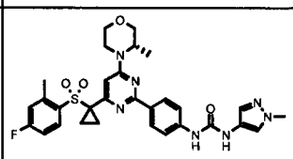
Phenyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.150 g, 0.25 mmol), triethylamine (0.104 mL, 0.75 mmol) and methylamine (0.75 mmol) were dissolved in dioxane (10 mL) and heated at 50°C overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.85 - 1.83 (2H, m), 2.44 (3H, s), 2.66 (3H, d), 3.13 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.42 (1H, s), 6.04 (1H, q), 6.62 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.40 (2H, d), 7.84 - 7.81 (3H, m), 8.71 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 540; HPLC tR= 2.34 min

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
82a		3-cyclopropyl-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	566	2.51
82b		1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	570	2.15
82c		3-(2-fluoroethyl)-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	572	2.50

Example	Structure	NAME	LCMS MH+	Retention time (min)
82d		3-(2,2-difluoroethyl)-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	590	2.62
82e		3-ethyl-1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	554	2.50
82f		1-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	606	2.36

Example 82a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.85 - 1.83 (2H, m), 2.44 (3H, s), 2.66 (3H, d), 3.13 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.42 (1H, s), 6.04 (1H, q), 6.62 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.40 (2H, d), 7.84 - 7.81 (3H, m), 8.71 (1H, s);

Example 82b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.85 - 1.83 (2H, m), 2.44 (3H, s), 3.20 - 3.09 (3H, m), 3.48 - 3.42 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.42 (1H, s), 4.73 (1H, t), 6.23 (1H, t), 6.62 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.39 (2H, d), 7.85 - 7.80 (3H, m), 8.77 (1H, s);

Example 82c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.85 - 1.83 (2H, m), 2.44 (3H, s), 3.13 (1H, ddd), 3.47 - 3.36 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.10 (1H, d), 4.55 - 4.40 (3H, m), 6.41 (1H, t), 6.63 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.40 (2H, d), 7.86 - 7.81 (3H, m), 8.78 (1H, s);

Example 82d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.86 - 1.83 (2H, m), 2.44 (3H, s), 3.13 (1H, ddd), 3.62 - 3.42 (4H, m), 3.74 (1H, d), 3.95 (1H, dd),

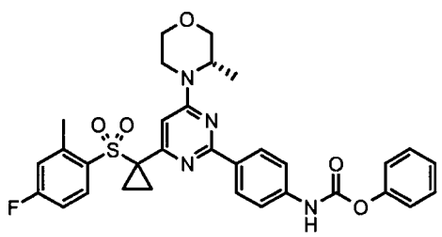
4.10 (1H, d), 4.42 (1H, s), 6.07 (1H, ddt), 6.50 (1H, t), 6.63 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.41 (2H, d), 7.86 - 7.80 (3H, m), 8.90 (1H, s);

Example 82e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.16 (3H, d), 1.63 - 1.60 (2H, m), 1.85 - 1.83 (2H, m), 2.44 (3H, s), 3.18 - 3.09 (3H, m), 3.44 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, ddd), 4.42 (1H, s), 6.13 (1H, t), 6.62 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.39 (2H, d), 7.84 - 7.81 (3H, m), 8.63 (1H, s);

Example 82f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.64 - 1.61 (2H, m), 1.86 - 1.83 (2H, m), 2.45 (3H, s), 3.14 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.79 (3H, s), 3.96 (1H, dd), 4.11 (1H, d), 4.43 (1H, s), 6.64 (1H, s), 7.18 (1H, ddd), 7.25 (1H, dd), 7.38 (1H, s), 7.45 (2H, d), 7.77 (1H, s), 7.88 - 7.81 (3H, m), 8.36 (1H, s), 8.81 (1H, s);

The preparation of phenyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

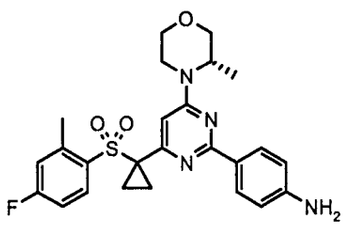


4-[4-[1-(4-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (1.80 g, 3.47 mmol) and sodium bicarbonate (2.91 g, 34.68 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.566 mL, 4.51 mmol) was added slowly and the reaction stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.73 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.65 - 1.62 (2H, m), 1.87 - 1.84 (2H, m), 2.45 (3H, s), 3.14 (1H, ddd), 3.49 - 3.42 (1H, m), 3.60 (1H, dd), 3.74

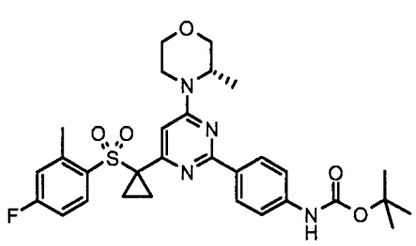
(1H, d), 3.95 (1H, dd), 4.12 (1H, d), 4.45 (1H, s), 6.67 (1H, s), 7.17 (1H, ddd), 7.30 - 7.23 (4H, m), 7.45 (2H, t), 7.54 (2H, d), 7.83 (1H, dd), 7.93 (2H, d), 10.40 (1H, s);
LCMS Spectrum: m/z (ES+) (M+H)+ = 603; HPLC tR= 3.15 min

4-[4-[1-(4-Fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



tert-Butyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.03 g, 3.48 mmol) was added to 6.0 N hydrogen chloride in propan-2-ol (30 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a white solid (1.80 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.04 (3H, d), 1.70 - 1.65 (2H, m), 1.89 - 1.86 (2H, m), 2.45 (3H, s), 3.22 (1H, ddd), 3.44 (1H, ddd), 3.59 (1H, dd), 3.75 (1H, d), 3.97 (1H, dd), 4.21 (1H, s), 4.50 (1H, s), 6.14 (2H, s), 6.70 (1H, s), 7.14 - 7.03 (2H, m), 7.21 (1H, t), 7.31 (1H, d), 7.82 (1H, dd), 7.93 (2H, d);
LCMS Spectrum: m/z (ES+) (M+H)+ = 483; HPLC tR= 2.67 min

tert-Butyl *N*-[4-[4-[1-(4-fluoro-2-methylphenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



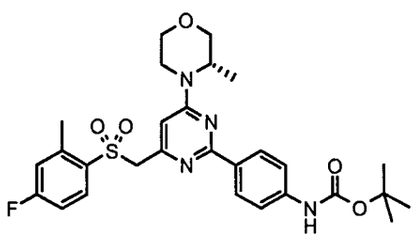
To *tert*-butyl *N*-[4-[4-[(4-fluoro-2-methylphenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.36 g, 6.04 mmol) in DMF (30 mL) was added rapidly sodium hydride (1.159 g, 24.14 mmol), this was stirred at RT for 10 minutes before

the slow addition 1,2-dibromoethane (2.081 mL, 24.14 mmol) in DMF (30 mL). The resulting suspension was stirred at RT for 1 hour. A further portion of sodium hydride (0.58 g, 12.07 mmol) and 1,2 dibromoethane (1.04 mL, 12.07 mmol) were rapidly added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a white foam (2.05 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.49 (9H, s), 1.63 - 1.60 (2H, m), 1.86 - 1.83 (2H, m), 2.44 (3H, s), 3.13 (1H, ddd), 3.45 (1H, ddd), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.11 (1H, d), 4.43 (1H, s), 6.65 (1H, s), 7.17 (1H, ddd), 7.24 (1H, dd), 7.47 (2H, d), 7.82 (1H, dd), 7.86 (2H, d), 9.50 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 583; HPLC tR= 3.17 min

tert-Butyl *N*-[4-[4-[(4-fluoro-2-methylphenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

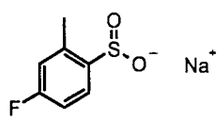


Sodium 4-fluoro-2-methylbenzenesulfinate (1.663 g, 7.84 mmol) and *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (4.0 g, 7.84 mmol) were dissolved in DMF (25 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid. This was partitioned between aqueous sodium thiosulphate solution (50 mL) and DCM (75 mL). The organics were purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a white foam (4.20 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.49 (9H, s), 2.65 (3H, s), 3.16 (1H, ddd), 3.48 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.11 (1H, d), 4.39 (1H, s), 4.67 (2H, s), 6.67 (1H, s), 7.15 (1H, ddd), 7.39 (1H, dd), 7.45 (2H, d), 7.68 (1H, dd), 7.80 (2H, d), 9.50 (1H, s);

LCMS Spectrum: m/z (ES+) (M+H)+ = 557; HPLC tR= 3.06 min

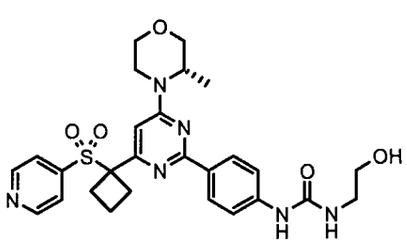
Sodium 4-fluoro-2-methylbenzenesulfinate



A solution of sodium sulfate (15.10 g, 119.82 mmol) in water (100 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (20.13 g, 239.65 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 4-Fluoro-2-methylbenzene-1-sulfonyl chloride (25 g, 119.82 mmol) was added portionwise to the solution and was stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and re-dissolved in ethanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (17.5 g). NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.46 (3H, s), 6.86 (1H, dd), 6.95 (1H, ddd), 7.66 (1H, dd);

The preparation of *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 83: 3-(2-Hydroxyethyl)-1-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea



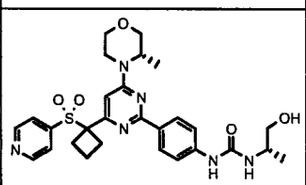
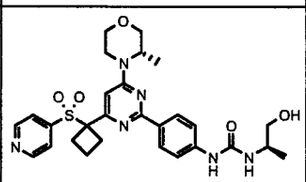
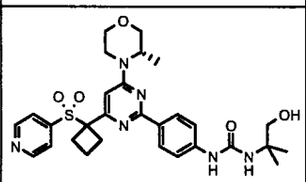
A solution of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) in NMP (2 mL) was treated with ethanolamine (11 mg, 0.18 mmol) and triethylamine (51 mg, 0.5 mmol) and stirred at RT overnight. The crude reaction mixture was purified by preparative HPLC, eluting

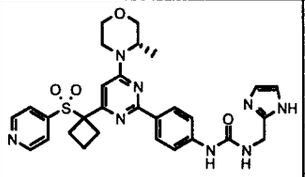
with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material (66mg).

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.20 - 1.22 (3H, m), 1.93 (1H, t), 2.11 - 2.16 (1H, m), 2.78 - 2.85 (2H, m), 3.09 - 3.19 (5H, m), 3.45 - 3.52 (3H, m), 3.63 - 3.66 (1H, m), 3.75 - 3.78 (1H, m), 3.97 (1H, d), 4.15 - 4.19 (1H, m), 4.51 (1H, s), 4.78 (1H, s), 6.26 (1H, t), 6.63 (1H, s), 7.35 (2H, d), 7.46 (2H, d), 7.68 (2H, d), 8.72 (2H, d), 8.80 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 553.48; HPLC tR = 1.93 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
83a		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	567.5	2.02
83b		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	567.5	2.02
83c		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	581.6	2.22

Example	Structure	NAME	LCMS MH+	Retention time (min)
83d		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]urea	589.5	1.43

Example 83a: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.07 - 1.09 (3H, m), 1.20 (3H, d), 1.91 - 1.93 (1H, m), 2.13 (1H, t), 2.78 - 2.85 (2H, m), 3.08 - 3.19 (3H, m), 3.38 - 3.41 (2H, m), 3.45 - 3.54 (1H, td), 3.60 - 3.82 (3H, m), 3.96 (1H, dd), 4.16 (1H, d), 4.50 (1H, s), 4.83 (1H, t), 6.09 - 6.11 (1H, m), 6.63 (1H, s), 7.34 (2H, d), 7.46 - 7.47 (2H, m), 7.68 (2H, d), 8.70 - 8.72 (3H, m)

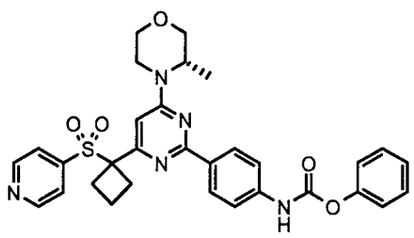
Example 83b: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.07 - 1.09 (3H, m), 1.20 (3H, d), 1.91 - 1.93 (1H, m), 2.13 (1H, t), 2.78 - 2.85 (2H, m), 3.08 - 3.19 (3H, m), 3.38 - 3.41 (2H, m), 3.45 - 3.54 (1H, td), 3.60 - 3.82 (3H, m), 3.96 (1H, dd), 4.16 (1H, d), 4.50 (1H, s), 4.83 (1H, t), 6.09 - 6.11 (1H, m), 6.63 (1H, s), 7.34 (2H, d), 7.46 - 7.47 (2H, m), 7.68 (2H, d), 8.70 - 8.72 (3H, m)

Example 83c: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.24 (6H, s), 1.91 - 1.93 (1H, m), 2.11 - 2.16 (1H, m), 2.77 - 2.84 (2H, m), 3.08 - 3.20 (3H, m), 3.39 (2H, d), 3.46 - 3.52 (1H, m), 3.62 - 3.66 (1H, m), 3.76 (1H, d), 3.95 - 3.99 (1H, m), 4.17 (1H, d), 4.51 (1H, s), 5.00 (1H, t), 6.00 (1H, s), 6.63 (1H, s), 7.29 - 7.32 (2H, m), 7.46 - 7.47 (2H, m), 7.65 - 7.67 (2H, m), 8.71 - 8.72 (3H, m)

Example 83d: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.92 (1H, q), 2.11 - 2.16 (1H, m), 2.81 (2H, s), 3.09 - 3.18 (3H, m), 3.49 (1H, t), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.17 (1H, d), 4.32 (2H, d), 4.51 (1H, s), 6.64 (2H, s), 6.84 (1H, s), 7.04 (1H, s), 7.38 (2H, d), 7.46 (2H, d), 7.69 (2H, d), 8.72 (2H, d), 8.92 (1H, s), 11.87 (1H, s)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]phenyl]carbamate



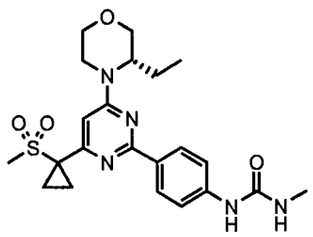
Phenyl chloroformate (0.241 mL, 1.92 mmol) was added dropwise to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline (894 mg, 1.92 mmol) and sodium bicarbonate (161 mg, 1.92 mmol) in dioxane (10 mL) at RT under air. The resulting solution was stirred at RT for 2hours. The reaction was evaporated to dryness and the residue was taken up in water (100 mL) and extracted with ethyl acetate (200 mL). The organic layer was washed with water, brine and then dried ($MgSO_4$). The solution was evaporated to dryness and the crude material was chromatographed on a silica, eluting with 50% ethyl acetate in isohexane, to give the desired material as a cream coloured solid (690 mg).

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17 - 1.23 (3H, m), 1.90 - 1.92 (1H, m), 2.00 (1H, s), 2.12 (1H, t), 2.77 - 2.83 (2H, m), 3.06 - 3.17 (3H, m), 3.47 - 3.50 (1H, m), 3.61 - 3.65 (1H, m), 3.75 (1H, d), 3.94 - 3.98 (1H, m), 4.15 (1H, d), 4.50 (1H, s), 5.54 (1H, d), 6.46 (1H, d), 6.53 (1H, s), 6.75 - 6.79 (2H, m), 7.15 - 7.19 (1H, m), 7.43 - 7.49 (2H, m), 7.49 (1H, d), 7.53 (1H, s), 8.70 - 8.72 (2H, m), 9.34 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 586.18; HPLC tR = 2.87 min.

The preparation of 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclobutyl)pyrimidin-2-yl]aniline was described earlier.

Example 84: 1-[4-[4-[(3*S*)-3-Ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea

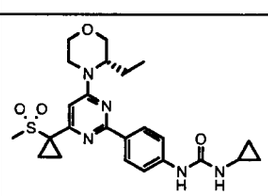


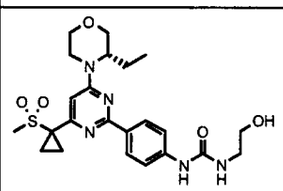
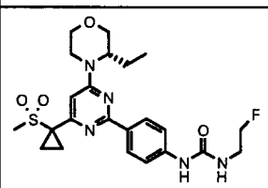
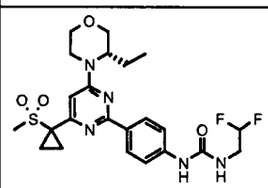
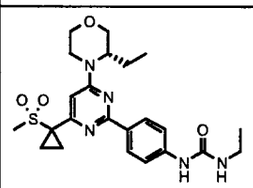
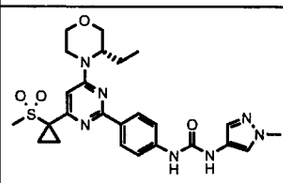
Phenyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (54.0 mg, 0.10 mmol), triethylamine (0.043 mL, 0.31 mmol) and methyl amine (-, 0.31 mmol) were dissolved in dioxane (10 mL) and heated at 50 °C over the weekend. The reaction was evaporated to dryness and was purified by preparative HPLC (Waters XTerra C18 column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford (S)-1-(4-(4-(3-ethylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)phenyl)-3-methylurea as a white solid.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.56 - 1.54 (2H, m), 1.69 - 1.64 (2H, m), 1.83 - 1.69 (2H, m), 2.66 (3H, d), 3.22 - 3.14 (1H, m), 3.27 (3H, s), 3.47 (1H, ddd), 3.55 (1H, dd), 3.87 (1H, d), 3.93 (1H, dd), 4.41 - 4.27 (2H, m), 6.07 (1H, q), 6.78 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.74 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 460; HPLC tR = 1.98 min.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
84a		3-cyclopropyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	486	2.15

Example	Structure	NAME	LCMS MH+	Retention time (min)
84b		1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	490	1.8
84c		1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	492	2.13
84d		3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	510	2.27
84e		3-ethyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea	474	2.13
84f		1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	526	2.03

Example 84a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.44 - 0.40 (2H, m), 0.65 - 0.64 (2H, m), 0.89 (3H, t), 1.57 - 1.53 (2H, m), 1.66 (2H, m), 1.68 - 1.64 (2H, m), 3.23 - 3.14 (1H, m), 3.50 - 3.44 (1H, m), 3.55 (1H, dd), 3.87 (1H, d), 3.94 - 3.92 (1H, m), 4.47 - 4.22 (2H, m), 6.44 (1H, s), 6.78 (1H, s), 7.51 (2H, d), 8.19 (2H, d), 8.54 (1H, s); 4 protons missing due to very weak sample!!

Example 84b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.57 - 1.53 (2H, m), 1.69 - 1.64 (2H, m), 1.83 - 1.71 (2H, m), 3.22 - 3.16 (3H, m), 3.27 (3H, s), 3.49 - 3.44 (3H, m), 3.55

(1H, dd), 3.87 (1H, d), 3.94 - 3.92 (1H, m), 4.39 - 4.24 (2H, m), 4.73 (1H, t), 6.25 (1H, t), 6.78 (1H, s), 7.49 (2H, d), 8.19 (2H, d), 8.80 (1H, s);

Example 84c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.58 - 1.54 (2H, m), 1.69 - 1.64 (2H, m), 1.83 - 1.69 (2H, m), 3.22 - 3.17 (1H, m), 3.29 (s, 3H), 3.49 - 3.37 (3H, m), 3.55 (1H, dd), 3.87 (1H, d), 3.94 - 3.92 (1H, m), 4.40 - 4.16 (2H, m), 4.48 (2H, dt), 6.44 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.81 (1H, s);

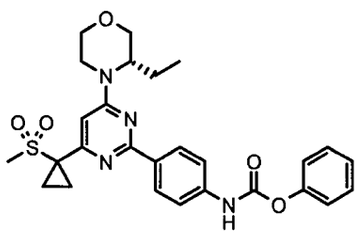
Example 84d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.57 - 1.54 (2H, m), 1.67 - 1.64 (2H, m), 1.83 - 1.69 (2H, m), 3.22 - 3.16 (1H, m), 3.29 (3H, s), 3.60 - 3.44 (4H, m), 3.87 (1H, d), 3.93 (1H, dd), 4.48 - 4.21 (2H, m), 6.07 (1H, tt), 6.53 (1H, t), 6.79 (1H, s), 7.51 (2H, d), 8.21 (2H, d), 8.92 (1H, s);

Example 84e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.07 (3H, t), 1.56 - 1.54 (2H, m), 1.68 - 1.65 (2H, m), 1.83 - 1.69 (2H, m), 3.22 - 3.09 (3H, m), 3.29 (3H, s), 3.47 (1H, ddd), 3.55 (1H, dd), 3.87 (1H, d), 3.93 (1H, dd), 4.40 - 4.24 (2H, m), 6.16 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.19 (2H, d), 8.66 (1H, s);

Example 84f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.57 - 1.54 (2H, m), 1.69 - 1.65 (2H, m), 1.84 - 1.70 (2H, m), 3.23 - 3.17 (1H, m), 3.47 (1H, ddd), 3.56 (1H, dd), 3.79 (3H, s), 3.88 (1H, d), 3.94 (1H, dd), 4.41 - 4.23 (2H, m), 6.80 (1H, s), 7.38 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.23 (2H, d), 8.39 (1H, s), 8.84 (1H, s); Methyl sulfone hidden under water peak (3H missing).

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

<u>Phenyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate</u>



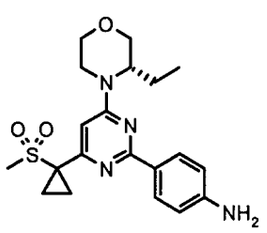
4-[4-[(3*S*)-3-Ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (as the hydrochloride salt) (0.43 g, 0.98 mmol) and sodium bicarbonate (0.823 g, 9.80 mmol)

were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.160 mL, 1.27 mmol) was added slowly and the reaction stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (0.46 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.58 - 1.55 (2H, m), 1.69 - 1.65 (2H, m), 1.84 - 1.70 (2H, m), 3.20 (1H, ddd), 3.27 (3H, s), 3.47 (1H, ddd), 3.56 (1H, dd), 3.87 (1H, d), 3.93 (1H, dd), 4.41 - 4.24 (2H, m), 6.82 (1H, s), 7.30 - 7.24 (3H, m), 7.45 (2H, t), 7.64 (2H, d), 8.29 (2H, d), 10.44 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 523; HPLC tR = 2.85 min.

4-[4-[(3*S*)-3-Ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline

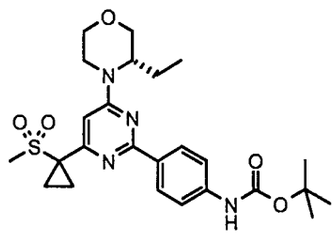


tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (0.5 g, 0.99 mmol) was added to 6.0 N hydrogen chloride in propan-2-ol (30 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a yellow solid (0.43 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.65 - 1.60 (2H, m), 1.75 - 1.67 (2H, m), 1.83 - 1.80 (2H, m), 3.24 (3H, s), 3.38 - 3.28 (1H, m), 3.52 - 3.46 (1H, m), 3.58 (1H, dd), 3.89 (1H, d), 3.96 (1H, dd), 4.48 - 4.33 (2H, m), 7.09 - 6.98 (3H, m), 8.21 - 8.08 (2H, m); NH2 missing;

LCMS Spectrum: m/z (ESI+) (M+H)+ = 403; HPLC tR = 2.23 min.

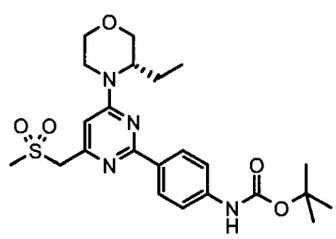
tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate



Sodium hydride (0.705 g, 14.69 mmol) was added rapidly to *tert*-butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate (1.75 g, 3.67 mmol) in DMF (30 mL) and the mixture stirred at RT for 10 minutes before the slow addition 1,2-dibromoethane (1.266 mL, 14.69 mmol) in DMF (30 mL). The resulting suspension was stirred at RT for 1 hour. The reaction was heated to 40°C and a further portion of sodium hydride (2.0 eq) and 1,2 dibromoethane (2.0 eq) were rapidly added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a yellow foam (0.30 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 (3H, t), 1.50 (9H, s), 1.57 - 1.54 (2H, m), 1.68 - 1.66 (2H, m), 1.83 - 1.70 (2H, m), 3.22 - 3.16 (1H, m), 3.50 - 3.44 (1H, m), 3.57 - 3.53 (1H, m), 3.87 (1H, d), 3.94 - 3.92 (1H, m), 4.38 - 4.24 (2H, m), 6.80 (1H, s), 7.57 (2H, d), 8.21 (2H, d), 9.55 (1H, s); methyl peak under water (3H missing).

tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidin-2-yl]phenyl]carbamate



tert-Butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(iodomethyl)pyrimidin-2-yl]phenyl]carbamate (2.0 g, 3.81 mmol) and sodium methanesulfinate (0.389 g, 3.81 mmol)

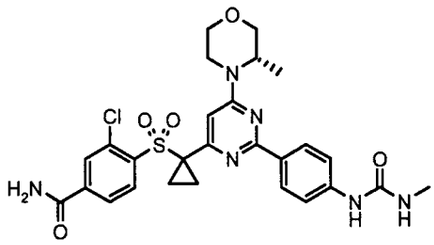
were dissolved in DMF (25 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid which was partitioned between aqueous sodium thiosulphate solution (50 mL) and DCM (75 mL). The layers were separated, the aquoes layer further extracted with DCM (75 mL), the combined organics purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a white foam (1.7 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90 (3H, t), 1.50 (9H, s), 1.73 - 1.64 (1H, m), 1.85 - 1.78 (1H, m), 3.24 - 3.18 (4H, m), 3.48 (1H, ddd), 3.57 (1H, dd), 3.89 (1H, d), 3.95 (1H, dd), 4.30 (2H, s), 4.48 (2H, s), 6.80 (1H, s), 7.57 (2H, d), 8.23 (2H, d), 9.55 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 477; HPLC tR = 2.67 min.

The preparation of *tert*-butyl *N*-[4-[4-[(3*S*)-3-ethylmorpholin-4-yl]-6-(iodomethyl)pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 85: 3-Chloro-4-[1-[2-[4-(methylcarbamoylamino)phenyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide

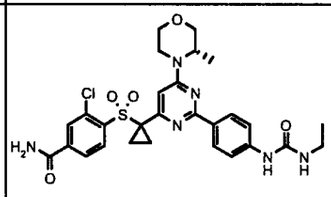
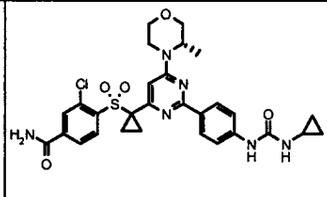
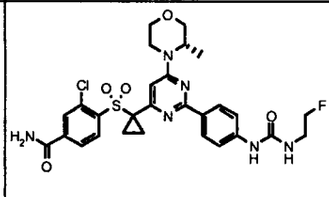
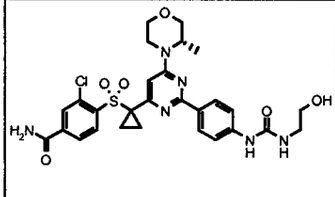
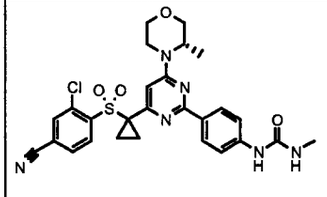


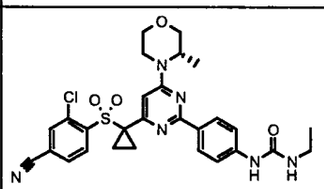
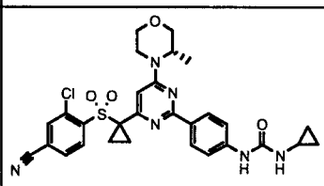
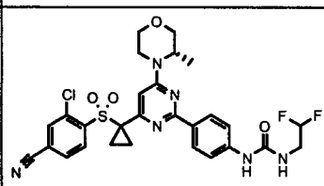
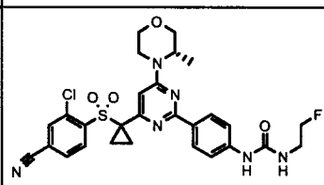
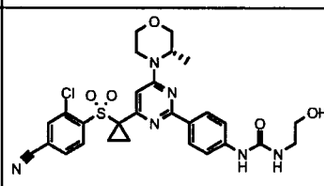
Methylamine (0.347 mL, 0.69 mmol) was added to phenyl *N*-[4-[4-[1-(4-carbamoyl-2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (150 mg, 0.23 mmol) and triethylamine (0.096 mL, 0.69 mmol) in DMF (0.714 mL) and resulting solution was stirred at 50°C for 2 hours. The crude mixture was purified by prep HPLC to give the desired material.

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.72 - 1.76 (2H, m), 1.99 - 2.02 (2H, m), 2.65 (3H, d), 3.09 - 3.17 (1H, m), 3.44 (1H, dt), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, d), 4.09 (1H, d), 4.41 (1H, s), 6.03 - 6.07 (1H, m), 6.61 (1H, s), 7.35 (2H, d), 7.67 (1H, s), 7.74 (2H, d), 7.88 (1H, dd), 7.99 (1H, d), 8.12 (1H, d), 8.20 (1H, s), 8.68 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 586; HPLC tR= 1.86 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(4-carbamoyl-2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
85a		3-chloro-4-[1-[2-[4-(ethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide	598 $(M-H)^-$	1.98
85b		3-chloro-4-[1-[2-[4-(cyclopropylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide	610 $(M-H)^-$	2.00
85c		3-chloro-4-[1-[2-[4-(2-fluoroethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide	616 $(M-H)^-$	1.98
85d		3-chloro-4-[1-[2-[4-(2-hydroxyethylcarbamoylamino)phenyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzamide	615	1.76
85e		1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	568	2.25

Example	Structure	NAME	LCMS MH+	Retention time (min)
85f		3-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	582	2.39
85g		1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	592 (M-H)	2.40
85h		1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	618	2.51
85i		1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	598 $(M-H)^-$	2.39
85j		1-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	598	2.06

Example 85a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.15 (3H, d), 1.72 - 1.76 (2H, m), 1.99 - 2.02 (2H, m), 3.09 - 3.18 (3H, m), 3.44 (1H, dt), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, d), 4.09 (1H, d), 4.41 (1H, s), 6.13 (1H, t), 6.61 (1H, s), 7.34 (2H, d), 7.67 (1H, s), 7.74 (2H, d), 7.88 (1H, dd), 7.99 (1H, d), 8.12 (1H, d), 8.21 (1H, s), 8.60 (1H, s)

Example 85b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.39 - 0.43 (2H, m), 0.62 - 0.67 (2H, m), 1.15 (3H, d), 1.72 - 1.76 (2H, m), 1.99 - 2.02 (2H, m), 2.54 - 2.55 (1H, m), 3.13 (1H, dt), 3.44 (1H, dt), 3.59 (1H, dd), 3.73 (1H, d), 3.94 (1H, dd), 4.09 (1H, d), 4.41 (1H, s), 6.40 (1H, d), 6.62 (1H, s), 7.35 (2H, d), 7.67 (1H, s), 7.74 (2H, d), 7.88 (1H, dd), 7.99 (1H, d), 8.12 (1H, d), 8.21 (1H, s), 8.48 (1H, s)

Example 85c: ^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.29 (3H, d), 1.54 - 1.56 (2H, m), 2.15 - 2.19 (2H, m), 3.27 (1H, dt), 3.51 - 3.62 (2H, m), 3.72 (1H, dd), 3.81 (1H, d), 4.02 (1H, dd), 4.08 (1H, d), 4.40 (1H, s), 4.46 (1H, t), 4.58 (1H, t), 5.63 (1H, t), 6.58 (1H, s), 7.17 (1H, s), 7.17 (1H, s), 7.24 (2H, d), 7.45 - 7.56 (2H, m), 7.64 - 7.69 (1H, m), 7.84 - 7.88 (2H, m), 7.90 (2H, d)

Example 85d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.72 - 1.76 (2H, m), 1.99 - 2.02 (2H, m), 3.09 - 3.12 (1H, m), 3.15 - 3.19 (2H, m), 3.43 - 3.48 (3H, m), 3.59 (1H, dd), 3.73 (1H, d), 3.93 (1H, dd), 4.09 (1H, d), 4.41 (1H, s), 4.72 (1H, t), 6.24 (1H, t), 6.61 (1H, s), 7.33 (2H, d), 7.66 (1H, s), 7.74 (2H, d), 7.88 (1H, dd), 7.99 (1H, d), 8.12 (1H, d), 8.21 (1H, s), 8.74 (1H, s)

Example 85e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.72 - 1.78 (2H, m), 2.00 - 2.03 (2H, m), 2.66 (3H, d), 3.10 - 3.15 (1H, m), 3.45 (1H, dt), 3.60 (1H, dd), 3.74 (1H, d), 4.06 (1H, q), 4.14 (1H, d), 4.47 (1H, s), 6.04 - 6.09 (1H, m), 6.66 (1H, s), 7.38 (2H, d), 7.66 (2H, d), 7.90 (1H, d), 8.02 (1H, d), 8.34 (1H, d), 8.71 (1H, s)

Example 85f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.18 (3H, d), 1.73 - 1.77 (2H, m), 1.99 - 2.03 (2H, m), 3.09 - 3.16 (2H, m), 3.16 - 3.19 (1H, m), 3.45 (1H, dt), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, d), 4.47 (1H, s), 6.16 (1H, t), 6.66 (1H, s), 7.37 (2H, d), 7.66 (2H, d), 7.90 (1H, dd), 8.02 (1H, d), 8.35 (1H, d), 8.62 (1H, s)

Example 85g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.67 (2H, m), 1.18 (3H, d), 1.73 - 1.77 (2H, m), 2.00 - 2.03 (2H, m), 2.53 - 2.59 (1H, m), 3.11 - 3.18 (1H, m), 3.45 (1H, dt), 3.58 - 3.62 (1H, m), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, d), 4.47 (1H, s), 6.42 (1H, d), 6.66 (1H, s), 7.38 (2H, d), 7.66 (2H, d), 7.90 (1H, dd), 8.02 (1H, d), 8.35 (1H, d), 8.50 (1H, s)

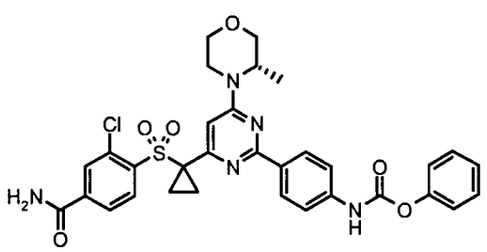
Example 85h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.73 - 1.77 (2H, m), 2.00 - 2.03 (2H, m), 3.15 (1H, dt), 3.42 - 3.51 (1H, m), 3.54 - 3.62 (3H, m), 3.74 (1H, d), 3.95 (1H, dd), 4.15 (1H, d), 4.47 (1H, s), 6.07 (1H, app t), 6.53 (1H, t), 6.67 (1H, s), 7.39 (2H, d), 7.68 (2H, d), 7.90 (1H, dd), 8.02 (1H, d), 8.35 (1H, d), 8.89 (1H, s)

Example 85i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.73 - 1.77 (2H, m), 2.00 - 2.03 (2H, m), 3.15 (1H, dt), 3.39 (1H, q), 3.42 - 3.48 (2H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.96 (1H, dd), 4.14 (1H, d), 4.42 (1H, t), 4.48 (1H, s), 4.53 (1H, t), 6.44 (1H, t), 6.66 (1H, s), 7.38 (2H, d), 7.67 (2H, d), 7.90 (1H, dd), 8.02 (1H, d), 8.35 (1H, d), 8.77 (1H, s)

Example 85j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.73 - 1.77 (2H, m), 2.00 - 2.03 (2H, m), 3.14 - 3.20 (3H, m), 3.43 - 3.48 (3H, m), 3.60 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.14 (1H, d), 4.48 (1H, s), 4.73 (1H, t), 6.26 (1H, t), 6.66 (1H, s), 7.37 (2H, d), 7.66 (2H, d), 7.90 (1H, dd), 8.02 (1H, d), 8.35 (1H, d), 8.77 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-(4-carbamoyl-2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(4-carbamoyl-2-chlorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

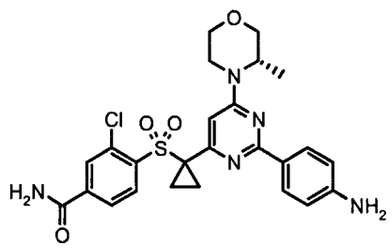


Sodium bicarbonate (0.263 g, 3.12 mmol) was added to 4-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-3-chlorobenzamide (1.1 g, 2.08 mmol), in 1,4-dioxane (10.15 mL) and to the resulting suspension was added phenyl chloroformate (0.262 mL, 2.08 mmol) dropwise over 2 minutes. The reaction was stirred at RT for 2 hours then evaporated to dryness and the residue redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as a beige solid (0.9 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.16 (3H, d), 1.73 - 1.77 (2H, m), 1.99 - 2.03 (2H, m), 3.12 - 3.17 (1H, m), 3.40 - 3.47 (1H, m), 3.57 - 3.61 (1H, m), 3.73 (1H, d), 3.91 - 3.96 (1H, m), 4.06 - 4.10 (1H, m), 4.44 (1H, s), 6.67 (1H, s), 7.24 - 7.30 (2H, m), 7.45 (2H, t), 7.50 (2H, d), 7.85 (2H, d), 7.88 - 7.90 (1H, m), 8.00 (1H, d), 8.13 (1H, d), 8.22 (1H, s), 10.40 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 648; HPLC tR= 2.62 min.

4-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-3-chlorobenzamide

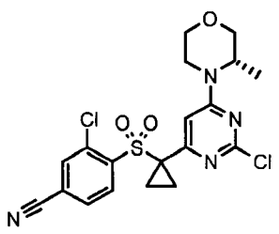


Bis(triphenylphosphine)palladium(II) chloride (0.271 g, 0.39 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.199 g, 10.04 mmol) and 3-chloro-4-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile (3.5 g, 7.72 mmol) and 2M aqueous solution of sodium carbonate (11.58 mL, 23.16 mmol) in a solvent mixture of DME (20 mL), ethanol (10 mL) and water (10 mL) and the resulting mixture stirred at 95°C for 16 hours. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (2 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a brown solid (1.1 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.71 - 1.73 (2H, m), 1.97 - 2.01 (2H, m), 3.06 - 3.13 (1H, m), 3.37 - 3.45 (1H, m), 3.58 (1H, dd), 3.72 (1H, d), 3.92 - 3.94 (1H, m), 4.04 - 4.08 (1H, m), 4.37 (1H, s), 5.48 (2H, s), 6.50 (1H, s), 7.58 (2H, d), 7.89 (1H, dd), 8.00 (2H, d), 8.11 (1H, d), 8.21 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 528; HPLC tR= 1.99 min.

3-Chloro-4-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylbenzonitrile

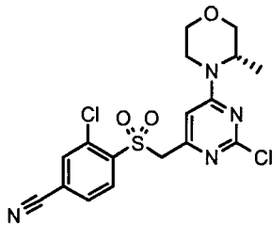


1,2-Dibromoethane (1.654 ml, 19.19 mmol) was added to 3-chloro-4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]benzonitrile (4.1 g, 9.60 mmol), sodium hydroxide (50% w/w) (9.60 mL, 95.95 mmol) and tetrabutylammonium bromide (0.619 g, 1.92 mmol) in DCM and the resulting solution stirred at 40°C for 5 hours. The reaction mixture was washed sequentially with water (200 mL) and saturated brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 50% ethyl acetate in DCM, to give the desired material as a cream solid (3.50 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.68 - 1.72 (2H, m), 1.95 - 1.98 (2H, m), 3.11 - 3.17 (1H, m), 3.29 - 3.30 (1H, m), 3.39 (1H, dt), 3.54 (1H, dd), 3.69 (1H, d), 3.91 (1H, dd), 4.30 (1H, s), 6.76 (1H, s), 8.03 (2H, s), 8.33 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 453; HPLC tR = 2.41 min.

3-Chloro-4-[[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]methylsulfonyl]benzonitrile

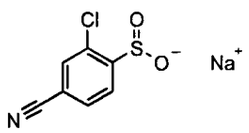


Sodium 2-chloro-4-cyanobenzenesulfinate (4.43 g, 19.80 mmol) was added in one portion to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (7 g, 19.80 mmol) in acetonitrile (99 mL) and the resulting suspension stirred at 80°C for 6 hours. The reaction mixture was evaporated to dryness, redissolved in DCM (200 mL) and washed with water (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in DCM, to give the desired material as a cream solid (6.20 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 3.15 - 3.21 (1H, m), 3.43 (1H, dt), 3.58 (1H, dd), 3.72 (1H, d), 3.93 (2H, m), 4.24 (1H, s), 4.86 (2H, s), 6.87 (1H, s), 7.96 (1H, d), 8.06 (1H, dd), 8.43 (1H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 427; HPLC tR = 2.28 min.

Sodium 2-chloro-4-cyanobenzenesulfinate



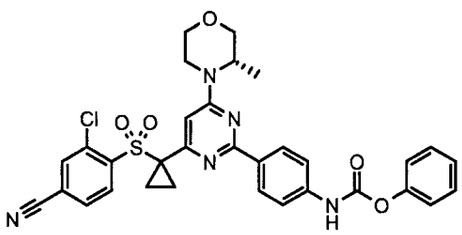
A solution of sodium sulfite (6.02 g, 47.74 mmol) in water (100 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (8.02 g, 95.48 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 10 minutes. 2-Chloro-4-cyanobenzene-1-sulfonyl chloride (11.27 g, 47.74 mmol) was added dropwise to the solution and was stirred at 50°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in ethanol (200 mL). The suspension was allowed to stir at RT for 20 minutes. The suspension was filtered and the filtrate evaporated to afford a white solid, this was stirred with acetonitrile (50 mL) and then filtered to afford the desired material as a white solid (10.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.80 - 7.77 (2H, m), 7.84 (1H, d)

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



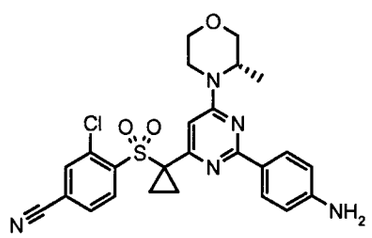
Sodium bicarbonate (1.400 g, 16.67 mmol) was added to 4-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-3-chlorobenzonitrile (1.7 g, 3.33 mmol), in 1,4-dioxane (16.25 mL) and to the resulting suspension was added phenyl chloroformate (0.42 mL, 3.33 mmol) dropwise over 2 minutes. The reaction was stirred at RT for 2 hours then evaporated to dryness, the residue redissolved in DCM (20 mL), and washed

with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as a cream solid (1.4 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.76 - 1.80 (2H, m), 2.01 - 2.04 (2H, m), 3.14 - 3.19 (1H, m), 3.43 - 3.48 (1H, m), 3.59 - 3.62 (1H, m), 3.74 (1H, d), 3.94 - 3.97 (1H, m), 4.16 (1H, d), 4.49 (1H, s), 6.71 (1H, s), 7.24 - 7.30 (3H, m), 7.45 (2H, t), 7.53 (2H, d), 7.77 (2H, d), 7.90 - 7.92 (1H, m), 8.02 (1H, d), 8.35 (1H, d), 10.44 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 630; HPLC tR= 3.02 min.

4-[1-[2-(4-Aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonyl-3-chlorobenzonitrile

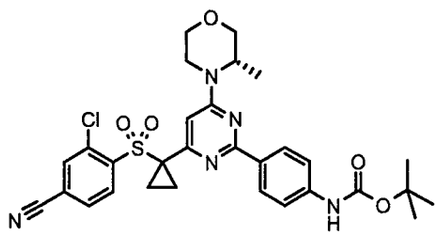


tert-Butyl *N*-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.4 g, 5.57 mmol) was dissolved in methanol (17.86 mL) and to this was added 6 N hydrogen chloride in propan-2-ol (10 mL) and the reaction stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material as a white solid (3.50 g). The material was used without further purification.

MR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.76 - 1.79 (2H, m), 2.01 - 2.04 (2H, m), 3.18 - 3.24 (1H, m), 3.42 - 3.48 (1H, m), 3.60 (1H, dd), 3.74 - 3.77 (1H, m), 3.94 - 3.98 (1H, m), 4.20 (1H, s), 4.51 (1H, s), 6.76 (1H, s), 7.11 - 7.14 (2H, m), 7.86 (2H, d), 7.95 - 7.97 (2H, m), 8.07 (1H, d), 8.37 (1H, d)

LCMS Spectrum: m/z (ES+) (M+H)+ = 510; HPLC tR= 2.49 min.

tert-Butyl *N*-[4-[4-[1-(2-chloro-4-cyanophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

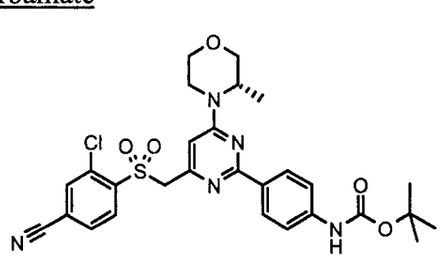


Sodium hydride (1.282 g, 26.71 mmol) was added rapidly to *tert*-butyl *N*-[4-[4-[(2-chloro-4-cyanophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.9 g, 6.68 mmol) in DMF (70 mL) and the mixture stirred at RT for 10 minutes before the slow addition 1,2-dibromoethane (2.302 mL, 26.71 mmol) in DMF (70 mL) at RT. The resulting suspension was stirred at RT for 90 minutes. A further portion of sodium hydride (1.0 eq) and 1,2 dibromoethane (1.0 eq) were rapidly added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (3.40 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.50 (9H, s), 1.73 - 1.78 (2H, m), 1.99 - 2.05 (2H, m), 3.12 - 3.18 (1H, m), 3.45 (1H, t), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.15 (1H, d), 4.48 (1H, s), 6.68 (1H, s), 7.45 (2H, d), 7.69 (2H, d), 7.90 (1H, d), 8.01 (1H, d), 8.35 (1H, s), 9.52 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 610; HPLC tR= 3.10 min.

tert-Butyl *N*-[4-[4-[(2-chloro-4-cyanophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



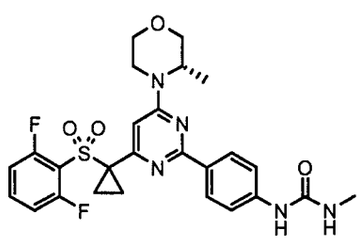
Sodium 2-chloro-4-cyanobenzenesulfinate (1.753 g, 7.84 mmol) and *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (4 g, 7.84 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid which was partitioned between water (50 mL) and DCM (75 mL). The layers were separated, the aqueous layer extracted with DCM (75 mL) and the combined organics concentrated *in vacuo* to give a yellow solid. This was rapidly stirred with ether (100 mL), to afford the desired material as an off white solid (3.90 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.49 (9H, s), 3.19 (1H, dt), 3.48 (1H, dt), 3.63 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.13 (1H, d), 4.41 (1H, s), 4.97 (2H, s), 6.79 (1H, s), 7.43 (2H, d), 7.61 (2H, d), 7.86 (1H, d), 7.91 (1H, dd), 8.53 (1H, d), 9.54 (1H, s)

LCMS Spectrum: m/z (ES+) (M+H)+ = 583.94; HPLC tR= 3.07 min.

The preparation of *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 86: 1-[4-[4-[1-(2,6-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea



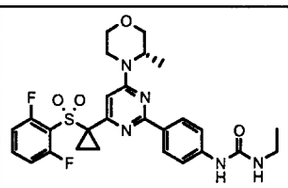
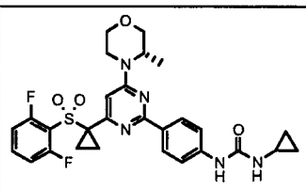
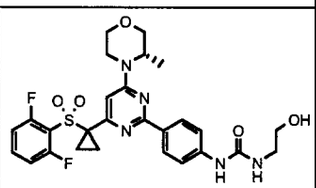
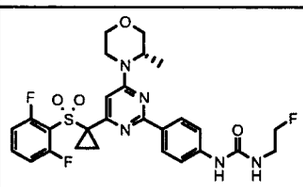
Phenyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (0.15 g, 0.25 mmol), triethylamine (0.103 mL, 0.74 mmol) and methylamine (0.74 mmol) were dissolved in dioxane (10 mL) and stirred at RT overnight. The reaction was evaporated to dryness and was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid.

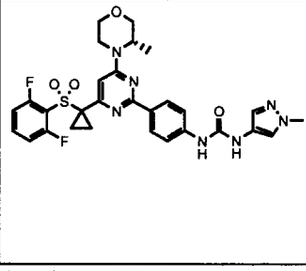
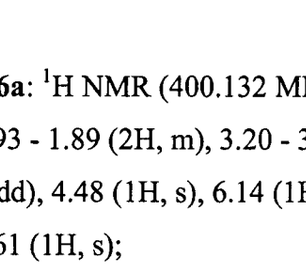
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.69 - 1.67 (2H, m), 1.94 - 1.91 (2H, m), 2.66 (3H, d), 3.17 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.75 (1H, d),

3.96 (1H, dd), 4.16 (1H, d), 4.49 (1H, s), 6.04 (1H, q), 6.74 (1H, s), 7.25 (2H, t), 7.35 (2H, d), 7.80 - 7.73 (3H, m), 8.69 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 544; HPLC tR = 1.82 min

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
86a		1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	558	2.43
86b*		3-cyclopropyl-1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	570	2.44
86c*		1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	574	2.07
86d*		1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	576	2.42

Example	Structure	NAME	LCMS MH+	Retention time (min)
86e*		3-(2,2-difluoroethyl)-1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	594	2.55
86f*		1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	610	2.28

* No triethylamine added

Example 86a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.20 (3H, d), 1.71 - 1.65 (2H, m), 1.93 - 1.89 (2H, m), 3.20 - 3.09 (3H, m), 3.47 (1H, ddd), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (2H, ddd), 4.48 (1H, s), 6.14 (1H, t), 6.74 (1H, s), 7.25 (2H, t), 7.35 (2H, d), 7.80 - 7.73 (3H, m), 8.61 (1H, s);

Example 86b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.43 - 0.39 (2H, m), 0.67 - 0.62 (2H, m), 1.20 (3H, d), 1.71 - 1.65 (2H, m), 1.92 - 1.91 (2H, m), 2.57 - 2.54 (1H, m), 3.17 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.40 (1H, s), 6.75 (1H, s), 7.25 (2H, t), 7.36 (2H, d), 7.80 - 7.73 (3H, m), 8.49 (1H, s);

Example 86c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.71 - 1.65 (2H, m), 1.94 - 1.88 (2H, m), 3.21 - 3.14 (3H, m), 3.50 - 3.44 (3H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 4.72 (1H, t), 6.23 (1H, t), 6.74 (1H, s), 7.25 (2H, t), 7.34 (2H, d), 7.80 - 7.73 (3H, m), 8.75 (1H, s);

Example 86d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.69 - 1.67 (2H, m), 1.93 - 1.89 (2H, m), 3.17 (1H, ddd), 3.50 - 3.36 (3H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.47 (2H, tt), 4.49 (1H, s), 6.41 (1H, t), 6.75 (1H, s), 7.25 (2H, t), 7.36 (2H, d), 7.80 - 7.74 (3H, m), 8.76 (1H, s);

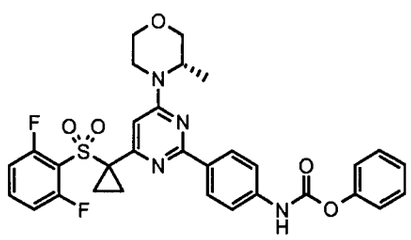
Example 86e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.69 - 1.67 (2H, m), 1.93 - 1.89 (2H, m), 3.17 (1H, ddd), 3.59 - 3.44 (3H, m), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd),

4.16 (1H, d), 4.48 (1H, s), 6.07 (1H, tt), 6.51 (1H, t), 6.75 (1H, s), 7.25 (2H, t), 7.37 (2H, d), 7.80 - 7.72 (3H, m), 8.87 (1H, s);

Example 86f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.70 - 1.68 (2H, m), 1.94 - 1.89 (2H, m), 3.18 (1H, ddd), 3.47 (1H, ddd), 3.63 (1H, dd), 3.76 (1H, d), 3.79 (3H, s), 3.97 (1H, dd), 4.16 (1H, d), 4.49 (1H, s), 6.76 (1H, s), 7.26 (2H, t), 7.41 - 7.38 (3H, m), 7.80 - 7.73 (4H, m), 8.36 (1H, s), 8.79 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

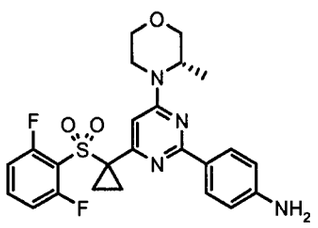


4-[4-[1-(2,6-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (as the hydrochloride salt) (1.67 g, 3.19 mmol) and sodium bicarbonate (2.68 g, 31.93 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.521 mL, 4.15 mmol) was added slowly and the reaction stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (1.4 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.72 - 1.66 (2H, m), 1.93 - 1.92 (2H, m), 3.18 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.76 (1H, d), 3.96 (1H, dd), 4.18 (1H, d), 4.50 (1H, s), 6.79 (1H, s), 7.30 - 7.23 (5H, m), 7.45 (2H, t), 7.49 (2H, d), 7.79 - 7.72 (1H, m), 7.84 (2H, d), 10.38 (1H, s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 607; HPLC tR = 3.02 min.

4-[4-[1-(2,6-Difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline

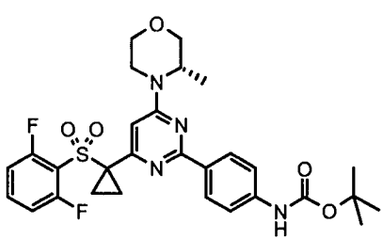


tert-Butyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (2.15 g, 3.66 mmol) was added to 6.0 N hydrogen chloride in propan-2-ol (30 mL) and stirred for 2 hours at RT. The crude solution was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a white solid (1.67 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.04 (3H, d), 1.76 - 1.72 (2H, m), 1.98 - 1.90 (2H, m), 3.24 (1H, ddd), 3.46 (1H, ddd), 3.60 (1H, dd), 3.76 (1H, d), 3.97 (1H, dd), 4.25 (1H, s), 4.53 (1H, s), 6.85 (1H, s), 7.15 - 7.02 (2H, m), 7.29 (2H, t), 7.84 - 7.77 (1H, m), 7.91 (2H, d); NH2 not visible)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 487; HPLC tR = 2.45 min.

tert-Butyl *N*-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



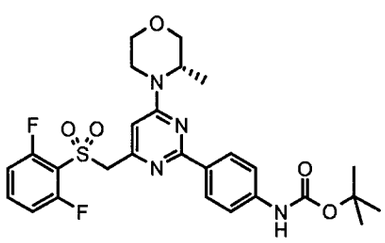
Sodium hydride (1.027 g, 21.41 mmol) was added rapidly to *tert*-butyl *N*-[4-[4-[(2,6-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3.0 g, 5.35 mmol) in DMF (70 mL) and stirred at RT for 10 minutes before the slow addition 1,2-dibromoethane (1.845 mL, 21.41 mmol) in DMF (70 mL). The resulting suspension was stirred at RT for 1.5 hours. A further portion of sodium hydride (2.0 eq) and 1,2 dibromoethane (2.0 eq) were rapidly added and the reaction was stirred for a further 30 minutes. The reaction mixture was quenched with water (50 mL), extracted with

ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford brown gum. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% ethyl acetate in isohexane, to afford a yellow foam. This was dissolved in 40% ethyl acetate in isohexane and upon stirring the desired material precipitated as a white solid (2.15 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.49 (9H, s), 1.71 - 1.65 (2H, m), 1.93 - 1.90 (2H, m), 3.17 (1H, ddd), 3.47 (1H, ddd), 3.62 (1H, dd), 3.75 (1H, d), 3.96 (1H, dd), 4.16 (1H, d), 4.48 (1H, s), 6.76 (1H, s), 7.25 (2H, t), 7.42 (2H, d), 7.80 - 7.72 (3H, m), 9.49 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 587; HPLC tR = 3.12 min.

tert-Butyl *N*-[4-[4-[(2,6-difluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



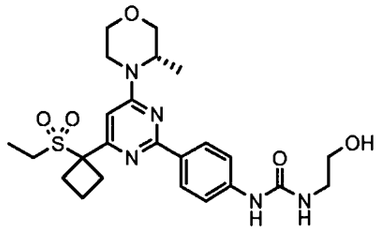
Sodium 2,6-difluorobenzenesulfonate (1.270 g, 5.88 mmol) and *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (3 g, 5.88 mmol) were dissolved in DMF (50 mL) and stirred for 1 hour at RT. The solvent was evaporated to afford a yellow solid which was partitioned between water (50 mL) and DCM (75 mL). The layers were separated, the aqueous layer extracted with DCM (75 mL) and the combined organics concentrated *in vacuo* to give a yellow solid. The solid was rapidly stirred with ether (100 mL), to afford a solid which was collected by filtration and dried under vacuum to give the desired material as an off white solid (3.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.49 (9H, s), 3.20 (1H, ddd), 3.49 (1H, ddd), 3.64 (1H, dd), 3.77 (1H, d), 3.98 (1H, dd), 4.14 (1H, d), 4.42 (1H, s), 4.78 (2H, s), 6.81 (1H, s), 7.32 (2H, t), 7.42 (2H, d), 7.73 (2H, d), 7.85 - 7.78 (1H, m), 9.50 (1H, s);

LCMS Spectrum: m/z (ESI+) (M+H)+ = 561; HPLC tR = 2.84 min.

The preparation of *tert*-butyl *N*-[4-[4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate was described earlier.

Example 87: 1-[4-[4-(1-Ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea

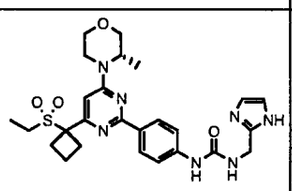


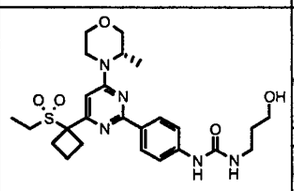
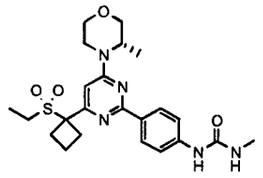
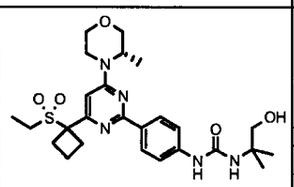
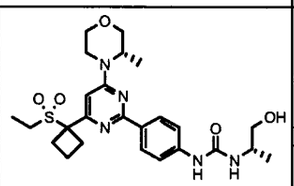
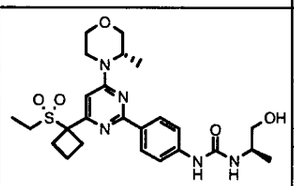
Ethanolamine (0.023 mL, 0.37 mmol) was added in one portion to phenyl *N*-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (101 mg, 0.19 mmol) and triethylamine (0.078 mL, 0.56 mmol) in NMP (2 mL) at RT and stirred for a period of 16 hours. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to afford desired material as a cream solid (71 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.23 (d, 3H), 1.86 - 1.97 (m, 1H), 2.01 - 2.11 (m, 1H), 2.77 - 2.87 (m, 2H), 2.90 - 2.99 (m, 4H), 3.16 - 3.25 (m, 2H), 3.46 (q, 1H), 3.52 (dd, 3H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.20 - 4.28 (m, 1H), 4.52 - 4.61 (m, 1H), 4.77 (t, 1H), 6.28 (t, 1H), 6.72 (s, 1H), 7.50 (d, 2H), 8.22 (d, 2H), 8.84 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 504; HPLC tR = 1.79 min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
87a		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)urea	540	1.87

Example	Structure	NAME	LCMS MH+	Retention time (min)
87b		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea	518	1.83
87c		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	474	1.95
87d		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-hydroxy-2-methylpropan-2-yl)urea	532	2.08
87e		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea	518	1.88
87f		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea	518	1.89

Example 87a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.23 (d, 3H), 1.87 - 1.97 (m, 1H), 2.02 - 2.10 (m, 1H), 2.77 - 2.87 (m, 2H), 2.90 - 3.01 (m, 4H), 3.17 - 3.25 (m, 1H), 3.50 (td, 1H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.21 - 4.29 (m, 1H), 4.33 (d, 2H), 4.52 - 4.61 (m, 1H), 6.65 (t, 1H), 6.73 (s, 1H), 6.82 - 6.86 (m, 1H), 7.02 - 7.07 (m, 1H), 7.52 (d, 2H), 8.24 (d, 2H), 8.97 (s, 1H), 11.87 (s, 1H)

Example 87b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.23 (d, 3H), 1.60 (quintet, 2H), 1.86 - 1.97 (m, 1H), 2.01 - 2.11 (m, 1H), 2.77 - 2.87 (m, 2H), 2.90 - 2.99 (m, 4H), 3.14 - 3.25 (m, 3H), 3.47 (q, 2H), 3.49 - 3.54 (m, 1H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H),

4.20 - 4.30 (m, 1H), 4.51 - 4.61 (m, 1H), 4.52 (t, 1H), 6.23 (t, 1H), 6.72 (s, 1H), 7.50 (d, 2H), 8.22 (d, 2H), 8.75 (s, 1H)

Example 87c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.23 (d, 3H), 1.85 - 1.97 (m, 1H), 2.00 - 2.10 (m, 1H), 2.66 (d, 3H), 2.77 - 2.87 (m, 2H), 2.90 - 3.00 (m, 4H), 3.21 (td, 1H), 3.50 (td, 1H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.20 - 4.29 (m, 1H), 4.52 - 4.60 (m, 1H), 6.09 (q, 1H), 6.72 (s, 1H), 7.51 (d, 2H), 8.22 (d, 2H), 8.79 (s, 1H)

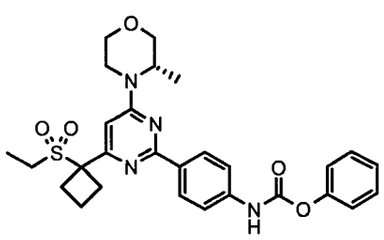
Example 87d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.23 (d, 3H), 1.24 (s, 6H), 1.86 - 1.97 (m, 1H), 2.01 - 2.11 (m, 1H), 2.76 - 2.87 (m, 2H), 2.90 - 3.01 (m, 4H), 3.22 (dd, 1H), 3.39 (d, 2H), 3.50 (td, 1H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.19 - 4.30 (m, 1H), 4.51 - 4.61 (m, 1H), 5.00 (t, 1H), 6.02 (s, 1H), 6.72 (s, 1H), 7.46 (d, 2H), 8.21 (d, 2H), 8.77 (s, 1H)

Example 87e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.09 (d, 3H), 1.15 (t, 3H), 1.23 (d, 3H), 1.86 - 1.97 (m, 1H), 2.01 - 2.11 (m, 1H), 2.77 - 2.87 (m, 2H), 2.90 - 3.00 (m, 4H), 3.21 (td, 1H), 3.32 - 3.42 (m, 2H), 3.50 (td, 1H), 3.65 (dd, 1H), 3.68 - 3.74 (m, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.20 - 4.29 (m, 1H), 4.52 - 4.61 (m, 1H), 4.83 (t, 1H), 6.12 (d, 1H), 6.72 (s, 1H), 7.49 (d, 2H), 8.22 (d, 2H), 8.75 (s, 1H)

Example 87f: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.08 (d, 3H), 1.15 (t, 3H), 1.23 (d, 3H), 1.86 - 1.97 (m, 1H), 2.01 - 2.11 (m, 1H), 2.77 - 2.87 (m, 2H), 2.90 - 3.00 (m, 4H), 3.21 (td, 1H), 3.32 - 3.42 (m, 2H), 3.50 (td, 1H), 3.65 (dd, 1H), 3.68 - 3.74 (m, 1H), 3.76 - 3.79 (m, 1H), 3.98 (dd, 1H), 4.20 - 4.29 (m, 1H), 4.52 - 4.61 (m, 1H), 4.83 (t, 1H), 6.12 (d, 1H), 6.72 (s, 1H), 7.48 (d, 2H), 8.22 (d, 2H), 8.75 (s, 1H)

The preparation of phenyl *N*-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below:

Phenyl *N*-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

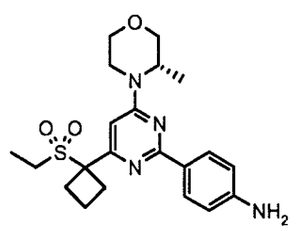


Phenyl chloroformate (0.211 mL, 1.68 mmol) was added dropwise to 4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (700 mg, 1.68 mmol) and sodium hydrogen carbonate (141 mg, 1.68 mmol) in dioxane (20 mL) and the resulting suspension stirred at RT for 3 hours. The reaction mixture was evaporated and DCM (50 mL) added and washed sequentially with water (20 mL) and saturated brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford desired material as a yellow oil which solidified on standing. (930 mg)

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.16 (t, 3H), 1.25 (d, 3H), 1.87 - 1.98 (m, 1H), 2.02 - 2.12 (m, 1H), 2.78 - 2.88 (m, 2H), 2.92 - 3.00 (m, 4H), 3.23 (td, 1H), 3.48 - 3.55 (m, 1H), 3.66 (dd, 1H), 3.78 (d, 1H), 3.99 (dd, 1H), 4.21 - 4.32 (m, 1H), 4.53 - 4.64 (m, 1H), 6.76 (s, 1H), 7.24 - 7.32 (m, 3H), 7.46 (dt, 2H), 7.64 (d, 2H), 8.32 (d, 2H), 10.44 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 537.15; HPLC tR = 2.95 min.

4-[4-(1-Ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



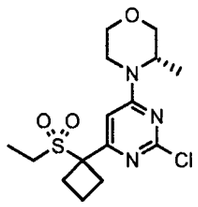
Bis(triphenylphosphine)palladium(II) chloride (0.137 g, 0.19 mmol) was added in one portion to 2-chloro-4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (1.4 g, 3.89 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.852 g, 3.89 mmol) and sodium carbonate (9.73 ml, 19.45 mmol) in a DMF / DME / water / ethanol solution at RT under nitrogen. The reaction mixture was thoroughly degassed and was stirred at 80°C for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (50 mL), and washed sequentially with water (50 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 100% ethyl acetate in DCM, to afford desired material as a yellow dry film (1.536 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.22 (d, 3H), 1.85 - 1.96 (m, 1H), 2.02 - 2.11 (m, 1H), 2.75 - 2.86 (m, 2H), 2.89 - 2.99 (m, 4H), 3.19 (td, 1H), 3.50 (td,

1H), 3.64 (dd, 1H), 3.76 (d, 1H), 3.97 (dd, 2H), 4.16 - 4.25 (m, 1H), 5.56 (s, 2H), 6.59 - 6.63 (m, 3H), 8.06 (d, 2H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 417.25; HPLC tR = 2.03 min.

2-Chloro-4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



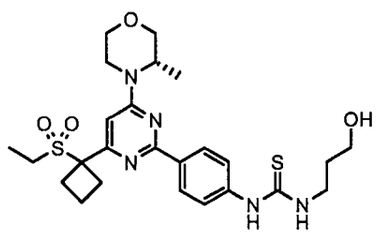
Sodium hydroxide (50% w/w solution) (27.4 g, 683.96 mmol) was added to 2-chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (3.977 g, 12.44 mmol), 1,3-dibromopropane (3.79 mL, 37.31 mmol) and tetrabutylammonium bromide (0.401 g, 1.24 mmol) in toluene (200 mL) and the resulting suspension stirred at 45°C for 3 hours. The organics were washed with water twice, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in DCM, to afford desired material as a colourless dry film (1.47 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.13 - 1.19 (m, 3H), 1.22 (d, 3H), 1.84 - 1.95 (m, 1H), 1.98 - 2.10 (m, 1H), 2.65 - 2.77 (m, 2H), 2.82 - 2.92 (m, 2H), 2.96 (q, 2H), 3.18 - 3.25 (m, 1H), 3.45 (td, 1H), 3.60 (dd, 1H), 3.73 (d, 1H), 3.94 (dd, 1H), 3.99 - 4.12 (m, 1H), 4.36 - 4.50 (m, 1H), 6.83 (s, 1H)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 360.22; HPLC tR = 2.13 min.

The preparation of 2-chloro-4-(ethylsulfonylmethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Example 88: 1-[4-[4-(1-Ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea

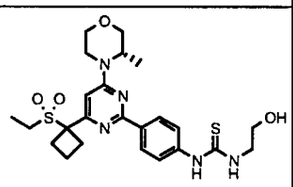
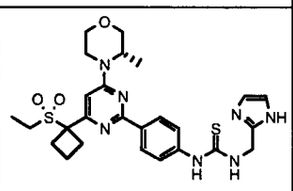


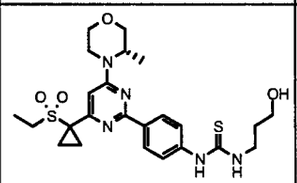
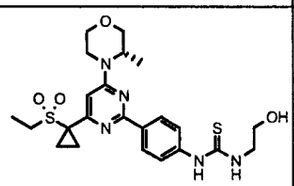
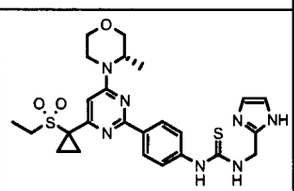
A solution of 1,1'-thiocarbonyldiimidazole (55.6 mg, 0.31 mmol) in DCM (2 mL) was added to a stirred solution of 4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (100 mg, 0.24 mmol) in THF (1 mL) and DCM (2 mL) at RT, over a period of 2 minutes under nitrogen. The resulting solution was stirred at RT for 2 hours. Triethylamine (0.033 mL, 0.24 mmol) and 3-amino-1-propanol (0.092 mL, 1.20 mmol) were added to the reaction mixture. The resulting solution was stirred at RT for 60 hours. The reaction mixture was evaporated to dryness and redissolved in acetonitrile (2 mL), filtered and purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to dryness to afford desired material as a beige solid. (100 mg)

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.24 (d, 3H), 1.72 (quintet, 2H), 1.86 - 1.97 (m, 1H), 2.03 - 2.12 (m, 1H), 2.77 - 2.88 (m, 2H), 2.91 - 3.00 (m, 4H), 3.18 - 3.26 (m, 1H), 3.45 - 3.59 (m, 5H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.19 - 4.29 (m, 1H), 4.49 - 4.63 (m, 2H), 6.75 (s, 1H), 7.57 (d, 2H), 7.86 - 7.94 (m, 1H), 8.28 (d, 2H), 9.65 - 9.74 (m, 1H)

LCMS Spectrum: m/z (ES+) (M+H)+= 534.8; HPLC tR= 2.16 min.

The compounds below were prepared in an analogous fashion from either 4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline or 4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
88a		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea	521	2.13
88b		1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea	557	1.51

Example	Structure	NAME	LCMS MH+	Retention time (min)
88c		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)thiourea	5.21	2.33
88d		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea	507	2.30
88e		1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea	543	2.36

Example 88a: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.24 (d, 3H), 1.86 - 1.97 (m, 1H), 2.03 - 2.11 (m, 1H), 2.77 - 2.88 (m, 2H), 2.91 - 3.00 (m, 4H), 3.18 - 3.27 (m, 1H), 3.51 (td, 1H), 3.55 - 3.60 (m, 4H), 3.65 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.18 - 4.30 (m, 1H), 4.54 - 4.63 (m, 1H), 4.77 - 4.86 (m, 1H), 6.75 (s, 1H), 7.62 (d, 2H), 7.84 - 7.90 (m, 1H), 8.28 (d, 2H), 9.81 (s, 1H)

Example 88b: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.15 (t, 3H), 1.24 (d, 3H), 1.86 - 1.97 (m, 1H), 2.02 - 2.12 (m, 1H), 2.78 - 2.88 (m, 2H), 2.91 - 3.00 (m, 4H), 3.18 - 3.26 (m, 1H), 3.51 (td, 1H), 3.66 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.19 - 4.30 (m, 1H), 4.53 - 4.63 (m, 1H), 4.71 (d, 2H), 6.75 (s, 1H), 6.99 (s, 2H), 7.69 (d, 2H), 8.18 - 8.25 (m, 1H), 8.30 (d, 2H), 9.98 - 10.09 (m, 1H), 11.84 - 12.09 (m, 1H)

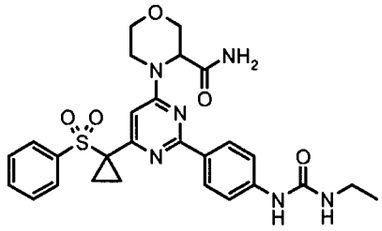
Example 88c: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.24 (d, 3H), 1.33 (t, 3H), 1.54 - 1.59 (m, 2H), 1.61 - 1.66 (m, 2H), 1.72 (quintet, 2H), 3.22 (td, 1H), 3.40 - 3.59 (m, 7H), 3.64 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.16 - 4.28 (m, 1H), 4.52 - 4.64 (m, 2H), 6.83 (s, 1H), 7.58 (d, 2H), 7.90 - 7.97 (m, 1H), 8.25 (d, 2H), 9.74 (s, 1H)

Example 88d: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.24 (d, 3H), 1.33 (t, 3H), 1.55 - 1.59 (m, 2H), 1.61 - 1.66 (m, 2H), 3.22 (td, 1H), 3.44 (q, 2H), 3.45 - 3.52 (m, 1H), 3.55 - 3.60 (m, 4H), 3.64 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.15 - 4.28 (m, 1H), 4.52 - 4.63 (m, 1H), 4.82 - 4.90 (m, 1H), 6.82 (s, 1H), 7.63 (d, 2H), 7.88 - 7.93 (m, 1H), 8.25 (d, 2H), 9.85 (s, 1H)

Example 88e: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.24 (d, 3H), 1.33 (t, 3H), 1.54 - 1.59 (m, 2H), 1.61 - 1.66 (m, 2H), 3.22 (td, 1H), 3.45 (q, 2H), 3.45 - 3.52 (m, 1H), 3.64 (dd, 1H), 3.77 (d, 1H), 3.98 (dd, 1H), 4.15 - 4.28 (m, 1H), 4.53 - 4.63 (m, 1H), 4.69 - 4.74 (m, 2H), 6.83 (s, 1H), 6.86 - 7.15 (m, 2H), 7.70 (d, 2H), 8.22 - 8.29 (m, 1H), 8.27 (d, 2H), 10.05 (s, 1H), 11.95 (s, 1H)

The preparation of both 4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline and 4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline were described earlier.

Example 89: 4-[6-[1-(Benzenesulfonyl)cyclopropyl]-2-[4-(ethylcarbamoylamino)phenyl]pyrimidin-4-yl]morpholine-3-carboxamide



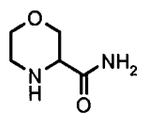
DIPEA (0.411 mL, 2.36 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.102 g, 0.20 mmol) and morpholine-3-carboxamide (as a mixture of the trifluoroacetic acid salts and the hydrochloride salt) (0.212 g, 1.63 mmol) in dioxane (5 mL) under nitrogen. The reaction was stirred at 70°C for several hours. The solvent was removed and then the gum was taken up in dioxane again. Ethyl isocyanate (0.032 mL, 0.41 mmol) was added and the reaction stirred at RT over the weekend. Further ethyl isocyanate (an excess) was added and the reaction stirred for several days. Methanol was added and the solvent was removed. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a yellow solid (0.027 g).

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.59-1.62 (1H, m), 1.65-1.68 (1H, m), 1.87-1.95 (2H, m), 3.09-3.17 (2H, m), 3.17-3.19 (1H, d), 3.41-3.54 (3H, m), 3.70-3.73 (1H, dd), 3.94-3.97 (1H, d), 4.30-4.33 (1H, d), 6.13-6.16 (1H, t), 6.72 (1H, s), 7.15 (1H, bs), 7.36-7.38 (2H, d), 7.52 (1H, bs), 7.57-7.61 (2H, t), 7.70-7.74 (1H, tt), 7.79-7.82 (4H, m), 8.62 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=551; HPLC tR=1.84min.

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier

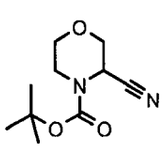
Morpholine-3-carboxamide



Hydrogen chloride (2.420 mL, 9.68 mmol) (4M solution in dioxane) was added to *tert*-butyl 3-cyanomorpholine-4-carboxylate (0.419 g, 1.98 mmol) in dioxane (15 mL) and the resulting solution stirred at RT over the weekend. The solvent was removed. The solid was taken up in dioxane and trifluoroacetic acid (1.2 eq) added. The reaction was allowed to stir at RT overnight. The solvent was removed, the crude material taken up in DCM and trifluoroacetic acid (0.734 mL, 9.88 mmol) added. The reaction was stirred overnight and then the solvent was removed to give the desired material (isolated as potentially a mixture of the trifluoroacetic acid salts and the hydrochloride salt). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.07-3.16 (1H, m), 3.58-3.70 (1H, m), 3.79-3.82 (1H, m), 3.87-3.93 (1H, m), 4.00-4.07 (1H, m), 4.11-4.22 (1H, m), 4.71-4.89 (1H, m), 7.76-8.16 (t) (TFA salt), 9.15-9.78 (bt) (HCl salt).

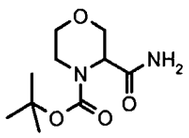
tert-Butyl 3-cyanomorpholine-4-carboxylate



tert-Butyl 3-carbamoylmorpholine-4-carboxylate (0.929 g, 4.03 mmol) was dissolved in dry DCM (10 mL) and triethylamine (1.181 mL, 8.47 mmol) was added. The solution was put under nitrogen and cooled to 0°C. Trifluoroacetic anhydride (0.627 mL, 4.44 mmol) was then added and the reaction was allowed to slowly warm up to RT, followed by stirring at RT for at least 3 hours. The solvent was removed and then ethyl acetate added. The organic layer was washed with brined, dried over $MgSO_4$, filtered and evaporated. he crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in DCM, to give the desired material as a light yellow crystalline solid (0.419 g).

NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (9H, s), 3.24 (1H, bt), 3.45-3.52 (1H, td), 3.60-3.64 (1H, dd), 3.80-3.83 (1H, d), 3.94-3.97 (1H, d), 4.04-4.07 (1H, d), 4.89 (1H, bs).

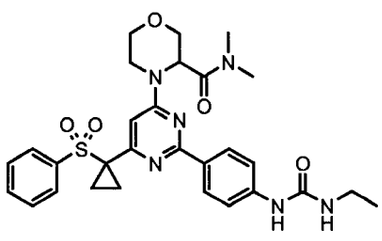
tert-butyl 3-carbamoylmorpholine-4-carboxylate



HATU (5.92 g, 15.57 mmol) was added to a solution of 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid (3 g, 12.97 mmol), DIPEA (3.40 mL, 19.46 mmol) and ammonium chloride (3.47 g, 64.87 mmol) in DMF (70 mL) and the resulting suspension stirred at RT for 12 hours under nitrogen. The reaction mixture was concentrated and diluted with ethyl acetate (150 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as an oil (4.0 g), which was used without further purification.

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.39 (9H, s), 3.15 (2H, m), 3.54 (2H, m), 3.63 (2H, m), 3.75 (1H, m), 4.17 (2H, m).

Example 90: 4-[6-[1-(Benzenesulfonyl)cyclopropyl]-2-[4-(ethylcarbamoylamino)phenyl]pyrimidin-4-yl]-*N*,*N*-dimethylmorpholine-3-carboxamide



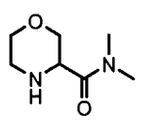
DIPEA (0.141 mL, 0.81 mmol) was added to [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate (0.101 g, 0.20 mmol) and *N,N*-dimethylmorpholine-3-carboxamide (as the hydrochloride salt) (0.079 g, 0.41 mmol) in dioxane (5 mL) under nitrogen. The reaction was stirred at 70°C for several hours then allowed to cool and ethyl isocyanate (0.321 mL, 4.05 mmol) added. The reaction was stirred at RT overnight, additional ethyl isocyanate added and the reaction stirred at RT overnight. Methanol was added and the solvent was removed. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a cream solid (0.047 g).

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05-1.08 (3H, t), 1.58-1.62 (1H, m), 1.68-1.73 (1H, m), 1.86-1.97 (2H, m), 2.82 (3H, bs), 3.09-3.16 (2H, m), 3.19 (3H, bs), 3.53-3.60 (1H, m), 3.67-3.71 (1H, m), 3.79-3.84 (1H, dd), 4.00-4.02 (1H, d), 4.14-4.17 (1H, d), 5.44 (1H, bs), 6.15-6.18 (1H, t), 6.77 (1H, s), 7.37-7.39 (2H, d), 7.56-7.60 (2H, t), 7.70-7.74 (1H, t), 7.76-7.80 (4H, m), 8.61 (1H, s). (1 peak under water or solvent peak).

LCMS Spectrum: m/z (ES+)(M+H)+=579; HPLC tR=2.01min.

The preparation of [2-(4-aminophenyl)-6-[1-(benzenesulfonyl)cyclopropyl]pyrimidin-4-yl] trifluoromethanesulfonate was described earlier

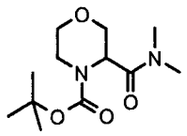
N,N-Dimethylmorpholine-3-carboxamide



Hydrogen chloride (3.57 mL, 14.28 mmol) (4M solution in dioxane) was added to *tert*-butyl 3-(dimethylcarbamoyl)morpholine-4-carboxylate (0.820 g, 3.17 mmol) in dioxane (25 mL) and the resulting solution stirred at RT overnight. The solvent was removed and the gum was triturated with diethyl ether to give the desired material (as the hydrochloride salt) as a solid which turned to a gum on standing (0.70 g).

NMR Spectrum: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (3H, s), 3.07 (3H, s), 3.13-3.16 (1H, dd), 3.20-3.23 (1H, dt), 3.42-3.48 (1H, m), 3.69-3.75 (1H, td), 3.92-3.96 (1H, dt), 4.15-4.19 (1H, dd), 4.57-4.61 (1H, dd), 9.47 (1H, bs).

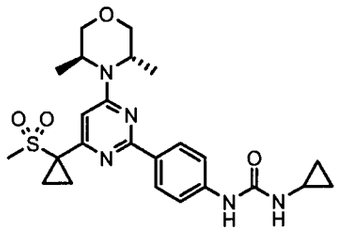
tert-Butyl 3-(dimethylcarbamoyl)morpholine-4-carboxylate



HATU (1.97 g, 5.19 mmol) was added to a solution of 4-(*tert*-butoxycarbonyl)morpholine-3-carboxylic acid (1 g, 4.32 mmol), DIPEA (1.133 ml, 6.49 mmol) and dimethylamine 2.0M in THF (10.81 mL, 21.62 mmol) in DMF and the resulting solution stirred at RT for 15 hours under nitrogen. The reaction mixture was concentrated and diluted with ethyl acetate (100 mL), and washed sequentially with water(25 mL), 5% aqueous citric acid solution (25 mL), and saturated brine (25 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product and dried under vacuum to the desired material as an oil (0.91 g), which was used without further purification.

NMR Spectrum: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.36 (9H, br s), 2.83 (3H, s), 2.98 (3H, s), 3.35 (1H, m), 3.48 (1H, m), 3.63 (1H, dd), 3.80 (1H, m), 3.90 - 4.04 (2H, m), 4.70 (1H, m).

Example 91: 3-Cyclopropyl-1-[4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea

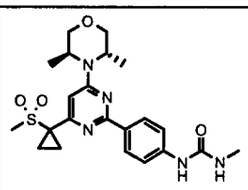
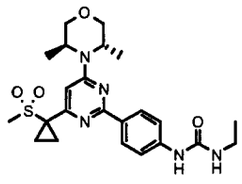
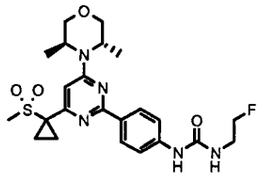
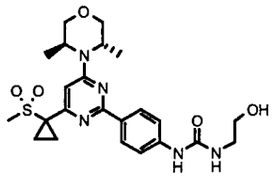


Cyclopropylamine (0.10 mmol) was added to phenyl *N*-[4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate (50 mg, 0.10 mmol) and triethylamine (0.027 mL, 0.19 mmol) in DMF (1 mL) at RT. The resulting solution was stirred at 50°C for 2 hours and the material purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (40mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 1.36 (6H, d), 1.53 - 1.61 (2H, m), 1.64 - 1.72 (2H, m), 2.54 - 2.59 (1H, m), 3.26 (3H, s), 3.72 (2H, dd), 4.16 (2H, dd), 4.25 - 4.31 (2H, m), 6.44 (1H, d), 6.72 (1H, s), 7.52 (2H, d), 8.21 (2H, d), 8.54 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=486; HPLC tR=2.13min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
91a		1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-methylurea	460	1.70
91b		1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-ethylurea	474	2.11
91c		1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	492	2.11
91d		1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	490	1.77

Example 91a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.36 (6H, d), 1.55 - 1.61 (2H, m), 1.64 - 1.70 (2H, m), 2.66 (3H, d), 3.26 (3H, s), 3.72 (2H, dd), 4.16 (2H, dd), 4.27 - 4.28 (2H, m), 6.07 - 6.08 (1H, m), 6.72 (1H, s), 7.51 (2H, d), 8.20 (2H, d), 8.74 (1H, s).

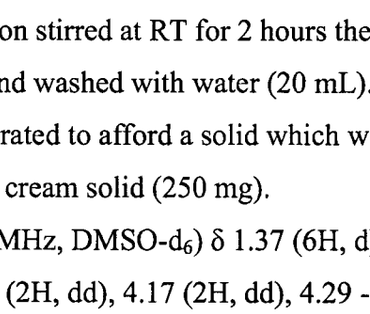
Example 91b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.36 (6H, d), 1.55 - 1.61 (2H, m), 1.64 - 1.73 (2H, m), 3.09 - 3.16 (2H, m), 3.26 (3H, s), 3.72 (2H, dd), 4.16 (2H, dd), 4.27 - 4.28 (2H, m), 6.17 (1H, t), 6.72 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.66 (1H, s).

Example 91c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.36 (6H, d), 1.55 - 1.59 (2H, m), 1.64 - 1.70 (2H, m), 3.26 (3H, s), 3.42 (2H, dq), 3.72 (2H, dd), 4.16 (2H, dd), 4.26 - 4.29 (2H, m), 4.42 (1H, t), 4.54 (1H, t), 6.44 (1H, t), 6.72 (1H, s), 7.51 (2H, d), 8.21 (2H, d), 8.81 (1H, s).

Example 91d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.36 (6H, d), 1.55 - 1.60 (2H, m), 1.65 - 1.72 (2H, m), 3.16 - 3.20 (2H, m), 3.26 (3H, s), 3.44 - 3.48 (2H, m), 3.72 (2H, dd), 4.16 (2H, dd), 4.24 - 4.31 (2H, m), 4.73 (1H, t), 6.26 (1H, t), 6.72 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.81 (1H, s).

The preparation of phenyl *N*-[4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]carbamate

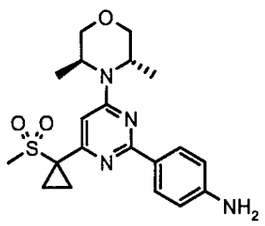


Sodium bicarbonate (104 mg, 1.24 mmol) was added to 4-[4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline (250 mg, 0.62 mmol) in 1,4-dioxane (3 mL) and phenyl chloroformate (0.078 mL, 0.62 mmol) was added dropwise to the resulting suspension. The reaction stirred at RT for 2 hours then evaporated to dryness, redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as a cream solid (250 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.37 (6H, d), 1.56 - 1.62 (2H, m), 1.65 - 1.71 (2H, m), 3.27 (3H, s), 3.73 (2H, dd), 4.17 (2H, dd), 4.29 - 4.31 (2H, m), 6.77 (1H, s), 7.24 - 7.30 (3H, m), 7.45 (2H, t), 7.65 (2H, d), 8.30 (2H, d), 10.45 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=523; HPLC tR=2.74min.

4-[4-[(3*S*,5*S*)-3,5-Dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]aniline

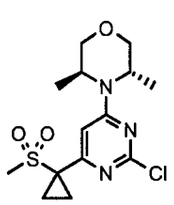


Bis(triphenylphosphine)palladium(II) chloride (35.5 mg, 0.05 mmol) was added to 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine (350 mg, 1.01 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (222 mg, 1.01 mmol) and 2M aqueous sodium carbonate solution (1.52 mL, 3.04 mmol), in ethanol (0.89 mL), DME (1.77 mL) and water (0.89 mL) and the reaction stirred at 90°C for 2 hours. The reaction mixture was diluted with ethyl acetate (20 mL), and washed sequentially with water (20 mL), and saturated brine(20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 2 to 10% methanol in DCM, to give the desired material as a beige solid (250 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.34 (6H, d), 1.50 - 1.58 (2H, m), 1.62 - 1.70 (2H, m), 3.25 (3H, s), 3.70 (2H, dd), 4.14 (2H, dd), 4.22 - 4.25 (2H, m), 5.56 (1H, s), 6.61 (2H, d), 8.04 (2H, d).

LCMS Spectrum: m/z (ES+)(M+H)+=403; HPLC tR=2.05min.

2-Chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidine



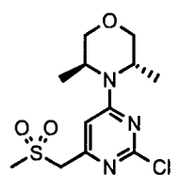
A solution of 50% w/v sodium hydroxide (6.12 mL, 154.44 mmol) was added portionwise to a stirred solution of 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine (898 mg, 2.81 mmol), tetrabutylammonium bromide (91 mg, 0.28 mmol) and 1,2-dibromoethane (0.726 mL, 8.42 mmol) in toluene (50 mL) and the

resulting suspension stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a solid (350 mg).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.43 (3H, d), 1.44 (3H, d), 1.50 (2H, m), 1.82 (2H, m), 3.02 (3H, s), 3.78 (2H, dd), 4.16 (2H, m), 4.24 (2H, dd), 6.77 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=346; HPLC tR=1.83min.

2-Chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(methylsulfonylmethyl)pyrimidine

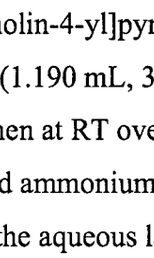


Sodium methanesulfinate (0.542 g, 5.31 mmol) was added portionwise to 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine (1.86 g, 5.06 mmol) in acetonitrile (50 mL) and the resulting suspension stirred at 80°C for 6 hours. Further sodium methanesulfinate (0.5 equivalents) was added and the reaction was heated a further 8 hours. The solvent was removed and the solid was taken up in DMF. Further sodium methanesulfinate (1 equivalent) was added and the mixture allowed to stir until the reaction was complete. The solvent was removed and ethyl acetate added. The mixture was washed with 10% sodium thiosulfate, brine and water and the organics dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 25% ethyl acetate in DCM, to give the desired material as a yellow gum (0.898 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.44-1.45 (6H, d), 3.02 (3H, s), 3.77-3.80 (2H, dd), 4.14-4.16 (2H, m), 4.17-4.18 (2H, d), 4.23-4.27 (2H, dd), 6.46 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=320; HPLC tR=1.59 min.

2-Chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine

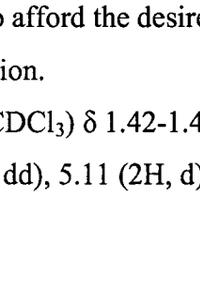


[2-Chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-4-yl]methyl methanesulfonate (5.21 g, 15.51 mmol) and lithium iodide (1.190 mL, 31.03 mmol) were added to dioxane (250 mL) and heated at 60°C for 1 hour and then at RT overnight. The mixture was evaporated to dryness and partitioned between saturated ammonium chloride solution (100 mL) and DCM (75 mL). The layers were separated and the aqueous layer further extracted with DCM (2 x 75 mL) then the combined organics washed sequentially with 10% sodium thiosulfate solution (100 mL) and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product as a brown oil (5.59 g). The material was used without further purification.

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.32 (6H, d), 3.69 (2H, dd), 4.08 (2H, m), 4.14 (2H, dd), 4.34 (2H, s), 6.84 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=368; HPLC tR=2.26min.

[2-Chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-4-yl]methyl methanesulfonate

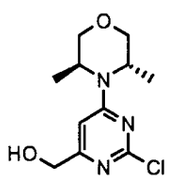


Methanesulfonyl chloride (1.802 mL, 23.28 mmol) was added dropwise to [2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-4-yl]methanol (4.00 g, 15.52 mmol) and DIPEA (4.03 mL, 23.28 mmol) in DCM (100 mL) at 0°C over a period of 2 minutes and the resulting solution allowed to gradually warm up to RT over a period of 2 hours. The reaction mixture was diluted with DCM (50 mL), and washed with water. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the desired material as a yellow gum (5.56 g). This was used without further purification.

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.42-1.44 (6H, d), 3.14 (3H, s), 3.76-3.80 (2H, dd), 4.13-4.18 (2H, m), 4.22-4.26 (2H, dd), 5.11 (2H, d), 6.48 (1H, s).

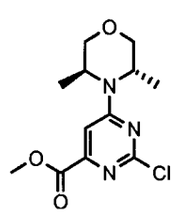
LCMS Spectrum: m/z (ES+)(M+H)+=336; HPLC tR=1.88min.

[2-Chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-4-yl]methanol



Lithium borohydride, 2M in THF (6.54 mL, 13.09 mmol) was added dropwise to methyl 2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine-4-carboxylate (4.40 g, 15.40 mmol) in THF (75 mL) at 0°C over a period of 30 minutes under nitrogen. The resulting solution was stirred at 0°C for 30 minutes then allowed to warm to RT. Water (250 mL) was added and the organics removed *in vacuo*. The aqueous residues were extracted with ethyl acetate then the combined organics were washed with brine. The organic layer was dried over $MgSO_4$ then evaporated to dryness to afford the desired material as a white solid (4.0 g).
NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.41-1.42 (6H, d), 2.69-2.71 (1H, t), 3.75-3.78 (2H, dd), 4.12-4.18 (2H, m), 4.21-4.25 (2H, dd), 4.59-4.60 (2H, d), 6.39 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=258; HPLC tR=1.38min.

Methyl 2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine-4-carboxylate

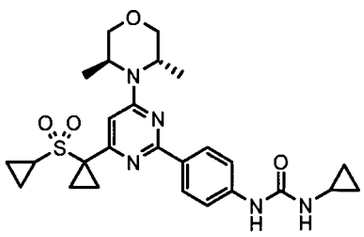


Methyl 2,4-dichloropyrimidine-6-carboxylate (4.45 g, 21.50 mmol) was dissolved in dry DCM (100mL) and DIPEA (9.67 mL, 55.89 mmol) was added. (3*S*,5*S*)-3,5-Dimethylmorpholine (as the hydrochloride salt) (3.42 g, 22.57 mmol)in DCM (20 mL) was added to this solution dropwise over several minutes and the reaction allowed to stir at RT for 5 days then at 50°C for several days. The crude reaction mixture was washed with water, dried over $MgSO_4$ and filtered. The crude product was purified by flash silica chromatography, elution gradient 0 to 25% ethyl acetate in DCM, to give the desired material as a cream solid (4.4 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.44-1.46 (6H, d), 3.78-3.81 (2H, dd), 3.98 (3H, s), 4.16-4.22 (2H, m), 4.24-4.28 (2H, dd), 7.10 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=286; HPLC tR=1.72min.

The preparation of (3*S*,5*S*)-3,5-dimethylmorpholine was described earlier.

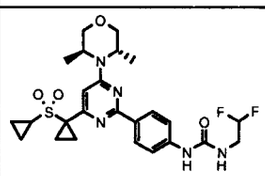
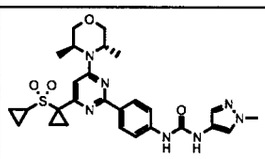
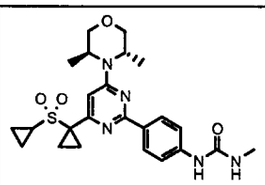
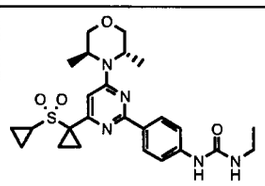
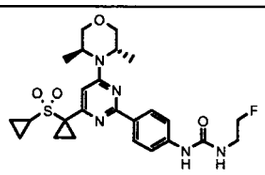
Example 92: 3-Cyclopropyl-1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea

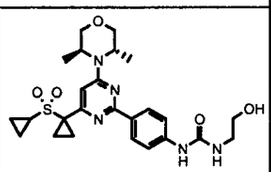


Cyclopropanamine (12.49 mg, 0.22 mmol) was added to phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (120 mg, 0.22 mmol) and triethylamine (0.091 mL, 0.66 mmol) in DMF (1 mL) at RT. The resulting solution was stirred at 50°C for 2 hours. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (82 mg).
NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.63 - 0.67 (2H, m), 0.87 - 1.04 (4H, m), 1.36 (6H, d), 1.57 - 1.70 (4H, m), 2.54 - 2.58 (1H, m), 2.91 - 2.97 (1H, m), 3.71 (2H, dd), 4.16 (2H, dd), 4.25 - 4.27 (2H, m), 6.43 (1H, s), 6.81 (1H, s), 7.51 (2H, d), 8.22 (2H, d), 8.52 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=512; HPLC tR=2.25min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)

Example	Structure	NAME	LCMS MH+	Retention time (min)
92a		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	537	2.39
92b		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	552	1.83
92c		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	486	2.06
92d		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	500	1.91
92e		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	518	1.94

Example	Structure	NAME	LCMS MH+	Retention time (min)
92f		1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	516	1.88

Example 92a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87 - 1.06 (4H, m), 1.36 (6H, d), 1.55 - 1.70 (4H, m), 2.91 - 2.97 (1H, m), 3.50 - 3.60 (2H, m), 3.72 (2H, dd), 4.16 (2H, dd), 4.25 - 4.28 (2H, m), 6.07 (1H, t), 6.54 (1H, t), 6.82 (1H, s), 7.52 (2H, d), 8.24 (2H, d), 8.91 (1H, s).

Example 92b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 - 1.07 (4H, m), 1.36 (6H, d), 1.56 - 1.71 (4H, m), 2.91 - 2.98 (1H, m), 3.72 (2H, dd), 3.79 (3H, s), 4.16 (2H, dd), 4.26 - 4.29 (2H, m), 6.82 (1H, s), 7.39 (1H, s), 7.55 (2H, d), 7.76 (1H, s), 8.25 (2H, d), 8.39 (1H, s), 8.83 (1H, s).

Example 92c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.89 - 1.04 (4H, m), 1.36 (6H, d), 1.57 - 1.68 (4H, m), 2.66 (3H, d), 2.91 - 2.97 (1H, m), 3.71 (2H, ddd), 4.16 (2H, dd), 4.25 - 4.27 (2H, m), 6.06 - 6.07 (1H, m), 7.50 (2H, d), 7.55 - 7.58 (1H, m), 8.21 (2H, d), 8.73 (1H, s).

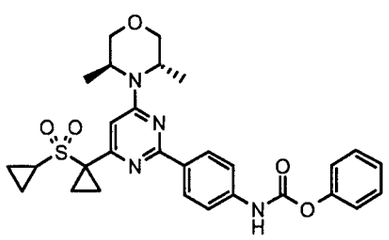
Example 92d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87 - 1.04 (4H, m), 1.07 (3H, t), 1.36 (6H, d), 1.55 - 1.70 (4H, m), 2.91 - 2.97 (1H, m), 3.09 - 3.16 (2H, m), 3.71 (2H, dd), 4.16 (2H, dd), 4.24 - 4.27 (2H, m), 6.16 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.21 (2H, d), 8.65 (1H, s).

Example 92e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87 - 1.06 (4H, m), 1.36 (6H, d), 1.55 - 1.70 (4H, m), 2.91 - 2.97 (1H, m), 3.39 (1H, q), 3.46 (1H, q), 3.72 (2H, dd), 4.16 (2H, dd), 4.22 - 4.29 (2H, m), 4.42 (1H, t), 4.54 (1H, t), 6.44 (1H, t), 6.81 (1H, s), 7.51 (2H, d), 8.23 (2H, d), 8.80 (1H, s).

Example 92f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87 - 1.04 (4H, m), 1.36 (6H, d), 1.55 - 1.69 (4H, m), 2.90 - 2.97 (1H, m), 3.16 - 3.20 (2H, m), 3.44 - 3.48 (2H, m), 3.71 (2H, dd), 4.16 (2H, dd), 4.24 - 4.29 (2H, m), 4.73 (1H, t), 6.26 (1H, t), 6.81 (1H, s), 7.49 (2H, d), 8.22 (2H, d), 8.79 (1H, s).

The preparation of phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

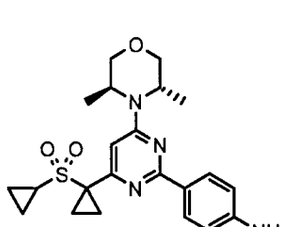
Phenyl *N*-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



Sodium bicarbonate (286 mg, 3.41 mmol) was added to 4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]aniline (730 mg, 1.70 mmol), in 1,4-dioxane (8.3 mL) and phenyl chloroformate (0.214 mL, 1.70 mmol) added dropwise to the resulting suspension. The mixture was stirred at RT for 2 hours. The reaction mixture was evaporated to dryness and redissolved in DCM (20 mL), and washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford a solid which was triturated with diethyl ether to give the desired material as a cream solid (800 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.88 - 1.05 (4H, m), 1.37 (6H, d), 1.59 - 1.70 (4H, m), 2.92 - 2.99 (1H, m), 3.73 (2H, dd), 4.17 (2H, dd), 4.28 - 4.30 (2H, m), 6.86 (1H, s), 7.24 - 7.30 (3H, m), 7.45 (2H, t), 7.64 (2H, d), 8.30 (2H, d), 10.45 (1H, s).
LCMS Spectrum: m/z (ES+)(M+H)+=549; HPLC tR=2.66min.

4-[4-(1-Cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]aniline



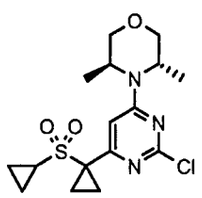
Bis(triphenylphosphine)palladium(II) chloride (60.4 mg, 0.09 mmol) was added to 2-chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine

(640 mg, 1.72 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (490 mg, 2.24 mmol) and 2M sodium carbonate solution (2.6 mL, 5.16 mmol) in water (1.5 mL), ethanol (1.5 mL), and DME (3 mL) and the resulting solution was stirred at 95°C for 2 hours. The reaction mixture was diluted with ethyl acetate (20 mL), and washed sequentially with water (10 mL) and saturated brine(10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM, to give the desired material as a beige solid (740 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.89 - 1.03 (4H, m), 1.34 (6H, d), 1.54 - 1.67 (4H, m), 2.89 - 2.96 (1H, m), 3.70 (2H, dd), 4.14 (2H, dd), 4.20 - 4.24 (2H, m), 6.61 (2H, d), 6.73 (1H, s), 8.05 (2H, d)

LCMS Spectrum: m/z (ES+)(M+H)+=429; HPLC tR=2.18min.

2-Chloro-4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine

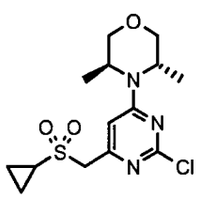


A solution of 50% w/v sodium hydroxide (7.06 mL, 176.52 mmol) was added portionwise to a stirred solution of 2-chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine (1.11 g, 3.21 mmol), tetrabutylammonium bromide (0.103 g, 0.32 mmol) and 1,2-dibromoethane (0.830 mL, 9.63 mmol) in toluene (50 mL) and the resulting suspension stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a solid (0.64 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.86 - 0.99 (2H, m), 1.01 (2H, m), 1.31 (3H, d), 1.33 (3H, d), 1.51 (2H, m), 1.63 (2H, m), 2.86 (1H, m), 3.70 (2H, dd), 4.13 (2H, m), 4.16 (2H, m), 6.90 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=372; HPLC tR=1.97min.

2-Chloro-4-(cyclopropylsulfonylmethyl)-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine



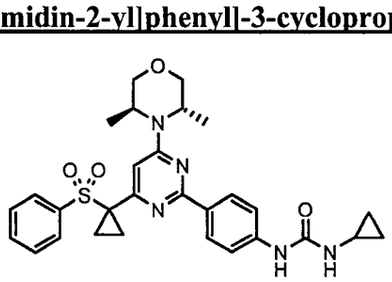
Sodium cyclopropanesulfinate (0.648 g, 5.06 mmol) was added portionwise to 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine (1.86 g, 5.06 mmol) in acetonitrile (50 mL) and the resulting suspension stirred at 80°C for 6 hours. Further sodium cyclopropanesulfinate (259mg, 2.02mmol) was added in one portion and the suspension was stirred at 80°C for a further 2 hours. The reaction mixture was concentrated and diluted with DCM (200 mL), and washed sequentially with water (50 mL), 10% sodium thiosulfate solution (50 mL), and saturated brine(50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0to 20% ethyl acetate in DCM, to give the desired material as a yellow solid (1.11 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.97 (2H, m), 1.03 (2H, m), 1.32 (3H, d), 1.34 (3H, d), 2.79 (1H, m), 3.70 (2H, dd), 4.09 (2H, m), 4.15 (2H, dd), 4.49 (2H, d), 6.82 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=346; HPLC tR=1.77 min.

The preparation of 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine was described earlier.

Example 93: 1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea

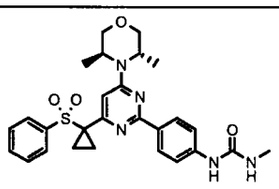
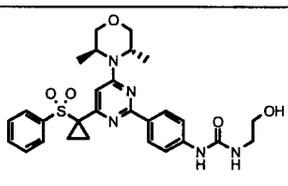


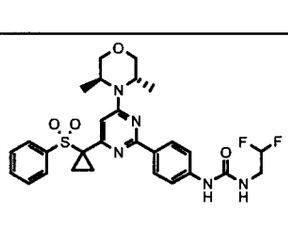
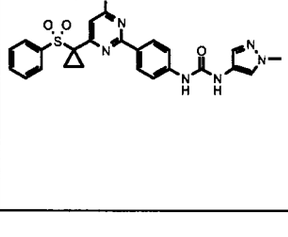
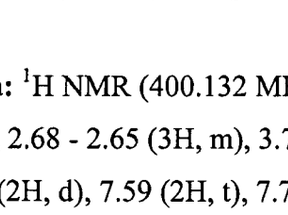
Cyclopropylamine (19.0 mg, 0.34 mmol) was added to phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (100 mg, 0.17 mmol) and triethylamine (52 mg, 0.51 mmol) in dioxane (10mL) at RT. The resulting solution was stirred at 50°C overnight. The crude product was purified by preparative HPLC, eluting with decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile, to give the desired material as a white solid (64 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 0.43 - 0.39 (2H, m), 0.67 - 0.62 (2H, m), 1.28 (6H, d), 1.69 - 1.62 (2H, m), 1.93 - 1.89 (2H, m), 2.59 - 2.50 (m, 1H), 3.70 - 3.67 (2H, m), 4.18 - 4.10 (4H, m), 6.41 (1H, s), 6.60 (1H, s), 7.41 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.79 (2H, d), 7.88 (2H, d), 8.49 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=548; HPLC tR=2.49min.

The compounds below were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
93a		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	522	2.32
93b		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	552	2.13

Example	Structure	NAME	LCMS MH+	Retention time (min)
93c		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	554	2.47
93d		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	572	2.60
93e		1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	588	2.34

1-[4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea (**Example 72**) can also be prepared in this fashion.

Example 93a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.28 (6H, d), 1.69 - 1.62 (2H, m), 1.93 - 1.89 (2H, m), 2.68 - 2.65 (3H, m), 3.70 - 3.67 (2H, m), 4.16 - 4.10 (4H, m), 6.05 (1H, q), 6.59 (1H, s), 7.40 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.79 (2H, d), 7.87 (2H, d), 8.69 (1H, s).

Example 93b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.28 (6H, d), 1.69 - 1.63 (2H, m), 1.93 - 1.89 (2H, m), 3.18 - 3.15 (2H, m), 3.46 (2H, q), 3.70 - 3.67 (2H, m), 4.18 - 4.10 (4H, m), 4.72 (1H, t), 6.24 (1H, t), 6.60 (1H, s), 7.39 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.79 (2H, d), 7.88 (2H, d), 8.76 (1H, s).

Example 93c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.28 (6H, d), 1.69 - 1.64 (2H, m), 1.93 - 1.89 (2H, m), 3.41 (2H, dq), 3.70 - 3.68 (2H, m), 4.18 - 4.10 (4H, m), 4.47 (2H, dt), 6.42 (1H,

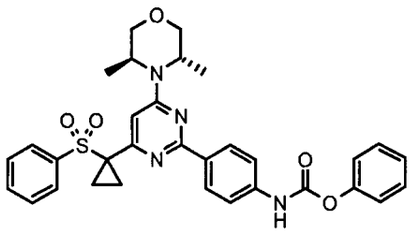
t), 6.60 (1H, s), 7.40 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.79 (2H, d), 7.88 (2H, d), 8.76 (1H, s).

Example 93d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.28 (6H, d), 1.69 - 1.61 (2H, m), 1.93 - 1.90 (2H, m), 3.59 - 3.49 (2H, m), 3.70 - 3.68 (2H, m), 4.18 - 4.10 (4H, m), 6.07 (1H, tt), 6.52 (1H, t), 6.60 (1H, s), 7.41 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.79 (2H, d), 7.89 (2H, d), 8.87 (1H, s).

Example 93e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.28 (6H, d), 1.72 - 1.62 (2H, m), 1.94 - 1.90 (2H, m), 3.70 - 3.68 (2H, m), 3.79 (3H, s), 4.18 - 4.10 (4H, m), 6.61 (1H, s), 7.38 (1H, s), 7.45 (2H, d), 7.59 (2H, t), 7.71 (1H, t), 7.76 (1H, s), 7.80 (2H, d), 7.91 (2H, d), 8.37 (1H, s), 8.79 (1H, s).

The preparation of phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate



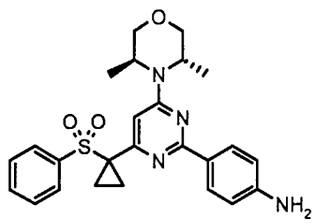
4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]aniline (0.6 g, 1.29 mmol) and sodium bicarbonate (1.085 g, 12.91 mmol) were added to DCM (60 mL) and stirred for 10 minutes. Phenyl chloroformate (0.211 mL, 1.68 mmol) was added slowly and the reaction was stirred for 1 hour. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL), extracted with ethyl acetate (3 x 50 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford an orange solid. The crude product was purified by flash silica chromatography, elution gradient 30 to 60% ethyl acetate in isohexane, to give the desired material as a yellow solid (0.73 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.29 (6H, d), 1.71 - 1.64 (2H, m), 1.94 - 1.89 (2H, m), 3.71 - 3.68 (2H, m), 4.18 - 4.11 (4H, m), 6.63 (1H, s), 7.30 - 7.23 (3H, m), 7.45

(2H, t), 7.54 (2H, d), 7.59 (2H, t), 7.70 (1H, t), 7.81 - 7.79 (2H, m), 7.97 (2H, d), 10.39 (1H, s).

LCMS Spectrum: m/z (ES+)(M+H)+=585; HPLC tR=3.02min.

4-[4-[1-(Benzenesulfonyl)cyclopropyl]-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]aniline

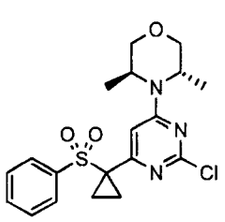


Bis(triphenylphosphine)palladium(II) chloride (0.053 g, 0.07 mmol) was added to 4-[1-(benzenesulfonyl)cyclopropyl]-2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine (0.611 g, 1.50 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.427 g, 1.95 mmol) and 2M sodium carbonate solution (2.247 mL, 4.49 mmol) in water (3 mL), ethanol (3 mL), and DME (6 mL) and the resulting solution stirred at 95°C overnight. The reaction mixture was diluted with ethyl acetate (75 mL), and washed sequentially with water (10 mL) and saturated brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 50% ethyl acetate in DCM, to give the desired material as a white foam (0.6 g).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.25 (6H, d), 1.69 - 1.60 (2H, m), 1.93 - 1.85 (2H, m), 3.68 - 3.64 (2H, m), 4.13 - 4.06 (4H, m), 5.50 (1H, s), 6.52 - 6.50 (4H, m), 7.58 (2H, t), 7.74 - 7.67 (3H, m), 7.80 - 7.78 (2H, m).

LCMS Spectrum: m/z (ES+)(M+H)+=465; HPLC tR=2.50min.

4-[1-(Benzenesulfonyl)cyclopropyl]-2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine

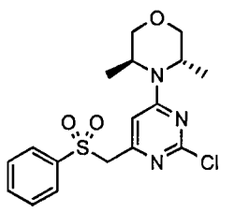


A solution of 50% w/v sodium hydroxide (4.99 mL, 124.73 mmol) was added portionwise to a stirred solution of 4-(benzenesulfonylmethyl)-2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine (866 mg, 2.27 mmol), tetrabutylammonium bromide (73.1 mg, 0.23 mmol) and 1,2-dibromoethane (0.586 mL, 6.80 mmol) in toluene (50 mL) and the resulting suspension stirred at 60°C for 6 hours. The reaction mixture was diluted with water (50 mL), and washed sequentially with water (2 x 50 mL), and saturated brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% ethyl acetate in DCM, to give the desired material as a solid (611 mg).

NMR Spectrum: ^{1}H NMR (400MHz, DMSO-d_6) δ 1.20 (6H, m), 1.59 (2H, m), 1.86 (2H, m), 3.66 (2H, dd), 4.02 (2H, m), 4.10 (2H, dd), 6.62 (1H, s), 7.61 (2H, m), 7.74 (1H, m), 7.75 (2H, m).

LCMS Spectrum: m/z (ES+)(M+H)+=408; HPLC tR=2.26min.

4-(Benzenesulfonylmethyl)-2-chloro-6-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]pyrimidine



Sodium benzenesulfinate (0.872 g, 5.31 mmol) was added portionwise to 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine (1.86 g, 5.06 mmol) in acetonitrile (50 mL) and the resulting suspension stirred at 80°C for 6 hours. Further sodium benzenesulfinate (0.5 equivalents) was added and the reaction was heated for a further 8 hours. The solvent was removed and the solid was taken up in DMF. Further sodium benzenesulfinate (1 equivalent) was added and the reaction allowed to stir until complete (some sodium iodide was added to speed up the reaction). 10% Aqueous sodium thiosulfate solution was added and the acetonitrile removed, ethyl acetate was added and the layers separated. The organic layer was washed with brine and water, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 25% ethyl acetate in DCM, to give the desired material as a white solid (0.866 g).

NMR Spectrum: ^{1}H NMR (400MHz, $CDCl_3$) δ 1.42-1.44(6H, d), 3.76-3.79(2H, dd), 4.10-4.16(2H, m), 4.22-4.26(2H, dd), 4.32(2H, s), 6.56(1H, s), 7.52-7.56(2H, t), 7.64-7.68(1H, t), 7.77-7.79(2H, d).

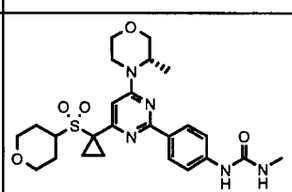
LCMS Spectrum: m/z (ES+)(M+H)+=382; HPLC tR=2.11min.

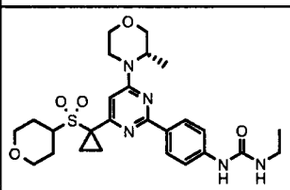
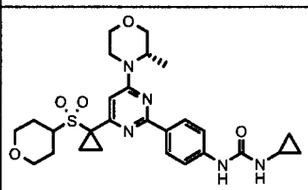
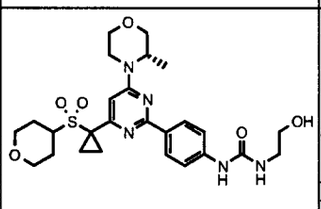
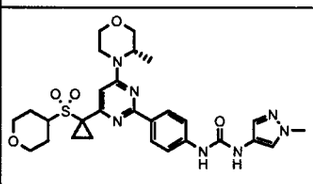
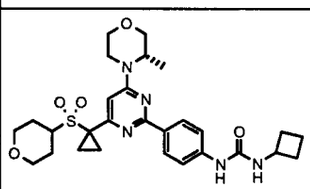
The preparation of 2-chloro-4-[(3*S*,5*S*)-3,5-dimethylmorpholin-4-yl]-6-(iodomethyl)pyrimidine was described earlier.

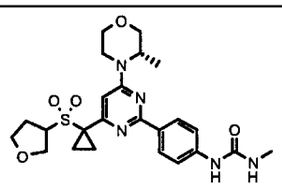
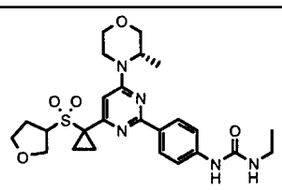
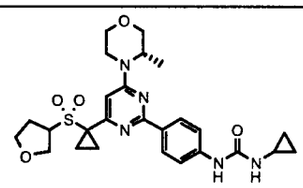
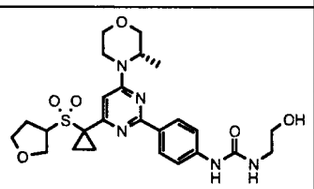
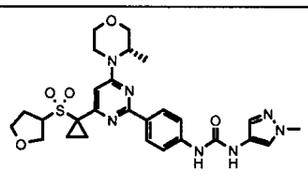
Example 94

The following samples were prepared by heating a mixture of the carbamate (1 equivalent), triethylamine (4 equivalents) and the amine (4 equivalents) in NMP (2 mL) at 70°C for 2 hours. The compounds were purified by preparative HPLC.

The following compounds were prepared in an analogous fashion from either phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
94a		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	516	1.98

Example	Structure	NAME	LCMS MH+	Retention time (min)
94b		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	530	2.14
94c		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	542	2.16
94d		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	546	1.80
94e		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	582	2.03
94f		3-cyclobutyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	556	2.44

Example	Structure	NAME	LCMS MH+	Retention time (min)
94g		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	502	1.98
94h		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	516	2.13
94i		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	528	2.15
94j		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea	532	1.81
94k		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	568	2.03

Example 94a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.52 - 1.56 (2H, m), 1.58 - 1.61 (2H, m), 1.65 - 1.77 (2H, m), 2.10 - 2.19 (2H, m), 3.17 - 3.33 (3H, m), 3.48 (1H, td),

3.63 (1H, d), 3.75 - 3.87 (2H, m), 3.95 - 4.05 (3H, m), 4.17 - 4.27 (1H, m), 4.55 (1H, s), 6.00 - 6.15 (1H, m), 6.78 (1H, s), 7.52 (2H, d), 8.18 (2H, d), 8.75 (1H, s)

Example 94b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.24 (3H, d), 1.52 - 1.56 (2H, m), 1.57 - 1.62 (2H, m), 1.65 - 1.78 (2H, m), 2.09 - 2.19 (2H, m), 3.09 - 3.24 (3H, m), 3.26 - 3.35 (2H, m), 3.48 (1H, td), 3.63 (1H, d), 3.74 - 3.88 (2H, m), 3.94 - 4.04 (3H, m), 4.22 (1H, d), 4.55 (1H, s), 6.17 (1H, t), 6.78 (1H, s), 7.51 (2H, d), 8.18 (2H, d), 8.67 (1H, s)

Example 94c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.38 - 0.46 (2H, m), 0.62 - 0.69 (2H, m), 1.24 (3H, d), 1.50 - 1.56 (2H, m), 1.56 - 1.62 (2H, m), 1.66 - 1.78 (2H, m), 2.09 - 2.19 (2H, m), 2.54 - 2.60 (1H, m), 3.21 (1H, td), 3.28 - 3.34 (2H, m), 3.48 (1H, td), 3.63 (1H, d), 3.76 (1H, d), 3.79 - 3.88 (1H, m), 3.94 - 4.04 (3H, m), 4.22 (1H, d), 4.55 (1H, s), 6.45 (1H, s), 6.78 (1H, s), 7.52 (2H, d), 8.19 (2H, d), 8.55 (1H, s)

Example 94d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.50 - 1.56 (2H, m), 1.56 - 1.62 (2H, m), 1.64 - 1.77 (2H, m), 2.09 - 2.20 (2H, m), 3.15 - 3.23 (2H, m), 3.25 - 3.35 (2H, m), 3.43 - 3.50 (2H, m), 3.61 - 3.66 (1H, m), 3.74 - 3.87 (2H, m), 3.94 - 4.04 (3H, m), 4.22 (1H, d), 4.55 (1H, s), 4.73 (1H, t), 6.27 (1H, t), 6.78 (1H, s), 7.50 (2H, d), 8.18 (2H, d), 8.82 (1H, s)

Example 94e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.51 - 1.57 (2H, m), 1.58 - 1.62 (2H, m), 1.67 - 1.78 (2H, m), 2.10 - 2.21 (2H, m), 3.18 - 3.34 (3H, m), 3.49 (1H, td), 3.64 (1H, d), 3.73 - 3.88 (5H, m), 3.95 - 4.05 (3H, m), 4.23 (1H, d), 4.55 (1H, s), 6.79 (1H, s), 7.39 (1H, s), 7.56 (2H, d), 7.77 (1H, s), 8.22 (2H, d), 8.40 (1H, s), 8.85 (1H, s)

Example 94f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.49 - 1.77 (8H, m), 1.81 - 1.91 (2H, m), 2.09 - 2.25 (4H, m), 3.21 (1H, td), 3.26 - 3.35 (2H, m), 3.48 (1H, td), 3.63 (1H, d), 3.71 - 3.89 (2H, m), 3.94 - 4.04 (3H, m), 4.08 - 4.25 (2H, m), 4.55 (1H, s), 6.47 (1H, d), 6.78 (1H, s), 7.49 (2H, d), 8.18 (2H, d), 8.57 (1H, s)

Example 94g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.52 - 1.58 (2H, m), 1.62 - 1.70 (2H, m), 2.17 - 2.30 (2H, m), 2.66 (3H, d), 3.14 - 3.28 (1H, m), 3.49 (1H, td), 3.61 - 3.72 (2H, m), 3.73 - 3.82 (2H, m), 3.93 - 4.04 (2H, m), 4.21 (1H, d), 4.27 - 4.39 (1H, m), 4.55 (1H, s), 6.07 (1H, t), 6.79 (1H, s), 7.51 (2H, d), 8.20 (2H, d), 8.74 (1H, s)

Example 94h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.23 (3H, d), 1.52 - 1.59 (2H, m), 1.63 - 1.69 (2H, m), 2.18 - 2.30 (2H, m), 3.09 - 3.17 (2H, m), 3.17 - 3.24 (1H, m), 3.49 (1H, td), 3.61 - 3.71 (2H, m), 3.73 - 3.83 (2H, m), 3.94 - 4.02 (3H, m), 4.21 (1H, d), 4.30 - 4.38 (1H, m), 4.54 (1H, s), 6.17 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.66 (1H, s)

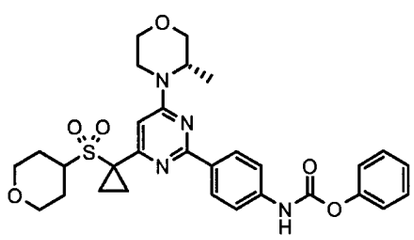
Example 94i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.40 - 0.44 (2H, m), 0.62 - 0.68 (3H, m), 1.23 (4H, d), 1.52 - 1.60 (4H, m), 1.63 - 1.70 (3H, m), 2.16 - 2.30 (3H, m), 2.52 - 2.61 (18H, m), 3.21 (3H, td), 3.49 (1H, td), 3.59 - 3.72 (3H, m), 3.72 - 3.84 (3H, m), 3.93 - 4.03 (3H, m), 4.21 (1H, d), 4.28 - 4.40 (1H, m), 4.54 (1H, s), 6.44 (1H, s), 6.80 (1H, s), 7.52 (2H, d), 8.20 (2H, d), 8.54 (1H, s)

Example 94j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.51 - 1.60 (2H, m), 1.62 - 1.69 (2H, m), 2.18 - 2.30 (2H, m), 3.14 - 3.24 (4H, m), 3.43 - 3.50 (2H, m), 3.61 - 3.71 (1H, m), 3.74 - 3.81 (2H, m), 3.94 - 4.02 (3H, m), 4.21 (1H, d), 4.30 - 4.38 (1H, m), 4.54 (1H, s), 4.69 - 4.77 (1H, m), 6.26 (1H, t), 6.79 (1H, s), 7.50 (2H, d), 8.20 (2H, d), 8.81 (1H, s)

Example 94k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.50 - 1.60 (2H, m), 1.63 - 1.68 (2H, m), 2.20 - 2.30 (2H, m), 3.16 - 3.28 (1H, m), 3.44 - 3.57 (1H, m), 3.61 - 3.70 (1H, m), 3.74 - 3.84 (4H, m), 3.94 - 4.05 (3H, m), 4.22 (1H, d), 4.31 - 4.38 (1H, m), 4.55 (1H, s), 6.81 (1H, s), 7.39 (1H, s), 7.56 (2H, d), 7.76 (1H, s), 8.24 (2H, d), 8.39 (1H, s), 8.84 (1H, s)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate



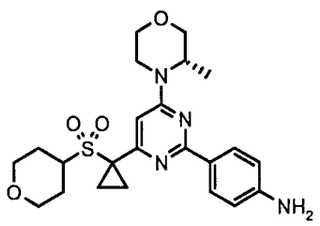
Phenyl chloroformate (0.436 mL, 3.47 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline (1.06 g, 2.31 mmol), sodium hydrogen carbonate (0.291 g, 3.47 mmol) in dioxane (40 mL) at 5°C under a nitrogen atmosphere. The resulting mixture was stirred at RT for 1.5 hours. The reaction mixture was diluted with ethyl acetate (150 mL), and washed sequentially with water (2 x 100 mL). The

organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product which was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (1.14 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.52 - 1.58 (2H, m), 1.58 - 1.64 (2H, m), 1.65 - 1.77 (2H, m), 2.10 - 2.20 (2H, m), 3.17 - 3.54 (2H, m), 3.63 (2H, d), 3.74 - 3.87 (3H, m), 3.96 - 4.04 (3H, m), 4.24 (1H, d), 4.56 (1H, s), 6.83 (1H, s), 7.20 - 7.32 (3H, m), 7.42 - 7.50 (2H, m), 7.63 (2H, d), 8.28 (2H, d), 10.45 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 579; HPLC tR = 2.8 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline



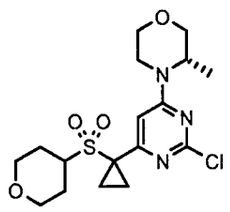
Bis(triphenylphosphine)palladium(II) chloride (0.187 g, 0.27 mmol) was added to 2-chloro-4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidine (1.6 g, 3.98 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.308 g, 5.97 mmol) and 2M aqueous sodium carbonate solution (1 mL, 2.00 mmol) in a solvent mixture of DMF (5 mL), DME (12 mL), water (1 mL) and ethanol (1 mL) at RT . The resulting mixture was stirred at 90°C for 7 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, and the crude product then further purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give a solid. The solid was further purified by trituration with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (1.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.48 - 1.53 (2H, m), 1.55 - 1.59 (2H, m), 1.66 - 1.76 (2H, m), 2.11 - 2.18 (2H, m), 3.18 (1H, dd), 3.30 - 3.34 (2H,

m), 3.47 (1H, td), 3.62 (1H, d), 3.75 (1H, d), 3.81 - 3.90 (1H, m), 3.93 - 4.05 (3H, m), 4.18 (1H, d), 4.51 (1H, s), 5.58 (2H, s), 6.62 (2H, d), 6.67 (1H, s), 8.02 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 459; HPLC tR = 2.11 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxan-4-ylsulfonyl)cyclopropyl]pyrimidine

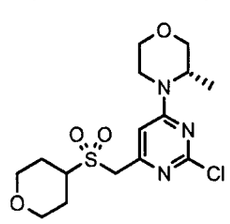


Aqueous sodium hydroxide solution (10 mL, 186.39 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxan-4-ylsulfonylmethyl)pyrimidine (1.5 g, 3.99 mmol), tetraethylammonium bromide (0.168 g, 0.80 mmol) and1,2-dibromoethane (2.75 mL, 31.93 mmol) in toluene (10 mL) at RT under a nitrogen atmosphere. After stirring at RT for 2 hours the reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 60% ethyl acetate in isohexane, to give the desired material as an oil which solidified on standing (1.64 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 - 1.25 (3H, m), 1.50 - 1.54 (2H, m), 1.55 - 1.59 (2H, m), 1.61 - 1.72 (2H, m), 1.97 - 2.07 (2H, m), 3.18 - 3.27 (1H, m), 3.26 - 3.36 (2H, m), 3.44 (1H, td), 3.58 (1H, d), 3.65 - 3.78 (2H, m), 3.90 - 4.01 (3H, m), 4.01 - 4.10 (1H, m), 4.39 (1H, s), 6.96 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 402; HPLC tR = 1.99 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxan-4-ylsulfonylmethyl)pyrimidine

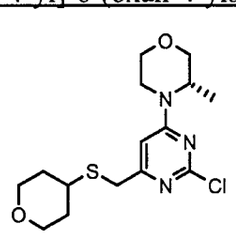


3-Chloroperoxybenzoic acid (381 mg, 2.21 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxan-4-ylsulfanylmethyl)pyrimidine (345 mg, 1.00 mmol)in DCM

(10 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 2 hours then diluted with DCM (100 mL), and washed sequentially with 10% aqueous sodium metabisulphite solution (200 mL), saturated aqueous sodium hydrogencarbonate (200 mL), dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (200 mg).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.19 - 1.26 (3H, m), 1.60 - 1.76 (2H, m), 1.95 - 2.06 (2H, m), 3.19 - 3.29 (1H, m), 3.31 - 3.39 (2H, m), 3.40 - 3.65 (3H, m), 3.74 (1H, d), 3.90 - 4.04 (3H, m), 4.30 (1H, s), 4.48 (2H, s), 6.93 (1H, s)

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxan-4-ylsulfanylmethyl)pyrimidine



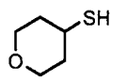
DIPEA (1.762 mL, 10.18 mmol) was added to oxane-4-thiol (1.203 g, 10.18 mmol), in acetonitrile (20 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 5mins then 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.4 g, 6.79 mmol) added. The resulting mixture was stirred at RT for 1 hour then diluted with ethyl acetate (75 mL), and washed sequentially with water (2 x 75 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give the desired material as a brown gum (2.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.39 - 1.51 (2H, m), 1.82 - 1.92 (2H, m), 2.92 - 3.02 (1H, m), 3.13 - 3.23 (1H, m), 3.26 - 3.37 (2H, m), 3.44 (1H, td), 3.54 - 3.66 (1H, m), 3.72 (1H, d), 3.78 - 3.88 (2H, m), 3.90 - 4.02 (2H, m), 4.31 (1H, s), 6.81 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 344; HPLC tR = 1.99 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Oxane-4-thiol

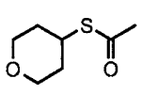


7M Ammonia in methanol (20 mL, 140.00 mmol) was added to *S*-(oxan-4-yl) ethanethioate (2.27 g, 14.17 mmol) at RT. The resulting solution was stirred at RT for 1 hour then the mixture concentrated *in vacuo* and used without further purifiaction.

NMR Spectrum: none

LCMS Spectrum: no mass ion; HPLC tR = 0.61 min.

S-(Oxan-4-yl) ethanethioate



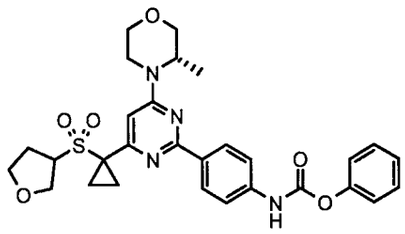
Potassium thioacetate (4.68 g, 40.98 mmol) was added to oxan-4-yl methanesulfonate (4.2 g, 23.30 mmol), in DMA (80 mL) at RT. The resulting mixture was stirred at 65°C for 18 hours. The reaction mixture was diluted with ethyl acetate (400 mL), and washed sequentially with water (2 x 150 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 30% ethyl acetate in isohexane, to give the desired material as a orange oil (2.27 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.47 - 1.65 (2H, m), 1.76 - 1.90 (2H, m), 2.35 (3H, s), 3.36 - 3.51 (2H, m), 3.53 - 3.69 (1H, m), 3.67 - 3.82 (2H, m).

LCMS Spectrum: no mass ion; HPLC tR = 1.45 min.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

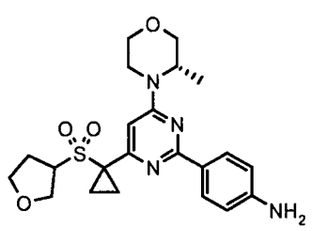
Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]carbamate



Phenyl chloroformate (0.297 mL, 2.36 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline (700 mg, 1.57 mmol), sodium hydrogen carbonate (198 mg, 2.36 mmol) in dioxane (30 mL) at 5°C under a nitrogen atmosphere. The resulting mixture was stirred at RT for 1.5 hours then diluted with ethyl acetate (150 mL), and washed sequentially with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (600 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.52 - 1.59 (2H, m), 1.64 - 1.71 (2H, m), 2.15 - 2.30 (2H, m), 3.22 (1H, td), 3.44 - 3.54 (1H, m), 3.61 - 3.70 (2H, m), 3.73 - 3.83 (2H, m), 3.94 - 4.03 (3H, m), 4.23 (1H, d), 4.30 - 4.38 (1H, m), 4.56 (1H, s), 6.84 (1H, s), 7.21 - 7.32 (3H, m), 7.41 - 7.50 (2H, m), 7.64 (2H, d), 8.30 (2H, d), 10.44 (1H, s)

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]aniline



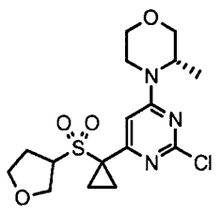
Bis(triphenylphosphine)palladium(II) chloride (0.233 g, 0.33 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidine (1.92 g, 4.95 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.627 g, 7.42 mmol) and sodium carbonate (1 mL, 2.00 mmol) in a solvent mixture of DMF (5 mL), DME (12 mL),

water (1 mL) and ethanol (1 mL) at RT. The resulting mixture was stirred at 90°C for 7 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed sequentially with water (2 x 100 mL).The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, to give a product that was further purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give a solid. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (0.821 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.22 (3H, d), 1.49 - 1.54 (2H, m), 1.61 - 1.66 (2H, m), 2.16 - 2.26 (2H, m), 3.18 (1H, dd), 3.39 - 3.53 (1H, m), 3.59 - 3.71 (3H, m), 3.70 - 3.83 (2H, m), 3.90 - 4.01 (3H, m), 4.17 (1H, d), 4.33 (1H, q), 4.51 (1H, s), 5.57 (2H, s), 6.61 (2H, d), 6.69 (1H, s), 8.03 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 447; HPLC tR = 1.91 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(oxolan-3-ylsulfonyl)cyclopropyl]pyrimidine

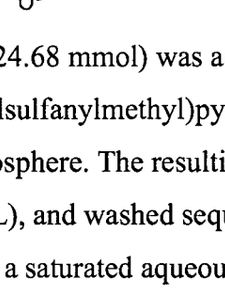


Aqueous sodium hydroxide solution (10 mL, 186.39 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxolan-3-ylsulfonylmethyl)pyrimidine (1.9 g, 5.25 mmol), tetraethylammonium bromide (0.221 g, 1.05 mmol), and1,2-dibromoethane (3.62 mL, 42.01 mmol) in toluene (30 mL) at RT under a nitrogen atmosphere. After being stirred at RT for 1.5 hours the reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (125 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 60% ethyl acetate in isohexane, to give the desired material as a colourless gum (1.92 g).

NMR Spectrum: none

LCMS Spectrum: m/z (ESI+)(M+H)+ = 388; HPLC tR = 1.91 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxolan-3-ylsulfonylmethyl)pyrimidine

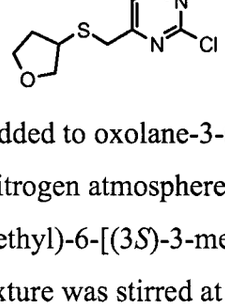


3-Chloroperoxybenzoic acid (4.26 g, 24.68 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxolan-3-ylsulfanylmethyl)pyrimidine (3.7 g, 11.22 mmol)in DCM (200 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred at RT for 2 hours then diluted with DCM (100 mL), and washed sequentially with 10% aqueous sodium metabisulphite solution (200 mL) and a saturated aqueous solution of sodium hydrogencarbonate (200 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (3.03 g).

NMR Spectrum: ^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.20 - 1.26 (3H, m), 2.18 - 2.31 (2H, m), 3.20 - 3.31 (1H, m), 3.37 - 3.52 (1H, m), 3.60 (1H, d), 3.65 - 3.77 (2H, m), 3.80 - 3.89 (1H, m), 3.90 - 3.99 (3H, m), 4.03 - 4.16 (2H, m), 4.31 (1H, s), 4.49 (2H, s), 6.94 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 362; HPLC tR = 1.59 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(oxolan-3-ylsulfanylmethyl)pyrimidine



DIPEA (3.67 mL, 21.21 mmol) was added to oxolane-3-thiol (2.210 g, 21.21 mmol), in acetonitrile (100 mL) at RT under a nitrogen atmosphere. The resulting solution was stirred for 5 minutes then 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol) added. The resulting mixture was stirred at RT for 1 hour then diluted with ethyl acetate (75 mL), and washed sequentially with water (2 x 75 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was

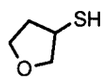
purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give the desired material as a brown gum (3.75 g).

NMR Spectrum: ^{1}H NMR (399.902MHz, DMSO-d_6) δ 1.17 - 1.24 (3H, m), 1.63 - 1.75 (2H, m), 2.17 - 2.30 (2H, m), 3.19 (1H, td), 3.40 - 3.50 (2H, m), 3.59 (1H, d), 3.63 - 3.80 (3H, m), 3.91 - 4.04 (4H, m), 4.33 (1H, s), 6.82 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 330; HPLC tR = 1.89 min.

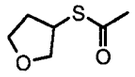
The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Oxolane-3-thiol



7M ammonia in methanol (20 mL, 140.00 mmol) was added to *S*-(Oxolan-3-yl) ethanethioate (20.47 g, 140.00 mmol) at RT. The resulting solution was stirred at RT for 1 hour then concentrated *in vacuo* to give the desired material which was used without further purification or characterisation.

S-(Oxolan-3-yl) ethanethioate

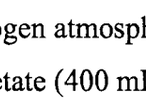


Potassium thioacetate (16.60 g, 145.31 mmol) was added to oxolan-3-yl methanesulfonate (13.8 g, 83.03 mmol), in DMA (150 mL) at RT. The resulting mixture was stirred at 65°C for 7 hours. The reaction mixture was diluted with ethyl acetate (400 mL), and washed sequentially with water (2 x 150 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 30% ethyl acetate in isohexane, to give the desired material as a brown oil (9.50 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.70 - 1.80 (1H, m), 2.25 - 2.40 (4H, m), 3.44 - 3.52 (1H, m), 3.67 - 3.81 (2H, m), 3.84 - 3.94 (1H, m), 3.97 - 4.08 (1H, m)

LCMS Spectrum: no mass ion; HPLC tR = 1.18 min.

Oxolan-3-yl methanesulfonate



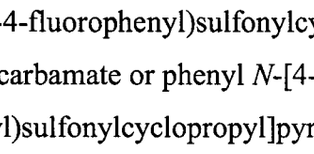
Methanesulfonyl chloride (11.86 mL, 153.23 mmol) was added dropwise to tetrahydrofuran-3-ol (9 g, 102.15 mmol) and triethylamine (21.36 mL, 153.23 mmol) in DCM (300 mL) at RT over a period of 30 minutes under a nitrogen atmosphere. The resulting mixture was stirred at RT for 1 hour then diluted with ethyl acetate (400 mL) and washed with water (250 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford the desired material, which was used without further purification.

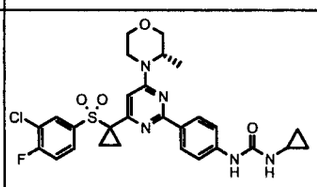
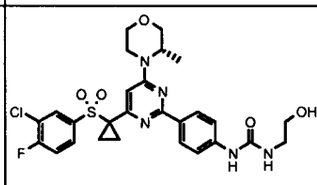
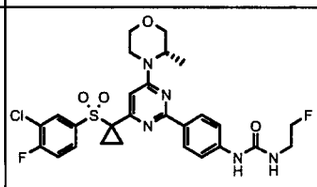
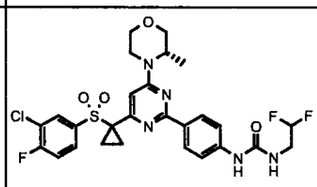
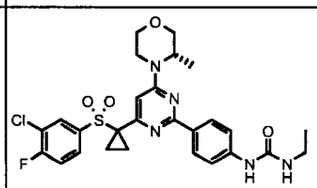
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.03 - 2.14 (1H, m), 2.17 - 2.29 (1H, m), 3.21 (3H, s), 3.69 - 3.92 (4H, m), 5.28 - 5.33 (1H, m)

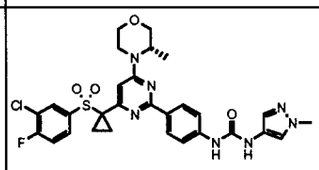
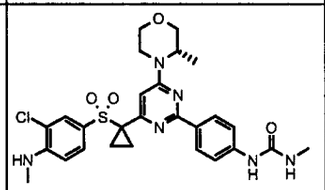
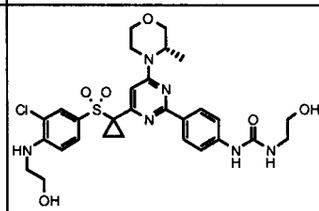
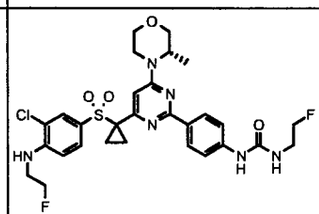
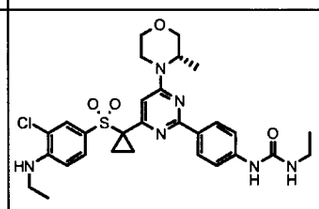
Example 95

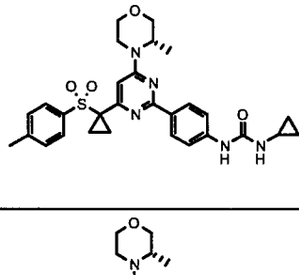
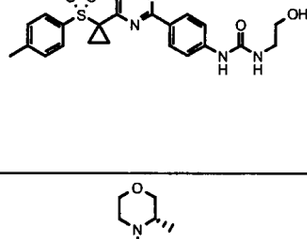
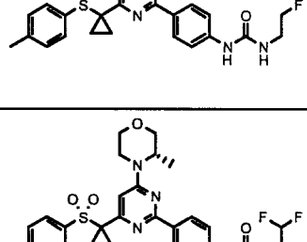
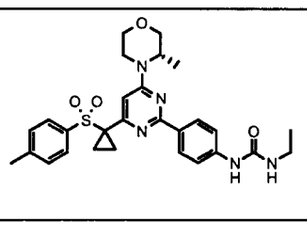
The following samples were prepared by heating a mixture of the carbamate (1 equivalent), triethylamine (4 equivalents) and the amine (1.2 equivalents) in NMP (2 mL) at 50°C for 2 hours. The compounds were purified by preparative HPLC.

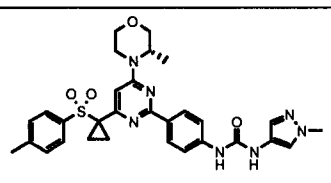
The following compounds were prepared in an analogous fashion from either phenyl *N*-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
95a		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	560	2.29

Example	Structure	NAME	LCMS MH+	Retention time (min)
95b		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea	586	2.44
95c		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	590	2.10
95d		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	592	2.41
95e		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea	610	2.54
95f		3-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-ethylurea	574	2.45

Example	Structure	NAME	LCMS MH+	Retention time (min)
95g		1-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	626	2.29
95h*		1-[4-[4-[1-(3-chloro-4-methylaminophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea	571	2.11
95i*		1-[4-[4-[1-[3-chloro-4-(2-hydroxyethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea	631	1.79
95j*		1-[4-[4-[1-[3-chloro-4-(2-fluoroethylamino)phenyl]sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	635	2.30
95k*		1-[4-[4-[1-(3-chloro-4-ethylaminophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	599	2.41

Example	Structure	NAME	LCMS MH+	Retention time (min)
95l		3-methyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	522	2.14
95m		3-cyclopropyl-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	548	2.29
95n		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	552	1.98
95o		3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	554	2.28
95p		3-(2,2-difluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	572	2.40
95q		1-ethyl-3-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea	536	2.28

Example	Structure	NAME	LCMS MH+	Retention time (min)
95r		1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	588	2.16

* 4 equivalents of amine used.

Example 95a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.64 (2H, m), 1.90 - 1.98 (2H, m), 2.68 (3H, s), 3.12 - 3.23 (1H, m), 3.46 (1H, dd), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.15 (1H, d), 4.48 (1H, s), 6.04 (1H, s), 6.67 (1H, s), 7.39 (2H, d), 7.58 - 7.68 (1H, m), 7.73 - 7.83 (3H, m), 7.99 (1H, d), 8.74 (1H, s)

Example 95b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.37 - 0.44 (2H, m), 0.60 - 0.69 (2H, m), 1.20 (3H, d), 1.60 - 1.64 (2H, m), 1.89 - 1.98 (2H, m), 2.56 - 2.60 (1H, m), 3.11 - 3.23 (1H, m), 3.42 - 3.52 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.95 (1H, d), 4.15 (1H, d), 4.49 (1H, s), 6.39 (1H, s), 6.67 (1H, s), 7.40 (2H, d), 7.57 - 7.68 (1H, m), 7.73 - 7.85 (3H, m), 7.92 - 8.03 (1H, m), 8.54 (1H, s)

Example 95c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.64 (2H, m), 1.91 - 1.96 (2H, m), 3.14 - 3.22 (2H, m), 3.40 - 3.50 (3H, m), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.16 (1H, d), 4.48 (1H, s), 4.72 (1H, t), 6.23 (1H, s), 6.67 (1H, s), 7.38 (2H, d), 7.63 (1H, t), 7.75 - 7.84 (3H, m), 7.98 (1H, d), 8.80 (1H, s)

Example 95d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.65 (2H, m), 1.88 - 1.97 (2H, m), 3.36 - 3.51 (4H, m), 3.62 (1H, d), 3.75 (1H, d), 3.95 (1H, d), 4.12 - 4.23 (1H, m), 4.41 (1H, t), 4.45 - 4.51 (1H, m), 4.53 (1H, t), 6.40 (1H, s), 6.68 (1H, s), 7.39 (2H, d), 7.60 - 7.69 (1H, m), 7.72 - 7.86 (3H, m), 7.99 (1H, d), 8.81 (1H, s)

Example 95e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.65 (2H, m), 1.89 - 1.97 (2H, m), 3.12 - 3.22 (1H, m), 3.41 - 3.64 (3H, m), 3.75 (1H, d), 3.96 (1H, d), 4.15 (1H, d), 4.49 (1H, s), 5.87 - 6.22 (1H, m), 6.49 (1H, t), 6.68 (1H, s), 7.40 (2H, d), 7.63 (1H, t), 7.77 - 7.86 (3H, m), 7.97 - 8.00 (1H, m), 8.92 (1H, s)

Example 95f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.07 (3H, t), 1.20 (3H, d), 1.59 - 1.65 (2H, m), 1.90 - 1.98 (2H, m), 3.09 - 3.21 (3H, m), 3.42 - 3.52 (1H, m), 3.61 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.09 - 4.21 (1H, m), 4.44 - 4.53 (1H, m), 6.12 (1H, t), 6.67 (1H, s), 7.39 (2H, d), 7.63 (1H, t), 7.75 - 7.85 (3H, m), 7.99 (1H, d), 8.66 (1H, s)

Example 95g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.59 - 1.66 (2H, m), 1.91 - 1.99 (2H, m), 3.11 - 3.21 (1H, m), 3.47 (1H, td), 3.62 (1H, d), 3.70 - 3.83 (4H, m), 3.96 (1H, d), 4.17 (1H, d), 4.49 (1H, s), 6.69 (1H, s), 7.38 (1H, s), 7.44 (2H, d), 7.64 (1H, t), 7.75 - 7.85 (3H, m), 7.99 (1H, d), 8.34 (1H, s), 8.84 (1H, s)

Example 95h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.53 - 1.59 (2H, m), 1.77 - 1.83 (2H, m), 2.63 - 2.67 (3H, m), 2.82 (3H, d), 3.10 - 3.19 (1H, m), 3.46 (1H, dd), 3.61 (1H, d), 3.75 (1H, d), 3.95 (1H, d), 4.09 (1H, d), 4.39 (1H, s), 6.00 - 6.08 (1H, m), 6.47 (1H, t), 6.59 (1H, s), 6.70 (1H, d), 7.41 (2H, d), 7.48 - 7.57 (2H, m), 7.94 (2H, d), 8.70 (1H, s)

Example 95i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.53 - 1.60 (2H, m), 1.77 - 1.83 (2H, m), 3.14 - 3.19 (2H, m), 3.25 - 3.32 (2H, m), 3.39 - 3.50 (3H, m), 3.55 - 3.65 (3H, m), 3.75 (1H, d), 3.96 (1H, d), 4.10 (1H, d), 4.38 (1H, s), 4.73 (1H, t), 4.82 (1H, t), 6.15 (1H, t), 6.24 (1H, t), 6.59 (1H, s), 6.84 (1H, d), 7.40 (2H, d), 7.48 (2H, d), 7.54 (1H, d), 7.95 (2H, d), 8.76 (1H, s)

Example 95j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.52 - 1.60 (2H, m), 1.78 - 1.83 (2H, m), 3.09 - 3.19 (1H, m), 3.35 - 3.49 (4H, m), 3.52 - 3.58 (1H, m), 3.57 - 3.65 (2H, m), 3.74 (1H, d), 3.95 (1H, d), 4.07 (1H, d), 4.37 - 4.44 (2H, m), 4.49 - 4.55 (1H, m), 4.63 (1H, t), 6.38 - 6.50 (2H, m), 6.58 (1H, s), 6.89 (1H, d), 7.40 (2H, d), 7.48 (2H, d), 7.53 (1H, s), 7.96 (2H, d), 8.76 (1H, s)

Example 95k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.13 - 1.21 (6H, m), 1.49 - 1.58 (2H, m), 1.78 - 1.82 (2H, m), 3.08 - 3.18 (2H, m), 3.22 - 3.33 (7H, m), 3.46 (1H, dd), 3.61 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.09 (1H, d), 4.39 (1H, s), 6.13 (1H, t), 6.28 (1H, t), 6.59 (1H, s), 6.77 (1H, d), 7.39 (2H, d), 7.46 (2H, d), 7.52 (1H, s), 7.96 (2H, d), 8.61 (1H, s)

Example 95l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.56 - 1.64 (2H, m), 1.82 - 1.89 (2H, m), 2.40 (3H, s), 2.68 (3H, s), 3.08 - 3.17 (1H, m), 3.45 (1H, td), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.10 (1H, d), 4.38 (1H, s), 6.04 (1H, t), 6.61 (1H, s), 7.33 - 7.44 (4H, m), 7.66 (2H, d), 7.82 (2H, d), 8.70 (1H, s)

Example 95m: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.42 - 0.50 (2H, m), 0.66 - 0.75 (2H, m), 1.23 (3H, d), 1.60 - 1.69 (2H, m), 1.87 - 1.98 (2H, m), 2.46 (3H, s), 2.62 - 2.70 (1H, m),

3.19 (1H, td), 3.46 - 3.57 (1H, m), 3.66 (1H, d), 3.80 (1H, d), 4.01 (1H, d), 4.16 (1H, d), 4.43 (1H, s), 6.46 (1H, s), 6.67 (1H, s), 7.39 - 7.49 (4H, m), 7.71 (2H, d), 7.88 (2H, d), 8.56 (1H, s)

Example 95n: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.57 - 1.65 (2H, m), 1.83 - 1.90 (2H, m), 2.42 (3H, s), 3.13 - 3.20 (3H, m), 3.40 - 3.50 (3H, m), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.09 (1H, d), 4.37 (1H, s), 4.72 (1H, t), 6.22 (1H, t), 6.61 (1H, s), 7.35 - 7.43 (4H, m), 7.66 (2H, d), 7.82 (2H, d), 8.77 (1H, s)

Example 95o: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.56 - 1.65 (2H, m), 1.81 - 1.90 (2H, m), 2.40 (3H, s), 3.07 - 3.22 (1H, m), 3.36 - 3.50 (3H, m), 3.60 (1H, d), 3.74 (1H, d), 3.96 (1H, d), 4.12 (1H, d), 4.33 - 4.45 (2H, m), 4.53 (1H, t), 6.41 (1H, t), 6.61 (1H, s), 7.34 - 7.43 (4H, m), 7.66 (2H, d), 7.83 (2H, d), 8.77 (1H, s)

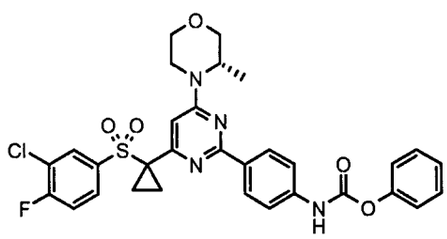
Example 95p: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.56 - 1.65 (2H, m), 1.82 - 1.91 (2H, m), 2.40 (3H, s), 3.10 - 3.18 (1H, m), 3.41 - 3.65 (4H, m), 3.74 (1H, d), 3.96 (1H, d), 4.09 (1H, d), 4.37 (1H, s), 5.91 - 6.23 (1H, m), 6.50 (1H, t), 6.62 (1H, s), 7.35 - 7.44 (4H, m), 7.66 (2H, d), 7.84 (2H, d), 8.89 (1H, s)

Example 95q: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.06 (3H, t), 1.17 (3H, d), 1.52 - 1.66 (2H, m), 1.85 - 1.90 (2H, m), 2.40 (3H, s), 3.07 - 3.20 (3H, m), 3.45 (1H, td), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.12 (1H, d), 4.37 (1H, s), 6.13 (1H, t), 6.61 (1H, s), 7.35 - 7.44 (4H, m), 7.66 (2H, d), 7.82 (2H, d), 8.62 (1H, s)

Example 95r: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.57 - 1.66 (2H, m), 1.84 - 1.90 (2H, m), 2.41 (3H, s), 3.08 - 3.18 (1H, m), 3.46 (1H, td), 3.61 (1H, d), 3.72 - 3.83 (4H, m), 3.96 (1H, d), 4.10 (1H, d), 4.37 (1H, s), 6.62 (1H, s), 7.35 - 7.49 (5H, m), 7.66 (2H, d), 7.76 (1H, s), 7.86 (2H, d), 8.35 (1H, s), 8.80 (1H, s)

The preparation of phenyl *N*-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

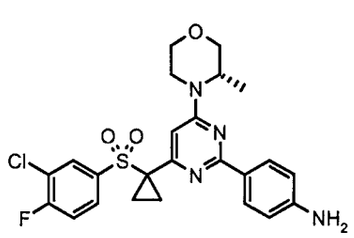


Sodium hydrogen carbonate (0.501 g, 5.96 mmol) was added to 4-[4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (2 g, 3.98 mmol) in dioxane (30 mL) at 5°C under nitrogen. Phenyl chloroformate (0.749 mL, 5.96 mmol) was then added and the resulting mixture stirred at RT for 2 hours. The reaction mixture was diluted with DCM (50 mL) and washed with water (75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (1.45 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.59 - 1.66 (2H, m), 1.91 - 1.96 (2H, m), 3.12 - 3.24 (1H, m), 3.40 - 3.52 (1H, m), 3.62 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.18 (1H, d), 4.50 (1H, s), 6.74 (1H, s), 7.23 - 7.32 (3H, m), 7.41 - 7.49 (2H, m), 7.54 (2H, d), 7.58 - 7.68 (1H, m), 7.79 - 7.83 (1H, m), 7.88 (2H, d), 7.96 - 8.02 (1H, m), 10.40 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 622; HPLC tR = 3.21 min.

4-[4-[1-(3-Chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



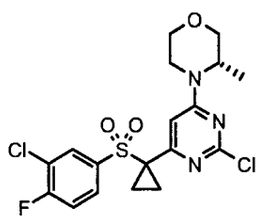
Bis(triphenylphosphine)palladium(II) chloride (0.242 g, 0.35 mmol) was added to 2-chloro-4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine (2.3 g, 5.15 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

(1.411 g, 6.44 mmol) and 2M aqueous sodium carbonate solution (3 mL, 6.00 mmol) in a solvent mixture of DMF (5 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT. The resulting mixture was stirred at 90°C, under an inert atmosphere for 5 hours then left at RT for 16 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and washed sequentially with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 80% ethyl acetate in isohexane, to give the desired material as a yellow gum (2.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.57 - 1.61 (2H, m), 1.87 - 1.96 (2H, m), 3.14 (1H, td), 3.41 - 3.50 (1H, m), 3.60 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.13 (1H, d), 4.44 (1H, s), 5.52 (1H, d), 6.49 (2H, d), 6.57 (1H, s), 7.57 - 7.68 (3H, m), 7.75 - 7.85 (1H, m), 7.99 (1H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 503; HPLC tR = 2.66 min.

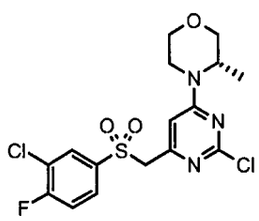
2-Chloro-4-[1-(3-chloro-4-fluorophenyl)sulfonylcyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine



Aqueous sodium hydroxide solution (20 mL, 142.76 mmol) was added to 2-chloro-4-[(3-chloro-4-fluorophenyl)sulfonylmethyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (2.5 g, 5.95 mmol), 1,2-dibromoethane (2.56 mL, 29.74 mmol) and tetrabutylammonium bromide (0.192 g, 0.59 mmol) in toluene (100 mL) at RT under a nitrogen atmosphere and the mixture stirred for 3 hours. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give the desired material as a colourless gum (2.3 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.98 (1H, d), 1.18 (3H, d), 1.54 - 1.61 (2H, m), 1.84 - 1.91 (2H, m), 3.15 (1H, td), 3.36 - 3.45 (1H, m), 3.55 (1H, d), 3.70 (1H, d), 3.90 (1H, d), 4.08 (1H, s), 4.31 (1H, s), 6.74 (1H, s), 7.62 - 7.71 (1H, m), 7.76 - 7.83 (1H, m)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 446; HPLC tR = 2.56 min.

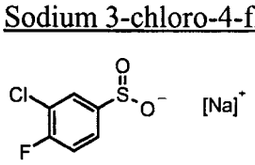
2-Chloro-4-[(3-chloro-4-fluorophenyl)sulfonylmethyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidine



Sodium 3-chloro-4-fluorobenzenesulfinate (3.52 g, 16.26 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol) in acetonitrile (150 mL) at RT under a nitrogen atmosphere. The resulting mixture was stirred at 80°C for 3 hours. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with water (100 mL), The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 70% ethyl acetate in isohexane, to give a colourless oil which solidified on standing. The crude solid was triturated with a mixture of diethyl ether and isohexane to give the desired material as a white solid (4.0 g).
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 3.18 (1H, dd), 3.28 (1H, d), 3.43 (1H, td), 3.58 (1H, d), 3.72 (1H, d), 3.94 (1H, d), 4.21 (1H, s), 4.73 (2H, s), 6.78 (1H, s), 7.66 - 7.74 (1H, m), 7.78 - 7.87 (1H, m), 8.02 (1H, d)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 420; HPLC tR = 2.38 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Sodium 3-chloro-4-fluorobenzenesulfinate

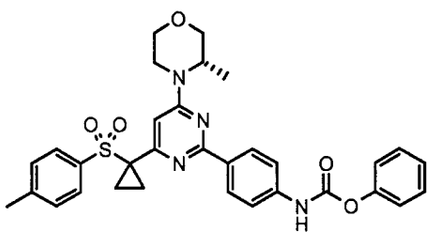


A solution of sodium sulfite (8.25 g, 65.49 mmol) in water (75 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (11.0 g, 130.97 mmol) was added to the stirred solution and the resulting solution stirred at 50°C for 1 hour. 3-Chloro-4-fluorobenzene-1-sulfonyl chloride (15 g, 65.49 mmol) was added portionwise to the solution and was stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (300 mL). The suspension was allowed to stir at RT for 20 minutes then filtered and the filtrate evaporated to afford the desired material as a white solid, which was air dried overnight under vacuum and used without further purification (16.5 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.34 (1H, t), 7.40 - 7.46 (1H, m), 7.58 (1H, d)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]carbamate



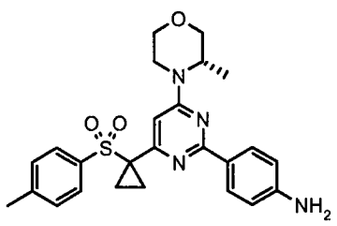
Sodium hydrogen carbonate (0.570 g, 6.78 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]aniline (2.1 g, 4.52 mmol) in dioxane (6 mL) at 5°C under a nitrogen atmosphere. Phenyl chloroformate (0.852 mL, 6.78 mmol) was then added and the resulting mixture stirred at RT for 2 hours. The reaction mixture was diluted with DCM (50 mL) and washed with water (75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (1.52 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.17 (3H, d), 1.58 - 1.64 (2H, m), 1.85 - 1.91 (2H, m), 2.40 (3H, s), 3.09 - 3.23 (1H, m), 3.41 - 3.51 (1H, m), 3.60 (1H, d), 3.75 (1H, d), 3.96 (1H, d), 4.12 (1H, d), 4.39 (1H, s), 6.65 (1H, s), 7.21 - 7.31 (3H, m), 7.36 - 7.41

(2H, m), 7.42 - 7.48 (2H, m), 7.50 - 7.56 (2H, m), 7.63 - 7.71 (2H, m), 7.89 (2H, d), 10.38 (1H, s)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 535; HPLC tR = 3.1 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]aniline

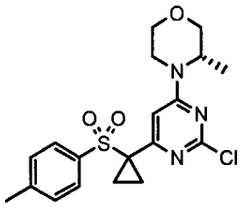


Bis(triphenylphosphine)palladium(II) chloride (0.225 g, 0.32 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidine (1.95 g, 4.78 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.362 g, 6.21 mmol) and 2M aqueous sodium carbonate solution (3 mL, 6.00 mmol) in a solvent mixture of DMF (5 mL), DME (8 mL), water (2 mL) and ethanol (1.5 mL) at RT. The resulting mixture was stirred at 90°C for 5 hours under an inert atmosphere, then left at RT for 16 hours. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 80% ethyl acetate in isohexane, to give crude material which was further purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give the desired material as a white solid (2.1 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 1.54 - 1.63 (2H, m), 1.81 - 1.89 (2H, m), 1.99 (3H, s), 3.11 (1H, td), 3.37 - 3.49 (1H, m), 3.59 (1H, d), 3.73 (1H, d), 3.94 (1H, d), 4.06 (1H, s), 4.32 (1H, s), 5.50 (1H, s), 6.50 (3H, d), 7.38 (2H, d), 7.62 - 7.72 (4H, m)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 465; HPLC tR = 2.48 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(4-methylphenyl)sulfonylcyclopropyl]pyrimidine

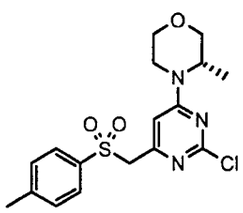


Aqueous sodium hydroxide solution (20 mL, 125.69 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine (2 g, 5.24 mmol), 1,2-dibromoethane (2.257 mL, 26.19 mmol) and tetrabutylammonium bromide (0.169 g, 0.52 mmol) in DCM (100 mL) at RT under a nitrogen atmosphere then stirred for 3 hours. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 60% ethyl acetate in isohexane, to give the desired material as a colourless gum (1.9 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.13 (3H, d), 1.52 - 1.56 (2H, m), 1.79 - 1.84 (2H, m), 1.99 (3H, s), 3.12 (1H, td), 3.35 - 3.47 (1H, m), 3.54 (1H, d), 3.71 (1H, d), 3.84 - 3.95 (2H, m), 4.17 (1H, s), 6.63 (1H, s), 7.41 (2H, d), 7.63 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 408; HPLC tR = 2.35 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methylphenyl)sulfonylmethyl]pyrimidine

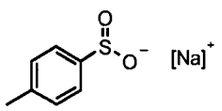


Sodium 4-methylbenzenesulfinate (2.9 g, 16.28 mmol) was added to 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine (5 g, 14.14 mmol), in acetonitrile (150 mL) at RT under a nitrogen atmosphere. The resulting mixture was stirred at 80°C for 3 hours. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with water (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 40% ethyl acetate in isohexane, to give the desired material as a beige solid (3.10 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.15 (3H, d), 2.41 (3H, s), 3.14 (1H, td), 3.38 - 3.46 (1H, m), 3.56 (1H, d), 3.71 (1H, d), 3.80 - 3.96 (2H, m), 4.13 (1H, s), 4.60 (2H, s), 6.60 (1H, s), 7.43 (2H, d), 7.66 (2H, d)
LCMS Spectrum: m/z (ESI+)(M+H)+ = 382; HPLC tR = 2.16 min.

The preparation of 2-chloro-4-(iodomethyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidine was described earlier.

Sodium 4-methylbenzenesulfinate

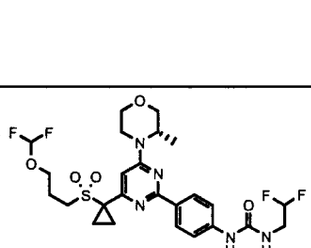
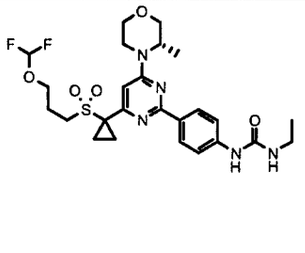
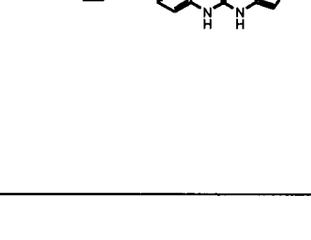


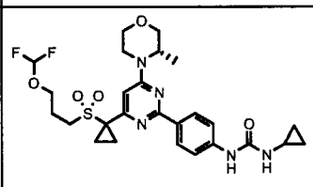
A solution of sodium sulfite (9.92 g, 78.68 mmol) in water (75 mL) was stirred at RT for 10 minutes. Sodium bicarbonate (13.22 g, 157.36 mmol) was added to the stirred solution. The resulting solution was stirred at 50°C for 1 hour. 4-Methylbenzene-1-sulfonyl chloride (15 g, 78.68 mmol) was added portionwise to the solution and was stirred at 50°C for 18 hours. The reaction mixture was evaporated to dryness and redissolved in methanol (400 mL). The suspension was allowed to stir at RT for 20 minutes then filtered and the filtrate evaporated to afford the desired material as a white solid, which was air dried overnight under vacuum and used without further purification (17.3 g).

Example 96

The following samples were prepared by heating a mixture of the carbamate (1 equivalent), triethylamine (4 equivalents) and the amine (4 equivalents) in NMP (2 mL) at RT for between 2 –16 hours. The compounds were purified by preparative HPLC.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate (contaminated with phenyl *N*-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]propyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate) and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
96a		1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea	572	2.28
96b.		3-(2,2-difluoroethyl)-1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	590	2.32
96c		1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-ethylurea	554	2.21
96d		1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1-methylpyrazol-4-yl)urea	606	2.09

Example	Structure	NAME	LCMS MH+	Retention time (min)
96e		3-cyclopropyl-1-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]urea	none	

Example 96a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.54 - 1.59 (2H, m), 1.62 - 1.69 (2H, m), 2.09 - 2.18 (2H, m), 3.17 - 3.25 (1H, m), 3.35 - 3.42 (1H, m), 3.43 - 3.52 (2H, m), 3.56 - 3.66 (3H, m), 3.78 (1H, d), 3.94 - 4.02 (3H, m), 4.21 (1H, d), 4.42 (1H, t), 4.52 - 4.60 (2H, m), 6.43 (1H, t), 6.47 - 6.89 (1H, m), 6.77 (1H, s), 7.49 (2H, d), 8.20 (2H, d), 8.81 (1H, s)

Example 96b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.23 (3H, d), 1.53 - 1.60 (2H, m), 1.62 - 1.69 (2H, m), 2.08 - 2.17 (2H, m), 3.16 - 3.25 (1H, m), 3.43 - 3.66 (6H, m), 3.76 (1H, d), 3.94 - 4.00 (3H, m), 4.22 (1H, d), 4.56 (1H, s), 5.91 - 6.23 (1H, m), 6.43 - 6.88 (1H, m), 6.52 (1H, t), 6.77 (1H, s), 7.50 (2H, d), 8.21 (2H, d), 8.93 (1H, s)

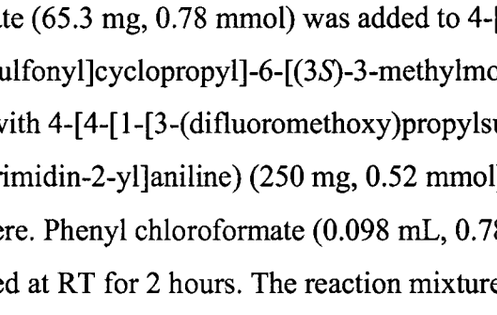
Example 96c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, t), 1.23 (3H, d), 1.54 - 1.60 (2H, m), 1.63 - 1.69 (2H, m), 2.09 - 2.18 (2H, m), 3.07 - 3.25 (3H, m), 3.48 (1H, td), 3.55 - 3.66 (3H, m), 3.76 (1H, d), 3.93 - 4.01 (3H, m), 4.21 (1H, d), 4.56 (1H, s), 6.15 (1H, t), 6.42 - 6.88 (1H, m), 6.76 (1H, s), 7.49 (2H, d), 8.18 (2H, d), 8.66 (1H, s)

Example 96d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.55 - 1.60 (2H, m), 1.63 - 1.69 (2H, m), 2.09 - 2.18 (2H, m), 3.18 - 3.26 (1H, m), 3.44 - 3.53 (1H, m), 3.55 - 3.67 (3H, m), 3.72 - 3.80 (4H, m), 3.93 - 4.03 (3H, m), 4.22 (1H, d), 4.57 (1H, s), 6.43 - 6.86 (1H, m), 6.78 (1H, s), 7.38 (1H, s), 7.54 (2H, d), 7.77 (1H, s), 8.22 (2H, d), 8.37 (1H, s), 8.85 (1H, s)

Example 96e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.38-0.40 (2H,m), 0.61-0.64 (2H,m), 1.20-1.22 (3H,d), 1.51-1.53 (2H,m), 1.61-1.64 (2H,m), 2.18-2.24 (2H,m), 2.52-2.58 (1H,m), 3.18-3.20 (1H,dd), 3.55-3.68 (3H,m), 3.72-3.78 (1H,m), 3.90-3.95 (3H,m), 4.20 (1H,s), 4.55 (1H,s), 6.40 (1H,s), 6.60 (1H,s), 7.45 (2H,d), 8.18 (2H,d), 8.54 (1H,s)

The preparation of phenyl *N*-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate

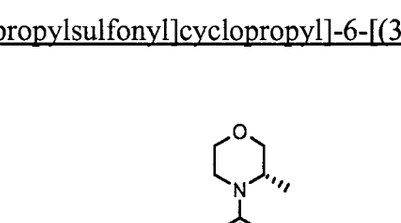


Sodium hydrogen carbonate (65.3 mg, 0.78 mmol) was added to 4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (contaminated with 4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]propyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline) (250 mg, 0.52 mmol) in dioxane (6 mL) at 5°C under a nitrogen atmosphere. Phenyl chloroformate (0.098 mL, 0.78 mmol) was added and the resulting mixture stirred at RT for 2 hours. The reaction mixture was diluted with DCM (50 mL), the organics dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude material was triturated with a mixture of diethyl ether and isohexane to give the desired material (contaminated with phenyl *N*-[4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]propyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]carbamate) as a cream solid (200 mg). The material was used without further purification.

NMR Spectrum: none

LCMS Spectrum: m/z (ESI+)(M+H)+ = 604; HPLC tR = 2.97 min.

4-[4-[1-[3-(Difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline



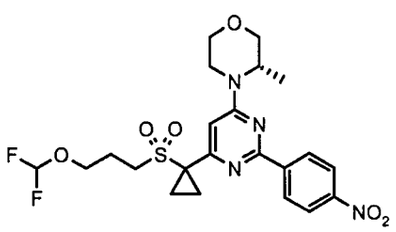
5% Palladium on charcoal (400 mg, 3.6 mmol) was added to 4-[1-[3-(difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]-2-(4-nitrophenyl)pyrimidine (2 g, 3.90 mmol) in ethyl acetate (200 mL) and methanol (30 mL) at RT. The flask was evacuated and the atmosphere replaced with first nitrogen and then hydrogen and the mixture left to stir under hydrogen at RT for 36 hours. The crude product was purified by flash silica chromatography, elution gradient 30 to 90% ethyl acetate in isohexane, to give a white solid (1.7 g) which appears to be the desired material (~30%) contaminated with 4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]propyl]-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline (~60%). The material was used without further purification.

NMR Spectrum: none

LCMS Spectrum: m/z (ESI+)(M+H)+ = 483; HPLC tR = 1.76 min.

LCMS Spectrum: (4-[4-[1-[3-(difluoromethoxy)propylsulfonyl]propyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]aniline) m/z (ESI+)(M+H)+ = 485; HPLC tR = 2.0 min.

4-[1-[3-(Difluoromethoxy)propylsulfonyl]cyclopropyl]-6-[(3*S*)-3-methylmorpholin-4-yl]-2-(4-nitrophenyl)pyrimidine

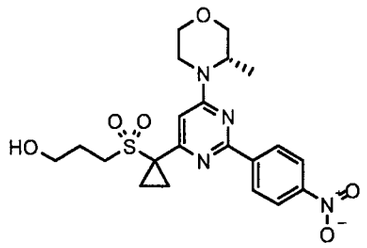


A solution of 2,2-difluoro-2-(fluorosulfonyl)acetic acid (4.56 mL, 44.11 mmol) in acetonitrile (25 mL) was added dropwise over 1.5 hours to a stirred solution of 3-[1-[6-[(3*S*)-3-methylmorpholin-4-yl]-2-(4-nitrophenyl)pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol (3.4g, 7.35 mmol) and copper(I) iodide (280 mg, 1.47 mmol) in acetonitrile (100 mL) at 55°C under a nitrogen atmosphere. The mixture was stirred at 55°C for a further 1 hour then diluted with ethyl acetate (300 mL) and washed with water (100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (2.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.26 (3H, d), 1.59 - 1.64 (2H, m), 1.67 - 1.72 (2H, m), 2.11 - 2.17 (2H, m), 3.22 - 3.28 (1H, m), 3.46 - 3.59 (3H, m), 3.65 (1H, d), 3.78 (1H, d), 3.93 - 4.01 (3H, m), 4.25 (1H, s), 4.61 (1H, s), 6.96 (1H, s), 8.33 (2H, d), 8.55 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 513; HPLC tR = 2.87 min.

3-[1-[6-[(3*S*)-3-Methylmorpholin-4-yl]-2-(4-nitrophenyl)pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol



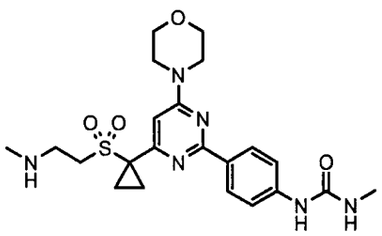
Bis(triphenylphosphine)palladium(II) chloride (0.636 g, 0.91 mmol) was added to 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane (7.2 g, 13.53 mmol), 2M aqueous sodium carbonate solution (15 mL, 30.00 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nitrobenzene (6.74 g, 27.06 mmol) in DME (100 mL) and water (5 mL) at RT. The mixture was stirred at 90°C for 16 hours under a nitrogen atmosphere then allowed to cool. The reaction mixture was diluted with ethyl acetate (400 mL), and washed sequentially with water (100 mL) then additional water (200 mL).The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was dissolved in DCM then tetrabutylammonium fluoride (67.6 mL, 67.64 mmol) added and left to stir for 1 hour. A saturated aqueous solution of ammonium chloride was added, the organics separated and dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 10 to 100% ethyl acetate in isohexane, to give crude material which was further purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, to give the desired material as a brown solid (3.60 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.26 (3H, d), 1.56 - 1.63 (2H, m), 1.66 - 1.70 (2H, m), 1.91 - 1.98 (2H, m), 3.22 - 3.29 (3H, m), 3.47 - 3.57 (3H, m), 3.65 (1H, d), 3.78 (1H, d), 3.99 (1H, dd), 4.25 (1H, d), 4.60 (1H, s), 4.72 (1H, t), 6.96 (1H, s), 8.33 (2H, d), 8.58 (2H, d)

LCMS Spectrum: m/z (ESI+)(M+H)+ = 463; HPLC tR = 2.37 min.

The preparation of 3-[1-[2-chloro-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropoxy-tri(propan-2-yl)silane was described earlier.

Example 97: 3-Methyl-1-[4-[4-[1-(2-methylaminoethylsulfonyl)cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea



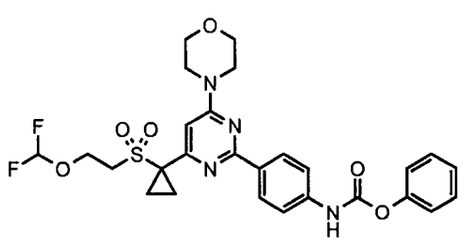
Methylamine (2 M in THF, 4 equivalents) was added to phenyl *N*-[4-[4-[1-[2-(difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate in NMP and resulting solution stirred at RT for 30 minutes then purified by preparative HPLC to give the desired material (0.012 g)

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.52 - 1.57 (2H, m), 1.62 - 1.66 (2H, m), 2.67 (3H, d), 2.92 - 3.01 (2H, m), 3.31 (3H, s), 3.55 - 3.64 (2H, m), 3.72 (8H, s), 6.06 (1H, t), 6.81 (1H, s), 7.50 (2H, d), 8.21 (2H, d), 8.75 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 475; HPLC tR = 1.65 min.

The preparation of phenyl *N*-[4-[4-[1-[2-(difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[1-[2-(difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]phenyl]carbamate

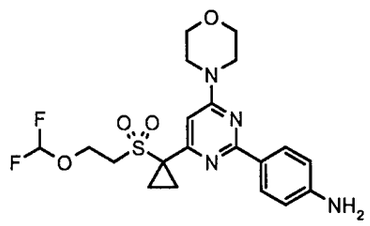


Sodium hydrogen carbonate (1.5 equivalents) was added to 4-[4-[1-[2-(difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline (1 equivalent) in dioxane at 5°C under nitrogen. Phenyl chloroformate (1.5 equivalents) was then added. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with DCM, the organics dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of ethyl acetate and isohexane to give the desired material as a cream solid.

NMR Spectrum: none

LCMS Spectrum: m/z (ESI+) (M+H)+ = 575; HPLC tR = 2.8 min.

4-[4-[1-[2-(Difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-ylpyrimidin-2-yl]aniline

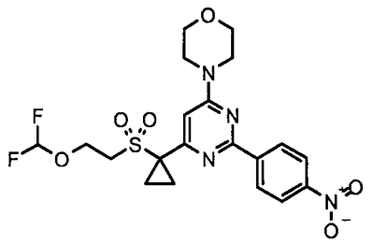


Palladium, 5% On Charcoal (6.59 mg, 0.06 mmol) was added to 4-[1-[2-(difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-yl-2-(4-nitrophenyl)pyrimidine (150 mg, 0.31 mmol), in ethyl acetate (20 mL) and methanol (3 mL) at RT and left to stir under an atmosphere of hydrogen for 24 hours. The mixture was filtered through celite® and the filtrate purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give the desired material as a yellow gum (90 mg).

NMR Spectrum: none

LCMS Spectrum: m/z (ESI+) (M+H)+ = 455; HPLC tR = 2.2 min.

4-[1-[2-(Difluoromethoxy)ethylsulfonyl]cyclopropyl]-6-morpholin-4-yl-2-(4-nitrophenyl)pyrimidine

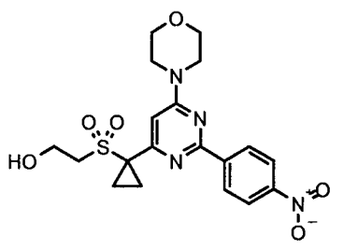


A solution of 2,2-difluoro-2-(fluorosulfonyl)acetic acid (0.856 mL, 8.29 mmol) in acetonitrile (4 mL) was added dropwise over 1 hour to a stirred solution of 2-[1-[6-morpholin-4-yl-2-(4-nitrophenyl)pyrimidin-4-yl]cyclopropyl]sulfonylethanol (480 mg, 1.10 mmol) and copper(I) iodide (742 mgl, 0.22 mmol) in acetonitrile (15 mL) at 55°C under a nitrogen atmosphere. The mixture was stirred at 55°C for 90 minutes, allowed to cool and diluted with ethyl acetate (300 mL) and washed with water (100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, to give the desired material as a yellow solid (195 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.59 - 1.68 (2H, m), 1.70 - 1.78 (2H, m), 3.70 - 3.81 (8H, m), 3.88 - 3.96 (2H, m), 4.28 - 4.35 (2H, m), 7.01 (1H, s), 8.33 (2H, d), 8.56 (2H, d)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 485; HPLC tR = 2.73 min.

2-[1-[6-Mrpholin-4-yl-2-(4-nitrophenyl)pyrimidin-4-yl]cyclopropyl]sulfonylethanol



Bis(triphenylphosphine)palladium(II) chloride (84 mg, 0.12 mmol) was added to 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane (900 mg, 1.79 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nitrobenzene (889 mg, 3.57 mmol) and 2M aqueous solution of sodium carbonate (3 mL, 6.00 mmol) in a solvent mixture of DME (25 mL) and water (1 mL). The mixture was stirred at 90°C for 18 hours

under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (100 mL), and washed with water (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was dissolved in DCM then 1M solution of tetrabutylammonium fluoride (8.93 mL, 8.93 mmol) added and left to stir 1 hour. A saturated aqueous solution of ammonium chloride was added, the layers separated and the organics dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash silica chromatography, elution gradient 10 to 70% ethyl acetate in isohexane, to give a material which was further purified by ion exchange chromatography using an SCX column, eluting with 7M ammonia in methanol, and finally triturated with a mixture of diethyl ether and isohexane to give the desired material as a beige solid (670 mg).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.53 - 1.62 (2H, m), 1.65 - 1.73 (2H, m), 3.56 - 3.67 (2H, m), 3.66 - 3.82 (8H, m), 3.80 - 3.97 (2H, m), 5.01 (1H, t), 7.01 (1H, s), 8.34 (2H, d), 8.57 (2H, d)

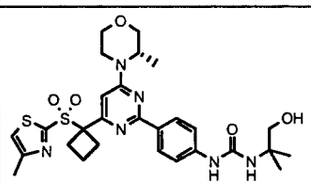
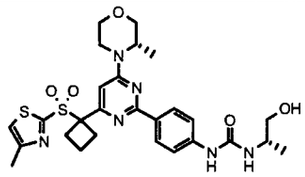
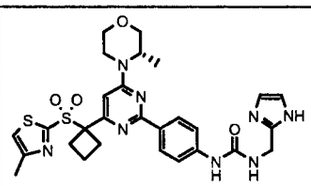
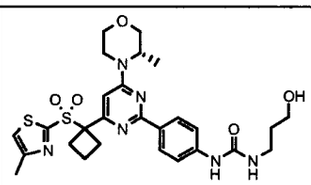
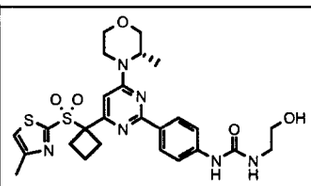
LCMS Spectrum: m/z (ESI+) (M+H)+ = 435; HPLC tR = 2.18 min.

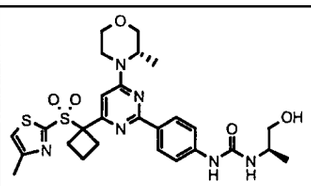
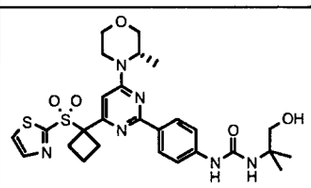
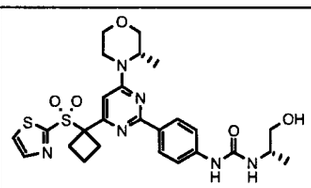
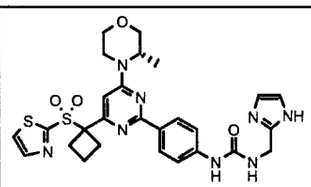
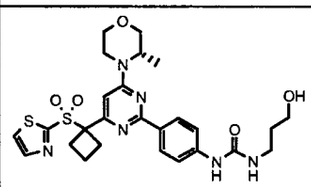
The preparation of 2-[1-(2-chloro-6-morpholin-4-ylpyrimidin-4-yl)cyclopropyl]sulfonylethoxy-tri(propan-2-yl)silane was described earlier.

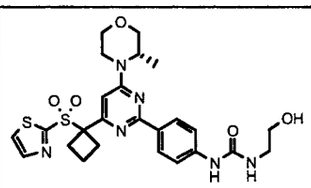
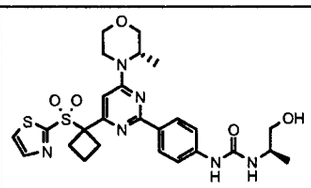
Example 98

The following samples were prepared by heating a mixture of the carbamate (1 equivalent), triethylamine (4 equivalents) and the amine (4 equivalents) in NMP (2 mL) at 50°C for 2 hours. The compounds were purified by preparative HPLC.

The following compounds were prepared in an analogous fashion from phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]carbamate or phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]carbamate and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
98a		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	601	2.49
98b		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	587	2.25
98c		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	609	2.22
98d		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	587	2.18
98e		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	573	2.14

Example	Structure	NAME	LCMS MH+	Retention time (min)
98f		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea	587	2.24
98g		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	587	2.41
98h		3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	573	2.20
98i		3-(1H-imidazol-2-ylmethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	595	2.17
98j		3-(3-hydroxypropyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	573	2.13

Example	Structure	NAME	LCMS MH+	Retention time (min)
98k		3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	559	2.09
98l		3-[(2R)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea	573	2.18

Example 98a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.24 (6H, s), 1.83 - 2.01 (1H, m), 2.12 - 2.20 (1H, m), 2.37 (3H, s), 2.83 - 2.92 (2H, m), 3.10 - 3.22 (4H, m), 3.36 - 3.41 (1H, m), 3.49 (1H, td), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.13 (1H, d), 4.48 (1H, s), 4.95 (1H, t), 5.99 (1H, s), 6.54 (1H, s), 7.36 (2H, d), 7.68 (1H, s), 7.86 (2H, d), 8.71 (1H, s)

Example 98b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.21 (3H, d), 1.88 - 1.99 (1H, m), 2.12 - 2.21 (1H, m), 2.82 - 2.92 (2H, m), 3.10 - 3.23 (2H, m), 3.31 (3H, s), 3.32 - 3.42 (3H, m), 3.44 - 3.54 (1H, m), 3.61 - 3.78 (3H, m), 3.97 (1H, d), 4.09 - 4.17 (1H, m), 4.49 (1H, s), 4.78 (1H, t), 6.08 (1H, d), 6.54 (1H, s), 7.39 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.68 (1H, s)

Example 98c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.89 - 1.99 (1H, m), 2.11 - 2.20 (1H, m), 2.37 (3H, s), 2.85 - 2.95 (2H, m), 3.10 - 3.22 (3H, m), 3.43 - 3.54 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.14 (1H, d), 4.33 (2H, s), 4.50 (1H, s), 6.53 - 6.63 (2H, m), 6.93 - 7.05 (1H, m), 7.43 (2H, d), 7.68 (1H, s), 7.85 - 7.93 (2H, m), 8.90 (1H, s)

Example 98d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.56 - 1.63 (2H, m), 1.86 - 1.97 (2H, m), 2.12 - 2.22 (2H, m), 2.77 - 2.92 (2H, m), 3.13 - 3.22 (3H, m), 3.25 - 3.34 (2H, m), 3.43 - 3.52 (3H, m), 3.64 (1H, d), 3.72 - 3.80 (1H, m), 3.97 (1H, d), 4.13 (1H, d), 4.44 - 4.53 (2H, m), 6.18 (1H, t), 6.54 (1H, s), 7.41 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.68 (1H, s)

Example 98e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.87 - 1.97 (1H, m), 2.15 - 2.21 (1H, m), 2.37 (3H, s), 2.79 - 2.94 (2H, m), 3.12 - 3.21 (3H, m), 3.27 - 3.34 (2H, m), 3.42 - 3.52 (3H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.13 (1H, d), 4.49 (1H, s), 4.72 (1H, t), 6.24 (1H, t), 6.54 (1H, s), 7.40 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.78 (1H, s)

Example 98f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.21 (3H, d), 1.87 - 1.99 (1H, m), 2.12 - 2.23 (1H, m), 2.37 (3H, s), 2.83 - 2.92 (2H, m), 3.12 - 3.23 (4H, m), 3.34 - 3.41 (1H, m), 3.45 - 3.52 (1H, m), 3.64 (1H, d), 3.75 (1H, d), 3.97 (1H, d), 4.13 (1H, d), 4.50 (1H, s), 4.78 (1H, t), 6.05 - 6.10 (1H, m), 6.54 (1H, s), 7.40 (2H, d), 7.68 (1H, s), 7.87 (2H, d), 8.68 (1H, s)

Example 98g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.25 (6H, s), 1.90 - 1.99 (1H, m), 2.14 - 2.21 (1H, m), 2.84 - 2.93 (2H, m), 3.17 - 3.25 (2H, m), 3.29 - 3.33 (1H, m), 3.45 - 3.52 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.13 (1H, d), 4.48 (1H, s), 4.95 (1H, t), 5.99 (1H, s), 6.53 (1H, s), 7.35 (2H, d), 7.83 (2H, d), 8.15 (1H, s), 8.70 (1H, s)

Example 98h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.20 (3H, d), 1.91 - 2.00 (1H, m), 2.13 - 2.22 (1H, m), 2.85 - 2.95 (2H, m), 3.14 - 3.21 (2H, m), 3.30 - 3.42 (4H, m), 3.44 - 3.52 (1H, m), 3.64 - 3.78 (2H, m), 3.96 (1H, d), 4.13 (1H, d), 4.49 (1H, s), 4.78 (1H, t), 6.06 - 6.13 (1H, m), 6.53 (1H, s), 7.38 (2H, d), 7.85 (2H, d), 8.14 (1H, s), 8.67 (1H, s)

Example 98i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.93 - 2.00 (1H, m), 2.13 - 2.20 (1H, m), 2.83 - 2.93 (2H, m), 3.14 - 3.24 (3H, m), 3.43 - 3.53 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.96 (1H, d), 4.15 (1H, d), 4.32 (2H, s), 4.48 (1H, s), 6.54 (1H, s), 6.63 (1H, t), 6.93 (1H, s), 7.42 (2H, d), 7.87 (2H, d), 8.14 (1H, s), 8.90 (1H, s)

Example 98j: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.56 - 1.63 (2H, m), 1.88 - 2.01 (1H, m), 2.09 - 2.22 (1H, m), 2.84 - 2.94 (2H, m), 3.12 - 3.24 (5H, m), 3.43 - 3.54 (3H, m), 3.65 (1H, d), 3.76 (1H, d), 3.95 (1H, d), 4.06 - 4.20 (1H, m), 4.46 - 4.51 (1H, m), 6.19 (1H, t), 6.53 (1H, s), 7.39 (2H, d), 7.85 (2H, d), 8.15 (1H, s), 8.67 (1H, s)

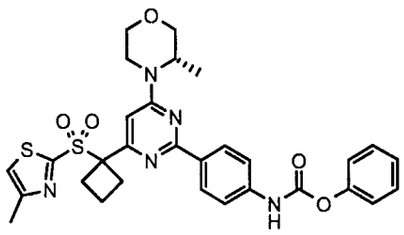
Example 98k: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.20 (3H, d), 1.90 - 2.00 (1H, m), 2.12 - 2.22 (1H, m), 2.84 - 2.94 (2H, m), 3.14 - 3.22 (3H, m), 3.25 - 3.34 (2H, m), 3.39 - 3.52 (3H, m), 3.63 (1H, d), 3.76 (1H, d), 3.96 (1H, d), 4.13 (1H, d), 4.48 (1H, s), 4.72 (1H, t), 6.24 (1H, t), 6.53 (1H, s), 7.39 (2H, d), 7.85 (2H, d), 8.15 (1H, s), 8.76 (1H, s)

Example 98l: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.08 (3H, d), 1.20 (3H, d), 1.89 - 1.98 (1H, m), 2.12 - 2.23 (1H, m), 2.80 - 2.93 (2H, m), 3.14 - 3.24 (3H, m), 3.30 - 3.40 (2H, m),

3.45 - 3.53 (1H, m), 3.60 - 3.77 (3H, m), 3.96 (1H, d), 4.13 (1H, d), 4.49 (1H, s), 4.78 (1H, t), 6.08 (1H, d), 6.53 (1H, s), 7.38 (2H, d), 7.85 (2H, d), 8.15 (1H, s), 8.67 (1H, s)

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]carbamate

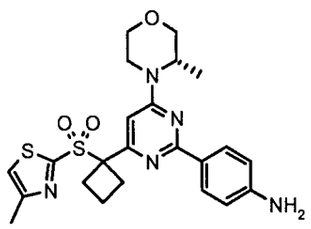


Sodium hydrogen carbonate (0.311 g, 3.71 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]aniline (1.2 g, 2.47 mmol) in dioxane (30 mL) at 5°C under nitrogen. Phenyl chloroformate (0.466 mL, 3.71 mmol) was then added and the resulting mixture stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water (75 mL) and the organic layer dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude gum was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (1.2 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.88 - 2.00 (1H, m), 2.10 - 2.21 (1H, m), 2.36 (3H, s), 2.83 - 2.95 (2H, m), 3.10 - 3.24 (3H, m), 3.44 - 3.53 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.15 (1H, d), 4.52 (1H, s), 6.59 (1H, s), 7.21 - 7.32 (3H, m), 7.39 - 7.47 (2H, m), 7.55 (2H, d), 7.68 (1H, s), 7.97 (2H, d), 10.39 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 606; HPLC tR = 3.12 min.

4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]aniline

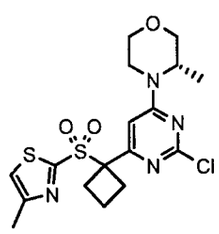


Bis(triphenylphosphine)palladium(II) chloride (0.115 g, 0.16 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidine (1.4 g, 3.26 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.073 g, 4.90 mmol) and 2M aqueous odium carbonate solution (5 mL, 10.00 mmol) in a solvent mixture of DMF (6 mL), DME (12 mL), ethanol (3 mL) and water (3.5 mL) and the resulting mixture stirred at 95°Cfor 5 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (250 mL), and washed with water (2 x 150 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 60% ethyl acetate in isohexane, to give the desired material as a beige solid (1.17 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (3H, d), 1.92 (1H, m), 1.99 (1H, s), 2.10 - 2.18 (1H, m), 2.39 (3H, s), 2.80 - 2.91 (2H, m), 3.09 - 3.24 (2H, m), 3.47 (1H, td), 3.62 (1H, d), 3.75 (1H, d), 3.95 (1H, d), 4.09 (1H, d), 4.45 (1H, s), 5.50 (2H, s), 6.43 (1H, s), 6.54 (2H, d), 7.61 - 7.80 (3H, m)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 486; HPLC tR = 2.51 min.

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidine



Tetrabutylammonium bromide (0.912 g, 2.83 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine (11 g, 28.29

mmol), 1,3-dibromopropane (17.23 mL, 169.71 mmol) and sodium hydroxide solution (50% w/w) (30 mL) in toluene (200 mL) and the resulting mixture stirred at 35°C for 2.5 hours under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% ethyl acetate in isohexane, to give the desired material as a yellow gum (1.7 g).

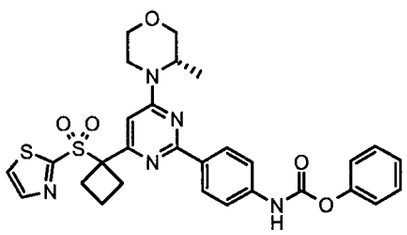
NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 7.88 (1H, s), 1.18 (3H, d), 1.85 - 1.97 (1H, m), 2.04 - 2.18 (1H, m), 2.70 - 2.85 (2H, m), 3.00 - 3.21 (3H, m), 3.29 (3H, s), 3.37 - 3.49 (1H, m), 3.57 (1H, d), 3.71 (1H, d), 3.86 - 4.01 (2H, m), 4.34 (1H, s), 6.59 (1H, s) 7.91(1H,s).

LCMS Spectrum: m/z (ESI+) (M+H)+ = 429; HPLC tR = 2.36 min.

The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[(4-methyl-1,3-thiazol-2-yl)sulfonylmethyl]pyrimidine was described earlier.

The preparation of phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]carbamate is described below.

Phenyl *N*-[4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]carbamate



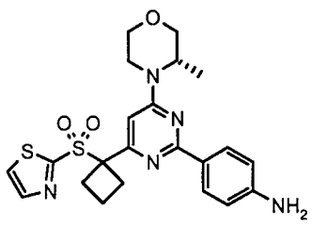
Sodium hydrogen carbonate (0.267 g, 3.18 mmol) was added to 4-[4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]aniline (1 g, 2.12 mmol) in dioxane (30 mL) at 5°C under nitrogen .Phenyl chloroformate (0.4 mL, 3.18 mmol) was then added. The resulting mixture was stirred at RT for 2 hours. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (75 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude gum

was triturated with a mixture of diethyl ether and isohexane to give the desired material as a cream solid (0.80 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.21 (3H, d), 1.89 - 2.01 (1H, m), 2.12 - 2.22 (1H, m), 2.84 - 2.97 (2H, m), 3.11 - 3.26 (3H, m), 3.44 - 3.54 (1H, m), 3.64 (1H, d), 3.76 (1H, d), 3.97 (1H, d), 4.15 (1H, d), 4.50 (1H, s), 6.57 (1H, s), 7.15 - 7.35 (3H, m), 7.38 - 7.48 (2H, m), 7.49 - 7.60 (2H, m), 8.15 (2H, s), 10.39 (1H, s)

LCMS Spectrum: m/z (ESI+) (M+H)+ = 592; HPLC tR = 3.06 min.

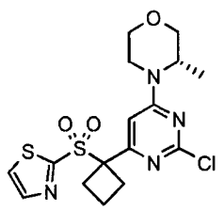
4-[4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]aniline



Bis(triphenylphosphine)palladium(II) chloride (0.093 g, 0.13 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidine (1.1 g, 2.65 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.871 g, 3.98 mmol) and 2M aqueous sodium carbonate solution (5 mL, 10.00 mmol) in a solvent mixture of DMF (6 mL), DME (12 mL), ethanol (3 mL) and water (3.5 mL) and the resulting mixture stirred at 95°Cfor 5 hours under an inert atmosphere. The reaction mixture was diluted with ethyl acetate (250 mL), and washed with water (2 x 150 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 70% ethyl acetate in isohexane, to give the desired material as a yellow solid (0.99 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.18 (3H, d), 1.88 - 1.96 (1H, m), 2.11 - 2.21 (1H, m), 2.82 - 2.91 (2H, m), 3.05 - 3.23 (3H, m), 3.47 (1H, td), 3.62 (1H, d), 3.74 (1H, d), 3.95 (1H, d), 4.10 (1H, s), 4.44 (1H, s), 5.50 (2H, s), 6.42 (1H, s), 6.51 (2H, d), 7.70 (2H, d), 8.15 (2H, s)

2-Chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidine



Tetrabutylammonium bromide (0.559 g, 1.73 mmol) was added to 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfonylmethyl)pyrimidine (6.5 g, 17.34 mmol), 1,3-dibromopropane (10.56 mL, 104.04 mmol) and sodium hydroxide (50% w/w) (10 mL) in toluene (20 mL) and the resulting mixture stirred at 70°C for 30 minutes. The reaction mixture was diluted with ethyl acetate (200 mL), and washed with water (100 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 20 to 60% ethyl acetate in isohexane, to give the desired material as a yellow gum (1.0 g).

NMR Spectrum: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.86 - 1.97 (1H, m), 2.07 - 2.18 (1H, m), 2.72 - 2.84 (2H, m), 3.04 - 3.19 (3H, m), 3.42 (1H, td), 3.57 (1H, d), 3.70 (1H, d), 3.89 - 3.99 (2H, m), 4.33 (1H, s), 6.60 (1H, s), 8.19 (1H, d), 8.30 (1H, d)

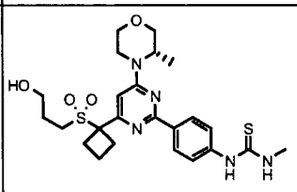
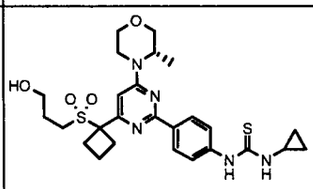
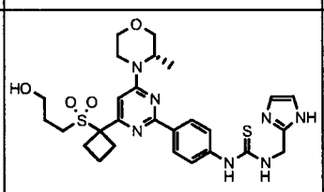
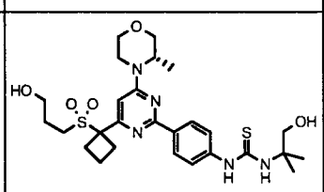
The preparation of 2-chloro-4-[(3*S*)-3-methylmorpholin-4-yl]-6-(1,3-thiazol-2-ylsulfonylmethyl)pyrimidine was described earlier.

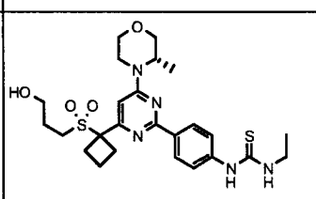
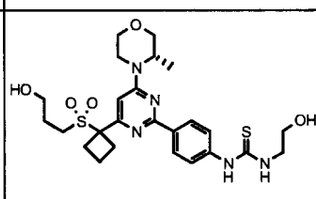
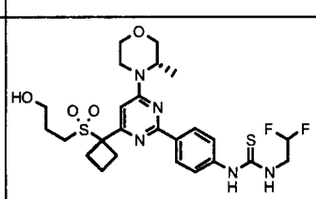
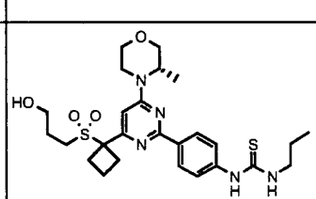
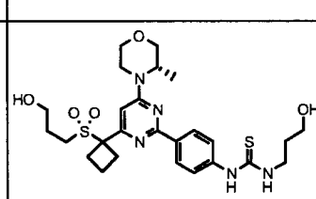
Example 99

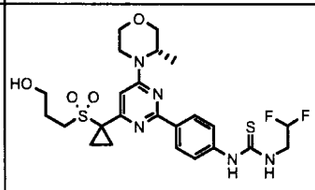
The following samples were prepared by heating a mixture of the aniline (1 equivalent) and 1,1 thiocarbonyldiimidazole (1.2 equivalents) in a mixture of DCM:THF (2:1) at RT for 30 minutes then adding the amine (5 equivalents) and stirring at 50°C for 2 hours. The compounds were purified by preparative HPLC.

The following compounds were prepared in an analogous fashion from either 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropan-1-

ol or 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol and the appropriate amine.

Example	Structure	NAME	LCMS MH+	Retention time (min)
99a		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea	520	1.92
99b		3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	546	2.07
99c		1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea	586	1.83
99d		3-(1-hydroxy-2-methylpropan-2-yl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	578	2.02

Example	Structure	NAME	LCMS MH+	Retention time (min)
99e		1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	534	2.07
99f		3-(2-hydroxyethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	550	1.75
99g		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	570	2.21
99h		3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-1-propylthiourea	548	2.38
99i		3-(3-hydroxypropyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	564	1.91

Example	Structure	NAME	LCMS MH+	Retention time (min)
99j		3-(2,2-difluoroethyl)-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea	556	2.06

Example 99a: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.73 - 1.81 (2H, m), 1.88 - 1.97 (1H, m), 2.03 - 2.10 (1H, m), 2.76 - 2.87 (2H, m), 2.89 - 3.05 (7H, m), 3.19 - 3.26 (1H, m), 3.36 - 3.41 (2H, m), 3.46 - 3.55 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.23 (1H, d), 4.52 - 4.61 (2H, m), 6.76 (1H, s), 7.55 (2H, d), 7.85 (1H, s), 8.28 (2H, d), 9.73 (1H, s)

Example 99b: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.56 - 0.64 (2H, m), 0.73 - 0.80 (2H, m), 1.25 (3H, d), 1.72 - 1.81 (2H, m), 1.88 - 1.96 (1H, m), 2.03 - 2.10 (1H, m), 2.80 - 3.04 (6H, m), 3.17 - 3.26 (1H, m), 3.34 - 3.41 (2H, m), 3.45 - 3.57 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.23 (1H, d), 4.49 - 4.64 (2H, m), 6.76 (1H, s), 7.59 - 7.66 (2H, m), 7.96 (1H, s), 8.28 (2H, d), 9.51 (1H, s)

Example 99c: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.73 - 1.82 (2H, m), 1.89 - 1.97 (1H, m), 2.04 - 2.11 (1H, m), 2.78 - 2.88 (2H, m), 2.92 - 2.99 (2H, m), 2.98 - 3.05 (2H, m), 3.20 - 3.26 (1H, m), 3.34 - 3.42 (2H, m), 3.46 - 3.57 (1H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.04 - 4.10 (1H, m), 4.25 (1H, d), 4.54 - 4.63 (2H, m), 4.71 (2H, s), 6.76 (1H, s), 6.99 (2H, s), 7.69 (2H, d), 8.21 (1H, s), 8.29 (2H, d), 10.03 (1H, s)

Example 99d: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (3H, d), 1.45 (6H, s), 1.73 - 1.80 (2H, m), 1.87 - 1.95 (1H, m), 2.03 - 2.10 (1H, m), 2.79 - 2.87 (2H, m), 2.92 - 2.98 (2H, m), 2.97 - 3.05 (2H, m), 3.20 - 3.24 (1H, m), 3.35 - 3.42 (2H, m), 3.48 - 3.57 (3H, m), 3.66 (1H, d), 3.77 (1H, d), 3.95 - 4.01 (1H, m), 4.03 - 4.09 (1H, m), 4.25 (1H, d), 4.52 - 4.62 (2H, m), 6.75 (1H, s), 7.61 (2H, d), 8.27 (2H, d), 9.92 (1H, s)

Example 99e: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.14 (3H, t), 1.24 (3H, d), 1.72 - 1.82 (2H, m), 1.88 - 1.98 (1H, m), 2.01 - 2.11 (1H, m), 2.76 - 2.87 (2H, m), 2.89 - 2.98 (2H, m), 2.98 - 3.06 (2H, m), 3.21 - 3.27 (1H, m), 3.35 - 3.42 (2H, m), 3.46 - 3.56 (3H, m), 3.66 (1H,

d), 3.77 (1H, d), 3.98 (1H, d), 4.24 (1H, d), 4.52 - 4.62 (2H, m), 6.75 (1H, s), 7.57 (2H, d), 7.89 (1H, s), 8.28 (2H, d), 9.63 (1H, s)

Example 99f: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.73 - 1.81 (2H, m), 1.86 - 1.97 (1H, m), 2.02 - 2.12 (1H, m), 2.79 - 2.87 (2H, m), 2.92 - 2.99 (2H, m), 2.97 - 3.05 (2H, m), 3.20 - 3.28 (1H, m), 3.35 - 3.43 (2H, m), 3.47 - 3.60 (3H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.25 (1H, d), 4.50 - 4.63 (2H, m), 4.81 (1H, s), 6.75 (1H, s), 7.63 (2H, d), 7.88 (1H, s), 8.28 (2H, d), 9.81 (1H, s)

Example 99g: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 10.01 (1H, s), 8.31 (2H, d), 8.12 (1H, s), 7.59 (2H, d), 6.77 (1H, s), 6.39 - 6.03 (1H, m), 4.64 - 4.54 (2H, m), 4.25 (1H, d), 4.05 - 3.94 (3H, m), 3.77 (1H, d), 3.66 (1H, d), 3.56 - 3.46 (1H, m), 3.42 - 3.36 (2H, m), 3.27 - 3.19 (1H, m), 3.05 - 2.98 (2H, m), 2.98 - 2.91 (2H, m), 2.89 - 2.79 (2H, m), 2.12 - 1.98 (1H, m), 1.97 - 1.87 (1H, m), 1.81 - 1.73 (2H, m), 1.25 (3H, d)

Example 99h: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 10.01 (1H, s), 8.31 (2H, d), 8.12 (1H, s), 7.59 (2H, d), 6.77 (1H, s), 6.39 - 6.03 (1H, m), 4.64 - 4.54 (2H, m), 4.25 (1H, d), 4.05 - 3.94 (3H, m), 3.77 (1H, d), 3.66 (1H, d), 3.56 - 3.46 (1H, m), 3.42 - 3.36 (2H, m), 3.27 - 3.19 (1H, m), 3.05 - 2.98 (2H, m), 2.98 - 2.91 (2H, m), 2.89 - 2.79 (2H, m), 2.12 - 1.98 (1H, m), 1.97 - 1.87 (1H, m), 1.81 - 1.73 (2H, m), 1.25 (3H, d)

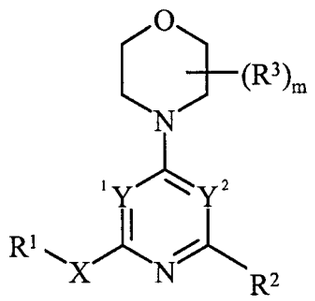
Example 99i: ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.24 (3H, d), 1.69 - 1.80 (4H, m), 1.88 - 1.98 (1H, m), 2.03 - 2.09 (1H, m), 2.78 - 2.89 (2H, m), 2.90 - 2.97 (2H, m), 2.98 - 3.05 (2H, m), 3.17 - 3.25 (1H, m), 3.35 - 3.42 (2H, m), 3.46 - 3.59 (5H, m), 3.66 (1H, d), 3.77 (1H, d), 3.98 (1H, d), 4.25 (1H, d), 4.52 - 4.61 (2H, m), 6.75 (1H, s), 7.58 (2H, d), 7.90 (1H, s), 8.28 (2H, d), 9.69 (1H, s)

Example 99j: Spectrum not recorded.

The preparations of 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclobutyl]sulfonylpropan-1-ol and 3-[1-[2-(4-aminophenyl)-6-[(3*S*)-3-methylmorpholin-4-yl]pyrimidin-4-yl]cyclopropyl]sulfonylpropan-1-ol were described earlier.

CLAIMS

1. A compound of formula (I)



formula (I)

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2, 3 or 4;

^{1}Y and **Y^2** are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$, and $-S(O)_2NR^4CR^6R^7-$;

R^1 is a group selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ and $-NR^9SO_2R^{10}$;

R^2 is a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is independently selected from halo, cyano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ and $-NR^{13}SO_2R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or R^1 and R^4 together with the atom or atoms to which they are attached form a 4- to 10-membered carbocyclic or heterocyclic ring wherein 1, 2 or 3 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is

optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$ and $\mathbf{R^{16}}$ are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

$\mathbf{R^{19}}$ is hydrogen, cyano or a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 3- to 10-membered heterocyclic ring wherein 1 or 2 ring carbon atoms is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-}

$_{6}$alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

2. A compound, or a pharmaceutically acceptable salt thereof, according to claim 1, wherein

m is 0, 1 or 2;

^{1}**Y** and **Y**^{2} are independently N or CR^8 provided that one of ^{1}Y and Y^2 is N and the other is CR^8;

X is a linker group selected from $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ and $-S(O)_2NR^4CR^6R^7$;

R^1 is a group selected from C_{1-6}alkyl, carbocyclyl, carbocyclylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, which group is optionally substituted by one or more substituent group selected from halo, cyano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ and $-NR^9COR^{10}$;

or **X-R^1** is $-CR^6R^7OH$;

R^2 is a group selected from carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent group independently selected from halo, cyano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ and $-NR^{17}CSNR^{18}R^{19}$;

each R^3, when present, is selected from cyano, R^{13}, and $-CONR^{13}R^{14}$;

R^4 and **R^5** are independently hydrogen or C_{1-6}alkyl;

or, when **X** is $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ or $-NR^4C(O)NR^5CR^6R^7-$, **R^1** and **R^4** together with the atom or atoms to which they are attached form a 5- or 6-membered heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^6 and R^7 together with the carbon atom to which they are attached form a 3- to 10-membered carbocyclic ring or heterocyclic ring wherein 1 ring carbon atom is optionally replaced with N, O or S and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

R^8 is selected from hydrogen, halo, cyano and C_{1-6}alkyl;

R^9 and R^{10} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{11}, R^{12}, R^{17} and R^{18} are independently hydrogen or a group selected from C_{1-6}alkyl, carbocyclyl and heterocyclyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino and bis(C_{1-6}alkyl)amino;

R^{13} and R^{14} are independently hydrogen or a C_{1-3}alkyl which is optionally substituted by one or more substituent groups selected from halo, cyano, hydroxy and C_{1-3}alkoxy; and

R^{19} is hydrogen, cyano or a group selected from C_{1-6}alkyl, C_{3-6}cycloakyl, aryl, heteroaryl, arylC_{1-6}alkyl and heteroarylC_{1-6}alkyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl;

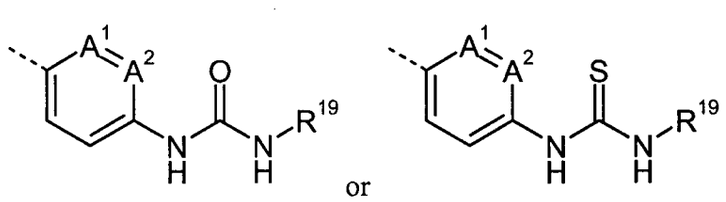
or $\mathbf{R^{18}}$ and $\mathbf{R^{19}}$ together with the nitrogen atom to which they are attached form a 6-membered heterocyclic ring wherein 1 ring carbon atoms is optionally replaced with N or O and which ring is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

3. A compound, or a pharmaceutically acceptable salt thereof, according to claim 1 or 2 wherein ^{1}Y is CH and Y^2 is N.

4 A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 wherein **X** is a -$S(O)_2CR^6R^7$- linker group

5. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 4 wherein R^1 is a group selected from methyl, ethyl, propyl, butyl, isobutyl, tert-butyl, cyclopropyl, cyclopentyl cyclohexyl, phenyl, benzyl, phenethyl, imidazolyl, pyrrolidinyl, thiadiazolyl, thiazolyl, pyridinyl, pyrazolylethyl, furanylmethyl, thienylmethyl, thiazolylmethyl, thiadiazolylmethyl and pyrazinylethyl, which group is optionally substituted by 1 or 2 substituent group selected from amino, halo, cyano, hydroxy, methyl, methoxy, trifluoromethyl, trifluoromethoxy, -$NHCOCH_3$, -$CONH_2$ and -$CONHCH_3$.

6. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5 wherein R^2 is



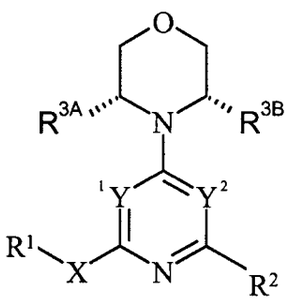
or

wherein A^1 and A^2 are selected from CH or N provided that at least one of A^1 or A^2 is CH

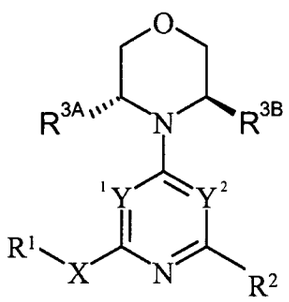
7. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6 wherein R^{19} is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, thienyl, imidazoylmethyl, isoxazolyl, pyrazolyl, pyrazolylmethyl, pyridinyl and pyrimidinyl which group is optionally substituted by one or more substituent groups selected from halo, cyano, nitro, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, hydroxyC_{1-6}alkyl, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkoxy, amino, C_{1-6}alkylamino, bis(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, bis(C_{1-6}alkyl)aminoC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylsulfonyl(C_{1-6}alkyl)amino, sulfamoyl, C_{1-6}alkylsulfamoyl, bis(C_{1-6}alkyl)sulfamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl(C_{1-6}alkyl)amino, carbamoyl, C_{1-6}alkylcarbamoyl and bis(C_{1-6}alkyl)carbamoyl.

8. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7 wherein **R^6** and **R^7** together with the carbon atom to which they are attached form a 3- to 5-membered carbocyclic ring

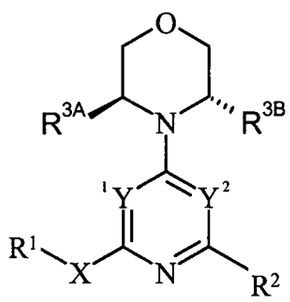
9. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

where

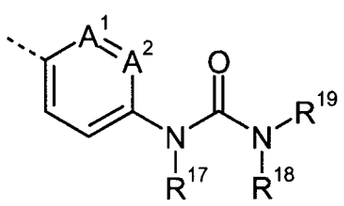
X is a $-S(O)_2CR^6R^7-$ linker group;

^1Y is CH and **Y^2** is N;

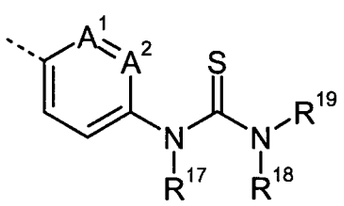
R^1 is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2CH_2NHMe$,

phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-fluoro-4-methylaminophenyl, 4-fluoro-2-methylphenyl, 5-fluoro-2-methylphenyl, 3-fluoro-4-(2-hydroxyethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-carbamoyl-2-chlorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3-chloro-4-fluorophenyl, 3-chloro-4-methylaminophenyl, 3-chloro-4-ethylaminophenyl, 3-chloro-4-(2-fluoroethylamino)phenyl, 3-chloro-4-(2-hydroxyethylamino)phenyl, 2-chloro-4-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-(trifluoromethyl)phenyl, 2-methylphenyl, 4-methylphenyl, 4-(2-hydroxyethylamino)phenyl, 1H-imidazol-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 1-(difluoromethyl)pyrazol-4-yl, 1-(difluoromethyl)-3,5-dimethylpyrazol-4-yl, 1,3-dimethylpyrazol-4-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, 5-fluoropyridin-3-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2,4-dimethylthiazol-5-yl, 5-methyl-1,3,4-thiadiazol-2-yl, terahydrofuran-3-yl and terahydropyran-4-yl;

R² is



or



wherein **A¹** and **A²** are CH;

R¹⁷ is hydrogen;

R¹⁸ is hydrogen; and

R¹⁹ is is hydrogen, cyano or a group selected from methyl, ethyl, propyl, i-propyl, i-butyl, t-butyl, cyclopropyl, cyclobutyl, -CH_2(cyclopropyl), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2C(CH_3)_2OH$, -$CH_2C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CH_2Cl, -$CH_2CH_2SO_2Me$, -$CH_2CH(OH)CF_3$, -CH_2CH_2CN, -CH_2CN, -CH_2CONMe_2, -CH_2CO_2H, 1-(methyl)cyclopropyl, -CH_2(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 4-

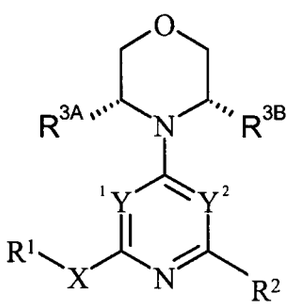
fluorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, -CH_2CH_2(pyrrolidin-1-yl),-CH_2(imidazol-2-yl), 1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 1,1-dioxothiolan-3-yl, 5-methylisoxazol-3-yl, -CH_2(1-methylpyrazol-4-yl), 1-methylpyrazol-4-yl, -CH_2(1-methylpyrazol-4-yl), 5-methylpyrazin-2-yl, -CH_2(2H-1,2,4-triazol-3-yl), 6-methoxypryridin-3-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl and 1-methylpyrazol-3-yl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

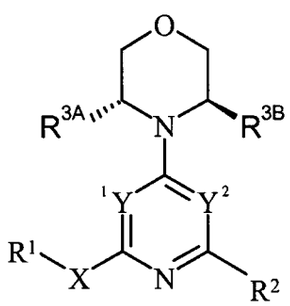
when $\mathbf{R^{3A}}$ is hydrogen, $\mathbf{R^{3B}}$ is hydrogen, methyl, ethyl, hydroxymethyl, dimethylcarbamoyl or carbamoyl; or

when $\mathbf{R^{3'}}$ is methyl, $\mathbf{R^3}$ is methyl.

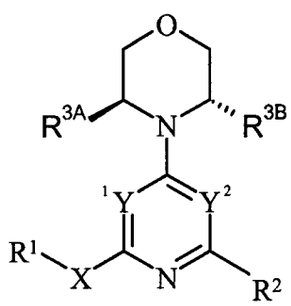
10. A compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

where

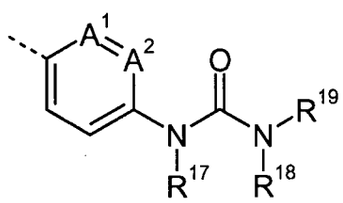
$\mathbf{X}$ is a -$S(O)_2CR^6R^7$- linker group;

$\mathbf{^1Y}$ is CH and $\mathbf{Y^2}$ is N;

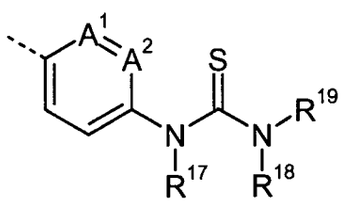
$\mathbf{R^1}$ is a group selected from methyl, ethyl, isopropyl, tert-butyl, cyclopropyl, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2C(OH)(CH_3)_2$, -$CH_2CH_2CH_2OCHF_2$, -$CH_2CH_2OCH_3$, -$CH_2CH_2NHC(O)CH_3$, -CH_2CH_2NHMe, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-fluoro-4-methylaminophenyl, 4-fluoro-2-methylphenyl, 5-fluoro-2-methylphenyl, 3-fluoro-4-(2-hydroxyethylamino)phenyl, 4-(difluoromethoxy)phenyl, 4-carbamoyl-2-chlorophenyl, 4-chlorophenyl, 2-chlorophenyl, 3-chloro-4-fluorophenyl,

3-chloro-4-methylaminophenyl, 3-chloro-4-ethylaminophenyl, 3-chloro-4-(2-fluoroethylamino)phenyl, 3-chloro-4-(2-hydroxyethylamino)phenyl, 2-chloro-4-cyanophenyl, 4-cyanophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-methylphenyl, 4-methylphenyl, 1H-imidazol-2-yl, 3,5-dimethylisoxazol-4-yl, 2-(dimethylcarbamoyl)pyridin-3-yl, 5-(dimethylcarbamoyl)pyridin-2-yl, 1-(difluoromethyl)pyrazol-4-yl, 1,3-dimethylpyrazol-4-yl, pyridin-4-yl, pyridin-2-yl, 5-fluoropyridin-2-yl, thiazol-2-yl, 4-methylthiazol-2-yl, 4,5-dimethylthiazol-2-yl, 2,4-dimethylthiazol-5-yl and 5-methyl-1,3,4-thiadiazol-2-yl;

$\mathbf{R^2}$ is



or



wherein $\mathbf{A^1}$ and $\mathbf{A^2}$ are CH;

$\mathbf{R^{17}}$ is hydrogen;

$\mathbf{R^{18}}$ is hydrogen; and

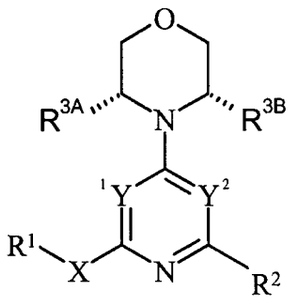
$\mathbf{R^{19}}$ is hydrogen or a group selected from methyl, ethyl, propyl, i-propyl, cyclopropyl, cyclobutyl, $-CH_2$(cyclopropyl), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CN$, $-CH_2$(1-hydroxycyclopropyl), 1-(hydroxymethyl)cyclopropyl, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4-difluorophenyl, $-CH_2CH_2$(pyrrolidin-1-yl),$-CH_2$(imidazol-2-yl), 1-methylimidazol-4-yl, oxazolyl-2-yl, isoxazolyl-3-yl, oxetan-3-yl, 5-methylisoxazol-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, 6-methoxypryridin-3-yl, thiazol-2-yl, 1,2,4-thiadiazol-5-yl and 1-methylpyrazol-3-yl;

$\mathbf{R^6}$ and $\mathbf{R^7}$ together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

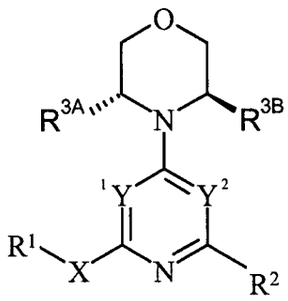
when $\mathbf{R^{3A}}$ is hydrogen, $\mathbf{R^{3B}}$ is hydrogen, methyl or ethyl; or

when $\mathbf{R^{3A}}$ is methyl, $\mathbf{R^{3B}}$ is methyl.

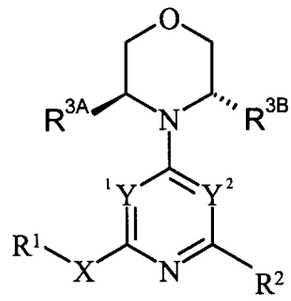
11. A compound according to claim 10, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (IA), (IB) or (IC)



(IA)



(IB)



(IC)

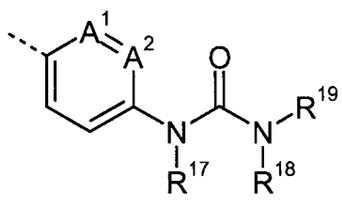
where

X is a $-S(O)_2CR^6R^7-$ linker group;

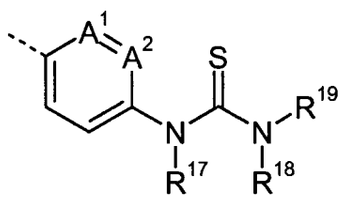
^{1}Y is CH and **Y^2** is N;

R^1 is a group selected from methyl, ethyl, cyclopropyl, $-CH_2CH_2CH_2OH$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 5-fluoropyridin-2-yl, pyridin-2-yl, thiazol-2-yl and 4-methylthiazol-2-yl;

R^2 is



or



wherein **A^1** and **A^2** are CH;

R^{17} is hydrogen;

R^{18} is hydrogen; and

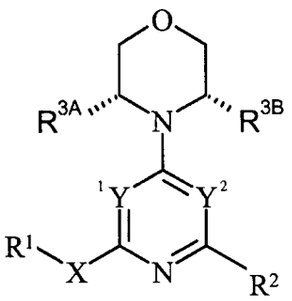
R^{19} is a group selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, $-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, thiazol-2-yl and 1,2,4-thiadiazol-5-yl;

R^6 and **R^7** together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

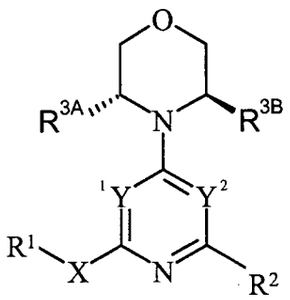
when **R^{3A}** is hydrogen, **R^{3B}** is hydrogen, methyl or ethyl; or

when $\mathbf{R^{3A}}$ is methyl, $\mathbf{R^{3B}}$ is methyl.

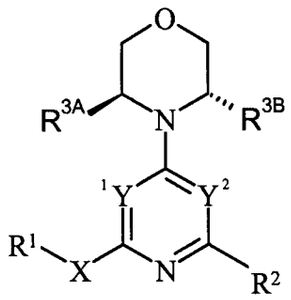
12. A compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (I) is a compound of formula (Ia), (Ib) or (Ic)



(IA)



(IB)



(IC)

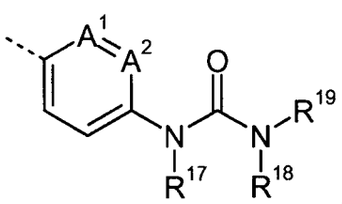
or a pharmaceutically acceptable salt thereof;

X is a $-S(O)_2CR^6R^7-$ linker group;

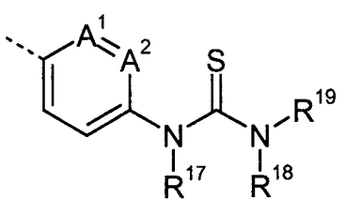
^{1}**Y** is CH and **Y**^{2} is N;

R^1 is a group selected from methyl, ethyl, cyclopropyl, $-CH_2CH_2CH_2OH$, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 2-methylphenyl, 5-fluoropyridin-2-yl, pyridin-2-yl, thiazol-2-yl and 4-methylthiazol-2-yl;

R^2 is



or



wherein **A**^{1} and **A**^{2} are CH;

R^{17} is hydrogen;

R^{18} is hydrogen; and

R^{19} is a group selected from methyl, ethyl, cyclopropyl, cyclobutyl, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hydroxy-1-methylethyl, (1S)-2-hydroxy-1-methylethyl, $-CH_2$(imidazol-2-yl), oxazolyl-2-yl, isoxazolyl-3-yl, 1-methylpyrazol-4-yl, 5-methylpyrazin-2-yl, thiazol-2-yl and 1,2,4-thiadiazol-5-yl;

R^6 and **R**^{7} together with the carbon atom to which they are attached form a cyclopropyl, cyclobutyl, cyclopentyl, tetrahydropyranyl or piperidyl ring; and

when R^{3A} is hydrogen, R^{3B} is methyl or ethyl; or
when R^{3A} is methyl, R^{3B} is methyl.

13. A compound according to any one of claims 1 to 12 where R^6 and R^7 together with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl ring

14. A compound of formula (I) according to claim 1 selected from any one of the Examples, or a pharmaceutically acceptable salt thereof.

15. A compound of formula (I) according to claim 1 selected from any one of
1-[4-[4-(1-ethylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methyl-urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,
3-cyclopropyl-1-[4-[4-(1-methylsulfonylcyclopropyl)-6-morpholin-4-ylpyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(4-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-2-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,

3-cyclopropyl-1-[4-[4-[1-(4-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,

3-cyclopropyl-1-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,

1-ethyl-3-[4-[4-[1-(3-hydroxypropylsulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]thiourea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylthiourea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(1H-imidazol-2-ylmethyl)thiourea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-(1-pyridin-4-ylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]thiourea,

1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,

1-[4-[4-[1-(2,4-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(3-fluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(2-methylphenyl)sulfonylcyclopropyl]pyrimidin-2-yl]phenyl]urea,

3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclopropyl]pyrimidin-2-yl]phenyl]urea,

1-[4-[4-[1-(2-chlorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,

1-[4-[4-(1-cyclopropylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclobutyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
3-(2-fluoroethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclopropyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-[(4-methyl-1,3-thiazol-2-yl)sulfonyl]cyclobutyl]pyrimidin-2-yl]phenyl]urea,
3-(2-hydroxyethyl)-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2,2-difluoroethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2R)-1-hydroxypropan-2-yl]urea,
3-cyclopropyl-1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S)-3-ethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(2,6-difluorophenyl)sulfonylcyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-(1-cyclopropylsulfonylcyclopropyl)-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,

3-cyclopropyl-1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]urea,
1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-methylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-cyclopropylurea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(2S)-1-hydroxypropan-2-yl]urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(3-hydroxypropyl)urea,
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S)-3-ethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-[(1-hydroxycyclopropyl)methyl]urea,
1-[4-[4-(1-ethylsulfonylcyclobutyl)-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-hydroxyethyl)thiourea,
1-[4-[4-[(3S,5S)-3,5-dimethylmorpholin-4-yl]-6-(1-methylsulfonylcyclopropyl)pyrimidin-2-yl]phenyl]-3-ethylurea,
3-[(2S)-1-hydroxypropan-2-yl]-1-[4-[4-[(3S)-3-methylmorpholin-4-yl]-6-[1-(1,3-thiazol-2-ylsulfonyl)cyclobutyl]pyrimidin-2-yl]phenyl]urea, and
1-[4-[4-[1-(benzenesulfonyl)cyclopropyl]-6-[(3S,5S)-3,5-dimethylmorpholin-4-yl]pyrimidin-2-yl]phenyl]-3-(2-fluoroethyl)urea,
or a pharmaceutically acceptable salt thereof.

16. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 15 for use as a medicament.

17. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 15 in the manufacture of a medicament for use in the treatment of proliferative disease.

18. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15 for the production of an anti-proliferative effect in a warm-blooded animal such as man.

19. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15 in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

20. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15 in the manufacture of a medicament for use in the providing a mTOR kinase inhibitory effect in a warm-blooded animal such as man.

21. A method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15.

22. A method for producing a mTOR kinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15.

23. A method for treating cancer, inflammatory diseases, obstructive airways diseases, immune diseases or cardiovascular diseases in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 15.

24. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

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(12) SOLICITUD INTERNACIONAL PUBLICADA EN VIRTUD DEL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual
Bureau International

(43) Fecha de publicación internacional
15 de Enero de 2009 (15.01.2009)

PCT

(10) Número de Publicación Internacional
WO 2009/007748 A2

(51) Clasificación Internacional de Patentes:
C07D 413/14 (2006.01) *A61P 35/00* (2006.01)
C07D 417/14 (2006.01) *C07D 413/04* (2006.01)
A61K 31/5377 (2006.01)

(21) Número de la solicitud internacional:
PCT/GB2008/050546

(22) Fecha de presentación internacional:
8 de Julio de 2008 (08.07.2008)

(25) Idioma de presentación: Inglés

(26) Idioma de publicación: Inglés

(30) Datos relativos a la prioridad:
60/948,566 9 de Julio de 2007 (09.07.2007) US
61/030,297 21 de Febrero de 2008 (21.02.2008) US

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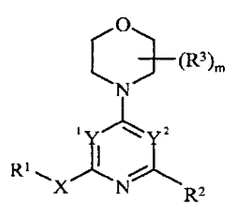
(81) Estados designados *(a menos que se indique otra cosa, para toda clase de protección nacional admisible)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Estados designados *(a menos que se indique otra cosa, para toda clase de protección regional admisible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicada:
- *sin informe de búsqueda internacional, será publicada nuevamente cuando se reciba dicho informe*

(54) Title: COMPOUNDS 945

(54) Título: COMPUESTOS 945



(I)

(57) Abstract: A compound of formula (I) or a pharamaceutically acceptable salt thereof, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, for example in the treatment of proliferative disease such as cancer and particularly in disease mediated by an mTOR kinase and/or one or more PI3K enzyme.

(57) Resumen: Un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, procesos para su preparación, composiciones farmacéuticas que los contienen y su uso en terapia, por ejemplo en el tratamiento de una enfermedad proliferativa tal como cáncer y particularmente en una enfermedad mediada por una mTOR quinasa y/o una o más enzimas PI3K.

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Compuestos – 945

La presente invención se refiere a derivados de morfolino pirimidina, procesos para su preparación, composiciones farmacéuticas que los contienen y su uso en terapia, por ejemplo, en el tratamiento de una enfermedad proliferativa tal como cáncer, y particularmente en una enfermedad mediada por una mTOR quinasa y/o una o más enzimas PI3K.

Se sabe ahora que la desregulación de oncogenes y genes supresores de tumores contribuye con la formación de tumores malignos, por ejemplo mediante el aumento de la proliferación celular o el aumento de la supervivencia celular. También se sabe que las vías de señalización mediadas por las familias PI3K/mTOR juegan un papel fundamental en distintos procesos celulares, incluidas la proliferación y supervivencia, y la desregulación de estas vías constituye un factor causante en una amplia gama de cánceres humanos y otras enfermedades.

El objetivo mamífero del antibiótico macrólido rapamicina (sirolimus) es la enzima mTOR. Esta enzima pertenece a la familia de proteína quinasas relacionada con la fosfatidilinositol (PI) quinasa, (PIKK), que también incluye ATM, ATR, DNA-PK y hSMG-1. La mTOR, al igual que otros integrantes de la familia PIKK, no posee actividad lípido quinasa detectable, pero en cambio presenta funciones de serina/treonina quinasa. Gran parte del conocimiento que se tiene sobre la señalización de la mTOR se basa en el uso de rapamicina. La rapamicina se une en primer lugar a la proteína de unión a la inmunofilina FK506 de 12 kDa (FKBP12) y este complejo inhibe la señalización de la mTOR (Tee and Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). La proteína mTOR consiste en un dominio quinasa catalítico, un dominio de unión a FKBP12-rapamicina (FRB), un dominio represor putativo cerca del extremo C y hasta 20 motivos HEAT repetidos en tándem en el extremo N, así como también un dominio FRAP-ATM-TRRAP (FAT) y FAT en el extremo C (Huang and Houghton, Current Opinion in Pharmacology, 2003, 3, 371-377).

La mTOR quinasa es un regulador clave del crecimiento celular y se ha demostrado que regula una amplia gama de funciones celulares, como la traducción, trascripción, recambio de ARNm, estabilidad proteica, reorganización citoesquelética y autofagia (Jacinto and Hall; Nature Reviews Molecular and Cell Biology, 2005, 4, 117-126). La mTOR quinasa integra señales de factores del crecimiento (como el factor de crecimiento de la insulina o similar a la insulina) y nutrientes (tales como aminoácidos y glucosa) para regular el crecimiento celular. La mTOR quinasa es activada por factores del crecimiento a través de la vía PI3K-Akt. La función mayormente descrita de la mTOR quinasa en células de mamíferos es la regulación de la traducción a través de dos vías, a saber, la activación de S6K1

ribosómica para mejorar la traducción de los ARNm que presentan un tracto de oligopirimidina en la región 5' terminal (TOP) y la supresión de 4E-BP1 para permitir la traducción de ARNm dependiente de CAP.

Generalmente, los investigadores han explorado las funciones fisiológicas y patológicas de la mTOR mediante la inhibición con rapamicina y análogos de rapamicina relacionados en base a su especificidad para la mTOR como objetivo intracelular. Sin embargo, datos recientes sugieren que la rapamicina exhibe acciones inhibitorias variables sobre las funciones de señalización de la mTOR, lo que sugiere que la inhibición directa del dominio de la mTOR quinasa puede exhibir actividades anti-cáncer sustantivamente mayores que las alcanzadas con la rapamicina (Edinger *et al.*, Cancer Research, 2003, 63, 8451-8460). Por este motivo, los inhibidores potentes y selectivos de la actividad de la mTOR quinasa serían de utilidad para poder comprender más cabalmente la función de la mTOR quinasa y así obtener agentes terapéuticos útiles.

Existe ahora considerable evidencia que indica que las vías corriente arriba de mTOR, tal como la vía de la PI3K, a menudo se activan en el cáncer (Vivanco and Sawyers, Nature Reviews Cancer, 2002, 2, 489-501; Bjornsti y Houghton, Nature Reviews Cancer, 2004, 4, 335-348; Inoki *et al.*, Nature Genetics, 2005, 37, 19-24). Por ejemplo, los componentes de la vía de la PI3K que mutan en distintos tumores humanos incluyen mutaciones activantes de receptores de factores de crecimiento y la amplificación y/o sobreexpresión de PI3K y Akt.

Además, existe evidencia de que la proliferación celular endotelial también puede depender de la señalización de la mTOR. La proliferación celular endotelial es estimulada por la activación del factor del crecimiento celular endotelial vascular (VEGF) de la vía de señalización PI3K-Akt-mTOR (Dancey, Expert Opinion on Investigational Drugs, 2005, 14, 313-328). Más aun, se cree que la señalización de la mTOR quinasa controla parcialmente la síntesis del VEGF a través de efectos en la expresión del factor-1α inducible por hipoxia (HIF-1α) (Hudson *et al.*, Molecular and Cellular Biology, 2002, 22, 7004-7014). Por lo tanto, la angiogénesis tumoral puede depender de la señalización de la mTOR de dos maneras: a través de la síntesis inducida por hipoxia del VEGF por parte de células tumorales y estromales y a través de la estimulación con el VEGF de la proliferación y supervivencia endoteliales a través de la señalización PI3K-Akt-mTOR.

Estos hallazgos sugieren que los inhibidores farmacológicos de la mTOR quinasa deberían ser valiosos desde el punto de vista terapéutico para el tratamiento de distintas formas de cáncer que comprenden tumores sólidos tales como carcinomas y sarcomas y las

leucemias y malignidades linfoides. En particular, los inhibidores de la mTOR quinasa deberían ser de valor terapéutico para el tratamiento de, por ejemplo, cáncer de mama, colorrectal, de pulmón (incluyendo cáncer de pulmón de célula pequeña, cáncer de pulmón de célula no pequeña y cáncer bronquioloalveolar) y de próstata y cáncer del conducto biliar, óseo, de vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículo, tiroides, útero, cuello de útero y vulva y de leucemias (incluidas LLA y LMC), mieloma múltiple y linfomas.

Además de la tumorigénesis, existe evidencia de que la mTOR quinasa participa en distintos síndromes de hamartoma. Estudios recientes han demostrado que las proteínas supresoras de tumores, como TSC1, TSC2, PTEN y LKB1, controlan fuertemente la señalización de la mTOR quinasa. La pérdida de estas proteínas supresoras de tumores conduce a distintas afecciones de hamartoma como resultado de una elevada señalización de la mTOR (Tee and Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). Entre los síndromes con una conexión molecular establecida con la desregulación de la mTOR quinasa se encuentran el síndrome de Peutz-Jeghers (PJS), la enfermedad de Cowden, el síndrome de Bannayan-Riley-Ruvalcaba (BRRS), el síndrome de Proteus, la enfermedad de Lhermitte-Duclos y la esclerosis tuberculosa (Inoki *et al.,* Nature Genetics, 2005, 37, 19-24). En general, los pacientes con estos síndromes desarrollan tumores hamartomatosos benignos en múltiples órganos.

Estudios recientes han revelado que la mTOR quinasa participa en otras enfermedades (Easton & Houghton, Expert Opinion on Therapeutic Targets, 2004, 8, 551-564). Se ha demostrado que la rapamicina es un potente inmunosupresor, ya que inhibe la producción de anticuerpos y la proliferación de células T y células B inducidas por antígenos (Sehgal, Transplantation Proceedings, 2003, 35, 7S-14S) y, por lo tanto, los inhibidores de la mTOR quinasa también pueden ser inmunosupresores útiles. La inhibición de la actividad quinasa de la mTOR también puede ser útil en la prevención de la reestenosis, es decir, el control de la proliferación indeseada de células normales en la vasculatura en respuesta a la introducción de stents en el tratamiento de enfermedades de la vasculatura (Morice *et al.,* New England Journal of Medicine, 2002, 346, 1773-1780). Más aun, el everolimus, análogo de la rapamicina, puede reducir la gravedad e incidencia de la vasculopatía de aloinjerto cardíaco (Eisen *et al.,* New England Journal of Medicine, 2003, 349,847-858). La elevada actividad de la mTOR quinasa se ha asociado con la hipertrofia cardíaca, que reviste importancia clínica como uno de los principales factores de riesgo para la insuficiencia cardíaca y es

consecuencia de un aumento del tamaño celular de los cardiomiocitos (Tee & Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). Por lo tanto, se espera que los inhibidores de la mTOR quinasa sean valiosos en la prevención y el tratamiento de una amplia variedad de enfermedades, además de cáncer.

Se cree también que varios de estos derivados de morfolino pirimidina pueden presentar actividad inhibidora contra la familia de quinasas de las fosfatidilinositol (PI) 3-quinasas.

Las fosfatidilinositol (PI) 3-quinasas (PI3Ks) son quinasas lipídicas omnipresentes que funcionan como transductores de señales corriente abajo de receptores de la superficie celular y en vías de tráfico intracelular de proteínas y membranas. Todas las PI3Ks son enzimas de especificidad dual con una actividad lípido quinasa que fosforila fosfoinositidas en la posición 3-hidroxi y una actividad proteína quinasa menos caracterizada. Los productos lípidos de las reacciones catalizadas por la PI3K que comprenden fosfatidilinositol 3,4,5-bisfosfato [$PI(3,4,5)P_3$], fosfatidilinositol 3,4-bisfosfato [$PI(3,4)P_2$] y fosfatidilinositol 3-monofosfato [PI(3)P] constituyen segundos mensajeros en una variedad de vías de transducción de señales, incluyendo aquellas que son esenciales para la proliferación, adhesión, supervivencia celular, reorganización citoesquelética y tráfico vesicular. El PI(3)P se encuentra constitutivamente presente en todas las células y sus niveles no cambian drásticamente luego de la estimulación con agonista. Por el contrario, el $PI(3,4)P_2$ y el $PI(3,4,5)P_3$ se encuentran teóricamente ausentes en la mayoría de las células pero se acumulan rápidamente con la estimulación con agonistas.

Los efectos corriente abajo de los segundos mensajeros de 3-fosfoinositida producidos por la PI3K son mediados por moléculas objetivo que contienen dominios de unión a 3-fosfoinositida, tales como el dominio de homología con pleckstrina (PH) y los recientemente identificados dominios FYVE y phox. Entre los objetivos proteicos bien descritos para la PI3K se encuentran la PDK1 y la proteína quinasa B (PKB). Además, tirosinas quinasas tales como Btk e Itk dependen de la actividad de la PI3K.

La familia de PI3K de quinasas lípidas pueden clasificarse en tres grupos, según sus especificidad de sustrato fisiológico (Vanhaesebroeck *et al.*, Trends in Biol. Sci., 1997, 22, 267). La Clase III de enzimas PI3K fosforila solamente PI. Por el contrario, la Clase II de enzimas PI3K fosforila tanto PI como PI 4-fosfato [PI(4)P]. La Clase I de enzimas PI3K fosforila PI, PI(4)P y PI 4,5-bisfosfato [$PI(4,5)P_2$], aunque se cree que solo $PI(4,5)P_2$ es el sustrato celular fisiológico. La fosforilación de $PI(4,5)P_2$ produce el segundo mensajero

lipídico $PI(3,4,5)P_3$. Integrantes de la superfamilia de quinasas lipídicas con una relación más lejana son las quinasas de la Clase IV, tales como la mTOR (analizada anteriormente) y la quinasa dependiente del ADN que fosforilan residuos de serina/treonina en sustratos proteicos. Las quinasas lipídicas PI3K más estudiadas y comprendidas son las enzimas PI3K de la Clase I.

Las enzimas PI3K de la Clase I son heterodímeros que consisten en una subunidad catalítica p110 y una subunidad reguladora. La familia se divide, además, en la Clase Ia y la Clase Ib según patrones reguladores y el mecanismo de regulación. La Clase Ia de enzimas consiste en tres subunidades catalíticas distintas (p110α, p110β y p110δ) que dimerizan con cinco subunidades reguladoras distintas (p85α, p55α, p50α, p85β y p55γ), siendo todas las subunidades catalíticas capaces de interactuar con todas las subunidades reguladoras para formar una variedad de heterodímeros. Las PI3Ks Clase Ia generalmente se activan en respuesta a la estimulación por parte del factor del crecimiento de receptores tirosina quinasas a través de la interacción de sus dominios de subunidad reguladora SH_2 con residuos de fosfo-tirosina específicos de proteínas receptoras o adaptadoras activadas, tales como IRS-1. Tanto la p110α como la p110β se expresan constitutivamente en todos los tipos de células, mientras que la expresión de la p110δ se encuentra más restringida a las poblaciones de leucocitos y algunas células epiteliales. Por el contrario, la enzima de Clase Ib consiste en una subunidad catalítica p110γ que interactúa con una subunidad reguladora p101. Más aun, la enzima Clase Ib se activa en respuesta a sistemas receptores acoplados a la proteína G (GPCRs) y su expresión parece limitarse a leucocitos y cardiomiocitos.

Actualmente existe considerable evidencia que indica que las enzimas PI3K Clase Ia participan en la tumorigénesis de una amplia gama de cánceres humanos, ya sea directamente o indirectamente (Vivanco and Sawyers, Nature Reviews Cancer, 2002, 2, 489-501). Por ejemplo, la subunidad p110α se amplifica en algunos tumores, como los de ovario (Shayesteh *et al.*, Nature Genetics, 1999, 21, 99-102) y cuello de útero (Ma *et al.*, Oncogene, 2000, 19, 2739-2744). Más recientemente se han asociado mutaciones activantes dentro del sitio catalítico de la subunidad catalítica p110α con otros tumores, como los de la región colorrectal y los de mama y pulmón (Samuels *et al.*, Science, 2004, 304, 554). También se han identificado las mutaciones relacionadas con tumores en la subunidad reguladora p85α en cánceres tales como cáncer de ovario y colon (Philp *et al.*, Cancer Research, 2001, 61, 7426-7429). Además de su participación en efectos directos, se cree que la activación de las PI3Ks Clase Ia participa en eventos tumorigénicos que se producen corriente arriba en las vías de

señalización, por ejemplo mediante la activación de receptores tirosina quinasa dependientes o independientes de ligandos, sistemas GPCR o integrinas (Vara *et al.,* Cancer Treatment Reviews, 2004, 30, 193-204). Ejemplos de dichas vías de señalización corriente arriba incluyen la sobreexpresión del receptor tirosina quinasa erbB2 en una variedad de tumores, lo que conduce a la activación de las vías mediadas por PI3K (Harari *et al.,* Oncogene, 2000, 19, 6102-6114) y la sobreexpresión del oncogén ras (Kauffmann-Zeh *et al.*, Nature, 1997, 385, 544-548). Además, las PI3Ks Clase Ia pueden contribuir indirectamente con la tumorigénesis causada por distintos eventos de señalización corriente abajo. Por ejemplo, la pérdida del efecto de la fosfatasa supresora de tumores PTEN, que cataliza la conversión de $PI(3,4,5)P_3$ de nuevo en $PI(4,5)P_2$, se asocia con una amplia gama de tumores a través de la desregulación de la producción de $PI(3,4,5)P_3$ mediada por la PI3K (Simpson and Parsons, Exp. Cell Res., 2001, 264, 29-41). Más aun, se cree que el aumento de los efectos de otros eventos de señalización mediados por la PI3K contribuye con una variedad de cánceres, por ejemplo, mediante la activación de Akt (Nicholson and Anderson, Cellular Signalling, 2002, 14, 381-395).

Además de su participación en la mediación de la señalización proliferativa y de supervivencia en células tumorales, existe evidencia que demuestra que las enzimas PI3K de Clase Ia contribuyen con la tumorigénesis en células estromales asociadas a tumores. Por ejemplo, se sabe que la señalización de la PI3K tiene un papel importante en la mediación de eventos angiogénicos en células endoteliales en respuesta a factores pro-angiogénicos tales como VEGF (Abid *et al.,* Arterioscler. Thromb. Vasc. Biol., 2004, 24, 294-300). Dado que las enzimas PI3K de Clase I también participan en la motilidad y la migración (Sawyer, Expert Opinion Investig. Drugs, 2004, 13, 1-19), los inhibidores de las enzimas PI3K deberían proporcionar beneficios terapéuticos a través de la inhibición de la invasión y metástasis de células tumorales. Además, las enzimas PI3K de Clase I también tienen una participación importante en la regulación de células inmunes, lo que contribuye con efectos pro-tumorigénicos de las células inflamatorias (Coussens and Werb, Nature, 2002, 420, 860-867).

Estos hallazgos sugieren que los inhibidores farmacológicos de las enzimas PI3K Clase I serán de valor terapéutico para el tratamiento de distintas enfermedades, incluidas formas de la enfermedad de cáncer que comprenden tumores sólidos tales como carcinomas y sarcomas y las leucemias y malignidades linfoides. En particular, los inhibidores de las enzimas PI3K de Clase I deberían ser valiosos desde el punto de vista terapéutico para el

tratamiento de, por ejemplo, cáncer de mama, colorrectal, de pulmón (incluyendo cáncer de pulmón de célula pequeña, cáncer de pulmón de célula no pequeña y cáncer bronquioloalveolar) y de próstata y cáncer del conducto biliar, óseo, de vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículo, tiroides, útero, cuello de útero y vulva y de leucemias (incluidas LLA y LMC), mieloma múltiple y linfomas.

La PI3K Clase Ib PI3Kγ es activada por los GPCRs, como quedó definitivamente demostrado en ratones que no tenían la enzima. Por lo tanto, los neutrófilos y macrófagos derivados de animales con deficiencia de PI3Kγ no lograron producir $PI(3,4,5)P_3$ en respuesta a la estimulación con distintas sustancias quimiotácticas (tales como IL-8, C5a, fMLP y MIP-1a), mientras que la señalización a través de receptores acoplados a la proteína tirosina quinasa hacia las PI3Ks Clase Ia se mantuvo intacta (Hirsch *et al.*, Science, 2000, 287(5455), 1049-1053; Li *et al.*, Science, 2002, 287(5455), 1046-1049; Sasaki *et al.*, Science 2002, 287(5455), 1040-1046). Más aun, la fosforilación de PKB mediada por $PI(3,4,5)P_3$ no fue iniciada por estos ligandos de GPCR en células nulas en PI3Kγ. Todos estos resultados demuestran que, al menos en células hematopoyéticas en reposo, la PI3Kγ es la única isoforma de PI3K que es activada por los GPCRs *in vivo*. Cuando se evaluaron neutrófilos derivados de médula ósea y macrófagos peritoneales de ratones de tipo silvestre y PI3Kγ *in vitro,* se observó un rendimiento reducido, pero no completamente suprimido, en ensayos de quimiotaxis y adherencia. Sin embargo, esto se tradujo en una drástica deficiencia en la infiltración de neutrófilos impulsada por IL-8 en tejidos (Hirsch *et al.*, Science, 2000, 287(5455), 1049-1053). Datos recientes sugieren que la PI3Kγ participa en el proceso de búsqueda de vías más que en la generación de fuerza mecánica para la motilidad, ya que la migración aleatoria no se vio afectada en células que carecían de PI3Kγ (Hannigan *et al.*, Proc. Nat. Acad. of Sciences of U.S.A., 2002, 99(6),3603-8). Los datos que vinculan la PI3Kγ con la patología de las enfermedades respiratorias demostraron que la PI3Kγ desempeña un papel fundamental en la regulación de la infiltración y activación de neutrófilos inducidas por endotoxinas que conducen a una lesión pulmonar aguda (Yum *et al.*, J. Immunology, 2001, 167(11), 6601-8). El hecho de que, si bien la PI3Kγ se expresa ampliamente en leucocitos, su pérdida no parece interferir con la hematopoyesis, y el hecho de que los ratones deficientes en PI3Kγ sean viables y fértiles convierten a esta isoforma de la PI3K en un posible objetivo para los fármacos. Los trabajos con ratones K.O. también establecieron que la PI3Kγ es un amplificador esencial de la activación de mastocitos (Laffargue *et al.*, Immunity, 2002, 16(3),

441-451).

Por lo tanto, además de tumorigénesis, existe evidencia de que las enzimas PI3K de Clase I desempeñan un papel en otras enfermedades (Wymann *et al.*, Trends in Pharmacological Science, 2003, 24, 366-376). Tanto las enzimas PI3K de Clase Ia como la enzima de Clase Ib desempeñan importantes papeles en células del sistema inmune (Koyasu, Nature Immunology, 2003, 4, 313-319) y, por lo tanto, son objetivos terapéuticos para indicaciones inflamatorias y alérgicas. Informes recientes demuestran que los ratones con deficiencia de PI3Kγ y PI3Kδ son viables pero tienen respuestas inflamatorias y alérgicas atenuadas (Ali *et al.*, Nature, 2004, 431(7011), 1007-11). La inhibición de la PI3K es útil también para tratar enfermedades cardiovasculares a través de efectos anti-inflamatorios o directamente mediante la afección de miocitos cardíacos (Prasad *et al.*, Trends in Cardiovascular Medicine, 2003, 13, 206-212). Por lo tanto, se espera que los inhibidores de las enzimas PI3K de Clase I sean valiosos en la prevención y el tratamiento de una amplia gama de enfermedades, además de cáncer.

Se han identificado varios compuestos que inhiben las PI3Ks y las quinasas relacionadas con la fosfatidilinositol (PI) quinasa (PI3KKs), entre los que se incluyen la wortmanina y el derivado de quercetina LY294002. Estos compuestos son inhibidores razonablemente específicos de las PI3Ks y PI3KKs con respecto a otras quinasas pero carecen de potencia y exhiben poca selectividad dentro de las familias PI3K.

Por lo tanto, sería deseable proporcionar inhibidores de mTOR y/o PI3K más eficaces para su uso en el tratamiento de cáncer, enfermedades inflamatorias u obstructivas de las vías respiratorias, inmunes o cardiovasculares.

Los derivados de morfolino pirimidina y los inhibidores de PI3K son conocidos en la técnica.

La Solicitud de Patente Internacional WO 2004/048365 describe compuestos que poseen actividad inhibitoria de la enzima PI3K y son útiles en el tratamiento de cáncer. Estos compuestos son pirimidinas arilamino- y heteroarilamino-sustituidas que difieren de los compuestos de la presente invención con respecto a sus sustituyentes arilamino- y heteroarilamino. Estos sustituyentes no son equivalentes a los $-XR^1$ de la presente invención.

Los inhibidores de la actividad de la PI3K útiles en el tratamiento de cáncer también se describen en la Solicitud de Patente Europea 1 277 738, que menciona compuestos heteroarilo bicíclicos 4-morfolino-substituidos tales como quinazolina y derivados de pirido[3,2-*d*]pirimidina y compuestos heteroarilo tricíclicos 4-morfolino-substituidos pero no derivados

de pirimidina monocíclicos.

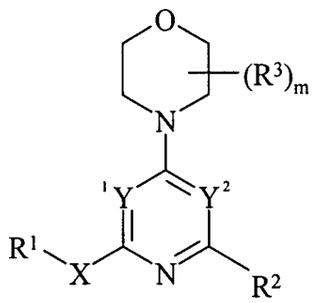
Los documentos WO2007/080382, WO2008/023180 y WO2008/023159 describen compuestos que poseen actividad inhibitoria de la enzima PI3K y/o mTOR y son útiles en el tratamiento de cáncer. Los documentos WO2007/080382, WO2008/023180 y WO2008/023159 no describen compuestos que comprenden un resto cíclico en el grupo X enlazante en el grupo $-XR^1$.

Se han registrado varios compuestos, tales como 4-morfolin-4-il-6-(fenilsulfonilmetil)-2-piridin-4-il-pirimidina y 4-{6-[(fenilsulfonil)metil]-2-piridin-2-ilpirimidin-4-il}morfolina, en la base de datos Chemical Abstracts pero no se ha indicado ninguna utilidad y no se sugiere que estos compuestos presenten actividad inhibitoria de la mTOR y/o PI3K o propiedades terapéuticas útiles.

De manera sorprendente, hemos encontrado que ciertos derivados de morfolino pirimidina, incluidos algunos compuestos conocidos previamente, poseen propiedades terapéuticas útiles. Sin querer quedar ligados a ninguna teoría en particular, se cree que la utilidad terapéutica de los derivados deriva de su actividad inhibitoria contra la mTOR quinasa y/o una o más de las enzimas PI3K (tal como la enzima Clase Ia y/o la enzima Clase Ib). Dado que las vías de señalización mediadas por las familias PI3K/mTOR desempeñan un papel central en distintos procesos celulares, incluida la proliferación y la supervivencia, y debido a que la desregulación de estas vías es un factor causante de una amplia gama de cánceres y otras enfermedades humanas, se espera que los derivados sean terapéuticamente útiles. En particular, se espera que los derivados tengan propiedades anti-proliferativas y/o apoptóticas, lo que significa que serán útiles en el tratamiento de enfermedades proliferativas, tal como cáncer. Los compuestos de la presente invención también pueden ser útiles para inhibir la proliferación celular descontrolada que surge en distintas enfermedades no malignas tales como enfermedades inflamatorias, enfermedades obstructivas de las vías respiratorias, enfermedades inmunológicas o enfermedades cardiovasculares.

En general, los compuestos de la presente invención poseen una potente actividad inhibitoria contra la mTOR quinasa pero el compuesto también puede poseer potente actividad inhibitoria contra una o más de las enzimas PI3K (tal como la enzima Clase Ia y/o la enzima Clase Ib).

De acuerdo con un aspecto de la presente invención, se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7-$;

R^1 es un grupo que se selecciona de hidrógeno, alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $-NR^9SO_2R^{10}$;

R^2 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S, y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-}

$_6$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^{11}, **R^{12}**, **R^{17}** y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo,

alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

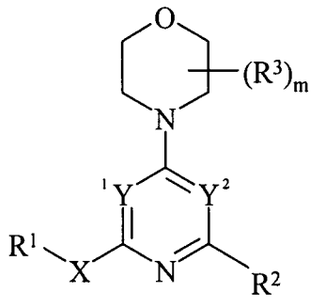
$\mathbf{R^{13}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$ y $\mathbf{R^{16}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

$\mathbf{R^{19}}$ es hidrógeno, ciano o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo

para su uso como un medicamento en el tratamiento de una enfermedad proliferativa.

De acuerdo con un aspecto de la presente invención, se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7-$;

R^1 es un grupo que se selecciona de hidrógeno, alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $-NR^9SO_2R^{10}$;

R^2 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o

más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^{11}, **R^{12}**, **R^{17}** y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$

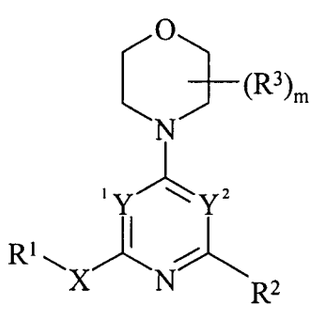
$_6$alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** y **R^{19}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo

para su uso como un medicamento en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona un compuesto de fórmula (I)



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fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7-$;

R^1 es un grupo que se selecciona de alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $-NR^9SO_2R^{10}$;

o **X-R^1** es $-CR^6R^7OH$;

R^2 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^{11}, **R^{12}**, **R^{17}** y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** y **R^{19}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se

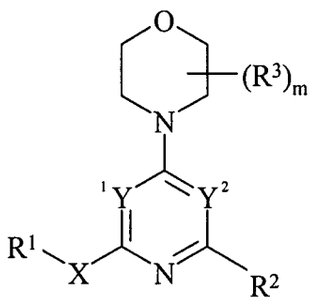
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seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo

para su uso como un medicamento en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

^1Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^1Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7-$;

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R^1 es un grupo que se selecciona de alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, -OR^9, -SR^9, -SOR^9, -SO_2R^9, -COR^9, -CO_2R^9, -$CONR^9R^{10}$, -NR^9R^{10}, –NR^9COR^{10}, -$NR^9CO_2R^{10}$, -$NR^9CONR^{10}R^{15}$, -$NR^9COCONR^{10}R^{15}$ y –$NR^9SO_2R^{10}$;

o **X-R^1** es -CR^6R^7OH;

R^2 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, -$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ y -$NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, -R^{13}, -OR^{13}, -SR^{13}, -SOR^{13}, -SO_2R^{13}, -COR^{13}, -CO_2R^{13}, -$CONR^{13}R^{14}$, -$NR^{13}R^{14}$, –$NR^{13}COR^{14}$, -$NR^{13}CO_2R^{14}$ y –$NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}

$_6$sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

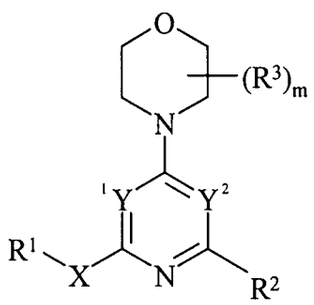
R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{13}, R^{14}, R^{15}, R^{16} y **R^{19}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo

para su uso como un medicamento en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona el uso de un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

$\mathbf{^1Y}$ e $\mathbf{Y^2}$ son independientemente N o CR^8 siempre que uno de ^1Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7-$;

$\mathbf{R^1}$ es un grupo que se selecciona de hidrógeno, alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $-NR^9SO_2R^{10}$;

R^2 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6},

hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{13}, R^{14}, R^{15} y **R^{16}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

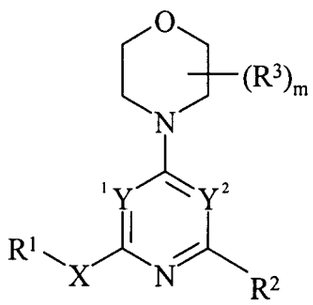
R^{19} es hidrógeno, ciano o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo,

alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo

en la fabricación de un medicamento para su uso en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona el uso de un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

^1Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^1Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7-$;

R^1 es un grupo que se selecciona de hidrógeno, alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este

grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $-NR^9SO_2R^{10}$;

R^2 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

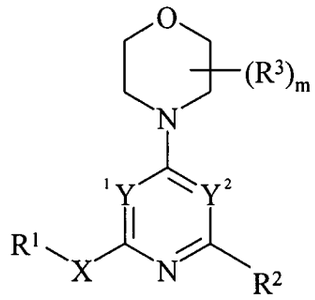
R^{13}, R^{14}, R^{15}, R^{16} y **R^{19}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6},

haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo

en la fabricación de un medicamento para su uso en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona el uso de un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7-, -NR^{4}S(O)$_2$CR^{6}R^7- y -S(O)$_2$NR^{4}CR^{6}R^7-;

R^1 es un grupo que se selecciona de alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, -R^9, -OR^9, -SR^9, -SOR^9, -SO$_2$R^9, -COR^9, -CO$_2$R^9, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} y –NR^{9}SO$_2$R^{10};

o **X-R^1** es –CR^{6}R^{7}OH;

R^2 es un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, - SR^{11}, -SOR^{11}, -SO$_2$R^{11}, -COR^{11}, -

CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, –$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ y -$NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, -R^{13}, -OR^{13}, -SR^{13}, -SOR^{13}, -SO_2R^{13}, -COR^{13}, -CO_2R^{13}, -$CONR^{13}R^{14}$, -$NR^{13}R^{14}$, –$NR^{13}COR^{14}$, -$NR^{13}CO_2R^{14}$ y –$NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6}

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$_{6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

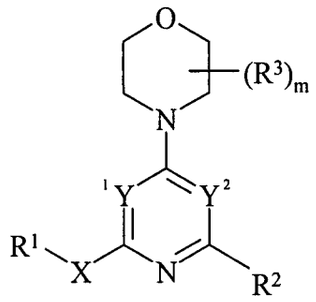
R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^{13}, R^{14}, R^{15}, R^{16} y **R^{19}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo

en la fabricación de un medicamento para su uso en el tratamiento de una enfermedad proliferativa.

De acuerdo con otro aspecto de la presente invención, se proporciona el uso de un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable; en donde

m es 0, 1, 2, 3 o 4;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7-$;

R^1 es un grupo que se selecciona de alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $-NR^9SO_2R^{10}$;

o **X-R^1** es $-CR^6R^7OH$;

R^2 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$ y $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-R^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

$\mathbf{R^8}$ se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$,

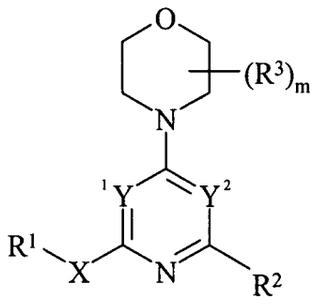
sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** y **R^{19}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo

en la fabricación de un medicamento para su uso en el tratamiento de una enfermedad proliferativa.

De acuerdo con un aspecto adicional de la presente invención, se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7-, -NR^{4}S(O)$_2$CR^{6}R^7- y -S(O)$_2$NR^{4}CR^{6}R^7-;

R^1 es un grupo que se selecciona de hidrógeno, alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, -R^9, -OR^9, -SR^9, -SOR^9, -O$_2$R^9, -COR^9, -CO$_2$R^9, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} y NR^{9}SO$_2$R^{10};

R^2 es un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO$_2$R^{11}, -COR^{11}, -CO$_2$R^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12}, -NR^{11}COR^{12}, -NR^{11}COCONR^{12}R^{16}, -NR^{11}SO$_2$R^{12}, -NR^{17}CONR^{18}R^{19} y -NR^{17}CSNR^{18}R^{19};

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, -R^{13}, -OR^{13}, -R^{13}, -SOR^{13}, -SO$_2$R^{13}, -COR^{13}, -CO$_2$R^{13}, -CONR^{13}R^{14}, -NR^{13}R^{14}, –NR^{13}COR^{14}, -NR^{13}CO$_2$R^{14} y –NR^{13}SO$_2$R^{14};

R^4 y **R^5** son independientemente hidrógeno o alquiloC$_{1-6}$;

o **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-}$

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$_6$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo,

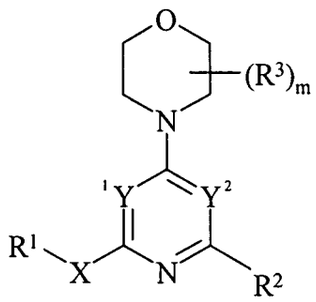
alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{13}, **R^{14}**, **R^{15}** y **R^{16}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{19} es hidrógeno, ciano o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

De acuerdo con un aspecto adicional de la presente invención, se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7-, -NR^{4}S(O)$_2$CR^{6}R^7- y -S(O)$_2$NR^{4}CR^{6}R^7-;

R^1 es un grupo que se selecciona de hidrógeno, alquiloC$_{1-6}$, alqueniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, -R^9, -OR^9, -SR^9, -SOR^9, -O$_2$R^9, -COR^9, -CO$_2$R^9, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} y NR^{9}SO$_2$R^{10};

R^2 es un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO$_2$R^{11}, -COR^{11}, -CO$_2$R^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12}, -NR^{11}COR^{12}, -NR^{11}COCONR^{12}R^{16}, -NR^{11}SO$_2$R^{12}, -NR^{17}CONR^{18}R^{19} y -NR^{17}CSNR^{18}R^{19};

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, -R^{13}, -OR^{13}, -R^{13}, -SOR^{13}, -SO$_2$R^{13}, -COR^{13}, -CO$_2$R^{13}, -CONR^{13}R^{14}, -NR^{13}R^{14}, –NR^{13}COR^{14}, -NR^{13}CO$_2$R^{14} y –NR^{13}SO$_2$R^{14};

R^4 y **R^5** son independientemente hidrógeno o alquiloC$_{1-6}$;

o **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o

más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

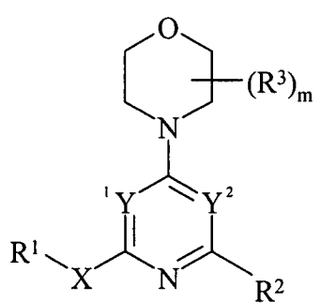
R^{11}, **R^{12}**, **R^{17}** y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$

$_6$alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** y **R^{19}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

De acuerdo con un aspecto adicional de la presente invención, se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^1Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7-$;

R^1 es un grupo que se selecciona de alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, $-R^9$, $-OR^9$, $-SR^9$, $-SOR^9$, $-O_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $NR^9SO_2R^{10}$;

o **X-R^1** es $-CR^6R^7OH$;

R^2 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-R^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

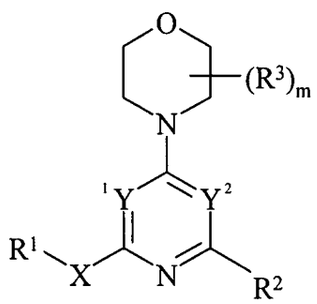
R^{11}, **R^{12}**, **R^{17}** y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{13}, **R^{14}**, **R^{15}**, **R^{16}** y **R^{19}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se

seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo.

De acuerdo con un aspecto adicional de la presente invención, se proporciona un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de -CR^4=CR^{5}CR^{6}R^7-, -CR^{6}R^{7}CR^5=CR^4-, -C≡CCR^{6}R^7-, -CR^{6}R^{7}C≡C-, -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7- y -S(O)$_2$NR^{4}CR^{6}R^7-;

R^{1} es un grupo que se selecciona de alquiloC$_{1-6}$, alquenniloC$_{2-6}$, alquiniloC$_{2-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, -R^{9}, -OR^{9}, -SR^{9}, -SOR^{9}, -O$_2$R^{9}, -COR^{9}, -CO$_2$R^{9}, -CONR^{9}R^{10}, -NR^{9}R^{10}, –NR^{9}COR^{10}, -NR^{9}CO$_2$R^{10}, -NR^{9}CONR^{10}R^{15}, -NR^{9}COCONR^{10}R^{15} y NR^{9}SO$_2$R^{10};

o **X-R**^{1} es –CR^{6}R^{7}OH;

R^{2} es un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO$_2$R^{11}, -COR^{11}, -CO$_2$R^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12}, -NR^{11}COR^{12} y -NR^{11}COCONR^{12}R^{16}, -NR^{11}SO$_2$R^{12}, -NR^{17}CONR^{18}R^{19} y -NR^{17}CSNR^{18}R^{19};

cada R^{3}, cuando está presente, se selecciona independientemente de halo, ciano, nitro, -R^{13}, -OR^{13}, -R^{13}, -SOR^{13}, -SO$_2$R^{13}, -COR^{13}, -CO$_2$R^{13}, -CONR^{13}R^{14}, -NR^{13}R^{14}, –NR^{13}COR^{14}, -NR^{13}CO$_2$R^{14} y –NR^{13}SO$_2$R^{14};

R^{4} y **R**^{5} son independientemente hidrógeno o alquiloC$_{1-6}$;

o **R**^{1} y **R**^{4} junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^{6} y **R**^{7} junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$

$_{6}$sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{13}, R^{14}, R^{15}, R^{16} y **R^{19}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

Ciertos compuestos de fórmula (I) son capaces de existir en formas estereoisoméricas. Se comprenderá que la invención abarca todos los isómeros geométricos y ópticos de los compuestos de fórmula (I) y mezclas de los mismos incluyendo racematos. Los tautómeros y mezclas de los mismos también forman un aspecto de la presente invención. Los solvatos y mezclas de los mismos también forman un aspecto de la presente invención. Por ejemplo, un solvato adecuado de un compuesto de fórmula (I) es, por ejemplo, un hidrato tal como un hemi-hidrato, un mono-hidrato, un di-hidrato o un tri-hidrato o una cantidad alternativa de los mismos.

La presente invención se refiere a los compuestos de fórmula (I) según se describen en la presente, así como sales de los mismos. Las sales para su uso en composiciones farmacéuticas serán sales farmacéuticamente aceptables, pero otras sales pueden ser útiles en la producción de los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables. Las sales farmacéuticamente aceptables de la invención pueden incluir, por ejemplo, sales de adición de ácido de compuestos de fórmula (I) según se describen en la presente que son lo suficientemente básicas para formar dichas sales. Dichas sales de adición de ácido incluyen, a modo no taxativo, sales de fumarato, metanosulfonato, clorhidrato, bromhidrato, citrato y maleato y sales formadas con ácido fosfórico y sulfúrico. Además, cuando los compuestos de fórmula (I) son lo suficientemente ácidos, las sales son sales básicas y ejemplos de las mismas incluyen, a modo no taxativo, una sal de metal alcalino, por ejemplo sodio o potasio, una sal de metal alcalinotérreo, por ejemplo calcio o magnesio, o una sal de amina orgánica, por ejemplo trietilamina, etanolamina, dietanolamina, trietanolamina, morfolina, *N*-metilpiperidina, *N*-etilpiperidina, dibencilamina, o aminoácidos tales como lisina.

Los compuestos de fórmula (I) también pueden proporcionarse como ésteres

hidrolizables *in vivo*. Un éster hidrolizable *in vivo* de un compuesto de fórmula (I) que contiene un grupo carboxi o hidroxi es, por ejemplo un éster farmacéuticamente aceptable que se escinde en el cuerpo humano o animal para producir el ácido o alcohol base. Dichos ésteres pueden identificarse mediante la administración, por ejemplo, por vía intravenosa a un animal de prueba, del compuesto en estudio y posteriormente del examen del fluido corporal del animal de prueba.

Entre los ésteres farmacéuticamente aceptables para carboxi se incluyen ésteres de alcoxiC_{1-6}metilo, por ejemplo metoximetilo, ésteres de alcanoilC_{1-6}oximetilo, por ejemplo ésteres de pivaloiloximetilo, ftalidilo, ésteres de cicloalcoxiC_{3-8}carboniloxiC_{1-6}alquilo, por ejemplo 1-ciclohexilcarboniloxietilo, ésteres de 1,3-dioxolen-2-onilmetilo, por ejemplo 5-metil-1,3-dioxolen-2-onilmetilo, y ésteres de alcoxiC_{1-6}carboniloxietilo, por ejemplo 1-metoxicarboniloxietilo; y pueden formarse en cualquier grupo carboxi en los compuestos de esta invención.

Entre los ésteres farmacéuticamente aceptables adecuados para hidroxi se incluyen ésteres inorgánicos tales como ésteres de fosfato (incluyendo ésteres cíclicos fosforamídicos) y éteres de α-aciloxialquilo y compuestos relacionados que, como resultado de la hidrólisis *in vivo* del éster, se desintegran para proporcionar el o los grupos hidroxi base. Ejemplos de ésteres de α-aciloxialquilo incluyen acetoximetoxi y 2,2-dimetilpropioniloximetoxi. Una selección de grupos formadores de ésteres hidrolizables *in vivo* incluyen alcanoiloC_{1-10}, por ejemplo formilo, acetilo, benzoilo, fenilacetilo, benzoilo sustituido y fenilacetilo; alcoxiC_{1-10}carbonilo (para proporcionar ésteres de alquil carbonato), por ejemplo etoxicarbonilo; di-alquilC_{1-4}carbamoilo y N-(di-alquilC_{1-4}aminoetil)-N-alquilC_{1-4}carbamoilo (para proporcionar carbamatos); di-alquilC_{1-4}aminoacetilo y carboxiacetilo. Ejemplos de sustituyentes del anillo en fenilacetilo y benzoilo incluyen aminometilo, alquilC_{1-4}aminometilo y di-(alquilC_{1-4})aminometilo, y morfolino o piperazino unidos desde un átomo de nitrógeno del anillo a través de un grupo de enlace metileno a la posición 3 o 4 del anillo de benzoilo. Otros ésteres hidrolizables *in vivo* incluyen, por ejemplo, R^AC(O)OalquilC_{1-6}-CO-, en donde R^A es, por ejemplo, benciloxi-alquiloC_{1-4}, o fenilo. Sustituyentes adecuados en un grupo fenilo en dichos ésteres incluyen, por ejemplo, 4-piperazinoC_{1-4}-alquiloC_{1-4}, piperazino-alquiloC_{1-4} y morfolino-alquiloC_{1-4}.

Los compuestos de fórmula (I) también pueden administrarse en forma de un profármaco que se desintegra en el cuerpo humano o animal para proporcionar un compuesto de la fórmula (I). En la técnica se conocen distintas formas de profármacos. Se remite al lector

a las siguientes publicaciones para ver más ejemplos:

a) Design of Prodrugs, editado por H. Bundgaard, (Elsevier, 1985) y Methods in Enzymology, Vol. 42, p. 309-396, editado por K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, editado por Krogsgaard-Larsen y H. Bundgaard, Capítulo 5 "Design and Application of Prodrugs", de H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); y

e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

En esta memoria descriptiva, el término genérico "alquiloC_{p-q}" incluye grupos alquilo de cadena recta y de cadena ramificada. Sin embargo, las referencias a grupos alquilo individuales tales como "propilo" son específicas para la versión de cadena recta solamente (es decir, n-propilo e isopropilo) y las referencias a grupos alquilo de cadena ramificada individuales tales como "*terc*-butilo" son específicas para la versión de cadena ramificada solamente.

El sufijo C_{p-q} en alquiloC_{p-q} y otros términos (en donde p y q son números enteros) indica el rango de átomos de carbono que se encuentran presentes en el grupo. Por ejemplo, alquilo C_{1-4} incluye alquiloC_1 (metilo), alquiloC_2 (etilo), alquiloC_3 (propilo como n-propilo e isopropilo) y alquiloC4 (n-butilo, sec-butilo, isobutilo y *terc*-butilo).

El término alcoxiC_{p-q} comprende grupos -O-alquiloC_{p-q}.

El término alcanoiloC_{p-q} comprende grupos -C(O)alquilo.

El término halo incluye fluoro, cloro, bromo y yodo.

"Carbociclilo" es un sistema anular monocíclico, bicíclico o tricíclico saturado, insaturado o parcialmente saturado que contiene de 3 a 14 átomos en el anillo, en donde un grupo CH_2 en el anillo puede reemplazarse por un grupo C=O. "Carbociclilo" incluye "arilo", "cicloalquiloC_{p-q}" y "cicloalqueniloC_{p-q}".

"Arilo" es un sistema anular carbociclilo monocíclico, bicíclico o tricíclico aromático.

"CicloalqueniloC_{p-q}" es un sistema anular carbociclilo monocíclico, bicíclico o tricíclico insaturado o parcialmente saturado que contiene al menos 1 enlace C=C y en donde un grupo CH_2 en el anillo puede reemplazarse por un grupo C=O.

"CicloalquiloC_{p-q}" es un sistema anular carbocíclico monocíclico, bicíclico o tricíclico saturado y en donde un grupo CH_2 en el anillo puede reemplazarse por un grupo C=O.

"Heterociclilo" es un sistema anular monocíclico, bicíclico o tricíclico saturado,

insaturado o parcialmente saturado que contiene de 3 a 14 átomos en el anillo de los que 1, 2, 3 o 4 átomos en el anillo se seleccionan de nitrógeno, azufre u oxígeno, pudiendo estar dicho anillo unido a carbono o nitrógeno y en donde un átomo de nitrógeno o azufre del anillo puede oxidarse y en donde un grupo CH_2 en el anillo puede reemplazarse por un grupo C=O. "Heterociclilo" incluye "heteroarilo", "cicloheteroalquilo" y "cicloheteroalquenilo".

"Heteroarilo" es un heterociclilo monocíclico, bicíclico o tricíclico aromático que en particular contiene 5 a 10 átomos en el anillo, de los que 1, 2, 3 o 4 átomos en el anillo se seleccionan de nitrógeno, azufre u oxígeno, en donde un nitrógeno o azufre del anillo puede oxidarse.

"Cicloheteroalquenilo" es un sistema anular heterociclilo monocíclico, bicíclico o tricíclico insaturado o parcialmente saturado, que en particular contiene de 5 a 10 átomos en el anillo, de los que 1, 2, 3 o 4 átomos en el anillo se seleccionan de nitrógeno, azufre u oxígeno, pudiendo estar dicho anillo unido a carbono o nitrógeno y en donde un átomo de nitrógeno o azufre en el anillo puede oxidarse y en donde un grupo CH_2 en el anillo puede reemplazarse por un grupo C=O.

"Cicloheteroalquilo" es un sistema anular heterocíclico monocíclico, bicíclico o tricíclico saturado, que en particular contiene de 5 a 10 átomos en el anillo, de los que 1, 2, 3 o 4 átomos en el anillo se seleccionan de nitrógeno, azufre u oxígeno, pudiendo estar dicho anillo unido a carbono o nitrógeno y en donde un átomo de nitrógeno o azufre en el anillo puede oxidarse y en donde un grupo CH_2 en el anillo puede reemplazarse por un grupo C=O.

Esta memoria descriptiva puede emplear términos compuestos para describir grupos que comprenden más de una funcionalidad. A menos que se describa de otra forma, dichos términos deben interpretarse según su acepción corriente en la técnica. Por ejemplo, carbociclilalquiloC_{p-q} comprende alquiloC_{p-q} sustituido por carbociclilo, heterociclilalquiloC_{p-q} comprende alquiloC_{p-q} sustituido por heterociclilo y bis(alquilC_{p-q})amino comprende amino sustituido por 2 grupos alquiloC_{p-q} que pueden ser iguales o diferentes.

HaloalquiloC_{p-q} es un grupo alquiloC_{p-q} que se sustituye por 1 o más sustituyentes halo y particularmente 1, 2 o 3 sustituyentes halo. De manera similar, otros términos genéricos que contienen halo, tal como haloalcoxiC_{p-q}, pueden contener 1 o más sustituyentes halo y particularmente 1, 2 o 3 sustituyentes halo.

HidroxialquiloC_{p-q} es un grupo alquiloC_{p-q} que se sustituye por 1 o más sustituyentes hidroxilo y particularmente por 1, 2 o 3 sustituyentes hidroxi. De manera similar, otros términos genéricos que contienen hidroxi, tal como hidroxialcoxiC_{p-q}, pueden contener 1 o

más, y particularmente 1, 2 o 3, sustituyentes hidroxi.

AlcoxiC_{p-q}alquiloC_{p-q} es un grupo alquiloC_{p-q} que se sustituye por 1 o más sustituyentes alcoxiC_{p-q} y particularmente 1, 2 o 3 sustituyentes alcoxiC_{p-q}. De manera similar, otros términos genéricos que contienen alcoxiC_{p-q}, tales como alcoxiC_{p-q}alcoxiC_{p-q}, pueden contener 1 o más sustituyentes alcoxiC_{p-q} y particularmente 1, 2 o 3 sustituyentes alcoxiC_{p-q}.

En los casos en los que los sustituyentes opcionales se seleccionan de "1 o 2", de "1, 2 o 3" o de "1, 2, 3 o 4" grupos o sustituyentes, debe entenderse que esta definición incluye a todos los sustituyentes que se seleccionan de uno de los grupos especificados, es decir, todos los sustituyentes son iguales, o los sustituyentes se seleccionan de dos o más de los grupos especificados, es decir, los sustituyentes no son iguales.

Los compuestos de la presente invención se nombraron con la ayuda del programa informático ACD/Name, versión 8.0.

"Enfermedad proliferativa" incluye enfermedades malignas tales como cáncer, así como también enfermedades no malignas tales como enfermedades inflamatorias, obstructivas de las vías respiratorias, inmunológicas o cardiovasculares.

Valores adecuados para cualquier grupo R o cualquier parte o sustituyente de dichos grupos incluyen:

para alquiloC_{1-4}: metilo, etilo, propilo, butilo, 2-metilpropilo y *terc*-butilo;

para alquiloC_{1-6}: alquiloC_{1-4}, pentilo, 2,2-dimetilpropilo, 3-metilbutilo y hexilo;

para cicloalquiloC_{3-6}: ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo;

para cicloalquilC_{3-6}alquiloC_{1-4}: ciclopropilmetilo, ciclopropiletilo, ciclobutilmetilo, ciclopentilmetilo y ciclohexilmetilo;

para arilo: fenilo y naftilo;

para arilalquiloC_{1-4}: bencilo, fenetilo, naftilmetilo y naftiletilo;

para carbocililo: arilo, ciclohexenilo y cicloalquiloC_{3-6};

para halo: fluoro, cloro, bromo y yodo;

para alcoxiC_{1-4}: metoxi, etoxi, propoxi e isopropoxi;

para alcoxiC_{1-6}: alcoxiC_{1-4}, pentiloxi, 1-etilpropoxi y hexiloxi;

para alcanoiloC_{1-6}: acetilo, propanoilo y 2-metilpropanoilo;

para heteroarilo: piridilo, imidazolilo, quinolinilo, cinnolilo, pirimidinilo, tienilo, pirrolilo, pirazolilo, tiazolilo, tiazolilo, triazolilo, oxazolilo, isoxazolilo, furanilo, piridazinilo, pirazinilo, indolilo, benzofuranilo, dibenzofuranilo y benzotienilo;

para heteroarilalquiloC_{1-4}: pirrolilmetilo, pirroliletilo, imidazolilmetilo, imidazoliletilo,

pirazolilmetilo, pirazoliletilo, furanilmetilo, furaniletilo, tienilmetilo, theiniletilo, piridilmetilo, piridiletilo, pirazinilmetilo, piraziniletilo, pirimidinilmetilo, pirimidiniletilo, pirimidinilpropilo, pirimidinilbutilo, imidazolilpropilo, imidazolilbutilo, quinolinilpropilo, 1,3,4-triazolilpropilo y oxazolilmetilo;

para heterociclilo: heteroarilo, pirrolidinilo, isoquinolinilo, quinoxalinilo, benzotiazolilo, benzoxazolilo, piperidinilo, piperazinilo, azetidinilo, morfolinilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, indolinilo, dihidro-2H-piranilo y tetrahidrofuranilo.

Cabe señalar que los ejemplos proporcionados para los términos utilizados en la memoria descriptiva no son taxativos.

A continuación se muestran valores particulares de m, X, ^{1}Y e Y^2, X, R^1, X-R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{17}, R^{18} y R^{19}. Dichos valores pueden utilizarse individualmente o combinados cuando corresponda con relación a cualquier aspecto de la invención, o parte de los mismos, y cualquiera de las definiciones, reivindicaciones o realizaciones definidas en la presente.

m

En un aspecto de la invención m es 0, 1, 2 o 3.

En otro aspecto m es 0, 1 o 2.

En un aspecto adicional m es 0 o 1.

En otro aspecto m es 0 para que R^3 esté ausente.

En otro aspecto m es 1 y R^3 es metilo.

En otro aspecto m es 1 y R^3 es hidroximetilo.

En otro aspecto m es 1 y R^3 es etilo.

En otro aspecto m es 1 y R^3 es dimetilcarbamoilo.

En otro aspecto m es 1 y R^3 es carbamoilo.

En otro aspecto m es 2 y cada R^3 es metilo.

^{1}Y e Y^2

En un aspecto de la invención ^{1}Y es N e Y^2 es CR^8.

En otro aspecto ^{1}Y es N e Y^2 es CH.

En otro aspecto ^{1}Y es CR^8 e Y^2 es N.

En un aspecto adicional ^{1}Y es CH o CF e Y^2 es N.

En otro un aspecto adicional ^{1}Y es CH e Y^2 es N.

X

En un aspecto de la invención X es un grupo enlazante que se selecciona de -$NR^4CR^6R^7$-, -OCR^6R^7-, -SCR^6R^7-, -$S(O)CR^6R^7$-, -$S(O)_2CR^6R^7$-, -$C(O)NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$- y -$S(O)_2NR^4CR^6R^7$-.

En otro aspecto **X** es un grupo enlazante que se selecciona de -$NR^4CR^6R^7$-, -OCR^6R^7-, -SCR^6R^7-, -$S(O)CR^6R^7$-, -$S(O)_2CR^6R^7$-, -$C(O)NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$- y -$S(O)_2NR^4CR^6R^7$.

En un aspecto adicional X es un grupo enlazante que se selecciona de -$NR^4CR^6R^7$-, -OCR^6R^7-, -SCR^6R^7-, -$S(O)CR^6R^7$- y -$S(O)_2CR^6R^7$-.

En un aspecto adicional X es un grupo enlazante que se selecciona de -$NR^4CR^6R^7$-, -OCR^6R^7-, -SCR^6R^7-, -$S(O)CR^6R^7$- y -$S(O)_2CR^6R^7$-.

En otro aspecto X es un grupo enlazante que se selecciona de -SCR^6R^7-, -$S(O)CR^6R^7$- y -$S(O)_2CR^6R^7$-.

En otro aspecto X es -SCR^6R^7- o -$S(O)_2CR^6R^7$-.

En otro aspecto X es -$S(O)_2CR^6R^7$-.

R^1

En un aspecto de la invención R^1 es un grupo que se selecciona de alquiloC_{1-4}, cicloalquiloC_{3-10}, arilo, cicloalquilC_{3-10}alquiloC_{1-4}, arilalquiloC_{1-4}, cicloheteroalquilo, heteroarilo, cicloheteroalquilalquiloC_{1-4}, heteroarilalquiloC_{1-4}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} y -NR^9COR^{10}.

En otro aspecto, R^1 es un grupo que se selecciona de adamantilo, metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopentilo, ciclohexilo, fenilo, bencilo, fenetilo, pirrolidinilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tiadiazolilo, tiazolilo, tienilo, piridinilo, pirimidinilo, pirazinilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolilmetilo, pirroliletilo, imidazolilmetilo, imidazoliletilo, pirazolilmetilo, pirazoliletilo, furanilmetilo, furaniletilo, tiadiazolilmetilo, tiadiazoliletilo, tiazolilmetilo, tiazoliletilo, tienilmetilo, tieniletilo, piridinilmetilo, piridiniletilo, pirimidinilmetilo, pirimidiniletilo, pirazinilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1, 2 o 3 grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} y –NR^9COR^{10}.

En otro aspecto, R^1 es un grupo que se selecciona de adamantilo, metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopentilo, ciclohexilo, fenilo, bencilo, fenetilo, pirrolidinilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, pirazinilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolilmetilo, pirroliletilo, imidazolilmetilo,

imidazoliletilo, pirazolilmetilo, pirazoliletilo, furanilmetilo, furaniletilo, tienilmetilo, tieniletilo, piridinilmetilo, piridiniletilo, pirimidinilmetilo, pirimidiniletilo, pirazinilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1, 2 o 3 grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} y –NR^9COR^{10}.

En un aspecto adicional, R^1 es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, imidazolilo, pirrolidinilo, tiadiazolilo, tiazolilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, hidroxi, metilo, metoxi, trifluorometilo, trifluorometoxi, -$NHCOCH_3$, -$CONH_2$ y -$CONHCH_3$.

En un aspecto adicional, R^1 es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, metilo, metoxi, trifluorometilo, trifluorometoxi, -$NHCOCH_3$, -$CONH_2$ y –$CONHCH_3$.

En otro aspecto R^1 es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, ciclopentilo, ciclohexilo, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2C(OH)(CH_3)_2$, -$CH_2CH_2CH_2OCHF_2$, -$CH_2CH_2OCH_3$, -$CH_2CH_2NHC(O)CH_3$, -$CH_2C(O)NH_2$, -$CH_2C(O)NHMe$, -CH_2CH_2NHMe, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-fluoro-4-metilaminofenilo, 4-fluoro-2-metilfenilo, 5-fluoro-2-metilfenilo, 3-fluoro-4-(2-hidroxietilamino)fenilo, 4-(difluorometoxi)fenilo, 4-carbamoil-2-clorofenilo, 4-clorofenilo, 2-clorofenilo, 3-cloro-4-fluorofenilo, 3-cloro-4-metilaminofenilo, 3-cloro-4-etilaminofenilo, 3-cloro-4-(2-fluoroetilamino)fenilo, 3-cloro-4-(2-hidroxietilamino)fenilo, 2-cloro-4-cianofenilo, 4-cianofenilo, 2,4-difluorofenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 3,4-difluorofenilo, 3,5-difluorofenilo, 2-(trifluorometil)fenilo, 2-metilfenilo, 4-metilfenilo, 4-(2-hidroxietilamino)fenilo, 1H-imidazol-2-ilo, 3,5-dimetilisoxazol-4-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, 1-(difluorometil)pirazol-4-ilo, 1-(difluorometil)-3,5-dimetilpirazol-4-ilo, 1,3-dimetilpirazol-4-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, 5-fluoropiridin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo, 4,5-dimetiltiazol-2-ilo, 2,4-dimetiltiazol-5-ilo, 5-metil-1,3,4-tiadiazol-2-ilo, tetrahidrofuran-3-ilo y tetrahidrofuran-4-ilo.

En otro aspecto R^1 es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, ciclopentilo, ciclohexilo, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, fenilo, 4-fluorofenilo, 4-clorofenilo, 2-clorofenilo, 3,5-difluorofenilo, 2-(trifluorometil)fenilo, 2-metoxifenilo, 2-metilfenilo, 4-(2-hidroxietilamino)fenilo, 1H-imidazol-2-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, 4-acetamidofenilo, 4-aminofenilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, 5-fluoropiridin-3-ilo, 2-oxopirolidin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo, 5-metil-1,3,4-tiadiazol-2-ilo y 3-metil-1,3,4-tiadiazol-2-ilo.

En otro aspecto R^1 es un grupo que se selecciona de metilo, isopropilo, ciclopropilo, ciclohexilo, $-CH_2CH_2OH$, $-CH_2CH_2NHC(O)CH_3$, fenilo, 4-fluorofenilo, 2-clorofenilo, 2-trifluorometilfenilo, 2-metoxifenilo, 2-metilfenilo, 4-acetamidofenilo, 4-aminofenilo, piridin-4-ilo, piridin-2-ilo, 2-oxopirolidin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo y 3-metil-1,3,4-tiadiazol-2-ilo.

En otro aspecto R^1 es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, ciclopentilo, ciclohexilo, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, fenilo, 4-fluorofenilo, 4-clorofenilo, 3,5-difluorofenilo, 2-(trifluorometil)fenilo, 4-(2-hidroxietilamino)fenilo, 1H-imidazol-2-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, 5-fluoropiridin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo y 5-metil-1,3,4-tiadiazol-2-ilo.

En otro aspecto R^1 es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2CH_2NHMe$, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-fluoro-4-metilaminofenilo, 4-fluoro-2-metilfenilo, 5-fluoro-2-metilfenilo, 3-fluoro-4-(2-hidroxietilamino)fenilo, 4-(difluorometoxi)fenilo, 4-carbamoil-2-clorofenilo, 4-clorofenilo, 2-clorofenilo, 3-cloro-4-fluorofenilo, 3-cloro-4-metilaminofenilo, 3-cloro-4-etilaminofenilo, 3-cloro-4-(2-fluoroetilamino)fenilo, 3-cloro-4-(2-hidroxietilamino)fenilo, 2-cloro-4-cianofenilo, 4-cianofenilo, 2,4-difluorofenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 3,4-difluorofenilo, 3,5-difluorofenilo, 2-metilfenilo, 4-metilfenilo, 1H-imidazol-2-ilo, 3,5-dimetilisoxazol-4-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, 1-(difluorometil)pirazol-4-ilo, 1,3-dimetilpirazol-4-ilo, piridin-4-ilo, piridin-2-ilo,

5-fluoropiridin-2-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo, 4,5-dimetiltiazol-2-ilo, 2,4-dimetiltiazol-5-ilo y 5-metil-1,3,4-tiadiazol-2-ilo.

En otro aspecto R^1 es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, fenilo, 4-fluorofenilo, 4-clorofenilo, 3,5-difluorofenilo, 1H-imidazol-2-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo y 5-metil-1,3,4-tiadiazol-2-ilo.

En otro aspecto R^1 es un grupo que se selecciona de metilo, etilo, ciclopropilo, $-CH_2CH_2CH_2OH$, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-clorofenilo, 2-metilfenilo, 5-fluoropiridin-2-ilo, piridin-2-ilo, tiazol-2-ilo y 4-metiltiazol-2-ilo. En otro aspecto R^1 es un grupo que se selecciona de $-CH_2CH_2CH_2OH$, fenilo, 4-fluorofenilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo y 4-metiltiazol-2-ilo.

En otro aspecto R^1 es metilo.

En otro aspecto R^1 es etilo.

En otro aspecto R^1 es ciclopropilo.

En otro aspecto R^1 es $-CH_2CH_2CH_2OH$.

En otro aspecto R^1 es fenilo.

En otro aspecto R^1 es 2-fluorofenilo.

En otro aspecto R^1 es 3-fluorofenilo.

En otro aspecto R^1 es 4-fluorofenilo.

En otro aspecto R^1 es 2-clorofenilo.

En otro aspecto R^1 es 2-metilfenilo.

En otro aspecto R^1 es 5-fluoropiridin-2-ilo.

En otro aspecto R^1 es piridin-2-ilo.

En otro aspecto R^1 es tiazol-2-ilo.

En otro aspecto R^1 es 4-metiltiazol-2-ilo.

X-R^1

En una realización X-R^1 es $-CR^6R^7OH$.

R^2

En un aspecto de la invención R^2 es un grupo que se selecciona de carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, -

SO_2R^{11}, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$.

En un aspecto de la invención R^2 se selecciona de carbociclilo o heterociclilo, sustituyéndose este grupo por $-NR^{17}CONR^{18}R^{19}$ o $-NR^{17}CSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 se selecciona de carbociclilo o heterociclilo, sustituyéndose este grupo por $-NHCONR^{18}R^{19}$ o $-NHCSNR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 se selecciona de carbociclilo o heterociclilo, sustituyéndose este grupo por $-NHCONHR^{19}$ o $-NHCSNHR^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 es un grupo que se selecciona de carbociclilo o heterociclilo de 5 o 6 miembros, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$.

En un aspecto de la invención R^2 se selecciona de carbociclilo o heterociclilo de 5 o 6 miembros, sustituyéndose este grupo por $-NR^{17}CONR^{18}R^{19}$ o $-NR^{17}CSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 se selecciona de carbociclilo o heterociclilo de 5 o 6 miembros, sustituyéndose este grupo por $-NHCONR^{18}R^{19}$ o $-NHCSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 se selecciona de carbociclilo o heterociclilo de 5 o 6 miembros, sustituyéndose este grupo por $-NHCONHR^{19}$ o $-NHCSNHR^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$.

En un aspecto de la invención R^2 se selecciona de un arilo de 6 miembros y un heteroarilo de 5 o 6 miembros, sustituyéndose este grupo opcionalmente por uno o más

grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, -$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ y -$NR^{17}CSNR^{18}R^{19}$.

En un aspecto de la invención R^2 se selecciona de un arilo de 6 miembros y un heteroarilo de 5 o 6 miembros, sustituyéndose este grupo por –$NR^{17}CONR^{18}R^{19}$ o -$NR^{17}CSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ y –$NR^{11}COR^{12}$.

En un aspecto de la invención R^2 se selecciona de un arilo de 6 miembros y un heteroarilo de 5 o 6 miembros, sustituyéndose este grupo por –$NHCONR^{18}R^{19}$ o -$NHCSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ y –$NR^{11}COR^{12}$.

En un aspecto de la invención R^2 se selecciona de un arilo de 6 miembros y un heteroarilo de 5 o 6 miembros, sustituyéndose este grupo por –$NHCONHR^{19}$ o -$NHCSNHR^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ y –$NR^{11}COR^{12}$.

En un aspecto de la invención R^2 se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, -$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ y -$NR^{17}CSNR^{18}R^{19}$.

En otro aspecto R^2 se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo por –$NR^{17}CONR^{18}R^{19}$ o -$NR^{17}CSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ y –$NR^{11}COR^{12}$.

En otro aspecto R^2 se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo por –$NHCONR^{18}R^{19}$ o -$NHCSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ y –$NR^{11}COR^{12}$.

En otro aspecto R^2 se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo por –$NHCONHR^{19}$ o -$NHCSNHR^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ y –$NR^{11}COR^{12}$.

En un aspecto de la invención R^2 se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, -$CONH_2$, –$CONHCH_3$ y -$CON(CH_3)_2$, -$NR^{11}COR^{12}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ y -$NR^{17}CSNR^{18}R^{19}$.

En otro aspecto R^2 se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo por –$NR^{17}CONR^{18}R^{19}$ o -$NR^{17}CSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, -$CONH_2$, –$CONHCH_3$ y -$CON(CH_3)_2$.

En otro aspecto R^2 se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo por –$NHCONR^{18}R^{19}$ o -$NHCSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, -$CONH_2$, –$CONHCH_3$ y -$CON(CH_3)_2$.

En otro aspecto R^2 se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo por –$NHCONHR^{19}$ o -$NHCSNHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, -$CONH_2$, –$CONHCH_3$ y -$CON(CH_3)_2$.

En un aspecto de la invención R^2 se selecciona de fenilo, piridinilo o pirimidinilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, -$CONH_2$, -$CONHCH_3$ y -$CON(CH_3)_2$, -$NR^{11}COR^{12}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ y -$NR^{17}CSNR^{18}R^{19}$.

En un aspecto de la invención R^2 se selecciona de fenilo o piridinilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan

independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$, $-NR^{11}COR^{12}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$.

En otro aspecto R^2 es fenilo, piridinilo o pirimidinilo sustituido por $-NR^{17}CONR^{18}R^{19}$ o $-NR^{17}CSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$.

En otro aspecto R^2 es fenilo o piridinilo sustituido por $-NR^{17}CONR^{18}R^{19}$ o $-NR^{17}CSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$.

En otro aspecto R^2 es fenilo o piridinilo sustituido por $-NHCONR^{18}R^{19}$ o $-NHCSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$.

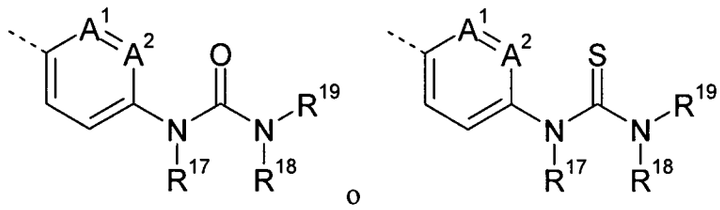
En otro aspecto R^2 es fenilo o piridinilo sustituido por $-NHCONHR^{19}$ o $-NHCSNHR^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$.

En otro aspecto R^2 es fenilo o piridinilo opcionalmente sustituido por $-NR^{17}CONR^{18}R^{19}$ o $-NR^{17}CSNR^{18}R^{19}$.

En otro aspecto R^2 es fenilo o piridinilo opcionalmente sustituido por $-NHCONR^{18}R^{19}$ o $-NHCSNR^{18}R^{19}$.

En otro aspecto R^2 es fenilo o piridinilo opcionalmente sustituido por $-NHCONHR^{19}$ o $-NHCSNHR^{19}$.

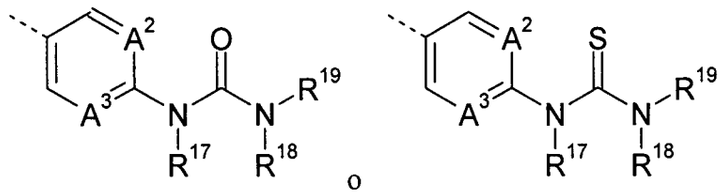
En otro aspecto R^2 es



o

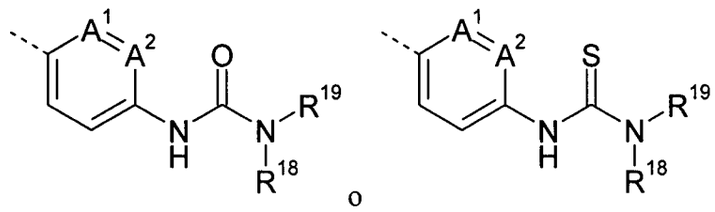
en donde A^1 y A^2 se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 sea CH.

En otro aspecto R^2 es



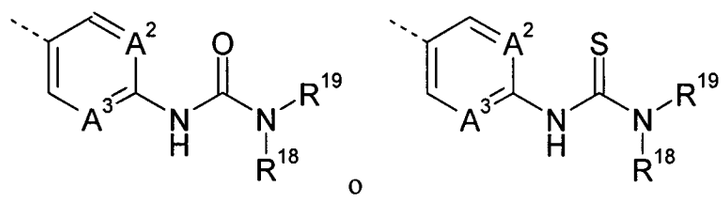
en donde A^2 y A^3 se seleccionan de CH o N.

En otro aspecto R^2 es



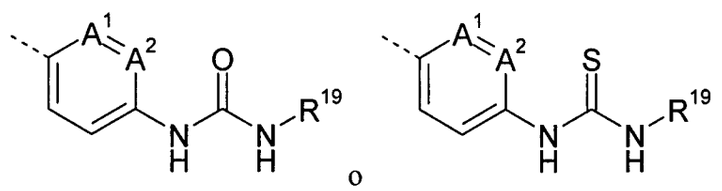
en donde A^1 y A^2 se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 sea CH.

En otro aspecto R^2 es



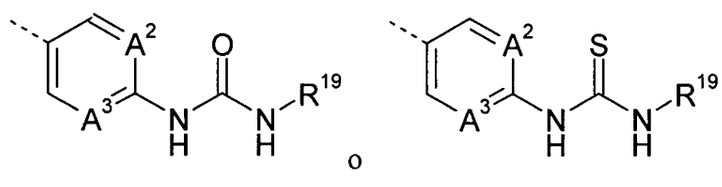
en donde A^2 y A^3 se seleccionan de CH o N.

En otro aspecto R^2 es



en donde A^1 y A^2 se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 sea CH.

En otro aspecto R^2 es



en donde A^2 y A^3 se seleccionan de CH o N.

En otro aspecto R^2 es 3-(hidroximetil)fenilo, 4-(hidroximetil)fenilo, 4-(cianometil)fenilo, 3,4-dimetoxifenilo, 3-fluoro-4-metoxifenilo, 4-fenoxifenilo, 3-pirrolidin-1ilfenilo, 3-(aminocarbonil)fenilo, 4-(dimetilaminocarbonil)fenilo, furan-3-ilo, tien-3-ilo, 5-

(hidroximetil)tien-2-ilo, piridin-2-ilo, piridin-4-ilo, 2-metoxipiridin-5-ilo, 2-metoxipirimidin-5-ilo, 2-metoxinaft-6-ilo, 5,7-diazabiciclo[4,3,0]nona-2,4,8,10-tetraenilo, azaindolilo, indol-5-ilo, 1-metilindol-5-ilo, quinolin-6-ilo, benzimidazolilo, benzofuran-2-ilo, dibenzofuran-1-ilo y benzotien-3-ilo.

En otro aspecto adicional R^2 es piridin-2-ilo, 3-hidroxifenilo, 4-hidroxifenilo, 3-hidroximetilfenilo, 4-hidroximetilfenilo o indol-5-ilo.

En otro aspecto adicional R^2 es azaindolilo, indol-5-ilo, benzimidazolilo, 3-hidroxifenilo, 4-hidroxifenilo, 3-hidroximetilfenilo o 4-hidroximetilfenilo.

En otro aspecto R^2 es piridin-2-ilo.

En un aspecto adicional R^2 es 3-hidroxifenilo o 4-hidroxifenilo.

En otro aspecto R^2 es 3-hidroximetilfenilo o 4-hidroximetilfenilo.

En otro aspecto adicional R^2 es indol-5-ilo.

En un aspecto R^2 es morfolinilo.

En otro aspecto R^2 es morfolino.

R^3

Cada R^3 se selecciona independientemente de ciano, R^{13} y $-CONR^{13}R^{14}$, en donde R^{13} y R^{14} son independientemente hidrógeno o un alquiloC_{1-3} que se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, hidroxi y alcoxiC_{1-3}.

Cada R^3 se selecciona independientemente de hidrógeno, alquiloC_{1-3}, hidroxialquiloC_{1-3} y $-CONR^{13}R^{14}$, en donde R^{13} y R^{14} son independientemente hidrógeno o un alquiloC_{1-3}.

Cada R^3 se selecciona independientemente de hidrógeno, metilo, etilo, hidroximetilo, carbamoilo y dimetilcarbamoilo.

R^4

En un aspecto de la invención R^4 es hidrógeno o metilo.

En otro aspecto R^4 es hidrógeno.

R^4 y R^1

En otro aspecto de la invención, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ o $-NR^4S(O)_2CR^6R^7-$, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6},

hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En otro aspecto de la invención, cuando **X** es -$NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$- o -$NR^4S(O)_2CR^6R^7$-, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5, 6 o 7 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En otro aspecto de la invención, cuando **X** es -$NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$- o -$NR^4S(O)_2CR^6R^7$-, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En otro aspecto de la invención, cuando **X** es -$NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$- o -$NR^4S(O)_2CR^6R^7$-, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo de morfolina o piperazina que se sustituye opcionalmente por uno o más grupos metilo.

En otro aspecto de la invención, cuando **X** es $-NR^4C(O)CR^6R^7-$, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los que están unidos forman un anillo de morfolina o piperazina que se sustituye opcionalmente por uno o más grupos metilo.

R^5

En un aspecto de la invención R^5 es hidrógeno o metilo.

En otro aspecto R^5 es hidrógeno.

En otro aspecto R^5 es metilo.

R^6 y R^7

En un aspecto de la invención $\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo.

En un aspecto de la invención $\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo.

En otro aspecto $\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico de 3 a 6 miembros.

En otro aspecto $\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico de 3 a 5 miembros.

En otro aspecto $\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico de 3 a 4 miembros.

En otro aspecto $\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico de 3 miembros.

En otro aspecto $\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo.

$\underline{\mathbf{R^8}}$

En un aspecto de la invención R^8 es hidrógeno o halo.

En otro aspecto R^8 es hidrógeno o fluoro.

En un aspecto adicional R^8 es hidrógeno.

$\underline{\mathbf{R^9}}$

En un aspecto de la invención R^9 es hidrógeno o alquiloC_{1-4} opcionalmente sustituido por 1, 2 o 3 grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alcoxiC_{1-4}, amino, alquilC_{1-4}amino y bis(alquilC_{1-4})amino.

En otro aspecto R^9 es hidrógeno o alquiloC_{1-4} opcionalmente sustituido por 1, 2 o 3 sustituyentes halo.

En un aspecto adicional R^9 es hidrógeno, metilo o trifluorometilo.

$\underline{\mathbf{R^{10}}}$

En un aspecto de la invención R^{10} es hidrógeno.

$\underline{\mathbf{R^{11}}}$

En un aspecto de la invención R^{11} es hidrógeno o un grupo que se selecciona de alquiloC_{1-4}, arilo y cicloheteroalquilo, sustituyéndose este grupo opcionalmente por 1, 2 o 3 grupos que se seleccionan de halo, hidroxi y ciano.

En otro aspecto R^{11} es hidrógeno, metilo opcionalmente sustituido por hidroxi o ciano, fenilo o pirrolidinilo.

En otro aspecto R^{11} es hidrógeno o metilo.

$\underline{\mathbf{R^{12}}}$

En un aspecto de la invención R^{12} es hidrógeno o metilo.

$\underline{\mathbf{R^{17}}}$

En un aspecto de la invención R^{17} es hidrógeno o un grupo que se selecciona de alquiloC_{1-4}, arilo y cicloheteroalquilo, sustituyéndose este grupo opcionalmente por 1, 2 o 3 grupos que se seleccionan de halo, hidroxi y ciano.

En otro aspecto R^{17} es hidrógeno, metilo opcionalmente sustituido por hidroxi o ciano, fenilo o pirrolidinilo.

En otro aspecto R^{17} es hidrógeno o metilo.

En otro aspecto R^{17} es hidrógeno.

R^{18}

En un aspecto de la invención R^{18} es hidrógeno o metilo.

En un aspecto de la invención R^{18} es hidrógeno

R^{19}

En un aspecto de la invención R^{19} es hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En un aspecto de la invención R^{19} es hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, fenilo, naftilo, pirrolilo, imidazolilo, isoxazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, azaindolilo, indolilo, quinolinilo, benzimidazolilo, benzofuranilo, dibenzofuranilo, benzotienilo, pirrolidinilo, pirazinilo, oxetanilo, dioxotiolanilo, tiazolilo, tiadiazolilo, fenilalquiloC_{1-6}, naftilalquiloC_{1-6}, pirrolilalquiloC_{1-6}, imidazolilalquiloC_{1-6}, isoxazolilalquiloC_{1-6}, pirazolilalquiloC_{1-6}, furanilalquiloC_{1-6}, tienilalquiloC_{1-6}, piridinilalquiloC_{1-6}, pirimidinilalquiloC_{1-6}, piridazinilalquiloC_{1-6}, azaindolilalquiloC_{1-6}, indolilalquiloC_{1-6}, quinolinilalquiloC_{1-6}, benzimidazolilalquiloC_{1-6}, benzofuranilalquiloC_{1-6}, dibenzofuranilalquiloC_{1-6}, benzotienilalquiloC_{1-6}, pirrolidinilalquiloC_{1-6}, pirazinilalquiloC_{1-6}, oxetanilalquiloC_{1-6}, dioxotiolanilalquiloC_{1-6}, tiazolilalquiloC_{1-6} y tiadiazolilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro,

hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo.

En un aspecto de la invención R^{19} es hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, cicloaquiloC$_{3-6}$, fenilo, naftilo, pirrolilo, imidazolilo, isoxazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, azaindolilo, indolilo, quinolinilo, benzimidazolilo, benzofuranilo, dibenzofuranilo, benzotienilo, fenilalquiloC$_{1-6}$, naftilalquiloC$_{1-6}$, pirrolilalquiloC$_{1-6}$, imidazolilalquiloC$_{1-6}$, isoxazolilalquiloC$_{1-6}$, pirazolilalquiloC$_{1-6}$, furanilalquiloC$_{1-6}$, tienilalquiloC$_{1-6}$, piridinilalquiloC$_{1-6}$, pirimidinilalquiloC$_{1-6}$, piridazinilalquiloC$_{1-6}$, azaindolilalquiloC$_{1-6}$, indolilalquiloC$_{1-6}$, quinolinilalquiloC$_{1-6}$, benzimidazolilalquiloC$_{1-6}$, benzofuranilalquiloC$_{1-6}$, dibenzofuranilalquiloC$_{1-6}$, benzotienilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo.

En un aspecto de la invención R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, tienilo, dioxotiolanilo, imidazoilmetilo, isoxazolilo, oxazolilo, oxetanilo, pirazinilo, pirazolilo, pirazolilmetilo, piridinilo, pirimidinilo, pirrolidinilo, tiadiazolilo, tiazolilo y triazolilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-}$

$_6$)amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En un aspecto de la invención R^{19} es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, tienilo, imidazoilmetilo, isoxazolilo, pirazolilo, pirazolilmetilo, piridinilo y pirimidinilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En un aspecto de la invención R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, -CH_2(ciclopropilo), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2C(CH_3)_2OH$, -$CH_2C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CH_2Cl, -$CH_2CH_2SO_2Me$, -$CH_2CH(OH)CF_3$, -CH_2CH_2CN, -CH_2CN, -CH_2CONMe_2, -CH_2CO_2H, 1-(metil)ciclopropilo, -CH_2(1-hidroxiciclopropilo), 1-(hidroximetil)ciclopropilo, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, tien-2-ilo, -CH_2CH_2(pirrolidin-1-ilo), -CH_2(imidazol-2-ilo), -CH_2(imidazol-3-ilo), 1-metilimidazol-4-ilo, oxazolil-2-ilo, isoxazolil-3-ilo, 6-oxo-1H-piridin-2-ilo, oxetan-3-ilo, 1,1-dioxotiolan-3-ilo, 5-metilisoxazol-3-ilo, -CH_2(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, -CH_2(1-metilpirazol-4-ilo), 5-metilpirazin-2-ilo, -CH_2(2H-1,2,4-triazol-3-ilo), 6-metoxipiridin-3-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, pirimidin-2-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo, 1-metilpirazol-3-ilo y 1H-pirazol-3-ilo.

En un aspecto de la invención R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, i-butilo, t-butilo, ciclopropilo, ciclobutilo, -CH_2(ciclopropilo), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2C(CH_3)_2OH$, -$CH_2C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CF_3, -CH_2CHF_2, -CH_2CH_2F, -CH_2CH_2Cl, -$CH_2CH_2SO_2Me$, -$CH_2CH(OH)CF_3$, -CH_2CH_2CN, -CH_2CN, -CH_2CONMe_2, -CH_2CO_2H, 1-(metil)ciclopropilo, -CH_2(1-hidroxiciclopropilo), 1-(hidroximetil)ciclopropilo,

(1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, $-CH_2CH_2$(pirrolidin-1-ilo), $-CH_2$(imidazol-2-ilo), 1-metilimidazol-4-ilo, oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 1,1-dioxotiolan-3-ilo, 5-metilisoxazol-3-ilo, $-CH_2$(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, $-CH_2$(1-metilpirazol-4-ilo), 5-metilpirazin-2-ilo, $-CH_2$(2H-1,2,4-triazol-3-ilo), 6-metoxipiridin-3-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo.

En un aspecto de la invención R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, 1-(metil)ciclopropilo, 1-(hidroximetil)ciclopropilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, tien-2-ilo, $-CH_2CH_2$(pirrolidin-1-ilo), $-CH_2$(imidazol-2-ilo), $-CH_2$(imidazol-3-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, 6-oxo-1H-piridin-2-ilo, oxetan-3-ilo, 1,1-dioxotiolan-3-ilo, 5-metilisoxazol-3-ilo, $-CH_2$(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, $-CH_2$(1-metilpirazol-4-ilo), 5-metilpirazin-2-ilo, $-CH_2$(2H-1,2,4-triazol-3-ilo), 6-metoxipiridin-3-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, pirimidin-2-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo, 1-metilpirazol-3-ilo y 1H-pirazol-3-ilo.

En un aspecto de la invención R^{19} es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, ciclopropilo, ciclobutilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CN$, $-CH_2$(1-hidroxiciclopropilo), 1-(hidroximetil)ciclopropilo, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, $-CH_2CH_2$(pirrolidin-1-il),-CH_2(imidazol-2-ilo), 1-metilimidazol-4-ilo, oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 5-metilisoxazol-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, 6-metoxipiridin-3-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo.

En un aspecto de la invención R^{19} es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, 4-metilfenilo, 4-clorofenilo, 4-

trifluorometilfenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, tien-2-ilo, -CH_2(imidazol-2-ilo), -CH_2(imidazol-3-ilo), isoxazolil-3-ilo, 6-oxo-1H-piridin-2-ilo, 5-metilisoxazol-3-ilo, -CH_2(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, -CH_2(1-metilpirazol-4-ilo), 6-metoxipiridin-3-ilo, 5-fluoropiridin-2-ilo, pirimidin-2-ilo y 1H-pirazol-3-ilo.

En un aspecto de la invención R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, i-butilo, t-butilo, ciclopropilo, ciclobutilo, -CH_2(ciclopropilo), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2C(CH_3)_2OH$, -$CH_2C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CHF_2, -$CH_2CH_2SO_2Me$, -$CH_2CH(OH)CF_3$, -CH_2CH_2CN, -CH_2CN, -CH_2CONMe_2, 1-(metil)ciclopropilo, 1-(hidroximetil)ciclopropilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, -CH_2CH_2(pirrolidin-1-il),-CH_2(imidazol-2-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 1,1-dioxotiolan-3-ilo, 5-metilisoxazol-3-ilo, -CH_2(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, -CH_2(2H-1,2,4-triazol-3-ilo), 6-metoxipiridin-3-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo.

En un aspecto de la invención R^{19} es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, ciclopropilo, ciclobutilo, -CH_2(ciclopropilo), -$CH_2CH_2NMe_2$, -$C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CH_2CN, 1-(hidroximetil)ciclopropilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, -CH_2CH_2(pirrolidin-1-ilo), -CH_2(imidazol-2-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 5-metilisoxazol-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, 6-metoxipiridin-3-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo.

En un aspecto de la invención R^{19} es un grupo que se selecciona de metilo, etilo, ciclopropilo, ciclobutilo, -$CH(CH_3)CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CHF_2, -CH_2CH_2F, -CH_2CH_2CN, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, -CH_2(imidazol-2-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, tiazol-2-ilo y 1,2,4-tiadiazol-5-ilo.

En un aspecto de la invención R^{19} es un grupo que se selecciona de metilo, etilo, ciclopropilo, ciclobutilo, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CH_2CN, -CH_2(imidazol-2-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, tiazol-2-ilo y 1,2,4-tiadiazol-5-ilo.

En un aspecto de la invención R^{19} es hidrógeno o un grupo que se selecciona de metilo, etilo, ciclopropilo, 1-metilpirazol-4-ilo y -CH_2(1-metilpirazol-4-ilo).

En un aspecto de la invención R^{19} es metilo.

En un aspecto de la invención R^{19} es etilo.

En un aspecto de la invención R^{19} es ciclopropilo.

En un aspecto de la invención R^{19} es ciclobutilo.

En un aspecto de la invención R^{19} es $-CH(CH_3)CH_2OH$.

En un aspecto de la invención R^{19} es $-CH_2CH_2OH$.

En un aspecto de la invención R^{19} es $-CH_2CH_2CH_2OH$.

En un aspecto de la invención R^{19} es $-CH_2CHF_2$.

En un aspecto de la invención R^{19} es $-CH_2CH_2F$.

En un aspecto de la invención R^{19} es $-CH_2CH_2CN$.

En un aspecto de la invención R^{19} es (1R)-2-hidroxi-1-metiletilo.

En un aspecto de la invención R^{19} es (1S)-2-hidroxi-1-metiletilo.

En un aspecto de la invención R^{19} es $-CH_2$(imidazol-2-ilo).

En un aspecto de la invención R^{19} es oxazolil-2-ilo.

En un aspecto de la invención R^{19} es isoxazolil-3-ilo.

En un aspecto de la invención R^{19} es 1-metilpirazol-4-ilo.

En un aspecto de la invención R^{19} es 5-metilpirazin-2-ilo.

En un aspecto de la invención R^{19} es tiazol-2-ilo.

En un aspecto de la invención R^{19} es 1,2,4-tiadiazol-5-ilo.

R^{18} y R^{19}

En un aspecto de la invención, R^{18} y R^{19} junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En un aspecto de la invención, R^{18} y R^{19} junto con el átomo de nitrógeno al que están unidos forman un anillo de morfolino.

En un aspecto de la invención, R^{18} y R^{19} junto con el átomo de nitrógeno al que están unidos forman un grupo 3-hidroxipirrolidin-1-ilo.

En un aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos;

m es 0, 1 o 2;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7$;

R^1 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X-R^1** es $-CR^6R^7OH$;

R^2 es un grupo que se selecciona de carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona de ciano, R^{13} y $-CONR^{13}R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ o $-NR^4C(O)NR^5CR^6R^7-$, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y R^7 junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

R^9 y R^{10} son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino;

R^{11}, R^{12}, R^{17} y R^{18} son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino;

R^{13} y R^{14} son independientemente hidrógeno o un alquiloC_{1-3} que se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, hidroxi y alcoxiC_{1-3}; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En otro aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos, en donde;

m es 0, 1 o 2;

$\mathbf{^1Y}$ e $\mathbf{Y^2}$ son independientemente N o CR^8 siempre que uno de ^1Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7$;

$\mathbf{R^1}$ es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o $\mathbf{X\text{-}R^1}$ es $-CR^6R^7OH$;

$\mathbf{R^2}$ es un grupo que se selecciona de carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada $\mathbf{R^3}$, cuando está presente, se selecciona de alquiloC_{1-3}, hidroxialquiloC_{1-3} y $-CONR^{13}R^{14}$;

$\mathbf{R^4}$ y $\mathbf{R^5}$ son independientemente hidrógeno o alquiloC_{1-6};

o, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ o $-NR^4C(O)NR^5CR^6R^7-$, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano,

nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino;

R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino;

R^{13} y **R^{14}** son independientemente hidrógeno o un alquiloC$_{1-3}$; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de alquiloC$_{1-6}$, cicloaquiloC$_{3-6}$, arilo, heteroarilo, arilalquiloC$_{1-6}$ y heteroarilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$,

alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo. En otro aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos, en donde;

m es 0, 1 o 2;

^1Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^1Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7$;

R^1 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X-R^1** es $-CR^6R^7OH$;

R^2 es un grupo que se selecciona de carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, es metilo o etilo;

$\mathbf{R^4}$ y $\mathbf{R^5}$ son independientemente hidrógeno o alquiloC$_{1-6}$;

o, cuando **X** es -NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7- o -NR^{4}C(O)NR^{5}CR^{6}R^7-, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

$\mathbf{R^8}$ se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino; y

$\mathbf{R^{19}}$ es hidrógeno, ciano o un grupo que se selecciona de alquiloC$_{1-6}$, cicloaquiloC$_{3-6}$, arilo, heteroarilo, arilalquiloC$_{1-6}$ y heteroarilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo.

En otro aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos, en donde;

m es 0, 1 o 2;

$\mathbf{^1Y}$ e $\mathbf{Y^2}$ son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7-, -S(O)$_2$CR^{6}R^7-, -C(O)NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7-, -NR^{4}C(O)NR^{5}CR^{6}R^7- y -S(O)$_2$NR^{4}CR^{6}R^7;

$\mathbf{R^1}$ es un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, -OR^9, -COR^9, -CONR^{9}R^{10}, -NR^{9}R^{10} y -NR^{9}COR^{10};

o **X-R^1** es –CR^{6}R^{7}OH;

$\mathbf{R^2}$ es un grupo que se selecciona de carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de

halo, ciano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, -$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ y -$NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, es metilo;

R^4 y **R^5** son independientemente hidrógeno o alquiloC$_{1-6}$;

o, cuando **X** es -$NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$- o -$NR^4C(O)NR^5CR^6R^7$-, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino;

R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En un aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos, en donde;

m es 0, 1 o 2;

^1Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^1Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7$;

R^1 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más

grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X-R^1** es $-CR^6R^7OH$;

R^2 es un grupo que se selecciona de carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, es metilo;

R^4 y **R^5** son independientemente hidrógeno o alquiloC$_{1-6}$;

o, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ o $-NR^4C(O)NR^5CR^6R^7-$, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

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R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino;

R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

R^{19} es hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En un aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos, en donde;

m es 0, 1 o 2;

^1Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^1Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7$;

R^1 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X-R^1** es $-CR^6R^7OH$;

R^2 es un grupo que se selecciona de arilo y heteroarilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, es metilo;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ o $-NR^4C(O)NR^5CR^6R^7-$, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-

$_{6}$sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

$\mathbf{R^8}$ se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

$\mathbf{R^{19}}$ es hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En un aspecto de la invención se proporciona subconjunto de compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos;

m es 0, 1 o 2;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7$;

R^1 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X-R^1** es $-CR^6R^7OH$;

R^2 se selecciona de arilo y heteroarilo, sustituyéndose este grupo por $-NR^{17}CONR^{18}R^{19}$ o $-NR^{17}CSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

cada R^3, cuando está presente, es metilo;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ o $-NR^4C(O)NR^5CR^6R^7-$, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6},

haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino;

R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino; y

R^{19} es hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, cicloaquiloC$_{3-6}$, arilo, heteroarilo, arilalquiloC$_{1-6}$ y heteroarilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo; o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo,

alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En otro aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos, en donde;

m es 0, 1 o 2;

^{1}Y e Y^2 son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$ y $-S(O)_2CR^6R^7-$;

R^1 es un grupo que se selecciona de adamantilo, metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopentilo, ciclohexilo, fenilo, bencilo, fenetilo, pirrolidinilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tiadiazolilo, tiazolilo, tienilo, piridinilo, pirimidinilo, pirazinilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolilmetilo, pirroliletilo, imidazolilmetilo, imidazoliletilo, pirazolilmetilo, pirazoliletilo, furanilmetilo, furaniletilo, tiadiazolilmetilo, tiadiazoliletilo, tiazolilmetilo, tiazoliletilo, tienilmetilo, tieniletilo, piridinilmetilo, piridiniletilo, pirimidinilmetilo, pirimidiniletilo, pirazinilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1, 2 o 3 grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X-R^1** es $-C(CH_3)_2OH$ o $-CH_2OH$;

R^2 se selecciona de arilo y heteroarilo de 5 o 6 miembros, sustituyéndose este grupo por $-NHCONR^{18}R^{19}$ o $-NHCSNR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

cada R^3, cuando está presente, es metilo;

R^4 es hidrógeno o alquiloC_{1-6};

o, cuando **X** es $-NR^4CR^6R^7-$, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}-

$_{6}$sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino;

R^{11}, **R^{12}** y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo.

En otro aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (I), o una sal farmacéuticamente aceptable de los mismos, en donde;

m es 0, 1 o 2;

$\mathbf{^1Y}$ e $\mathbf{Y^2}$ son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7- y -S(O)$_2$CR^{6}R^7-;

$\mathbf{R^1}$ es un grupo que se selecciona de adamantilo, metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopentilo, ciclohexilo, fenilo, bencilo, fenetilo, pirrolidinilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, pirazinilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolilmetilo, pirroliletilo, imidazolilmetilo, imidazoliletilo, pirazolilmetilo, pirazoliletilo, furanilmetilo, furaniletilo, tienilmetilo, tieniletilo, piridinilmetilo, piridiniletilo, pirimidinilmetilo, pirimidiniletilo, pirazinilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1, 2 o 3 grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, -OR^9, -COR^9, -CONR^{9}R^{10}, -NR^{9}R^{10} y –NR^{9}COR^{10};

o $\mathbf{X\text{-}R^1}$ es –C(CH$_3$)$_2$OH o –CH$_2$OH;

$\mathbf{R^2}$ se selecciona de arilo y heteroarilo de 5 o 6 miembros, sustituyéndose este grupo por -NHCONR^{18}R^{19} o –NHCSNR^{18}R^{19} y opcionalmente sustituido por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12} y –NR^{11}COR^{12};

cada $\mathbf{R^3}$, cuando está presente, es metilo;

$\mathbf{R^4}$ es hidrógeno o alquiloC$_{1-6}$;

o, cuando **X** es -NR^{4}CR^{6}R^7-, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se

reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino;

R^{11}, **R^{12}** y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino; y

R^{19} es hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, cicloaquiloC$_{3-6}$, arilo, heteroarilo, arilalquiloC$_{1-6}$ y heteroarilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$,

alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En otra clase particular de compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

m es 0 o 1;

$^{1}\mathbf{Y}$ es CH e $\mathbf{Y^{2}}$ es N;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

$\mathbf{R^1}$ es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, imidazolilo, pirrolidinilo, tiadiazolilo, tiazolilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, hidroxi, metilo, metoxi, trifluorometilo, trifluorometoxi, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

o $-\mathbf{XR^1}$ es $-C(CH_3)_2OH$ o $-CH_2OH$;

$\mathbf{R^2}$ se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo por $-NHCONHR^{19}$ o $-NHCSNHR^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

$\mathbf{R^3}$, cuando está presente, es metilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{11}, **R^{12}** y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En otra clase particular de compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

m es 0 o 1;

^1Y es CH e **Y^2** es N;

X es grupo enlazante -$S(O)_2CR^6R^7$-;

R^1 es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este

grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, metilo, metoxi, trifluorometilo, trifluorometoxi, -$NHCOCH_3$, -$CONH_2$ y –$CONHCH_3$;

o **–XR^1** es –$C(CH_3)_2OH$ o –CH_2OH;

R^2 se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo por –$NHCONHR^{19}$ o -$NHCSNHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$ y -$NR^{11}COR^{12}$;

R^3, cuando está presente, es metilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{11}, R^{12} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

R^{19} es hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

m es 0, 1 o 2;

X es un grupo enlazante $-S(O)_2CR^6R^7-$ seleccionado;

^{1}**Y** es CH e **Y**^{2} es N;

R^1 es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, imidazolilo, pirrolidinilo, tiadiazolilo, tiazolilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, hidroxi, metilo, metoxi, trifluorometilo, trifluorometoxi, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

R^2 es fenilo o piridinilo sustituido por $-NHCONHR^{19}$ o $-NHCSNHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$;

R^3, cuando está presente, es metilo o etilo;

R^6 y **R**^{7} junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, tienilo, dioxotiolanilo, imidazoilmetilo, isoxazolilo, oxazolilo, oxetanilo, pirazinilo, pirazolilo, pirazolilmetilo, piridinilo, pirimidinilo, pirrolidinilo, tiadiazolilo, tiazolilo y triazolilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})

$_6$)aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

m es 1;

X es un grupo enlazante -$S(O)_2CR^6R^7$- seleccionado;

^{1}**Y** es CH e **Y**^{2} es N.

R^1 es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, imidazolilo, pirrolidinilo, tiadiazolilo, tiazolilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, hidroxi, metilo, metoxi, trifluorometilo, trifluorometoxi, -$NHCOCH_3$, -$CONH_2$ y -$CONHCH_3$;

R^2 es fenilo o piridinilo sustituido por –NHCONHR^{19} o –NHCSNHR^{19} y opcionalmente sustituido por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, -$CONH_2$, –$CONHCH_3$ y -$CON(CH_3)_2$;

R^3 es metilo;

R^6 y **R**^{7} junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, tienilo, dioxotiolanilo, imidazoilmetilo, isoxazolilo, oxazolilo, oxetanilo, pirazinilo, pirazolilo, pirazolilmetilo, piridinilo, pirimidinilo, pirrolidinilo, tiadiazolilo, tiazolilo y triazolilo,

sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

m es 1;

X es grupo enlazante -$S(O)_2CR^6R^7$- seleccionado;

^{1}**Y** es CH e **Y**^{2} es N.

R^1 es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, metilo, metoxi, trifluorometilo, trifluorometoxi, -$NHCOCH_3$, -$CONH_2$ y –$CONHCH_3$;

R^2 es fenilo o piridinilo sustituido por –$NHCONHR^{19}$ o –$NHCSNHR^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, -$CONH_2$, –$CONHCH_3$ y -$CON(CH_3)_2$;

R^3 es metilo;

R^6 y **R**^{7} junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; y

R^{19} es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, tienilo, imidazoilmetilo, isoxazolilo, pirazolilo, pirazolilmetilo, piridinilo y pirimidinilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

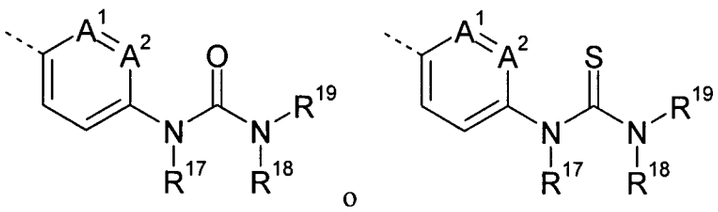
m es 1;

X es un grupo enlazante -$S(O)_2CR^6R^7$-;

^1Y es CH e **Y^2** es N.

R^1 es un grupo que se selecciona de metilo, isopropilo, ciclopropilo, ciclohexilo, -CH_2CH_2OH, -$CH_2CH_2NHC(O)CH_3$, fenilo, 4-fluorofenilo, 2-clorofenilo, 2-trifluorometilfenilo, 2-metoxifenilo, 2-metilfenilo, 4-acetamidofenilo, 4-aminofenilo, piridin-4-ilo, piridin-2-ilo, 2-oxopirolidin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo y 3-metil-1,3,4-tiadiazol-2-ilo;

R^2 es



o

en donde **A^1** y **A^2** se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 sea CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno;

R^{19} es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, -CH_2(ciclopropilo), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$,

-CH_2CH_2OH, -$CH_2CH_2CH_2OH$, 4-metilfenilo, 4-clorofenilo, 4-trifluorometilfenilo, 4-flurofenilo, 4-metoxifenilo, 3,4-difluorofenilo, tien-2-ilo, -CH_2(imidazol-2-ilo), -CH_2(imidazol-3-ilo), isoxazolil-3-ilo, 6-oxo-1H-piridin-2-ilo, 5-metilisoxazol-3-ilo, 1-metilpirazol-4-ilo, -CH_2(1-metilpirazol-4-ilo), -CH_2(1-metilpirazol-4-ilo), 6-metoxipiridin-3-ilo, 5-fluoropiridin-2-ilo, pirimidin-2-ilo y 1H-pirazol-3-ilo;

$\mathbf{R^3}$ es metilo; y

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

m es 0, 1 o 2;

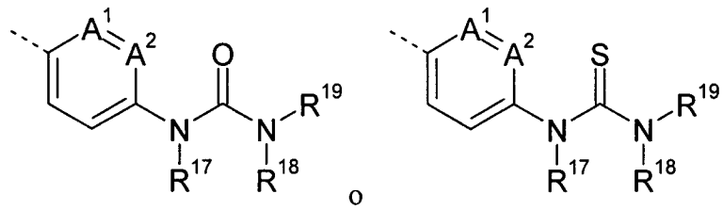
X es un grupo enlazante -$S(O)_2CR^6R^7$-;

$\mathbf{^1Y}$ es CH e $\mathbf{Y^2}$ es N.

$\mathbf{R^1}$ es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, ciclopentilo, ciclohexilo, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2C(OH)(CH_3)_2$, -$CH_2CH_2CH_2OCHF_2$, -$CH_2CH_2OCH_3$, -$CH_2CH_2NHC(O)CH_3$, -$CH_2C(O)NH_2$, -$CH_2C(O)NHMe$, -CH_2CH_2NHMe, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-fluoro-4-metilaminofenilo, 4-fluoro-2-metilfenilo, 5-fluoro-2-metilfenilo, 3-fluoro-4-(2-hidroxietilamino)fenilo, 4-(difluorometoxi)fenilo, 4-carbamoil-2-clorofenilo, 4-clorofenilo, 2-clorofenilo, 3-cloro-4-fluorofenilo, 3-cloro-4-metilaminofenilo, 3-cloro-4-etilaminofenilo, 3-cloro-4-(2-fluoroetilamino)fenilo, 3-cloro-4-(2-hidroxietilamino)fenilo, 2-cloro-4-cianofenilo, 4-cianofenilo, 2,4-difluorofenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 3,4-difluorofenilo, 3,5-difluorofenilo, 2-(trifluorometil)fenilo, 2-metilfenilo, 4-metilfenilo, 4-(2-hidroxietilamino)fenilo, 1H-imidazol-2-ilo, 3,5-dimetilisoxazol-4-ilo, 2-(dimetilcarbamoil)piridin-3-ilo,

5-(dimetilcarbamoil)piridin-2-ilo, 1-(difluorometil)pirazol-4-ilo, 1-(difluorometil)-3,5-dimetilpirazol-4-ilo, 1,3-dimetilpirazol-4-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, 5-fluoropiridin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo, 4,5-dimetiltiazol-2-ilo, 2,4-dimetiltiazol-5-ilo, 5-metil-1,3,4-tiadiazol-2-ilo, tetrahidrofuran-3-ilo y tetrahidropiran-4-ilo;

R^2 es



o

en donde **A^1** y **A^2** se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 es CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno;

R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, i-butilo, t-butilo, ciclopropilo, ciclobutilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, $-CH_2CO_2H$, 1-(metil)ciclopropilo, $-CH_2$(1-hidroxiciclopropilo), 1-(hidroximetil)ciclopropilo, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, $-CH_2CH_2$(pirrolidin-1-ilo), $-CH_2$(imidazol-2-ilo), 1-metilimidazol-4-ilo, oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 1,1-dioxotiolan-3-ilo, 5-metilisoxazol-3-ilo, $-CH_2$(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, $-CH_2$(1-metilpirazol-4-ilo), 5-metilpirazin-2-ilo, $-CH_2$(2H-1,2,4-triazol-3-ilo), 6-metoxipiridin-3-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo;

R^3, cuando está presente, es metilo o etilo; y

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6},

alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo;

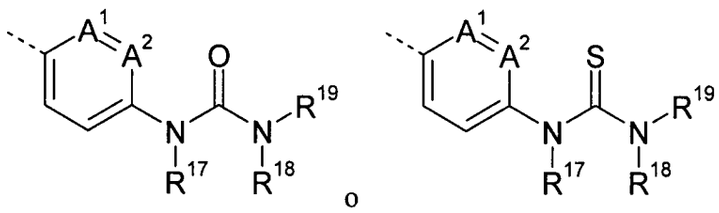
m es 1;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

^{1}**Y** es CH e **Y**^{2} es N.

R^1 es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, ciclopentilo, ciclohexilo, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, fenilo, 4-fluorofenilo, 4-clorofenilo, 3,5-difluorofenilo, 2-(trifluorometil)fenilo, 4-(2-hidroxietilamino)fenilo, 1H-imidazol-2-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, 5-fluoropiridin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo y 5-metil-1,3,4-tiadiazol-2-ilo;

R^2 es



o

en donde **A**^{1} y **A**^{2} se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 sea CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno;

R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, i-butilo, t-butilo, ciclopropilo, ciclobutilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, 1-(metil)ciclopropilo, 1-(hidroximetil)ciclopropilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, $-CH_2CH_2$(pirrolidin-1-ilo),

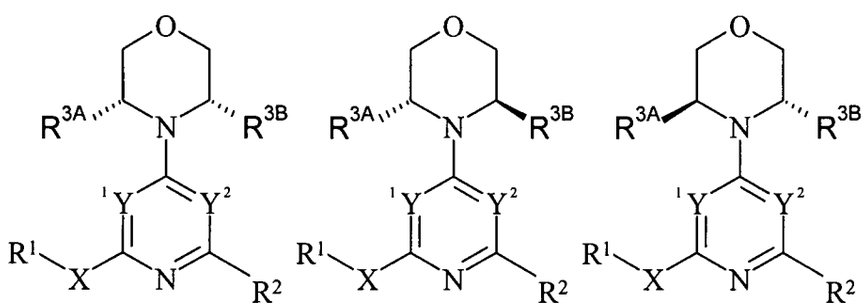
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-CH_2(imidazol-2-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 1,1-dioxotiolan-3-ilo, 5-metilisoxazol-3-ilo, -CH_2(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, -CH_2(2H-1,2,4-triazol-3-ilo), 6-metoxipiridin-3-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo;

R^3 es metilo; y

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En un aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (IA), (IB) o (IC)



(IA) (IB) (IC)

o una sal farmacéuticamente aceptable del mismo;

^1Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^1Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de -$NR^4CR^6R^7$-, -OCR^6R^7-, -SCR^6R^7-, -$S(O)CR^6R^7$-, -$S(O)_2CR^6R^7$-, -$C(O)NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$- y -$S(O)_2NR^4CR^6R^7$;

R^1 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} y -NR^9COR^{10};

o **X-R^1** es $-C(CH_3)_2OH$ o $-CH_2OH$;

R^2 se selecciona de arilo y heteroarilo, sustituyéndose este grupo por $-NR^{17}CONR^{18}R^{19}$ o $-NR^{17}CSNR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC$_{1-6}$

o, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ o $-NR^4C(O)NR^5CR^6R^7-$, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino;

R^{11}, R^{12}, R^{17} y R^{18} son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino;

R^{19} es hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, cicloaquiloC$_{3-6}$, arilo, heteroarilo, arilalquiloC$_{1-6}$ y heteroarilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

o R^{18} y R^{19} junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo; y

cuando R^{3A} es hidrógeno, R^{3B} es hidrógeno, metilo, etilo, hidroximetilo, dimetilcarbamoilo o carbamoilo; o

cuando R^{3A} es metilo, R^{3B} es metilo.

En un aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (IA), (IB) o (IC)

alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y R^7 junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

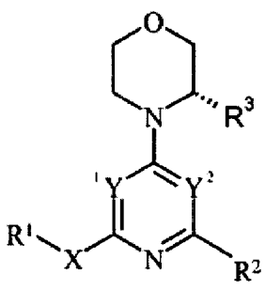
R^9 y R^{10} son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino;

R^{11}, R^{12}, R^{17} y R^{18} son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

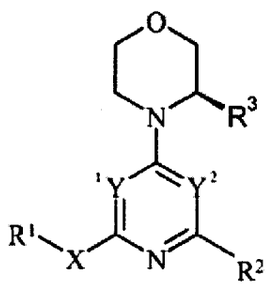
R^{19} es hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En un aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable de los mismos, en donde;

$\mathbf{^1Y}$ e $\mathbf{Y^2}$ son independientemente N o CR^8 siempre que uno de ^1Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7$;

$\mathbf{R^1}$ es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X-$\mathbf{R^1}$** es $-C(CH_3)_2OH$ o $-CH_2OH$;

$\mathbf{R^2}$ se selecciona de arilo y heteroarilo, sustituyéndose este grupo por $-NR^{17}CONR^{18}R^{19}$ o $-NR^{17}CSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

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$\mathbf{R^3}$ es hidrógeno, metilo o etilo;

$\mathbf{R^4}$ y $\mathbf{R^5}$ son independientemente hidrógeno o alquiloC$_{1-6}$

o, cuando **X** es -NR^{4}CR^{6}R^7-, -NR^{4}C(O)CR^{6}R^7- o -NR^{4}C(O)NR^{5}CR^{6}R^7-, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

$\mathbf{R^8}$ se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

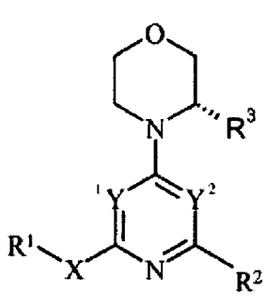
$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$,

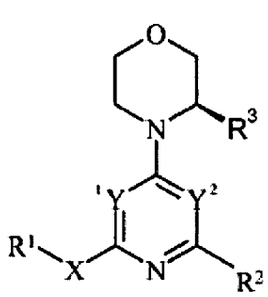
alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

$\mathbf{R^{19}}$ es hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En un aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable de los mismos;

$\mathbf{^1Y}$ e $\mathbf{Y^2}$ son independientemente N o CR^8 siempre que uno de ^1Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7$;

$\mathbf{R^1}$ es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X-R¹** es $-C(CH_3)_2OH$ o $-CH_2OH$;

$\mathbf{R^2}$ se selecciona de arilo y heteroarilo, sustituyéndose este grupo por $-NR^{17}CONR^{18}R^{19}$ o $-NR^{17}CSNR^{18}R^{19}$ y opcionalmente sustituido por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

$\mathbf{R^3}$ es metilo;

$\mathbf{R^4}$ y $\mathbf{R^5}$ son independientemente hidrógeno o alquiloC_{1-6}

o, cuando **X** es $-NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$ o $-NR^4C(O)NR^5CR^6R^7-$, $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}

$_{6}$sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

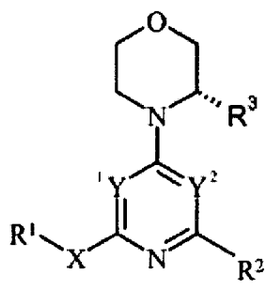
$\mathbf{R^8}$ se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino;

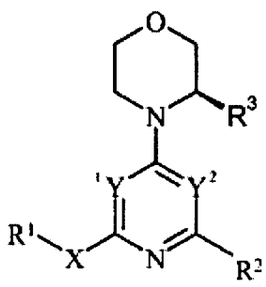
$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

$\mathbf{R^{19}}$ es hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; o $\mathbf{R^{18}}$ y $\mathbf{R^{19}}$ junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En otro aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

^{1}**Y** e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7- y -S(O)$_2$CR^{6}R^7-;

R^1 es un grupo que se selecciona de adamantilo, metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopentilo, ciclohexilo, fenilo, bencilo, fenetilo, pirrolidinilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tiadiazolilo, tiazolilo, tienilo, piridinilo, pirimidinilo, pirazinilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolilmetilo, pirroliletilo, imidazolilmetilo, imidazoliletilo, pirazolilmetilo, pirazoliletilo, furanilmetilo, furaniletilo, tiadiazolilmetilo, tiadiazoliletilo, tiazolilmetilo, tiazoliletilo, tienilmetilo, tieniletilo, piridinilmetilo, piridiniletilo, pirimidinilmetilo, pirimidiniletilo, pirazinilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1, 2 o 3 grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, -OR^9, -COR^9, -CONR^{9}R^{10}, -NR^{9}R^{10} y –NR^{9}COR^{10};

o **X-R^1** es –C(CH$_3$)$_2$OH o –CH$_2$OH;

R^2 se selecciona de arilo y heteroarilo de 5 o 6 miembros, sustituyéndose este grupo por -NHCONR^{18}R^{19} o -NHCSNR^{18}R^{19} y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -COR^{11}, -CONR^{11}R^{12}, -NR^{11}R^{12} y –NR^{11}COR^{12};

R^3 es metilo;

R^4 es hidrógeno o alquiloC$_{1-6}$;

o, cuando **X** es -NR^{4}CR^{6}R^7-, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$,

alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

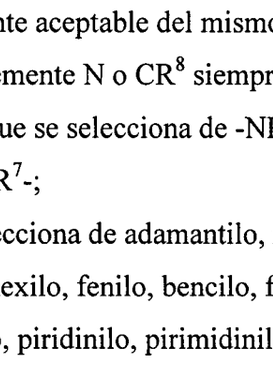
R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino;

R^{11}, R^{12} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

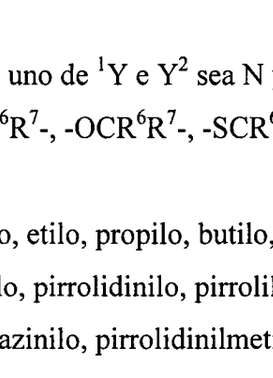
R^{19} es hidrógeno, ciano o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6},

cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo; o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo.

En otro aspecto de la invención se proporciona un subconjunto de compuestos de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de -NR^{4}CR^{6}R^7-, -OCR^{6}R^7-, -SCR^{6}R^7-, -S(O)CR^{6}R^7- y -S(O)$_2$CR^{6}R^7-;

R^1 es un grupo que se selecciona de adamantilo, metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopentilo, ciclohexilo, fenilo, bencilo, fenetilo, pirrolidinilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, pirazinilo, pirrolidinilmetilo, pirrolidiniletilo, pirrolilmetilo, pirroliletilo, imidazolilmetilo, imidazoliletilo, pirazolilmetilo, pirazoliletilo, furanilmetilo, furaniletilo, tienilmetilo, tieniletilo, piridinilmetilo, piridiniletilo, pirimidinilmetilo, pirimidiniletilo, pirazinilmetilo y piraziniletilo, sustituyéndose este grupo

opcionalmente por 1, 2 o 3 grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, OR^9, $-COR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$ y $-NR^9COR^{10}$;

o **X-R^1** es $-C(CH_3)_2OH$ o $-CH_2OH$;

R^2 se selecciona de arilo y heteroarilo de 5 o 6 miembros, sustituyéndose este grupo por $-NHCONR^{18}R^{19}$ o $-NHCSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

R^3 es metilo;

R^4 es hidrógeno o alquiloC_{1-6};

o, cuando **X** es $-NR^4CR^6R^7-$, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6},

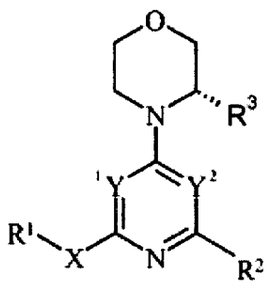
haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino;

R^{11}, R^{12} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino y bis(alquilC$_{1-6}$)amino; y

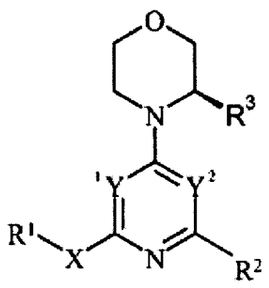
R^{19} es hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, cicloaquiloC$_{3-6}$, arilo, heteroarilo, arilalquiloC$_{1-6}$ y heteroarilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo.

En otra clase particular de compuesto de fórmula (Ia) o (Ib),



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

^{1}Y es CH e **Y^2** es N;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

R^1 es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, imidazolilo, pirrolidinilo, tiadiazolilo, tiazolilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, hidroxi, metilo, metoxi, trifluorometilo, trifluorometoxi, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

o $-XR^1$ es $-C(CH_3)_2OH$ o $-CH_2OH$;

R^2 se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo por $-NHCONHR^{19}$ o $-NR^{17}CSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

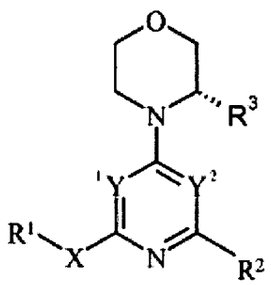
R^3 es metilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

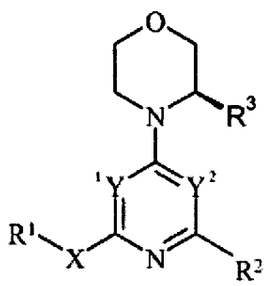
R^{11}, R^{12} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En otra clase particular de compuesto de fórmula (Ia) o (Ib),



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

^1Y es CH e **Y^2** es N;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

R^1 es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, metilo, metoxi, trifluorometilo, trifluorometoxi, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

o $-XR^1$ es $-C(CH_3)_2OH$ o $-CH_2OH$;

R^2 se selecciona de fenilo, pirrolilo, imidazolilo, pirazolilo, furanilo, tienilo, piridinilo, pirimidinilo, piridazinilo, tiazolilo, sustituyéndose este grupo por $-NHCONHR^{19}$ o

$-NR^{17}CSNR^{18}R^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-COR^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$ y $-NR^{11}COR^{12}$;

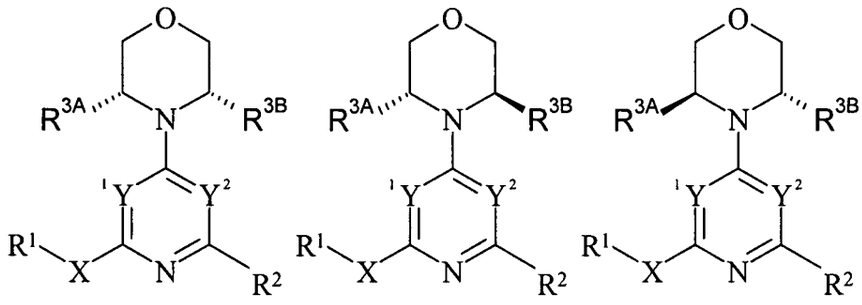
R^3 es metilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^{11}, R^{12} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino; y

R^{19} es hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (IA), (IB) o (IC)



(IA) (IB) (IC)

o una sal farmacéuticamente aceptable del mismo;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

^{1}**Y** es CH e **Y**^{2} es N.

R^1 es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, imidazolilo, pirrolidinilo, tiadiazolilo, tiazolilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, hidroxi, metilo, metoxi, trifluorometilo, trifluorometoxi, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

R^2 es fenilo o piridinilo sustituido por $-NHCONHR^{19}$ o $-NHCSNHR^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$;

R^{3A} y **R**^{3B} cada uno independientemente es hidrógeno, metilo o etilo;

R^6 y **R**^{7} junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

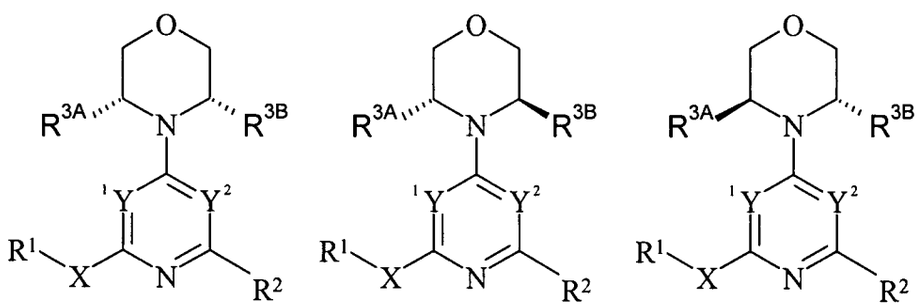
R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, tienilo, dioxotiolanilo, imidazoilmetilo, isoxazolilo, oxazolilo, oxetanilo, pirazinilo, pirazolilo,

pirazolilmetilo, piridinilo, pirimidinilo, pirrolidinilo, tiadiazolilo, tiazolilo y triazolilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; y

cuando $\mathbf{R^{3A}}$ es hidrógeno, $\mathbf{R^{3B}}$ es hidrógeno, metilo, etilo, hidroximetilo, dimetilcarbamoilo o carbamoilo; o

cuando $\mathbf{R^{3A}}$ es metilo, $\mathbf{R^{3B}}$ es metilo.

En una clase particular adicional de compuesto de fórmula (Ia) o (Ib)



(IA) (IB) (IC)

o una sal farmacéuticamente aceptable del mismo;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

^{1}**Y** es CH e **Y^2** es N.

R^1 es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, imidazolilo, pirrolidinilo, tiadiazolilo, tiazolilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, hidroxi, metilo, metoxi, trifluorometilo, trifluorometoxi, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

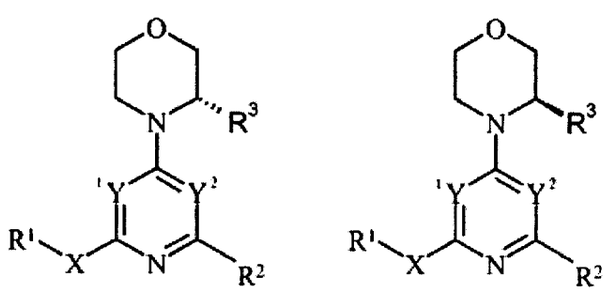
R^2 es fenilo o piridinilo sustituido por $-NHCONHR^{19}$ o $-NHCSNHR^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$;

R^{3A} y **R^{3B}** cada uno independientemente es hidrógeno, metilo o etilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; y

$\mathbf{R^{19}}$ es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, tienilo, dioxotiolanilo, imidazoilmetilo, isoxazolilo, oxazolilo, oxetanilo, pirazinilo, pirazolilo, pirazolilmetilo, piridinilo, pirimidinilo, pirrolidinilo, tiadiazolilo, tiazolilo y triazolilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (Ia) o (Ib)



(Ia) (Ib)

o una sal farmacéuticamente aceptable del mismo;

X es un grupo enlazante -$S(O)_2CR^6R^7$-;

^{1}**Y** es CH e $\mathbf{Y^2}$ es N.

R[1] es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, imidazolilo, pirrolidinilo, tiadiazolilo, tiazolilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, hidroxi, metilo, metoxi, trifluorometilo, trifluorometoxi, -$NHCOCH_3$, -$CONH_2$ y -$CONHCH_3$;

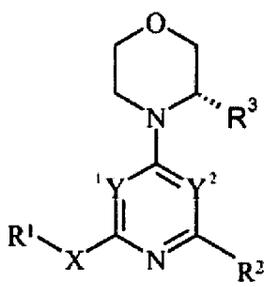
R[2] es fenilo o piridinilo sustituido por –$NHCONHR^{19}$ o -$NHCSNHR^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, -$CONH_2$, –$CONHCH_3$ y -$CON(CH_3)_2$;

R[3] es metilo;

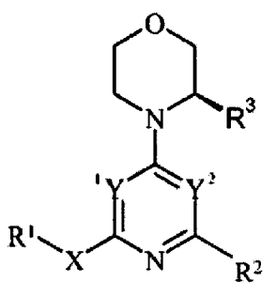
R[6] y **R[7]** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; y

R[19] es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, tienilo, dioxotiolanilo, imidazoilmetilo, isoxazolilo, oxazolilo, oxetanilo, pirazinilo, pirazolilo, pirazolilmetilo, piridinilo, pirimidinilo, pirrolidinilo, tiadiazolilo, tiazolilo y triazolilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

^{1}**Y** es CH e Y^2 es N.

$\mathbf{R^1}$ es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, metilo, metoxi, trifluorometilo, trifluorometoxi, $-NHCOCH_3$, $-CONH_2$ y $-CONHCH_3$;

$\mathbf{R^2}$ es fenilo o piridinilo sustituido por $-NHCONHR^{19}$ o $-NHCSNHR^{19}$ y opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de fluoro, metilo, metoxi, hidroximetilo, cianometilo, $-CONH_2$, $-CONHCH_3$ y $-CON(CH_3)_2$;

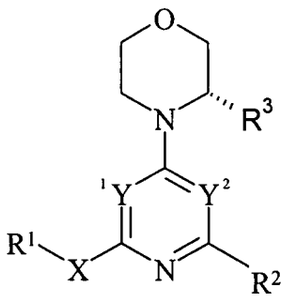
$\mathbf{R^3}$ es metilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; y

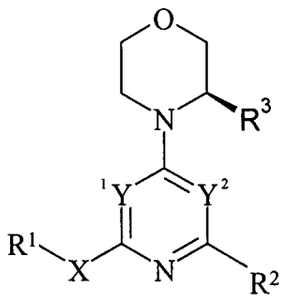
$\mathbf{R^{19}}$ es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, tienilo, imidazoilmetilo, isoxazolilo, pirazolilo, pirazolilmetilo, piridinilo y pirimidinilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se

seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

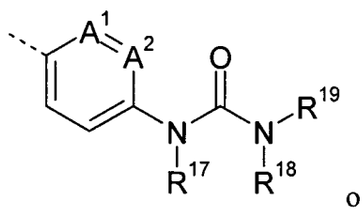
m es 1;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

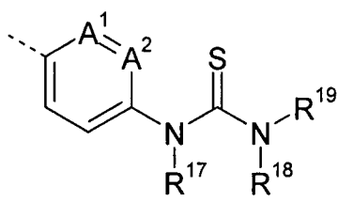
^{1}Y es CH e **Y^2** es N.

R^1 es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, ciclopentilo, ciclohexilo, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, fenilo, 4-fluorofenilo, 4-clorofenilo, 2-clorofenilo, 3,5-difluorofenilo, 2-(trifluorometil)fenilo, 4-(2-hidroxietilamino)fenilo, 2-metoxifenilo, 2-metilfenilo, 1H-imidazol-2-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, 4-acetamidofenilo, 4-aminofenilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, 5-fluoropiridin-3-ilo, 2-oxopirolidin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo, 5-metil-1,3,4-tiadiazol-2-ilo y 3-metil-1,3,4-tiadiazol-2-ilo;

R^2 es



o



en donde $\mathbf{A^1}$ y $\mathbf{A^2}$ se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 sea CH;

$\mathbf{R^{17}}$ es hidrógeno;

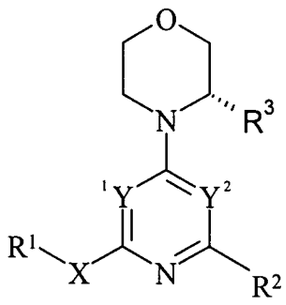
$\mathbf{R^{18}}$ es hidrógeno; y

$\mathbf{R^{19}}$ es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, 1-(metil)ciclopropilo, 1-(hidroximetil)ciclopropilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, tien-2-ilo, $-CH_2CH_2$(pirrolidin-1-ilo), $-CH_2$(imidazol-2-ilo), $-CH_2$(imidazol-3-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, 6-oxo-1H-piridin-2-ilo, oxetan-3-ilo, 1,1-dioxotiolan-3-ilo, 5-metilisoxazol-3-ilo, $-CH_2$(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, $-CH_2$(1-metilpirazol-4-ilo), 5-metilpirazin-2-ilo, $-CH_2$(2H-1,2,4-triazol-3-ilo), 6-metoxipiridin-3-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, pirimidin-2-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo, 1-metilpirazol-3-ilo y 1H-pirazol-3-ilo;

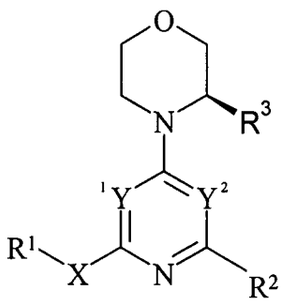
$\mathbf{R^3}$ es metilo; y

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

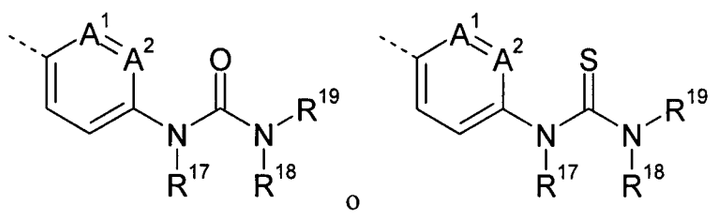
m es 1;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

^{1}Y es CH e Y^2 es N;

R^1 es un grupo que se selecciona de metilo, isopropilo, ciclopropilo, ciclohexilo, $-CH_2CH_2OH$, $-CH_2CH_2NHC(O)CH_3$, fenilo, 4-fluorofenilo, 2-clorofenilo, 2-trifluorometilfenilo, 2-metoxifenilo, 2-metilfenilo, 4-acetamidofenilo, 4-aminofenilo, piridin-4-ilo, piridin-2-ilo, 2-oxopirolidin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo y 3-metil-1,3,4-tiadiazol-2-ilo;

R^2 es



en donde **A^1** y **A^2** se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 sea CH;

R^{17} es hidrógeno;

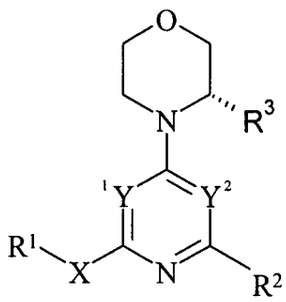
R^{18} es hidrógeno; y

R^{19} es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, 4-metilfenilo, 4-clorofenilo, 4-trifluorometilfenilo, 4-flurofenilo, 4-metoxifenilo, 3,4-difluorofenilo, tien-2-ilo, $-CH_2$(imidazol-2-ilo), $-CH_2$(imidazol-3-ilo), isoxazolil-3-ilo, 6-oxo-1H-piridin-2-ilo, 5-metilisoxazol-3-ilo, 1-metilpirazol-4-ilo, $-CH_2$(1-metilpirazol-4-ilo), $-CH_2$(1-metilpirazol-4-ilo), 6-metoxipiridin-3-ilo, 5-fluoropiridin-2-ilo, pirimidin-2-ilo y 1H-pirazol-3-ilo;

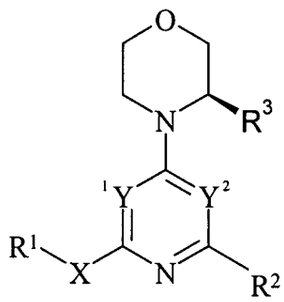
$\mathbf{R^3}$ es metilo; y

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}C$_{-6}$alcoxi, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

En una clase particular adicional de compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

o una sal farmacéuticamente aceptable del mismo;

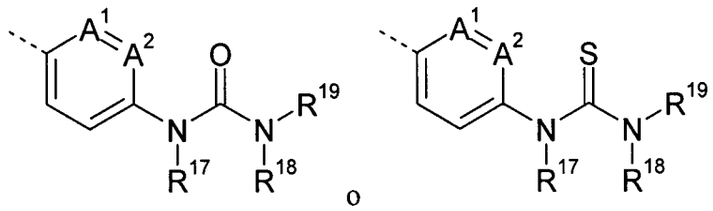
m es 1;

X es un grupo enlazante -$S(O)_2CR^6R^7$-;

^{1}**Y** es CH e Y^2 es N.

$\mathbf{R^1}$ es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, ciclopentilo, ciclohexilo, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2OCH_3$, -$CH_2CH_2NHC(O)CH_3$, -$CH_2C(O)NH_2$, -$CH_2C(O)NHMe$, fenilo, 4-fluorofenilo, 4-clorofenilo, 3,5-difluorofenilo, 2-(trifluorometil)fenilo, 4-(2-hidroxietilamino)fenilo, 1H-imidazol-2-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, 5-fluoropiridin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo y 5-metil-1,3,4-tiadiazol-2-ilo;

$\mathbf{R^2}$ es



en donde **A**^{1} y **A**^{2} se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 sea CH;

R^{17} es hidrógeno;

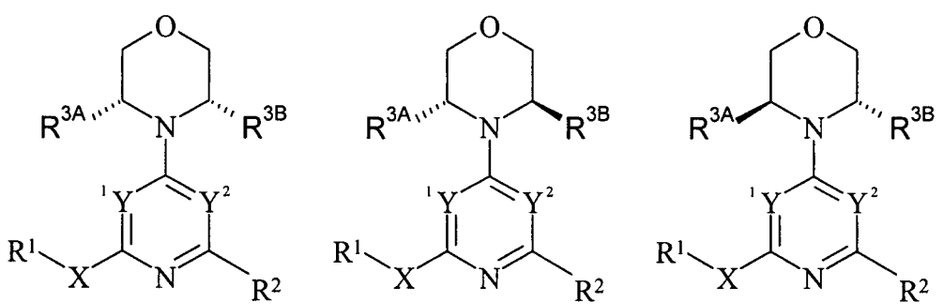
R^{18} es hidrógeno; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, i-butilo, t-butilo, ciclopropilo, ciclobutilo, -CH_2(ciclopropilo), -$CH_2CH_2NMe_2$, -$CH(CH_3)CH_2OH$, -$C(CH_3)_2CH_2OH$, -$CH_2C(CH_3)_2OH$, -$CH_2C(CH_3)_2CH_2OH$, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -CH_2CHF_2, -$CH_2CH_2SO_2Me$, -$CH_2CH(OH)CF_3$, -CH_2CH_2CN, -CH_2CN, -CH_2CONMe_2, 1-(metil)ciclopropilo, 1-(hidroximetil)ciclopropilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, -CH_2CH_2(pirrolidin-1-il),-CH_2(imidazol-2-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 1,1-dioxotiolan-3-ilo, 5-metilisoxazol-3-ilo, -CH_2(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, -CH_2(2H-1,2,4-triazol-3-ilo), 6-metoxipiridin-3-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo;

R^3 es metilo; y

R^6 y **R**^{7} junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo.

En una clase particular adicional de compuesto de fórmula (IA), (IB) o (IC)



(IA) (IB) (IC)

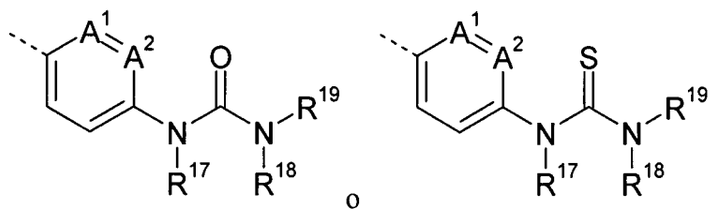
o una sal farmacéuticamente aceptable del mismo;

X es un grupo enlazante -$S(O)_2CR^6R^7$-;

^{1}**Y** es CH e Y^2 es N;

R^1 es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, ciclopentilo, ciclohexilo, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2CH_2NHMe$, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-fluoro-4-metilaminofenilo, 4-fluoro-2-metilfenilo, 5-fluoro-2-metilfenilo, 3-fluoro-4-(2-hidroxietilamino)fenilo, 4-(difluorometoxi)fenilo, 4-carbamoil-2-clorofenilo, 4-clorofenilo, 2-clorofenilo, 3-cloro-4-fluorofenilo, 3-cloro-4-metilaminofenilo, 3-cloro-4-etilaminofenilo, 3-cloro-4-(2-fluoroetilamino)fenilo, 3-cloro-4-(2-hidroxietilamino)fenilo, 2-cloro-4-cianofenilo, 4-cianofenilo, 2,4-difluorofenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 3,4-difluorofenilo, 3,5-difluorofenilo, 2-(trifluorometil)fenilo, 2-metilfenilo, 4-metilfenilo, 4-(2-hidroxietilamino)fenilo, 1H-imidazol-2-ilo, 3,5-dimetilisoxazol-4-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, 1-(difluorometil)pirazol-4-ilo, 1-(difluorometil)-3,5-dimetilpirazol-4-ilo, 1,3-dimetilpirazol-4-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, 5-fluoropiridin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo, 4,5-dimetiltiazol-2-ilo, 2,4-dimetiltiazol-5-ilo, 5-metil-1,3,4-tiadiazol-2-ilo, tetrahidrofuran-3-ilo y tetrahidropiran-4-ilo;

R^2 es



o

en donde **A^1** y **A^2** se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 sea CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, i-butilo, t-butilo, ciclopropilo, ciclobutilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, $-CH_2CO_2H$, 1-(metil)ciclopropilo, $-CH_2$(1-hidroxiciclopropilo), 1-(hidroximetil)ciclopropilo, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo,

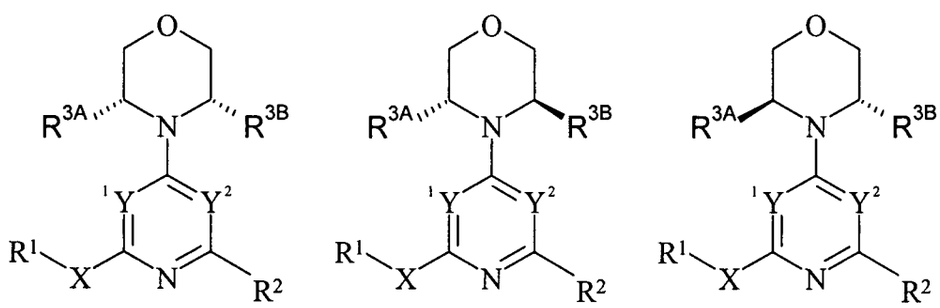
fenilo, 4-metilfenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, $-CH_2CH_2$(pirrolidin-1-il),$-CH_2$(imidazol-2-ilo), 1-metilimidazol-4-ilo, oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 1,1-dioxotiolan-3-ilo, 5-metilisoxazol-3-ilo, $-CH_2$(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, $-CH_2$(1-metilpirazol-4-ilo), 5-metilpirazin-2-ilo, $-CH_2$(2H-1,2,4-triazol-3-ilo), 6-metoxipiridin-3-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo; y

cuando $\mathbf{R^{3A}}$ es hidrógeno, $\mathbf{R^{3B}}$ es hidrógeno, metilo, etilo, hidroximetilo, dimetilcarbamoilo o carbamoilo; o

cuando $\mathbf{R^{3A}}$ es metilo, $\mathbf{R^{3B}}$ es metilo.

En una clase particular adicional de compuesto de fórmula (IA), (IB) o (IC)



(IA) (IB) (IC)

o una sal farmacéuticamente aceptable del mismo;

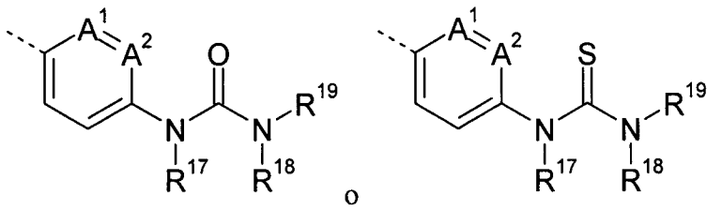
X es un grupo enlazante $-S(O)_2CR^6R^7-$;

^{1}**Y** es CH e Y^2 es N;

$\mathbf{R^1}$ es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2CH_2NHMe$, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-fluoro-4-metilaminofenilo, 4-fluoro-2-metilfenilo, 5-fluoro-2-metilfenilo, 3-fluoro-4-(2-hidroxietilamino)fenilo, 4-(difluorometoxi)fenilo, 4-carbamoil-2-clorofenilo, 4-clorofenilo, 2-clorofenilo, 3-cloro-4-fluorofenilo, 3-cloro-4-metilaminofenilo, 3-cloro-4-etilaminofenilo, 3-cloro-4-(2-fluoroetilamino)fenilo, 3-cloro-4-(2-hidroxietilamino)fenilo, 2-cloro-4-cianofenilo, 4-cianofenilo, 2,4-difluorofenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 3,4-difluorofenilo, 3,5-difluorofenilo, 2-metilfenilo, 4-metilfenilo, 1H-imidazol-2-ilo, 3,5-dimetilisoxazol-4-ilo, 2-(dimetilcarbamoil)piridin-3-ilo,

5-(dimetilcarbamoil)piridin-2-ilo, 1-(difluorometil)pirazol-4-ilo, 1,3-dimetilpirazol-4-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo, 4,5-dimetiltiazol-2-ilo, 2,4-dimetiltiazol-5-ilo y 5-metil-1,3,4-tiadiazol-2-ilo;

R^2 es



o

en donde **A^1** y **A^2** se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 sea CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno; y

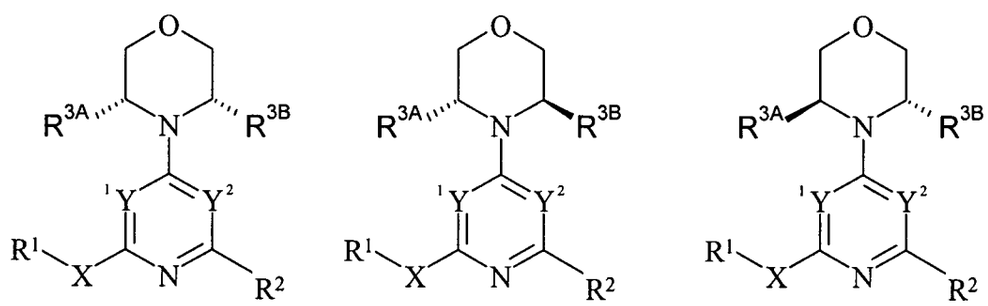
R^{19} es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, ciclopropilo, ciclobutilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CN$, $-CH_2$(1-hidroxiciclopropilo), 1-(hidroximetil)ciclopropilo, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, $-CH_2CH_2$(pirrolidin-1-ilo), $-CH_2$(imidazol-2-ilo), 1-metilimidazol-4-ilo, oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 5-metilisoxazol-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, 6-metoxipiridin-3-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo; y

cuando **R^{3A}** es hidrógeno, **R^{3B}** es hidrógeno, metilo o etilo; o

cuando **R^{3A}** es metilo, **R^{3B}** es metilo.

En una clase particular adicional de compuesto de fórmula (IA), (IB) o (IC)



(IA) (IB) (IC)

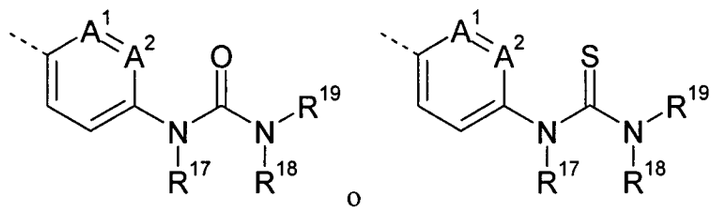
o una sal farmacéuticamente aceptable del mismo;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

^{1}**Y** es CH e **Y**^{2} es N;

R^1 es un grupo que se selecciona de metilo, etilo, ciclopropilo, $-CH_2CH_2CH_2OH$, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-clorofenilo, 2-metilfenilo, 5-fluoropiridin-2-ilo, piridin-2-ilo, tiazol-2-ilo y 4-metiltiazol-2-ilo;

R^2 es



o

en donde **A**^{1} y **A**^{2} se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 es CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno; y

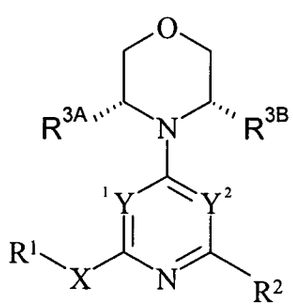
R^{19} es un grupo que se selecciona de metilo, etilo, ciclopropilo, ciclobutilo, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, $-CH_2$(imidazol-2-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, tiazol-2-ilo y 1,2,4-tiadiazol-5-ilo;

R^6 y **R**^{7} junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo; y

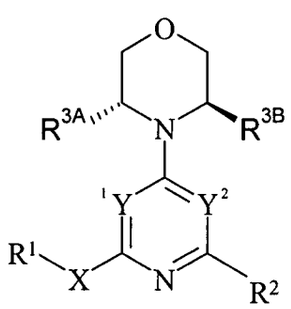
cuando **R**^{3A} es hidrógeno, **R**^{3B} es hidrógeno, metilo o etilo; o

cuando **R**^{3A} es metilo, **R**^{3B} es metilo.

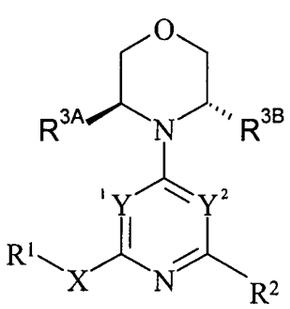
En una clase particular adicional de compuesto de fórmula (IA), (IB) o (IC)



(IA)



(IB)



(IC)

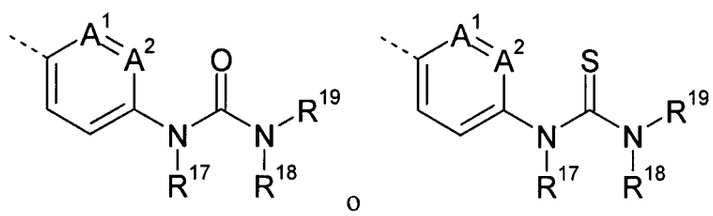
o una sal farmacéuticamente aceptable del mismo;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

^{1}Y es CH e **Y^2** es N;

R^1 es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, ciclopentilo, ciclohexilo, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2CH_2NHMe$, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-fluoro-4-metilaminofenilo, 4-fluoro-2-metilfenilo, 5-fluoro-2-metilfenilo, 3-fluoro-4-(2-hidroxietilamino)fenilo, 4-(difluorometoxi)fenilo, 4-carbamoil-2-clorofenilo, 4-clorofenilo, 2-clorofenilo, 3-cloro-4-fluorofenilo, 3-cloro-4-metilaminofenilo, 3-cloro-4-etilaminofenilo, 3-cloro-4-(2-fluoroetilamino)fenilo, 3-cloro-4-(2-hidroxietilamino)fenilo, 2-cloro-4-cianofenilo, 4-cianofenilo, 2,4-difluorofenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 3,4-difluorofenilo, 3,5-difluorofenilo, 2-(trifluorometil)fenilo, 2-metilfenilo, 4-metilfenilo, 4-(2-hidroxietilamino)fenilo, 1H-imidazol-2-ilo, 3,5-dimetilisoxazol-4-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, 1-(difluorometil)pirazol-4-ilo, 1-(difluorometil)-3,5-dimetilpirazol-4-ilo, 1,3-dimetilpirazol-4-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, 5-fluoropiridin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo, 4,5-dimetiltiazol-2-ilo, 2,4-dimetiltiazol-5-ilo, 5-metil-1,3,4-tiadiazol-2-ilo, tetrahidrofuran-3-ilo y tetrahidropiran-4-ilo;

R^2 es



o

en donde **A^1** y **A^2** son CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, i-butilo, t-butilo, ciclopropilo, ciclobutilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, $-CH_2CO_2H$, 1-(metil)ciclopropilo, $-CH_2$(1-hidroxiciclopropilo), 1-(hidroximetil)ciclopropilo, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo,

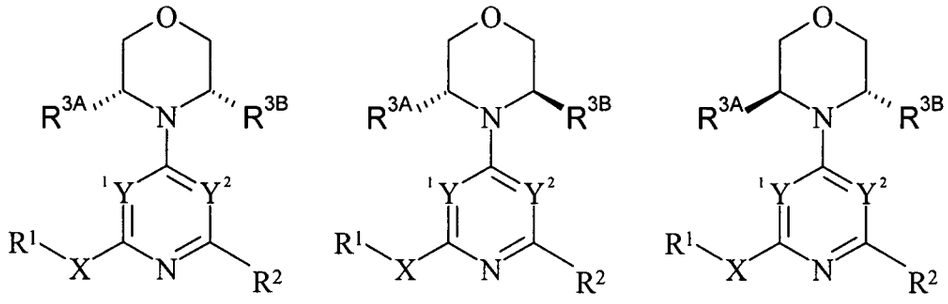
fenilo, 4-metilfenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, -CH_2CH_2(pirrolidin-1-ilo), -CH_2(imidazol-2-ilo), 1-metilimidazol-4-ilo, oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 1,1-dioxotiolan-3-ilo, 5-metilisoxazol-3-ilo, -CH_2(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, -CH_2(1-metilpirazol-4-ilo), 5-metilpirazin-2-ilo, -CH_2(2H-1,2,4-triazol-3-ilo), 6-metoxipiridin-3-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo; y

cuando $\mathbf{R^{3A}}$ es hidrógeno, $\mathbf{R^{3B}}$ es hidrógeno, metilo, etilo, hidroximetilo, dimetilcarbamoilo o carbamoilo; o

cuando $\mathbf{R^{3'}}$ es metilo, $\mathbf{R^3}$ es metilo.

En una clase particular adicional de compuesto de fórmula (IA), (IB) o (IC)



(IA) (IB) (IC)

o una sal farmacéuticamente aceptable del mismo;

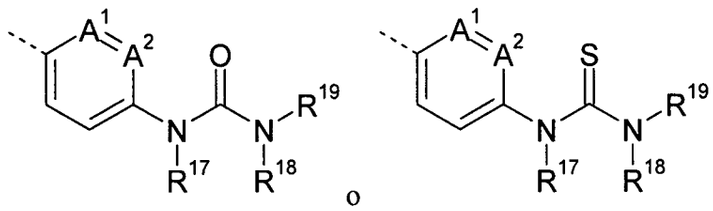
X es un grupo enlazante -$S(O)_2CR^6R^7$-;

^{1}**Y** es CH e Y^2 es N;

$\mathbf{R^1}$ es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2C(OH)(CH_3)_2$, -$CH_2CH_2CH_2OCHF_2$, -$CH_2CH_2OCH_3$, -$CH_2CH_2NHC(O)CH_3$, -CH_2CH_2NHMe, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-fluoro-4-metilaminofenilo, 4-fluoro-2-metilfenilo, 5-fluoro-2-metilfenilo, 3-fluoro-4-(2-hidroxietilamino)fenilo, 4-(difluorometoxi)fenilo, 4-carbamoil-2-clorofenilo, 4-clorofenilo, 2-clorofenilo, 3-cloro-4-fluorofenilo, 3-cloro-4-metilaminofenilo, 3-cloro-4-etilaminofenilo, 3-cloro-4-(2-fluoroetilamino)fenilo, 3-cloro-4-(2-hidroxietilamino)fenilo, 2-cloro-4-cianofenilo, 4-cianofenilo, 2,4-difluorofenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 3,4-difluorofenilo, 3,5-difluorofenilo, 2-metilfenilo, 4-metilfenilo, 1H-imidazol-2-ilo, 3,5-dimetilisoxazol-4-ilo, 2-(dimetilcarbamoil)piridin-3-ilo,

5-(dimetilcarbamoil)piridin-2-ilo, 1-(difluorometil)pirazol-4-ilo, 1,3-dimetilpirazol-4-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo, 4,5-dimetiltiazol-2-ilo, 2,4-dimetiltiazol-5-ilo y 5-metil-1,3,4-tiadiazol-2-ilo;

$\mathbf{R^2}$ es



o

en donde $\mathbf{A^1}$ y $\mathbf{A^2}$ son CH;

$\mathbf{R^{17}}$ es hidrógeno;

$\mathbf{R^{18}}$ es hidrógeno; y

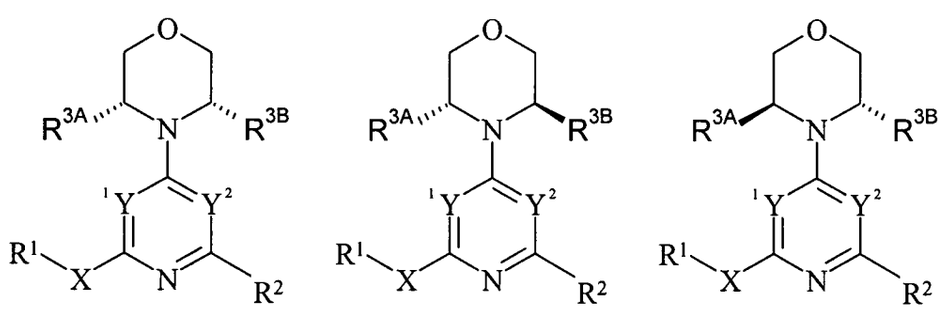
$\mathbf{R^{19}}$ es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, ciclopropilo, ciclobutilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CN$, $-CH_2$(1-hidroxiciclopropilo), 1-(hidroximetil)ciclopropilo, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, $-CH_2CH_2$(pirrolidin-1-il), $-CH_2$(imidazol-2-ilo), 1-metilimidazol-4-ilo, oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 5-metilisoxazol-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, 6-metoxipiridin-3-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo; y

cuando $\mathbf{R^{3A}}$ es hidrógeno, $\mathbf{R^{3B}}$ es hidrógeno, metilo o etilo; o

cuando $\mathbf{R^{3A}}$ es metilo, $\mathbf{R^{3B}}$ es metilo.

En una clase particular adicional de compuesto de fórmula (IA), (IB) o (IC)



(IA) (IB) (IC)

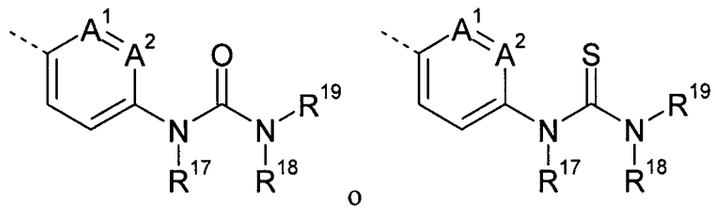
o una sal farmacéuticamente aceptable del mismo;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

^{1}**Y** es CH e Y^2 es N;

$\mathbf{R^1}$ es un grupo que se selecciona de metilo, etilo, ciclopropilo, $-CH_2CH_2CH_2OH$, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-clorofenilo, 2-metilfenilo, 5-fluoropiridin-2-ilo, piridin-2-ilo, tiazol-2-ilo y 4-metiltiazol-2-ilo;

$\mathbf{R^2}$ es



o

en donde $\mathbf{A^1}$ y $\mathbf{A^2}$ son CH;

$\mathbf{R^{17}}$ es hidrógeno;

$\mathbf{R^{18}}$ es hidrógeno; y

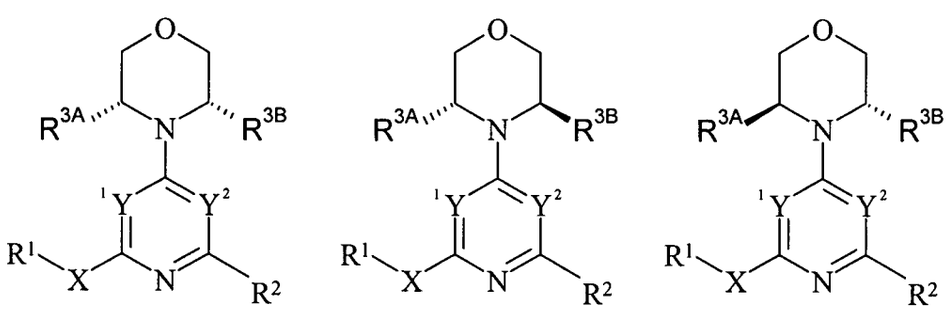
$\mathbf{R^{19}}$ es un grupo que se selecciona de metilo, etilo, ciclopropilo, ciclobutilo, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, $-CH_2$(imidazol-2-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, tiazol-2-ilo y 1,2,4-tiadiazol-5-ilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo; y

cuando $\mathbf{R^{3A}}$ es hidrógeno, $\mathbf{R^{3B}}$ es hidrógeno, metilo o etilo; o

cuando $\mathbf{R^{3A}}$ es metilo, $\mathbf{R^{3B}}$ es metilo.

En una clase particular adicional de compuesto de fórmula (IA), (IB) o (IC)



(IA) (IB) (IC)

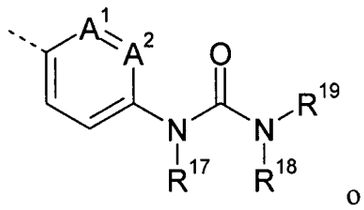
o una sal farmacéuticamente aceptable del mismo;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

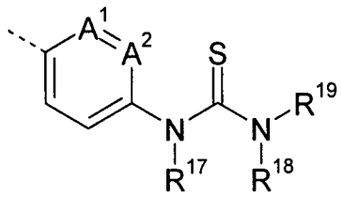
^{1}**Y** es CH e Y^2 es N;

$\mathbf{R^1}$ es un grupo que se selecciona de metilo, etilo, ciclopropilo, $-CH_2CH_2CH_2OH$, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-clorofenilo, 2-metilfenilo, 5-fluoropiridin-2-ilo, piridin-2-ilo, tiazol-2-ilo y 4-metiltiazol-2-ilo;

$\mathbf{R^2}$ es



o



en donde $\mathbf{A^1}$ y $\mathbf{A^2}$ son CH;

$\mathbf{R^{17}}$ es hidrógeno;

$\mathbf{R^{18}}$ es hidrógeno; y

$\mathbf{R^{19}}$ es un grupo que se selecciona de metilo, etilo, ciclopropilo, ciclobutilo, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, $-CH_2$(imidazol-2-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, tiazol-2-ilo y 1,2,4-tiadiazol-5-ilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo; y

cuando $\mathbf{R^{3A}}$ es hidrógeno, $\mathbf{R^{3B}}$ es metilo o etilo; o

cuando $\mathbf{R^{3A}}$ es metilo, $\mathbf{R^{3B}}$ es metilo.

Otro aspecto de la invención proporciona un compuesto, o una combinación de compuestos, que se selecciona de cualquiera de the Ejemplos o una sal farmacéuticamente aceptable del mismo.

En otro aspecto de la invención se proporciona un compuesto, o una combinación de compuestos, que se selecciona de cualquiera de

3-Etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-Ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-fenil-urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propan-2-il-urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propil-urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

3-(ciclopropilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(1-hidroxipropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(6-metoxipiridin-3-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(4-fluorofenil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(3,4-difluorofenil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(4-metilfenil)urea,

3-(4-clorofenil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(4-metoxifenil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(5-metil-1,2-oxazol-3-il)urea,

3-(5-fluoropiridin-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(3-hidroxi-2,2-dimetilpropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-pirrolidin-1-iletil)urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(3,3,3-trifluoro-2-hidroxipropil)urea,

3-(2-hidroxi-2-metilpropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-[1-(hidroximetil)ciclopropil]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(oxetan-3-il)urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-3-il)urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

3-(cianometil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2H-1,2,4-triazol-3-ilmetil)urea,

3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-ciclobutil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-il-urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-il-urea,

3-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etil-urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propil-urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metil-propan-2-il)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxi-2,2-dimetilpropil)urea,

3-(2-cianoetil)-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-pirrolidin-1-iletil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3,3,3-trifluoro-2-hidroxipropil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxi-2-metilpropil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[1-(hidroximetil)ciclopropil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(oxetan-3-il)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-3-il)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

3-etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-propan-2-il-urea,

3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-propil-urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-piridin-2-il-urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-propan-2-il-urea,

3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-propil-urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-piridin-2-il-urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-piridin-2-il-urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propan-2-il-urea,

3-etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propil-urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propan-2-il-urea,

3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-1-propil-urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-piridin-2-il-urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea,

1-etil-3-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-il-urea,

3-ciclobutil-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metil-propan-2-il)urea,

3-(2-dimetilaminoetil)-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propil-urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-il-urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropil-urea,

3-ciclobutil-1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-il-urea,

1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-il-urea,

3-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etil-urea,

1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea,

1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propil-urea,

1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea,

1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metil-propan-2-il)urea,

1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-3-piridin-2-il-urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-3-propan-2-il-urea,

1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-1-propil-urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea,

1-etil-3-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-il-urea,

3-ciclobutil-1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metil-propan-2-il)urea,

3-(2-dimetilaminoetil)-1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propil-urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-il-urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-etil-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-ciclobutil-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-propilurea,

3-(3-hidroxipropil)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(1-metilpirazol-4-il)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-etilurea,

3-ciclobutil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-propilurea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

3-ciclopropil-1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]urea,

1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-metilurea,

1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-(2-dimetilaminoetil)urea,

1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-(2-hidroxietil)urea,

1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]urea,

1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-metilurea,

1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-(2-hidroxietil)urea,

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1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]urea,

1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-metilurea,

3-(2-dimetilaminoetil)-1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]urea,

1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-(2-hidroxietil)urea,

1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]urea,

3-metil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]urea,

3-(2-dimetilaminoetil)-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]urea,

3-(2-hidroxietil)-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]urea,

1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-il]urea,

3-metil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-il]urea,

3-(2-hidroxietil)-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-il]urea,

1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-il]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]urea,

1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-metilurea,

1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-(2-hidroxietil)urea,

1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-(1-metilpirazol-4-il)urea,

3-(2-hidroxietil)-1-[5-[4-[1-[4-(2-hidroxietilamino)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]urea,

3-ciclopropil-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-etil-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclobutil-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea,

1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

3-(2-cianoetil)-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea,

1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[1-(hidroximetil)ciclopropil]urea,

1-[4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-etil-1-[4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclobutilurea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-ilurea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-ilurea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propilurea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-ciclobutil-1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-ilurea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-ilurea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propilurea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfonilpiperidin-4-il)pirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfonilpiperidin-4-il)pirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfonilpiperidin-4-il)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfonilpiperidin-4-il)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfonilpiperidin-4-il)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-(4-ciclopropilsulfonilpiperidin-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(4-ciclopropilsulfonilpiperidin-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-(4-ciclopropilsulfonilpiperidin-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-(4-ciclopropilsulfonilpiperidin-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-Benzil-4-(3,5-difluorofenil)sulfonilpiperidin-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea,

1-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea,

1-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-piridin-2-ilurea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-propan-2-ilurea,

1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-1-propilurea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

3-ciclobutil-1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea,

1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclobutilurea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-ilurea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-ilurea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-piridin-2-ilurea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propan-2-ilurea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-1-propilurea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea

[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-[4-(3,5-difluorofenil)sulfonilpiperidin-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-ilurea,

3-ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-ciclobutil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-ilurea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea,

1-etil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea,

3-(2-dimetilaminoetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea

3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea

N,N-dimetil-1-[2-[4-(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropane-1-carboxamida

3-metil-1-[4-[4-[1-[(3S)-3-metilmorfolina-4-carbonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea

N-ciclopropil-1-[2-[4-(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropane-1-carboxamida

N-ciclopropil-N-metil-1-[2-[4-(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropane-1-carboxamida

3-metil-1-[4-[4-[1-(4-metilpiperazina-1-carbonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea

1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]-N,N-dimetilciclopropane-1-carboxamida

3-ciclopropil-1-[4-[4-[1-[(3S)-3-metilmorfolina-4-carbonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea

N-ciclopropil-1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropane-1-carboxamida

N-ciclopropil-1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]-N-metilciclopropane-1-carboxamida

3-ciclopropil-1-[4-[4-[1-(4-metilpiperazina-1-carbonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea

1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]-N,N-dimetilciclopropane-1-carboxamida

3-(2-hidroxietil)-1-[4-[4-[1-[(3S)-3-metilmorfolina-4-carbonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea

N-ciclopropil-1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropane-1-carboxamida

N-ciclopropil-1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]-N-metilciclopropane-1-carboxamida,

3-(2-hidroxietil)-1-[4-[4-[1-(4-metilpiperazina-1-carbonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

3-etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

3-[1-(hidroximetil)ciclopropil]-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

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1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-cianoetil)-1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea,

3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-cianoetil)-1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

3-[1-(hidroximetil)ciclopropil]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[1-(hidroximetil)ciclopropil]urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[1-(hidroximetil)ciclopropil]urea,

3-(2-cianoetil)-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

1-etil-3-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-metilurea,

3-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-(1-metilpirazol-4-il)urea,

3-(2-hidroxietil)-1-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-(1-metilpirazol-4-il)-3-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-metil-3-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-etil-3-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,3-tiazol-2-il)urea,

3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-1-(5-metilpirazin-2-il)urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,3-oxazol-2-il)urea,

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3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclobutilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3,3,3-trifluoro-2-hidroxipropil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-ilurea,

3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-cianoetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[1-(hidroximetil)ciclopropil]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(oxetan-3-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-cianoetil)urea,

1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-etil-3-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-ciclobutil-1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea,

3-(2-hidroxietil)-1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

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1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,3-tiazol-2-il)urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,3-tiazol-2-il)urea,

1-ciclopropil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-metilurea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilciclopropil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-*terc*-butil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-ciano-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-hidroxi-N-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]pirrolidina-1-carboxamida,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilsulfoniletil)urea,

3-(1,1-dioxotiolan-3-il)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

2-[[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamoilamino]-N,N-dimetilacetamida,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-[1-(hidroximetil)ciclopropil]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-[1-(hidroximetil)ciclopropil]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[4-(bencenosulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-[4-[4-[4-(bencenosulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[4-(bencenosulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[4-(bencenosulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-ciclopropilurea,

3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-metilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-cianoetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]fenil]urea,

N-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-hidroxipirrolidina-1-carboxamida,

2-[[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamoilamino]ácido acético,

2-[[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamoilamino]-N,N-dimetilacetamida,

3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-ciclopropil-1-metilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-cianoetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-3-il)urea,

3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-(5-metil-1,2-oxazol-3-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,3-oxazol-2-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2,2-trifluoroetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilimidazol-4-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea,

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1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-cloroetil)urea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

3-(2,2-difluoroetil)-1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea,

3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea,

3-ciclobutil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

3-(2-cianoetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

3-(3-hidroxipropil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea,

3-ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)tiourea,

1-etil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propiltiourea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

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1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propiltiourea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)tiourea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]tiourea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]tiourea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]tiourea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea,

3-ciclopropil-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropiltiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)tiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)tiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-cianoetil)tiourea,

3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etiltiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)tiourea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)tiourea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(1H-imidazol-2-ilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[1-(1H-imidazol-2-ilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

3-ciclopropil-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(1-metilpirazol-4-il)-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-etil-3-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-ciclobutil-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-propilurea,

1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-propan-2-ilurea,

3-ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea,

3-ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2-cianoetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-etil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea,

3-(3-hidroxipropil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea,

3-(2-fluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,3-tiazol-2-il)urea,

N-[2-[1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletil]acetamida,

N-[2-[1-[2-[4-(etilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletil]acetamida,

2-[1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropil]sulfonilacetamida,

2-[1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropil]sulfonil-N-metilacetamida,

3-ciclopropil-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-metilurea,

3-etil-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-[4-[4-[1-(5-fluoropiridin-2-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[1-(5-fluoropiridin-2-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

N,N-dimetil-6-[1-[2-[4-(metilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpiridina-3-carboxamida,

6-[1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-N,N-dimetilpiridina-3-carboxamida,

N,N-dimetil-3-[1-[2-[4-(metilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpiridina-2-carboxamida,

3-[1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-N,N-dimetilpiridina-2-carboxamida,

1-[4-[4-[1-(2-metoxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[2-fluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[2-fluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-metilurea,

3-etil-1-[2-fluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[2-fluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[2-fluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-fluoroetil)-1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-etil-3-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2,2-difluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-etil-1-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(1-metilpirazol-4-il)-1-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2-fluoro-4-metilaminofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclop,ropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-hidroxiciclopropil)metil]urea,

1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-fluoroetil)-1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-etil-3-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-hidroxiciclopropil)metil]urea,

1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-hidroxiciclopropil)metil]urea,

3-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-43-il)urea,

1-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-43-il)urea

1-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-fluoroetil)-1-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-etil-3-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-43-il)urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea,

3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea,

3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea,

3-ciclopropil-1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

3-ciclopropil-1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-[3-fluoro-4-(2-hidroxietilamino)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2,2-difluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-(2,2-difluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea,

3-(2-fluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea,

1-[4-[4-[1-[1-(difluorometil)pirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]tiourea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclobutil]pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclobutil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3R)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[3-(hidroximetil)morfolin-4-il]pirimidin-2-il]fenil]-3-etilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3R,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-hidroxiciclopropil)metil]urea,

3-Ciclopropil-1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea,

1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea,

1-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2-fluoroetil)-1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-etil-3-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

3-ciclopropil-1-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-fluoroetil)-1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-etil-1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-metilurea,

3-ciclopropil-1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-etil-1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea

3-cloro-4-[1-[2-[4-(metilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzamida

3-cloro-4-[1-[2-[4-(etilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzamida

3-cloro-4-[1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzamida

3-cloro-4-[1-[2-[4-(2-fluoroetilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzamida

3-cloro-4-[1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzamida

1-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea

3-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea

1-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea

1-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea

1-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea

1-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea

1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea

1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea

3-ciclopropil-1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea

1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)tiourea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)tiourea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)tiourea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea,

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)tiourea,

4-[6-[1-(bencenosulfonil)ciclopropil]-2-[4-(etilcarbamoilamino)fenil]pirimidin-4-il]morfolina-3-carboxamida,

4-[6-[1-(bencenosulfonil)ciclopropil]-2-[4-(etilcarbamoilamino)fenil]pirimidin-4-il]-N,N-dimetilmorfolina-3-carboxamida,

3-ciclopropil-1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-etilurea,

1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea

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1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea

1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea

3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea

1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea,

3-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea,

1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-(3-cloro-4-metilaminofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[1-[3-cloro-4-(2-hidroxietilamino)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-[3-cloro-4-(2-fluoroetilamino)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-(3-cloro-4-etilaminofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea,

3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2,2-difluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

1-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

3-(2,2-difluoroetil)-1-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]piramidin-2-il]fenil]-3-etilurea,

1-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea,

3-ciclopropil-1-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea,

3-metil-1-[4-[4-[1-(2-metilaminoetilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea,

3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea,

3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea,

3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea,

3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea,

3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea,

3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea,

3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea,

3-ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)tiourea,

3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

1-etil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

3-(2,2-difluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propiltiourea,

3-(3-hidroxipropil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea y

3-(2,2-difluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

or una sal farmacéuticamente aceptable del mismo.

En otro aspecto de la invención there is provided un compuesto, o a combination of compuestos, selected from any one of

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

3-ciclopropil-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea,

3-ciclopropil-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

3-ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

1-etil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)tiourea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea,

3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea,

3-ciclopropil-1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-ciclopropil-1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea y

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-hidroxiciclopropil)metil]urea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea,

1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-etilurea,

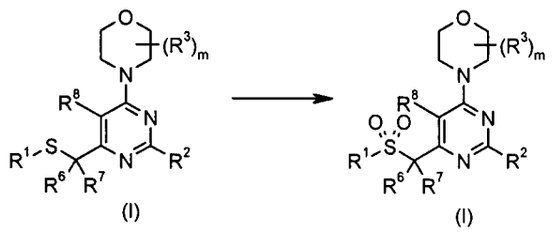
3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea y

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

o una sal farmacéuticamente aceptable del mismo.

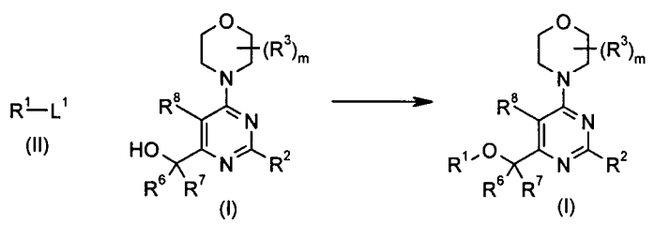
La invención también proporciona procesos para la preparación de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

Un compuesto de fórmula (I), en donde X = $-S(O)_2CR^6R^7-$, puede prepararse mediante la oxidación de un compuesto de la fórmula (I), en donde X = SCR^6R^7-, por ejemplo utilizando Oxone® a temperatura ambiente en un sistema de disolventes mezclado de agua y etanol



(I) (I)

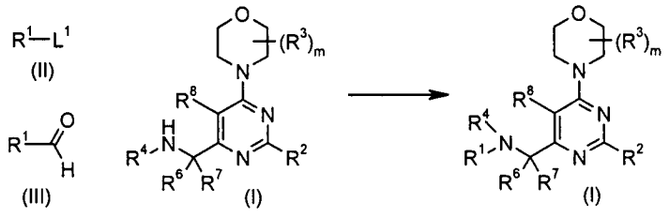
Un compuesto de fórmula (I), en donde $R^1X = R^1OCR^6R^7-$, puede prepararse mediante la reacción de un compuesto de fórmula (I), en donde $R^1X = HOCR^6R^7-$, con un compuesto de fórmula (II), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.) opcionalmente en presencia de una base adecuada tal como trietilamina y un disolvente tal como tetrahidrofurano o *N,N*-dimetilformamida.



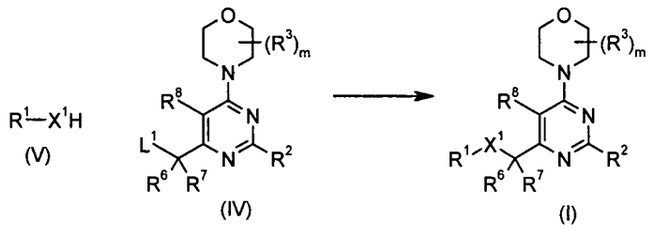
R^1-L^1 (II) (I) (I)

Un compuesto de fórmula (I), en donde $R^1X = R^1R^4NCR^6R^7-$, puede prepararse mediante la reacción de un compuesto de fórmula (I), en donde $R^1X = HR^4NCR^6R^7-$, con un compuesto de fórmula (II), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.) opcionalmente en presencia de una base adecuada tal como trietilamina y un disolvente tal como tetrahidrofurano o *N,N*-dimetilformamida; o mediante la reacción de un compuesto

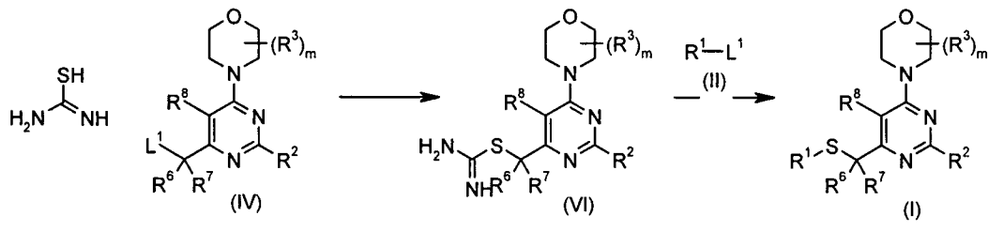
de fórmula (I), en donde $R^1X = HR^4NCR^6R^7$-, con un compuesto de fórmula (III) en presencia de un agente reductor adecuado tal como $NaCNBH_3$.



Un compuesto de fórmula (I), en donde X^1 = $-S(O)_2CR^6R^7$-, $-SCR^6R^7$-, $-OCR^6R^7$-, $-R^4NCR^6R^7$-, $-S(O)CR^6R^7$-, puede prepararse mediante la reacción de un compuesto de fórmula (IV), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con un compuesto de fórmula (V) opcionalmente en presencia de una base adecuada tal como trietilamina y un disolvente tal como tetrahidrofurano o *N,N*-dimetilformamida.

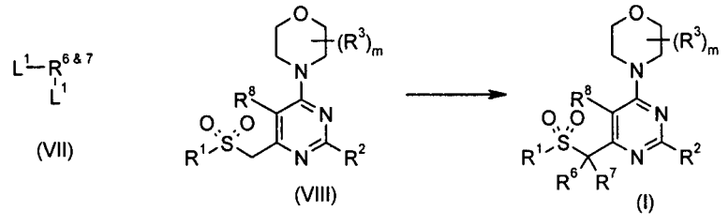


Un compuesto de fórmula (I), en donde X= $-SCR^6R^7$-, puede prepararse mediante la reacción de un compuesto de fórmula (IV), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con tiourea en un disolvente adecuado tal como etanol para generar un compuesto de fórmula (VI) que luego se hace reaccionar con un compuesto de fórmula (II) en presencia de una base adecuada tal como hidróxido de sodio y un disolvente tal como *N,N*-dimetilformamida.



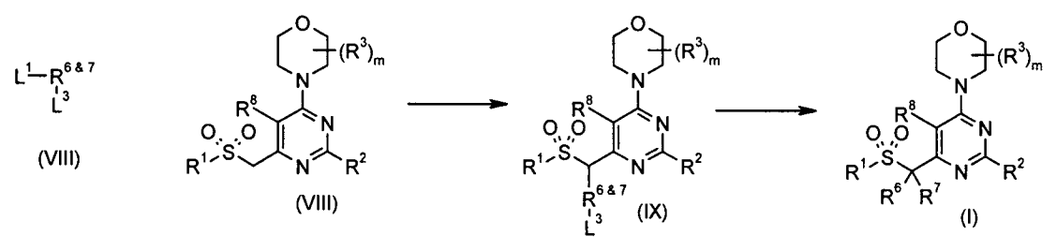
Un compuesto de fórmula (I), en donde X = $-S(O)_2CR^6R^7$-, puede prepararse mediante la reacción de un compuesto de fórmula (VIII) con un compuesto de fórmula (VII), en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S y en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), en presencia de una base adecuada tal como hidruro de sodio o *terc*-butóxido de potasio en un disolvente adecuado tal como tetrahidrofurano o *N,N*-dimetilformamida, o utilizando una solución acuosa de hidróxido de sodio y DCM como

disolvente con un agente de transferencia de fase adecuado tal como bromuro de tetrabutilamonio.



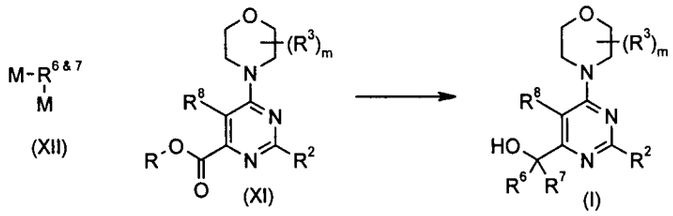
(VII) (VIII) (I)

Un compuesto de fórmula (I), en donde X = $-S(O)_2CR^6R^7-$, puede prepararse mediante la reacción de un compuesto de fórmula (VIII) con un compuesto de fórmula (IX), en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S y en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.) y L^3 es un grupo que puede transformarse en un grupo saliente adecuado (tal como halo, tosilo, mesilo) en una etapa posterior, para proporcionar un compuesto de fórmula (X) en presencia de una base adecuada tal como hidruro de sodio o *terc*-butóxido de potasio en un disolvente adecuado tal como tetrahidrofurano o *N,N*-dimetilformamida, o utilizando una solución acuosa de hidróxido de sodio y DCM como disolvente con un agente de transferencia de fase adecuado tal como bromuro de tetrabutilamonio y a continuación convertir L^3 en un grupo saliente adecuado (tal como halo, tosilo, mesilo etc.) y luego exponer a una base adecuada tal como hidruro de sodio o *terc*-butóxido de potasio en un disolvente adecuado tal como tetrahidrofurano o *N,N*-dimetilformamida, o utilizando una solución acuosa de hidróxido de sodio y DCM como disolvente con un agente de transferencia de fase adecuado tal como bromuro de tetrabutilamonio.

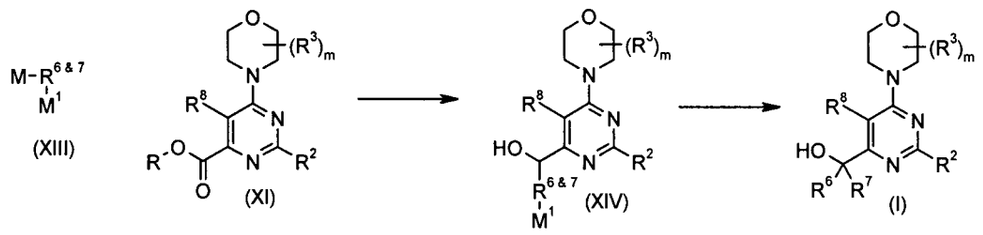


(VIII) (VIII) (IX) (I)

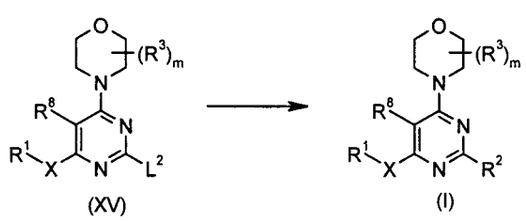
Un compuesto de fórmula (I), en donde R^1X = $HOCR^6R^7-$, puede prepararse mediante la reacción de un compuesto de fórmula (XI) con un reactivo organometálico adecuado de fórmula (XII) en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S, tal como el reactivo de Grignard en un disolvente adecuado.



Un compuesto de fórmula (I), en donde R^1X = $HOCR^6R^7$-, puede prepararse mediante la reacción de un compuesto de fórmula (XI), con un reactivo organometálico adecuado de fórmula (XIII) en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S y M^1 es un grupo que puede transformarse en un reactivo organometálico adecuado (tal como un reactivo de Grignard) en una fecha posterior, tal como el reactivo de Grignard en un disolvente adecuado, para proporcionar un compuesto de fórmula (XIV) y luego convertir M^1 en un reactivo organometálico adecuado y posterior reacción.

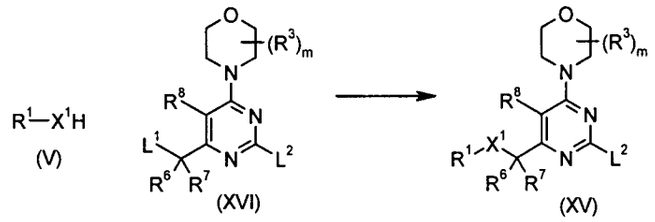


Un compuesto de fórmula (I) puede prepararse a partir de un compuesto de fórmula (XV), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), con un reactivo organometálico adecuado (tal como el ácido borónico $R^2B(OH)_2$ o el éster borónico $R^2B(O)_2$, etc.) en presencia de un catalizador de metal adecuado (tal como paladio o cobre) en un disolvente adecuado tal como 1,4-dioxano. De forma alternativa, en donde R^2 se conecta al anillo de pirimidina a través de un átomo de nitrógeno, oxígeno o azufre, un compuesto de fórmula (I) puede prepararse a partir de un compuesto de fórmula (XIII), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), mediante reacción con la amina, alcohol o tiol necesarios en presencia de una base adecuada, tal como carbonato de potasio, en un disolvente adecuado tal como *N,N*-dimetilformamida.

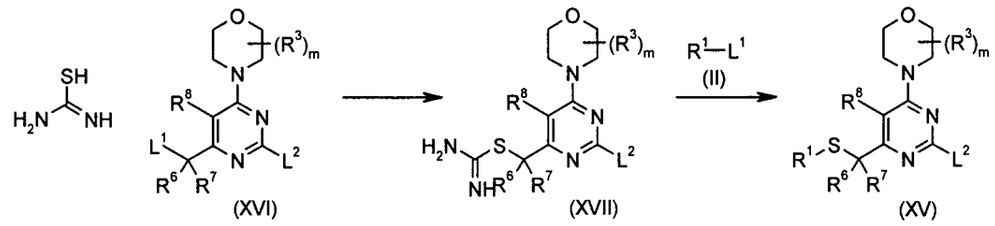


Se apreciará que un compuesto de fórmula (XV) puede transformarse en otro compuesto de fórmula (XV) mediante técnicas tales como oxidación, alquilación, aminación reductiva, etc., enumeradas anteriormente o conocidas en la bibliografía.

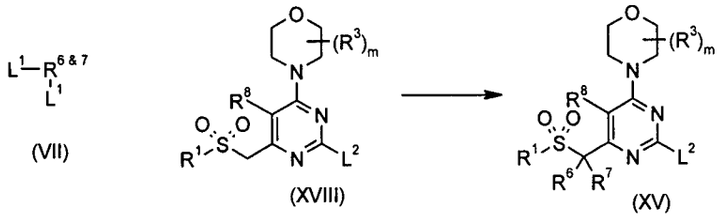
Un compuesto de fórmula (XV), en donde X^1 = $-S(O)_2CR^6R^7-$, $-SCR^6R^7-$, $-OCR^6R^7-$, $-R^4NCR^6R^7-$, $-S(O)CR^6R^7-$, puede prepararse mediante la reacción de un compuesto de fórmula (XVI), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con un compuesto de fórmula (V), opcionalmente en presencia de una base adecuada tal como trietilamina y un disolvente tal como tetrahidrofurano o *N,N*-dimetilformamida.



Un compuesto de fórmula (XV), en donde X = $-SCR^6R^7-$, puede prepararse mediante la reacción de un compuesto de fórmula (XVI), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con tiourea en un disolvente adecuado tal como etanol para generar un compuesto de fórmula (XVII) que luego se hace reaccionar con un compuesto de fórmula (II) en presencia de una base adecuada tal como hidróxido de sodio y un disolvente tal como *N,N*-dimetilformamida.

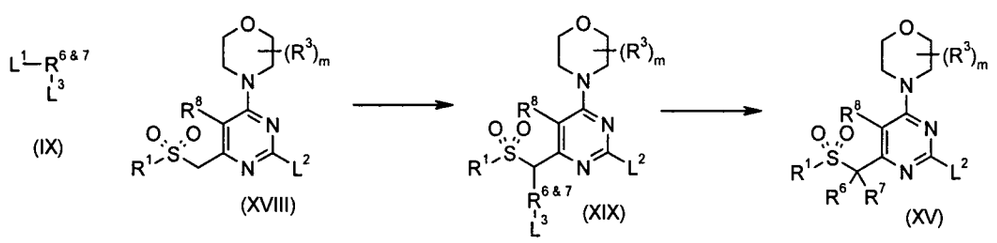


Un compuesto de fórmula (XV), en donde X = $-S(O)_2CR^6R^7-$, puede prepararse mediante la reacción de un compuesto de fórmula (XVIII), en donde X = $-S(O)_2CH_2-$, con un compuesto de fórmula (VII), en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S y en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), en presencia de una base adecuada tal como hidruro de sodio o *terc*-butóxido de potasio en un disolvente adecuado tal como tetrahidrofurano o *N,N*-dimetilformamida, o utilizando una solución acuosa de hidróxido de sodio y DCM como disolvente con un agente de transferencia de fase adecuado tal como bromuro de tetrabutilamonio.



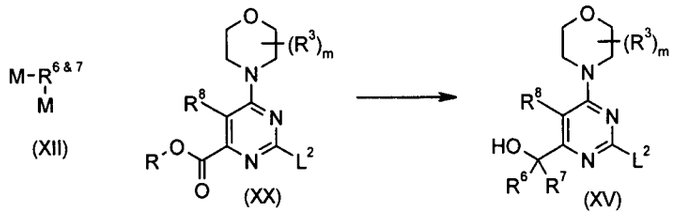
(VII) (XVIII) (XV)

Un compuesto de fórmula (XV), en donde X = $-S(O)_2CR^6R^7-$, puede prepararse mediante la reacción de un compuesto de fórmula (XVIII), en donde X = $-S(O)_2CH_2-$, con un compuesto de fórmula (IX), en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S y en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.) y L^3 es un grupo que puede transformarse en un grupo saliente adecuado (tal como halo, tosilo, mesilo) en una etapa posterior, para proporcionar un compuesto de fórmula (XIX) en presencia de una base adecuada tal como hidruro de sodio o *terc*-butóxido de potasio en un disolvente adecuado tal como tetrahidrofurano o *N,N*-dimetilformamida, o utilizando una solución acuosa de hidróxido de sodio y DCM como disolvente con un agente de transferencia de fase adecuado tal como bromuro de tetrabutilamonio y a continuación convirtiendo L^3 en un grupo saliente adecuado (tal como halo, tosilo, mesilo etc.) y luego exponiendo a una base adecuada tal como hidruro de sodio o *terc*-butóxido de potasio en un disolvente adecuado tal como tetrahidrofurano o *N,N*-dimetilformamida, o utilizando una solución acuosa de hidróxido de sodio y DCM como disolvente con un agente de transferencia de fase adecuado tal como bromuro de tetrabutilamonio.

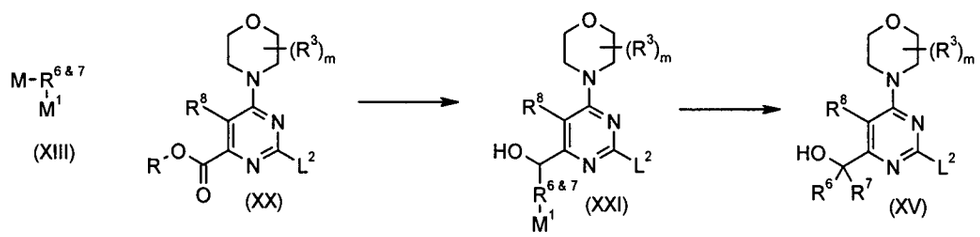


(IX) (XVIII) (XIX) (XV)

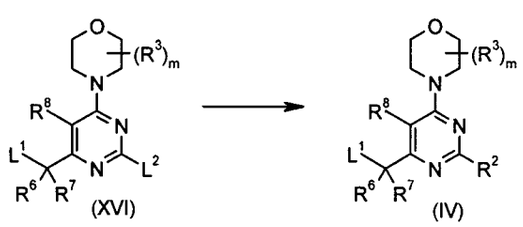
Un compuesto de fórmula (XV), en donde R^1X = $HOCR^6R^7-$, puede prepararse mediante la reacción de un compuesto de fórmula (XX), con un reactivo organometálico adecuado de fórmula (XII) en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S, tal como el reactivo de Grignard en un disolvente adecuado.



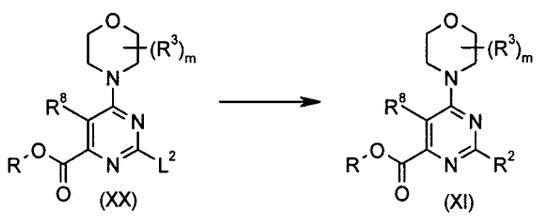
Un compuesto de fórmula (XV), en donde R^1X = $HOCR^6R^7$-, puede prepararse mediante la reacción de un compuesto de fórmula (XX) con un reactivo organometálico adecuado de fórmula (XIII) en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S y M^1 es un grupo que puede transformarse en un reactivo organometálico adecuado (tal como un reactivo de Grignard) en una fecha posterior, tal como el reactivo de Grignard en un disolvente adecuado, para proporcionar un compuesto de fórmula (XXI) y luego la subsiguiente conversión de M^1 en un reactivo organometálico adecuado y posterior reacción.



Un compuesto de fórmula (IV) puede prepararse a partir de un compuesto de fórmula (XVI), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.) y L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con un reactivo organometálico adecuado (tal como el ácido borónico $R^2B(OH)_2$ o el éster borónico $R^2B(O)_2$, etc.) en presencia de un catalizador de metal adecuado (tal como paladio o cobre) en un disolvente adecuado tal como 1,4-dioxano. De forma alternativa, en donde R^2 se conecta al anillo de pirimidina a través de un átomo de nitrógeno, oxígeno o azufre, un compuesto de fórmula (IV) puede prepararse a partir de un compuesto de fórmula (XVI), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), mediante reacción con la amina, alcohol o tiol necesarios en presencia de una base adecuada tal como carbonato de potasio en un disolvente adecuado tal como *N,N*-dimetilformamida.

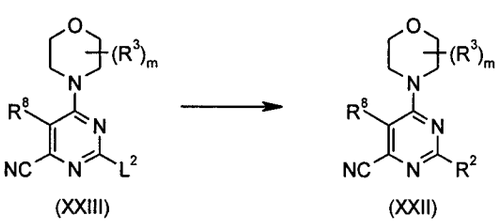


Un compuesto de fórmula (XI) puede prepararse a partir de un compuesto de fórmula (XX), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.) y R es un grupo hidrógeno o alquilo C_{1-4}, con un reactivo organometálico adecuado (tal como el ácido borónico $R^2B(OH)_2$ o el éster borónico $R^2B(O)_2$ etc.) en presencia de un catalizador de metal adecuado (tal como paladio o cobre) en un disolvente adecuado tal como 1,4-dioxano. De forma alternativa, en donde R^2 se conecta al anillo de pirimidina a través de un átomo de nitrógeno, oxígeno o azufre, un compuesto de fórmula (XI) puede prepararse a partir de un compuesto de fórmula (XX), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), mediante reacción con la amina, alcohol o tiol necesarios en presencia de una base adecuada tal como carbonato de potasio en un disolvente adecuado tal como *N,N*-dimetilformamida.



(XX) (XI)

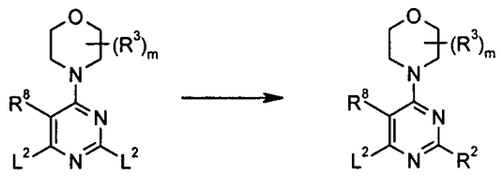
Un compuesto de fórmula (XXII) puede prepararse a partir de un compuesto de fórmula (XXIII), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), con un reactivo organometálico adecuado (tal como el ácido borónico $R^2B(OH)_2$ o el éster borónico $R^2B(O)_2$ etc.) en presencia de un catalizador de metal adecuado (tal como paladio o cobre) en un disolvente adecuado tal como 1,4-dioxano. De forma alternativa en donde R^2 se conecta al anillo de pirimidina a través de un átomo de nitrógeno, oxígeno o azufre, un compuesto de fórmula (XXII) puede prepararse a partir de un compuesto de fórmula (XXIII), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), mediante reacción con la amina, alcohol o tiol necesarios en presencia de una base adecuada tal como carbonato de potasio en un disolvente adecuado tal como *N,N*-dimetilformamida.



(XXIII) (XXII)

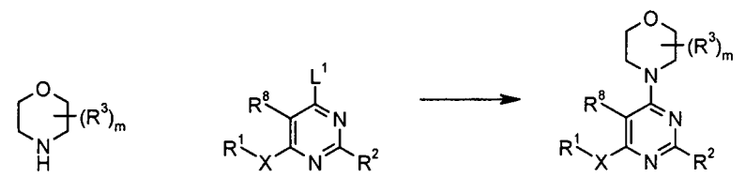
Un compuesto de fórmula (XXIV) puede prepararse a partir de un compuesto de fórmula (XXV), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), con un reactivo organometálico adecuado (tal como el ácido borónico

$R^2B(OH)_2$ o el éster borónico $R^2B(O)_2$ etc.) en presencia de un catalizador de metal adecuado (tal como paladio o cobre) en un disolvente adecuado tal como 1,4-dioxano. De forma alternativa en donde R^2 se conecta al anillo de pirimidina a través de un átomo de nitrógeno, oxígeno o azufre, un compuesto de fórmula (XXIV) puede prepararse a partir de un compuesto de fórmula (XXV), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), mediante reacción con la amina, alcohol o tiol necesarios en presencia de una base adecuada tal como carbonato de potasio en un disolvente adecuado tal como *N,N*-dimetilformamida.



(XXV) (XXIV)

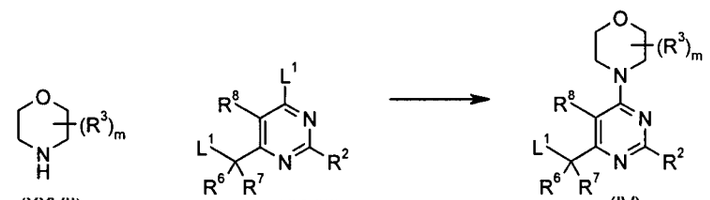
Un compuesto de fórmula (I), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), puede prepararse mediante la reacción de un compuesto de fórmula (XXVI) con un compuesto de fórmula (XXVII), opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



(XXVII) (XXVI) (I)

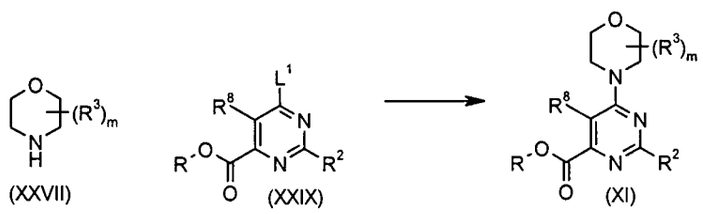
Se apreciará que un compuesto de fórmula (XXV) puede transformarse en otro compuesto de fórmula (XXV) mediante técnicas tales como oxidación, alquilación, aminación reductiva etc., enumeradas anteriormente o conocidas en la bibliografía.

Un compuesto de fórmula (IV), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), puede prepararse mediante la reacción de un compuesto de fórmula (XXVIII) con un compuesto de fórmula (XXVII) opcionalmente en presencia de una base adecuada tal como trietilamina, en un disolvente adecuado tal como *N,N*-dimetilformamida.



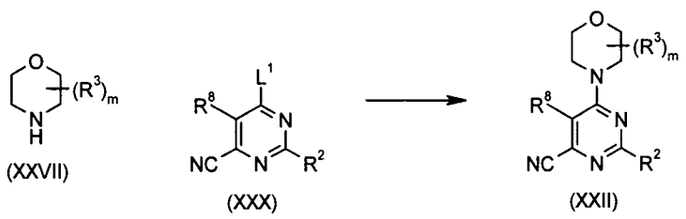
(XXVII) (XXVIII) (IV)

Un compuesto de fórmula (XI), en donde R es un grupo hidrógeno o alquilo C_{1-4}, puede prepararse mediante la reacción de un compuesto de fórmula (XXIX), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con un compuesto de fórmula (XXVII), opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



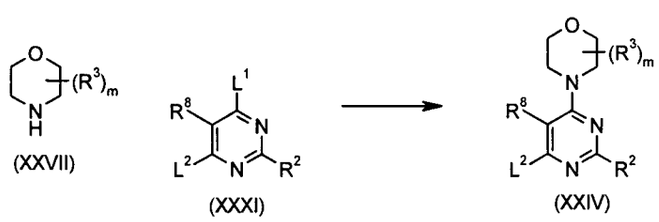
(XXVII) (XXIX) (XI)

Un compuesto de fórmula (XXII) puede prepararse mediante la reacción de un compuesto de fórmula (XXX), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con un compuesto de fórmula (XXVII) opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



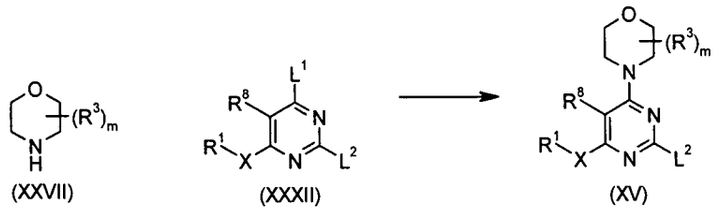
(XXVII) (XXX) (XXII)

Un compuesto de fórmula (XXIV), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse mediante la reacción de un compuesto de fórmula (XXXI), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.) con un compuesto de fórmula (XXVII), opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



(XXVII) (XXXI) (XXIV)

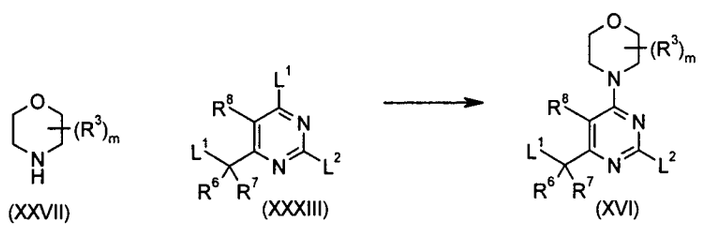
Un compuesto de fórmula (XV), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse mediante la reacción de un compuesto de fórmula (XXXII), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.) con un compuesto de fórmula (XXVII) opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



(XXVII) (XXXII) (XV)

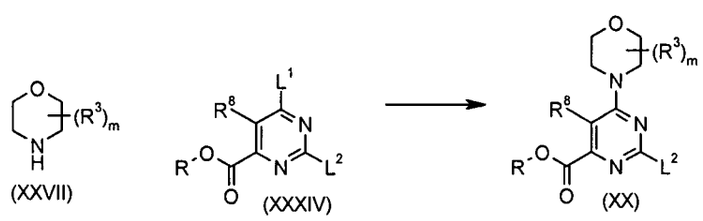
Se apreciará que un compuesto de fórmula (XXXII) puede transformarse en otro compuesto de fórmula (XXXII) mediante técnicas tales como oxidación, alquilación, aminación reductiva etc., enumeradas anteriormente o conocidas en la bibliografía.

Un compuesto de fórmula (XVI), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.) y L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse mediante la reacción de un compuesto de fórmula (XXXIII) con un compuesto de fórmula (XXVII) opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



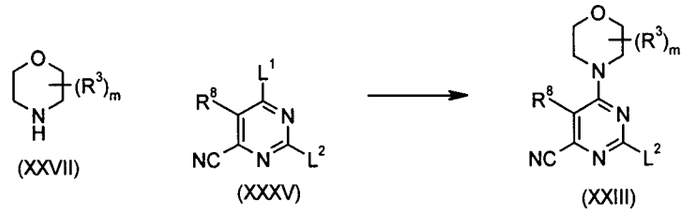
(XXVII) (XXXIII) (XVI)

Un compuesto de fórmula (XX), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.) y R es un grupo hidrógeno o alquilo C_{1-4}, puede prepararse mediante la reacción de un compuesto de fórmula (XXXIV), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con un compuesto de fórmula (XXVII), opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



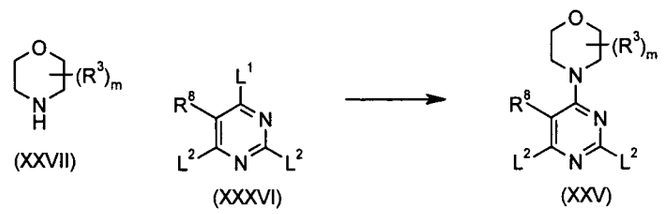
(XXVII) (XXXIV) (XX)

Un compuesto de fórmula (XXIII), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse mediante la reacción de un compuesto de fórmula (XXXV), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con un compuesto de fórmula (XXVII), opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



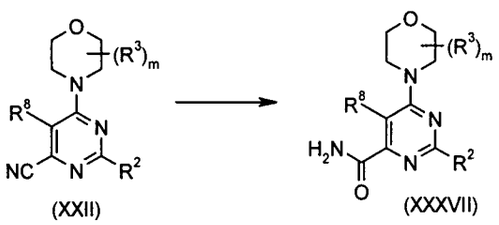
(XXVII) (XXXV) (XXIII)

Un compuesto de fórmula (XXV), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse mediante la reacción de un compuesto de fórmula (XXXVI), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con un compuesto de fórmula (XXVII), opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



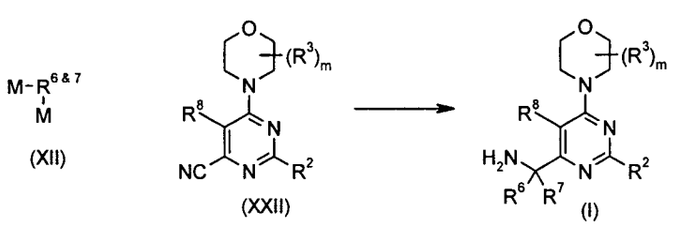
(XXVII) (XXXVI) (XXV)

Un compuesto de fórmula (XXXVII), en donde $R^1X = H_2NC(O)$-, puede prepararse a partir de un compuesto de fórmula (XXII) mediante hidrólisis con, por ejemplo, hidróxido de sodio en un disolvente adecuado tal como una mezcla de agua y etanol.



(XXII) (XXXVII)

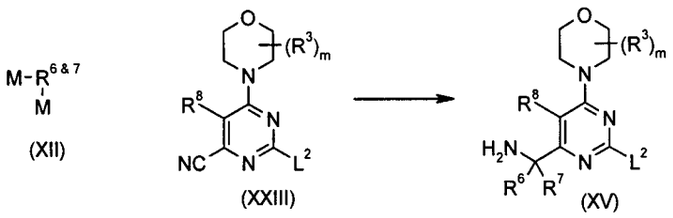
Un compuesto de fórmula (I), en donde $R^1X = H_2NCR^6R^7$-, puede prepararse mediante la reacción de un compuesto de fórmula (XXII) con un reactivo organometálico adecuado de fórmula (XII), en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S, tal como el reactivo de Grignard o reactivo de alquillitio en un disolvente adecuado.



(XII) (XXII) (I)

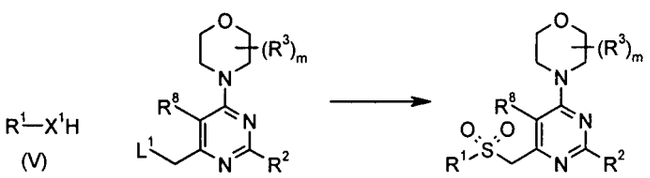
Un compuesto de fórmula (XV), en donde $R^1X = H_2NCR^6R^7$-, puede prepararse mediante la reacción de un compuesto de fórmula (XXIII), con un reactivo organometálico adecuado de fórmula (XII) en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente

sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S, tal como el reactivo de Grignard o reactivo de alquillitio en un disolvente adecuado.



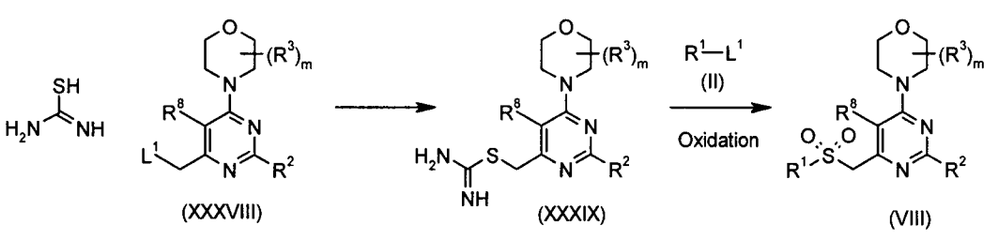
(XII) (XXIII) (XV)

Un compuesto de fórmula (VIII) puede prepararse mediante la reacción de un compuesto de fórmula (XXXVIII), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con un compuesto de fórmula (V), en donde X^1 = -S-, -SO_2-, opcionalmente en presencia de una base adecuada tal como trietilamina y un disolvente tal como tetrahidrofurano o *N,N*-dimetilformamida. Cuando X^1 = -SH será necesaria una etapa posterior de oxidación, por ejemplo utilizando Oxone® a temperatura ambiente en un sistema disolvente de agua y etanol, o por ejemplo utilizando ácido 3-cloroperbenzoico con diclorometano como disolvente.



(V) (XXXVIII) (VIII)

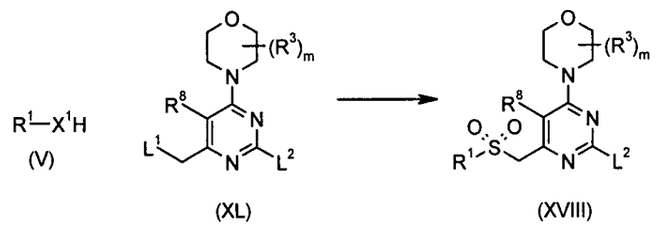
Un compuesto de fórmula (VIII) puede prepararse mediante la reacción de un compuesto de fórmula (XXXVIII), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con tiourea en un disolvente adecuado tal como etanol para generar un compuesto de fórmula (XXXIX), que luego se hace reaccionar con un compuesto de fórmula (II) en presencia de una base adecuada tal como hidróxido de sodio y un disolvente tal como *N,N*-dimetilformamida y a continuación se oxida, por ejemplo utilizando Oxone® a temperatura ambiente en un sistema disolvente de agua y etanol, o por ejemplo utilizando ácido 3-cloroperbenzoico con diclorometano como disolvente.



(XXXVIII) (XXXIX) (II) Oxidation (VIII)

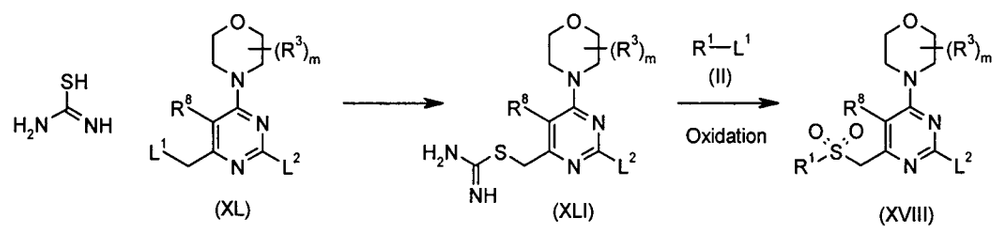
Un compuesto de fórmula (XVIII), en donde L^2 es un grupo saliente (tal como halo, tosilo mesilo, -SMe, -$S(O)_2$Me, etc.), puede prepararse mediante la reacción de un compuesto

de fórmula (XL), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con un compuesto de fórmula (V), en donde X^1 = -S-, -SO_2-, opcionalmente en presencia de una base adecuada tal como trietilamina y un disolvente tal como tetrahidrofurano o *N,N*-dimetilformamida. Cuando X^1 = -S-, se requerirá una posterior etapa de oxidación, por ejemplo utilizando Oxone® a temperatura ambiente en un sistema disolvente de agua y etanol, o por ejemplo utilizando ácido 3-cloroperbenzoico con diclorometano como disolvente.



(V) (XL) (XVIII)

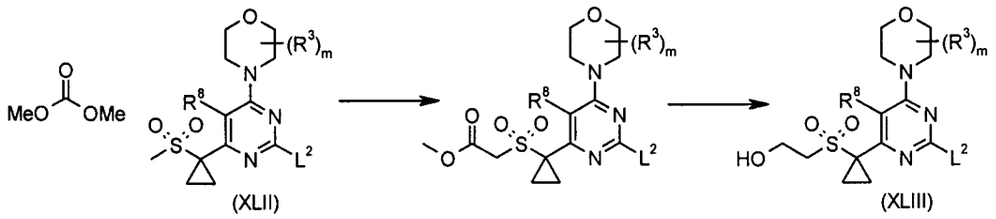
Un compuesto de fórmula (XVIII), en donde L^2 es un grupo saliente (tal como halo, tosilo mesilo, -SMe, -$S(O)_2$Me, etc.), puede prepararse mediante la reacción de un compuesto de fórmula (XL), en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), con tiourea en un disolvente adecuado tal como etanol para generar un compuesto de fórmula (XLI) que luego se hace reaccionar con un compuesto de fórmula (II) en presencia de una base adecuada tal como hidróxido de sodio y un disolvente tal como *N,N*-dimetilformamida y a continuación se oxida, por ejemplo utilizando Oxone® a temperatura ambiente en un sistema disolvente de agua y etanol, o por ejemplo utilizando ácido 3-cloroperbenzoico con diclorometano como disolvente.



(XL) (XLI) (II) Oxidation (XVIII)

Se apreciará que el sustituyente R^1 presente en un compuesto de fórmula (I) y fórmula (XV) puede transformarse en otro sustituyente R^1 mediante una serie de transformaciones químicas conocidas en la bibliografía, tal como oxidación, reducción, reacciones nucelofílicas o electrofílicas y reacciones de adición y eliminación. Un ejemplo de dichas transformaciones sería la reacción de un compuesto de fórmula (XLII), en donde L^2 es un grupo saliente (tal como halo, tosilo mesilo, -SMe, -$S(O)_2$Me, etc.), con un electrófilo tal como dimetil carbonato en presencia de una base tal como hidruro de sodio en un disolvente adecuado tal como tetrahidrofurano, seguido por una reducción, tal como la conversión en un anhídrido mezclado

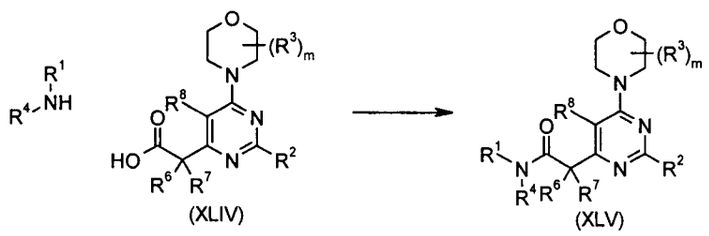
seguida por tratamiento con una fuente de hidruro, para proporcionar un compuesto de fórmula (XLIII).



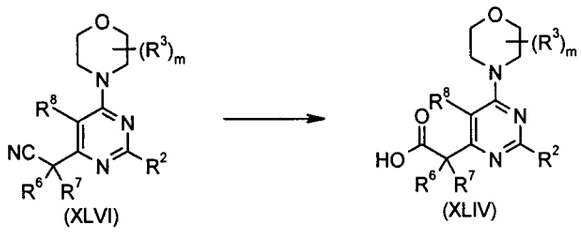
Se apreciará que el grupo R^2 puede introducirse y luego convertirse en otro grupo de la fórmula R^2 en una etapa posterior de la síntesis utilizando métodos conocidos en la bibliografía. Por ejemplo, a modo no taxativo, un R^2 que contiene una alquil o arilamina (que puede protegerse adecuadamente, por ejemplo, como un nitro o t-butoxicarbamato) puede introducirse en cualquier etapa y luego convertirse, por ejemplo, en una urea mediante reacción con un isocianato adecuado (o mediante activación en un grupo adecuado, tal como isocianato o fenoxicarbamato y la posterior reacción con una amina); o en una tiourea mediante reacción con un isotiocianato adecuado (o mediante activación en un grupo adecuado, tal como un isotiocianato y la posterior reacción con una amina); o en una amida o sulfonamida mediante reacción con un derivado de ácido carboxílico o ácido sulfónico adecuadamente activado; o mediante otros métodos conocidos en la bibliografía.

Se apreciará que en donde R^6 y R^7, junto con el carbono al que están unidos, forman un anillo heterocíclico de 3 a 10 miembros que contiene un átomo de nitrógeno, éste puede protegerse adecuadamente (por ejemplo un grupo t-butoxicarbamato o bencilo) y que el grupo protector puede eliminarse y, si es necesario, puede llevarse a cabo una reacción adicional en el nitrógeno (por ejemplo una alquilación, aminación o amidación reductiva) en cualquier etapa de la síntesis.

Un compuesto de fórmula (XLV) puede prepararse mediante la reacción de una amina de fórmula R^1R^4NH con un compuesto de fórmula (XLIV) en presencia de un agente de acoplamiento adecuado, tal como HATU, o siguiendo la activación adecuada de (XLIV), tal como la conversión en un cloruro de ácido.

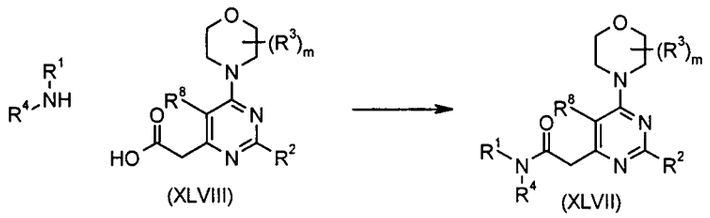


Un compuesto de fórmula (XLIV) puede prepararse a partir de un compuesto de fórmula (XLVI) mediante hidrólisis, por ejemplo con hidróxido de sodio en un disolvente adecuado tal como una mezcla etanol:agua.



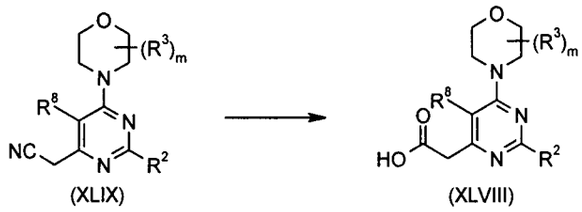
(XLVI) (XLIV)

Un compuesto de fórmula (XLVII) puede prepararse mediante la reacción de una amina de fórmula R^1R^4NH con un compuesto de fórmula (XLVIII) en presencia de un agente de acoplamiento adecuado, tal como HATU, o siguiendo la activación adecuada de (XLVIII), tal como la conversión en un cloruro de ácido.



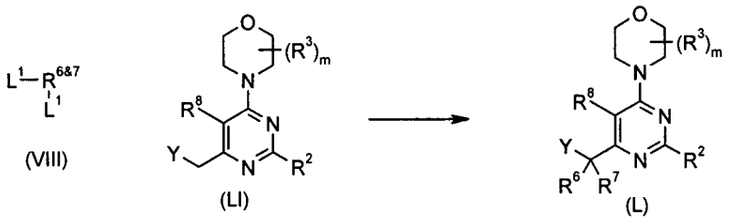
(XLVIII) (XLVII)

Un compuesto de fórmula (XLIX) puede prepararse a partir de un compuesto de fórmula (XLVIII) mediante hidrólisis, por ejemplo con hidróxido de sodio en un disolvente adecuado tal como una mezcla etanol:agua.



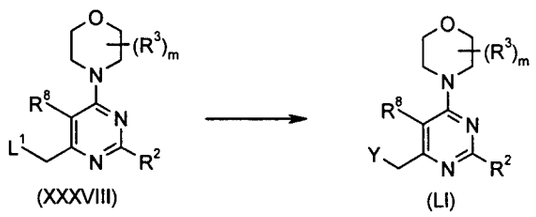
(XLIX) (XLVIII)

Un compuesto de fórmula (L), en donde Y = $R^1R^4NC(O)$-, ROC(O)-, NC-, puede prepararse mediante la reacción de un compuesto de fórmula (VIII) con un compuesto de fórmula (LI), en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S y en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), en presencia de una base adecuada tal como hidruro de sodio o *terc*-butóxido de potasio en un disolvente adecuado tal como tetrahidrofurano o *N,N*-dimetilformamida, o utilizando una solución acuosa de hidróxido de sodio y DCM como disolvente con un agente de transferencia de fase adecuado tal como bromuro de tetrabutilamonio.



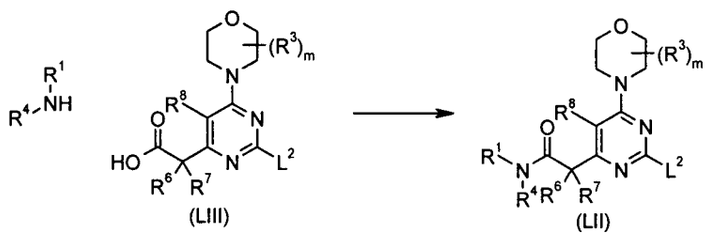
(VIII) (LI) (L)

Un compuesto de fórmula (LI), en donde Y = NC-, HOC(O)-, puede prepararse mediante la reacción de un compuesto de fórmula (XXXVIII) con un nucleófilo adecuado, tal como por ejemplo cianuro de sodio o por ejemplo anión de tris(feniltio)metano seguido por una hidrólisis adecuada.



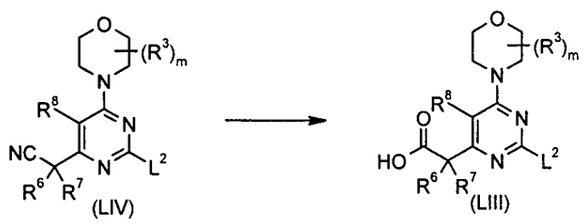
(XXXVIII) (LI)

Un compuesto de fórmula (LII), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse mediante la reacción de una amina de fórmula R^1R^4NH con un compuesto de fórmula (LIII) en presencia de un agente de acoplamiento adecuado, tal como HATU, o siguiendo la activación adecuada de (LIII), tal como la conversión en un cloruro de ácido.



(LIII) (LII)

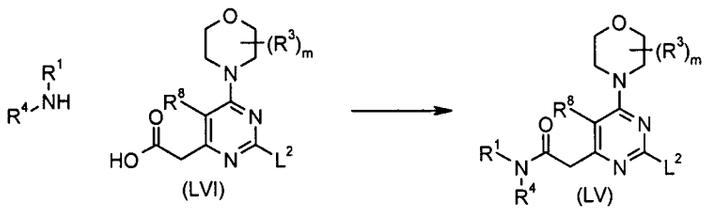
Un compuesto de fórmula (LIII), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse a partir de un compuesto de fórmula (LIV) mediante hidrólisis, por ejemplo con hidróxido de sodio en un disolvente adecuado tal como una mezcla etanol:agua.



(LIV) (LIII)

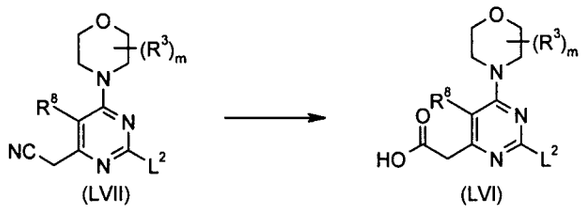
Un compuesto de fórmula (LV), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse mediante la

reacción de una amina de fórmula R^1R^4NH con un compuesto de fórmula (LVI) en presencia de un agente de acoplamiento adecuado, tal como HATU, o siguiendo la activación adecuada de (LVI), tal como la conversión en un cloruro de ácido.



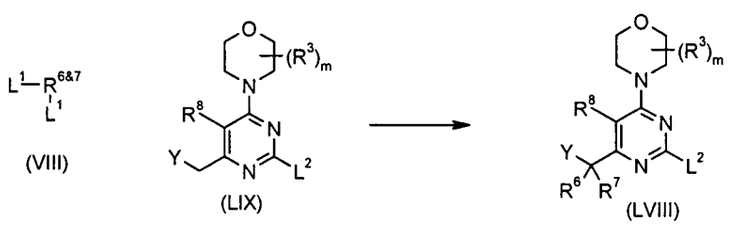
(LVI) (LV)

Un compuesto de fórmula (LVI), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse a partir de un compuesto de fórmula (LVII) mediante hidrólisis, por ejemplo con hidróxido de sodio en un disolvente adecuado tal como una mezcla etanol:agua.



(LVII) (LVI)

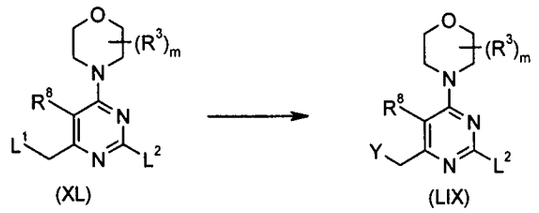
Un compuesto de fórmula (LVIII), en donde Y = $R^1R^4NC(O)$-, ROC(O)-, NC- y L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse mediante la reacción de un compuesto de fórmula (VIII) con un compuesto de fórmula (LIX), en donde $R^{6\ y\ 7}$ es una cadena de alquileno, opcionalmente sustituida, de 2 a 9 miembros en donde 1 carbono puede reemplazarse opcionalmente por O, N o S y en donde L^1 es un grupo saliente (tal como halo, tosilo, mesilo etc.), en presencia de una base adecuada tal como hidruro de sodio o *terc*-butóxido de potasio en un disolvente adecuado tal como tetrahidrofurano o *N,N*-dimetilformamida, o utilizando una solución acuosa de hidróxido de sodio y DCM como disolvente con un agente de transferencia de fase adecuado tal como bromuro de tetrabutilamonio.



(VIII) (LIX) (LVIII)

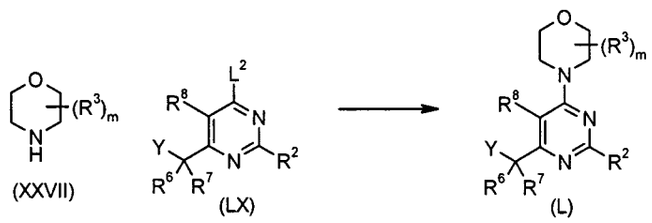
Un compuesto de fórmula (LIX), en donde Y = NC-, HOC(O)- y L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse mediante la reacción de un compuesto de fórmula (XL) con un nucleófilo

adecuado, tal como por ejemplo cianuro de sodio o por ejemplo un anión de tris(feniltio)metano seguido por una hidrólisis adecuada.



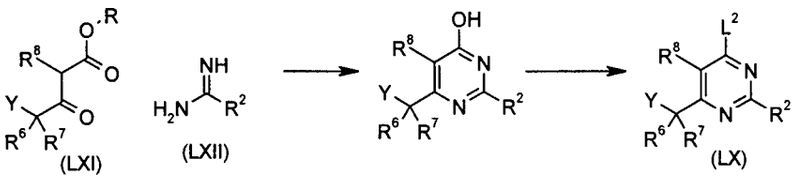
(XL) (LIX)

Un compuesto de fórmula (L), en donde Y = NC-, ROC(O)-, puede prepararse mediante la reacción de un compuesto de fórmula (XXVII) con un compuesto de fórmula (LX), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.), opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



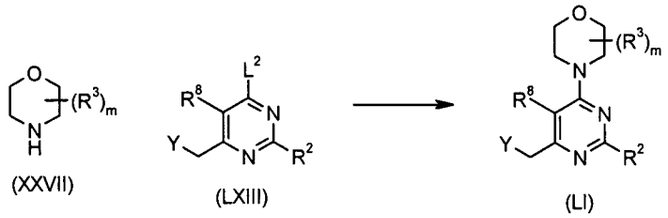
(XXVII) (LX) (L)

Un compuesto de fórmula (LX), en donde Y = NC-, ROC(O)- y L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.), puede prepararse mediante la reacción de un compuesto de fórmula (LXI) con un compuesto de fórmula (LXII) y la posterior conversión del grupo OH en un grupo saliente adecuado, tal como mediante reacción con *N*-feniltrifluorometanosulfonimida en presencia de una base adecuada tal como DBU y un disolvente adecuado tal como diclorometano.



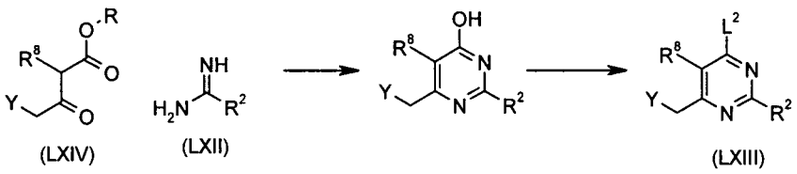
(LXI) (LXII) (LX)

Un compuesto de fórmula (LI), en donde Y = NC-, ROC(O)-, puede prepararse mediante la reacción de un compuesto de fórmula (XXVII) con un compuesto de fórmula (LXIII), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.), opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



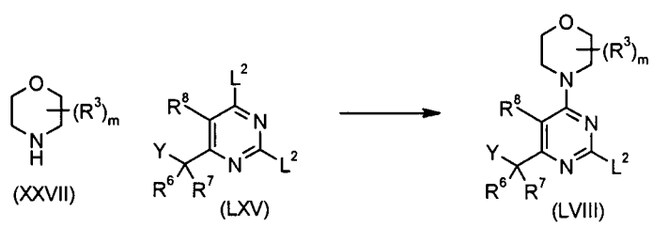
(XXVII) (LXIII) (LI)

Un compuesto de fórmula (LXIII), en donde Y = NC-, ROC(O)- y L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.) puede prepararse mediante la reacción de un compuesto de fórmula (LXIV) con un compuesto de fórmula (LXII) y la posterior conversión del grupo OH en un grupo saliente adecuado, tal como mediante reacción con *N*-feniltrifluorometanosulfonimida en presencia de una base adecuada tal como DBU y un disolvente adecuado tal como diclorometano.



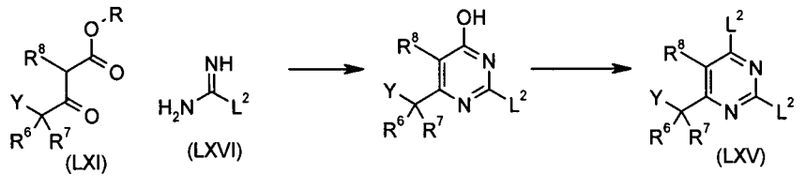
(LXIV) (LXII) (LXIII)

Un compuesto de fórmula (LVIII), en donde Y = NC-, ROC(O)- y L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.) puede prepararse mediante la reacción de un compuesto de fórmula (XXVII) con un compuesto de fórmula (LXV), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.), opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



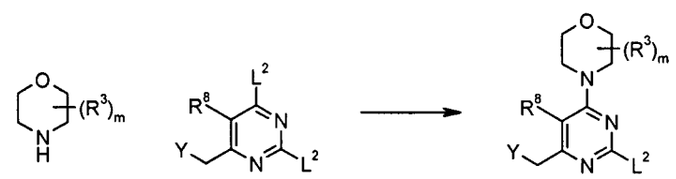
(XXVII) (LXV) (LVIII)

Un compuesto de fórmula (LXV), en donde Y = NC-, ROC(O)- y L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.) puede prepararse mediante la reacción de un compuesto de fórmula (LXI) con un compuesto de fórmula (LXVI) y la posterior conversión del grupo OH en un grupo saliente adecuado, tal como mediante reacción con *N*-feniltrifluorometanosulfonimida en presencia de una base adecuada tal como DBU y un disolvente adecuado tal como diclorometano.



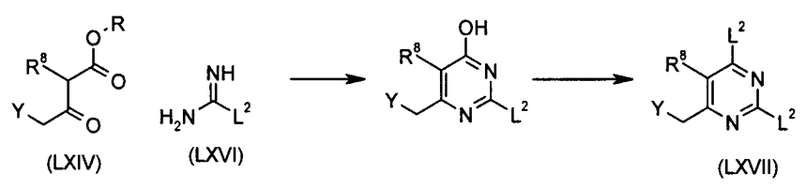
(LXI) (LXVI) (LXV)

Un compuesto de fórmula (LIX), en donde Y = NC-, ROC(O)- y L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.) puede prepararse mediante la reacción de un compuesto de fórmula (XXVII) con un compuesto de fórmula (LXVII), en donde L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.), opcionalmente en presencia de una base adecuada tal como trietilamina en un disolvente adecuado tal como *N,N*-dimetilformamida.



(XXVII) (LXVII) (LIX)

Un compuesto de fórmula (LXVII), en donde Y = NC-, ROC(O)- y L^2 es un grupo saliente (tal como halo, tosilo, mesilo, trifluorometilsulfonilo, -SMe, $-S(O)_2Me$, etc.) puede prepararse mediante la reacción de un compuesto de fórmula (LXIV) con un compuesto de fórmula (LXVI) y la posterior conversión del grupo OH en un grupo saliente adecuado, tal como mediante reacción con *N*-feniltrifluorometanosulfonimida en presencia de una base adecuada tal como DBU y un disolvente adecuado tal como diclorometano.



(LXIV) (LXVI) (LXVII)

Se apreciará que algunos de los distintos sustituyentes anulares en los compuestos de la presente invención pueden introducirse mediante reacciones de sustitución aromáticas convencionales o generarse mediante modificaciones de grupos funcionales antes o inmediatamente después de los procesos mencionados anteriormente y, como tales, se incluyen en el aspecto de proceso de la invención. Por ejemplo, los compuestos de fórmula (I) pueden convertirse en otros compuestos de fórmula (I) mediante reacciones de sustitución aromáticas convencionales o mediante modificaciones de grupos funcionales convencionales. Dichas reacciones y modificaciones incluyen, por ejemplo, la introducción de un sustituyente mediante una reacción de sustitución aromática, reducción de sustituyentes, alquilación de

sustituyentes y oxidación de sustituyentes. Los reactivos y las condiciones de reacción para dichos procedimientos son bien conocidos en la técnica química. Ejemplos particulares de reacciones de sustitución aromática incluyen la introducción de un grupo nitro utilizando ácido nítrico concentrado, la introducción de un grupo acilo utilizando, por ejemplo, un haluro de acilo y ácido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts; la introducción de un grupo alquilo utilizando un haluro de alquilo y ácido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts; y la introducción de un grupo halógeno. Ejemplos particulares de modificaciones incluyen la reducción de un grupo nitro a un grupo amino mediante, por ejemplo, hidrogenación catalítica con un catalizador de níquel o tratamiento con hierro en presencia de ácido clorhídrico con calentamiento; la oxidación de alquiltio en alquilsulfinilo o alquilsulfonilo.

También se apreciará que en algunas de las reacciones mencionadas en la presente puede ser necesario/deseable proteger los grupos sensibles en los compuestos. Las instancias en donde la protección es necesaria o deseable y los métodos adecuados para la protección son conocidos por los expertos en la técnica. Pueden utilizarse grupos protectores convencionales de acuerdo con la práctica estándar (por más detalles ver T. W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). De esta manera, si los reactivos incluyen grupos tales como amino, carboxi o hidroxi, puede ser deseable proteger el grupo en alguna de las reacciones mencionadas en la presente.

Un grupo protector adecuado para un grupo amino o alquilamino es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como acetilo, un grupo alcoxicarbonilo, por ejemplo un grupo metoxicarbonilo, etoxicarbonilo o t-butoxicarbonilo, un grupo arilmetoxicarbonilo, por ejemplo benciloxicarbonilo, o un grupo aroilo, por ejemplo benzoilo. Las condiciones de desprotección para los grupos protectores precedentes variarán necesariamente con la elección del grupo protector. Así, por ejemplo, un acilo tal como un grupo alcanoilo o alcoxicarbonilo o un grupo aroilo puede eliminarse, por ejemplo, mediante hidrólisis con una base adecuada tal como un hidróxido de metal alcalino, por ejemplo hidróxido de sodio o litio. De manera alternativa, un grupo acilo tal como un grupo t-butoxicarbonilo puede eliminarse, por ejemplo, mediante tratamiento con un ácido adecuado tal como ácido clorhídrico, sulfúrico o fosfórico o ácido trifluoroacético y un grupo arilmetoxicarbonilo tal como un grupo benciloxicarbonilo puede eliminarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio sobre carbono, o mediante tratamiento con un ácido de Lewis, por ejemplo tris(trifluoroacetato) de boro. Un grupo

protector alternativo adecuado para un grupo amino primario es, por ejemplo, un grupo ftaloilo que puede eliminarse mediante tratamiento con una alquilamina, por ejemplo dimetilaminopropilamina, o con hidrazina.

Un grupo protector adecuado para un grupo hidroxi es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como acetilo, un grupo aroilo, por ejemplo benzoilo, o un grupo arilmetilo, por ejemplo bencilo. Las condiciones de desprotección para los grupos protectores precedentes variarán necesariamente con la elección del grupo protector. Así, por ejemplo, un grupo acilo tal como un grupo alcanoilo o un grupo aroilo puede eliminarse, por ejemplo, mediante hidrólisis con una base adecuada tal como un hidróxido de metal alcalino, por ejemplo hidróxido de sodio o litio. De manera alternativa, un grupo arilmetilo tal como un grupo bencilo puede eliminarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio sobre carbono.

Un grupo protector adecuado para un grupo carboxi es, por ejemplo, un grupo esterificador, por ejemplo un grupo metilo o etilo que puede eliminarse, por ejemplo, mediante hidrólisis con una base tal como hidróxido de sodio, o por ejemplo un grupo *terc*-butilo que puede eliminarse, por ejemplo, mediante tratamiento con un ácido, por ejemplo un ácido orgánico tal como ácido trifluoroacético, o por ejemplo un grupo bencilo que puede eliminarse, por ejemplo, mediante hidrogenación sobre un catalizador tal como paladio sobre carbono.

Los grupos protectores pueden eliminarse en cualquier etapa conveniente de la síntesis utilizando técnicas convencionales conocidas en la técnica.

Muchos de los intermedios descritos en la presente son nuevos y, por lo tanto, se proporcionan como una característica adicional de la invención.

Ensayos biológicos

Pueden usarse los siguientes ensayos para medir los efectos de los compuestos de la presente invención como inhibidores de la mTOR quinasa, como inhibidores de la PI3 quinasa, como inhibidores *in vitro* de la activación de las vías de señalización de la PI3 quinasa y como inhibidores *in vitro* de la proliferación de células de adenocarcinoma de mama humanas MDA-MB-468.

(a)(i) Ensayo de mTOR quinasa *in vitro*

En este ensayo se utilizó la tecnología AlphaScreen (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) para determinar la capacidad de los compuestos de prueba de inhibir la fosforilación por parte de la mTOR recombinante.

Se expresó establemente un truncamiento C terminal de mTOR que abarcaba los residuos aminoácidos 1362 a 2549 de mTOR (No. de acceso EMBL L34075) como una fusión etiquetada con FLAG en células HEK293 como lo describen Vilella-Bach *et al.*, Journal of Biochemistry, 1999, 274, 4266-4272. La línea celular estable de mTOR (1362-2549) etiquetada con FLAG de HEK293 se mantuvo a 37°C con CO_2 al 5% hasta una confluencia de 70-90% en medio de crecimiento de Eagle modificado por Dulbecco (DMEM; Invitrogen Limited, Paisley, UK, No. de catálogo 41966-029) que contenía suero de bovino fetal inactivado con calor al 10% (FCS; Sigma, Poole, Dorset, UK, No. de catálogo F0392), 1% L-glutamina (Gibco, No. de catálogo 25030-024) y 2 mg/ml geneticina (sulfato G418; Invitrogen Limited, UK No. de catálogo 10131-027). Luego de la expresión en la línea celular de HEK293 de mamífero, la proteína expresada se purificó utilizando la etiqueta del epítopo FLAG utilizando técnicas de purificación convencionales.

Los compuestos de prueba se prepararon como soluciones concentradas de 10 mM en DMSO y se diluyeron en agua según fuera necesario para proporcionar una gama de concentraciones finales de ensayo. Se colocaron alícuotas (2 µl) de cada dilución de compuesto en un pocillo de una placa Greiner de poliestireno blanco de bajo volumen de 384 pocillos (Greiner Bio-one). Una mezcla de 30 µl de enzima de mTOR purificada recombinante, sustrato de péptido biotinilado 1 µM (Biotin-Ahx-Lys-Lys-Ala-Asn-Gln-Val-Phe-Leu-Gly-Phe-Thr-Tyr-Val-Ala-Pro-Ser-Val-Leu-Glu-Ser-Val-Lys-Glu-NH_2; Bachem UK Ltd), ATP (20 µM) y solución tampón [que contenía Tris-HCl pH7,4 tampón (50 mM), EGTA (0,1 mM), albúmina de suero bovino (0,5 mg/ml), DTT (1,25 mM) y cloruro de manganeso (10 mM)] se agitó a temperatura ambiente durante 90 minutos.

Los pocillos testigo que produjeron una señal máxima correspondiente a la actividad enzimática máxima se crearon utilizando DMSO al 5% en lugar de compuesto de prueba. Los pocillos testigo que produjeron una señal mínima correspondiente a la enzima totalmente inhibida fueron creados mediante la adición de EDTA (83 mM) en lugar de compuesto de prueba. Estas soluciones de ensayo se incubaron durante 2 horas a temperatura ambiente.

Cada reacción se detuvo mediante la adición de 10 µl de una mezcla de EDTA (50 mM), albúmina de suero bovino (BSA; 0,5 mg/ml) y tampón de Tris-HCl pH7,4 (50 mM) que contenía Anticuerpo Monoclonal 1A5 de p70 S6 Quinasa (T389) (Cell Signalling Technology, No. de catálogo 9206B) y perlas donantes de Estreptavidina AlphaScreen y aceptoras de Proteína A (200 ng; Perkin Elmer, No. de catálogo 6760002B y 6760137R respectivamente) y las placas de ensayo se dejaron durante aproximadamente 20 horas a

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temperatura ambiente en la oscuridad. Las señales resultantes de la excitación de la luz láser a 680 nm se leyeron utilizando un instrumento Packard Envision.

El péptido biotinilado fosforilado se forma *in situ* como resultado de la fosforilación mediada por mTOR. El péptido biotinilado fosforilado que está asociado a las perlas donantes de Estreptavidina AlphaScreen forma un complejo con el Anticuerpo Monoclonal 1A5 de la p70 S6 Quinasa (T389) asociado a las perlas aceptoras de Proteína A Alphascreen. Con la excitación de la luz láser a 680 nm, el complejo perla donante : perla aceptora produce una señal que puede medirse. Por consiguiente, la presencia de la actividad mTOR quinasa resulta en una señal de ensayo. En presencia de un inhibidor de la mTOR quinasa, la fuerza de la señal disminuye.

La inhibición de la enzima de mTOR para un compuesto de prueba determinado se expresó como un valor de CI_{50}.

(a)(ii) Ensayo de mTOR quinasa *in vitro* (Echo)

En este ensayo se utilizó la tecnología AlphaScreen (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) para determinar la capacidad de los compuestos de prueba de inhibir la fosforilación por parte de la mTOR recombinante.

Se expresó establemente un truncamiento C terminal de mTOR que abarcaba los residuos aminoácidos 1362 a 2549 de mTOR (No. de acceso EMBL L34075) como una fusión etiquetada con FLAG en células HEK293 como lo describen Vilella-Bach *et al.*, Journal of Biochemistry, 1999, 274, 4266-4272. La línea celular estable de mTOR (1362-2549) etiquetada con FLAG de HEK293 se mantuvo a 37°C con CO_2 al 5% hasta una confluencia de 70-90% en medio de crecimiento de Eagle modificado por Dulbecco (DMEM; Invitrogen Limited, Paisley, UK, No. de catálogo 41966-029) que contenía suero de bovino fetal inactivado con calor al 10% (FCS; Sigma, Poole, Dorset, UK, No. de catálogo F0392), 1% L-glutamina (Gibco, No. de catálogo 25030-024) y 2 mg/ml geneticina (sulfato G418; Invitrogen Limited, UK No. de catálogo 10131-027). Luego de la expresión en la línea celular de HEK293 de mamífero, la proteína expresada se purificó utilizando la etiqueta del epítopo FLAG utilizando técnicas de purificación convencionales.

Los compuestos de prueba se prepararon como soluciones concentradas de 10 mM en aguaDMSO y se diluyeron en agua según fuera necesario para proporcionar una gama de concentraciones finales de ensayo. Se colocaron acústicamente utilizando un Labcyte Echo 550 alícuotas (120nl2 µl) de cada dilución de compuesto en un pocillo de una placa Greiner de poliestireno blanco de bajo volumen de 384 pocillos (Greiner Bio-one). Una mezcla de

1230 µl de enzima de mTOR purificada recombinante, sustrato de péptido biotinilado 1 µM (Biotin-Ahx-Lys-Lys-Ala-Asn-Gln-Val-Phe-Leu-Gly-Phe-Thr-Tyr-Val-Ala-Pro-Ser-Val-Leu-Glu-Ser-Val-Lys-Glu-NH_2; Bachem UK Ltd), ATP (20 µM) y solución tampón [que contenía Tris-HCl pH7,4 tampón (50 mM), EGTA (0,1 mM), albúmina de suero bovino (0,5 mg/ml), DTT (1,25 mM) y cloruro de manganeso (10 mM)] se incubó a temperatura ambiente durante 12090 minutos.

Los pocillos testigo que produjeron una señal máxima correspondiente a la actividad enzimática máxima se crearon utilizando DMSO al 1005% en lugar de compuesto de prueba. Los pocillos testigo que produjeron una señal mínima correspondiente a la enzima totalmente inhibida fueron creados mediante la adición de compuesto LY294002EDTA (100uM83 mM). Estas soluciones de ensayo se incubaron durante 2 horas a temperatura ambiente.

Cada reacción se detuvo mediante la adición de 510 µl de una mezcla de EDTA (50 mM), albúmina de suero bovino (BSA; 0,5 mg/ml) y tampón de Tris-HCl pH7,4 (50 mM) que contenía Anticuerpo Monoclonal 1A5 de p70 S6 Quinasa (T389) (Cell Signalling Technology, No. de catálogo 9206B) y perlas donantes de Estreptavidina AlphaScreen y aceptoras de Proteína A (200 ng; Perkin Elmer, No. de catálogo 6760002B y 6760137R respectivamente) y las placas de ensayo se dejaron durante aproximadamente 20 horas a temperatura ambiente en la oscuridad. Las señales resultantes de la excitación de la luz láser a 680 nm se leyeron utilizando un instrumento Packard Envision.

El péptido biotinilado fosforilado se forma *in situ* como resultado de la fosforilación mediada por mTOR. El péptido biotinilado fosforilado que está asociado a las perlas donantes de Estreptavidina AlphaScreen forma un complejo con el Anticuerpo Monoclonal 1A5 de la p70 S6 Quinasa (T389) asociado a las perlas aceptoras de Proteína A Alphascreen. Con la excitación de la luz láser a 680 nm, el complejo perla donante : perla aceptora produce una señal que puede medirse. Por consiguiente, la presencia de la actividad mTOR quinasa resulta en una señal de ensayo. En presencia de un inhibidor de la mTOR quinasa, la fuerza de la señal disminuye.

La inhibición de la enzima de mTOR para un compuesto de prueba determinado se expresó como un valor de CI_{50}.

(b)(i) Ensayo de enzima PI3K *in vitro*

En este ensayo se utilizó la tecnología AlphaScreen (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) para determinar la capacidad de los compuestos de prueba de inhibir la fosforilación por parte de las enzimas PI3K Tipo I del lípido PI(4,5)P2.

Se aislaron fragmentos de ADN que codificaban subunidades catalíticas y reguladores de PI3K a partir de bibliotecas de ADNc utilizando técnicas de biología molecular y clonación por PCR convencionales. Los fragmentos de ADN seleccionados se usaron para generar vectores de expresión de baculovirus. En particular, se subclonó ADN total de cada una de las isoformas p110 de PI3K humana Tipo I p110α, p110β y p110δ (Nos. de acceso de EMBL HSU79143, S67334, Y10055 para p110α, p110β y p110δ, respectivamente) en un vector pDEST10 (Invitrogen Limited, Fountain Drive, Paisley, UK). El vector es una versión de FastbacI adaptada con Gateway que contiene una etiqueta de epítopo 6-His. También se subclonaron una forma truncada de la isoforma p110γ de la PI3K humana Tipo Ib correspondiente a los residuos de 144-1102 (No. de acceso EMBL X8336A) y la subunidad reguladora p85α humana (No. de acceso EMBL HSP13KIN) en el vector pFastBacl que contiene una etiqueta de epítopo 6-His. Los constructos de p110 de Tipo Ia se co-expresaron con la subunidad reguladora p85α. Luego de la expresión en el sistema de baculovirus utilizando técnicas convencionales de expresión con baculovirus, las proteínas expresadas se purificaron utilizando la etiqueta de epítopo His mediante técnicas de purificación convencionales.

Se aisló ADN correspondiente a los aminoácidos 263 a 380 para el dominio PH de receptor general humano para fosfoinositidas (Grp 1) a partir de una biblioteca de ADNc utilizando técnicas de biología molecular y clonación por PCR convencionales. El fragmento de ADN resultante se subclonó en un vector de expresión de *E. coli* pGEX 4T1 que contenía una etiqueta de epítopo GST (Amersham Pharmacia Biotech, Rainham, Essex, UK) como describe Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245). El dominio PH de Grp1 etiquetado con GST se expresó y purificó utilizando técnicas convencionales.

Los compuestos de prueba se prepararon como soluciones concentradas 10 mM en DMSO y se diluyeron en agua según fue necesario para proporcionar un rango de concentraciones de ensayo finales. Se colocaron alícuotas (2 µl) de cada dilución de compuesto en un pocillo de una placa Greiner de poliestireno blanca de bajo volumen de 384 pocillos (Greiner Bio-one, Brunel Way, Stonehouse, Gloucestershire, UK, No. de catálogo 784075). Se agitó una mezcla de cada enzima PI3K purificada recombinante (15 ng), sustrato de DiC8-PI(4,5)P2 (40 µM; Cell Signals Inc., Kinnear Road, Columbus, USA, No. de catálogo 901), adenosina trifosfato (ATP; 4 µM) y una solución tampón [que contenía tampón Tris-HCl pH7,6 (40 mM, 10 µl), 3-[(3-colamidopropil)dimetilamonio]-1-propanesulfonato (CHAPS; 0,04%), ditiotreitol (DTT; 2 mM) y cloruro de magnesio (10 mM)] a temperatura

ambiente durante 20 minutos.

Se crearon los pocillos testigo que produjeron una mínima señal correspondiente a la máxima actividad enzimática utilizando 5% DMSO en lugar de compuesto de prueba. Se crearon los pocillos testigo que produjeron una señal máxima correspondiente a la enzima totalmente inhibida mediante la adición de wortmannina (6 μM; Calbiochem / Merck Bioscience, Padge Road, Beeston, Nottingham, UK, No. de catálogo 681675) en lugar de compuesto prueba. Estas soluciones de ensayo también se agitaron durante 20 minutos a temperatura ambiente.

Cada una de las reacciones se detuvo mediante la adición de 10 μl de una mezcla de EDTA (100 mM), albúmina de suero bovino (BSA, 0,045 %) y tampón Tris-HCl pH7,6 (40 mM).

Se agregaron DiC8-PI(3,4,5)P3 biotinilado (50 nM; Cell Signals Inc., No. de catálogo 107), proteína PH GST-GrpI recombinante purificada (2,5 nM) y perlas donantes y aceptoras Anti-GST AlphaScreen (100 ng; Packard Bioscience Limited, Station Road, Pangbourne, Berkshire, UK, No. de catálogo 6760603M) y las placas de ensayo se dejaron durante aproximadamente 5 a 20 horas a temperatura ambiente en la oscuridad. Las señales resultantes que surgieron de la excitación de la luz láser a 680 nm se leyeron utilizando un instrumento Packard AlphaQuest.

Se formó PI(3,4,5)P3 *in situ* como resultado de la fosforilación mediada por la P13K de PI(4,5)P2. La proteína del dominio PH GST-GrpI que se asocia con las perlas donantes Anti-GST AlphaScreen forma un complejo con el PI(3,4,5)P3 biotinilado que se asocia con las perlas aceptoras de estreptavidina Alphascreen. El PI(3,4,5)P3 producido enzimáticamente compite con el PI(3,4,5)P3 biotinilado para unirse a la proteína del dominio PH. Inmediatamente luego de la excitación de la luz láser a 680 nm, el complejo perla donante : perla aceptora produce una señal que puede medirse. Por lo tanto, la actividad de la enzima PI3K para formar el PI(3,4,5)P3 y la posterior competencia con el PI(3,4,5)P3 biotinilado resulta en una señal reducida. La fuerza de la señal se recupera en presencia de un inhibidor de la enzima PI3K.

La inhibición de la enzima PI3K para un determinado compuesto de prueba se expresó como un valor de CI_{50}.

(b)(ii)Ensayo de enzima PI3K *in vitro* (Echo)

En este ensayo se utilizó la tecnología AlphaScreen (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) para determinar la capacidad de los compuestos de prueba

de inhibir la fosforilación por parte de las enzimas PI3K Tipo I del lípido PI(4,5)P2.

Se aislaron fragmentos de ADN que codificaban subunidades catalíticas y reguladores de PI3K a partir de bibliotecas de ADNc utilizando técnicas de biología molecular y clonación por PCR convencionales. Los fragmentos de ADN seleccionados se usaron para generar vectores de expresión de baculovirus. En particular, se subclonó ADN total de cada una de las isoformas p110 de PI3K humana Tipo I p110α, p110β y p110δ (Nos. de acceso de EMBL HSU79143, S67334, Y10055 para p110α, p110β y p110δ, respectivamente) en un vector pDEST10 (Invitrogen Limited, Fountain Drive, Paisley, UK). El vector es una versión de FastbacI adaptada con Gateway que contiene una etiqueta de epítopo 6-His. También se subclonaron una forma truncada de la isoforma p110γ de la PI3K humana Tipo Ib correspondiente a los residuos de 144-1102 (No. de acceso EMBL X8336A) y la subunidad reguladora p85α humana (No. de acceso EMBL HSP13KIN) en el vector pFastBacI que contiene una etiqueta de epítopo 6-His. Los constructos de p110 de Tipo Ia se co-expresaron con la subunidad reguladora p85α. Luego de la expresión en el sistema de baculovirus utilizando técnicas convencionales de expresión con baculovirus, las proteínas expresadas se purificaron utilizando la etiqueta de epítopo His mediante técnicas de purificación convencionales.

Se aisló ADN correspondiente a los aminoácidos 263 a 380 para el dominio PH de receptor general humano para fosfoinositidas (Grp 1) a partir de una biblioteca de ADNc utilizando técnicas de biología molecular y clonación por PCR convencionales. El fragmento de ADN resultante se subclonó en un vector de expresión de *E. coli* pGEX 4T1 que contenía una etiqueta de epítopo GST (Amersham Pharmacia Biotech, Rainham, Essex, UK) como describe Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245). El dominio PH de Grp1 etiquetado con GST se expresó y purificó utilizando técnicas convencionales.

Los compuestos de prueba se prepararon como soluciones concentradas 10 mM en DMSO y se diluyeron en DMSO a agua según fue necesario para proporcionar un rango de concentraciones de ensayo finales. Se dispensaron acústicamente con un Labcyte Echo 550 alícuotas (120nl2 µl) de cada dilución de compuesto en un pocillo de una placa Greiner de poliestireno blanca de bajo volumen de 384 pocillos (Greiner Bio-one, Brunel Way, Stonehouse, Gloucestershire, UK, No. de catálogo 784075). Se agitó una mezcla de cada enzima PI3K purificada recombinante (15 ng), sustrato de DiC8-PI(4,5)P2 (40 µM; Cell Signals Inc., Kinnear Road, Columbus, USA, No. de catálogo 901), adenosina trifosfato (ATP; 4 µM) y una solución tampón [que contenía tampón Tris-HCl pH7,6 (40 mM, 10 µl),

3-[(3-colamidopropil)dimetilamonio]-1-propanesulfonato (CHAPS; 0,04%), ditiotreitol (DTT; 2 mM) y cloruro de magnesio (10 mM)] a temperatura ambiente durante 20 minutos.

Se crearon los pocillos testigo que produjeron una mínima señal correspondiente a la máxima actividad enzimática utilizando 1005% DMSO en lugar de compuesto de prueba. Se crearon los pocillos testigo que produjeron una señal máxima correspondiente a la enzima totalmente inhibida mediante la adición de wortmannina (6 µM; Calbiochem / Merck Bioscience, Padge Road, Beeston, Nottingham, UK, No. de catálogo 681675) en lugar de compuesto prueba. Estas soluciones de ensayo también se agitaron durante 20 minutos a temperatura ambiente.

Cada una de las reacciones se detuvo mediante la adición de 10 µl de una mezcla de EDTA (100 mM), albúmina de suero bovino (BSA, 0,045 %) y tampón Tris-HCl pH7,6 (40 mM).

Se agregaron DiC8-PI(3,4,5)P3 biotinilado (50 nM; Cell Signals Inc., No. de catálogo 107), proteína PH GST-GrpI recombinante purificada (2,5 nM) y perlas donantes y aceptoras Anti-GST AlphaScreen (100 ng; Packard Bioscience Limited, Station Road, Pangbourne, Berkshire, UK, No. de catálogo 6760603M) y las placas de ensayo se dejaron durante aproximadamente 5 a 20 horas a temperatura ambiente en la oscuridad. Las señales resultantes que surgieron de la excitación de la luz láser a 680 nm se leyeron utilizando un instrumento Packard AlphaQuest.

Se formó PI(3,4,5)P3 *in situ* como resultado de la fosforilación mediada por la P13K de PI(4,5)P2. La proteína del dominio PH GST-GrpI que se asocia con las perlas donantes Anti-GST AlphaScreen forma un complejo con el PI(3,4,5)P3 biotinilado que se asocia con las perlas aceptoras de estreptavidina Alphascreen. El PI(3,4,5)P3 producido enzimáticamente compite con el PI(3,4,5)P3 biotinilado para unirse a la proteína del dominio PH. Inmediatamente luego de la excitación de la luz láser a 680 nm, el complejo perla donante : perla aceptora produce una señal que puede medirse. Por lo tanto, la actividad de la enzima PI3K para formar el PI(3,4,5)P3 y la posterior competencia con el PI(3,4,5)P3 biotinilado resulta en una señal reducida. La fuerza de la señal se recupera en presencia de un inhibidor de la enzima PI3K.

La inhibición de la enzima PI3K para un determinado compuesto de prueba se expresó como un valor de CI_{50}.

(c) Ensayo de fosfo-Ser473 Akt *in vitro*

Este ensayo determina la capacidad de los compuestos de prueba de inhibir la

fosforilación de la Serina 473 en Akt según evaluación con la tecnología Acumen Explorer (Acumen Bioscience Limited), un lector de placas que puede usarse para cuantificar rápidamente las características de las imágenes generadas por escaneo con láser.

Se mantuvo de manera rutinaria una línea celular de adenocarcinoma de mama humano MDA-MB-468 (LGC Promochem, Teddington, Middlesex, UK, No. de catálogo HTB-132) a 37°C con CO_2 al 5% hasta una confluencia de 70-90% en DMEM que contenía FCS inactivado con calor al 10% y L-glutamina al 1%.

Para este ensayo se despegaron las células del matraz de cultivo 'Accutase' (Innovative Cell Technologies Inc., San Diego, CA, EUA; No. de catálogo AT104) utilizando métodos de cultivo tisular convencionales y se resuspendieron en medio para proporcionar $1,7x10^5$ células por ml. Se sembraron alícuotas (90 µl) en cada uno de los 60 pocillos internos de una placa de 96 pocillos negra Packard 96 (PerkinElmer, Boston, MA, EUA; No. de catálogo 6005182) para proporcionar una densidad de ~15000 células por pocillo. Las alícuotas (90 µl) del medio de cultivo se colocaron en los pocillos externos para evitar efectos borde. Las células se incubaron durante toda la noche a 37°C con CO_2 al 5% para permitir su adherencia.

En el día 2, las células se trataron con compuestos de prueba y se incubaron durante 2 horas a 37°C con CO_2 al 5%. Los compuestos de prueba se prepararon como soluciones concentradas 10 mM en DMSO y se diluyeron en series según fue necesario con medio de crecimiento para proporcionar un rango de concentraciones 10 veces mayor que las concentraciones de prueba finales requeridas. Las alícuotas (10 µl) de cada dilución de compuesto se colocaron en un pocillo (por triplicado) para proporcionar las concentraciones finales requeridas. A modo de testigo de respuesta mínima, cada placa contuvo pocillos con una concentración final de 100 µM LY294002 (Calbiochem, Beeston, UK, No. de catálogo 440202). A modo de testigo de respuesta máxima, los pocillos contuvieron DMSO al 1% en lugar de compuesto de prueba. Luego de la incubación, el contenido de las placas se fijó mediante tratamiento con una solución acuosa de formaldehído al 1,6% (Sigma, Poole, Dorset, UK, No. de catálogo F1635) a temperatura ambiente durante 1 hora.

Todas las etapas subsiguientes de aspiración y lavado se llevaron a cabo utilizando una lavadora de placas de 96 pocillos Tecan (velocidad de aspiración 10 mm/seg). La solución de fijación se retiró y el contenido de las placas se lavó con solución salina tamponada con fosfato (PBS; 50 µl; Gibco, No. de catálogo 10010015). El contenido de las placas se trató durante 10 minutos a temperatura ambiente con una alícuota (50 µl) de una solución tampón de permeabilización celular que consistía en mezcla de PBS y Tween-20 al 0,5%. La solución

tampón de 'permeabilización' se retiró y los sitios de unión no específica se bloquearon mediante tratamiento durante 1 hora a temperatura ambiente de una alícuota (50 µl) de una solución tampón de bloqueo que consistía en leche descremada deshidratada al 5% ['Marvel' (marca registrada); Premier Beverages, Stafford, GB] en una mezcla de PBS y Tween-20 al 0,05%. La solución tampón de 'bloqueo' se retiró y las células se incubaron durante 1 hora a temperatura ambiente con solución de anticuerpo anti fosfo-Akt (Ser473) de conejo (50 µl por pocillo; Cell Signalling, Hitchin, Herts, U.K., No. de catálogo 9277) que se había diluido 1:500 en tampón de 'bloqueo'. Las células se lavaron tres veces en una mezcla de PBS y Tween-20 al 0,05%. Posteriormente las células se incubaron durante 1 hora a temperatura ambiente con IgG anti-conejo de cabra marcado con Alexafluor488 (50 µl por pocillo; Molecular Probes, Invitrogen Limited, Paisley, UK, No. de catálogo A11008) que se había diluido 1:500 en tampón de 'bloqueo'. Las células se lavaron 3 veces con una mezcla de PBS y Tween-20 al 0,05%. Se agregó una alícuota de PBS (50 µl) a cada pocillo y las placas se sellaron con selladores de placa negros y se detectó y analizó la señal de fluorescencia.

Se analizaron los datos de respuesta de las dosis a la fluorescencia obtenidos para cada compuesto y se expresó el grado de inhibición de la Serina 473 en Akt como un valor de CI_{50}.

(d) Ensayo de proliferación de adenocarcinoma de mama humano MDA-MB-468 *in vitro*

Este ensayo determina la capacidad de los compuestos de prueba de inhibir la proliferación celular según se evaluó utilizando la tecnología Cellomics Arrayscan. Se mantuvo rutinariamente una línea celular de adenocarcinoma de mama humano MDA-MB-468 (LGC Promochem, No. de catálogo HTB-132) como se describe en el ensayo biológico (b) precedente.

Para el ensayo de proliferación se desprendieron las células del matraz de cultivo utilizando Accutase y se sembraron en los 60 pocillos interiores de una placa negra de 96 pocillos Packard a una densidad de 8000 células por pocillo en 100 µl de medio de crecimiento completo. Los pocillos exteriores contenían 100 µl de PBS estéril. Las células se incubaron durante toda la noche a 37°C con 5% CO_2 para permitir su adhesión.

En el día 2 las células se trataron con compuestos de prueba y se incubaron durante 48 horas a 37°C con 5% CO_2. Los compuestos de prueba se prepararon como soluciones concentradas 10 mM en DMSO y se diluyeron serialmente según fuera necesario con medio de crecimiento para proporcionar una gama de concentraciones de prueba. Se colocaron

alícuotas (50 µl) de cada dilución de compuesto en un pocillo y las células se incubaron durante 2 días a 37°C con 5% CO_2. Cada placa contenía pocillos testigo sin compuesto de prueba.

En el día 4 se agregó reactivo de marcaje BrdU (Sigma, No. de catálogo B9285) a una dilución final de 1:1000 y las células se incubaron durante 2 horas a 37°C. El medio se retiró y las células de cada pocillo se fijaron mediante tratamiento con 100 µl de una mezcla de etanol y ácido acético glacial (90% etanol, 5% ácido acético glacial y 5% agua) durante 30 minutos a temperatura ambiente. Las células de cada pocillo se lavaron dos veces con PBS (100 µl). Se agregó ácido clorhídrico acuoso (2M, 100 µl) a cada pocillo. Después de 20 minutos a temperatura ambiente, las células se lavaron dos veces con PBS. Se agregó peróxido de hidrógeno (3%, 50 µl; Sigma, No. de catálogo H1009) a cada pocillo. Después de 10 minutos a temperatura ambiente, los pocillos se lavaron nuevamente con PBS.

La incorporación de BrdU se detectó mediante incubación durante 1 hora a temperatura ambiente con anticuerpo anti-BrdU de ratón(50 µl; Caltag, Burlingame, CA, US; No. de catálogo MD5200) que se diluyó 1:40 en PBS que contenía 1% BSA y 0,05% Tween-20. El anticuerpo sin unir se retiró con dos lavados de PBS. Para la visualización de la BrdU se trataron las células durante 1 hora a temperatura ambiente con PBS (50 µl) y 0,05% tampón Tween-20 que contenía una dilución 1:1000 de IgG anti-ratón de cabra etiquetado con Alexa Fluor 488. Para la visualización del núcleo celular se agregó una dilución 1:1000 de tinción de Hoechst (Molecular Probes, No. de catálogo H_3570). Cada una de las placas se lavó con PBS. Posteriormente se agregó PBS (100 µl) a cada pocillo y las placas se analizaron utilizando la tecnología Cellomics Arrayscan para evaluar el número total de células y de células BrdU positivas.

Se analizaron los datos de respuesta a la dosis de fluorescencia obtenidos con cada compuesto y se expresó el grado de inhibición del crecimiento celular de MDA-MB-468 como un valor de CI_{50}.

Si bien las propiedades farmacológicas de los compuestos de fórmula (I) varían, como se esperaba, con el cambio estructural, en general se cree que la actividad que poseen los compuestos de fórmula (I) puede demostrarse en las siguientes concentraciones o dosis en uno o más de las pruebas (a) a (d) precedentes:-

Prueba (a)(i): CI_{50} versus mTOR quinasa a menos de 10 µM, en particular 0,001 - 0,5 µM para muchos compuestos; para el ejemplo 2b, la CI_{50} se midió en tres ocasiones y los valores fueron de 0,059, 0,005 y 0,23µM.

Prueba (b)(i): CI_{50} versus PI3K humana Tipo Ib p110γ a menos de 10 μM, en particular 0,001 - 0,5 μM para muchos compuestos; CI_{50} versus PI3K humana Tipo Ia p110α a menos de 10 μM, en particular 0,001 - 0,5 μM para muchos compuestos;

para el ejemplo 2b, la CI_{50} se midió y el valor fue de 1,044μM.

Prueba (c): CI_{50} versus Serina 473 en Akt a menos de 10 μM, en particular 0,1 - 20 μM para muchos compuestos; para el ejemplo 2b, la CI_{50} se midió en dos ocasiones y los valores fueron de 0,052 y 0,025 μM.

Prueba (d): CI_{50} a menos de 20 μM;

Los siguientes ejemplos se evaluaron en el ensayo de prueba enzimático (a)(ii):

Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)
1	0,00276	23l	0,00888	52	0,0184
1a	0,00279	23m	0,0577	52a	0,0103
2	0,0015	24	0,00517	52b	0,0307
2a	0,0932	25	0,00155	52c	0,0296
2b	0,000169	25a	0,00224	52d	0,00588
2c	0,00186	25b	0,000817	53	0,00218
2d	0,0239	25c	0,00385	53a	0,00229
2e	0,279	25d	0,00152	53b	0,000669
2f	0,00433	25e	0,000277	53c	0,000688
2g	0,000231	25f	0,0547	53d	0,0031
2h	0,000272	25g	0,00143	53e	0,00198
2i	0,00207	25h	0,000993	53f	0,00634
2j	0,012	25i	0,001	54	0,00217
2k	0,00381	25j	0,00576	54a	0,00918
2l	0,0116	25k	0,00292	54b	0,00317
2m	0,00589	25l	0,000956	54c	0,00453
2n	0,00844	25m	0,00025	54d	0,00882
2o	0,000403	26	0,00605	54e	0,00762
2p	0,0027	26a	0,00672	54f	0,0107
2q	0,000379	26b	0,0039	55	0,00296
2r	0,00103	26c	0,119	55a	0,0213

Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)
2s	0,00155	26d	0,0012	55b	0,0161
2t	0,000656	26e	0,00395	55c	0,0189
2u	0,00118	26f	0,00457	55d	0,0351
2v	0,00866	26g	0,00746	55e	0,0204
2w	0,0685	26h	0,004	55f	0,0156
2x	0,00164	27	0,00111	56	0,00231
2y	0,23	27a	0,00388	56a	0,00226
2z	0,0181	27b	0,00425	56b	0,00165
2aa	0,0274	27c	0,014	56c	0,00623
2ab	0,0553	27d	0,00307	56d	0,0043
2ac	0,00641	27e	0,000351	57	0,0119
2ad	0,000705	27f	0,000997	57a	0,0104
2ae	0,00072	27g	0,0213	57b	0,00457
2af	0,0462	27h	0,000244	57c	0,00695
2ag	0,0149	27i	0,00302	57d	0,01
3	0,00195	27j	0,00761	57e	0,00728
3a	0,00445	27k	0,00462	57f	0,0106
3b	0,00385	27l	0,00112	57g	0,0585
3c	0,0124	27m	0,00144	58	0,00115
3d	0,0135	28	0,00187	58a	0,00339
3e	0,00166	28a	0,00253	58b	0,002
3f	0,0214	28b	0,00149	58c	0,00327
3g	0,00126	28c	0,00847	58d	0,00293
3h	0,0165	28d	0,00237	58e	0,00256
3i	0,000932	28e	0,000434	58f	0,00267
3j	0,00422	28f	0,0674	58g	0,0102
3k	0,00227	28g	0,00118	59	0,00882
3l	0,00257	28h	0,00093	59a	0,0222
3m	0,000497	28i	0,00153	59b	0,00993
3n	0,0396	28j	0,00557	59c	0,0226

Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)
3o	0,00596	28k	0,000954	59d	0,032
3p	0,193	28l	0,000442	59e	0,293
3q	0,00839	29	0,0042	59f	0,0491
3r	0,0488	30	0,025	59g	0,101
3s	0,0263	31	0,00452	60	0,012
3t	0,00479	31a	0,00265	60a	0,0191
3u	0,000604	31b	0,00497	60b	0,00862
3w	0,00089	31c	0,00131	60c	0,00695
4	0,000699	31d	0,00955	60d	0,0183
4a	0,00217	31e	0,00107	60e	0,0116
4b	0,00203	31f	0,0016	60f	0,0173
4c	0,0169	31g	0,00323	61	0,0269
4d	0,01	31h	0,000209	61a	0,0326
4e	0,000767	31i	0,00326	61b	0,0136
4f	0,01	31j	0,00103	61c	0,0211
4g	0,0626	31k	0,00191	61d	0,0438
4h	0,00146	31l	0,214	61e	0,0237
4i	0,0115	31m	0,00591	61f	0,0328
4j	0,00379	32	0,00315	62	0,00205
4k	0,00905	32a	0,0425	62a	0,0393
4l	0,00369	32b	0,00829	62b	0,00546
4m	0,00245	32c	0,00288	62c	0,0375
4n	0,0392	32d	0,0131	62d	0,022
5	0,000802	33	0,00929	63	0,0725
5a	0,000289	33a	0,0584	64	0,00785
5b	0,00052	33b	0,012	64a	0,0052
5c	0,00681	33c	0,00258	64b	0,00678
5d	0,00274	33d	0,133	64c	0,00215
5e	0,000864	34	0,00405	64d	0,0067
5f	0,00485	34a	0,0387	64e	0,00537

Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)
5g	0,0668	34b	0,0109	64f	0,00521
5h	0,00234	34c	0,00345	64g	0,0342
5i	0,00988	34d	0,0863	64h	0,00148
5j	0,000173	35	0,00531	64i	0,00135
5k	0,00333	35a	0,00552	64j	0,0012
5l	0,000237	35b	0,000577	64k	0,00144
5m	0,000604	35c	0,108	64l	0,00111
5n	0,00828	35d	0,00411	64m	0,0408
6	0,001	36a	0,142	64n	0,0161
6a	0,00293	36b	0,00179	64o	0,00345
6b	0,00612	36c	0,114	64p	0,00398
6c	0,00321	36d	0,00317	64q	0,00467
6d	0,000874	36e	0,00667	64r	0,00418
6e	0,0673	36f	0,00278	64s	0,00296
6f	0,000794	36g	0,00841	64t	0,0114
6g	0,00225	36h	0,00314	64u	0,0139
6h	0,000799	36i	0,0518	64v	0,146
6i	0,00462	36j	0,018	64w	0,0161
6j	0,00593	36k	0,0131	64x	0,00761
6k	0,00186	36l	0,0428	64y	0,0125
6l	0,00119	36m	0,0347	64z	0,00866
6m	0,000936	36n	0,0248	64aa	0,00388
7	0,00315	36o	0,00358	64ab	0,0094
7a	0,00231	36p	0,00161	64ac	0,00529
7b	0,0181	36q	0,0889	64ad	0,00298
7c	0,00646	36r	0,00733	64ae	0,00213
7d	0,0038	36s	0,00475	64af	0,00339
7e	0,00212	36t	0,194	64ag	0,00281
7f	0,00915	36u	0,00922	64ah	0,00684
7g	0,211	36v	0,467	64ai	0,00567

Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)
7h	0,0116	36w	0,11	64aj	0,00778
7i	0,0182	36x	0,182	64ak	0,00161
7j	0,0105	36y	0,00131	64al	0,00558
7k	0,00482	36z	0,00208	65	0,03
7l	0,00913	36aa	0,0749	65a	0,00688
7m	0,00504	36ab	0,011	65b	0,00342
8	0,000959	36ac	0,00441	65c	0,0151
8a	0,00096	36ad	0,0323	65d	0,00448
8b	0,00123	36ae	0,0151	65e	0,0114
8c	0,00185	36af	0,00275	66	0,00303
8d	0,00134	36ag	0,0013	66a	0,00415
8e	0,000342	36ah	0,00247	66b	0,0246
8f	0,00882	36ai	0,00561	67	0,001
8g	0,0784	36aj	0,00255	68	0,00141
8h	0,00176	36ak	0,00245	68a	0,00174
8i	0,0198	36al	0,0161	69	0,00788
8j	0,000751	36am	0,0259	70	0,002
8k	0,0173	36an	0,0104	71	0,0182
8l	0,00813	36ao	0,014	72	0,00432
8m	0,00136	36ap	0,0156	73	0,00744
9	0,0018	36aq	0,0157	74	0,00237
9a	0,0129	36ar	0,00945	74a	0,00398
9b	0,0215	36as	0,00911	74b	0,00244
9c	0,0483	36at	0,00639	74c	0,00314
9d	0,0151	36au	0,0121	74d	0,00279
9e	0,00187	36av	0,00995	74e	0,00506
9f	0,144	36aw	0,0164	74f	0,00399
9g	0,00127	36ax	0,0211	74g	0,00433
9h	0,0057	36ay	0,00117	74h	0,00321
9i	0,0024	36az	0,00105	74i	0,00925

Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)
9j	0,046	36ba	0,00167	75	0,029
9k	0,0115	36bb	0,00513	75a	0,0435
9l	0,00395	36bc	0,00285	75b	0,0381
9m	0,00401	36bd	0,00258	75c	0,0339
10	0,00448	36be	0,00376	75d	0,0399
10a	0,0395	36bf	0,00457	75e	0,037
10b	0,0266	36bg	0,00189	75f	0,0608
10c	0,147	36bh	0,00137	76	0,00687
10d	0,0432	36bi	0,00231	76a	0,00407
10e	0,00691	36bj	0,00106	76b	0,00719
10f	0,174	36bk	0,00433	76c	0,00319
10g	0,00156	36bl	0,00333	76d	0,00924
10h	0,0268	36bm	0,00193	76e	0,00566
10i	0,00591	36bn	0,00637	76f	0,00678
10j	0,11	36bo	0,0176	77	0,00821
10k	0,0502	36bp	0,00198	77a	0,00524
10l	0,0183	36bq	0,00131	77b	0,0086
10m	0,00497	36br	0,00188	77c	0,00437
11	0,00165	36bs	0,00264	77d	0,0101
11a	0,0059	36bt	0,00188	77e	0,00517
11b	0,00333	36bu	0,00118	77f	0,00919
11c	0,0247	36bv	0,00264	78	0,0418
11d	0,00642	36bw	0,00909	78a	0,0153
11e	0,00197	36bx	0,00269	78b	0,0333
11f	0,00337	36by	0,012	78c	0,0209
11g	0,313	36bz	0,0143	78d	0,0175
11h	0,00913	36ca	0,31	78e	0,0239
11i	0,0294	36cb	0,163	78f	0,0291
11j	0,0122	36cc	0,129	79	0,0186
11k	0,00332	36cd	0,147	79a	0,0222

Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)
11l	0,00356	36ce	0,42	79b	0,0109
11m	0,00437	36cf	0,286	79c	0,0299
12	0,00421	36cg	0,136	79d	0,0161
12a	0,00167	36ch	0,208	79e	0,0259
12b	0,00271	36ci	0,0386	79f	0,0398
12c	0,00751	36cj	0,00333	80	0,0197
12d	0,00155	36ck	2,62	80a	0,0146
12e	0,00459	36cl	0,0681	80b	0,0103
12f	0,35	36cm	0,00946	80c	0,00921
12g	0,00273	36cn	0,0858	80d	0,00951
12h	0,00392	36co	1,62	80e	0,0143
12i	0,000771	36cp	1,26	81	0,0137
12j	0,00167	36cq	0,114	82	0,00939
12k	0,0043	36cr	0,0435	82a	0,0265
12l	0,00138	36cs	1,17	82b	0,00757
12m	0,0101	36ct	0,00157	82c	0,0185
12n	0,238	36cu	0,0686	82d	0,0243
12o	0,00509	36v	0,259	82e	0,0208
12p	0,0014	36cw	0,0493	82f	0,0273
12q	0,00162	36cx	0,284	83	0,00346
12r	0,000991	36cy	0,0478	83a	0,00483
12s	0,117	36cz	0,0384	83b	0,0114
12t	0,0366	36da	0,0331	83c	0,0124
13	0,00357	36db	0,0209	83d	0,0472
13a	0,00341	36dc	0,00989	84	0,00956
13b	0,0037	36dd	0,00291	84a	0,00909
13c	0,00173	36de	0,00389	84b	0,00385
13d	0,00351	36df	0,00712	84c	0,00829
13e	0,0301	36dg	0,0164	84d	0,00959
13f	0,386	36dh	0,0034	84e	0,00818

Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)
13g	0,00479	36di	0,00923	84f	0,0134
13h	0,0106	36dj	0,00891	85	0,00477
13i	0,00275	36dk	0,00905	85a	0,00313
13j	0,0178	36dl	0,00399	85b	0,00526
13k	0,0179	36dm	0,0298	85c	0,00509
13l	0,0108	36dn	0,0138	85d	0,00323
13m	0,0532	36do	0,0277	85e	0,0183
13n	0,997	36dp	0,0106	85f	0,0202
13o	0,0287	36dq	0,0245	85g	0,0259
13p	0,00202	36dr	0,294	85h	0,0426
13q	0,00192	36ds	0,000973	85i	0,0153
13r	0,00198	36dt	0,00037	85j	0,0124
13s	0,00846	36du	0,0152	86	0,00247
13t	0,172	36dv	0,0043	86a	0,00522
13u	0,00477	36dw	0,00624	86b	0,00725
14	0,0465	36dx	0,00262	86c	0,00247
14a	0,0136	36dy	0,00636	86d	0,00382
14b	1,39	36dz	0,00277	86e	0,00223
14c	0,0401	36ea	0,00884	86f	0,00345
14d	0,0143	36eb	0,00311	87	0,00487
14e	0,11	36ec	0,00321	87a	0,0887
14f	0,189	36ed	0,00704	87b	0,0177
14g	0,0857	36ee	0,00958	87c	0,00775
14h	0,14	36ef	0,00841	87d	0,0177
14i	0,0339	36eg	0,00877	87e	0,0103
14j	0,0129	37a	0,026	87f	0,00907
14k	0,275	37b	0,0124	88	0,0321
14l	0,0137	37c	0,0033	88a	0,00448
14m	0,0143	37d	0,00439	88b	0,0567
14n	0,0363	37e	0,0049	88c	0,047

Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)
14o	0,0217	37f	0,12	88d	0,004
14p	0,537	37g	0,0179	88e	0,131
14q	0,0265	37h	0,0198	89	0,485
14r	0,0103	37i	0,00379	90	0,0189
14s	0,122	37j	0,0309	91	0,00498
14t	0,197	37k	0,0161	91a	0,00198
14u	0,123	37l	0,032	91b	0,00521
14v	0,0823	37m	0,0506	91c	0,00368
14w	0,208	37n	0,0393	91d	0,00356
14x	0,63	37o	0,033	92	0,00793
14y	0,152	37p	0,00534	92a	0,00551
14z	0,171	37q	0,00294	92b	0,00746
14aa	0,0186	37r	0,00162	92c	0,0078
15	0,00154	37s	0,00756	92d	0,00807
15a	0,000591	37t	0,00889	92e	0,00599
16	0,00142	37u	0,000395	92f	0,00625
16a	0,0101	37v	0,00549	93	0,00505
16b	0,00577	37w	0,00137	93a	0,00303
16c	0,0016	37x	0,00944	93b	0,0023
16d	0,00364	37y	0,00686	93c	0,0029
16e	0,0214	37z	0,00481	93d	0,000818
16f	0,0212	37aa	0,00567	93e	0,00541
16g	0,0176	37ab	0,00488	94a	0,0136
16h	0,186	37ac	0,0438	94b	0,0122
16i	0,845	37ad	0,00263	94c	0,0118
17	0,00116	37ae	0,00952	94d	0,011
17a	0,000942	37af	0,0233	94e	0,0135
17b	0,000584	37ag	0,0134	94f	0,0151
17c	0,00179	38	0,00131	94g	0,0127
18	0,00135	38a	0,000918	94h	0,0116

Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)
18a	0,00714	39	0,000351	94i	0,0121
18b	0,0147	39a	0,000502	94j	0,00605
18c	0,032	40	0,00436	94k	0,0106
18d	0,0151	40a	0,00221	95a	0,0139
18e	0,000654	41	0,0308	95b	0,019
18f	0,12	42	0,000705	95c	0,00706
18g	0,00123	42a	0,00261	95d	0,0126
18h	0,00664	42b	0,00535	95e	0,016
18i	0,00555	42c	0,0036	95f	0,0109
18j	0,0303	42d	0,000607	95g	0,0164
18k	0,0113	42e	0,00257	95h	0,013
18l	0,0102	42f	0,00264	95i	0,00479
18m	0,00315	42g	0,00401	95j	0,0131
19	0,00131	42h	0,00412	95k	0,0272
19a	0,00425	43	0,00539	95l	0,00109
19b	0,00119	43a	0,00479	95m	0,00202
19c	0,0214	43b	0,00751	95n	0,000668
19d	0,00318	43c	0,0288	95o	0,00473
19e	0,00135	43d	0,011	95p	0,00543
19f	0,0804	43e	0,188	95q	0,00168
19g	0,000274	43f	0,0392	95r	0,00631
19h	0,00246	43g	0,029	96a	0,0177
19i	0,00152	43h	0,133	96b	0,0268
19j	0,0199	43i	0,102	96c	0,0272
19k	0,00415	43j	0,012	96d	0,0209
19l	0,00152	43k	0,0257	96e	0,00862
19m	0,000944	43l	0,0236	97	0,0882
20	0,0128	43m	0,00531	98a	0,011
20a	0,0163	43n	0,0119	98b	0,00413
20b	0,874	43o	0,0157	98c	0,0267

Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)	Ej. No.	Prueba (a)(ii) CI_{50} (μM)
20c	0,00559	43p	0,0555	98d	0,00441
20d	0,0133	43q	0,028	98e	0,00335
21	0,0253	43r	0,0577	98f	0,00229
21a	0,0378	43s	0,00629	98g	0,0127
21b	0,0133	43t	0,00545	98h	0,00362
21c	0,0234	44	0,0234	98i	0,0285
22	0,503	45	0,00717	98j	0,00374
23	0,00492	46	0,00456	98k	0,00246
23a	0,00459	46a	0,0126	98l	0,00789
23b	0,197	47	0,0155	99a	0,0438
23c	0,000831	47a	0,0054	99b	0,0316
23d	0,00534	47b	0,0149	99c	0,239
23e	0,00876	48	0,00072	99d	0,219
23f	0,0199	48a	0,00116	99e	0,0317
23g	1,21	49	0,00187	99f	0,00589
23h	0,00808	49a	0,00267	99g	0,0152
23i	0,0254	50	0,0104	99h	0,0782
23j	0,0314	50a	0,00794	99i	0,0594
23k	1,14	51	0,00332	99j	0,0124

Los compuestos pueden seleccionarse adicionalmente en base a otras propiedades biológicas o físicas que pueden medirse con técnicas conocidas en la técnica y que pueden utilizarse en la evaluación o selección de compuestos para su aplicación terapéutica o profiláctica.

Los compuestos de la presente invención son ventajosos, ya que poseen actividad farmacológica. En particular, los compuestos de la presente invención modulan (en particular, inhiben) la mTOR quinasa y/o las enzimas fosfatidilinositol-3-quinasa (PI3K), tales las enzimas PI3K Clase Ia (por ejemplo PI3Kalfa, PI3Kbeta y PI3Kdelta) y la enzima PI3K Clase Ib (PI3Kgamma). Más particularmente, los compuestos de la presente invención modulan (en particular, inhiben) la mTOR quinasa. Más particularmente, los compuestos de la presente invención modulan (en particular, inhiben) una o más enzimas PI3K. Las propiedades

inhibitorias de los compuestos de fórmula (I) pueden demostrarse utilizando los procedimientos de prueba establecidos en esta sección y en la sección experimental. Por lo tanto, los compuestos de fórmula (I) pueden utilizarse en el tratamiento (terapéutico o profiláctico) de afecciones/enfermedades en animales humanos y no humanos que son mediadas por la mTOR quinasa y/o una o más enzimas PI3K, y en particular mediadas por la mTOR quinasa.

La invención también proporciona una composición farmacéutica que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en asociación con un portador o diluyente farmacéuticamente aceptable.

Las composiciones de la invención pueden presentarse en formas adecuadas para uso oral (por ejemplo, como comprimidos, grageas, cápsulas duras o blandas, suspensiones acuosas u oleosas, emulsiones, gránulos o polvos dispersables, jarabes o elixires), para uso tópico (por ejemplo, como cremas, ungüentos, geles o soluciones o suspensiones acuosas u oleosas), para administración mediante inhalación (por ejemplo, como un polvo dividido finamente o un aerosol líquido), para administración mediante insuflación (por ejemplo, como un polvo dividido finamente) o para administración parenteral (por ejemplo, como una solución oleosa u acuosa estéril para dosificación intravenosa, subcutánea, intraperitoneal o intramuscular o como un supositorio para dosificación rectal).

Las composiciones de la invención pueden obtenerse mediante procedimientos convencionales utilizando excipientes farmacéuticos convencionales bien conocidos en la técnica. De esta manera, las composiciones para uso oral pueden contener, por ejemplo, uno o más agentes colorantes, edulcorantes, saborizantes y/o conservantes.

La cantidad de ingrediente activo que se combina con uno o más excipientes para producir una forma de dosificación única variará necesariamente según el huésped tratado y la vía de administración particular. Por ejemplo, una formulación para la administración oral en humanos contendrá generalmente, por ejemplo, entre 1 mg a 1 g de agente activo (más adecuadamente de 1 a 250 mg, por ejemplo de 1 a 100 mg) combinado con una cantidad apropiada y conveniente de excipientes, la cual puede variar de entre aproximadamente 5 a aproximadamente 98 por ciento en peso de la composición total.

El tamaño de la dosis con fines terapéuticos o profilácticos de un compuesto de Fórmula I naturalmente variará de acuerdo con la naturaleza y gravedad de los síntomas o condiciones, la edad y el sexo del animal o paciente y la vía de administración de acuerdo con principios bien conocidos en la medicina.

Cuando se utiliza un compuesto de la fórmula (I) con fines terapéuticos o profilácticos generalmente se administrará en una dosis diaria entre, por ejemplo, 1 mg/kg a 100 mg/kg por kilo de peso corporal, el cual podrá administrarse en dosis divididas si es necesario. En general se administrarán dosis más bajas cuando se emplee una vía parenteral. Así, por ejemplo, para la administración intravenosa se utilizará generalmente una dosis entre por ejemplo, 1 mg/kg a 25 mg/kg por kilo de peso corporal. En forma similar, para la administración por inhalación, se utilizará una dosis entre, por ejemplo, 1 mg/kg a 25 mg/kg por kilo de peso corporal. Típicamente, las formas de dosificación unitarias contendrán aproximadamente 10 mg a 0,5 g de un compuesto de esta invención.

Tal como se indica en la presente, se sabe que la mTOR quinasa y las enzimas PI3K desempeñan un papel en la tumorigénesis, así como en numerosas enfermedades. Hemos encontrado que los compuestos de fórmula (I) presentan una potente actividad anti-tumoral que se cree se obtiene mediante la inhibición de la mTOR quinasa y/o una o más de las enzimas PI3K.

Por lo tanto, los compuestos de la presente invención son de valor como agentes antitumorales. Particularmente, los compuestos de la presente invención son de valor como agentes anti-proliferativos, apoptóticos y/o antiinvasivos en la contención y/o el tratamiento de enfermedades de tumor sólido y/o líquido. Particularmente, se espera que los compuestos de la presente invención sean útiles en la prevención o tratamiento de los tumores sensibles a la inhibición de mTOR y/o una o más de las enzimas PI3K, tales como las enzimas PI3K de la Clase Ia y/o las enzimas PI3K de la Clase Ib. Adicionalmente, se espera que los compuestos de la presente invención sean útiles en la prevención o tratamiento de los tumores que son mediados exclusivamente o en parte por la mTOR y/o una o más de las enzimas PI3K, tales como las enzimas PI3K de la Clase Ia y/o las enzimas PI3K de la Clase Ib. Los compuestos, por lo tanto, pueden utilizarse para producir un efecto inhibitorio de la enzima mTOR en un animal de sangre caliente que necesita dicho tratamiento. Ciertos compuestos pueden utilizarse para producir un efecto inhibitorio de la enzima PI3K en un animal de sangre caliente que necesita dicho tratamiento.

Tal como se indica en la presente, los inhibidores de la mTOR quinasa y/o una o más enzimas PI3K pueden tener valor terapéutico para el tratamiento de una enfermedad proliferativa tal como cáncer y en particular tumores sólidos tales como carcinoma y sarcomas y las leucemias y malignidades linfoides y en particular para el tratamiento de, por ejemplo, cáncer de mama, colorrectal, de pulmón (incluyendo cáncer de pulmón de célula pequeña,

cáncer de pulmón de célula no pequeña y cáncer bronquioloalveolar) y de próstata y cáncer del conducto biliar, óseo, de vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículo, tiroides, útero, cuello de útero y vulva y de leucemias [incluyendo leucemia linfocítica aguda (LLA) y leucemia mielógena crónica (LMC)], mieloma múltiple y linfomas.

Los efectos anticáncer que son por lo tanto útiles en el tratamiento de cáncer en un paciente incluyen, a modo no taxativo, efectos antitumorales, la tasa de respuesta, el tiempo que transcurre hasta comenzar el avance de la enfermedad y la tasa de supervivencia. Los efectos antitumorales de un método de tratamiento de la presente invención incluyen, a modo no taxativo, la inhibición del crecimiento tumoral, el retardo del crecimiento tumoral, el retroceso del tumor, la reducción del tumor, el tiempo que transcurre hasta el nuevo crecimiento del tumor luego de la finalización del tratamiento y la ralentización del avance de la enfermedad. Los efectos anticáncer incluyen el tratamiento profiláctico así como también el tratamiento de la enfermedad existente.

Un inhibidor de la mTOR quinasa, o una sal farmacéuticamente aceptable del mismo, también puede ser útil para el tratamiento de pacientes con cánceres, incluidos, a modo no taxativo, malignidades hematológicas tales como leucemia, mieloma múltiple, linfomas tales como enfermedad de Hodgkin, linfomas no Hodgkin (incluyendo linfoma de células del manto) y síndromes mielodisplásicos y también tumores sólidos y sus metástasis tales como cáncer de mama, cáncer de pulmón (cáncer de pulmón de células no pequeñas (CPCNP), cáncer de pulmón de células pequeñas (CPCP), carcinoma de células escamosas), cáncer de endometrio, tumores del sistema nervioso central tales como gliomas, tumor neuroepitelial disembrioplásico, glioblastoma multiforme, gliomas mixtos, meduloblastoma, retinoblastoma, neuroblastoma, germinoma y teratoma, cánceres del tracto gastrointestinal tales como cáncer gástrico, cáncer esofágico, carcinoma hepatocelular (hígado), colangiocarcinomas, carcinomas de colon y recto, cánceres del intestino delgado, cánceres pancreáticos, cánceres de la piel tales como melanomas (en particular melanoma metastásico), cánceres de tiroides, cánceres de cabeza y cuello y cánceres de las glándulas salivares, próstata, testículos, ovario, cuello del útero, útero, vulva, vejiga, riñón (incluidos carcinoma de células renales, oncocitoma de células claras y renal), carcinomas de células escamosas, sarcomas tales como osteosarcoma, condrosarcoma, leiomiosarcoma, sarcoma de tejidos blandos, sarcoma de Ewing, tumor estromal gastrointestinal (TEGI), sarcoma de Kaposi y cánceres pediátricos tales como rabdomiosarcomas y neuroblastomas.

Se espera que los compuestos de la presente invención y los métodos de tratamiento que comprenden la administración o el uso de un inhibidor de mTOR quinasa, o una sal farmacéuticamente aceptable del mismo, sean particularmente útiles para el tratamiento de pacientes con cáncer de pulmón, cáncer de próstata, melanoma, cáncer de ovario, cáncer de mama, cáncer de endometrio, cáncer de riñón, cáncer gástrico, sarcomas, cánceres de cabeza y cuello, tumores del sistema nervioso central y su metástasis y también para el tratamiento de pacientes con leucemia mielógena aguda.

De acuerdo con un aspecto adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso como un medicamento en un animal de sangre caliente tal como el hombre.

De acuerdo con un aspecto adicional de la invención, se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso en la producción de un efecto antiproliferativo en un animal de sangre caliente tal como el hombre.

De acuerdo con un aspecto adicional de la invención, se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso en la producción de un efecto apoptótico en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso en un animal de sangre caliente tal como el hombre como un agente antiinvasivo en la contención y/o el tratamiento de una enfermedad proliferativa tal como cáncer.

De acuerdo con un aspecto adicional de la invención, se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para la producción de un efecto antiproliferativo en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en la fabricación de un medicamento para su uso en la producción de un efecto antiproliferativo en un animal de sangre caliente tal como el hombre.

De acuerdo con un aspecto adicional de la invención, se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para la producción de un efecto apoptótico en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en la fabricación de un medicamento para su uso en la producción de un efecto apoptótico en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en la fabricación de un medicamento para su uso en un animal de sangre caliente tal como el hombre como un agente antiinvasivo en la contención y/o el tratamiento de una enfermedad proliferativa tal como cáncer.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método para producir un efecto antiproliferativo en un animal de sangre caliente, tal como el hombre, que necesita dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método para producir un efecto antiinvasivo mediante la contención y/o el tratamiento de una enfermedad de tumor sólido en un animal de sangre caliente, tal como el hombre, que necesita dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente.

De acuerdo con un aspecto adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en la fabricación de un medicamento para su uso en la prevención o tratamiento de una enfermedad proliferativa tal como cáncer en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método para la prevención o tratamiento de una enfermedad proliferativa tal como cáncer en un animal de sangre caliente, tal como el hombre, que necesita dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto

de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente.

De acuerdo con un aspecto adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso en la prevención o tratamiento de los tumores sensibles a la inhibición de la mTOR quinasa y/o una o más enzimas PI3K (tal como la enzima PI3K de la Clase Ia y/o la enzima PI3K de la Clase Ib) que participan en las etapas de la transducción de señales que conducen a la proliferación, supervivencia, invasividad y capacidad migratoria de células tumorales.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en la fabricación de un medicamento para su uso en la prevención o tratamiento de los tumores sensibles a la inhibición de la mTOR quinasa y/o una o más enzimas PI3K (tal como la enzima PI3K de la Clase Ia y/o la enzima PI3K de la Clase Ib) que participan en las etapas de la transducción de señales que conducen a la proliferación, supervivencia, invasividad y capacidad migratoria de células tumorales.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método para la prevención o tratamiento de los tumores sensibles a la inhibición de la mTOR quinasa y/o una o más enzimas PI3K (tal como la enzima PI3K de la Clase Ia y/o la enzima PI3K de la Clase Ib) que participan en las etapas de la transducción de señales que conducen a la proliferación, supervivencia, invasividad y capacidad migratoria de células tumorales que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente.

De acuerdo con un aspecto adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso para proporcionar un efecto inhibitorio de la mTOR quinasa y/o un efecto inhibitorio de la enzima PI3K (tal como un efecto inhibitorio de la enzima PI3K de la Clase Ia y/o la enzima PI3K de la Clase Ib).

De acuerdo con una característica adicional de este aspecto de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en la fabricación de un medicamento para su uso para proporcionar un efecto inhibitorio de la mTOR quinasa y/o un efecto inhibitorio de la

enzima PI3K (tal como un efecto inhibitorio de la enzima PI3K de la Clase Ia y/o la enzima PI3K de la Clase Ib).

De acuerdo con un aspecto adicional de la invención también se proporciona un método para proporcionar un efecto inhibitorio de la mTOR quinasa y/o un efecto inhibitorio de la enzima PI3K (tal como un efecto inhibitorio de la enzima PI3K de la Clase Ia y/o la enzima PI3K de la Clase Ib) que comprende administrar una cantidad efectiva de un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso en el tratamiento de cáncer, enfermedades inflamatorias, enfermedades obstructivas de las vías respiratorias, enfermedades inmunológicas o enfermedades cardiovasculares.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso en el tratamiento de tumores sólidos tales como carcinoma y sarcomas y las leucemias y malignidades linfoides.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso en el tratamiento de cáncer de mama, colorrectal, de pulmón (incluyendo cáncer de pulmón de célula pequeña, cáncer de pulmón de célula no pequeña y cáncer bronquioloalveolar) y de próstata.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso en el tratamiento de cáncer del conducto biliar, óseo, de vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículo, tiroides, útero, cuello de útero y vulva y de leucemias (incluidas LLA y LMC), mieloma múltiple y linfomas.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso en el tratamiento de cáncer del conducto biliar, óseo, de vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, endometrio,

páncreas, piel, testículo, tiroides, útero, cuello de útero y vulva y de leucemias (incluidas LLA y LMC), mieloma múltiple y linfomas.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente para su uso en el tratamiento de cáncer de pulmón, cáncer de próstata, melanoma, cáncer de ovario, cáncer de mama, cáncer de endometrio, cáncer de riñón, cáncer gástrico, sarcomas, cánceres de cabeza y cuello, tumores del sistema nervioso central y su metástasis y también para el tratamiento de leucemia mielógena aguda.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en la fabricación de un medicamento para su uso en el tratamiento de cáncer, enfermedades inflamatorias u obstructivas de las vías respiratorias, inmunes o cardiovasculares.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en la fabricación de un medicamento para su uso en el tratamiento de tumores sólidos tales como carcinomas y sarcomas y las leucemias y malignidades linfoides.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en la fabricación de un medicamento para su uso en el tratamiento de cáncer de mama, colorrectal, de pulmón (incluyendo cáncer de pulmón de célula pequeña, cáncer de pulmón de célula no pequeña y cáncer bronquioloalveolar) y de próstata.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en la fabricación de un medicamento para su uso en el tratamiento de cáncer del conducto biliar, óseo, de vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículo, tiroides, útero, cuello de útero y vulva y de leucemias (incluidas LLA y LMC), mieloma múltiple y linfomas.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente en la fabricación de un medicamento para su uso en el tratamiento de cáncer de pulmón, cáncer de próstata, melanoma, cáncer de ovario, cáncer de mama, cáncer de endometrio, cáncer de riñón, cáncer gástrico, sarcomas, cánceres de cabeza y cuello,

tumores del sistema nervioso central y su metástasis y también para el tratamiento de leucemia mielógena aguda.

De acuerdo con una característica adicional de la invención se proporciona un método para el tratamiento de cáncer, enfermedades inflamatorias u obstructivas de las vías respiratorias, inmunes o cardiovasculares en un animal de sangre caliente tal como el hombre que necesita dicho tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente.

De acuerdo con una característica adicional de la invención se proporciona un método para el tratamiento de tumores sólidos tales como carcinoma y sarcomas y las leucemias y malignidades linfoides en un animal de sangre caliente tal como el hombre que necesita dicho tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente.

De acuerdo con una característica adicional de la invención se proporciona un método para el tratamiento de cáncer de mama, colorrectal, de pulmón (incluyendo cáncer de pulmón de célula pequeña, cáncer de pulmón de célula no pequeña y cáncer bronquioloalveolar) y de próstata en un animal de sangre caliente tal como el hombre que necesita dicho tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente.

De acuerdo con una característica adicional de la invención se proporciona un método para el tratamiento de cáncer del conducto biliar, óseo, de vejiga, cabeza y cuello, riñón, hígado, tejido gastrointestinal, esófago, ovario, páncreas, piel, testículo, tiroides, útero, cuello de útero y vulva y de leucemias (incluidas LLA y LMC), mieloma múltiple y linfomas en un animal de sangre caliente tal como el hombre que necesita dicho tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente.

De acuerdo con una característica adicional de la invención se proporciona un método para el tratamiento de cáncer de pulmón, cáncer de próstata, melanoma, cáncer de ovario, cáncer de mama, cáncer de endometrio, cáncer de riñón, cáncer gástrico, sarcomas, cánceres de cabeza y cuello, tumores del sistema nervioso central y su metástasis y leucemia mielógena aguda en un animal de sangre caliente tal como el hombre que necesita dicho tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente.

Como se señala en la presente, los efectos *in vivo* de un compuesto de fórmula (I) pueden ser ejercidos, en parte, por uno o más metabolitos que se forman en el cuerpo humano o animal después de la administración de un compuesto de fórmula (I).

La invención adicionalmente se refiere a terapias de combinación en donde un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, o una composición farmacéutica o formulación que comprende un compuesto de fórmula (I), se administra concurrentemente o secuencialmente o como una preparación combinada con otro tratamiento utilizado en el control de una enfermedad oncológica.

En particular, el tratamiento definido anteriormente en la presente puede aplicarse como terapia única o puede implicar, además del compuesto de la invención, cirugía convencional o radioterapia o quimioterapia. Por lo tanto, los compuestos de la invención también pueden utilizarse en combinación con agentes terapéuticos existentes para el tratamiento de cáncer.

Los agentes adecuados a ser utilizados en combinación incluyen

(i) fármacos antiproliferativos/antineoplásicos y combinaciones de los mismos, tal como se emplean en la oncología médica, como agentes alquilantes (por ejemplo cis-platina, carboplatina, ciclofosfamida, mostaza de nitrógeno, melfalán, clorambucil, busulfán y nitrosoureas); antimetabolitos (por ejemplo, antifolatos como fluoropirimidinas tal como 5-fluorouracilo y tegafur, raltitrexed, metotrexato, citosina arabinosida, hidroxiurea y gemcitabina); antibióticos antitumorales (por ejemplo: antraciclinas como adriamicina, bleomicina, doxorubicina, daunomicina, epirubicina, idarubicina, mitomicina-C, dactinomicina y mitramicina); agentes antimitóticos (por ejemplo alcaloides de la vinca como vincristina, vinblastina, vindesina y vinorelbina y taxoides como paclitaxel y taxotere); e inhibidores de topoisomerasa (por ejemplo epipodofilotoxinas como etoposida y teniposida, amsacrina, topotecán y camptotecinas);

(ii) agentes citostáticos tales como antiestrógenos (por ejemplo tamoxifeno, toremifeno, raloxifeno, droloxifeno y yodoxifeno), reguladores hacia abajo del receptor de estrógenos (por ejemplo, fulvestrant), antiandrógenos (por ejemplo bicalutamida, flutamida, nilutamida y acetato de ciproterona), antagonistas de LHRH o agonistas de LHRH (por ejemplo goserelina, leuprorelina y buserelina), progestógenos (por ejemplo acetato de megestrol), inhibidores de aromatasa (por ejemplo anastrozol, letrozol, vorazol y exemestano) e inhibidores de 5α-reductasa como finasterida;

(iii) agentes anti-invasión (por ejemplo inhibidores de la familia de las c-Src quinasas como 4-

(6-cloro-2,3-metilenodioxianilino)-7-[2-(4-metilpiperazin-1-il)etoxi]-5-tetrahigotairan-4-iloxiquinazolina (AZD0530; Solicitud de Patente Internacional WO 01/94341) y *N*-(2-cloro-6-metilfenil)-2-{6-[4-(2-hidroxietil)piperazin-1-il]-2-metilpirimidin-4-ilamino)tiazol-5-carboxamida (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661) e inhibidores de metaloproteinasa tales como marimastat e inhibidores de la función del receptor activador del plasminógeno de uroquinasa);

(iv) inhibidores de la función del factor de crecimiento: por ejemplo, dichos inhibidores incluyen anticuerpos del factor de crecimiento, anticuerpos del receptor del factor de crecimiento (por ejemplo el anticuerpo anti-erbB2 trastuzumab) [Herceptin™] y el anticuerpo anti erbB1 cetuximab [C225]; dichos inhibidores también incluyen, por ejemplo, inhibidores de tirosina quinasa, por ejemplo, inhibidores de la familia del factor de crecimiento epidérmico (por ejemplo, inhibidores de la familia de la tirosina quinasa EGFR como *N*-(3-cloro-4-fluorofenil)-7-metoxi-6-(3-morfolinopropoxi)quinazolin-4-amina (gefitinib, ZD1839), *N*-(3-etinilfenil)-6,7-bis(2-metoxietoxi)quinazolin-4-amina (erlotinib, OSI-774) y 6-acrilamido-*N*-(3-cloro-4-fluorofenil)-7-(3-morfolinopropoxi)quinazolin-4-amina (CI 1033) e inhibidores de tirosina quinasa de erbB2 tales como lapatinib), inhibidores de la familia del factor de crecimiento de hepatocitos, inhibidores de la familia del factor de crecimiento derivado de plaquetas tales como imatinib, inhibidores de serina/treonina quinasas (por ejemplo inhibidores de la señalización de Ras/Raf tales como inhibidores de la farnesiltransferasa, por ejemplo sorafenib (BAY 43-9006)), inhibidores de la señalización celular a través MEK y/o AKT quinasas;

(v) agentes antiangiogénicos como los que inhiben los efectos del factor de crecimiento endotelial vascular, [por ejemplo el anticuerpo del factor de crecimiento celular endotelial anti-vascular bevacizumab [Avastin™] e inhibidores de tirosina quinasa del receptor VEGF tales como 4-(4-bromo-2-fluoroanilino)-6-metoxi-7-(1-metilpiperidin-4-ilmetoxi)quinazolina (ZD6474; Ejemplo 2 en WO 01/32651), 4-(4-fluoro-2-metilindol-5-iloxi)-6-metoxi-7-(3-pirrolidin-1-ilpropoxi)quinazolina (AZD2171; Ejemplo 240 en WO 00/47212), vatalanib (PTK787; WO 98/35985) y SU11248 (sunitinib; WO 01/60814) y compuestos que operan mediante otros mecanismos (por ejemplo: linomida, inhibidores de la función integrina $\alpha v\beta 3$ y angiostatina);

(vi) agentes que producen daños vasculares como Combretastatina A4 y los compuestos revelados en las Solicitudes de Patente Internacionales WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 y WO 02/08213;

(vii) terapias anti-sentido, por ejemplo, aquellas dirigidas a los objetivos mencionados anteriormente, como ISIS 2503, un anti-sentido anti-ras;

(viii) abordajes de terapia genética, incluyendo por ejemplo, el reemplazo de genes aberrantes como el aberrante p53 o los aberrantes BRCA1 o BRCA2, los abordajes de la GDEPT (terapia de profármaco de enzimas dirigidas por genes) como los que emplean citosina deaminasa, timidina quinasa o una enzima nitrorreductasa bacterial y abordajes para incrementar la tolerancia de los pacientes a la quimioterapia o la radioterapia, como la terapia genética de resistencia a múltiples fármacos; y

(ix) abordajes de inmunoterapia, incluyendo, por ejemplo, abordajes *ex vivo* e *in vivo* para incrementar la inmunogenicidad de las células tumorales de los pacientes, como en la transfección con citoquinas como interleuquina 2, interleuquina 4 o el factor de estimulación de la colonia de granulocitos-macrófagos, abordajes para disminuir la anergia de las células T, abordajes que utilizan células inmunes transfectadas como células dendríticas transfectadas con citoquina, abordajes que emplean líneas de células tumorales transfectadas con citoquinas y abordajes que emplean anticuerpos anti-idiotípicos.

La presente invención se ilustrará adicionalmente mediante los siguientes ejemplos.

A menos que se indique de otra forma, los materiales de partida se encontraban comercialmente disponibles. Todos los disolventes y reactivos comerciales eran de laboratorio y se usaron tal como se recibieron.

En los ejemplos, los espectros de ^{1}H NMR se registraron en un instrumento Bruker DPX 300 (300 MHz), un instrumento Bruker DRX 400 (400 MHz) o un instrumento Bruker DRX 500 (500 MHz). Los picos centrales de cloroformo-d (δ_H 7,27 ppm), dimetilsulfóxido-d_6 (δ_H 2,50 ppm) o acetona-d_6 (δ_H 2,05 ppm) se utilizaron como referencias internas. Se utilizaron las siguientes abreviaturas: s, singulete; d, doblete; t, triplete; q, cuartete; m, multiplete; br, ancho.

La cromatografía en columna se llevó a cabo utilizando gel de sílice (0,04-0,063 mm, Merck). En general, se utilizó una columna Kromasil KR-100-5-C18 de fase inversa (250 x 20 mm, Akzo Nobel) para la HPLC preparativa con mezclas de acetonitrilo y agua [que contenían ácido trifluoroacético (TFA) al 0,1%] utilizadas como eluyente a una tasa de flujo de 10 mL/min.

Se utilizaron los siguientes métodos para el análisis de cromatografía líquida (LC) / espectro de masas (MS):

HPLC: Agilent 1100 o Waters Alliance HT (2790 y 2795)

Espectrómetro de Masas: Waters ZQ ESCi

Columna de HPLC

La columna de HPLC convencional utilizada fue Phemonenex Gemini C18 5µm, 50 x 2 mm.

Métodos de HPLC ácidos

Las fases móviles son: Fase Móvil A: Agua

Fase Móvil B: Acetonitrilo

Fase Móvil C: Ácido fórmico al 1% en 50:50 Agua:MeCN (v/v)

A cada método siguió un rápido equilibrio utilizando una tasa de flujo de 5 mL durante 0,45 min.

Se encuentran disponibles cuatro métodos de HPLC genéricos:

Método ácido monitor de 5 minutos

Tiempo/min	Fase Móvil A:	Fase Móvil B:	Fase Móvil C:	Curva	Tasa de Flujo/mL/min
0,00	95	0	5	1	1,1
4	0	95	5	6	1,1
4,5	0	95	5	6	1,1

Método ácido temprano para compuestos que eluyen primero

Tiempo/min	Fase Móvil A:	Fase Móvil B:	Fase Móvil C:	Curva	Tasa de Flujo/mL/min
0,00	95	0	5	1	1,1
4	57,5	37,5	5	6	1,1
4,5	57,5	37,5	5	6	1,1

Método ácido medio para compuestos que eluyen en el medio

Tiempo/min	Fase Móvil A:	Fase Móvil B:	Fase Móvil C:	Curva	Tasa de Flujo/mL/min
0,00	95	0	5	1	1,1
0,01	67,5	27,5	5	6	1,1
4,5	27,5	67,5	5	6	1,1

Método ácido tardío para compuestos que eluyen más tarde

Tiempo/min	Fase Móvil	Fase Móvil	Fase Móvil	Curva	Tasa de

	A:	B:	C:		Flujo/mL/min
0,00	95	0	5	1	1,1
0,01	27,5	67,5	5	6	1,1
4,5	5	95	5	6	1,1

Métodos de HPLC básicos

En algunas instancias, los métodos ácidos convencionales pueden no ser adecuados para la ionización del compuesto o la separación cromatográfica necesarias. Para estos casos se encuentran disponibles cuatro métodos de HPLC básicos.

Las fases móviles utilizadas son: Fase Móvil A: Agua

Fase Móvil B: Acetonitrilo

Fase Móvil D: Amoníaco 880 al 0,1% en acetonitrilo

A cada método siguió un rápido equilibrio utilizando una tasa de flujo de 5 mL durante 0,45 min.

Método básico monitor de minutos

Tiempo/min	Fase Móvil A:	Fase Móvil B:	Fase Móvil D:	Curva	Tasa de Flujo/mL/min
0,00	95	0	5	1	1,1
4	0	95	5	6	1,1
4,5	0	95	5	6	1,1

Método básico temprano para compuestos que eluyen primero

Tiempo/min	Fase Móvil A:	Fase Móvil B:	Fase Móvil D:	Curva	Tasa de Flujo/mL/min
0,00	95	0	5	1	1,1
4	57,5	37,5	5	6	1,1
4,5	57,5	37,5	5	6	1,1

Método básico medio para compuestos que eluyen en el medio

Tiempo/min	Fase Móvil A:	Fase Móvil B:	Fase Móvil D:	Curva	Tasa de Flujo/mL/min
0,00	95	0	5	1	1,1

0,01	67,5	27,5	5	6	1,1
4,5	27,5	67,5	5	6	1,1

Método básico tardío para compuestos que eluyen más tarde

Tiempo/min	**Fase Móvil A:**	**Fase Móvil B:**	**Fase Móvil D:**	**Curva**	**Tasa de Flujo/mL/min**
0,00	95	0	5	1	1,1
0,01	27,5	67,5	5	6	1,1
4,5	5	95	5	6	1,1

El siguiente método se utilizó para el análisis de cromatografía líquida (LC) / espectro de masas (MS):- Instrumento: Agilent 1100; Columna: Waters "Symmetry" 2,1 x 30 mm; Análisis de espectros de masa utilizando ionización química (APCI); Tasa de Flujo: 0,7 mL/min; Longitud de Onda de Absorción: 254 nm; Disolvente A: agua + 0,1% TFA; Disolvente B: acetonitrilo + 0,1% TFA ; Gradiente de Disolvente: 15-95% Disolvente B durante 2,7 minutos y luego 95% Disolvente B durante 0,3 minutos.

Se utilizaron los siguientes métodos para el análisis de LC:-

Método A:- Instrumento: Agilent 1100; Columna: Kromasil C18 de fase inversa en sílice, 100 x 3 mm, tamaño de partícula 5µm; Disolvente A: 0,1% TFA/agua, disolvente B: 0,08% TFA/acetonitrilo; Tasa de flujo: 1 mL/min; Gradiente de disolvente: 10-100% Disolvente B durante 20 minutos y luego 100% Disolvente B durante 1 minuto; Longitudes de Onda de Absorción: 220, 254 y 280 nm. En general, se registró el tiempo de retención del producto.

Método B :- Instrumento: Agilent 1100; Columna: Waters "Xterra" C8 de fase inversa en sílice, 100 x 3 mm, tamaño de partícula 5µm; Disolvente A: amoníaco 0,015M en agua, el disolvente B: acetonitrilo; Tasa de flujo: 1 ml/min, el Gradiente de Disolvente: 10-100% Disolvente B durante 20 minutos y luego 100% Disolvente B durante 1 minuto; Longitud de Onda de Absorción: 220, 254 y 280 nm. En general, se registró el tiempo de retención del producto.

Las siguientes abreviaturas se usan en esta sección o en los siguientes ejemplos ilustrativos:-

HPLC Cromatografía líquida de alto rendimiento;

HBTU O-(benzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluorofosfato;

HATU O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluorofosfato;

HOBT 1-hidroxibenzotriazol;

HOAT 1-hidroxi-7-azabenzotriazol;

NMP N-metilpirrolidin-2-ona;

DMSO dimetilsulfóxido;

DMF N,N-dimetilformamida;

DMA N,N-dimetilacetamida;

THF tetrahidrofurano;

DME 1,2-dimetoxietano;

DCCI diciclohexilcarbodiimida;

MeOH metanol;

MeCN acetonitrilo;

DCM diclorometano;

DIPEA *N,N*-diisopropiletilamina;

DBU 1,8-diazabiciclo[5,4,0]undec-7-eno;

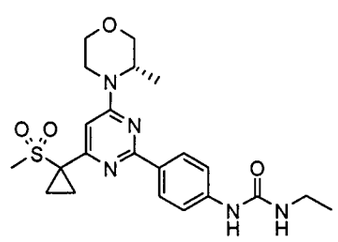
TA temperatura ambiente (aproximadamente 17 a 25°C);

tR tiempo de retención;

m/z relación masa/carga.

Los nombres químicos se generaron con el software que utiliza el Lexichem Toolkit (v. 1.60) de OpenEye Scientific Software (www.eyesopen.com) para generar nombres de acuerdo con la IUPAC.

Ejemplo 1: 3-Etil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea



A una solución de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina (200 mg, 0,60 mmol) en etanol se agregó tolueno (1,00 mL), agua (1,00 mL), ácido [4-(3-etilureido)fenil]borónico, pinacol éster (262 mg, 0,90 mmol), ortofosfato de tri-potasio (448 mg, 2,11 mmol) y paladiobis(tri-*terc*-butilfosfina) (18,55 mg, 0,04 mmol). La reacción se desgasificó y luego se purgó con nitrógeno y se

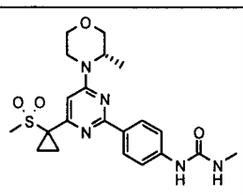
calentó a 80°C durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (10 mL) y se lavó con agua (5 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% (3,5M amoníaco en metanol) en DCM, para proporcionar el material deseado como un sólido blanco (109 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, m), 1,23 (3H, d), 1,56 (2H, s), 1,67 (2H, s), 3,14 (2H, t), 3,22 (1H, m), 3,30 (3H, s), 3,48 (1H, t), 3,63 (1H, m), 3,76 (1H, d), 3,97 (1H, d), 4,21 (1H, d), 4,57 (1H, s), 6,16 (1H, t), 6,76 (1H, s), 7,50 (2H, d), 8,20 (2H, d), 8,66 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 460 ; HPLC tR = 1,83 min

Ensayo de mTOR Quinasa (Echo): 0,00276μM

El siguiente compuesto se elaboró en forma análoga a partir del éster borónico apropiado.

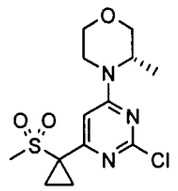
Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
1a		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	446	1,68

Ejemplo 1a: ^{1}H NMR (400,132 MHz, DMSO) δ 1,23 (3H, d), 1,31 (3H, s), 1,56 (2H, m), 1,67 (2H, m), 2,66 (3H, d), 3,22 (1H, m), 3,48 (1H, m), 3,63 (1H, m), 3,76 (1H, d), 3,97 (1H, m), 4,21 (1H, d), 4,57 (1H, s), 6,07 (1H, m), 6,76 (1H, s), 7,51 (2H, d), 8,19 (2H, d), 8,75 (1H, s)

Ensayo de mTOR Quinasa (Echo): 0,00279μM

La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina se describe a continuación.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina

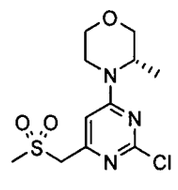


Se disolvió 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina (1,2 g, 3,9 mmol) en DMF (20 mL) y se agregó *terc*-butóxido de sodio (755 mg, 7,85 mmol) a la reacción, seguido por dibromoetano (738 mg, 3,9 mmol). La reacción se agitó a TA durante 4 horas luego a 60°C durante toda la noche. Se agregó más *terc*-butóxido de sodio (378 mg, 3,9 mmol) a la reacción, seguido por dibromoetano (369 mg, 1,9 mmol) y la reacción se agitó a 60°C durante otras 24 horas. Se agregó DCM (20 mL) y la reacción se lavó con ácido clorhídrico acuoso 2M (20 mL). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío. El sólido bruto se cromatografió sobre sílice, eluyendo con 0-50% acetato de etilo en DCM, para proporcionar el material deseado (400 mg, 31 %).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (d, 3H), 1,51 (m, 2H), 1,64 (m, 2H), 3,18 (s, 3H), 3,22 (m, 1H), 3,43 (m, 1H), 3,58 (m, 1H), 3,72 (d, 1H), 3,93 (m, 1H), 4,05 (d, 1H), 4,41 (s, 1H), 6,93 (s, 1H)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 332, HPLC tR = 1,6 min

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina



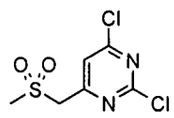
Se disolvió 2,4-dicloro-6-(metilsulfonilmetil)pirimidina (30 g, 0,13 mol) en diclorometano y se agitó (bajo nitrógeno) a -5°C. Se agregó trietilamina (17,4 mL, 0,13 mol) para proporcionar una solución marrón clara. Se disolvió (3*S*)-3-metilmorfolina en diclorometano y se agregó gota a gota manteniendo la reacción por debajo de -5°C. Luego se retiró el baño de enfriamiento y la mezcla se agitó durante 1 hora. La mezcla de reacción se calentó a reflujo durante 2 horas, luego la mezcla de reacción se lavó con agua, se secó y luego se evaporó. El material bruto se purificó mediante HPLC preparativa para proporcionar el material deseado como un sólido (19,3 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,21 - 1,23 (m, 3H), 3,11 (s, 3H), 3,19 - 3,26 (m, 1H), 3,42 - 3,49 (m, 1H), 3,58 - 3,62 (1H, m), 3,73 (d, 1H), 3,92 - 3,96 (m,

2H), 4,27 - 4,31 (m, 1H), 4,45 (s, 2H), 6,92 (s, 1H)

Espectro de LCMS: MH+ 306, tiempo de retención 1,42 min, Método 5 Min Ácido

2,4-Dicloro-6-(metilsulfonilmetil)pirimidina

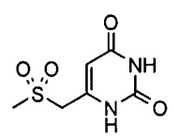


Se agregó 6-(metilsulfonilmetil)-1*H*-pirimidina-2,4-diona (132 g, 0,65 mol) a oxicloruro de fósforo (1,2 L) y la mezcla se calentó hasta alcanzar reflujo durante 16 horas, luego se enfrió hasta alcanzar temperatura ambiente. El exceso de oxicloruro de fósforo se retiró al vacío, el residuo se sometió a azeotropía con tolueno (2 x 500 mL) y se disolvió en diclorometano. Esta mezcla luego se vertió lentamente en hielo (4 L) y se agitó durante 20 minutos, luego se extrajo con diclorometano (3 x 1 L) (el material insoluble negro se retiró mediante filtración y se descartó) y acetato de etilo (2 x 1 L). Los extractos se combinaron, se secaron, luego se evaporaron para proporcionar el material deseado como un sólido marrón oscuro (51 g). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 3,13 (s, 3H), 4,79 (s, 2H), 7,87 (s, 1H)

Espectro de LCMS: MH+ 239, tiempo de retención 1,21 min, Método 5 Min Ácido

6-(Metilsulfonilmetil)-1*H*-pirimidina-2,4-diona



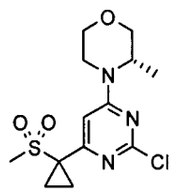
Se disolvió 6-(clorometil)-1*H*-pirimidina-2,4-diona (175 g, 1,09 mol) en DMF (2 L) y se agregó sal de sodio de ácido metanosulfínico (133,5 g, 1,31 mol). La reacción se calentó hasta alcanzar 125°C durante 2 horas y luego se dejó enfriar y la suspensión se filtró y se concentró al vacío para proporcionar un sólido amarillo. El material bruto se lavó con agua, se filtró, luego se trituró con tolueno. El sólido se filtró y luego se trituró con isohexano para proporcionar el compuesto deseado como un sólido amarillo (250 g). El material se utilizó sin purificación adicional.

6-(Clorometil)-1*H*-pirimidina-2,4-diona es un material comercialmente disponible.

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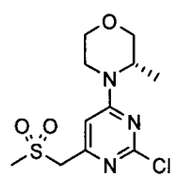
2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina también puede prepararse mediante el método descrito a continuación.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina



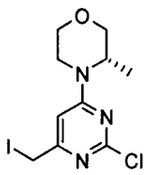
Se agregó hidróxido de sodio (solución 50% p/p) (115 g, 2877,88 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina (16 g, 52,33 mmol), 1,2-dibromoetano (13,53 ml, 156,98 mmol) y bromuro de tetrabutilamonio (1,687 g, 5,23 mmol) en tolueno (128 mL) y la suspensión resultante se agitó a TA durante 4 horas. Se agregó agua y la mezcla se extrajo dos veces con tolueno. El tolueno se secó sobre $MgSO_4$, se filtró y se evaporó. El producto bruto, 15g se purificó mediante cromatografía instantánea sobre sílice, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado (13 g) como un sólido blanco que fue idéntico a las muestras anteriores.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina



Se agregó ácido metanosulfínico, sal de sodio (11,75 g, 115,11 mmol) en una porción a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (37 g, 104,64 mmol), en acetonitrilo (900 mL) y la solución resultante se agitó a 85°C durante 24 horas. Se combinaron las capas orgánicas y se lavaron con agua (3 x 100 mL), se secaron sobre $MgSO_4$, se filtraron y el disolvente se retiró mediante evaporación para proporcionar el producto bruto como un aceite marrón oscuro, que solidificó (36 g). El sólido bruto se purificó mediante cromatografía instantánea sobre sílice, gradiente de elución de 0 a 30% acetato de etilo en DCM, para proporcionar el material deseado (22 g) como un sólido crema que fue idéntico a las muestras anteriores.

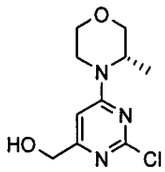
2-Cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó cloruro de metanosulfonilo (0,245 mL, 3,14 mmol) gota a gota durante un período de 5 minutos a una solución de trietilamina (0,875 mL, 6,28 mmol) y [2-cloro-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]metanol (510 mg, 2,09 mmol) en DCM (30 mL) a 0°C bajo nitrógeno. La solución resultante se agitó a TA durante 45 minutos. La mezcla de reacción se diluyó con agua (20 mL). La capa orgánica se secó ($MgSO_4$) y se filtró. Se agregó yoduro de sodio (1569 mg, 10,46 mmol) y la reacción se calentó hasta alcanzar 50°C durante 20 horas. La mezcla de reacción se filtró y se evaporó para proporcionar el material deseado (761 mg).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO) δ 1,19 - 1,25 (3H, m), 3,18 - 3,22 (1H, m), 3,40 - 3,47 (1H, m), 3,57 - 3,60 (1H, m), 3,71 (1H, d), 3,90 - 3,94 (1H, m), 3,96 - 3,98 (1H, m), 4,28 - 4,32 (3H, m), 6,94 (1H, s).
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 354; HPLC tR = 2,10 min.

2-Cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina también puede prepararse mediante la adición gota a gota de cloruro de metanosulfonilo (91 mL, 1169,52 mmol) a [2-cloro-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]metanol (190 g, 779,68 mmol) y trietilamina (163 mL, 1169,52 mmol) en DCM (2293 mL) a 0°C al aire. La solución resultante se dejó entibiar lentamente hasta alcanzar TA durante un período de 4 horas. La mezcla de reacción se aplacó con agua, se extrajo con DCM y la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar [2-cloro-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]metil metanosulfonato como una goma amarilla (251 g). Se agregó yoduro de sodio (234 g, 1560,07 mmol) a este material en acetona (3679 mL) y la suspensión resultante se agitó a TA durante 16 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM y se lavó tres veces con agua, luego con una solución saturada acuosa de tiosulfato de sodio. La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto deseado bruto (270 g). Esto se purificó mediante cromatografía para proporcionar un sólido blancuzco que se trituró adicionalmente con éter para proporcionar el material deseado que fue idéntico a las muestras anteriores.

[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metanol



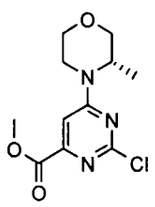
Se disolvió metil 2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina-4-carboxilato (3,15 g) en THF seco (20 mL) y se enfrió hasta alcanzar 0°C bajo nitrógeno. Una solución de borohidruro de litio (2,0M en THF, 6,09mL) se agregó gota a gota y la solución se dejó entibiar hasta alcanzar TA y se agitó durante 1 hora. La reacción se aplacó con agua (20 mL) luego se evaporó hasta secarse, el residuo se disolvió en acetato de etilo (150 mL) y se lavó con agua (150 mL) seguido por salmuera (50 mL). Los orgánicos se evaporaron hasta secarse para proporcionar el material deseado como un sólido blanco (2,44 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO) δ 1,20 - 1,21 (3H, m), 3,18 - 3,22 (1H, m), 3,40 - 3,47 (1H, m), 3,56 - 3,60 (1H, m), 3,71 (1H, d), 3,91 - 3,94 (1H, m), 3,98 (1H, d), 4,35 (3H, d), 5,51 (1H, t), 6,74 (1H, s).

Espectro de Masa; $M+H^+$ 244.

El [2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metanol también puede prepararse mediante la adición gota a gota de borohidruro de litio (2M en THF) (454 mL, 908,17 mmol) durante un período de 15 minutos a una solución de metil 2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina-4-carboxilato (235 g, 864,92 mmol) en el THF (4701 mL) a 0°C. La mezcla se agitó a TA durante 2 horas y luego se agregó lentamente agua (1500 mL). Se formó un sólido blanco que se retiró por decantación y el THF se retiró al vacío. Al residuo se agregó más agua (500 mL) y se extrajo con acetato de etilo (3 x 700 mL). Los orgánicos combinados se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron hasta proporcionar un sólido blanco que fue idéntico a las muestras anteriores.

Metil 2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina-4-carboxilato



Se disolvió metil 2,6-dicloropirimidina-4-carboxilato (5 g) en DCM (120 mL). Se disolvió (3*S*)-3-metilmorfolina (2,49 g) en trietilamina (3,70 mL) y se agregó gota a gota DCM (10

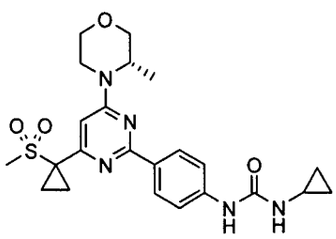
mL) a la solución durante 10 minutos. La reacción se dejó agitar a temperatura ambiente durante 1 hora. La reacción luego se evaporó hasta secarse y se disolvió en DCM (300 mL). Los orgánicos se lavaron una vez con agua (150 mL) y se secó ($MgSO_4$), se filtró y se evaporó. El material bruto se cromatografió sobre sílice, eluyendo con 2,5% metanol en DCM, para proporcionar el material deseado como un sólido blanco (3,15 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO) δ 1,22 - 1,24 (3H, m), 3,25 (1H, d), 3,41 - 3,48 (1H, m), 3,57 - 3,61 (1H, m), 3,71 (1H, d), 3,87 (3H, s), 3,91 - 3,95 (1H, m), 4,25 (1H, s), 4,45 (1H, s), 7,29 (1H, s).

Espectro de Masa: $M+H^+$ 272.

Metil 2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina-4-carboxilato también puede prepararse mediante la adición de metil 2,6-dicloropirimidina-4-carboxilato (250 g, 1207,65 mmol) al DCM (2500 mL). Se agregó trietilamina (185 mL, 1328,41 mmol) y la reacción se enfrió hasta alcanzar 0°C. Se disolvió (3*S*)-3-metilmorfolina (128 g, 1268,03 mmol) en DCM (300 mL), se agregó gota a gota durante 30 minutos y la mezcla se agitó a 5° durante toda la noche. Se agregó agua (800 mL), las fases se separaron y la capa acuosa se extrajo con DCM (300 mL). Los orgánicos combinados se lavaron con salmuera (300 mL), se secaron sobre $MgSO_4$, se filtraron y se concentraron hasta proporcionar un sólido crema. El sólido bruto se disolvió en acetato de etilo caliente (3 volúmenes) luego se agregó isohexano (5 volúmenes) y la mezcla se dejó enfriar con agitación durante el fin de semana para proporcionar el material deseado como un sólido que fue idéntico a las muestras anteriores.

Ejemplo 2: 3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea



A una solución de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato (200 mg, 0,39 mmol) en DMF (2 mL) se agregó trietilamina (0,164 mL, 1,18 mmol) seguido por ciclopropilamina (0,136 mL, 1,97 mmol) y la reacción se calentó a 50°C durante 2 horas. El disolvente se retiró bajo presión reducida para proporcionar el producto bruto que se purificó mediante cromatografía de sílice

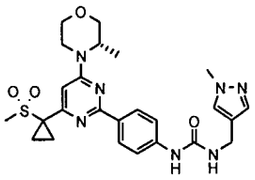
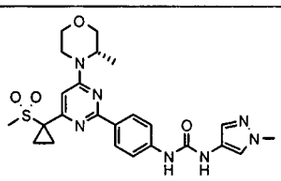
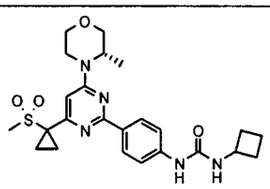
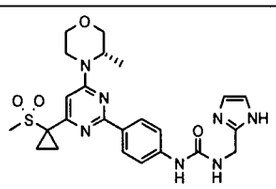
instantánea, gradiente de elución de 0 a 10% (amoníaco 3,5M en metanol) en DCM, para proporcionar el producto deseado como un sólido blanco (168 mg).

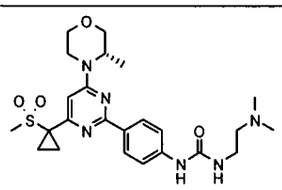
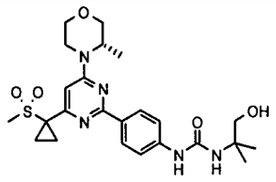
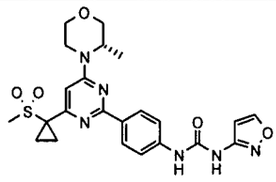
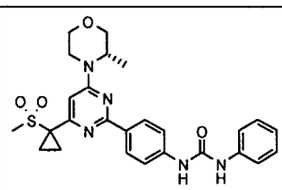
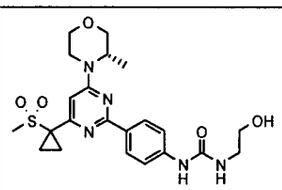
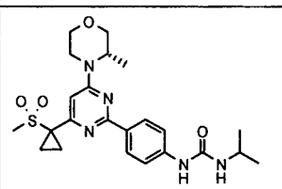
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,42 (2H, m), 0,65 (2H, m), 1,24 (3H, d), 1,56 (2H, m), 1,67 (2H, m), 2,56 (3H, m), 3,21 (1H, m), 3,48 (1H, m), 3,63 (1H, m), 3,78 (1H, d), 3,97 (1H, m), 4,21 (1H, d), 4,57 (1H, s), 6,43 (1H, d), 6,77 (1H, s), 7,51 (2H, d), 8,20 (2H, d), 8,54 (1H, s)

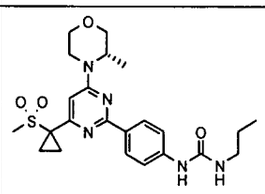
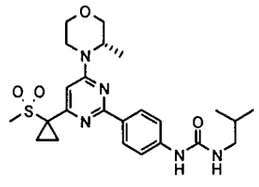
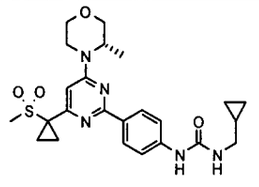
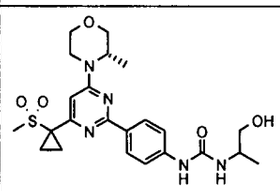
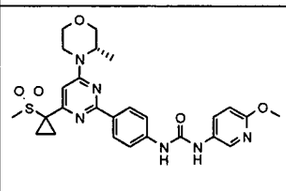
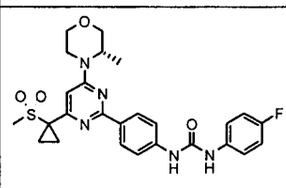
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 472; HPLC tR = 1,93 min.

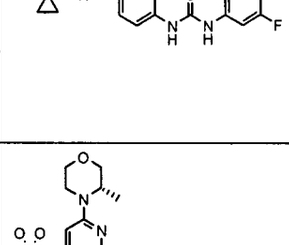
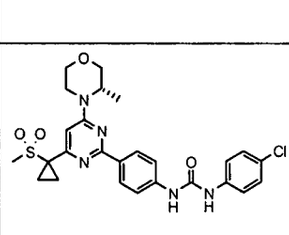
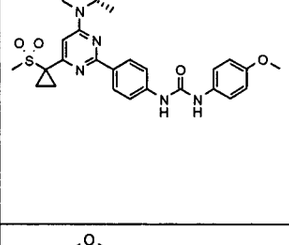
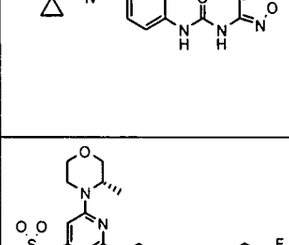
Ensayo de mTOR Quinasa (Echo): 0,0015μM

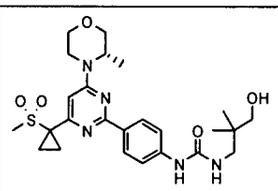
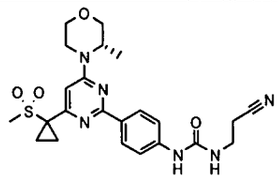
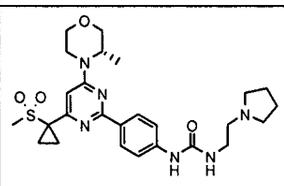
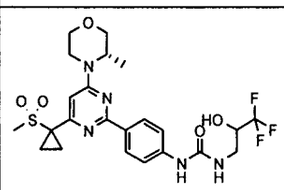
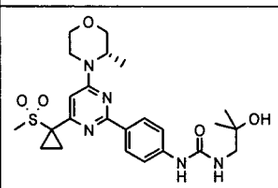
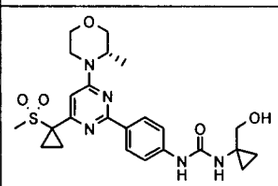
Los compuestos a continuación se prepararon en forma análoga utilizando la amina apropiada.

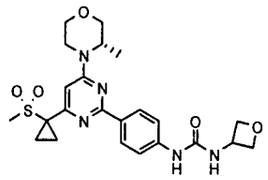
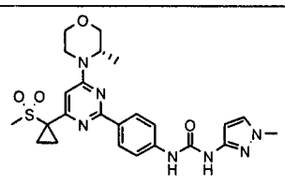
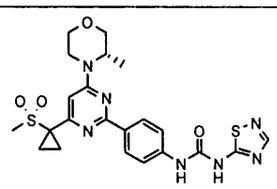
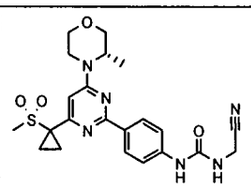
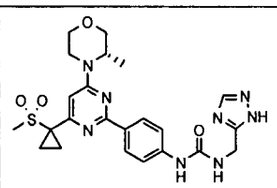
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
2a		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-[(1-metilpirazol-4-il)metil]urea	526	1,73
2b		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	512	1,75
2c		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	486	2,21
2d		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	512	1,66

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
2e		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	502	1,89
2f		3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	503	1,83
2g		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea	498	2,03
2h		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-fenil-urea	507	2,35
2i		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	475	1,54
2j		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propan-2-il-urea	473	2,0

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
2k		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propil-urea	473	2,02
2l		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea	487	2,18
2m		3-(ciclopropilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	485	2,06
2n		3-(1-hidroxipropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	489	1,63
2o		3-(6-metoxipiridin-3-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	538	2,11
2p		3-(4-fluorofenil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	525	2,4

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
2q		3-(3,4-difluorofenil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	543	2,52
2r		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(4-metilfenil)urea	521	2,49
2s		3-(4-clorofenil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	541	2,59
2t		3-(4-metoxifenil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	537	2,29
2u		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(5-metil-1,2-oxazol-3-il)urea	512	2,16
2v		3-(5-fluoropiridin-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	527	2,35

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
2w		3-(3-hidroxi-2,2-dimetilpropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	518	2,05
2x		3-(2-cianoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	485	1,91
2y		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-pirrolidin-1-iletil)urea	529	2,21
2z		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(3,3,3-trifluoro-2-hidroxipropil)urea	544	2,11
2aa		3-(2-hidroxi-2-metilpropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	530	1,91
2ab		3-[1-(hidroximetil)ciclopropil]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	502	1,81

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
2ac		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(oxetan-3-il)urea	488	2,25
2ad		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-3-il)urea	512	2,11
2ae		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	515	1,43
2af		3-(cianometil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	471	1,54
2ag		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2H-1,2,4-triazol-3-ilmetil)urea	513	1,58

El **Ejemplo 2** y el **Ejemplo 1a** pueden prepararse en forma análoga a la descrita anteriormente pero utilizando THF como un disolvente. El **Ejemplo 1a** también puede prepararse en forma análoga a la descrita anteriormente pero utilizando NMP como un disolvente.

Ejemplo 2a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,56 (2H, s), 1,67 (2H, s),

3,21 (1H, m), 3,48 (1H, t), 3,63 (1H, d), 3,76 (4H, m), 3,80 (3H, s), 3,97 (1H, d), 4,13 (2H, d), 4,20 (1H, s), 4,57 (1H, s), 6,42 (1H, t), 6,77 (1H, s), 7,35 (1H, s), 7,51 (2H, d), 7,59 (1H, s), 8,20 (2H, d), 8,70 (1H, s)

Ensayo de mTOR Quinasa (Echo): 0,0932μM

Ejemplo 2b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,58 (2H, m), 1,66 - 1,69 (2H, m), 3,21 (1H, dt), 3,27 - 3,29 (1H, m), 3,29 (3H, s), 3,49 (1H, dt), 3,64 (1H, dd), 3,79 (3H, s), 3,98 (1H, dd), 4,22 (1H, d), 4,58 (1H, s), 6,78 (1H, s), 7,38 (1H, s), 7,55 (2H, d), 7,76 (1H, s), 8,23 (2H, d), 8,38 (1H, s), 8,84 (1H, s)

Ensayo de mTOR Quinasa (Echo): 0,000169μM

Ejemplo 2c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,24 (3H, d), 1,54-1,69 (6H, m), 1,81-1,91 (2H, m), 2,18-2,25 (2H, m), 3,17-3,24 (1H, td), 3,29 (3H, s), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,10-4,23 (2H, m), 4,57 (1H, bs), 6,45-6,47 (1H, d), 6,77 (1H, s), 7,47-7,50 (2H, d), 8,18-8,21 (2H, d), 8,57 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00121μM

Ejemplo 2d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,55-1,66 (2H, q), 1,67-1,69 (2H, q), 3,17-3,25 (1H, td), 3,30 (3H, s), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,32-4,34 (2H, d), 4,57 (1H, bs), 6,61-6,64 (1H, t), 6,77 (1H, s), 6,77 (2H, bs), 7,51-7,54 (2H, d), 8,21-8,22 (2H, d), 8,94 (1H, s), 11,84 (1H, bs).

Ensayo de mTOR Quinasa (Echo): 0,0239μM

Ejemplo 2e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,24 (3H, d), 1,54-1,58 (2H, q), 1,66-1,69 (2H, q), 2,19 (6H, s), 2,33-2,36 (2H, t), 3,18-3,22 (2H, t), 3,20-3,25 (1H, td), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,57 (1H, bs), 6,15-6,18 (1H, t), 6,77 (1H, s), 7,49-7,51 (2H, d), 8,19-8,21 (2H, d), 8,90 (1H, s). Nota: Señal de metilo oscurecida por pico de agua a 3,29.

Ensayo de mTOR Quinasa (Echo): 0,279μM

Ejemplo 2f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25(9H, d), 1,54-1,58 (2H, q), 1,66-1,69 (2H, q), 3,17-3,25 (1H, td), 3,39-3,40 (2H, d), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-4,00 (1H, dd), 4,20-4,23 (1H, d), 4,56 (1H, bs), 4,94-4,97 (1H, t), 6,01 (1H, s), 6,77 (1H, s), 7,45-7,47 (2H, d), 8,18-8,20 (2H, d), 8,74 (1H, s).

Nota: Señal de metilo oscurecida por pico de agua a 3,29.

Ensayo de mTOR Quinasa (Echo): 0,00433μM

Ejemplo 2g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,25 (3H, d), 1,56-1,59 (2H, q),

1,67-1,70 (2H, q), 3,19-3,26 (1H, td), 3,46-3,53 (1H, td), 3,62-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,97-4,00 (1H, dd), 4,21-4,24 (1H, d), 4,58 (1H, bs), 6,81 (1H, s), 6,87-6,88 (1H, d), 7,57-7,59 (2H, d), 8,27-8,29 (2H, d), 8,75-8,76 (1H, d), 9,08 (1H,s), 9,62 (1H, s).

Nota: Señal de metilo oscurecida por pico de agua a 3,29.

Ensayo de mTOR Quinasa (Echo): 0,000137μM

Ejemplo 2h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,56-1,59 (2H, q), 1,67-1,70 (2H, q), 3,18-3,26 (1H, td), 3,31 (3H, s), 3,46-3,53 (1H, td), 3,63-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,96-4,00 (1H, dd), 4,21-4,24 (1H, d), 4,59 (1H, bs), 6,79 (1H, s), 6,98-7,01 (1H, t), 7,28-7,32 (2H, t), 7,46-7,48 (2H, d), 7,57-7,59 (2H, d), 8,25-8,27 (2H, d), 8,71 (1H, s), 8,92 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000272μM

Ejemplo 2i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,24 (3H, d), 1,54-1,58 (2H, q), 1,65-1,70 (2H, q), 3,16-3,25 (1H, td), 3,16-3,21 (2H, q), 3,45-3,52 (1H, td), 3,45-3,49 (2H, q), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,57 (1H, bs), 4,72-4,74 (1H, t), 6,25-6,27 (1H, t), 6,77 (1H, s), 7,49-7,51 (2H, d), 8,19-8,21 (2H, d), 8,82 (1H, s).

Nota: Señal de metilo oscurecida por pico de agua a 3,29.

Ensayo de mTOR Quinasa (Echo): 0,00207μM

Ejemplo 2j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11-1,12 (6H, d), 1,23-1,24 (3H, d), 1,54-1,58 (2H, q), 1,66-1,69 (2H, q), 3,17-3,25 (1H, td), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,74-3,82 (2H, m), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,57 (1H, bs), 6,06-6,07 (1H, d), 6,77 (1H, s), 7,48-7,50 (2H, d), 8,19-8,21 (2H, d), 8,54 (1H, s).

Nota: Señal de metilo oscurecida por pico de agua a 3,29.

Ensayo de mTOR Quinasa (Echo): 0,012μM

Ejemplo 2k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,87-0,91 (3H, t), 1,23-1,25 (3H, d), 1,42-1,51 (2H, m), 1,54-1,58 (2H, q), 1,66-1,69 (2H, q), 3,05-3,09 (2H, q), 3,17-3,25 (1H, td), 3,45-3,52 (1H, td), 3,61-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,57 (1H, bs), 6,19-6,22 (1H, t), 6,77 (1H, s), 7,49-7,51 (2H, d), 8,19-8,21 (2H, d), 8,66 (1H, s).

Nota: Señal de metilo oscurecida por pico de agua a 3,29.

Ensayo de mTOR Quinasa (Echo): 0,00406μM

Ejemplo 2l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,88-0,90 (6H, d), 1,23-1,25 (3H, d), 1,54-1,58 (2H, q), 1,66-1,68 (2H, q), 1,67-1,76 (1H, m), 2,93-2,96 (2H, t), 3,17-3,25 (1H, td),

3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,57 (1H, bs), 6,24-6,27 (1H, t), 6,77 (1H, s), 7,49-7,51 (2H, d), 8,19-8,21 (2H, d), 8,66 (1H, s).

Nota: Señal de metilo oscurecida por pico de agua a 3,29.

Ensayo de mTOR Quinasa (Echo): 0,0116μM

Ejemplo 2m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,18-0,22 (2H, m), 0,42-0,46 (2H, m), 0,93-1,00 (1H, m), 1,23-1,25 (3H, d), 1,54-1,58 (2H, q), 1,66-1,69 (2H, q), 2,98-3,01 (2H, t), 3,17-3,25 (1H, td), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,57 (1H, bs), 6,25-6,28 (1H, t), 6,77 (1H, s), 7,49-7,51 (2H, d), 8,19-8,21 (2H, d), 8,70 (1H, s).

Nota: Señal de metilo oscurecida por pico de agua a 3,29.

Ensayo de mTOR Quinasa (Echo): 0,00589μM

Ejemplo 2n: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,08-1,10 (3H, d), 1,23-1,25 (3H, d), 1,54-1,57 (2H, q), 1,66-1,69 (2H, q), 2,98-3,01 (2H, t), 3,18-3,25 (1H, td), 3,30 (3H, s), 3,34-3,43 (2H, m), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,69-3,75 (1H, m), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,57 (1H, bs), 4,77-4,80 (1H, t), 6,09-6,11 (1H, d), 6,77 (1H, s), 7,48-7,50 (2H, d), 8,19-8,21 (2H, d), 8,72 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00844μM

Ejemplo 2o: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,56-1,59 (2H, q), 1,67-1,70 (2H, q), 3,18-3,26 (1H, td), 3,30 (3H, s), 3,46-3,53 (1H, td), 3,62-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,83 (3H, s), 3,96-4,00 (1H, dd), 4,21-4,24 (1H, d), 4,58 (1H, bs), 6,79(s, 1H), 6,79-6,81 (1H, d), 7,56-7,58 (2H, d), 7,83-7,86 (1H, dd), 8,21-8,22 (1H, d), 8,25-8,27 (2H, d), 8,62 (1H, s), 8,98 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000851μM

Ejemplo 2p: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,55-1,58 (2H, q), 1,66-1,69 (2H, q), 3,18-3,25 (1H, td), 3,30 (3H, s), 3,46-3,52 (1H, td), 3,62-3,66 (1H, dd), 3,76-3,78 (1H, d), 3,96-4,00 (1H, dd), 4,21-4,24 (1H, d), 4,58 (1H, bs), 6,79(s, 1H), 7,11-7,16 (2H, t), 7,46-7,50 (2H, m), 7,56-7,58 (2H, d), 8,24-8,27 (2H, d), 8,74 (1H, s), 8,92 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0027μM

Ejemplo 2q: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,25 (3H, d), 1,56-1,59 (2H, q), 1,67-1,70 (2H, q), 3,18-3,26 (1H, td), 3,30 (3H, s), 3,46-3,53 (1H, td), 3,62-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,96-4,00 (1H, dd), 4,21-4,24 (1H, d), 4,58 (1H, bs), 6,80(s, 1H), 7,14-7,17 (1H, m), 7,32-7,39 (1H, q), 7,56-7,59 (2H, d), 7,65-7,71 (1H, qd), 8,26-8,28 (2H, d), 8,93

(1H, s), 9,00 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,001μM

Ejemplo 2r: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,25 (3H, d), 1,56-1,59 (2H, q), 1,67-1,70 (2H, q), 2,26 (3H, s), 3,18-3,26 (1H, td), 3,30 (3H, s), 3,46-3,53 (1H, td), 3,62-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,96-4,00 (1H, dd), 4,21-4,24 (1H, d), 4,58 (1H, bs), 6,79(s, 1H), 7,09-7,12 (2H, d), 7,34-7,36 (2H, d), 7,56-7,58 (2H, d), 8,24-8,27 (2H, d), 8,59 (1H, s), 8,87 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00066μM

Ejemplo 2s: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,25 (3H, d), 1,56-1,59 (2H, q), 1,67-1,70 (2H, q), 3,18-3,26 (1H, td), 3,46-3,53 (1H, td), 3,62-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,96-4,00 (1H, dd), 4,21-4,24 (1H, d), 4,58 (1H, bs), 6,79(s, 1H), 7,33-7,36 (2H, d), 7,50-7,52 (2H, d), 7,56-7,59 (2H, d), 8,25-8,27 (2H, d), 8,87 (1H, s), 8,97 (1H, s).

Nota: Señal de metilo oscurecida por pico de agua a 3,29

Ensayo de mTOR Quinasa (Echo): 0,00138μM

Ejemplo 2t: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,25 (3H, d), 1,56-1,58 (2H, q), 1,67-1,69 (2H, q), 3,18-3,25 (1H, td), 3,46-3,53 (1H, td), 3,62-3,66 (1H, dd), 3,73 (3H, s), 3,76-3,79 (1H, d), 3,96-4,00 (1H, dd), 4,21-4,24 (1H, d), 4,58 (1H, bs), 6,79(s, 1H), 6,88-6,90 (2H, d), 7,36-7,38 (2H, d), 7,55-7,57 (2H, d), 8,24-8,26 (2H, d), 8,51 (1H, s), 8,84 (1H, s).

Nota: Señal de metilo oscurecida por pico de agua a 3,29

Ensayo de mTOR Quinasa (Echo): 0,00145μM

Ejemplo 2u: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,25 (3H, d), 1,56-1,59 (2H, q), 1,67-1,70 (2H, q), 2,38 (3H, s), 3,18-3,26 (1H, td), 3,46-3,53 (1H, td), 3,62-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,96-4,00 (1H, dd), 4,21-4,24 (1H, d), 4,58 (1H, bs), 6,57 (1H, s), 6,80 (s, 1H), 7,56-7,58 (2H, d), 8,27-8,29 (2H, d), 9,06 (1H, s), 9,47 (1H, s).

Nota: Señal de metilo oscurecida por pico de agua a 3,29

Ensayo de mTOR Quinasa (Echo): 0,00118μM

Ejemplo 2v: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,56-1,59 (2H, q), 1,67-1,70 (2H, q), 3,19-3,26 (1H, td), 3,31 (3H, s), 3,46-3,53 (1H, td), 3,63-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,97-4,00 (1H, dd), 4,22-4,25 (1H, d), 4,58 (1H, bs), 6,80 (1H, s), 7,60-7,63 (2H, d), 7,72-7,77 (1H, td), 7,79-7,82 (1H, dd), 8,28-8,30 (3H, m), 9,40 (1H, s), 9,89 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00866μM

Ejemplo 2w: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,82 (6H, s), 1,23 (3H, d), 1,54 - 1,57

(2H, m), 3,00 (2H, d), 3,15 (2H, d), 3,18 - 3,24 (1H, m), 3,29 (3H, s), 3,48 (1H, dt), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 (1H, d), 4,21 (1H, d), 4,55 - 4,62 (2H, m), 6,24 (1H, t), 6,76 (1H, s), 7,49 (2H, d), 8,20 (2H, d), 8,77 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0685μM

Ejemplo 2x: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,54 - 1,57 (2H, m), 1,66 - 1,68 (2H, m), 2,70 (2H, t), 3,21 (1H, dt), 3,27 (3H, s), 3,35 - 3,40 (2H, m), 3,48 (1H, dt), 3,64 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,22 (1H, d), 4,57 (1H, s), 6,53 (1H, t), 6,77 (1H, s), 7,52 (2H, d), 8,21 (2H, d), 8,93 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00164μM

Ejemplo 2y: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,54 - 1,57 (2H, m), 1,65 - 1,67 (2H, m), 1,70 - 1,73 (4H, m), 2,46 - 2,50 (4H, m), 3,20 - 3,24 (4H, m), 3,27 (3H, s), 3,48 (1H, dt), 3,63 (1H, dd), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 3,97 (1H, dd), 4,21 (1H, d), 4,56 (1H, s), 6,19 (1H, t), 6,76 (1H, s), 7,50 (2H, d), 8,19 (2H, d), 8,88 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,23μM

Ejemplo 2z: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,54 - 1,57 (2H, m), 1,66 - 1,68 (2H, m), 3,14 - 3,27 (1H, m), 3,29 (3H, s), 3,45 - 3,56 (2H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,05 - 4,11 (1H, m), 4,21 (1H, d), 4,57 (1H, s), 6,39 (1H, t), 6,49 (1H, d), 6,77 (1H, s), 7,51 (2H, d), 8,21 (2H, d), 8,94 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0181μM

Ejemplo 2aa: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11 (6H, s), 1,23 (3H, d), 1,54 - 1,57 (2H, m), 1,66 - 1,68 (2H, m), 3,06 (2H, d), 3,18 (1H, d), 3,22 (1H, dd), 3,29 (3H, s), 3,48 (1H, dt), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,21 (1H, d), 4,52 (1H, s), 4,57 (1H, s), 6,25 (1H, t), 6,76 (1H, s), 7,49 (2H, d), 8,20 (2H, d), 8,90 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0274μM

Ejemplo 2ab: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,63 - 0,67 (2H, m), 0,69 - 0,73 (2H, m), 1,23 (3H, d), 1,54 - 1,57 (2H, m), 1,66 - 1,68 (2H, m), 3,18 - 3,24 (1H, m), 3,29 (3H, s), 3,43 - 3,52 (3H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,21 (1H, d), 4,56 (1H, s), 4,83 (1H, s), 6,57 (1H, s), 6,77 (1H, s), 7,48 (2H, d), 8,20 (2H, d), 8,69 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0553μM

Ejemplo 2ac: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,54 - 1,57 (2H, m), 1,66 - 1,68 (2H, m), 3,17 - 3,24 (1H, m), 3,29 (3H, s), 3,48 (1H, dt), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,21 (1H, d), 4,44 (2H, t), 4,56 (1H, s), 4,72 - 4,82 (3H, m), 6,77 (1H, s), 6,95 (1H, d), 7,50 (2H, d), 8,20 (2H, d), 8,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00641μM

Ejemplo 2ad: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,58 (2H, m), 1,66 - 1,69 (2H, m), 3,17 - 3,25 (1H, m), 3,27 (3H, s), 3,49 (1H, dt), 3,64 (1H, dd), 3,74 (3H, s), 3,77 (1H, d), 3,98 (1H, dd), 4,22 (1H, d), 4,57 (1H, s), 6,25 (1H, d), 6,79 (1H, s), 7,54 (1H, t), 7,57 (2H, d), 8,25 (2H, d), 8,92 (1H, s), 9,18 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000705μM

Ejemplo 2ae: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,25 (3H, d), 1,56 - 1,59 (2H, m), 1,67 - 1,70 (2H, m), 3,17 - 3,23 (1H, m), 3,27 (3H, s), 3,49 (1H, dt), 3,64 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,24 (1H, d), 4,58 (1H, s), 6,81 (1H, s), 7,64 (2H, d), 8,30 (2H, d), 8,35 (1H, s), 9,46 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00072μM

Ejemplo 2af: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,25 (3H, d), 1,57 - 1,60 (2H, m), 1,68 - 1,71 (2H, m), 3,18 - 3,24 (1H, m), 3,27 (3H, s), 3,50 (1H, d), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,08 (2H, s), 4,25 (1H, d), 4,61 (1H, s), 6,86 (1H, s), 7,55 (2H, d), 8,14 (1H, s), 8,35 (2H, d), 8,44 (1H, d).

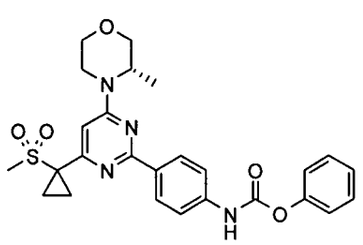
Ensayo de mTOR Quinasa (Echo): 0,0462μM

Ejemplo 2ag: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,54 - 1,57 (2H, m), 1,66 - 1,68 (2H, m), 3,18 (1H, d), 3,22 (1H, dd), 3,49 (1H, dt), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,21 (1H, d), 4,38 (2H, s), 4,44 (1H, s), 4,57 (1H, s), 6,66 (1H, d), 6,77 (1H, s), 7,52 (2H, d), 8,19 (1H, d), 8,21 (2H, d), 8,95 (1H, s), 13,83 (1H, s), 13,83 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0149μM

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato



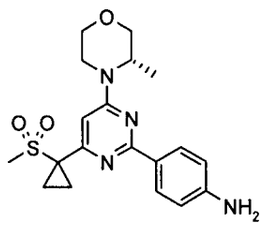
A una solución de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina (1,35 g, 3,48 mmol) en 1,4-dioxano (17,4 mL) se agregó bicarbonato de sodio

(0,438 g, 5,21 mmol) y fenil cloroformiato (0,437 mL, 3,48 mmol) y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con DCM (20 mL) y se lavó con agua (20 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (1,058 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO) δ 1,24 (3H, d), 1,57 (2H, m), 1,68 (2H, m), 3,23 (1H, m), 3,49 (1H, m), 3,58 (3H, s), 3,64 (1H, m), 3,77 (1H, d), 3,97 (1H, m), 4,23 (1H, d), 4,58 (1H, s), 6,81 (1H, s), 7,25 (2H, d), 7,30 (1H, d), 7,45 (2H, m), 7,64 (2H, d), 8,30 (2H, d), 10,44 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+ = 509$; HPLC tR = 2,48 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina

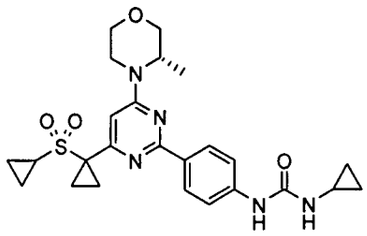


A una solución de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina (1,52 g, 4,58 mmol) en DMF (0,24 mL), DME (9,33 mL), agua (4,0 mL) y etanol (2,67 mL) se agregó ácido 4-(*terc*-butoxicarbonilamino)fenilborónico (1,629 g, 6,87 mmol), carbonato de sodio (5,73 mL, 11,45 mmol) y diclorobis(trifenilfosfina)paladio(II) (0,161 g, 0,23 mmol) y la suspensión se calentó a 80°C durante 2 horas. La mezcla de reacción se enfrió hasta alcanzar TA, se diluyó con acetato de etilo (10 mL) y se lavó con agua (10 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se disolvió en DCM (6,67 mL) y se agregó ácido trifluoroacético (0,353 mL, 4,58 mmol) y la reacción se agitó a TA durante 16 horas. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% (amoníaco 7,5N en metanol) en DCM, para proporcionar el material deseado como un sólido beige (1,283 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO) δ 1,24 (3H, d), 1,55 (2H, m), 1,67 (2H, m), 3,23 (1H, m), 3,27 (3H, s), 3,47 (1H, m), 3,63 (1H, m), 3,77 (1H, d), 3,97 (1H, m), 4,24 (1H, s), 4,58 (1H, s), 5,75 (1H, s), 6,68 (2H, d), 8,04 (2H, d)

Espectro de LCMS: m/z (ESI+) $(M+H)^+ = 389$; HPLC tR = 1,82 min.

Ejemplo 3: 3-Ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



Se disolvieron ácido [4-(3-ciclopropilureido)fenil]borónico, pinacol éster (199 mg, 0,66 mmol), 2-cloro-4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (189mg, 0,53 mmol), diclorobis(trifenilfosfina)paladio(II) (37,1 mg, 0,05 mmol) y carbonato de sodio (1,32 mL, 2,64 mmol) en una solución de 18% DMF en DME:agua:etanol 7:3:2 (4 mL) y se sellaron en un tubo de microondas. La reacción se calentó hasta alcanzar 100°C durante 20 minutos en el reactor de microondas y se enfrió hasta alcanzar TA. El producto bruto se purificó mediante cromatografía de intercambio iónico, utilizando una columna SCX. El producto deseado se eluyó de la columna utilizando amoníaco 7M en metanol y las fracciones puras se evaporaron hasta secarse para proporcionar un producto bruto. El producto bruto se purificó mediante HPLC preparativa utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes. Las fracciones que contenían el compuesto deseado se evaporaron hasta secarse para proporcionar el material deseado como una goma incolora (69,0 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO) δ 0,40 - 0,44 (2H, m), 0,62 - 0,67 (2H, m), 0,91 - 0,97 (1H, m), 0,94 (1H, s), 1,02 - 1,04 (2H, m), 1,23 (3H, t), 1,55 - 1,58 (2H, m), 1,64 - 1,66 (2H, m), 2,56 (1H, s), 2,98 - 3,02 (1H, m), 3,18 (1H, d), 3,46 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,17 - 4,21 (1H, m), 4,53 (1H, s), 6,42 (1H, d), 6,85 (1H, s), 7,49 - 7,51 (2H, m), 8,20 - 8,22 (2H, m), 8,53 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 498; HPLC tR = 1,95 min.

Ensayo de mTOR Quinasa (Echo): 0,00195μM

El **Ejemplo 3**, 3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea, también puede prepararse como se describe a continuación.

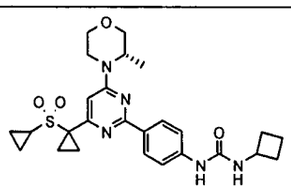
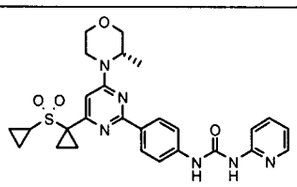
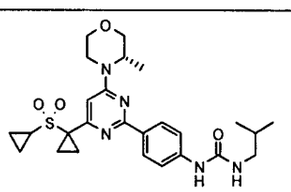
A una solución de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (150 mg, 0,28 mmol) en DMF (2 mL) se agregó trietilamina

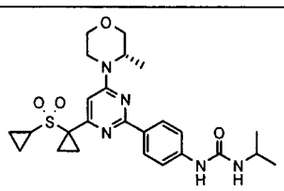
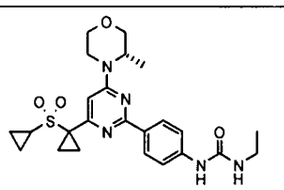
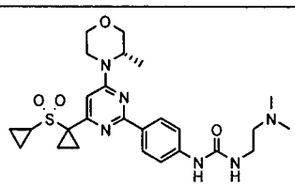
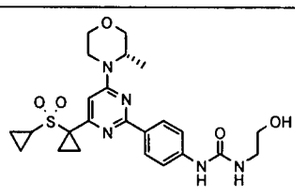
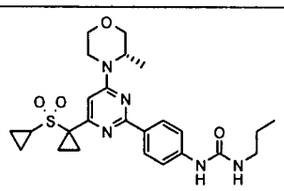
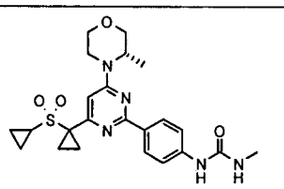
(0,177 mL, 0,84 mmol) seguido por ciclopropilamina (0,097 mL, 1,40mmol) y la reacción se calentó a 50ºÇ durante 2 horas. El producto bruto se purificó mediante HPLC preparativa utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (103 mg).

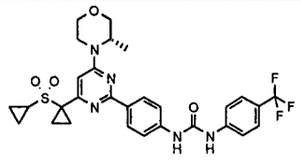
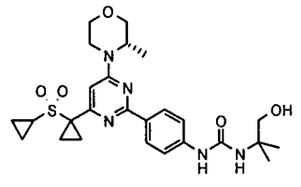
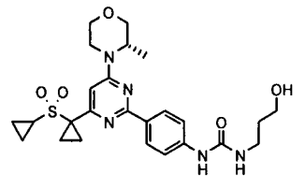
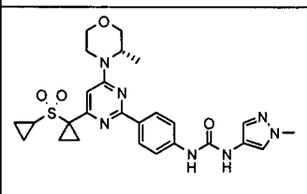
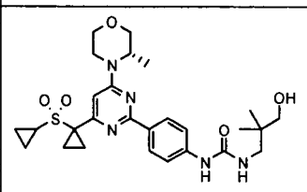
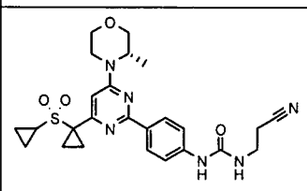
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,62 - 0,67 (2H, m), 0,90 - 0,97 (2H, m), 1,02 - 1,04 (2H, m), 1,24 (3H, d), 1,56 - 1,60 (2H, m), 1,65 (2H, d), 2,60 (1H, t), 2,96 - 3,02 (1H, m), 3,20 - 3,24 (1H, m), 3,46 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,19 (1H, d), 4,53 (1H, s), 6,42 (1H, d), 6,85 (1H, s), 7,50 (2H, d), 8,21 (2H, d), 8,53 (1H, s)

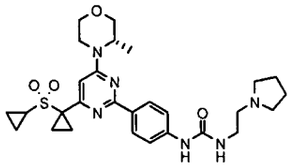
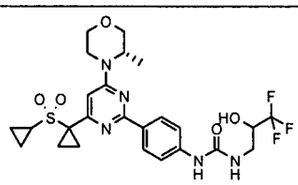
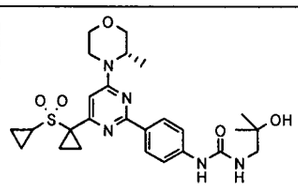
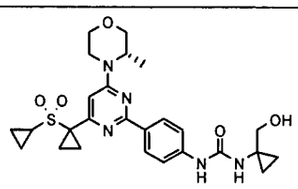
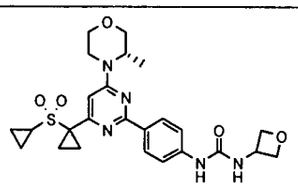
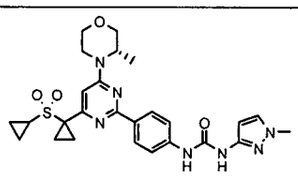
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 498; HPLC tR = 2,13 min.

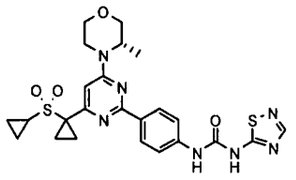
Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
3a		3-ciclobutil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	512	2,38
3b		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-il-urea	535	2,58
3c		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea	514	2,46

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
3d		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-il-urea	500	2,28
3e		3-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etil-urea	486	2,12
3f		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	529	2,04
3g		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	502	1,79
3h		3-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propil-urea	500	2,29
3i		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea	472	1,96

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
3j		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	602	3,00
3k		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metil-propan-2-il)urea	530	2,10
3l		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	516	1,83
3m		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	538	2,00
3n		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxi-2,2-dimetilpropil)urea	544	2,02
3o		3-(2-cianoetil)-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	511	1,92

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
3p		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-pirrolidin-1-iletil)urea	555	2,17
3q		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3,3,3-trifluoro-2-hidroxipropil)urea	570	2,01
3r		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxi-2-metilpropil)urea	530	1,91
3s		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[1-(hidroximetil)ciclopropil]urea	528	1,91
3t		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(oxetan-3-il)urea	514	1,92
3u		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-3-il)urea	538	2,22

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
3w		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	542	1,50

Ejemplo 3a: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,90 - 0,97 (2H, m), 1,02 - 1,04 (2H, m), 1,23 (3H, d), 1,56 - 1,59 (2H, m), 1,63 (2H, d), 1,65 (2H, d), 1,83 (1H, d), 1,86 (1H, t), 2,17 - 2,25 (2H, m), 2,97 - 3,01 (1H, m), 3,17 - 3,24 (1H, m), 3,46 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 3,99 (1H, m), 4,11 - 4,17 (1H, m), 4,20 (1H, s), 4,53 (1H, d), 6,45 (1H, d), 6,84 (1H, s), 7,46 - 7,48 (2H, m), 8,20 (2H, d), 8,55 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00445μM

Ejemplo 3b: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,88 - 0,98 (2H, m), 0,99 - 1,06 (2H, m), 1,25 (3H, d), 1,57 - 1,62 (2H, m), 1,65 - 1,68 (2H, m), 2,99 - 3,05 (1H, m), 3,19 - 3,23 (1H, m), 3,47 - 3,54 (1H, m), 3,63 - 3,67 (1H, m), 3,78 (1H, d), 3,97 - 4,01 (1H, m), 4,21 (1H, d), 4,54 (1H, d), 6,88 (1H, s), 7,02 - 7,05 (1H, m), 7,56 (1H, d), 7,63 (2H, d), 7,75 - 7,77 (1H, m), 8,29 - 8,31 (3H, m), 9,44 (1H, d), 10,58 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00385μM

Ejemplo 3c: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,88 - 0,90 (6H, m), 0,94 (2H, t), 1,00 - 1,06 (2H, m), 1,24 (3H, d), 1,55 - 1,58 (2H, m), 1,64 - 1,66 (2H, m), 1,67 - 1,74 (1H, m), 2,94 (2H, t), 2,98 - 3,02 (1H, m), 3,20 - 3,24 (1H, m), 3,46 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,19 (1H, d), 4,53 (1H, s), 6,23 (1H, t), 6,84 (1H, s), 7,47 - 7,50 (2H, m), 8,20 - 8,22 (2H, m), 8,63 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0124μM

Ejemplo 3d: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,91 - 0,97 (2H, m), 1,00 - 1,05 (2H, m), 1,11 (6H, d), 1,23 (3H, d), 1,55 - 1,58 (2H, m), 1,64 - 1,66 (2H, m), 2,97 - 3,03 (1H, m), 3,17 - 3,24 (1H, m), 3,46 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,76 (2H, d), 3,96 - 4,00 (1H, m), 4,19 (1H, d), 4,53 (1H, s), 6,05 (1H, d), 6,84 (1H, s), 7,46 - 7,49 (2H, m), 8,19 - 8,22 (2H, m), 8,52 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0135μM

Ejemplo 3e: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,92 - 0,94 (2H, t), 1,02 - 1,04 (2H, m), 1,07 (3H, t), 1,23 (3H, d), 1,58 (2H, d), 1,64 - 1,66 (2H, m), 2,98 - 3,02 (1H, m), 3,17 - 3,18 (1H, m), 3,14 - 3,24 (2H, m), 3,47 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,19 (1H, d), 4,53 (1H, s), 6,15 (1H, t), 6,84 (1H, s), 7,47 - 7,51 (2H, m), 8,19 - 8,22 (2H, m), 8,65 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00166μM

Ejemplo 3f: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,91 - 0,97 (2H, m), 0,98 - 1,05 (2H, m), 1,23 (3H, d), 1,55 - 1,58 (2H, m), 1,64 - 1,66 (2H, m), 2,18 (6H, s), 2,34 (2H, t), 2,97 - 3,03 (1H, m), 3,19 (3H, q), 3,46 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,19 (1H, d), 4,53 (1H, s), 6,15 (1H, t), 6,84 (1H, s), 7,47 - 7,50 (2H, m), 8,19 - 8,22 (2H, m), 8,88 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0214μM

Ejemplo 3g: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,91 - 0,97 (2H, m), 1,00 - 1,05 (2H, m), 1,23 (3H, d), 1,55 - 1,58 (2H, m), 1,64 - 1,66 (2H, m), 2,97 - 3,03 (1H, m), 3,16 - 3,21 (3H, m), 3,44 - 3,52 (3H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,17 - 4,21 (1H, m), 4,53 (1H, s), 4,72 (1H, t), 6,25 (1H, t), 6,84 (1H, s), 7,47 - 7,50 (2H, m), 8,20 - 8,22 (2H, m), 8,79 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00134μM

Ejemplo 3h: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,89 (3H, t), 0,91 - 0,95 (2H, m), 1,02 - 1,04 (2H, m), 1,23 (3H, d), 1,41 - 1,50 (2H, m), 1,56 - 1,60 (2H, m), 1,64 - 1,66 (2H, m), 2,98 - 3,02 (1H, m), 3,04 - 3,09 (2H, m), 3,20 - 3,24 (1H, m), 3,47 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,19 (1H, d), 4,53 (1H, s), 6,20 (1H, t), 6,84 (1H, s), 7,47 - 7,50 (2H, m), 8,20 - 8,22 (2H, m), 8,64 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0165μM

Ejemplo 3i: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,92 - 0,95 (2H, m), 1,02 - 1,05 (2H, m), 1,23 (3H, d), 1,56 - 1,60 (2H, m), 1,63 - 1,66 (2H, m), 2,66 (3H, d), 2,98 - 3,02 (1H, m), 3,17 - 3,24 (1H, m), 3,46 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,19 (1H, d), 4,53 (1H, s), 6,05 (1H, t), 6,84 (1H, s), 7,48 - 7,51 (2H, m), 8,19 - 8,22 (2H, m), 8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000932μM

Ejemplo 3j: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,92 - 0,98 (2H, m), 1,01 - 1,05 (2H, m), 1,25 (3H, d), 1,57 - 1,62 (1H, m), 1,61 (1H, d), 1,65 - 1,68 (2H, m), 2,97 - 3,04 (1H, m), 3,22 - 3,26 (1H, m), 3,47 - 3,53 (1H, m), 3,63 - 3,67 (1H, m), 3,78 (1H, d), 3,97 - 4,00 (1H, m),

4,21 (1H, d), 4,55 (1H, s), 6,87 (1H, s), 7,57 - 7,59 (2H, m), 7,63 - 7,70 (4H, m), 8,29 (2H, d), 9,04 (1H, s), 9,13 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00422μM

Ejemplo 3k: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,94 (2H, t), 1,04 (2H, d), 1,23 (6H, d), 1,24 (3H, d), 1,56 - 1,59 (2H, m), 1,64 - 1,66 (2H, m), 2,98 - 3,02 (1H, m), 3,18 (1H, d), 3,39 (2H, d), 3,46 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,19 (1H, d), 4,52 (1H, s), 4,95 (1H, t), 6,00 (1H, s), 6,84 (1H, s), 7,43 - 7,47 (2H, m), 8,19 - 8,21 (2H, m), 8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00227μM

Ejemplo 3l: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,91 - 0,94 (2H, m), 1,01 - 1,05 (2H, m), 1,23 (3H, d), 1,55 - 1,58 (2H, m), 1,60 -1,61 (2H, m), 1,65 (1H, m), 2,98 - 3,02 (1H, m), 3,17 (1H, d), 3,18 - 3,23 (2H, m), 3,45 - 3,49 (3H, m), 3,50 (1H, d), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,17 (1H, s), 4,47 (1H, t), 4,53 (1H, s), 6,20 (1H, t), 6,84 (1H, s), 7,48 - 7,50 (2H, m), 8,21 (2H, d), 8,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00257μM

Ejemplo 3m: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,93 - 0,95 (2H, m), 1,02 - 1,05 (2H, m), 1,24 (3H, d), 1,57 - 1,60 (2H, m), 1,65 - 1,67 (2H, m), 2,98 - 3,02 (1H, m), 3,18 (1H, t), 3,46 - 3,50 (1H, m), 3,63 - 3,66 (1H, m), 3,76 (1H, s), 3,79 (3H, s), 3,96 - 4,00 (1H, m), 4,18 (1H, s), 4,53 (1H, s), 6,86 (1H, s), 7,38 - 7,38 (1H, m), 7,55 (2H, t), 7,76 (1H, s), 8,25 (2H, d), 8,38 (1H, s), 8,83 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000497μM

Ejemplo 3n: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,81 (6H, s), 0,91 - 0,95 (2H, m), 1,01 - 1,05 (2H, m), 1,23 (3H, d), 1,56 - 1,60 (3H, m), 1,63 - 1,66 (2H, m), 2,98 - 3,02 (2H, m), 3,15 (2H, d), 3,21 (1H, dt), 3,49 (1H, dt), 3,64 (1H, dd), 3,77 (1H, d), 4,19 (1H, d), 4,53 (1H, s), 4,61 (1H, t), 6,26 (1H, t), 6,84 (1H, s), 7,48 (2H, d), 8,21 (2H, d), 8,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0396μM

Ejemplo 3o: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,90 - 0,95 (2H, m), 1,00 - 1,06 (2H, m), 1,24 (3H, d), 1,56 - 1,60 (2H, m), 1,63 - 1,66 (2H, m), 2,70 (2H, t), 2,96 - 3,03 (1H, m), 3,17 - 3,25 (1H, m), 3,35 - 3,39 (2H, m), 3,49 (1H, dt), 3,64 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,19 (1H, d), 4,53 (1H, s), 6,52 (1H, t), 6,85 (1H, s), 7,51 (2H, d), 8,22 (2H, d), 8,91 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00596μM

Ejemplo 3p: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,93 - 0,94 (2H, m), 1,02 - 1,04 (2H, m), 1,23 (3H, d), 1,56 - 1,58 (2H, m), 1,64 - 1,67 (2H, m), 1,72 (8H, m), 2,94 - 3,02 (1H, m), 3,18

- 3,24 (5H, m), 3,49 (1H, t), 3,64 (1H, d), 3,77 (1H, d), 3,97 (1H, d), 4,19 (1H, d), 4,53 (1H, s), 6,22 (1H, s), 6,84 (1H, s), 7,49 (2H, d), 8,21 (2H, d), 8,88 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,193μM

Ejemplo 3q: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,91 - 0,95 (2H, m), 1,00 - 1,06 (2H, m), 1,23 (3H, d), 1,56 - 1,60 (2H, m), 1,63 - 1,66 (2H, m), 2,96 - 3,03 (1H, m), 3,14 - 3,25 (2H, m), 3,46 - 3,55 (2H, m), 3,64 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,07 - 4,08 (1H, m), 4,19 (1H, d), 4,52 (1H, s), 6,42 (1H, t), 6,49 (1H, s), 6,85 (1H, s), 7,50 (2H, d), 8,22 (2H, d), 8,95 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00839μM

Ejemplo 3r: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,91 - 0,95 (2H, m), 1,00 - 1,06 (2H, m), 1,10 (6H, s), 1,23 (3H, d), 1,56 - 1,60 (2H, m), 1,61 - 1,66 (2H, m), 2,97 - 3,02 (1H, m), 3,06 (2H, d), 3,22 (1H, dd), 3,49 (1H, dt), 3,64 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,19 (1H, d), 4,52 (1H, s), 4,54 (1H, s), 6,24 (1H, t), 6,84 (1H, s), 7,48 (2H, d), 8,21 (2H, d), 8,88 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0488μM

Ejemplo 3s: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,63 - 0,67 (2H, m), 0,69 - 0,73 (2H, m), 0,91 - 0,95 (2H, m), 1,02 - 1,04 (2H, m), 1,23 (3H, d), 1,56 - 1,60 (2H, m), 1,63 - 1,66 (2H, m), 2,97 - 3,03 (1H, m), 3,17 - 3,25 (2H, m), 3,44 (1H, d), 3,46 - 3,52 (1H, m), 3,64 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,19 (1H, d), 4,52 (1H, s), 4,83 (1H, s), 6,56 (1H, s), 6,85 (1H, s), 7,47 (2H, d), 8,21 (2H, d), 8,67 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0263μM

Ejemplo 3t: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,91 - 0,95 (2H, m), 1,00 - 1,07 (2H, m), 1,23 (3H, d), 1,56 - 1,61 (2H, m), 1,63 - 1,66 (2H, m), 2,96 - 3,02 (1H, m), 3,21 (1H, dt), 3,49 (1H, dt), 3,64 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,19 (1H, d), 4,45 (2H, t), 4,52 (1H, s), 4,72 - 4,83 (3H, m), 6,85 (1H, s), 6,95 (1H, d), 7,49 (2H, d), 8,22 (2H, d), 8,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00479μM

Ejemplo 3u: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,91 - 0,95 (2H, m), 1,00 - 1,07 (2H, m), 1,23 (3H, d), 1,56 - 1,61 (2H, m), 1,63 - 1,66 (2H, m), 2,96 - 3,02 (1H, m), 3,21 (1H, dt), 3,49 (1H, dt), 3,64 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,19 (1H, d), 4,45 (2H, t), 4,52 (1H, s), 4,72 - 4,83 (3H, m), 6,85 (1H, s), 6,95 (1H, d), 7,49 (2H, d), 8,22 (2H, d), 8,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000604μM

Ejemplo 3v: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,94 - 0,96 (2H, m), 1,03 - 1,05 (2H, m), 1,24 (3H, d), 1,57 - 1,59 (2H, m), 1,64 - 1,66 (2H, m), 2,98 - 3,03 (1H, m), 3,19 - 3,25 (1H, m), 3,50 (1H, t), 3,65 (1H, d), 3,74 (3H, s), 3,77 (1H, d), 3,98 (1H, d), 4,21 (1H, d), 4,54 (1H,

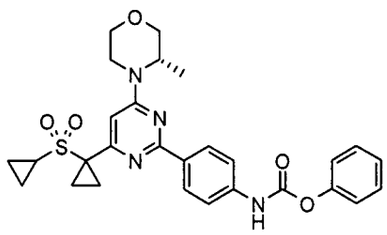
s), 6,24 (1H, d), 6,86 (1H, s), 7,54 - 7,55 (1H, m), 7,56 (2H, d), 8,26 (2H, d), 8,92 (1H, s), 9,17 (1H, s).

Ejemplo 3w: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,92 - 0,96 (2H, m), 1,02 - 1,06 (2H, m), 1,25 (3H, d), 1,58 - 1,60 (2H, m), 1,66 - 1,67 (2H, m), 2,98 - 3,05 (1H, m), 3,20 - 3,23 (1H, m), 3,50 (1H, t), 3,65 (1H, d), 3,78 (1H, d), 3,99 (1H, d), 4,21 (1H, d), 4,55 (1H, s), 6,89 (1H, s), 7,63 (2H, d), 8,31 - 8,36 (3H, m), 9,43 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00089μM

La preparación de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

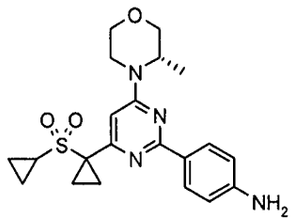


Se agregó gota a gota fenil cloroformiato (0,729 mL, 5,79 mmol) a 4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (2,40 g, 5,79 mmol) y bicarbonato de sodio (0,730 g, 8,68 mmol) en dioxano (45 mL) bajo nitrógeno. La suspensión resultante se agitó a 20°C durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetato de etilo (200 mL) y se lavó con agua (200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un sólido blanco (3,03 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,92 - 0,95 (2H, m), 1,03 - 1,05 (2H, m), 1,25 (3H, d), 1,57 - 1,61 (1H, m), 1,61 (1H, d), 1,65 - 1,68 (2H, m), 2,99 - 3,03 (1H, m), 3,46 - 3,47 (1H, m), 3,49 - 3,53 (1H, m), 3,63 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,22 (1H, d), 4,56 (1H, s), 6,89 (1H, s), 7,26 (1H, t), 7,24 - 7,30 (2H, m), 7,43 - 7,47 (2H, m), 7,60 - 7,65 (2H, m), 8,29 - 8,32 (2H, m), 10,43 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 535; HPLC tR = 2,84 min.

4-[4-(1-Ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

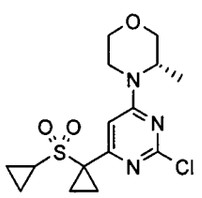


Se agregó diclorobis(trifenilfosfina)paladio(II) (0,524 g, 0,75 mmol) a una solución desgasificada de 2-cloro-4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,67 g, 7,46 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (2,043 g, 9,33 mmol) y carbonato de sodio (18,65 mL, 37,31 mmol) en 18% DMF en 7:3:2 DME:agua:etanol (20 mL). La solución resultante se agitó a 85°C durante 1 hora. La mezcla de reacción se concentró y se diluyó con DCM (150 mL) y se lavó con agua (100 mL) y salmuera (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 2,5% metanol en DCM, para proporcionar el material deseado como un sólido marrón (2,40 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,90 - 0,98 (2H, m), 0,98 - 1,05 (2H, m), 1,22 (3H, d), 1,52 - 1,59 (2H, m), 1,62 - 1,64 (2H, m), 2,95 - 3,02 (1H, m), 3,14 - 3,22 (1H, m), 3,45 - 3,51 (1H, m), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,98 (1H, m), 4,14 - 4,17 (1H, m), 4,48 - 4,51 (1H, m), 5,53 (2H, d), 6,60 (2H, d), 6,75 (1H, s), 8,03 - 8,06 (2H, m).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 415; HPLC tR = 2,13 min.

2-Cloro-4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

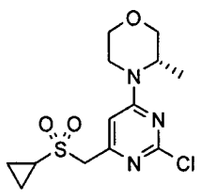


Se agregó solución de hidróxido de sodio 5N (1,74 mL, 8,68 mmol) a bromuro de tetrabutilamonio (0,140 g, 0,43 mmol), 1,2-dibromoetano (0,374 mL, 4,34 mmol) y 2-cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,44 g, 4,34 mmol) en DCM (20 mL). La mezcla resultante se agitó a 40°C durante 2 horas. Se agregó más hidróxido de sodio sólido (4 g, 0,1 mol) directamente a la reacción y se agitó a 40°C durante 1 hora más. La mezcla de reacción se diluyó con DCM (20 mL) y se lavó con agua (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado (1,68

g).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 358; HPLC tR = 1,87 min.

2-Cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



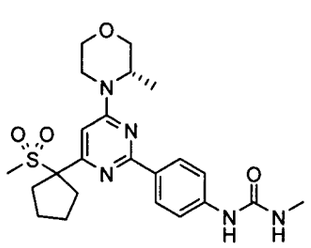
Se agregó ácido ciclopropanosulfínico, sal de sodio (381 mg, 2,97 mmol) en una porción a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (700 mg, 1,98 mmol) en acetonitrilo (20 mL) a TA. La suspensión resultante se agitó a 90°C durante 3 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (50 mL) y se lavó con agua (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (458 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO) δ 0,95 - 0,98 (2H, m), 1,02 - 1,06 (2H, m), 1,18 - 1,23 (3H, m), 2,77 - 2,83 (1H, m), 3,19 - 3,25 (1H, m), 3,42 - 3,49 (1H, m), 3,58 - 3,62 (1H, m), 3,73 (1H, d), 3,92 - 3,96 (2H, m), 4,30 (1H, s), 4,48 (2H, s), 6,92 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 332; HPLC tR = 1,68 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 4: 3-Metil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea



Se agregó trietilamina (0,15 mL, 1,1 mmol) a una solución de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]carbamato (200 mg, 0,37

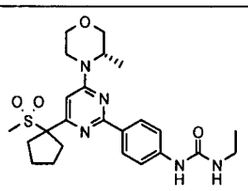
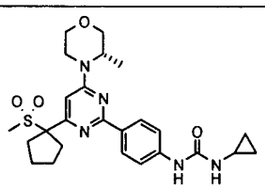
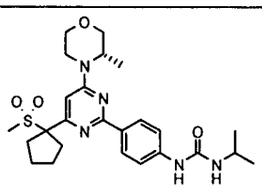
mmol) y metilamina (2M en THF, 1,48 mmol) en NMP (2 mL). La reacción se calentó a 80°C durante 2 horas y luego se purificó mediante HPLC prep, utilizando una mezcla de agua (conteniendo 1% NH_3) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido (126 mg).

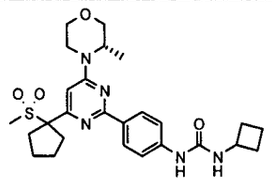
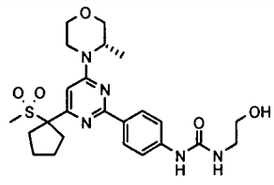
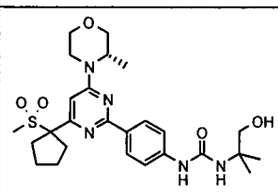
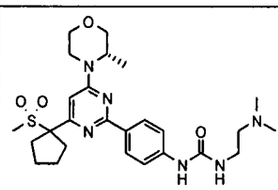
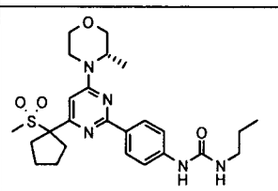
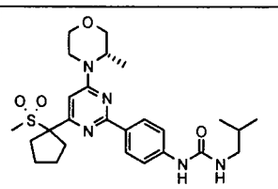
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,52-1,62 (2H, m), 1,75-1,90 (2H, m), 2,38-2,50 (2H, m), 2,65 (3H, d), 2,65-2,78 (2H, m), 2,89 (3H, s), 3,20 (1H, dd), 3,50 (1H, dd), 3,64 (1H, d), 3,75 (1H, d), 3,95 (1H, dd), 4,25 (1H, d), 4,55 (1H, s), 6,05 (1H, q), 6,79 (1H, s), 7,50 (2H, d), 8,22 (2H, d), 8,72 (1H, s).

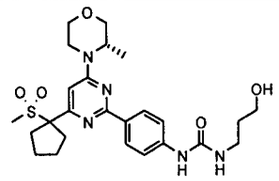
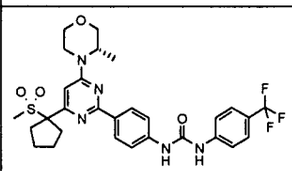
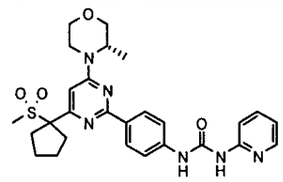
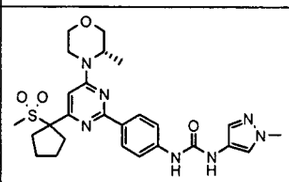
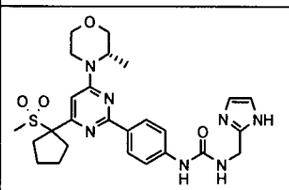
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 474; HPLC tR = 1,96 min

Ensayo de mTOR Quinasa (Echo): 0,000699μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
4a		3-etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea	488	2,13
4b		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea	500	2,13
4c		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-propan-2-il-urea	502	2,29

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
4d		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea	514	2,35
4e		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea	504	1,80
4f		3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea	532	2,09
4g		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea	531	2,07
4h		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-propil-urea	502	2,28
4i		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea	517	2,45

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
4j		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea	518	1,84
4k		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	604	2,95
4l		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-piridin-2-il-urea	537	2,55
4m		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	540	1,99
4n		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]urea	540	1,92

Ejemplo 4a: ^{1}H NMR (400,132 MHz, DMSO) δ 1,05 (3H, t), 1,21 (3H, d), 1,50-1,62 (2H, m), 1,78-1,85 (2H, m), 2,35-2,45 (2H, m), 2,65-2,75 (2H, m), 2,89 (3H, s), 3,12 (2H, q), 3,18 (1H, dd), 3,50 (1H, dd), 3,65 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,24 (1H, d), 4,55 (1H, s), 6,15 (1H, t), 6,78 (1H, s), 7,48 (2H, d), 8,22 (2H, d), 8,65 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00216μM

Ejemplo 4b: ^{1}H NMR (400,132 MHz, DMSO) δ 0,41 (2H, q), 0,62 (2H, q), 1,21 (3H, d), 1,51-1,61 (2H, m), 1,75-1,86 (2H, m), 2,35-2,45 (2H, m), 2,55 (1H, m), 2,65-2,85 (2H, m), 2,89 (3H, s), 3,20 (1H, dd), 3,50 (1H, dd), 3,65 (1H, dd), 3,75 (1H, d), 3,97 (1H, dd), 4,25 (1H, d), 4,55 (1H, s), 6,41 (1H, d), 6,78 (1H, s), 7,50 (2H, d), 8,25 (2H, d), 8,55 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00203μM

Ejemplo 4c: ^{1}H NMR (400,132 MHz, DMSO) δ 1,11 (6H, d), 1,21 (3H, d), 1,50-1,62 (2H, m), 1,75-1,85 (2H, m), 2,38-2,50 (3H, m), 2,65-2,80 (2H, m), 2,89 (3H, s), 3,20 (1H, dd), 3,50 (1H, dd), 3,65 (1H, dd), 3,75 (1H, dd), 3,99 (1H, dd), 4,23 (1H, d), 4,55 (1H, s), 6,05 (1H, d), 6,79 (1H, s), 7,48 (2H, d), 8,22 (2H, d), 8,54 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0169μM

Ejemplo 4d: ^{1}H NMR (400,132 MHz, DMSO) δ 1,21 (3H, d), 1,50-1,65 (4H, m), 1,75-1,90 (4H, m), 2,15-2,20 (2H, m), 2,35-2,50 (2H, m), 2,65-2,80 (2H, m), 2,88 (3H, s), 3,20 (1H, dd), 3,50 (1H, dd), 3,65 (1H, dd), 3,75 (1H, dd), 3,95 (1H, dd), 4,15 (1H, q), 4,22 (1H, d), 4,55 (1H, s), 6,42 (1H, d), 6,79 (1H, s), 7,45 (2H, d), 8,22 (2H, d), 8,55 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,01μM

Ejemplo 4e: ^{1}H NMR (400,132 MHz, DMSO) δ 1,21 (3H, d), 1,50-1,62 (2H, m), 1,78-1,85 (2H, m), 2,38-2,50 (2H, m), 2,65-2,80 (2H, m), 2,89 (3H, s), 3,15-3,22 (3H, m), 3,40-3,50 (3H, m), 3,65 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,22 (1H, d), 4,55 (1H, s), 4,71 (1H, t), 6,22 (1H, t), 6,78 (1H, s), 7,45 (2H, d), 8,22 (2H, d), 8,80 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00119μM

Ejemplo 4f: ^{1}H NMR (400,132 MHz, DMSO) δ 1,21 (3H, d), 1,50-1,62 (2H, m), 1,75-1,85 (2H, m), 2,38-2,50 (2H, m), 2,65-2,80 (2H, m), 2,89 (3H, s), 3,20 (1H, dd), 3,35-3,40 (2H, m), 3,50 (1H, dd), 3,65 (1H, dd), 3,75 (1H, d), 3,95 (1H, dd), 4,22 (1H, d), 4,55 (1H, s), 4,95 (1H, t), 6,0 (1H, s), 6,78 (1H, s), 7,45 (2H, d), 8,22 (2H, d), 8,72 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,01μM

Ejemplo 4g: ^{1}H NMR (400,132 MHz, DMSO) δ 1,21 (3H, d), 1,50-1,60 (2H, m), 1,75-1,85 (2H, m), 2,18 (6H, s), 2,31 (2H, t), 2,38-2,50 (2H, m), 2,65-2,75 (2H, m), 2,89 (3H, s), 3,15-3,22 (3H, m), 3,50 (1H, dd), 3,65 (1H, dd), 3,75 (1H, dd), 3,96 (1H, dd), 4,22 (1H, dd), 4,55 (1H, s), 6,15 (1H, t), 6,79 (1H, s), 7,48 (2H, d), 8,22 (2H, d), 8,87 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0626μM

Ejemplo 4h: ^{1}H NMR (400,132 MHz, DMSO) δ 0,88 (3H, t), 1,21 (3H, d), 1,45 (2H, q), 1,50-1,62 (2H, m), 1,75-1,85 (2H, m), 2,38-2,50 (2H, m), 2,65-2,80 (2H, m), 2,89 (3H, s),

3,05 (2H, m), 3,20 (1H, dd), 3,50 (1H, dd), 3,65 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,22 (1H, d), 4,55 (1H, s), 6,20 (1H, t), 6,78 (1H, s), 7,48 (2H, d), 8,21 (2H, d), 8,62 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00157μM

Ejemplo 4i: ^{1}H NMR (400,132 MHz, DMSO) δ 0,88 (6H, d), 1,21 (3H, d), 1,50-1,62 (2H, m), 1,70 (1H, m), 1,75-1,85 (2H, m), 2,35-2,50 (2H, m), 2,65-2,80 (2H, m), 2,90 (3H, s), 2,94 (2H, t), 3,20 (1H, dd), 3,50 (1H, dd), 3,65 (1H, dd), 3,75 (1H, dd), 3,97 (1H, dd), 4,24 (1H, d), 4,54 (1H, s), 6,22 (1H, t), 6,78 (1H, s), 7,50 (2H, d), 8,22 (2H, d), 8,63 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0115μM

Ejemplo 4j: ^{1}H NMR (400,132 MHz, DMSO) δ 1,21 (3H, d), 1,50-1,62 (4H, m), 1,75-1,85 (2H, m), 2,38-2,50 (2H, m), 2,65-2,80 (2H, m), 2,89 (3H, s), 3,10-3,22 (3H, m), 3,45-3,52 (3H, m), 3,65 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,22 (1H, d), 4,45 (1H, t), 4,55 (1H, s), 6,1991H, t), 6,79 (1H, s), 7,49 (2H, d), 8,22 (2H, d), 8,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00461μM

Ejemplo 4k: ^{1}H NMR (400,132 MHz, DMSO) δ 1,21 (3H, d), 1,50-1,62 (2H, m), 1,75-1,85 (2H, m), 2,38-2,50 (2H, m), 2,65-2,80 (2H, m), 2,89 (3H, s), 3, 22 (1H, dd), 3,50 (1H, dd), 3,65 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,25 (1H, d), 4,55 (1H, s), 6,80 (1H, s), 7,58 (2H, d), 7,62-7,70 (4H, m), 8,30 (2H, d), 9,04 (1H, s), 9,10 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00905μM

Ejemplo 4l: ^{1}H NMR (400,132 MHz, DMSO) δ 1,21 (3H, d), 1,55-1,62 (2H, m), 1,78-1,90 (2H, m), 2,38-2,50 (2H, m), 2,65-2,80 (2H, m), 2,89 (3H, s), 3,20 (1H, dd), 3,50 (1H, dd), 3,65 (1H, dd), 3,75 (1H, d), 3,9791H, dd), 4,2591H, d), 4,55 (1H, s), 6,80 (1H, s), 7,02 (1H, dd), 7,58 (1H, d), 7,61 (2H, d), 7,74 (1H, dd), 8,25-8,35 (4H, m), 9,41 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00369μM

Ejemplo 4m: ^{1}H NMR (400,132 MHz, DMSO) δ 1,20 (3H, d), 1,50-1,62 (2H, m), 1,78-1,85 (2H, m), 2,38-2,50 (2H, m), 2,65-2,80 (2H, m), 2,89 (3H, s), 3,20 (1H, dd), 3,50 (1H, dd), 3,65 (1H, dd), 3,75-40 (4H, m), 3,97 (1H, dd), 4,25 (1H, d), 4,55 (1H, s), 6,80 (1H, s), 7,38 (1H, s), 7,55 (2H, d), 7,73 (1H, s), 8,25 (2H, d), 8,35 (1H, s), 8,85 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00245μM

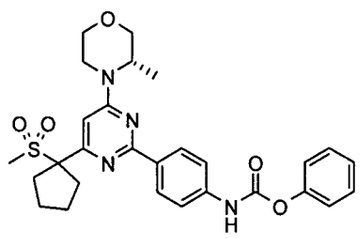
Ejemplo 4n: ^{1}H NMR (400,132 MHz, DMSO) δ 1,21 (3H, d), 1,50-1,62 (2H, m), 1,75-1,85 (2H, m), 2,35-2,50 (2H, m), 2,65-2,80 (2H, m), 2,89 (3H, s), 3,20 (1H, dd), 3,50 (1H, dd), 3, 65 (1H, dd), 3,75 (1H, d), 3,97 (1H, dd), 4,24 (1H, d), 4,35 (1H, d), 4,55 (1H, s), 6,65 (1H, t), 6,78 (1H, s), 7,04 (2H, s), 7,52 (2H, d), 8,25 (2H, d), 9,0 (1H, s), 12,6 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0392μM

1294

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]fenil]carbamato

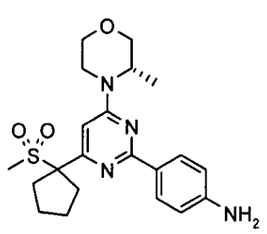


Se agregó hidrogenocarbonato de sodio (1,150 g, 13,68 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]anilina (3,8 g, 9,12 mmol), en dioxano (100 mL) a 21°C bajo nitrógeno. La mezcla resultante se enfrió hasta alcanzar 10°C y se agregó lentamente fenil cloroformiato (1,72 mL, 13,68 mmol) luego la reacción se agitó durante 3 horas y se dejó entibiar hasta alcanzar TA y se dejó durante 16 horas. La mezcla de reacción se diluyó con acetato de etilo (250 mL) y se lavó con agua (150 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se trituró con una mezcla de éter dietílico, iso-hexano y acetona para proporcionar el material deseado como un sólido blanco (4,50 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,50-1,62 (2h, m), 1,75-1,85 (2H, m), 2,38-2,50 (2H, m), 2,65-2,80 (2H, m), 3,21 (1H, dd), 3,30 (3H, s), 3,50 (1H, dd), 3,63 (1H, dd), 3,75 (1H, d), 3,97 (1H, dd), 4,28 (1H, d), 4,57 (1H, s), 6,81 (1H, s), 7,22-7,30 (3Hh, m), 7,43 (2H, dd), 7,61 (1H, d), 8,32 (2H, d), 10,45 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 537 ; HPLC tR = 2,98 min

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]anilina



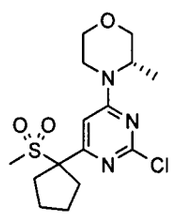
Se agregó cloruro de bis(trifenilfosfina)paladio (II) (0,390 g, 0,56 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidina (4,0g, 11,12 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (3,17 g, 14,45 mmol) y carbonato de sodio (20 mL,

40,0 mmol) en una mezcla de DMF (20 mL), DME (50 mL), etanol (20 mL) y agua (20 mL) a TA bajo nitrógeno. La mezcla resultante se agitó a 95°C durante 12 horas. La mezcla de reacción se diluyó con acetato de etilo (400 mL), se lavó dos veces con agua (200 mL seguido por 250 mL), la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se cromatografió sobre sílice, eluyendo con 5 - 50% acetato de etilo en iso-hexano, para proporcionar un sólido amarillo que a continuación se trituró con una mezcla de éter dietílico e iso-hexano para proporcionar el material deseado como un sólido blanco (4,25 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,50-1,60 (2H, m), 1,75-1,90 (2H, m), 2,34-2,43 (2H, m), 2,62-2,78 (2H, m), 2,88 (3H, s), 3,18 (1H, dd), 3,48 (1H, dd), 3,65 (1H, dd), 3,75 (1H, dd), 3,95 (1H, dd), 4,20 (1H, d), 4,51 (1H, s), 5,55 (2H, s), 6,62 (2H, d), 6,68 (1H, s), 8,09 (1H, d).

Espectro de Masa: m/z (ESI+)$(M+H)^+$ = 417

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidina



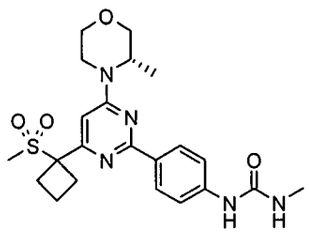
Se agregó bromuro de tetrabutilamonio (0,495 g, 1,54 mmol) a una mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6- (metilsulfonilmetil)pirimidina (4,7 g, 15,37 mmol), 1,4-dibromobutano (1,84 mL, 15,37 mmol) y solución acuosa de hidróxido de sodio (30 mL, 368,9 mmol) en DCM (150 mL) a TA bajo nitrógeno. La mezcla resultante se agitó a 40°C durante 6 horas. La mezcla de reacción se diluyó con DCM (200 mL) y se lavó con agua (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se cromatografió sobre sílice, eluyendo con 5 - 50% acetato de etilo en iso-hexano, para proporcionar el material deseado como un sólido amarillo (3,90 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,50-1,60 (2H, m), 1,72-1,82 (2H, m), 2,30-2,41 (2H, m,), 2,50-2,60 (2H, m), 2,88 (3H, s), 3,20 (1H, dd), 3,45 (1H, dd), 3,60 (1H, dd), 3,71 (1H, d), 3,94 (1H, dd), 4,0-4,10 (1H, m), 4,42 (1H, s), 6,89 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 360 ; HPLC tR = 2,22 min

La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6- (metilsulfonilmetil)pirimidina se describió anteriormente.

Ejemplo 5: 3-Metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea



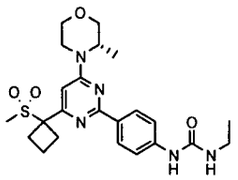
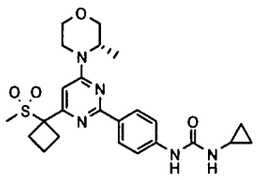
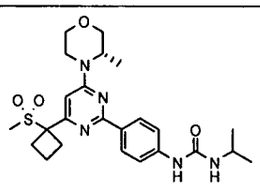
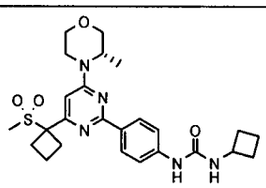
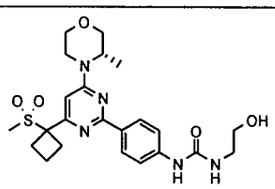
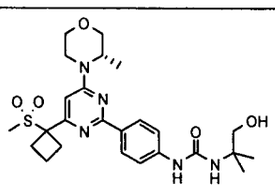
Se agregó trietilamina (0,07 mL, 0,48mmol) a una solución de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]carbamato (86 mg, 0,16 mmol) y metilamina (2M en THF, 0,65 mmol) en NMP (2 mL). La reacción se calentó a 80°C durante 2 horas y luego se purificó mediante HPLC prep, utilizando una mezcla de agua (conteniendo 1% NH_3) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido (48 mg).

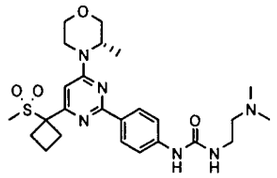
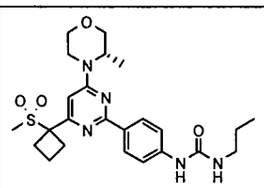
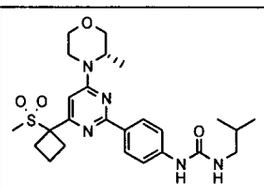
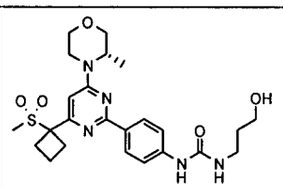
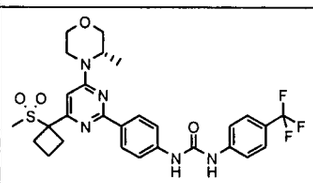
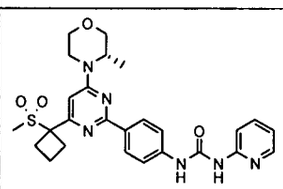
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,91 (2H, m), 2,08 (2H, m), 2,62(3H,d), 2,80 (2H, m), 2,87 (3H, s), 3,21 (1H, td), 3,50 (1H, td), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,24 (1H, d), 4,60 (1H, s), 6,07 (1H, d), 6,71 (1H, s), 7,50 (2H, d), 8,22 (2H, d), 8,75 (1H, s).

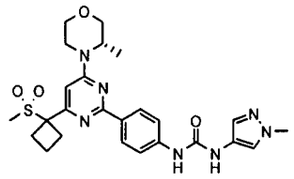
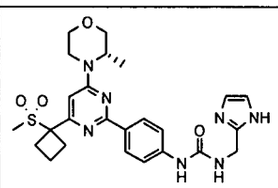
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 460; HPLC tR = 1,5 min

Ensayo de mTOR Quinasa (Echo): 0,000802μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
5a		3-etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea	474	1,98
5b		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea	486	2,01
5c		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-propan-2-il-urea	488	2,15
5d		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea	500	2,24
5e		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea	490	1,69
5f		3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea	518	1,97

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
5g		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea	517	1,98
5h		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-propil-urea	488	2,16
5i		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea	502	2,33
5j		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea	504	1,73
5k		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	590	2,84
5l		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-piridin-2-il-urea	523	2,42

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
5m		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	526	1,88
5n		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]urea	526	1,79

Ejemplo 5a: ^{1}H NMR (400,132 MHz, DMSO) δ 1,07 (3H, t), 1,24 (3H, d), 1,91 (2H, m), 2,07 (2H, m), 2,81 (2H, m), 2,87 (3H, s), 3,12 (2H, m), 3,22 (1H, m), 3,50 (1H, td), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,24 (1H, d), 4,59 (1H, s), 6,16 (1H, t), 6,71 (1H, s), 7,49 (2H, d), 8,22 (2H, d), 8,68 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000289μM

Ejemplo 5b: ^{1}H NMR (400,132 MHz, DMSO) δ 0,42 (2H, m), 0,65 (2H, m), 1,24 (3H, d), 1,92 (2H, m), 2,08 (2H, m), 2,56 (2H, m), 2,80 (2H, m), 2,88 (3H, s), 3,21 (1H, td), 3,54 (1H, s), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,24 (1H, d), 4,59 (1H, s), 6,45 (1H, s), 6,72 (1H, s), 7,51 (2H, d), 8,22 (2H, d), 8,55 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000383μM

Ejemplo 5c: ^{1}H NMR (400,132 MHz, DMSO) δ 1,11 (6H, d), 1,24 (3H, d), 1,86 - 1,96 (2H, m), 2,03 - 2,13 (2H, m), 2,76 - 2,84 (2H, m), 2,86 (3H, s), 3,21 (1H, td), 3,50 (1H, td), 3,65 (1H, dd), 3,73 - 3,80 (2H, m), 3,98 (1H, dd), 4,25 (1H, d), 4,61 (1H, s), 6,05 (1H, d), 6,72 (1H, s), 7,48 (2H, d), 8,21 (2H, d), 8,54 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00681μM

Ejemplo 5d: ^{1}H NMR (400,132 MHz, DMSO) δ 1,23 (3H, d), 1,58 - 1,67 (3H, m), 1,81 - 1,94 (4H, m), 2,02 - 2,11 (2H, m), 2,20 (2H, m), 2,76 - 2,84 (2H, m), 2,87 (3H, s), 3,21 (1H, td), 3,50 (1H, td), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,13 (1H, quinteto), 4,25 (1H, d), 4,61 (1H, s), 6,45 (1H, d), 6,71 (1H, s), 7,47 (2H, d), 8,21 (3H, d), 8,58 (2H, s).

Ensayo de mTOR Quinasa (Echo): 0,00385μM

Ejemplo 5e: ^{1}H NMR (400,132 MHz, DMSO) δ 1,24 (3H, d), 1,87 - 1,97 (2H, m), 2,01 - 2,12 (2H, m), 2,77 - 2,85 (2H, m), 2,88 (3H, s), 3,15 - 3,25 (3H, m), 3,43 - 3,54 (3H, m), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,24 (1H, d), 4,60 (1H, s), 4,72 (1H, t), 6,26 (1H, t), 6,71 (1H, s), 7,49 (2H, d), 8,23 (2H, d), 8,82 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000864μM

Ejemplo 5f: ^{1}H NMR (400,132 MHz, DMSO) δ 1,25 (14H, s), 1,87 - 1,95 (2H, m), 2,03 - 2,11 (2H, m), 2,76 - 2,83 (7H, m), 2,88 (7H, s), 3,17 - 3,25 (15H, m), 3,39 (2H, d), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, d), 4,24 (1H, d), 4,59 (1H, s), 4,95 (1H, t), 6,02 (1H, s), 6,72 (1H, s), 7,44 (2H, d), 8,21 (2H, d), 8,75 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00736μM

Ejemplo 5g: ^{1}H NMR (400,132 MHz, DMSO) δ 1,24 (3H, d), 1,87 - 1,96 (2H, m), 2,02 - 2,12 (2H, m), 2,21 (6H, s), 2,34 (2H, t), 2,74 - 2,85 (2H, m), 2,88 (3H, s), 3,15 - 3,26 (3H, m), 3,50 (1H, td), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,24 (1H, d), 4,60 (1H, s), 6,15 (1H, t), 6,72 (1H, s), 7,48 (2H, d), 8,21 (2H, d), 8,91 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0668μM

Ejemplo 5h: ^{1}H NMR (400,132 MHz, DMSO) δ 0,89 (3H, t), 1,24 (3H, d), 1,40 - 1,51 (2H, m), 1,87 - 1,97 (2H, m), 2,01 - 2,12 (2H, m), 2,76 - 2,84 (2H, m), 2,89 (3H, s), 3,06 (2H, q), 3,17 - 3,27 (1H, m), 3,50 (1H, td), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,24 (1H, d), 4,57 (1H, s), 6,20 (1H, t), 6,72 (1H, s), 7,49 (2H, d), 8,21 (2H, d), 8,66 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00234μM

Ejemplo 5i: ^{1}H NMR (400,132 MHz, DMSO) δ 0,89 (6H, d), 1,24 (3H, d), 1,65 - 1,75 (2H, m), 1,85 - 1,96 (2H, m), 2,01 - 2,12 (2H, m), 2,75 - 2,84 (2H, m), 2,88 (3H, s), 2,89 - 2,99 (3H, m), 3,16 - 3,26 (1H, m), 3,50 (1H, td), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,24 (1H, d), 4,56 (1H, s), 6,24 (1H, t), 6,72 (1H, s), 7,49 (2H, d), 8,22 (2H, d), 8,65 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00988μM

Ejemplo 5j: ^{1}H NMR (400,132 MHz, DMSO) δ 1,24 (3H, d), 1,59 (2H, q), 1,86 - 1,96 (2H, m), 2,02 - 2,14 (2H, m), 2,76 - 2,85 (2H, m), 2,88 (3H, s), 3,13 - 3,26 (3H, m), 3,45 - 3,54 (3H, m), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,24 (1H, d), 4,48 (1H, t), 4,56 (1H, s), 6,20 (1H, t), 6,72 (1H, s), 7,49 (2H, d), 8,21 (2H, d), 8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000239μM

Ejemplo 5k: Ensayo de mTOR Quinasa (Echo): 0,00333μM

Ejemplo 5l: Ensayo de mTOR Quinasa (Echo): 0,000248μM

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Ejemplo 5m: ^{1}H NMR (400,132 MHz, DMSO) δ 1,24 (3H, d), 1,87 - 1,98 (2H, m), 2,03 - 2,12 (2H, m), 2,76 - 2,84 (2H, m), 2,88 (3H, s), 3,17 - 3,30 (4H, m), 3,51 (1H, td), 3,65 (1H, dd), 3,73 - 3,80 (1H, m), 3,98 (1H, dd), 4,25 (1H, d), 4,62 (1H, s), 6,73 (1H, s), 7,39 (1H, s), 7,54 (2H, d), 7,77 (1H, s), 8,27 (2H, d), 8,40 (1H, s), 8,86 (1H, s).

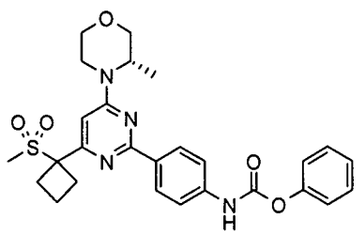
Ensayo de mTOR Quinasa (Echo): 0,00069μM

Ejemplo 5n: ^{1}H NMR (400,132 MHz, DMSO) δ 1,24 (3H, d), 1,87 - 1,97 (2H, m), 2,03 - 2,12 (2H, m), 2,75 - 2,85 (2H, m), 2,88 (3H, s), 3,21 (1H, td), 3,50 (1H, td), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,25 (1H, d), 4,32 (2H, d), 4,60 (1H, s), 6,62 (1H, t), 6,98 (2H, s), 7,52 (2H, d), 8,24 (2H, d), 11,88 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00828μM

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]carbamato

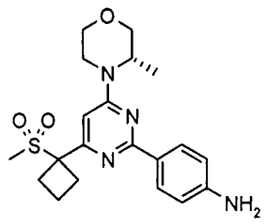


Se agregó hidrogenocarbonato de sodio (0,313 g, 3,73 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]anilina (1 g, 2,48 mmol), en dioxano (20 mL) a TA bajo nitrógeno. La mezcla resultante se enfrió hasta alcanzar 10°C y se agregó lentamente fenil cloroformiato (0,468 mL, 3,73 mmol). La reacción se agitó durante 3 horas y luego se diluyó con acetato de etilo (150 mL) y se lavó con agua (100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó. El sólido bruto se trituró con una mezcla de éter dietílico, iso-hexano y acetona para proporcionar el material deseado como un sólido blanco (1,35 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,21 (3H,d), 1,88-1,96 (2H,m), 2,02-2,11 (2H,m), 2,75-2,85 (2H,m), 2,85 (3H,s), 3,21 (1H,dd), 3,50 (1H,dd), 3,64 (1H,d), 3,75 (1H,d), 3,98 (1H,dd), 4,25 (1H,d), 4,57 (1H,s), 6,72 (1H,s), 7,20-7,30 (3H,m), 7,42 (2H,dd), 7,61 (2H,d), 8,32 (2H,m), 10,44 (1H,s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 523; HPLC tR = 2,88 min

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]anilina

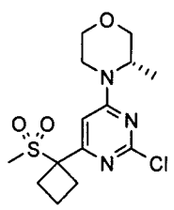


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,101 g, 0,14 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidina (1 g, 2,89 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,824 g, 3,76 mmol) y carbonato de sodio (5 mL, 10,00 mmol) en una mezcla de DMF (5 mL), DME (50 mL), etanol (20 mL) y agua (20 mL) a TA bajo nitrógeno. La mezcla resultante se agitó a 95°C durante 12 horas. La mezcla de reacción se diluyó con acetato de etilo (400 mL) y se lavó dos veces con agua (200 mL seguido por 250 mL), la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó. El producto bruto se cromatografió sobre sílice, eluyendo con 5 - 60% acetato de etilo en iso-hexano, para proporcionar el material deseado como un sólido crema (0,98 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,21 (3H,d), 1,85-1,95 (2H,m), 2,0-2,10 (2H,m), 2,71-2,82 (2H,m), 2,82 (3H,s), 3,18 (1H,dd), 3,50 (1H,dd), 3,62 (1H,dd), 3,75 (1H,d), 3,95 (1H,dd), 4,20 (1H,d), 4,53 (1H,s), 5,55 (2H,s), 6,60 (3H,d), 8,05 (2H,d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 403; HPLC tR = 2,17 min

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidina

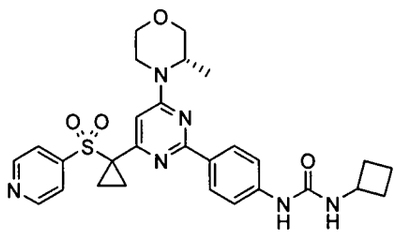


Se agregó bromuro de tetrabutilamonio (0,45 g, 1,40 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina (4,27 g, 13,96 mmol), 1,3-dibromopropano (1,42 mL, 13,96 mmol) y solución acuosa de hidróxido de sodio (30 mL, 368,9 mmol) en DCM (100 mL) a TA bajo nitrógeno. La mezcla resultante se agitó a 35°C durante 5 horas y luego se diluyó con DCM (50 mL) y se lavó con agua (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se cromatografió sobre sílice, eluyendo con 5 - 50% acetato de etilo en iso-hexano, para proporcionar el material deseado (1,0 g).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 346; HPLC tR = 1,92 min

La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina se describió anteriormente.

Ejemplo 6: 3-Ciclobutil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea



A una solución de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato (122 mg, 0,21 mmol) en DMF (2 mL) se agregó trietilamina (0,088 mL, 0,63 mmol) seguido por ciclobutilamina (0,090 mL, 1,05 mmol) y la reacción se calentó a 50°C durante toda la noche. El producto bruto se purificó mediante HPLC preparativa utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (90 mg).

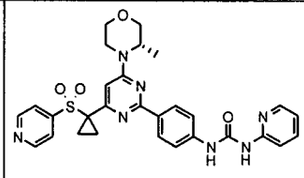
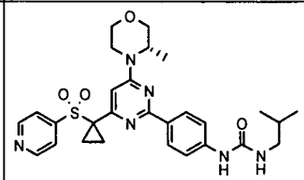
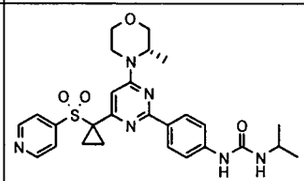
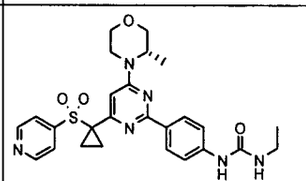
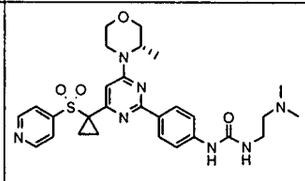
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18-1,20 (3H, d), 1,57-1,70 (4H, m), 1,82-1,91 (2H, m), 1,95-1,98 (2H, q), 2,18-2,25 (2H, m), 3,12-3,20 (1H, td), 3,43-3,50 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,11-4,17 (2H, m), 4,46 (1H, bs), 6,42-6,44 (1H, d), 6,67 (1H, s), 7,33-7,35 (2H, q), 7,65-7,67 (2H, d), 7,76-7,78 (2H, q), 8,53 (1H, s), 8,85-8,87 (2H, q).

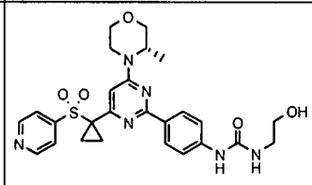
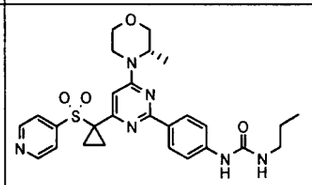
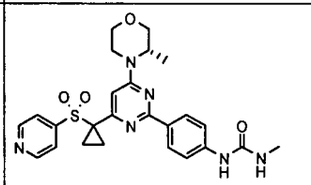
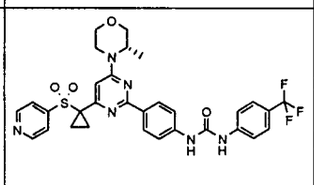
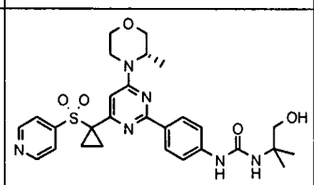
Espectro de LCMS: m/z (ESI+) $(M+H)^+$549 = HPLC tR = 2,25 min.

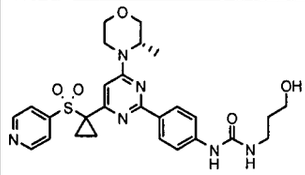
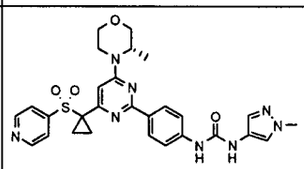
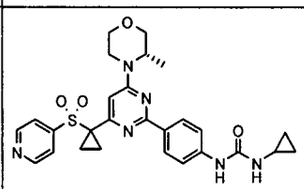
Ensayo de mTOR Quinasa (Echo): 0,001μM

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

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Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
6a		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-piridin-2-il-urea	572	2,44
6b		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea	551	2,33
6c		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propan-2-il-urea	537	2,17
6d		3-etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	523	2,03
6e		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	566	1,32

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
6f		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	539	1,75
6g		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propil-urea	537	2,18
6h		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	509	1,89
6i		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	639	2,84
6j		3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	567	2,01

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
6k		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	553	1,80
6l		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	575	1,96
6m		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	535	2,12

Ejemplo 6a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19-1,21 (3H, d), 1,69-1,72 (2H, q), 1,97-2,00 (2H, q), 3,15-3,22 (1H, td), 3,44-3,51 (1H, td), 3,61-3,64 (1H, dd), 3,74-3,77 (1H, d), 3,95-3,99 (1H, dd), 4,17-4,20 (1H, d), 4,48 (1H, bs), 6,71 (1H, s), 7,02-7,06 (1H, m), 7,49-7,51 (2H, d), 7,56-7,58 (1H, d), 7,74-7,79 (5H, m), 8,30-8,32 (1H, d), 8,88-8,89 (2H, q), 9,43 (1H, s), 10,55 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00293μM

Ejemplo 6b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,88-0,90 (6H, d), 1,18-1,20 (3H, d), 1,68-1,74 (3H, m), 1,96-1,98 (2H, q), 2,93-2,96 (2H, t), 3,13-3,20 (1H, td), 3,43-3,50 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,99 (1H, dd), 4,15-4,18 (1H, d), 4,45 (1H, bs), 6,20-6,23 (1H, t), 6,67 (1H, s), 7,34-7,36 (2H, d), 7,65-7,67 (2H, d), 7,77-7,78 (2H, q), 8,62 (1H, s), 8,86-8,87 (2H, q).

Ensayo de mTOR Quinasa (Echo): 0,00612μM

Ejemplo 6c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11-1,12 (6H, d), 1,18-1,20 (3H, d),

1,67-1,71 (2H, q), 1,96-1,98 (2H, q), 3,13-3,20 (1H, td), 3,43-3,50 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,82 (2H, m), 3,94-3,98 (1H, dd), 4,14-4,18 (1H, d), 4,46 (1H, bs), 6,02-6,04 (1H, d), 6,67 (1H, s), 7,32-7,36 (2H, q), 7,64-7,67 (2H, q), 7,76-7,78 (2H, q), 8,50 (1H, s), 8,86-8,87 (2H, q).

Ensayo de mTOR Quinasa (Echo): 0,00321μM

Ejemplo 6d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,05-1,09 (2H, t), 1,18-1,20 (3H, d), 1,67-1,71 (2H, q), 1,96-1,98 (2H, q), 3,09-3,20 (4H, m), 3,43-3,50 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,15-4,17 (1H, d), 4,46 (1H, bs), 6,12-6,15 (1H, t), 6,67 (1H, s), 7,35-7,37 (2H, q), 7,65-7,67 (2H, d), 7,77-7,78 (2H, q), 8,63 (1H, s), 8,86-8,87 (2H, q).

Ensayo de mTOR Quinasa (Echo): 0,000874μM

Ejemplo 6e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18-1,20 (3H, d), 1,67-1,71 (2H, q), 1,96-1,98 (2H, q), 2,18 (6H, s), 2,32-2,35 (2H, t), 3,13-3,21 (3H, m), 3,43-3,50 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,15-4,18 (1H, d), 4,47 (1H, bs), 6,12-6,15 (1H, t), 6,67 (1H, s), 7,34-7,37 (2H, q), 7,65-7,67 (2H, d), 7,76-7,78 (2H, q), 8,86-8,87 (3H, m).

Ensayo de mTOR Quinasa (Echo): 0,0673μM

Ejemplo 6f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18-1,20 (3H, d), 1,67-1,71 (2H, q), 1,96-1,98 (2H, q), 3,13-3,20 (3H, m), 3,43-3,50 (3H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,15-4,18 (1H, d), 4,46 (1H, bs), 4,71-4,74 (1H, t), 6,21-6,24 (1H, t), 6,67 (1H, s), 7,34-7,36 (2H, q), 7,65-7,67 (2H, d), 7,76-7,78 (2H, q), 8,77 (1H, s), 8,86-8,87 (2H, q).

Ensayo de mTOR Quinasa (Echo): 0,000794μM

Ejemplo 6g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,87-0,91 (3H, t), 1,18-1,20 (3H, d), 1,41-1,50 (2H, m), 1,67-1,71 (2H, q), 1,96-1,98 (2H, q), 3,04-3,09 (2H, q), 3,13-3,19 (1H, td), 3,43-3,50 (1H, td), 3,59-3,63 (1H, td), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,14-4,18 (1H, d), 4,47 (1H, bs), 6,16-6,19 (1H, t), 6,67 (1H, s), 7,34-7,36 (2H, d), 7,65-7,67 (2H, d0, 7,77-7,78 (2H, q), 8,62 (1H, s), 8,86-8,87 (2H, q).

Ensayo de mTOR Quinasa (Echo): 0,00225μM

Ejemplo 6h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18-1,20 (3H, d), 1,67-1,71 (2H, q), 1,96-1,98 (2H, q), 2,65-2,67 (3H, d), 3,13-3,20 (1H, td), 3,43-3,50 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,15-4,17 (1H, d), 4,46 (1H, bs), 6,02-6,06 (1H, q), 6,67 (1H, s), 7,35-7,38 (2H, q), 7,65-7,67 (2H, d), 7,77-7,78 (2H, q), 8,71 (1H, s), 8,86-8,87

(2H, q).

Ensayo de mTOR Quinasa (Echo): 0,000799μM

Ejemplo 6i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19-1,21 (3H, d), 1,69-1,72 (2H, q), 1,97-2,00 (2H, q), 3,14-3,21 (1H, td), 3,44-3,50 (1H, td), 3,61-3,64 (1H, dd), 3,74-3,77 (1H, d), 3,95-3,98 (1H, dd), 4,16-1,20 (1H, d), 4,48 (1H, bs), 6,70 (1H, s), 7,44-7,46 (2H, d), 7,64-7,70 (4H, q), 7,72-7,75 (2H, q), 7,78-7,79 (2H, q), 8,87-8,89 (2H, q), 9,03 (1H, s), 9,11 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00462μM

Ejemplo 6j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18-1,20 (3H, d), 1,24 (6H, s), 1,67-1,70 (2H, q), 1,96-1,99 (2H, q), 3,13-3,20 (1H, td), 3,38-3,40 (2H, d), 3,43-3,50 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,15-4,18 (1H, d), 4,46 (1H, bs), 4,94-4,96 (1H, t), 5,97 (1H, s), 6,67 (1H, s), 7,30-7,32 (2H, d), 7,63-7,65 (2H, q), 7,76-7,78 (2H, q), 8,71 (1H, s), 8,86-8,87 (2H, q).

Ensayo de mTOR Quinasa (Echo): 0,00593μM

Ejemplo 6k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18-1,20 (3H, d), 1,57-1,63 (2H, m), 1,67-1,71 (2H, q), 1,96-1,98 (2H, q), 3,13-3,20 (3H, m), 3,43-3,50 (3H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,14-4,18 (1H, d), 4,46 (1H, bs), 4,46-4,49 (1H, t), 6,16-6,19 (1H, t), 6,67 (1H, s), 7,34-7,36 (2H, q), 7,65-7,67 (2H, d), 7,76-7,78 (2H, q), 8,68 (1H, s), 8,86-8,87 (2H, q).

Ensayo de mTOR Quinasa (Echo): 0,00186μM

Ejemplo 6l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19-1,20 (3H, d), 1,68-1,71 (2H, q), 1,96-1,99 (2H, q), 3,13-3,21 (1H, td), 3,44-3,50 (1H, td), 3,60-3,63 (1H, dd), 3,74-3,77 (1H, d), 3,79 (3H, s), 3,95-3,98 (1H, dd), 4,16-4,19 (1H, d), 4,47 (1H, bs), 6,68 (1H, s), 7,39-7,42 (3H, m), 7,68-7,70 (2H, d), 7,77-7,79 (3H, m), 8,37 (1H, s), 8,82 (1H, s), 8,86-8,88 (2H, q).

Ensayo de mTOR Quinasa (Echo): 0,00119μM

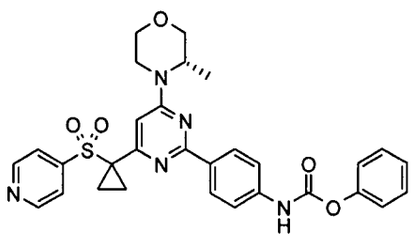
Ejemplo 6m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40-0,44 (2H, m), 0,63-0,67 (2H, m), 1,18-1,20 (3H, d), 1,68-1,71 (2H, q), 1,96-1,99 (2H, q), 2,53-2,59 (1H, m), 3,13-3,20 (1H, td), 3,43-3,63 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,15-4,18 (1H, d), 4,46 (1H, bs), 6,40-6,41 (1H, d), 6,67 (1H, s), 7,36-7,38 (2H, q), 7,65-7,68 (2H, q), 7,77-7,78 (2H, q), 8,51 (1H, s), 8,86-8,87 (2H, q).

Ensayo de mTOR Quinasa (Echo): 0,000936μM

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-

ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato

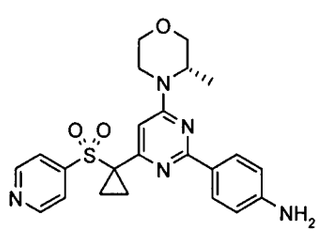


Se agregó fenil cloroformiato (0,341 mL, 2,71 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]anilina (1,224 g, 2,71 mmol) y bicarbonato de sodio (0,342 g, 4,07 mmol) en dioxano (175 mL) a TA al aire. La suspensión resultante se agitó a TA durante 2 horas. Se agregaron porciones adicionales de fenil cloroformiato (2 x 0,005 mL) a la reacción. Se agregó agua a la mezcla de reacción y el material se extrajo con DCM. Los orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 4% metanol en DCM, para proporcionar el material deseado como un sólido beige (1,72 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,28-1,29 (3H, d), 1,60-1,69 (2H, m), 1,97-2,05 (2H, m), 3,22-3,30 (1H, td), 3,52-3,59 (1H, td), 3,71-3,72 (1H, dd), 3,78-3,81 (1H, d), 3,99-4,03 (1H, dd), 4,09-4,13 (1H, d), 4,38-4,39 (1H, bs), 6,72 (1H, s), 7,13-7,15 (2H, d), 7,19-7,21 (1H, t), 7,32-7,36 (2H, t), 7,46-7,48 (2H, d), 7,61-7,63 (2H, q), 7,97-7,99 (2H, d), 8,74-8,75 (2H, q).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 450; HPLC tR = 2,66 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]anilina

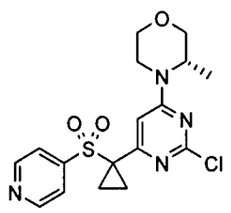


Se agregó trans-diclorobis(trifenilfosfina)paladio (II) (0,095 g, 0,14 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidina (1,07 g, 2,71 mmol), 4-

(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,89 g, 4,06 mmol) y carbonato de sodio (6,77 mL, 13,55 mmol) en 18% DMF en una mezcla 7:3:2 de DME:agua:etanol (50 mL) a TA bajo nitrógeno. La solución resultante se agitó a 80°C durante 5 horas. La reacción se enfrió y se diluyó con acetato de etilo y agua. La mezcla de reacción se extrajo con acetato de etilo, los orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el material deseado (1,224 g).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 452; HPLC tR = 2,03 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidina

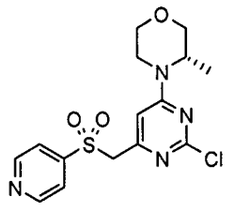


Se agregó hidróxido de sodio acuoso 50% v/v (23 mL, 9,52 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfonilmetil)pirimidina (3,51 g, 9,52 mmol), 1,2-dibromoetano (0,820 mL, 9,52 mmol) y bromuro de tetrabutilamonio (0,307 g, 0,95 mmol) en DCM (100 mL) y la reacción se entibió hasta alcanzar 30°C al aire. La suspensión resultante se agitó a 30°C durante 4 horas y luego se dejó enfriar, se agregó DCM y las capas se separaron. La capa orgánica se lavó con agua, se secó ($MgSO_4$) y se filtró. La solución resultante se evaporó en sílice y se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 60% acetato de etilo en DCM, para proporcionar el material deseado como un sólido amarillo (1,07 g).

Espectro de NMR: ^1H NMR (400,132 MHz, DMSO-D_6) δ 1,15-1,16 (3H, d), 1,61-1,65 (2H, m), 1,90-1,93 (2H, m), 3,11-3,19 (1H, td), 3,37-3,44 (1H, td), 3,53-3,57 (1H, dd), 3,68-3,71 (1H, d), 3,89-3,96 (1H, dd), 3,96 (1H, bs), 4,28 (1H, bs), 6,75 (1H, s), 7,74-7,75 (2H, dd), 8,88-8,90 (2H, dd).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 395; HPLC tR = 1,65 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfonilmetil)pirimidina

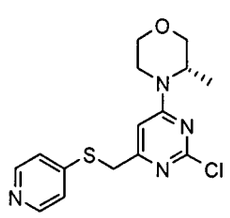


Una solución de peróxido de hidrógeno (1,799 mL, 58,19 mmol) se agregó gota a gota a una solución agitada de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfanilmetil)pirimidina (0,980 g, 2,91 mmol), tungstato de sodio dihidrato (0,005 mL, 0,06 mmol) y ácido sulfúrico 2N (0,075 mL) en dioxano (200 mL) a 55°C, durante un período de 5 minutos al aire. La solución resultante se agitó a 55 °C durante 3 horas. Se agregó agua (200mL) y la reacción se enfrió, los sólidos se filtraron, se lavaron con agua y se secaron en el horno de vacío a 50°C durante toda la noche para proporcionar el material deseado como un sólido blanco (0,580 g). Se obtuvo material adicional mediante extracción de la capa acuosa con DCM. Los extractos se secaron ($MgSO_4$), se filtraron, se evaporaron y se cromatografiaron sobre sílice, eluyendo con 0 - 3% metanol en DCM, para proporcionar una porción adicional del material deseado (0,144 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,17-1,19 (3H, d), 3,14-3,22 (1H, td), 3,40-3,47 (1H, td), 3,56-3,60 (1H, dd), 3,71-3,74 (1H, d), 3,90 (1H, bs), 3,91-3,95 (1H, dd), 4,20 (1H, bs), 4,79 (2H, s), 6,79 (1H, s), 7,77-7,79 (2H, q), 8,92-8,93 (2H, q).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 369; HPLC tR = 1,40 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfanilmetil)pirimidina



Se agregó 4-mercaptopiridina (0,752 g, 6,77 mmol) a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,596 g, 4,51 mmol) en acetonitrilo (100 mL) a TA al aire. Luego se agregó DBU (0,3 mL, 2,01 mmol) y la solución resultante se agitó a TA durante 2 minutos. El disolvente se retiró y se agregó DCM. La mezcla de reacción se lavó secuencialmente con agua, la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se cromatografió sobre sílice, eluyendo con 0 - 2% metanol en DCM. Las fracciones puras se cromatografiaron adicionalmente sobre sílice, eluyendo con 0 – 4,5%

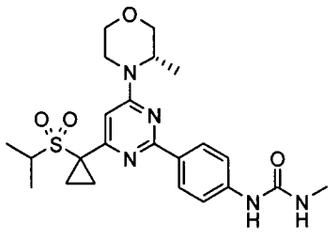
metanol en DCM y se combinaron con las fracciones puras iniciales para proporcionar el material deseado como una goma amarilla (0,980 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,14-1,16 (3H, d), 3,11-3,18 (1H, td), 3,37-3,44 (1H, td), 3,53-3,57 (1H, dd), 3,64-3,67 (1H, d), 3,86-3,90 (2H, dd), 4,01 (2H, s), 4,14 (1H, bs), 6,43 (1H, s), 7,04-7,06 (2H, d), 8,29-8,30 (2H, d).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 337; HPLC tR = 1,62 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente

Ejemplo 7: 3-Metil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea



A una solución de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato (120 mg, 0,22 mmol) en DMF (2 mL) se agregó trietilamina (0,094 mL, 0,67 mmol) seguido por metilamina (0,5 mL, 1,1 mmol) y la reacción se calentó a 50°C durante 2 horas. El producto bruto se purificó mediante HPLC preparativa utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (71 mg).

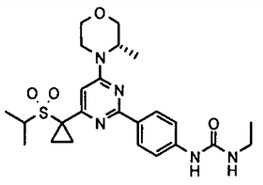
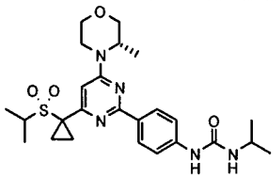
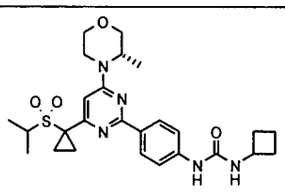
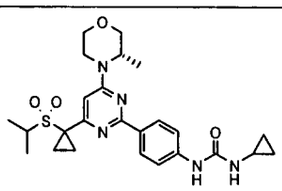
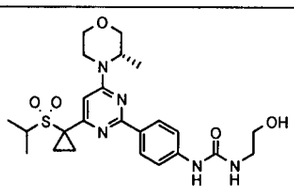
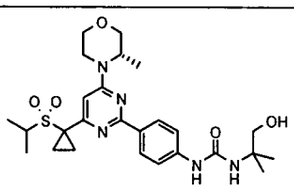
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,34 (6H, dd), 1,55 - 1,62 (4H, m), 2,66 (3H, d), 3,17 - 3,24 (1H, m), 3,48 (1H, dt), 3,60 - 3,67 (2H, m), 3,76 (1H, d), 3,98 (1H, dd), 4,19 (1H, d), 4,53 (1H, s), 6,07 (1H, d), 6,79 (1H, s), 7,50 (2H, d), 8,18 (2H, d), 8,74 (1H, s)

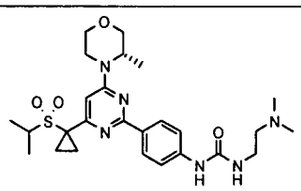
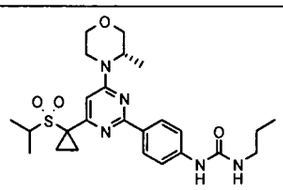
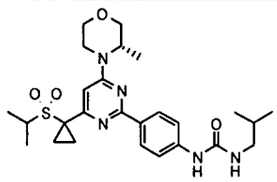
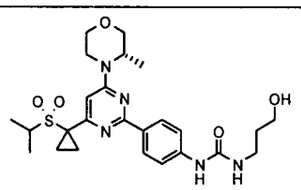
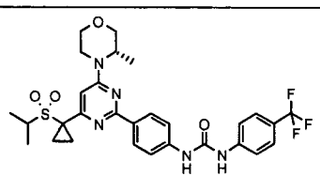
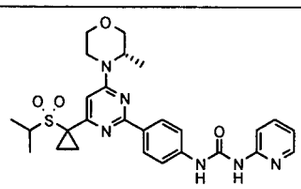
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 474; HPLC tR = 1,92 min.

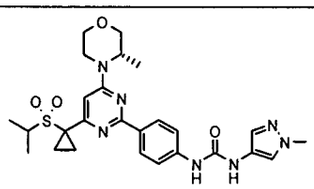
Ensayo de mTOR Quinasa (Echo): 0,00315μM

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato

utilizando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
7a		1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	488	1,92
7b		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propan-2-il-urea	502	2,08
7c		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	514	2,24
7d		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	500	2,34
7e		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	504	2,09
7f		3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	532	1,77

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
7g		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	531	2,06
7h		3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-1-propil-urea	502	2,00
7i		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea	516	2,26
7j		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	518	2,43
7k		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	604	1,81
7l		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-piridin-2-il-urea	537	2,95

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
7m		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	540	2,54

Ejemplo 7a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,23 (3H, d), 1,34 (6H, dd), 1,52 - 1,61 (4H, m), 3,09 - 3,16 (2H, m), 3,16 - 3,23 (1H, m), 3,49 (1H, dt), 3,62 - 3,67 (2H, m), 3,76 (1H, d), 3,97 (1H, d), 4,19 (1H, d), 4,53 (1H, s), 6,17 (1H, t), 6,79 (1H, s), 7,50 (2H, d), 8,18 (2H, d), 8,66 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00231μM

Ejemplo 7b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11 (6H, d), 1,23 (3H, d), 1,34 (6H, dd), 1,52 - 1,61 (4H, m), 3,15 - 3,24 (1H, m), 3,49 (1H, dt), 3,60 - 3,67 (2H, m), 3,73 - 3,82 (2H, m), 3,97 (1H, dd), 4,19 (1H, d), 4,53 (1H, s), 6,07 (1H, d), 6,79 (1H, s), 7,48 (2H, d), 8,18 (2H, d), 8,53 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0181μM

Ejemplo 7c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,33 (3H, d), 1,35 (3H, d), 1,52 - 1,66 (6H, m), 1,81 - 1,91 (2H, m), 2,18 - 2,25 (2H, m), 3,20 (1H, dt), 3,48 (1H, dt), 3,60 - 3,67 (2H, m), 3,76 (1H, d), 3,97 (1H, dd), 4,09 - 4,21 (2H, m), 4,53 (1H, s), 6,47 (1H, d), 6,79 (1H, s), 7,48 (2H, d), 8,18 (2H, d), 8,56 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00646μM

Ejemplo 7d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,63 - 0,67 (2H, m), 1,23 (3H, d), 1,33 (3H, d), 1,35 (3H, d), 1,53 - 1,62 (4H, m), 2,54 - 2,58 (1H, m), 3,17 - 3,24 (1H, m), 3,49 (1H, dt), 3,60 - 3,67 (2H, m), 3,76 (1H, d), 3,97 (1H, dd), 4,20 (1H, d), 4,53 (1H, s), 6,44 (1H, d), 6,80 (1H, s), 7,51 (2H, d), 8,19 (2H, d), 8,53 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0038μM

Ejemplo 7e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,33 (3H, d), 1,35 (3H, d), 1,54 - 1,61 (4H, m), 3,16 - 3,24 (3H, m), 3,44 - 3,52 (3H, m), 3,60 - 3,67 (2H, m), 3,76 (1H, d), 3,97 (1H, dd), 4,19 (1H, d), 4,52 (1H, s), 4,73 (1H, t), 6,26 (1H, t), 6,79 (1H, s), 7,50 (2H,

d), 8,19 (2H, d), 8,80 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00212μM

Ejemplo 7f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,24 (6H, s), 1,34 (3H, d), 1,35 (3H, d), 1,55 - 1,62 (4H, m), 3,15 - 3,23 (1H, m), 3,39 (2H, d), 3,49 (1H, dt), 3,62 - 3,68 (2H, m), 3,76 (1H, d), 3,97 (1H, d), 4,20 (1H, d), 4,52 (1H, s), 4,95 (1H, t), 6,01 (1H, s), 6,79 (1H, s), 7,46 (2H, d), 8,18 (2H, d), 8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00915μM

Ejemplo 7g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,33 (3H, d), 1,35 (3H, d), 1,52 - 1,61 (4H, m), 2,18 (6H, s), 2,34 (2H, t), 3,17 - 3,24 (3H, m), 3,49 (1H, dt), 3,60 - 3,67 (2H, m), 3,76 (1H, d), 3,97 (1H, dd), 4,19 (1H, d), 4,52 (1H, s), 6,16 (1H, t), 6,79 (1H, s), 7,49 (2H, d), 8,18 (2H, d), 8,89 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,211μM

Ejemplo 7h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,23 (3H, d), 1,33 (3H, d), 1,35 (3H, d), 1,43 - 1,49 (2H, m), 1,53 - 1,62 (4H, m), 3,07 (2H, q), 3,16 - 3,23 (1H, m), 3,49 (1H, dt), 3,60 - 3,67 (2H, m), 3,76 (1H, d), 3,97 (1H, d), 4,20 (1H, d), 4,54 (1H, s), 6,21 (1H, t), 6,79 (1H, s), 7,50 (2H, d), 8,19 (2H, d), 8,64 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0116μM

Ejemplo 7i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (6H, d), 1,23 (3H, d), 1,33 (3H, d), 1,35 (3H, d), 1,55 - 1,62 (4H, m), 1,67 - 1,74 (1H, m), 2,94 (2H, t), 3,18 - 3,23 (1H, m), 3,46 - 3,51 (1H, m), 3,60 - 3,67 (2H, m), 3,76 (1H, d), 3,97 (1H, dd), 4,20 (1H, d), 4,51 (1H, s), 6,25 (1H, t), 6,79 (1H, s), 7,49 (2H, d), 8,19 (2H, d), 8,64 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0182μM

Ejemplo 7j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,33 (3H, d), 1,35 (3H, d), 1,53 - 1,63 (4H, m), 3,15 - 3,23 (4H, m), 3,45 - 3,51 (4H, m), 3,60 - 3,67 (2H, m), 3,76 (1H, d), 3,97 (1H, d), 4,19 (1H, d), 4,47 (1H, t), 4,53 (1H, s), 6,21 (1H, t), 6,79 (1H, s), 7,50 (2H, d), 8,18 (2H, d), 8,71 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0105μM

Ejemplo 7k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,34 (3H, d), 1,36 (3H, d), 1,54 - 1,64 (4H, m), 3,19 - 3,25 (1H, m), 3,50 (1H, t), 3,61 - 3,66 (2H, m), 3,77 (1H, d), 3,98 (1H, d), 4,22 (1H, d), 4,55 (1H, s), 6,82 (1H, s), 7,59 (2H, d), 7,64 - 7,70 (4H, m), 8,27 (2H, d), 9,04 (1H, s), 9,14 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00482μM

Ejemplo 7l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,35 (3H, d), 1,37 (3H, d),

1,57 - 1,61 (4H, m), 3,18 - 3,27 (1H, m), 3,50 (1H, dt), 3,63 - 3,70 (2H, m), 3,77 (1H, d), 3,98 (1H, dd), 4,21 (1H, d), 4,55 (1H, s), 6,82 (1H, s), 7,02 - 7,05 (1H, m), 7,55 - 7,58 (1H, m), 7,65 (2H, d), 7,77 (1H, t), 8,27 - 8,31 (3H, m), 9,47 (1H, s), 10,62 (1H, s).

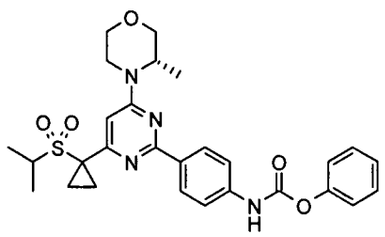
Ensayo de mTOR Quinasa (Echo): 0,00913μM

Ejemplo 7m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,34 (3H, d), 1,36 (3H, d), 1,53 - 1,63 (4H, m), 3,17 - 3,25 (1H, m), 3,49 (1H, t), 3,61 - 3,68 (2H, m), 3,77 (1H, d), 3,79 (3H, s), 3,97 (1H, d), 4,20 (1H, d), 4,53 (1H, s), 6,81 (1H, s), 7,38 (1H, s), 7,55 (2H, d), 7,76 (1H, s), 8,22 (2H, d), 8,39 (1H, s), 8,83 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00504μM

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato

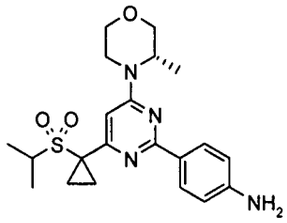


A una solución de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]anilina (1,47 g, 3,53 mmol) en 1,4-dioxano (17,65 mL) se agregó bicarbonato de sodio (0,445 g, 5,29 mmol) y fenil cloroformiato (0,474 mL, 3,77 mmol) y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con DCM (20 mL) y se lavó con agua (20 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El sólido bruto se trituró con éter dietílico para proporcionar un sólido que se recogió mediante filtración y se secó al vacío para proporcionar el producto deseado como un sólido blanco (1,56 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,27 (3H, d), 1,28 (3H, d), 1,49 - 1,55 (4H, m), 3,14 (1H, dt), 3,39 - 3,44 (1H, m), 3,53 - 3,60 (2H, m), 3,70 (1H, d), 3,90 (1H, dd), 4,14 (1H, d), 4,47 (1H, s), 6,77 (1H, s), 7,17 - 7,23 (3H, m), 7,38 (2H, t), 7,57 (2H, d), 8,22 (2H, d), 10,37 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 537; HPLC tR = 2,39 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidin-2-il]anilina

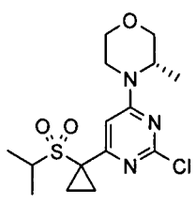


A una solución de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidina (1,6 g, 4,45 mmol) en DMF (0,24 mL), DME (9,33 mL), agua (4,0 mL) y etanol (2,67 mL) se agregaron 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,266 g, 5,78 mmol), carbonato de sodio (5 mL, 10,00 mmol) y diclorobis(trifenilfosfina)paladio(II) (0,156 g, 0,22 mmol) y la suspensión se calentó a 95°C durante 2 horas. La mezcla de reacción se enfrió hasta alcanzar TA, se diluyó con acetato de etilo (10 mL) y se lavó con agua (2 x 10 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 5 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido crema (1,47 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,32 (3H, d), 1,34 (3H, d), 1,50 - 1,59 (4H, m), 3,17 (1H, dt), 3,44 - 3,51 (1H, m), 3,59 - 3,66 (2H, m), 3,75 (1H, d), 3,96 (1H, dd), 4,16 (1H, d), 4,49 (1H, d), 5,56 (2H, s), 6,61 (2H, d), 6,69 (1H, s), 8,02 (2H, d)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 417; HPLC tR = 2,09 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-propan-2-ilsulfonilciclopropil)pirimidina



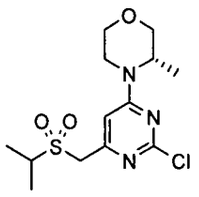
Se disolvió 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(propan-2-ilsulfonilmetil)pirimidina (2,4 g, 7,19 mmol) en DCM (40 mL) y se agregó a la reacción hidróxido de sodio concentrado (7,2 mL, 71,89 mmol), seguido por dibromoetano (0,325 mL, 14,38 mmol). La reacción se agitó a 40°C durante 10 horas. La mezcla de reacción se lavó con agua (50 mL) y la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (1,49

g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,27 (6H, d), 1,52 - 1,54 (2H, m), 1,56 - 1,59 (2H, m), 3,21 - 3,24 (1H, m), 3,41 - 3,47 (1H, m), 3,55 - 3,61 (2H, m), 3,72 (1H, d), 3,93 (1H, dd), 4,02 (1H, d), 4,37 (1H, s), 6,94 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 360, HPLC tR = 1,89 min

2-Cloro-4-[(3S)-3-metilmorfolin-4-il]-6-(propan-2-ilsulfonilmetil)pirimidina

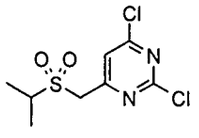


Se disolvió 2,4-dicloro-6-[(isopropilsulfonil)metil]pirimidina (2,65 g, 9,85 mmol) en DCM (50 mL) y se agitó (bajo nitrógeno) a -5°C. Se agregó trietilamina (1,5 mL, 10,84 mmol) para proporcionar una solución marrón clara. Se disolvió (3*S*)-3-metil morfolina (997 mg, 9,85 mmol) en DCM y se agregó gota a gota manteniendo la reacción por debajo de -5°C. Luego se retiró el baño de enfriamiento y la mezcla de reacción se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción luego se lavó con agua (50 mL), se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El material bruto se cromatografió sobre sílice, eluyendo con 0-50% acetato de etilo en DCM para proporcionar el material deseado como un sólido blanco (2 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (d, 3H), 1,31 (d, 6H), 3,22 (m, 1H), 3,43 (m, 2H), 3,60 (m, 1H), 3,74 (d, 1H), 3,98 (m, 1H), 4,30 (s, 1H), 4,43 (s, 2H), 6,91 (s, 1H)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 332, HPLC tR = 1,70 min

2,4-Dicloro-6-[(isopropilsulfonil)metil]pirimidina



Se disolvió 2,4-dicloro-6-[(isopropiltio)metil]pirimidina (6,2 g, 26,16 mmol) en DCM (100 mL) y ácido 3,5-diclorobencenocarboperoxoico (13,5 g, 78,4 mmol) se agregó en porciones durante 10 minutos. La reacción se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción luego se lavó con bicarbonato de sodio acuoso saturado (50 mL), se secó sobre

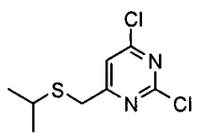
320

sulfato de magnesio, se filtró y se concentró al vacío para proporcionar un sólido crema. La purificación mediante cromatografía de fase normal, eluyendo con 0-50% acetato de etilo en iso-hexano proporcionó el material deseado como un sólido crema (5,3 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,25 (d, 6H), 3,43 (m, 1H), 4,77 (s, 2H), 7,87 (s, 1H)

Espectro de LCMS: m/z $(M-H)^-$ 267, HPLC tR = 1,64 min

2,4-Dicloro-6-[(isopropiltio)metil]pirimidina

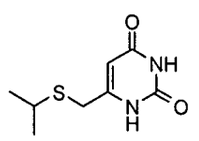


6-[(Isopropiltio)metil]pirimidina-2,4(1*H*,3*H*)-diona (8 g, 40 mmol) se agregó a oxicloruro de fósforo (100 mL) y la mezcla se calentó hasta alcanzar reflujo durante 16 horas. La reacción luego se enfrió hasta alcanzar temperatura ambiente y el exceso de oxicloruro de fósforo se retiró al vacío. El residuo se sometió a azeotropía con tolueno (2 x 100 mL) y se disolvió en DCM. Esta mezcla luego se vertió lentamente en hielo (1 L) y se agitó durante 20 minutos, luego se extrajo con DCM (3 x 500 mL). Los extractos se combinaron, se secaron sobre sulfato de magnesio, luego se concentraron al vacío para proporcionar el material deseado como un aceite marrón (6,5 g). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (d, 6H), 2,96 (m, 1H), 3,85 (s, 2H), 7,82 (s, 1H)

Espectro de LCMS: No se observó ion másico, HPLC tR = 2,51 min

6-[(Isopropiltio)metil]pirimidina-2,4(1*H*,3*H*)-diona



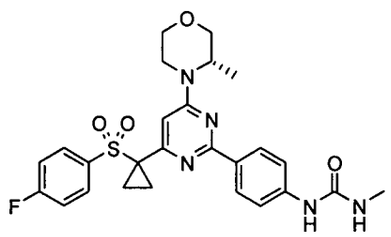
Se disolvió 6-(clorometil)-1*H*-pirimidina-2,4-diona (8 g, 50 mmol) en acetonitrilo (200 mL) y se agregó 1,8-diazabiciclo[5,4,0]undec-7-eno (13 mL, 87,19 mmol) y la reacción se agitó a temperatura ambiente durante 15 minutos. Luego se agregó isopropil mercaptano (8,1 mL, 87,19 mmol) y la reacción se agitó a temperatura ambiente durante otras 2 horas. El disolvente se retiró al vacío y el aceite marrón resultante se disolvió en DCM y se lavó con

agua. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El aceite resultante se cromatografió sobre sílice, eluyendo con 0-10% metanol en DCM para proporcionar el material deseado como un sólido blanco (8 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (d, 6H), 2,90 (m, 1H), 3,42 (s, 2H), 5,49 (s, 1H), 10,82 (s, 1H), 10,94 (s, 1H)

Espectro de LCMS: m/z $(M-H)^-$ 199, HPLC tR = 0,63 min

Ejemplo 8: 1-[4-[4-[1-(4-Fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea



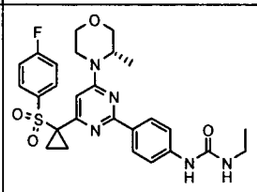
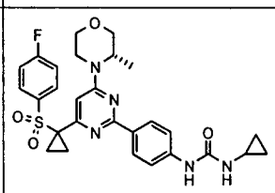
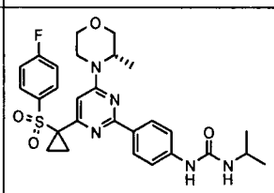
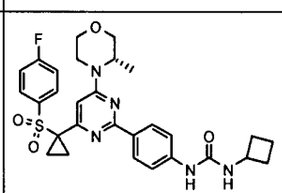
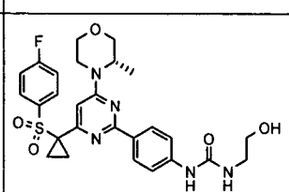
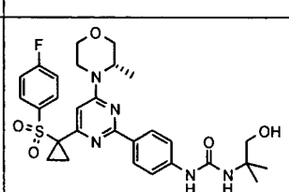
A una solución de fenil *N*-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (100 mg, 0,17 mmol) en DMF (2 mL) se agregó trietilamina (0,071 mL, 0,51 mmol) seguido por metilamina (0,5 mL, 1,1 mmol) y la reacción se calentó a 50°C durante 2 horas. El producto bruto se purificó mediante HPLC preparativa utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (51 mg).

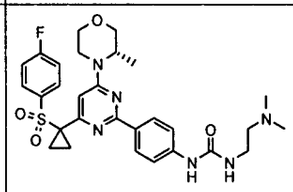
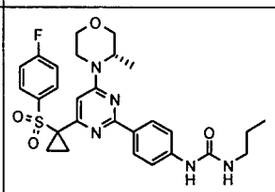
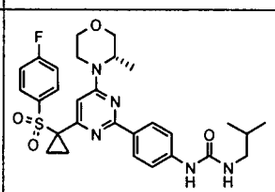
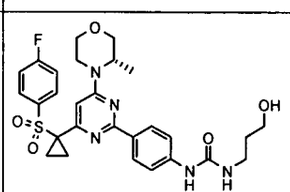
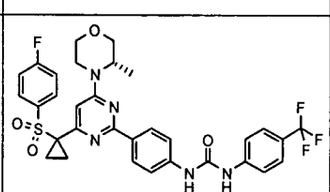
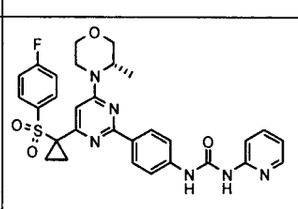
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,59 - 1,62 (2H, m), 1,88 - 1,90 (2H, m), 2,66 (3H, d), 3,15 (1H, dt), 3,46 (1H, dt), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,13 (1H, d), 4,42 (1H, s), 6,03 (1H, d), 6,65 (1H, s), 7,38 - 7,44 (4H, m), 7,79 - 7,86 (4H, m), 8,71 (1H, s)

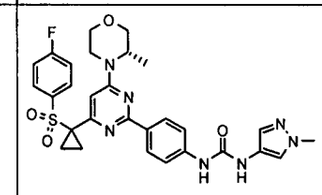
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 526; HPLC tR = 2,09 min.

Ensayo de mTOR Quinasa (Echo): 0,000576μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
8a		1-etil-3-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	540	2,23
8b		3-ciclopropil-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	552	2,25
8c		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-il-urea	554	2,40
8d		3-ciclobutil-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	566	2,47
8e		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	556	1,92
8f		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metil-propan-2-il)urea	584	2,22

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
8g		3-(2-dimetilaminoetil)-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	583	2,17
8h		3-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propil-urea	554	2,40
8i		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea	568	2,55
8j		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	570	1,97
8k		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	656	3,01
8l		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-	589	2,63

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		2-il-urea		
8m		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	592	2,12

El **Ejemplo 8** también puede prepararse en forma análoga a la descrita anteriormente pero utilizando NMP como disolvente y agitando a 75°C durante 30 minutos. El material luego puede dividirse entre acetato de etilo y agua y los materiales orgánicos se purificaron mediante cromatografía en sílice, eluyendo con 0-3% metanol en acetato de etilo. El material luego puede disolverse en DCM y evaporarse rápidamente para proporcionar el material deseado como una espuma o dejarse reposar durante aproximadamente 6 semanas, tiempo durante el cual el material deseado se precipita de la solución.

Ejemplo 8a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06 (3H, t), 1,18 (3H, d), 1,59 - 1,62 (2H, m), 1,88 - 1,90 (2H, m), 3,09 - 3,18 (3H, m), 3,46 (1H, dt), 3,61 (1H, dd), 3,75 (1H, d), 3,95 (1H, dd), 4,13 (1H, d), 4,42 (1H, s), 6,12 (1H, t), 6,65 (1H, s), 7,37 - 7,46 (4H, m), 7,79 - 7,86 (4H, m), 8,63 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00096μM

Ejemplo 8b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,19 (3H, d), 1,58 - 1,63 (2H, m), 1,89 - 1,91 (2H, m), 2,55 - 2,58 (1H, m), 3,15 (1H, t), 3,46 (1H, t), 3,61 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,14 (1H, d), 4,42 (1H, s), 6,39 (1H, s), 6,65 (1H, s), 7,39 - 7,44 (4H, m), 7,80 - 7,86 (4H, m), 8,51 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00123μM

Ejemplo 8c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11 (6H, d), 1,18 (3H, d), 1,58 - 1,62 (2H, m), 1,88 - 1,90 (2H, m), 3,15 (1H, t), 3,46 (1H, t), 3,61 (1H, d), 3,73 - 3,81 (2H, m), 3,96 (1H, d), 4,13 (1H, d), 4,42 (1H, s), 6,02 (1H, d), 6,65 (1H, s), 7,37 (2H, d), 7,42 (2H, t), 7,79 - 7,86 (4H, m), 8,51 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00185μM

Ejemplo 8d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,59 - 1,66 (4H, m), 1,83 - 1,91 (4H, m), 2,18 - 2,26 (2H, m), 3,12 - 3,19 (1H, m), 3,46 (1H, t), 3,61 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,11 - 4,17 (2H, m), 4,42 (1H, s), 6,42 (1H, d), 6,65 (1H, s), 7,37 (2H, d), 7,42 (2H, t), 7,79 - 7,86 (4H, m), 8,54 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00134μM

Ejemplo 8e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,59 - 1,62 (2H, m), 1,88 - 1,90 (2H, m), 3,15 - 3,18 (2H, m), 3,40 - 3,48 (2H, m), 3,61 (2H, dd), 3,74 (1H, d), 3,95 (1H, d), 4,05 - 4,16 (2H, m), 4,13 (1H, d), 4,73 (1H, t), 6,22 (1H, t), 6,64 (1H, s), 7,37 - 7,44 (4H, m), 7,79 - 7,86 (4H, m), 8,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000342μM

Ejemplo 8f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,24 (6H, s), 1,57 - 1,63 (2H, m), 1,86 - 1,91 (2H, m), 3,10 - 3,18 (1H, m), 3,38 (2H, d), 3,46 (1H, t), 3,61 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,14 (1H, d), 4,41 (1H, s), 4,95 (1H, t), 5,97 (1H, s), 6,64 (1H, s), 7,34 (2H, d), 7,42 (2H, t), 7,78 - 7,86 (4H, m), 8,71 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00882μM

Ejemplo 8g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,59 - 1,62 (2H, m), 1,88 - 1,90 (2H, m), 2,18 (6H, s), 2,33 (2H, t), 3,15 - 3,21 (3H, m), 3,46 (1H, dt), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,13 (1H, d), 4,42 (1H, s), 6,13 (1H, t), 6,65 (1H, s), 7,37 - 7,43 (4H, m), 7,79 - 7,86 (4H, m), 8,86 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0613μM

Ejemplo 8h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,18 (3H, d), 1,45 (2H, sexteto), 1,59 - 1,62 (2H, m), 1,88 - 1,90 (2H, m), 3,06 (2H, q), 3,12 - 3,16 (1H, m), 3,40 - 3,49 (1H, m), 3,61 (1H, dd), 3,74 (1H, d), 3,96 (1H, dd), 4,13 (1H, d), 4,42 (1H, s), 6,17 (1H, t), 6,64 (1H, s), 7,37 - 7,44 (4H, m), 7,79 - 7,86 (4H, m), 8,63 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00176μM

Ejemplo 8i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,88 (6H, d), 1,19 (3H, d), 1,59 - 1,62 (2H, m), 1,67 - 1,74 (1H, m), 1,88 - 1,90 (2H, m), 2,94 (2H, t), 3,12 - 3,19 (1H, m), 3,46 (1H, dt), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,14 (1H, d), 4,42 (1H, s), 6,21 (1H, t), 6,65 (1H, s), 7,37 - 7,43 (4H, m), 7,79 - 7,85 (4H, m), 8,62 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0198μM

Ejemplo 8j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,56 - 1,63 (4H, m), 1,88 - 1,90 (2H, m), 3,12 - 3,19 (3H, m), 3,47 (2H, q), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd),

4,13 (1H, d), 4,43 (1H, s), 4,47 (2H, t), 6,17 (1H, t), 6,65 (1H, s), 7,37 - 7,45 (4H, m), 7,79 - 7,86 (4H, m), 8,68 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000751μM

Ejemplo 8k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,60 - 1,63 (2H, m), 1,89 - 1,92 (2H, m), 3,13 - 3,21 (1H, m), 3,47 (1H, dt), 3,62 (1H, dd), 3,75 (1H, d), 3,97 (1H, dd), 4,15 (1H, d), 4,43 (1H, s), 6,68 (1H, s), 7,41 - 7,49 (4H, m), 7,63 - 7,69 (4H, m), 7,84 - 7,89 (4H, m), 9,02 (1H, s), 9,10 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0173μM

Ejemplo 8l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,61 - 1,63 (2H, m), 1,89 - 1,92 (2H, m), 3,14 - 3,21 (1H, m), 3,47 (1H, t), 3,62 (1H, d), 3,76 (1H, d), 3,96 (1H, d), 4,16 (1H, d), 4,44 (1H, s), 6,68 (1H, s), 7,02 - 7,05 (1H, m), 7,43 (2H, t), 7,53 (2H, d), 7,57 - 7,62 (1H, m), 7,75 - 7,79 (1H, m), 7,83 - 7,91 (4H, m), 8,30 (1H, d), 9,40 (1H, s), 10,50 (1H, s).

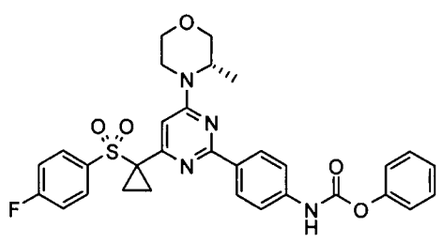
Ensayo de mTOR Quinasa (Echo): 0,00813μM

Ejemplo 8m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,60 - 1,62 (2H, m), 1,89 - 1,91 (2H, m), 3,12 - 3,20 (1H, m), 3,47 (1H, dt), 3,62 (1H, dd), 3,75 (1H, d), 3,79 (3H, s), 3,96 (1H, dd), 4,14 (1H, d), 4,43 (1H, s), 6,66 (1H, s), 7,38 - 7,45 (5H, m), 7,77 (1H, s), 7,83 - 7,87 (4H, m), 8,35 (1H, s), 8,82 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00136μM

La preparación de fenil *N*-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



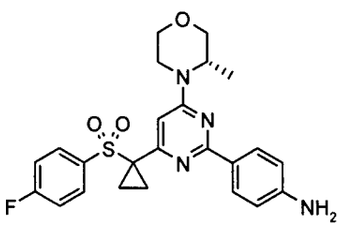
A una solución de 4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (1,33 g, 2,84 mmol) en 1,4-dioxano (15 mL) se agregó bicarbonato de sodio (0,358 g, 4,26 mmol) y fenil cloroformiato (0,357 mL, 2,84 mmol) y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con DCM (20 mL) y se lavó con agua (20 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El sólido bruto se

trituró con éter dietílico para proporcionar un sólido que se recogió mediante filtración y se secó al vacío para proporcionar el producto deseado como un sólido blanco (1,46 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,60 - 1,65 (2H, m), 1,89 - 1,92 (2H, m), 3,18 (1H, dt), 3,47 (1H, dt), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,17 (1H, d), 4,45 (1H, s), 6,69 (1H, s), 7,25 (3H, d), 7,40 - 7,47 (4H, m), 7,55 (2H, d), 7,83 - 7,87 (2H, m), 7,92 (2H, d), 10,42 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 589; HPLC tR = 2,92 min.

4-[4-[1-(4-Fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

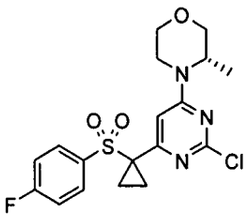


A una solución de 2-cloro-4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,5 g, 3,64 mmol) en DMF (0,48 mL), DME (9,33 mL), agua (4,0 mL) y etanol (2,67 mL) se agregaron 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,037 g, 4,73 mmol), carbonato de sodio (5 mL, 10,00 mmol) y diclorobis(trifenilfosfina)paladio(II) (0,128 g, 0,18 mmol) y la suspensión se calentó a 95°C durante 2 horas. La mezcla de reacción se enfrió hasta alcanzar TA, se diluyó con acetato de etilo (10 mL) y se lavó con agua (2 x 10 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 5 a 60% acetato de etilo en isohexano, para proporcionar lo deseado como un sólido crema (1,33 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,57 - 1,59 (2H, m), 1,86 - 1,88 (2H, m), 3,12 (1H, dt), 3,45 (1H, dt), 3,60 (1H, dd), 3,73 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,38 (1H, s), 5,52 (2H, s), 6,49 (2H, d), 6,55 (1H, s), 7,41 (2H, t), 7,64 (2H, d), 7,82 - 7,85 (2H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 469; HPLC tR = 2,47 min.

2-Cloro-4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

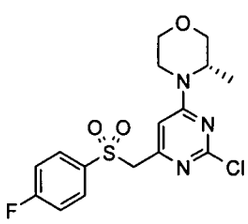


Se disolvió 2-cloro-4-[(4-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,0 g, 7,78 mmol) en DCM (40 mL) y se agregó hidróxido de sodio concentrado (7,8 mL, 77,75 mmol) a la reacción, seguido por dibromoetano (0,352 mL, 15,55 mmol). La reacción se agitó a 40°C durante 16 horas. La mezcla de reacción se lavó con agua (50 mL) y la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (1,50 g,).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15 (3H, d), 1,53 - 1,56 (2H, m), 1,82 - 1,85 (2H, m), 3,14 (1H, dt), 3,40 (1H, dt), 3,55 (1H, dd), 3,70 (1H, d), 3,91 (2H, dd), 4,25 (1H, s), 6,70 (1H, s), 7,45 (2H, t), 7,79 - 7,84 (2H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 412, HPLC tR = 2,14 min

2-Cloro-4-[(4-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



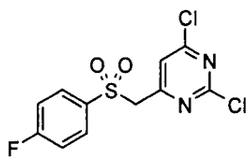
Se agregó trietilamina (1,117 ml, 8,01 mmol) a 2,4-dicloro-6-[(4-fluorofenil)sulfonilmetil]pirimidina (2,34 g, 7,29 mmol) en DCM (36,4 mL) a 0°C seguido por (3*S*)-3-metilmorfolina (0,737 g, 7,29 mmol) en DCM (20 mL) durante 15 minutos. La reacción luego se agitó a TA durante 16 horas. La mezcla de reacción se lavó con agua (50 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido beige (1,530 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 3,13 - 3,20 (1H, m),

3,27 - 3,28 (1H, m), 3,39 - 3,46 (1H, m), 3,57 (1H, dd), 3,72 (1H, d), 3,93 (1H, dd), 4,17 (1H, s), 4,65 (2H, s), 6,71 (1H, s), 7,48 (2H, t), 7,83 - 7,87 (2H, m)

Espectro de LCMS: MH+ 386, tiempo de retención 1,94 min.

2,4-Dicloro-6-[(4-fluorofenil)sulfonilmetil]pirimidina

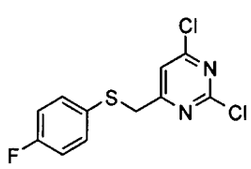


Se agregó en porciones ácido 3-cloroperoxibenzoico (3,78 g, 21,89 mmol) a 2,4-dicloro-6-[(4-fluorofenil)sulfanilmetil]pirimidina (2,11 g, 7,30 mmol), en DCM (36,5 mL) y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se lavó con una solución saturada acuosa de hidrogenocarbonato de sodio (50 mL) y la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto deseado (2,35 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 4,99 (2H, s), 7,48 - 7,52 (2H, m), 7,76 (1H, s), 7,85 - 7,88 (2H, m)

Espectro de LCMS: MH+ 319, tiempo de retención 2,01 min.

2,4-Dicloro-6-[(4-fluorofenil)sulfanilmetil]pirimidina



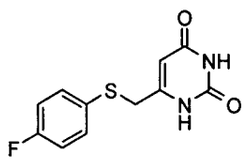
Se agregó oxicloruro de fósforo (15,2 g, 99,1 mmol) a 6-[(4-fluorofenil)sulfanilmetil]-1*H*-pirimidina-2,4-diona (2,5 g, 9,91 mmol) y la solución resultante se agitó a reflujo durante 7 horas. La reacción se dejó enfriar y el oxicloruro de fósforo se eliminó bajo presión reducida para proporcionar un aceite marrón. Esto se disolvió en DCM y se agregó agua helada (50 mL) y luego bicarbonato de sodio sólido (hasta que se detuvo la efervescencia). La capa acuosa se extrajo con DCM (2 x 50 mL) y los orgánicos se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (2,11 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 4,21 (2H, s), 7,09 - 7,14 (2H, m),

7,34 - 7,38 (2H, m), 7,58 (1H, s)

Espectro de LCMS: M-H+ 287, tiempo de retención 2,51 min.

6-[(4-Fluorofenil)sulfanilmetil]-1*H*-pirimidina-2,4-diona

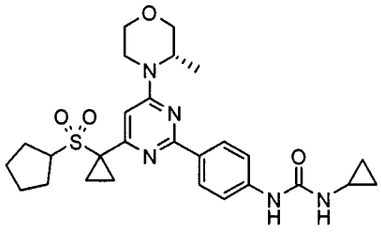


Se agregó DBU (4,02 mL, 26,91 mmol) a 4-fluorobencenotiol (3,45 g, 26,91 mmol), en DMF (90 mL) a TA. La solución resultante se agitó a 20°C durante 15 minutos. Luego se agregó 6-(clorometil)-1*H*-pirimidina-2,4-diona (2,88 g, 17,94 mmol) y la reacción se agitó durante 4 horas. La mezcla de reacción se concentró y se diluyó con DCM (100 mL) y se lavó con agua (100 mL). La capa acuosa se acidificó con ácido clorhídrico 2M para proporcionar un sólido blanco que se filtró y se lavó con agua y luego se secó al vacío para proporcionar el producto deseado (2,5 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 3,80 (2H, s), 5,20 (1H, s), 7,18 - 7,23 (2H, m), 7,45 - 7,49 (2H, m), 10,90 (1H, s), 10,93 (1H, s)

Espectro de LCMS: M-H- 251, tiempo de retención 0,80 min.

Ejemplo 9: 1-[4-[4-(1-Ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropil-urea



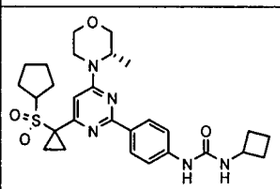
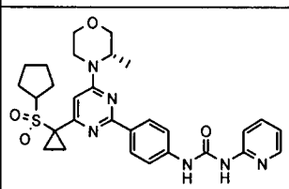
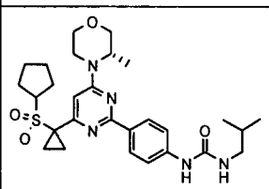
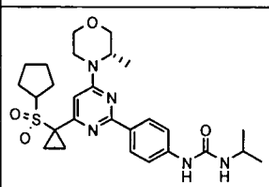
A una solución de fenil *N*-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (200 mg, 0,36 mmol) y amina (1,44 mmol) en NMP (2 mL) se agregó trietilamina (0,198 mL, 1,44 mmol) y la mezcla se calentó a 75°C durante 6 horas. La reacción se dejó enfriar y se purificó mediante HPLC prep utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido (130 mg).

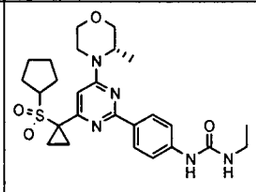
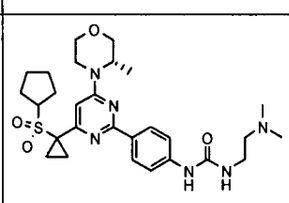
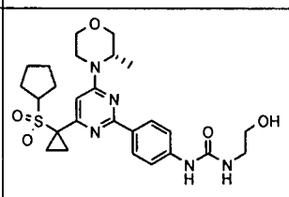
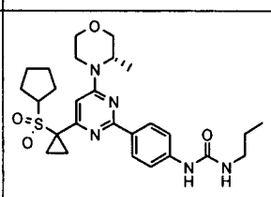
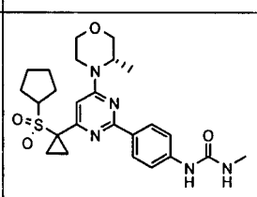
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,23 (3H, d), 1,50 - 1,70 (8H, m), 1,85 - 1,94 (2H, m), 1,99 - 2,07 (2H, m), 3,16 - 3,25 (1H, m), 3,49 (1H, dd), 3,63 (1H, dd), 3,76 (1H, d), 3,89 - 4,00 (2H, m), 4,20 (1H, d), 4,55 (1H, s), 6,46 (1H, s), 6,82 (1H, s), 7,51 (2H, d), 8,20 (2H, d), 8,54 (1H, s)

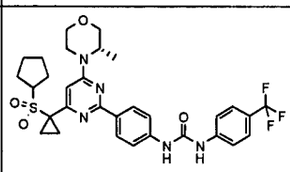
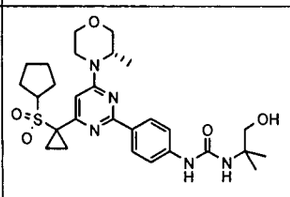
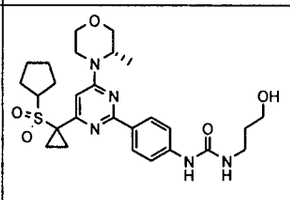
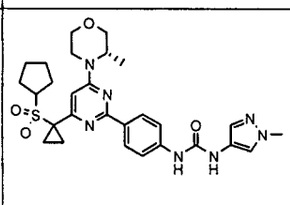
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 526; HPLC tR = 2,42 min

Ensayo de mTOR Quinasa (Echo): 0,0018μM

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
9a		1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-il-urea	540	2,67
9b		1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea	563	2,89
9c		1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-il-urea	542	2,77
9d		3-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etil-	528	2,59

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		urea		
9e		1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	514	2,40
9f		1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	557	2,33
9g		3-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propil-urea	530	2,02
9h		1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea	528	2,59
9i		1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	500	2,25

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
9j		1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metil-propan-2-il)urea	630	3,25
9k		1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	558	2,37
9l		1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	544	2,07
9m		1-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-il-urea	566	2,26

Ejemplo 9a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,51 - 1,70 (10H, m), 1,82 - 1,94 (4H, m), 1,98 - 2,08 (2H, m), 2,17 - 2,25 (2H, m), 3,17 - 3,25 (1H, m), 3,49 (1H, td), 3,63 (1H, dd), 3,76 (1H, d), 3,88 - 4,00 (2H, m), 4,10 - 4,22 (2H, m), 4,55 (1H, s), 6,47 (1H, d), 6,81 (1H, s), 7,48 (2H, d), 8,19 (2H, d), 8,56 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0129μM

Ejemplo 9b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,53 - 1,70 (8H, m), 1,86 - 1,96 (2H, m), 2,00 - 2,09 (2H, m), 3,18 - 3,25 (1H, m), 3,46 - 3,54 (1H, m), 3,65 (1H, dd), 3,77 (1H, d), 3,90 - 4,01 (2H, m), 4,22 (1H, d), 4,57 (1H, s), 6,85 (1H, s), 7,04 (1H, t), 7,56

(1H, d), 7,65 (2H, d), 7,77 (1H, t), 8,26 - 8,32 (5H, m), 9,48 (1H, s), 10,63 (3H, s).

Ensayo de mTOR Quinasa (Echo): 0,0215μM

Ejemplo 9c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (6H, d), 1,23 (3H, d), 1,51 - 1,75 (8H, m), 1,85 - 1,96 (2H, m), 1,99 - 2,08 (2H, m), 2,94 (2H, t), 3,16 - 3,25 (1H, m), 3,49 (1H, td), 3,63 (1H, dd), 3,76 (1H, d), 3,89 - 4,00 (2H, m), 4,20 (1H, d), 4,55 (1H, s), 6,24 (1H, t), 6,82 (1H, s), 7,49 (2H, d), 8,19 (2H, d), 8,65 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0483μM

Ejemplo 9d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11 (6H, d), 1,23 (3H, d), 1,51 - 1,69 (8H, m), 1,85 - 1,94 (2H, m), 1,98 - 2,08 (2H, m), 3,20 (1H, td), 3,49 (1H, td), 3,63 (1H, dd), 3,73 - 3,81 (2H, m), 3,89 - 4,00 (2H, m), 4,19 (1H, d), 4,55 (1H, s), 6,07 (1H, d), 6,83 (1H, s), 7,48 (2H, d), 8,19 (2H, d), 8,54 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0151μM

Ejemplo 9e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,23 (3H, d), 1,49 - 1,71 (8H, m), 1,86 - 1,96 (2H, m), 1,99 - 2,07 (2H, m), 3,12 (2H, q), 3,17 - 3,25 (1H, m), 3,45 - 3,53 (1H, m), 3,61 - 3,66 (1H, m), 3,89 - 3,99 (2H, m), 4,19 (1H, d), 4,56 (1H, s), 6,17 (1H, t), 6,82 (1H, s), 7,50 (2H, d), 8,18 (2H, d), 8,67 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00187μM

Ejemplo 9f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,50 - 1,70 (8H, m), 1,84 - 1,95 (2H, m), 1,98 - 2,08 (2H, m), 2,20 (6H, s), 2,33 (2H, t), 3,17 - 3,23 (2H, m), 3,49 (1H, td), 3,63 (1H, dd), 3,76 (1H, d), 3,90 - 4,00 (2H, m), 4,20 (1H, d), 4,56 (1H, s), 6,16 (1H, t), 6,82 (1H, s), 7,49 (2H, d), 8,19 (2H, d), 8,90 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,144μM

Ejemplo 9g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,50 - 1,71 (8H, m), 1,85 - 1,95 (2H, m), 1,98 - 2,07 (2H, m), 3,14 - 3,24 (3H, m), 3,43 - 3,52 (3H, m), 3,63 (1H, d), 3,76 (1H, d), 3,89 - 4,00 (2H, m), 4,19 (1H, d), 4,55 (1H, s), 4,73 (1H, t), 6,26 (1H, t), 6,82 (1H, s), 7,49 (2H, d), 8,19 (2H, d), 8,81 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00127μM

Ejemplo 9h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,23 (3H, d), 1,42 - 1,70 (10H, m), 1,84 - 1,94 (2H, m), 1,98 - 2,08 (2H, m), 3,03 - 3,09 (2H, m), 3,16 - 3,25 (1H, m), 3,50 (1H, d), 3,63 (1H, d), 3,76 (1H, d), 3,90 - 4,00 (2H, m), 4,20 (1H, d), 4,55 (1H, s), 6,21 (1H, t), 6,82 (1H, s), 7,49 (2H, d), 8,19 (2H, d), 8,66 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0057μM

Ejemplo 9i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,49 - 1,71 (8H, m), 1,85 -

1,95 (2H, m), 1,99 - 2,08 (2H, m), 3,16 - 3,24 (1H, m), 3,49 (1H, td), 3,63 (1H, dd), 3,76 (1H, d), 3,87 - 4,01 (2H, m), 4,20 (1H, d), 4,56 (1H, s), 6,09 (1H, q), 6,82 (1H, s), 7,50 (2H, d), 8,19 (2H, d), 8,75 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0024μM

Ejemplo 9j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,52 - 1,70 (8H, m), 1,87 - 1,96 (2H, m), 1,99 - 2,07 (2H, m), 3,17 - 3,27 (1H, m), 3,46 - 3,54 (1H, m), 3,64 (1H, d), 3,77 (1H, d), 3,89 - 4,01 (2H, m), 4,21 (1H, d), 4,57 (1H, s), 6,85 (1H, s), 7,59 (2H, d), 7,67 (4H, q), 8,27 (2H, d), 9,05 (1H, s), 9,15 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,046μM

Ejemplo 9k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 - 1,26 (9H, m), 1,51 - 1,71 (8H, m), 1,86 - 1,93 (2H, m), 1,98 - 2,09 (2H, m), 3,16 - 3,24 (1H, m), 3,39 (2H, d), 3,49 (1H, dd), 3,63 (1H, dd), 3,76 (1H, d), 3,90 - 4,01 (2H, m), 4,20 (1H, d), 4,55 (1H, s), 4,95 (1H, t), 6,02 (1H, s), 6,81 (1H, s), 7,45 (2H, d), 8,18 (2H, d), 8,75 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0115μM

Ejemplo 9l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,50 - 1,70 (8H, m), 1,85 - 1,95 (2H, m), 1,98 - 2,07 (2H, m), 3,12 - 3,25 (3H, m), 3,23 - 3,33 (2H, m), 3,43 - 3,53 (3H, m), 3,63 (1H, d), 3,77 (1H, d), 3,89 - 4,01 (2H, m), 4,20 (1H, d), 4,48 (1H, t), 4,56 (1H, s), 6,21 (1H, t), 6,81 (1H, s), 7,49 (2H, d), 8,19 (2H, d), 8,72 (1H, s).

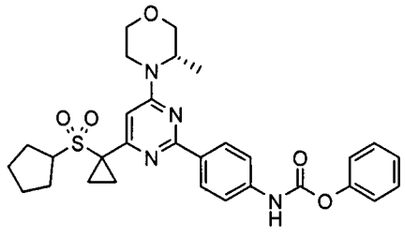
Ensayo de mTOR Quinasa (Echo): 0,00395μM

Ejemplo 9m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (9H, d), 1,51 - 1,70 (20H, m), 1,86 - 1,95 (6H, m), 1,99 - 2,07 (4H, m), 3,15 - 3,25 (25H, m), 3,50 (1H, d), 3,64 (1H, d), 3,78 (1H, d), 3,90 - 4,01 (2H, m), 4,20 (1H, d), 4,56 (1H, s), 6,86 (1H, s), 7,43 (1H, s), 7,56 (2H, d), 7,81 (1H, s), 8,23 (2H, d), 8,44 (1H, s), 8,87 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00401μM

La preparación de fenil *N*-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

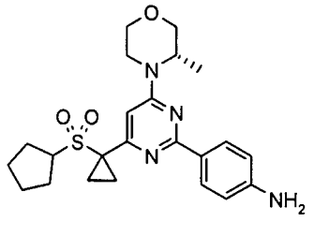


Se agregó fenil cloroformiato (1,701 mL, 13,56 mmol) a 4-[4-(1-ciclopentilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (4 g, 9,04 mmol) e hidrogenocarbonato de sodio (1,139 g, 13,56 mmol) en dioxano (120 mL) se enfrió hasta alcanzar 5°C bajo nitrógeno. La mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (125 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material bruto que se trituró con éter dietílico e isohexano para proporcionar el material deseado como un sólido blanco (4,77 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,51 - 1,70 (4H, m), 1,85 - 1,95 (2H, m), 1,98 - 2,08 (2H, m), 3,21 (1H, td), 3,49 (1H, td), 3,64 (1H, dd), 3,77 (1H, d), 3,90 - 4,00 (2H, m), 4,21 (1H, d), 4,58 (1H, s), 6,88 (1H, s), 7,22 - 7,32 (3H, m), 7,41 - 7,49 (2H, m), 7,64 (2H, d), 8,30 (2H, d), 10,45 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 563; HPLC tR = 3,02 min

4-[4-(1-Ciclopentilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



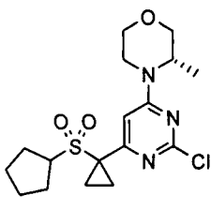
Se agregó cloruro de bis(trifenilfosfina)paladio(II) (300 mg, 0,43 mmol) a 2-cloro-4-(1-ciclopentilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4,15 g, 10,75 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (3,53 g, 16,13 mmol) y carbonato de sodio (25 mL, 50,0 mmol) en etanol (20 mL), DMF (40 mL), agua (25 mL) y DME (40 mL) a TA y la mezcla resultante se desgasificó y luego se agitó a 95°C durante 18 horas. La mezcla de reacción se diluyó con acetato de etilo (400 mL) y se lavó con agua (2 x 150 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 80% acetato de etilo en isohexano, para proporcionar el material deseado como un

sólido crema (4,00 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,46 - 1,72 (7H, m), 1,84 - 1,95 (2H, m), 3,13 - 3,22 (1H, m), 3,47 (1H, td), 3,62 (1H, dd), 3,75 (1H, d), 3,89 - 3,99 (2H, m), 4,15 (1H, d), 4,54 (1H, s), 5,58 (2H, s), 6,61 (2H, d), 6,72 (1H, s), 8,02 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 443; HPLC tR = 2,4 min

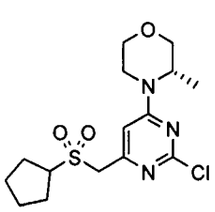
2-Cloro-4-(1-ciclopentilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó hidróxido de sodio (62,5 mL, 125,04 mmol) a 2-cloro-4-(ciclopentilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4,50 g, 12,50 mmol), 1,2-dibromoetano (4,31 mL, 50,02 mmol) y bromuro de tetrabutilamonio (0,403 g, 1,25 mmol) en tolueno (100 mL) a 30°C bajo nitrógeno. La mezcla resultante se agitó a 60°C durante 3 horas. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 5 a 45% acetato de etilo en isohexano, para proporcionar el material deseado como una goma incolora (4,47 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,47 - 1,68 (8H, m), 1,80 - 1,89 (2H, m), 1,91 - 1,98 (2H, m), 3,21 (1H, dt), 3,44 (1H, td), 3,58 (1H, dd), 3,72 (1H, d), 3,82 (1H, q), 3,93 (1H, dd), 3,98 - 4,06 (1H, m), 4,41 (1H, s), 6,97 (1H, s)

2-Cloro-4-(ciclopentilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



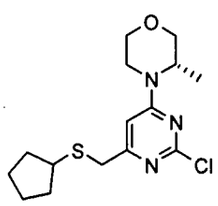
Se agregó peróxido de hidrógeno (19,54 mL, 632 mmol) a 2- cloro-4-(ciclopentilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (10,36 g, 31,60 mmol),

tungstato de sodio dihidrato (0,208 g, 0,63 mmol) (disuelto en una cantidad mínima de agua) y solución de ácido sulfúrico 2M (0,177 mL) en dioxano (100 mL) a 55°C al aire. La solución resultante se agitó a 55°C durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó con agua y luego una solución acuosa de metabisulfito de sodio al 10%. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 5 a 70% acetato de etilo en isohexano, para proporcionar el material deseado como una goma incolora (9,7 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,64 (4H, m), 1,95 (4H, m), 3,24 (1H, m), 3,45 (1H, td), 3,60 (1H, dd), 3,71 (1H, m), 3,95 (2H, m), 4,35 (1H, s), 4,40 (2H, s), 6,91 (1H, s)

Espectro de Masa: m/z (ESI+)$(M+H)^+$ = 360

2-Cloro-4-(ciclopentilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



DIPEA (9,62 mL, 55,57 mmol) se agregó a ciclopentanotiol (5,93 mL, 55,57 mmol), en DMF (80 mL) a TA bajo nitrógeno. La solución resultante se agitó a TA durante 20 minutos. Se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (13,1g, 37,05 mmol) a la reacción y se agitó durante 2 horas a TA. La mezcla de reacción se diluyó con acetato de etilo (500 mL) y se lavó con agua (2 x 200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 30% acetato de etilo en isohexano, para proporcionar el material deseado como una goma incolora (11,13 g).

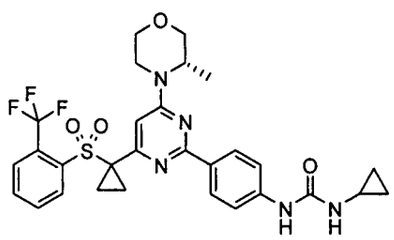
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,43 (2H, m), 1,53 (2H, m), 1,65 (2H, m), 1,94 (2H, m), 3,16 (2H, m), 3,44 (1H, td), 3,71 (1H, d), 3,95 (2H, m), 4,35 (1H, s), 6,79 (1H, s)

Espectro de Masa: m/z (ESI+)$(M+H)^+$ = 328

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió

anteriormente

Ejemplo 10: 3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea



A una solución de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]carbamato (200 mg,0,31 mmol) y ciclopropilamina (1,25 mmol) en NMP (2 mL) se agregó trietilamina (0,175 mL,1,25 mmol). La mezcla de reacción se calentó a 75°C durante 6 horas. La mezcla de reacción se purificó mediante HPLC prep, utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y acetonitrilo como eluyentes, para proporcionar el material deseado (140 mg).

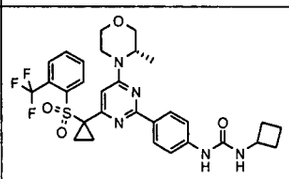
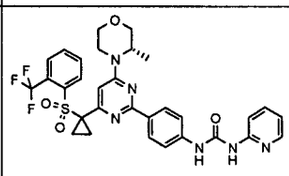
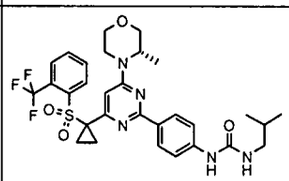
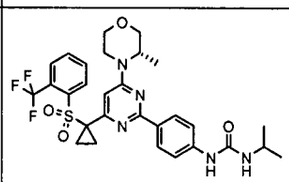
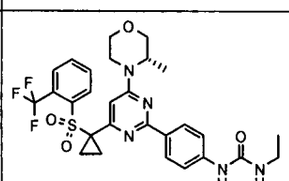
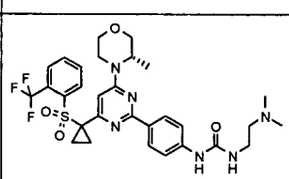
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,39 - 0,44 (2H, m), 0,63 - 0,67 (2H, m), 1,14 (3H, d), 1,70 - 1,75 (2H, m), 1,92 - 1,95 (2H, m), 3,11 (1H, td), 3,39 - 3,48 (1H, m), 3,59 (1H, dd), 3,73 (1H, d), 3,94 (1H, dd), 4,09 (1H, d), 4,43 (1H, s), 6,41 (1H, d), 6,62 (1H, s), 7,37 (2H, d), 7,76 (2H, d), 7,82 - 7,86 (2H, m), 7,91 - 7,95 (1H, m), 8,16 - 8,19 (1H, m), 8,49 (1H, s)

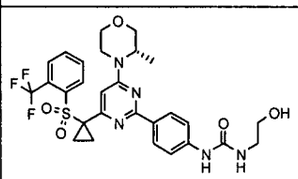
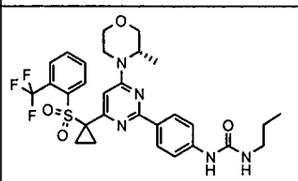
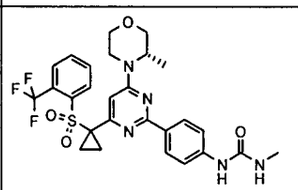
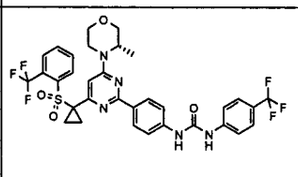
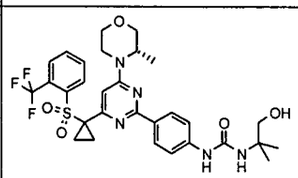
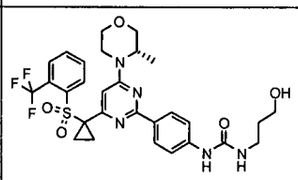
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 602; HPLC tR = 2,52 min.

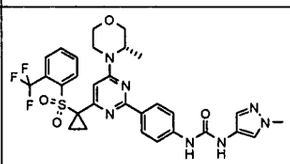
Ensayo de mTOR Quinasa (Echo): 0,00448μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
10a		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea	616	2,73
10b		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-3-piridin-2-il-urea		
10c		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-3-(2-metilpropil)urea	618	2,81
10d		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-3-propan-2-il-urea	604	2,66
10e		1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea	590	2,51
10f		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea	633	2,46

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
10g		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea	606	2,16
10h		3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-1-propil-urea	604	2,62
10i		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea	576	2,34
10j		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	706	3,22
10k		3-(1-hidroxi-2-metil-propan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea	634	2,43
10l		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]urea	620	2,17

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
10m		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	642	2,35

Ejemplo 10a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 (3H, d), 1,56 - 1,75 (4H, m), 1,80 - 1,96 (4H, m), 2,17 - 2,25 (2H, m), 3,11 (1H, td), 3,39 - 3,48 (1H, m), 3,59 (1H, dd), 3,73 (1H, d), 3,94 (1H, dd), 4,04 - 4,18 (2H, m), 4,43 (1H, s), 6,44 (1H, d), 6,61 (1H, s), 7,34 (2H, d), 7,75 (2H, d), 7,82 - 7,86 (2H, m), 7,92 - 7,95 (1H, m), 8,15 - 8,20 (1H, m), 8,52 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0395μM

Ejemplo 10b: Ensayo de mTOR Quinasa (Echo): 0,0266μM

Ejemplo 10c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,88 (6H, d), 1,14 (3H, d), 1,67 - 1,75 (2H, m), 1,91 - 1,95 (2H, m), 2,94 (2H, t), 3,11 (1H, td), 3,44 (1H, td), 3,59 (1H, dd), 3,73 (1H, d), 3,94 (1H, dd), 4,09 (1H, d), 4,43 (1H, s), 6,22 (1H, t), 6,61 (1H, s), 7,35 (2H, d), 7,76 (2H, d), 7,81 - 7,87 (2H, m), 7,92 - 7,96 (1H, m), 8,16 - 8,21 (1H, m), 8,60 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,147μM

Ejemplo 10d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,09 - 1,15 (9H, m), 1,68 - 1,77 (2H, m), 1,92 - 1,95 (2H, m), 3,11 (1H, td), 3,44 (1H, td), 3,59 (1H, dd), 3,71 - 3,82 (2H, m), 3,94 (1H, dd), 4,09 (1H, d), 4,42 (1H, s), 6,04 (1H, d), 6,61 (1H, s), 7,34 (2H, d), 7,75 (2H, d), 7,82 - 7,87 (2H, m), 7,91 - 7,95 (1H, m), 8,16 - 8,20 (1H, m), 8,49 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0432μM

Ejemplo 10e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06 (3H, t), 1,13 (3H, d), 1,69 - 1,75 (2H, m), 1,91 - 1,95 (2H, m), 3,07 - 3,19 (3H, m), 3,44 (1H, td), 3,59 (1H, dd), 3,73 (1H, d), 3,94 (1H, dd), 4,04 - 4,12 (1H, m), 4,44 (1H, s), 6,14 (1H, t), 6,62 (1H, s), 7,36 (2H, d), 7,75 (2H, d), 7,81 - 7,85 (2H, m), 7,91 - 7,95 (1H, m), 8,16 - 8,20 (1H, m), 8,62 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00691μM

Ejemplo 10f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 (3H, d), 1,69 - 1,74 (2H, m), 1,91 - 1,95 (2H, m), 2,19 (6H, s), 2,33 (2H, t), 3,11 (1H, td), 3,16 - 3,22 (2H, m), 3,44 (1H, td), 3,59

(1H, dd), 3,73 (1H, d), 3,94 (1H, dd), 4,09 (1H, d), 4,43 (1H, s), 6,15 (1H, t), 6,62 (1H, s), 7,35 (2H, d), 7,75 (2H, d), 7,82 - 7,87 (2H, m), 7,91 - 7,96 (1H, m), 8,16 - 8,20 (1H, m), 8,86 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,174μM

Ejemplo 10g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 (3H, d), 1,68 - 1,76 (2H, m), 1,92 - 1,95 (2H, m), 3,08 - 3,20 (3H, m), 3,39 - 3,48 (3H, m), 3,59 (1H, dd), 3,74 (1H, d), 3,94 (1H, dd), 4,09 (1H, d), 4,43 (1H, s), 4,72 (1H, t), 6,23 (1H, t), 6,62 (1H, s), 7,35 (2H, d), 7,75 (2H, d), 7,82 - 7,85 (2H, m), 7,92 - 7,95 (1H, m), 8,16 - 8,19 (1H, m), 8,76 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00156μM

Ejemplo 10h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,88 (3H, t), 1,14 (3H, d), 1,45 (2H, q), 1,70 - 1,74 (2H, m), 1,90 - 1,95 (2H, m), 3,03 - 3,15 (3H, m), 3,40 - 3,48 (1H, m), 3,59 (1H, dd), 3,73 (1H, d), 3,94 (1H, dd), 4,09 (1H, d), 4,41 (1H, s), 6,18 (1H, t), 6,62 (1H, s), 7,36 (2H, d), 7,75 (2H, d), 7,82 - 7,87 (2H, m), 7,92 - 7,95 (1H, m), 8,17 - 8,20 (1H, m), 8,61 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0268μM

Ejemplo 10i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 (3H, d), 1,69 - 1,75 (2H, m), 1,92 - 1,95 (2H, m), 2,66 (3H, d), 3,11 (1H, td), 3,44 (1H, td), 3,59 (1H, dd), 3,73 (1H, d), 3,94 (1H, dd), 4,09 (1H, d), 4,43 (1H, s), 6,04 (1H, q), 6,61 (1H, s), 7,37 (2H, d), 7,76 (2H, d), 7,82 - 7,85 (2H, m), 7,92 - 7,95 (1H, m), 8,16 - 8,19 (1H, m), 8,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00591μM

Ejemplo 10j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 (3H, d), 1,71 - 1,76 (2H, m), 1,91 - 1,96 (2H, m), 3,09 - 3,17 (1H, m), 3,45 (1H, dd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, d), 4,11 (1H, d), 4,44 (1H, s), 6,64 (1H, s), 7,45 (2H, d), 7,63 - 7,70 (4H, m), 7,81 - 7,87 (4H, m), 7,93 - 7,96 (1H, m), 8,17 - 8,21 (1H, m), 9,01 (1H, s), 9,12 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,11μM

Ejemplo 10k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 (3H, d), 1,25 (6H, s), 1,69 - 1,75 (2H, m), 1,91 - 1,95 (2H, m), 3,11 (1H, td), 3,37 - 3,48 (3H, m), 3,59 (1H, dd), 3,74 (1H, d), 3,94 (1H, dd), 4,09 (1H, d), 4,42 (1H, s), 4,95 (1H, t), 5,99 (1H, s), 6,62 (1H, s), 7,32 (2H, d), 7,74 (2H, d), 7,82 - 7,87 (2H, m), 7,92 - 7,95 (1H, m), 8,17 - 8,20 (1H, m), 8,69 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0502μM

Ejemplo 10l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 (3H, d), 1,56 - 1,63 (2H, m), 1,69 - 1,74 (2H, m), 1,91 - 1,95 (2H, m), 3,07 - 3,19 (3H, m), 3,40 - 3,50 (3H, m), 3,59 (1H, dd), 3,73 (1H, d), 3,94 (1H, dd), 4,09 (1H, d), 4,43 (1H, s), 4,47 (1H, t), 6,18 (1H, t), 6,62 (1H, s),

7,36 (2H, d), 7,76 (2H, d), 7,82 - 7,86 (2H, m), 7,91 - 7,96 (1H, m), 8,15 - 8,20 (1H, m), 8,67 (1H, s).

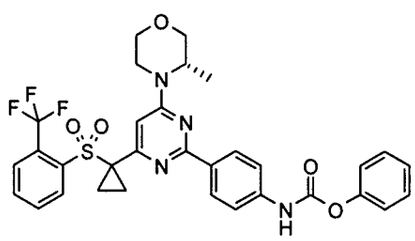
Ensayo de mTOR Quinasa (Echo): 0,0183μM

Ejemplo 10m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 (3H, d), 1,70 - 1,75 (2H, m), 1,90 - 1,96 (2H, m), 3,12 (1H, td), 3,44 (1H, td), 3,59 (1H, dd), 3,73 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,43 (1H, s), 6,62 (1H, s), 7,37 - 7,44 (3H, m), 7,76 - 7,81 (3H, m), 7,83 - 7,87 (2H, m), 7,92 - 7,95 (1H, m), 8,17 - 8,20 (1H, m), 8,38 (1H, s), 8,80 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00497μM

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]carbamato se describe a continuación.

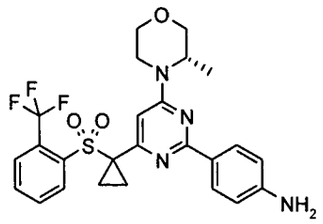
Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]fenil]carbamato



Se agregó fenil cloroformiato (1,669 mL, 13,31 mmol) a 4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]anilina (4,6 g, 8,87 mmol) e hidrogenocarbonato de sodio (1,118 g, 13,31 mmol) en dioxano (20 mL) a 5°C bajo nitrógeno. La mezcla resultante se agitó a TA durante 2 horas luego la mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (125 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto que se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado (4,55 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 (3H, d), 1,71 - 1,76 (2H, m), 1,92 - 1,96 (2H, m), 3,12 (1H, td), 3,41 - 3,47 (1H, m), 3,59 (1H, d), 3,73 (1H, d), 3,95 (1H, dd), 4,11 (1H, d), 4,45 (1H, s), 6,65 (1H, s), 7,22 - 7,31 (2H, m), 7,43 - 7,52 (3H,

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidin-2-il]anilina

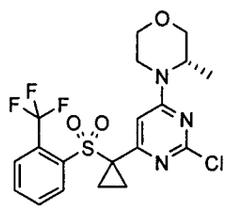


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (300 mg, 0,43 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidina (5 g, 10,83 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (3,56 g, 16,24 mmol) y carbonato de sodio (20 mL, 40,0 mmol) en una mezcla de etanol (10 mL), DMF (20 mL), agua (15 mL) y DME (40 mL) a TA. La mezcla resultante se desgasificó y luego se agitó a 95°C durante 18 horas. La reacción se dejó enfriar, se diluyó con acetato de etilo (400 mL) y se lavó con agua (2 x 200 mL). Los orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 70% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido crema (5,40 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11 (3H, d), 1,68 - 1,73 (2H, m), 1,90 - 1,93 (2H, m), 3,07 (1H, td), 3,38 - 3,47 (1H, m), 3,58 (1H, dd), 3,72 (1H, d), 3,93 (2H, dd), 4,02 - 4,07 (1H, m), 4,39 (1H, s), 5,50 (2H, s), 6,45 - 6,50 (3H, m), 7,61 (2H, d), 7,81 - 7,85 (2H, m), 7,93 (1H, dd), 8,17 (1H, dd)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 519; HPLC tR = 2,51 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[2-(trifluorometil)fenil]sulfonilciclopropil]pirimidina



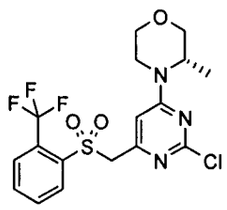
Una solución acuosa de hidróxido de sodio (30 mL, 247,8 mmol) se agregó a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil]sulfonilmetil]pirimidina (4,5 g, 10,32 mmol), 1,2-dibromoetano (4,45 mL, 51,62 mmol) y bromuro de tetrabutilamonio (0,333 g, 1,03 mmol) en tolueno (100 mL) a 30°C bajo nitrógeno. La mezcla resultante se agitó a 30°C

durante 3 horas. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 5 a 60% acetato de etilo en isohexano, para proporcionar el material deseado (4,70 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,10 (3H, d), 1,61 - 1,66 (2H, m), 1,86 - 1,91 (2H, m), 3,09 (1H, td), 3,37 (1H, td), 3,52 (1H, dd), 3,68 (1H, d), 3,84 - 3,93 (2H, m), 4,27 (1H, s), 6,69 (1H, s), 7,85 - 7,93 (2H, m), 8,00 (1H, d), 8,07 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 462; HPLC tR = 2,43 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[[2-(trifluorometil)fenil]sulfonilmetil]pirimidina

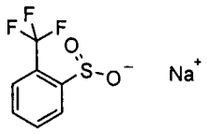


Se agregó 2-(trifluorometil)bencenosulfinato de sodio (10,24 g, 44 mmol) a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (13 g, 36,77 mmol), en acetonitrilo (500 mL) a TA bajo nitrógeno. La mezcla resultante se agitó a 80°C durante 3 horas. Se agregó más 2-(trifluorometil)bencenosulfinato de sodio (10,2 g, 44 mmol) y la reacción se calentó a 80°C durante 1 hora. La mezcla de reacción se dejó enfriar y se concentró al vacío. El material se disolvió en acetato de etilo (500 mL) y se lavó con agua (200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido naranja/crema (9,48 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 3,17 (1H, td), 3,43 (1H, td), 3,58 (1H, dd), 3,72 (1H, d), 3,93 (2H, m), 4,27 (1H, s), 4,68 (2H, s), 6,79 (1H, s), 7,94 (3H, m), 8,08 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 436; HPLC tR = 2,35 min.

2-(Trifluorometil)bencenosulfinato de sodio

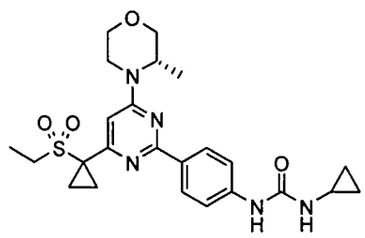


Se disolvió sulfito de sodio (3,92 mL, 81,88 mmol) en agua y se agitó a TA 10 minutos. Se agregó bicarbonato de sodio (13,74 g, 163,52 mmol) y la mezcla se agitó a 50°C durante 1 hora. Se agregó gota a gota cloruro de 2-(trifluorometil)benceno-1-sulfonilo (12,62 mL, 81,76 mmol) a la mezcla de reacción que luego se agitó a 50°C durante 18 horas. La mezcla de reacción se evaporó hasta secarse y el residuo se suspendió en metanol (250 mL) y se agitó a TA durante 20 minutos. El sólido se retiró mediante filtración y el filtrado se evaporó para proporcionar el material deseado (20,00 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 7,40 (1H, d), 7,51 (1H, d), 7,64 (1H, d), 8,05 (1H, d)

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 11: 3-Ciclopropil-1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



A una solución de fenil *N*-[4-[4-(1-etilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (150 mg, 0,29 mmol) en DMF (2 mL) se agregó trietilamina (0,120 mL, 0,86 mmol) seguido por ciclopropilamina (0,100 mL, 1,44 mmol) y la reacción se calentó a 50°C durante 2 horas. El producto bruto se purificó mediante HPLC preparativa utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (90 mg).

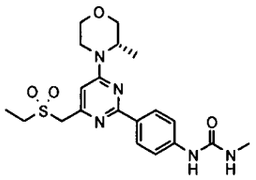
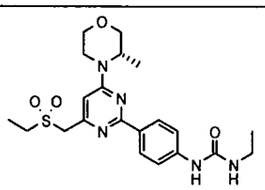
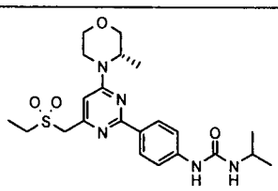
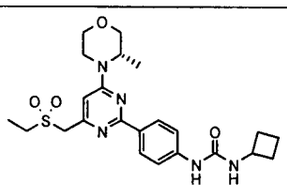
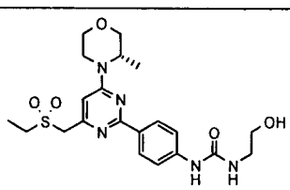
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,63 - 0,67 (2H, m), 1,23 (3H, d), 1,32 (3H, t), 1,55 (2H, t), 1,62 - 1,65 (2H, m), 2,52 - 2,58 (1H, m), 3,17 - 3,24 (1H, m), 3,43 (2H, q), 3,45 - 3,52 (1H, m), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,19 - 4,22 (1H, m), 4,56 (1H, s), 6,44 (1H, d), 6,78 (1H, s), 7,50 - 7,52 (2H, m),

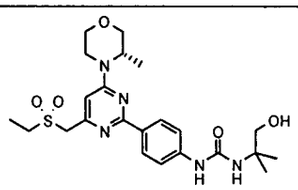
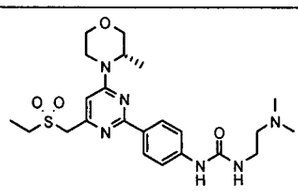
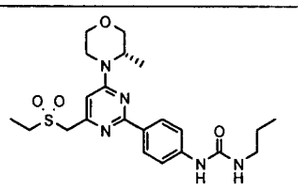
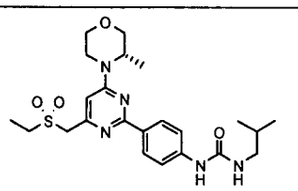
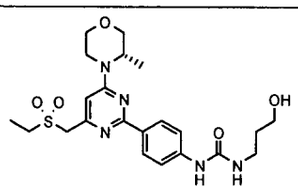
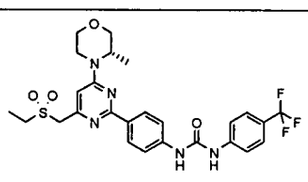
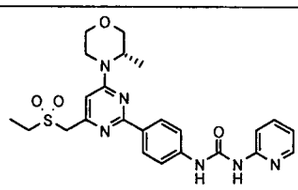
8,18 - 8,20 (2H, m), 8,54 (1H, s).

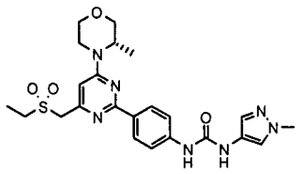
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 486; HPLC tR = 1,96 min.

Ensayo de mTOR Quinasa (Echo): 0,00165μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-(1-etilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
11a		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea	460	1,79
11b		1-etil-3-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	474	1,93
11c		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-il-urea	488	2,11
11d		3-ciclobutil-1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	500	2,19
11e		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	490	1,63

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
11f		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metil-propan-2-il)urea	518	1,92
11g		3-(2-dimetilaminoetil)-1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	517	1,90
11h		3-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propil-urea	488	2,11
11i		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea	502	2,29
11j		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	504	1,68
11k		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	590	2,80
11l		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-il-urea	523	2,37

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
11m		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	526	1,84

El **Ejemplo 11m** también puede prepararse en forma análoga pero utilizando DMA como disolvente y agitando a 50°C durante 18 horas.

Ejemplo 11a: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,32 (3H, t), 1,55 (2H, t), 1,62 - 1,64 (2H, m), 2,67 (3H, t), 3,20 - 3,24 (1H, m), 3,43 (2H, q), 3,45 - 3,52 (1H, m), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,19 - 4,22 (1H, m), 4,55 (1H, s), 6,07 (1H, d), 6,77 (1H, s), 7,49 - 7,52 (2H, m), 8,17 - 8,19 (2H, m), 8,74 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00418μM

Ejemplo 11b: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,23 (3H, d), 1,32 (3H, t), 1,55 (2H, t), 1,62 - 1,65 (2H, m), 3,09 - 3,16 (2H, m), 3,20 - 3,24 (1H, m), 3,43 (2H, q), 3,45 - 3,52 (1H, m), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,20 (1H, d), 4,56 (1H, s), 6,16 (1H, t), 6,77 (1H, s), 7,48 - 7,52 (2H, m), 8,17 - 8,19 (2H, m), 8,66 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00333μM

Ejemplo 11c: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,11 (6H, d), 1,23 (3H, d), 1,32 (3H, t), 1,55 (2H, t), 1,60 - 1,65 (2H, m), 3,20 - 3,24 (1H, m), 3,43 (2H, q), 3,45 - 3,52 (1H, m), 3,61 - 3,65 (1H, m), 3,77 (1H, d), 3,80 (1H, m), 3,95 - 3,99 (1H, m), 4,19 - 4,22 (1H, m), 4,55 (1H, s), 6,07 (1H, d), 6,77 (1H, s), 7,47 - 7,50 (2H, m), 8,17 - 8,19 (2H, m), 8,53 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0247μM

Ejemplo 11d: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,32 (3H, t), 1,53 - 1,58 (2H, m), 1,62 - 1,64 (2H, m), 1,81 - 1,89 (3H, m), 2,18 - 2,24 (3H, m), 3,20 - 3,24 (1H, m), 3,43 (2H, q), 3,48 - 3,51 (1H, m), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,16 (2H, m), 4,55 (1H, s), 6,46 - 6,48 (1H, m), 6,78 (1H, s), 7,46 - 7,50 (2H, m), 8,18 (2H, d), 8,56 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00642μM

Ejemplo 11e: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,32 (3H, t), 1,55 (2H, t),

1,62 - 1,64 (2H, m), 3,18 (1H, q), 3,20 (2H, d), 3,40 - 3,51 (2H, m), 3,46 (1H, d), 3,42 - 3,52 (2H, m), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,20 (1H, d), 4,56 (1H, s), 4,73 (1H, t), 6,26 (1H, t), 6,78 (1H, s), 7,48 - 7,50 (2H, m), 8,19 (2H, d), 8,80 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00135μM

Ejemplo 11f: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,24 (6H, s), 1,32 (3H, d), 1,53 - 1,58 (2H, m), 1,62 - 1,64 (2H, m), 3,17 - 3,24 (1H, m), 3,39 (2H, d), 3,45 (2H, q), 3,45 - 3,52 (1H, m), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,19 - 4,22 (1H, m), 4,54 (1H, s), 4,95 (1H, t), 6,01 (1H, s), 6,77 (1H, s), 7,44 - 7,48 (2H, m), 8,18 (2H, d), 8,74 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00337μM

Ejemplo 11g: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,32 (3H, t), 1,53 - 1,58 (2H, m), 1,62 - 1,64 (2H, m), 2,18 (6H, s), 2,34 (2H, t), 3,17 - 3,23 (3H, m), 3,43 (2H, q), 3,45 - 3,52 (1H, m), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,19 (1H, s), 4,56 (1H, s), 6,16 (1H, t), 6,77 (1H, s), 7,48 - 7,51 (2H, m), 8,17 - 8,19 (2H, m), 8,89 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,313μM

Ejemplo 11h: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,23 (3H, d), 1,32 (3H, t), 1,41 - 1,50 (2H, m), 1,55 (2H, t), 1,62 - 1,65 (2H, m), 3,04 - 3,09 (2H, m), 3,17 - 3,24 (1H, m), 3,43 (2H, q), 3,45 - 3,52 (1H, m), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,20 (1H, d), 4,55 (1H, s), 6,21 (1H, t), 6,77 (1H, s), 7,48 - 7,51 (2H, m), 8,17 - 8,20 (2H, m), 8,65 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00913μM

Ejemplo 11i: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,89 (6H, d), 1,23 (3H, d), 1,32 - 1,38 (3H, m), 1,55 (2H, t), 1,62 - 1,65 (2H, m), 1,69 - 1,76 (1H, m), 2,94 (2H, t), 3,17 - 3,24 (1H, m), 3,43 (2H, q), 3,45 - 3,52 (1H, m), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,20 (1H, d), 4,56 (1H, s), 6,25 (1H, t), 6,78 (1H, s), 7,48 - 7,51 (2H, m), 8,18 (1H, t), 8,20 (1H, s), 8,64 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0294μM

Ejemplo 11j: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,32 (3H, t), 1,55 (2H, q), 1,58 (2H, m), 1,62 - 1,64 (2H, m), 3,15 - 3,19 (3H, m), 3,43 (2H, q), 3,46 - 3,47 (2H, m), 3,50 (1H, d), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,20 (1H, d), 4,47 (1H, t), 4,55 (1H, s), 6,21 (1H, t), 6,77 (1H, s), 7,48 - 7,51 (2H, m), 8,17 - 8,20 (2H, m), 8,71 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0122μM

Ejemplo 11k: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,33 (3H, t), 1,56 (2H, t),

1,63 - 1,66 (2H, m), 3,18 - 3,26 (1H, m), 3,44 (2H, q), 3,46 - 3,53 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,22 (1H, d), 4,57 (1H, s), 6,81 (1H, s), 7,58 - 7,60 (2H, m), 7,64 - 7,70 (4H, m), 8,27 (2H, d), 9,05 (1H, s), 9,14 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00332μM

Ejemplo 11l: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,25 (3H, d), 1,34 (3H, t), 1,55 - 1,59 (2H, m), 1,63 - 1,66 (2H, m), 3,18 - 3,23 (1H, m), 3,45 (2H, q), 3,47 - 3,53 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,20 - 4,24 (1H, m), 4,57 (1H, s), 6,81 (1H, s), 7,02 - 7,05 (1H, m), 7,56 (1H, d), 7,65 (2H, d), 7,75 - 7,77 (1H, m), 8,26 - 8,31 (1H, m), 8,27 - 8,31 (2H, m), 9,45 (1H, d), 10,61 (1H, s).

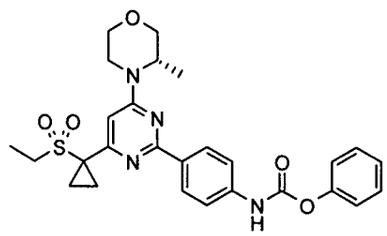
Ensayo de mTOR Quinasa (Echo): 0,00356μM

Ejemplo 11m: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,33 (3H, t), 1,56 (2H, t), 1,63 - 1,65 (2H, m), 3,17 - 3,25 (1H, m), 3,44 (2H, q), 3,46 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,75 (1H, s), 3,79 (3H, s), 3,96 - 4,00 (1H, m), 4,21 (1H, d), 4,56 (1H, s), 6,79 (1H, s), 7,38 - 7,39 (1H, m), 7,53 - 7,57 (2H, m), 7,76 (1H, s), 8,22 (2H, d), 8,39 (1H, s), 8,84 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00437μM

La preparación de fenil *N*-[4-[4-(1-etilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-(1-etilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



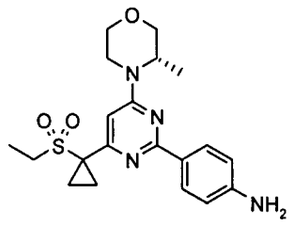
Se agregó gota a gota fenil cloroformiato (0,566 mL, 4,50 mmol) a 4-[4-(1-etilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (1,81 g, 4,50 mmol) y bicarbonato de sodio (0,567 g, 6,75 mmol) en dioxano (30 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetato de etilo (200 mL) y se lavó con agua (200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un sólido blanco (2,36 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,33 (3H, t), 1,55 -

1,59 (2H, m), 1,63 - 1,65 (2H, m), 3,21 - 3,25 (1H, m), 3,43 - 3,48 (2H, m), 3,41 - 3,52 (1H, m), 3,62 - 3,65 (1H, m), 3,77 (1H, d), 3,96 - 3,99 (1H, m), 4,21 (1H, s), 4,57 (1H, s), 6,82 (1H, s), 7,24 - 7,30 (3H, m), 7,43 - 7,47 (2H, m), 7,64 (2H, d), 8,27 - 8,30 (2H, m), 10,44 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 523; HPLC tR = 2,83 min.

4-[4-(1-Etilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

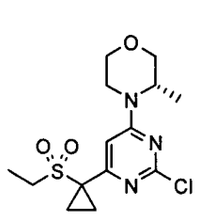


Se agregó diclorobis(trifenilfosfina)paladio(II) (0,317 g, 0,45 mmol) a una solución desgasificada de 2-cloro-4-(1-etilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,56 g, 4,51 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,235 g, 5,64 mmol) y carbonato de sodio (11,28 ml, 22,55 mmol) en una mezcla de 18% DMF en DME:agua:etanol (7:3:2) (20 mL). La solución resultante se agitó a 85°C durante 30 minutos. La mezcla de reacción se concentró y se repartió entre DCM (100 mL) y agua (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 2,5% metanol en DCM, para proporcionar el material deseado como un aceite marrón (2,15 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,31 (3H, t), 1,53 (2H, m), 1,60 - 1,62 (2H, m), 3,17 - 3,21 (1H, m), 3,37 - 3,47 (2H, m), 3,50 (1H, m), 3,60 - 3,64 (1H, m), 3,75 (1H, d), 3,94 - 3,98 (1H, m), 4,15 - 4,19 (1H, m), 4,51 - 4,53 (1H, m), 5,55 (2H, d), 6,60 - 6,62 (2H, m), 6,67 (1H, s), 8,00 - 8,04 (2H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 403; HPLC tR = 2,14 min.

2-Cloro-4-(1-etilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

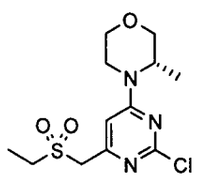


Una solución acuosa de hidróxido de sodio (25,4 mL, 254,1 mmol) se agregó a bromuro de tetrabutilamonio (0,328 g, 1,02 mmol), 1,2-dibromoetano (0,876 mL, 10,16 mmol) y 2-cloro-4-(etilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,25 g, 10,16 mmol) en DCM (75 mL). La mezcla resultante se agitó a 40°C durante 4 horas. La mezcla de reacción se diluyó con DCM (50 mL) y se lavó con agua (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (1,56 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,23 (3H, s), 1,49 - 1,52 (2H, m), 1,55 - 1,62 (2H, m), 3,18 - 3,23 (1H, m), 3,35 (2H, t), 3,41 - 3,46 (1H, m), 3,56 - 3,60 (1H, m), 3,72 (1H, d), 3,91 - 3,95 (1H, m), 4,15 - 4,19 (1H, m), 4,40 (1H, s), 6,93 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 346; HPLC 1,97 tR = min.

2-Cloro-4-(etilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



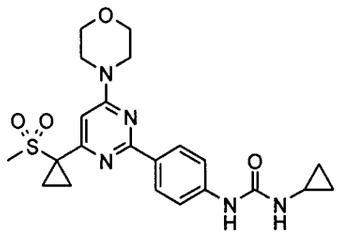
Se agregó sal de sodio de ácido etanosulfínico (3,94 g, 33,94 mmol) en una porción a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (12,0 g, 33,94 mmol) en acetonitrilo (250 mL) a TA. La suspensión resultante se agitó a 80°C durante 16 horas. La mezcla de reacción se evaporó hasta secarse y el residuo se repartió entre DCM (250mL) y agua (200mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido amarillo (5,94 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, m), 1,28 (3H, t), 3,22 (2H, d), 3,32 (1H, s), 3,42 - 3,49 (1H, m), 3,58 - 3,62 (1H, m), 3,73 (1H, d), 3,92 - 3,96 (2H, m), 4,25 - 4,31 (1H, m), 4,43 (2H, s), 6,92 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 320; HPLC tR = 1,46 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 12: 3-Ciclopropil-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea



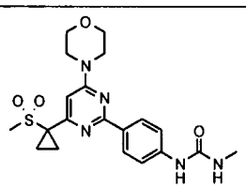
A una solución de fenil *N*-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato (150 mg, 0,29 mmol) en DMF (2 mL) se agregó trietilamina (0,127 mL, 0,91 mmol) seguida por ciclopropilamina (0,106 mL, 1,52 mmol) y la reacción se calentó a 50°C durante 20 horas. El producto bruto se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes, para proporcionar el material deseado como un sólido blanco (80 mg).

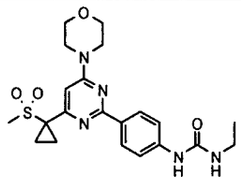
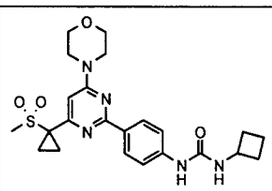
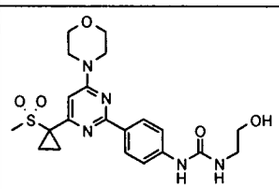
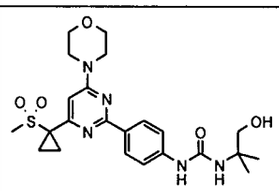
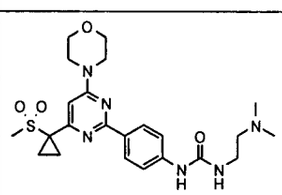
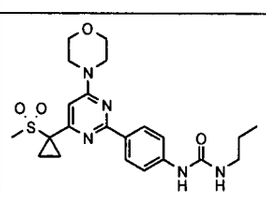
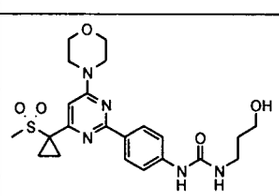
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,64 - 0,66 (2H, m), 1,54 - 1,57 (1H, m), 1,55 (1H, d), 1,67 (1H, d), 1,65 - 1,68 (1H, m), 2,60 (1H, m), 3,30 (3H, s), 3,72 (8H, s), 6,43 (1H, d), 6,81 (1H, s), 7,50 - 7,52 (2H, m), 8,19 - 8,22 (2H, m), 8,55 (1H, s)

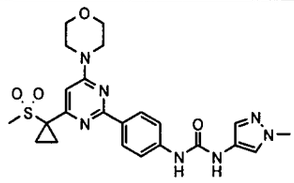
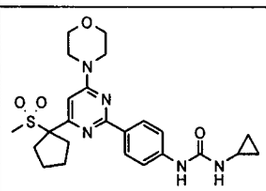
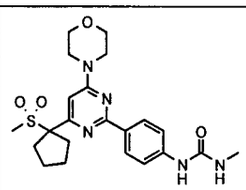
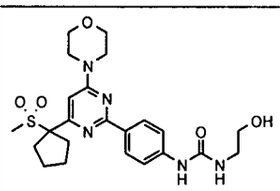
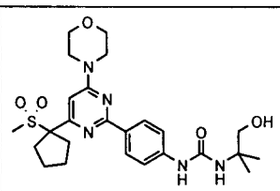
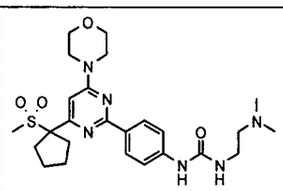
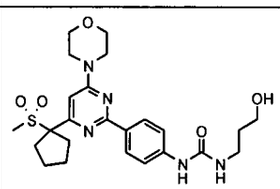
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 458; HPLC tR = 1,44 min.

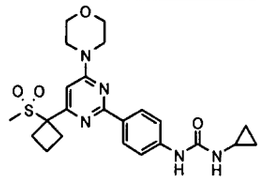
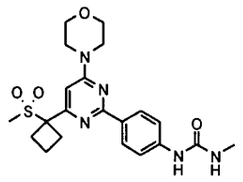
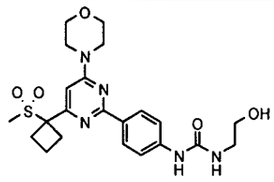
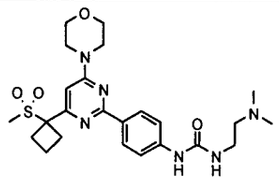
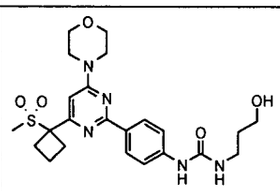
Ensayo de mTOR Quinasa (Echo): 0,00421μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato, fenil *N*-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
12a		3-metil-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	432,5	1,27

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
12b		3-etil-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	446,5	1,39
12c		3-ciclobutil-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	471,5	1,73
12d		3-(2-hidroxietil)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	462,5	1,15
12e		3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	490,5	1,43
12f		3-(2-dimetilaminoetil)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	489,5	1,05
12g		1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-propilurea	460,5	1,6
12h		3-(3-hidroxipropil)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	476,5	1,18

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
12i		3-(1-metilpirazol-4-il)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	498,5	1,38
12j*		3-ciclopropil-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	486	2,04
12k*		3-metil-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	460	1,88
12l*		3-(2-hidroxietil)-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	490	1,73
12m*		3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	518	2,00
12n*		3-(2-dimetilaminoetil)-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	517	1,98
12o*		3-(3-hidroxipropil)-1-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	504	1,77

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
12p**		3-ciclopropil-1-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	472	2,06
12q**		3-metil-1-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	446	1,88
12r**		3-(2-hidroxietil)-1-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	476	1,72
12s**		3-(2-dimetilaminoetil)-1-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	503	1,92
12t**		3-(3-hidroxipropil)-1-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	490	1,77

* La reacción se agitó a 55°C durante 6 horas

** La reacción se agitó a 40°C durante 6 horas

El material bruto del **Ejemplo 12** también puede purificarse mediante cromatografía en sílice, eluyendo con 50-80% acetato de etilo en isohexano, o disolviendo el material en acetato de etilo y dejando que el material deseado se precipite de la solución al agitarse.

Ejemplo 12a: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,53 - 1,57 (1H, m), 1,55 - 1,56 (1H, m), 1,67 (1H, d), 1,65 - 1,68 (1H, m), 2,66 (3H, d), 3,30 (3H, s), 3,72 (8H, s), 6,06 (1H, d), 6,81 (1H, s), 7,49 - 7,52 (2H, m), 8,19 - 8,21 (2H, m), 8,75 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00167μM

Ejemplo 12b: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,54 - 1,57 (1H, m), 1,55 (1H, d), 1,67 (1H, d), 1,65 - 1,68 (1H, m), 3,11 - 3,14 (2H, m), 3,30 (3H, s), 3,72 (8H, s), 6,16 (1H, s), 6,81 (1H, s), 7,49 - 7,51 (2H, m), 8,19 - 8,21 (2H, m), 8,67 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00271μM

Ejemplo 12c: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,53 - 1,57 (2H, m), 1,55 (2H, d), 1,59 - 1,67 (2H, m), 1,82 - 1,85 (1H, m), 1,89 (1H, t), 2,18 - 2,25 (2H, m), 3,30 (3H, s), 3,72 (8H, s), 4,14 (1H, d), 6,46 (1H, d), 6,81 (1H, s), 7,47 - 7,49 (2H, m), 8,20 (2H, d), 8,57 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00152μM

Ejemplo 12d: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,54 - 1,57 (1H, m), 1,55 - 1,56 (1H, m), 1,67 (1H, d), 1,65 - 1,68 (1H, m), 3,18 (2H, q), 3,30 (3H, s), 3,46 (2H, q), 3,72 (8H, s), 4,73 (1H, t), 6,25 (1H, t), 6,81 (1H, s), 7,48 - 7,50 (2H, m), 8,19 - 8,22 (2H, m), 8,81 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00155μM

Ejemplo 12e: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (6H, s), 1,54 - 1,57 (1H, m), 1,55 (1H, d), 1,67 (1H, d), 1,65 - 1,68 (1H, m), 3,30 (3H, s), 3,39 (2H, d), 3,72 (8H, s), 4,95 (1H, t), 6,00 (1H, s), 6,80 (1H, s), 7,44 - 7,47 (2H, m), 8,18 - 8,20 (2H, m), 8,74 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00459μM

Ejemplo 12f: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,54 - 1,57 (1H, m), 1,55 - 1,56 (1H, m), 1,67 (1H, d), 1,65 - 1,68 (1H, m), 2,18 (6H, s), 2,34 (2H, t), 3,20 (2H, t), 3,30 (3H, s), 3,72 (8H, s), 6,16 (1H, t), 6,80 (1H, s), 7,47 - 7,51 (2H, m), 8,20 (2H, d), 8,90 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0605μM

Ejemplo 12g: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,41 - 1,50 (2H, m), 1,54 - 1,57 (1H, m), 1,55 (1H, d), 1,67 (1H, d), 1,65 - 1,68 (1H, m), 3,04 - 3,09 (2H, m), 3,30 (3H, s), 3,72 (8H, s), 6,20 (1H, t), 6,81 (1H, s), 7,48 - 7,51 (2H, m), 8,18 - 8,22 (2H, m), 8,66 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00273μM

Ejemplo 12h: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,53 - 1,58 (2H, m), 1,61 (2H, d), 1,65 - 1,68 (2H, m), 3,17 (2H, d), 3,30 (3H, s), 3,45 - 3,48 (2H, m), 3,72 (8H, s), 4,47 (1H, t), 6,20 (1H, s), 6,81 (1H, s), 7,48 - 7,51 (2H, m), 8,19 - 8,21 (2H, m), 8,72 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00392μM

Ejemplo 12i: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,54 - 1,58 (1H, m), 1,56 - 1,56 (1H, m), 1,67 (2H, t), 3,30 (3H, s), 3,72 (8H, s), 3,79 (3H, s), 6,82 (1H, s), 7,38 - 7,38 (1H, m), 7,54 - 7,56 (2H, m), 7,76 (1H, s), 8,23 - 8,25 (2H, m), 8,38 (1H, s), 8,84 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000771μM

Ejemplo 12j: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,63 - 0,67 (2H, m), 1,58 (2H, t), 1,81 (2H, d), 2,39 - 2,47 (2H, m), 2,57 (1H, t), 2,74 (2H, t), 2,91 (3H, s), 3,73 (8H, s), 6,42 (1H, d), 6,84 (1H, s), 7,49 - 7,53 (2H, m), 8,22 - 8,26 (2H, m), 8,54 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00167μM

Ejemplo 12k: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,56 - 1,57 (2H, m), 1,80 - 1,82 (2H, m), 2,42 (2H, d), 2,46 (2H, d), 2,67 (3H, t), 2,91 (3H, s), 3,73 (8H, s), 6,06 (1H, d), 6,84 (1H, s), 7,49 - 7,52 (2H, m), 8,22 - 8,25 (2H, m), 8,74 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0043μM

Ejemplo 12l: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,58 (2H, t), 1,81 (2H, d), 2,41 - 2,44 (2H, m), 2,73 (2H, d), 2,91 (3H, s), 3,18 (2H, q), 3,46 (2H, q), 3,73 (8H, s), 4,72 (1H, t), 6,25 (1H, s), 6,84 (1H, s), 7,48 - 7,50 (2H, m), 8,23 - 8,25 (2H, m), 8,81 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00138μM

Ejemplo 12m: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (6H, s), 1,58 (2H, t), 1,81 (2H, d), 2,41 - 2,44 (2H, m), 2,71 - 2,75 (2H, m), 2,91 (3H, s), 3,39 (2H, d), 3,73 (8H, s), 4,95 (1H, t), 6,00 (1H, s), 6,84 (1H, s), 7,44 - 7,47 (2H, m), 8,22 - 8,24 (2H, m), 8,74 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0101μM

Ejemplo 12n: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,56 - 1,57 (2H, m), 1,81 (2H, d), 2,18 (6H, s), 2,34 (2H, t), 2,39 - 2,46 (2H, m), 2,73 (2H, q), 2,91 (3H, s), 3,19 (2H, q), 3,73 (8H, s), 6,15 (1H, t), 6,84 (1H, s), 7,48 - 7,50 (2H, m), 8,23 - 8,25 (2H, m), 8,90 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,238μM

Ejemplo 12o: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,56 - 1,59 (2H, m), 1,57 - 1,63 (2H, m), 1,81 (2H, d), 2,39 - 2,46 (2H, m), 2,72 - 2,74 (2H, t), 2,91 (3H, s), 3,15 - 3,19 (2H, m), 3,45 - 3,50 (2H, m), 3,73 (8H, s), 4,47 (1H, t), 6,20 (1H, t), 6,84 (1H, s), 7,48 - 7,51 (2H, m), 8,22 - 8,25 (2H, m), 8,71 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00509μM

Ejemplo 12p: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,41 - 0,43 (2H, m), 0,63 - 0,66 (2H, m), 1,90 (1H, m), 2,08 (1H, m), 2,33 (1H, t), 2,68 (1H, t), 2,80 - 2,82 (1H,m), 2,87 (3H, s), 2,90 (2H, m), 3,73 (8H, s), 6,43 - 6,44 (1H, m), 6,77 (1H, s), 7,49 - 7,51 (2H, m), 8,21 - 8,24 (2H, m), 8,56 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0014μM

Ejemplo 12q: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,99 - 2,06 (1H, m), 2,09 (1H, m), 2,32 - 2,34 (3H, m), 2,87 (3H, s), 2,90 (2H, s), 2,93 (2H, s), 3,73 (8H, s), 6,06 (1H, d), 6,76 (1H, s),

7,50 (2H, d), 8,22 (2H, d), 8,74 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00162μM

Ejemplo 12r: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,89 (1H, t), 2,07 (1H, d), 2,76 - 2,83 (2H, m), 2,87 (3H, s), 2,90 - 2,93 (2H, m), 3,18 (2H, m), 3,46 (2H, m), 3,73 (8H, s), 4,72 (1H, t), 6,25 (1H, t), 6,76 (1H, s), 7,48 - 7,50 (2H, m), 8,21 - 8,23 (2H, m), 8,81 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000991μM

Ejemplo 12s: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,89 (1H, t), 2,07 (1H, t), 2,18 (6H, s), 2,34 (2H, t), 2,80 (2H, d), 2,87 (3H, s), 2,90 (2H, m), 3,19 (2H, t), 3,73 (8H, s), 6,16 (1H, s), 6,76 (1H, s), 7,47 - 7,50 (2H, m), 8,21 - 8,23 (2H, m), 8,90 (1H, s).

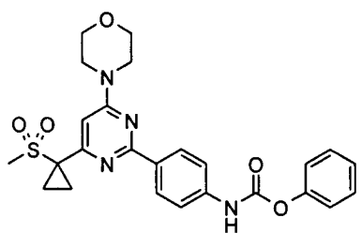
Ensayo de mTOR Quinasa (Echo): 0,134μM

Ejemplo 12t: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,58 (2H, t), 1,87 - 1,92 (1H, m), 2,06 - 2,10 (1H, m), 2,76 - 2,82 (2H, m), 2,87 (3H, s), 2,90 - 2,93 (2H, m), 3,14 - 3,19 (2H, m), 3,45 - 3,49 (2H, m), 3,73 (8H, s), 4,47 (1H, t), 6,20 (1H, t), 6,76 (1H, s), 7,48 - 7,50 (2H, m), 8,21 - 8,23 (2H, m), 8,71 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0366μM

La preparación de fenil *N*-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato



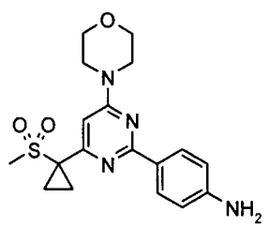
Se agregó gota a gota fenil cloroformiato (0,4 mL, 3,18 mmol) a 4-(4-(1-(metilsulfonil)ciclopropil)-6-morfolinopirimidin-2-il)anilina (1,19 g, 3,18 mmol) y bicarbonato de sodio (0,40 g, 4,77 mmol) en dioxano (30 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetato de etilo (100mL) y se lavó con agua (100mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un sólido amarillo (1,68 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,57 (1H, d), 1,55 - 1,62 (1H, m),

1,68 (1H, d), 1,66 - 1,69 (1H, m), 3,40 (3H, s), 3,73 (8H, s), 6,86 (1H, s), 7,24 - 7,30 (3H, m), 7,43 - 7,47 (2H, m), 7,63 - 7,65 (2H, m), 8,29 - 8,31 (2H, m), 10,44 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 495; HPLC tR = 2,58 min.

4-[4-(1-Metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]anilina

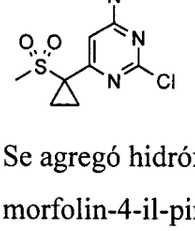


Se agregó diclorobis(trifenilfosfina)paladio(II) (0,636 g, 0,91 mmol) a 2-cloro-4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidina (2,88 g, 9,06 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (2,482 g, 11,33 mmol) y carbonato de sodio (22,66 mL, 45,31 mmol) en 18% DMF en 7:3:2 DME:agua:etanol (40mL). La solución resultante se agitó a 85°C durante 1 hora. La mezcla de reacción se concentró, se diluyó con DCM (200 mL) y se lavó con agua (200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 2,5% metanol en DCM, para proporcionar el material deseado como un sólido amarillo (1,19 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,51 - 1,53 (2H, m), 1,65 - 1,66 (2H, m), 3,40 (3H, s), 3,70 (8H, s), 5,56 (2H, d), 6,61 (2H, d), 6,70 (1H, s), 8,04 (2H, d)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 375; HPLC tR = 1,65 min.

2-Cloro-4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidina



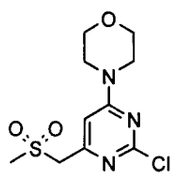
Se agregó hidróxido de sodio (9,60 mL, 95,97 mmol) a 2-cloro-4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidina (2,80 g, 9,60 mmol), 1,2-dibromoetano (1,654 mL, 19,19 mmol) y bromuro de tetrabutilamonio (0,619 g, 1,92 mmol) en tolueno (120 mL) a TA. La solución resultante se agitó a 60°C durante 3 horas. La mezcla de reacción se evaporó hasta secarse, se

disolvió nuevamente en acetato de etilo (200 mL) y se lavó secuencialmente con agua (200 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 2,5% metanol en DCM, para proporcionar el material deseado como un sólido amarillo (2,88 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,49 -1,51 (2H, m), 1,62 - 1,65 (2H, m), 3,19 (3H, s), 3,67 (8H, d), 6,96 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 318; HPLC 1,37 tR = min.

2-Cloro-4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidina

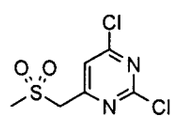


Una suspensión de 2,4-dicloro-6-(metilsulfonilmetil)pirimidina (10,56 g) en DCM (230 mL) se agitó magnéticamente (bajo nitrógeno) y se enfrió hasta alcanzar -5°C. Se agregó trietilamina (6,78 mL) seguido por adición gota a gota de una solución de morfolina (3,85 mL) en DCM (30 mL) manteniendo la reacción temperatura por debajo de -5°C. La reacción se agitó a temperatura ambiente durante 1 hora y luego la mezcla orgánica se lavó con agua (300 mL). La fase orgánica se secó ($MgSO_4$), se filtró y se evaporó hasta proporcionar un sólido marrón que se cromatografió sobre sílice, eluyendo con 50% acetato de etilo en DCM, para proporcionar el material deseado (6,81g) como un sólido blanco.

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 3,12 (3H, s), 3,63 (4H, s), 3,68 - 3,70 (4H, m), 4,45 (2H, s), 6,96 (1H, s)

Espectro de Masa: MH+ 292.

2,4-Dicloro-6-(metilsulfonilmetil)pirimidina



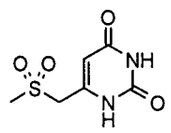
Se agregó 6-(metilsulfonilmetil)-1*H*-pirimidina-2,4-diona (132 g, 0,65 mol) a oxicloruro de fósforo (1,2 L) y la mezcla se calentó hasta alcanzar reflujo durante 16 horas, luego se enfrió hasta alcanzar temperatura ambiente. El exceso de oxicloruro de fósforo se retiró al vacío, el

residuo se sometió a azeotropía con tolueno (2 x 500 mL) y se disolvió en diclorometano. Esta mezcla luego se vertió lentamente en hielo (4 L) y se agitó durante 20 minutos, luego se extrajo con diclorometano (3 x 1 L) (el material insoluble negro se retiró mediante filtración y se descartó) y acetato de etilo (2 x 1 L). Los extractos se combinaron, se secaron, luego se evaporaron para proporcionar el material deseado como un sólido marrón oscuro (51 g). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 3,13 (s, 3H), 4,79 (s, 2H), 7,87 (s, 1H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 239; HPLC 1,21 tR = min.

6-(Metilsulfonilmetil)-1*H*-pirimidina-2,4-diona

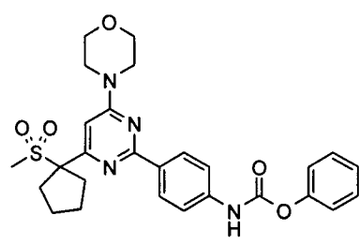


Se disolvió 6-(clorometil)-1*H*-pirimidina-2,4-diona (175 g, 1,09 mol) en DMF (2 L) y se agregó sal de sodio de ácido metanosulfínico (133,5 g, 1,31 mol). La reacción se calentó hasta alcanzar 125°C durante 2 horas y luego se dejó enfriar y la suspensión se filtró y se concentró al vacío para proporcionar un sólido amarillo. El material bruto se lavó con agua, se filtró, luego se trituró con tolueno. El sólido se filtró y luego se trituró con isohexano para proporcionar el compuesto deseado como un sólido amarillo (250 g). El material se utilizó sin purificación adicional.

6-(Clorometil)-1*H*-pirimidina-2,4-diona es un material comercialmente disponible.

La preparación de fenil *N*-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato

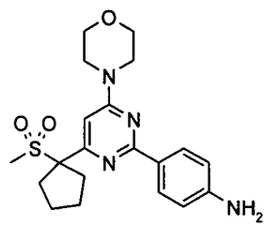


Se agregó gota a gota fenil cloroformiato (0,541 mL, 4,30 mmol) a 4-[4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]anilina (1,73 g, 4,30 mmol) y bicarbonato de sodio (0,542 g, 6,45 mmol) en dioxano (50 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 1 hora. La mezcla de reacción se evaporó hasta secarse y se repartió entre acetato de etilo (100 mL) y agua (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un sólido amarillo (1,7 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,58 (2H, t), 1,82 (2H, d), 2,40 - 2,47 (2H, m), 2,73 - 2,75 (2H, m), 2,91 (3H, s), 3,74 (8H, s), 6,88 (1H, s), 7,24 - 7,30 (3H, m), 7,43 - 7,47 (2H, m), 7,64 (2H, d), 8,33 - 8,35 (2H, m), 10,43 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 523; HPLC tR = 2,90 min.

4-[4-(1-Metilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]anilina

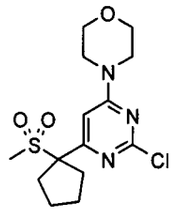


Se agregó diclorobis(trifenilfosfina)paladio (II) (0,224 g, 0,32 mmol) a una solución de 2-cloro-4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidina (2,21 g, 6,39 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,75 g, 7,99 mmol) y solución de carbonato de sodio acuoso (15,98 mL, 31,95 mmol) en una mezcla de disolventes de 18% DMF en 7:3:2 DME:agua:etanol (40 mL). La solución resultante se agitó a 85°C durante 1 hora. La mezcla de reacción se concentró y se diluyó con DCM (200 mL) y se lavó con agua (200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 2,5% metanol en DCM, para proporcionar el material deseado como un sólido amarillo (1,73 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,57 (2H, t), 1,80 (2H, d), 2,37 - 2,44 (2H, m), 2,69 - 2,74 (2H, m), 2,90 (3H, s), 3,71 (8H, s), 5,55 (2H, d), 6,59 - 6,63 (2H, m), 6,74 (1H, s), 8,05 - 8,09 (2H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 403; HPLC tR = 2,22 min.

2-Cloro-4-(1-metilsulfonilciclopentil)-6-morfolin-4-ilpirimidina



Se agregó solución de hidróxido de sodio 10N (8,57 mL, 85,69 mmol) a 2-cloro-4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidina (2,50 g, 8,57 mmol), 1,4-dibromobutano (1,014 mL, 8,57 mmol) y bromuro de tetrabutilamonio (0,552 g, 1,71 mmol) en tolueno (120 mL) a TA. La solución resultante se agitó a 60ºC durante 4 horas. La mezcla de reacción se evaporó hasta secarse y el residuo se repartió entre acetato de etilo (200 mL) y agua (200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (2,215 g).

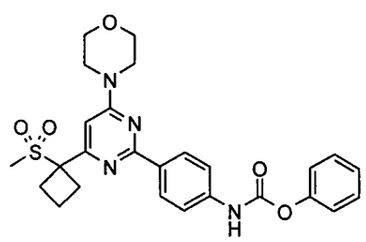
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,51 - 1,58 (2H, m), 1,76 - 1,80 (2H, m), 2,33 - 2,40 (2H, m), 2,52 - 2,59 (2H, m), 2,89 (3H, s), 3,67 (8H, s), 6,96 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 346; HPLC 2,12 tR = min.

La preparación de 2-cloro-4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato



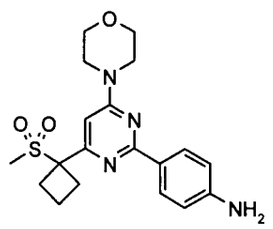
Se agregó gota a gota fenil cloroformiato (0,084 mL, 0,67 mmol) a 4-[4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]anilina (260 mg, 0,67 mmol) y bicarbonato de sodio (84 mg, 1,00 mmol) en dioxano (20 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse, se

disolvió nuevamente en acetato de etilo (100 mL) y se lavó con agua (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un sólido crema (380 mg).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,91 (1H, d), 2,06 (1H, t), 2,80 - 2,84 (2H, m), 2,88 (3H, s), 2,93 (2H, d), 3,74 (8H, d), 6,80 (1H, s), 7,24 - 7,26 (2H, m), 7,25 - 7,30 (1H, m), 7,43 - 7,47 (2H, m), 7,63 (2H, d), 8,32 (2H, d), 10,43 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 509; HPLC tR = 2,77 min.

4-[4-(1-Metilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]anilina

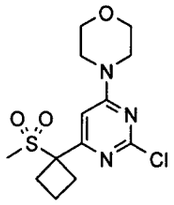


Se agregó diclorobis(trifenilfosfina)paladio(II) (0,167 g, 0,24 mmol) a una solución desgasificada de 2-cloro-4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidina (0,790 g, 2,38 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,652 g, 2,98 mmol) y una solución acuosa de carbonato de sodio (5,95 mL, 11,90 mmol) en una mezcla de disolventes de 18% DMF en 7:3:2 DME:agua:etanol (40 mL). La solución resultante se agitó a 85°C durante 1 hora. La mezcla de reacción se concentró, se diluyó con DCM (200 mL) y se lavó con agua (200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blanco (0,22 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,89 (1H, d), 2,03 - 2,07 (1H, m), 2,74 - 2,81 (2H, m), 2,86 (3H, s), 2,88 - 2,93 (2H, m), 3,71 (8H, s), 5,54 (2H, d), 6,59 - 6,62 (2H, m), 6,66 (1H, s), 8,04 - 8,07 (2H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 389; HPLC tR = 2,05 min.

2-Cloro-4-(1-metilsulfonilciclobutil)-6-morfolin-4-ilpirimidina

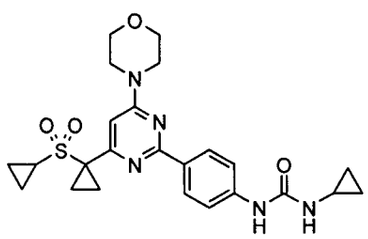


Se agregó solución de hidróxido de sodio 10N (9,60 mL, 95,97 mmol) a 1,3-dibromopropano (0,979 mL, 9,60 mmol), 2-cloro-4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidina (2,80 g, 9,60 mmol) y bromuro de tetrabutilamonio (0,619 g, 1,92 mmol) en tolueno (120 mL) a TA. La solución resultante se agitó a 60°C durante 18 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (200 mL) y se lavó secuencialmente con agua (200 mL) y solución de salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en isohexano, para proporcionar el Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,87 - 1,89 (1H, m), 2,01 (1H, d), 2,66 - 2,73 (2H, m), 2,81 - 2,84 (2H, m), 2,86 (3H, s), 3,67 (8H, s), 6,88 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 332; HPLC 1,44 tR = min.

La preparación de 2-cloro-4-(metilsulfonilmetil)-6-morfolin-4-il-pirimidina se describió anteriormente.

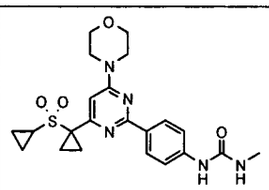
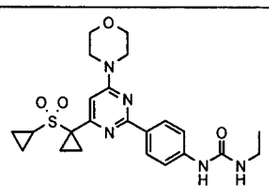
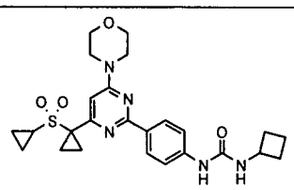
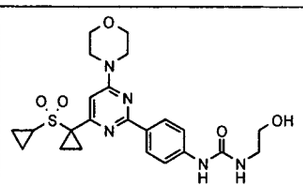
Ejemplo 13: 3-Ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea

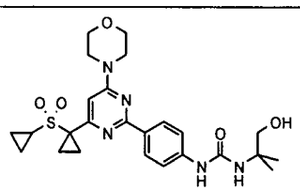
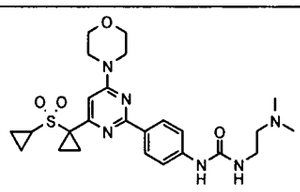
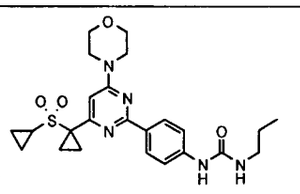
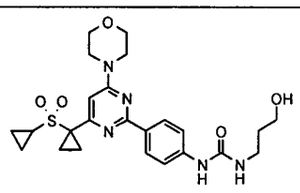
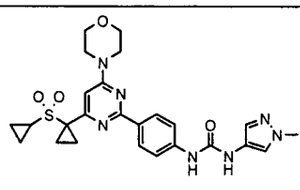
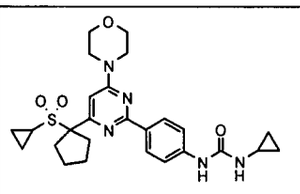


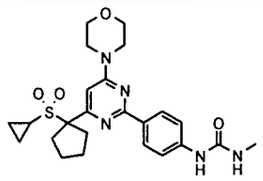
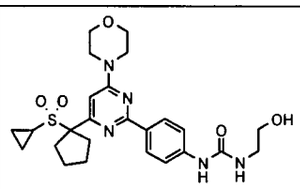
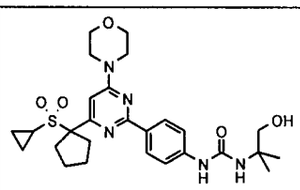
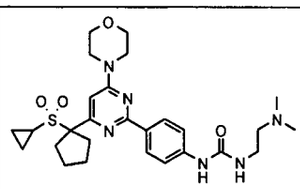
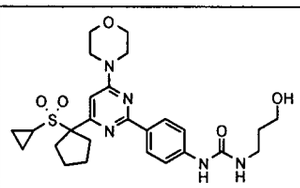
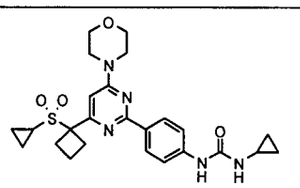
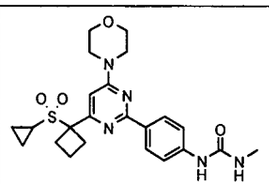
A una solución de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato (100 mg, 0,19 mmol) en DMF (2 mL) se agregó trietilamina (0,08 mL, 0,58 mmol) seguido por ciclopropilamina (55 mg, 0,96 mmol) y la reacción se calentó a 50°C durante 8 horas. El producto bruto se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes, para proporcionar el material deseado como un sólido blanco (60 mg).

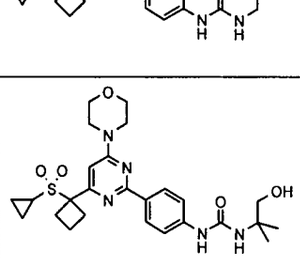
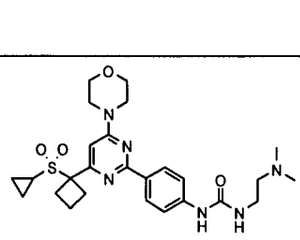
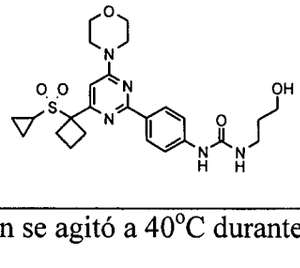
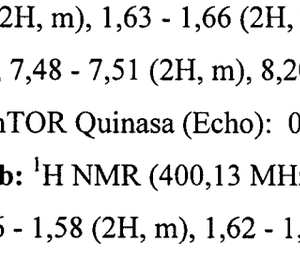
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,41 - 0,43 (2H, m), 0,64 - 0,66 (2H, m), 0,93 - 0,95 (2H, m), 1,02 - 1,05 (2H, m), 1,57 (2H, d), 1,65 (2H, d), 2,56 (1H, m), 3,02 (1H, s), 3,71 (8H, s), 6,42 (1H, s), 6,88 (1H, s), 7,50 (2H, d), 8,22 (2H, d), 8,53 (1H, s)
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 484; HPLC tR = 1,80 min.
Ensayo de mTOR Quinasa (Echo): 0,00357μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato, fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
13a		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-metilurea	458,3	1,63
13b		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-etilurea	472,4	1,78
13c		3-ciclobutil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	498,4	2,04
13d		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-hidroxietil)urea	488,4	1,5

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
13e		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	516,4	1,78
13f		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	515,4	1,71
13g		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-propilurea	486,4	1,96
13h		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	502,4	1,54
13i		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	524,4	1,71
13j*		3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	512	2,30

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
13k*		1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-metilurea	486	2,13
13l*		1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-hidroxietil)urea	516	1,92
13m*		1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	544	2,25
13n*		1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	543	2,18
13o*		1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	530	1,97
13p*		3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	498	2,05
13q*		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-metilurea	498	2,05

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
13r*		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-hidroxietil)urea	502	1,72
13s*		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	530	2,01
13t*		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	529	1,98
13u*		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	516	1,76

* La reacción se agitó a 40°C durante 6 horas

Ejemplo 13a: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,93 - 0,95 (2H, m), 1,02 - 1,05 (2H, m), 1,55 - 1,58 (2H, m), 1,63 - 1,66 (2H, m), 2,66 (3H, d), 3,02 (1H, s), 3,71 (8H, s), 6,06 (1H, d), 6,88 (1H, s), 7,48 - 7,51 (2H, m), 8,20 - 8,22 (2H, m), 8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00341μM

Ejemplo 13b: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,93 - 0,96 (2H, m), 1,02 (2H, m), 1,06 (3H, q), 1,56 - 1,58 (2H, m), 1,62 - 1,66 (2H, m), 3,00 - 3,04 (1H, m), 3,10 - 3,16 (2H, m), 3,71 (8H, s), 6,15 (1H, t), 6,88 (1H, s), 7,47 - 7,51 (2H, m), 8,20 - 8,23 (2H, m), 8,65 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0037μM

Ejemplo 13c: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,93 - 1,00 (2H, m), 1,02 - 1,05 (2H, m), 1,56 (2H, d), 1,56 - 1,60 (2H, m), 1,61 - 1,68 (2H, m), 1,82 - 1,88 (2H, m), 2,17 - 2,24 (2H,

m), 3,00 - 3,04 (1H, m), 3,71 (8H, s), 4,14 (1H, d), 6,45 (1H, d), 6,88 (1H, s), 7,46 - 7,48 (2H, m), 8,20 - 8,22 (2H, m), 8,55 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0024μM

Ejemplo 13d: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,93 - 0,95 (2H, m), 1,03 - 1,04 (2H, d), 1,55 - 1,58 (2H, m), 1,63 - 1,66 (2H, m), 3,02 (1H, s), 3,18 (2H, d), 3,45 (2H, t), 3,71 (8H, s), 4,73 (1H, s), 6,25 (1H, s), 6,88 (1H, s), 7,47 - 7,49 (2H, m), 8,22 (2H, d), 8,80 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00351μM

Ejemplo 13e: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,93 - 0,95 (2H, m), 1,03 - 1,05 (2H, m), 1,24 (6H, s), 1,56 (2H, d), 1,63 -1,65 (2H, d), 3,02 (1H, m), 3,38 - 3,40 (2H, m), 3,71 (8H, s), 4,95 (1H, s), 5,99 (1H, s), 6,88 (1H, s), 7,45 (2H, d), 8,20 (2H, d), 8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0301μM

Ejemplo 13f: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,93 - 0,96 (2H, m), 1,03 - 1,05 (2H, m), 1,55 - 1,58 (2H, m), 1,63 - 1,66 (2H, m), 2,18 (6H, s), 2,34 (2H, t), 3,02 (1H, t), 3,19 (2H, q), 3,71 (8H, s), 6,15 (1H, s), 6,88 (1H, s), 7,47 - 7,49 (2H, m), 8,20 - 8,22 (2H, m), 8,88 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,386μM

Ejemplo 13g: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,89 (3H, t), 0,93 - 0,96 (2H, m), 1,03 (2H, d), 1,41 - 1,50 (2H, m), 1,56 - 1,58 (2H, t), 1,62 - 1,66 (2H, m), 3,00 - 3,02 (1H, m), 3,06 (2H, s), 3,71 (8H, s), 6,19 (1H, t), 6,88 (1H, s), 7,49 (2H, d), 8,21 (2H, d), 8,64 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00479μM

Ejemplo 13h: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,92 - 0,98 (2H, m), 0,98 - 1,07 (2H, m), 1,55 - 1,56 (2H, m), 1,58 (2H, d), 1,61 - 1,66 (2H, m), 2,99 - 3,05 (1H, m), 3,15 - 3,19 (2H, m), 3,45 - 3,50 (2H, m), 3,71 (8H, s), 4,47 (1H, t), 6,19 (1H, t), 6,88 (1H, s), 7,47 - 7,51 (2H, m), 8,20 - 8,23 (2H, m), 8,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0106μM

Ejemplo 13i: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,94 (2H, t), 1,03 - 1,06 (2H, m), 1,55 - 1,59 (2H, m), 1,64 - 1,67 (2H, m), 3,02 (1H, s), 3,72 (8H, s), 3,79 (3H, s), 6,89 (1H, s), 7,38 (1H, s), 7,54 (2H, d), 7,76 (1H, s), 8,25 (2H, d), 8,38 (1H, s), 8,84 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00275μM

Ejemplo 13j: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,39 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 0,71 - 0,73 (2H, m), 0,84 - 0,87 (2H, m), 1,55 (2H, t), 1,81 (2H, d), 2,33 (1H, t), 2,43 - 2,45 (2H, m), 2,57 - 2,61 (1H, m), 2,82 (2H, t), 3,72 (8H, s), 6,45 (1H, d), 6,87 (1H, s), 7,50 (2H, d), 8,25 (2H, d), 8,56 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0178μM

Ejemplo 13k: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,71 - 0,73 (2H, m), 0,84 - 0,87 (2H, m), 1,55 (2H, t), 1,79 (1H, d), 1,82 (1H, s), 2,43 (2H, t), 2,57 - 2,61 (1H, m), 2,65 (3H, d), 2,82 (2H, d), 3,72 (8H, s), 6,08 (1H, d), 6,86 (1H, s), 7,49 - 7,51 (2H, m), 8,23 - 8,25 (2H, m), 8,77 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0179μM

Ejemplo 13l: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,71 - 0,73 (2H, m), 0,83 - 0,88 (2H, m), 1,55 (2H, t), 1,77 - 1,82 (2H, m), 2,43 - 2,48 (2H, m), 2,55 - 2,62 (1H, m), 2,81 (1H, t), 2,84 (1H, s), 3,15 - 3,18 (2H, m), 3,45 (2H, q), 3,72 (8H, s), 4,77 (1H, t), 6,26 (1H, t), 6,86 (1H, s), 7,47 - 7,50 (2H, m), 8,23 - 8,26 (2H, m), 8,83 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0108μM

Ejemplo 13m: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,72 - 0,74 (2H, m), 0,85 - 0,88 (2H, m), 1,24 (6H, s), 1,55 (2H, t), 1,79 (2H, d), 2,42 (1H, s), 2,45 (1H, d), 2,59 (1H, s), 2,80 (2H, s), 3,38 (2H, d), 3,72 (8H, s), 4,99 (1H, t), 6,01 (1H, s), 6,86 (1H, s), 7,44 - 7,46 (2H, m), 8,22 - 8,24 (2H, m), 8,75 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0532μM

Ejemplo 13n: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,71 - 0,73 (2H, m), 0,85 - 0,87 (2H, m), 1,55 (2H, t), 1,79 (2H, d), 2,17 (6H, s), 2,33 (2H, t), 2,42 (1H, s), 2,45 (1H, d), 2,59 (1H, s), 2,81 (2H, s), 3,19 (2H, q), 3,72 (8H, s), 6,17 (1H, s), 6,86 (1H, s), 7,47 - 7,49 (2H, m), 8,23 - 8,25 (2H, m), 8,92 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,997μM

Ejemplo 13o: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,71 - 0,73 (2H, m), 0,83 - 0,88 (2H, m), 1,53 - 1,62 (4H, m), 1,79 - 1,82 (1H, m), 1,81 (1H, d), 2,44 (2H, d), 2,57 - 2,61 (1H, m), 2,81 (1H, t), 2,84 (1H, s), 3,14 - 3,18 (2H, m), 3,44 - 3,49 (2H, m), 3,72 (8H, s), 4,52 (1H, t), 6,21 (1H, t), 6,86 (1H, s), 7,48 - 7,50 (2H, m), 8,23 - 8,25 (2H, m), 8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0287μM

Ejemplo 13p: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,62 - 0,67 (2H, m), 0,74 - 0,78 (2H, m), 0,85 - 0,87 (2H, m), 1,88 - 1,91 (1H, m), 2,07 (1H, t), 2,50 (1H, s), 2,53 - 2,58 (1H, m), 2,85 - 2,89 (2H, m), 2,94 - 2,99 (2H, m), 3,73 (8H, s), 6,42 (1H, d), 6,77 (1H, s), 7,48 - 7,52 (2H, m), 8,23 - 8,26 (2H, m), 8,53 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00202μM

Ejemplo 13q: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,74 - 0,78 (2H, m), 0,84 - 0,89 (2H, m), 1,88 - 1,91 (1H, m), 2,07 (1H, t), 2,50 (1H, m), 2,66 (3H, d), 2,85 - 2,89 (2H, m), 2,94 - 2,99 (2H, m), 3,72 (8H, s), 6,06 (1H, q), 6,76 (1H, s), 7,48 - 7,51 (2H, m), 8,22 - 8,26 (2H, m),

8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00192μM

Ejemplo 13r: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,76 - 0,78 (2H, m), 0,85 - 0,88 (2H, m), 1,91 (1H, s), 2,07 (1H, t), 2,50 (1H, s), 2,85 - 2,89 (2H, m), 2,94 - 2,97 (2H, m), 3,17 (2H, q), 3,46 (2H, q), 3,72 (8H, s), 4,72 (1H, t), 6,24 (1H, t), 6,76 (1H, s), 7,47 - 7,49 (2H, m), 8,23 - 8,25 (2H, m), 8,79 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00198μM

Ejemplo 13s: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,76 - 0,79 (2H, m), 0,85 - 0,88 (2H, m), 1,24 (6H, s), 1,91 (1H, s), 2,07 (1H, t), 2,50 (1H, s), 2,85 - 2,89 (2H, m), 2,94 (1H, d), 2,96 - 2,97 (1H, m), 3,39 (2H, d), 3,72 (8H, s), 4,95 (1H, t), 6,00 (1H, s), 6,76 (1H, s), 7,44 - 7,46 (2H, m), 8,22 - 8,24 (2H, m), 8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00846μM

Ejemplo 13t: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,75 - 0,77 (2H, m), 0,85 - 0,88 (2H, m), 1,88 - 1,91 (1H, m), 2,07 (1H, t), 2,18 (6H, s), 2,32 (1H, s), 2,34 (2H, t), 2,86 (1H, d), 2,88 (1H, s), 2,94 (1H, d), 2,96 (1H, s), 3,20 (2H, t), 3,72 (8H, s), 6,15 (1H, s), 6,76 (1H, s), 7,47 - 7,49 (2H, m), 8,23 - 8,25 (2H, m), 8,88 (1H, s).

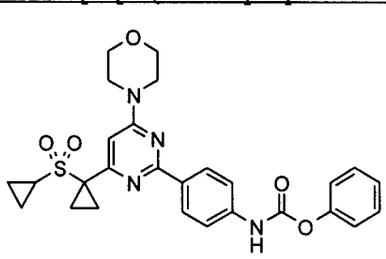
Ensayo de mTOR Quinasa (Echo): 0,172μM

Ejemplo 13u: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,74 - 0,78 (2H, m), 0,84 - 0,89 (2H, m), 1,57 (1H, d), 1,61 (1H, t), 1,88 - 1,91 (1H, m), 2,06 (1H, d), 2,50 (1H, m), 2,85 - 2,89 (2H, m), 2,94 - 2,99 (2H, m), 3,14 - 3,19 (2H, m), 3,45 - 3,49 (2H, m), 3,72 (8H, s), 4,47 (1H, t), 6,19 (1H, t), 6,76 (1H, s), 7,47 - 7,50 (2H, m), 8,23 - 8,25 (2H, m), 8,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00477μM

La preparación de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato se describe a continuación:

<u>Fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato</u>



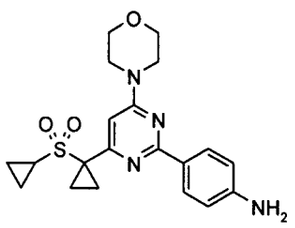
Se agregó gota a gota fenil cloroformiato (0,440 mL, 3,50 mmol) a 4-[4-(1-

ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]anilina (1,40g, 3,50 mmol) y bicarbonato de sodio (0,440 g, 5,24 mmol) en dioxano (50 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (100 mL) y se lavó con agua (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un sólido amarillo (1,82 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,93 - 0,95 (2H, m), 1,05 (2H, d), 1,59 (1H, s), 1,60 (1H, t), 1,65 (1H, t), 1,67 (1H, d), 3,01 - 3,05 (1H, m), 3,58 (1H, s), 3,73 (8H, s), 6,94 (1H, s), 7,24 - 7,30 (3H, m), 7,43 - 7,47 (2H, m), 7,64 (2H, d), 8,31 (2H, d), 10,44 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 521; HPLC tR = 2,68 min.

4-[4-(1-Ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]anilina

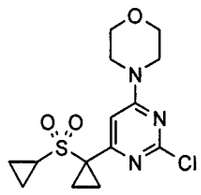


Se agregó diclorobis(trifenilfosfina)paladio(II) (0,376 g, 0,54 mmol) a 2-cloro-4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidina (1,84 g, 5,35 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,466 g, 6,69 mmol) y carbonato de sodio (13,38 mL, 26,76 mmol) en 18% DMF en 7:3:2 DME:agua:etanol (40 mL). La solución resultante se agitó a 85°C durante 1 hora. La mezcla de reacción se concentró y se diluyó con DCM (200 mL) y se lavó con agua (200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (1,40 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,91 - 0,97 (2H, m), 0,98 - 1,06 (2H, m), 1,52 - 1,58 (2H, m), 1,59 - 1,64 (2H, m), 2,97 - 3,04 (1H, m), 3,68 (4H, d), 3,71 - 3,71 (4H, m), 5,54 (2H, d), 6,58 - 6,62 (2H, m), 6,79 (1H, s), 8,03 (2H, d)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 401; HPLC tR = 1,62 min.

2-Cloro-4-(1-ciclopropilsulfonilciclopropil)-6-morfolin-4-ilpirimidina

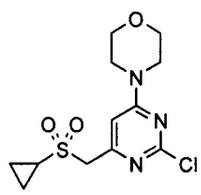


Se agregó hidróxido de sodio (8,81 mL, 88,11 mmol) a 2-cloro-4-(ciclopropilsulfonilmetil)-6-morfolin-4-ilpirimidina (2,80 g, 8,81 mmol), 1,2-dibromoetano (1,519 mL, 17,62 mmol) y bromuro de tetrabutilamonio (0,568 g, 1,76 mmol) en tolueno (120 mL) a TA. La solución resultante se agitó a 60°C durante 3 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (200 mL) y se lavó secuencialmente con agua (200 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (1,84 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,89 - 0,93 (2H, m), 1,00 - 1,05 (2H, m),), 1,50 (2H, d), 1,62 (2H, d), 2,89 - 2,96 (1H, m), 3,65 (4H, m), 3,66 - 3,67 (4H, m), 7,01 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 344; HPLC 1,48 tR = min.

2-Cloro-4-(ciclopropilsulfonilmetil)-6-morfolin-4-ilpirimidina

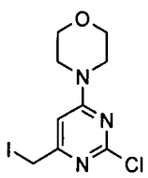


Se agregó sal de sodio de ácido ciclopropanosulfínico (5,66 g, 44,17 mmol) en una porción a 2-cloro-4-(yodometil)-6-morfolin-4-ilpirimidina (12,5 g, 36,81 mmol) en acetonitrilo (300 mL) a TA. La suspensión resultante se agitó a 80 °C durante 24 horas. La mezcla resultante se evaporó hasta secarse y el residuo se sometió a azeotropía con MeCN para proporcionar el material deseado (7,12 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,94 - 0,99 (2H, m), 1,01 - 1,07 (2H, m), 2,77 - 2,84 (1H, m), 3,62 (4H, s), 3,67 - 3,69 (4H, s), 4,47 (2H, s), 6,95 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 318; HPLC tR = 1,46 min.

2-Cloro-4-(yodometil)-6-morfolin-4-ilpirimidina

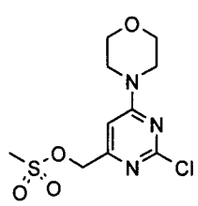


Se agregó yoduro de sodio (27,2 g, 181,31 mmol) a (2-cloro-6-morfolin-4-ilpirimidin-4-il)metil metanosulfonato (27,9 g, 90,66 mmol) en acetona (400 mL) a TA bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en DCM (400 mL) y se lavó con agua (200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un sólido marrón (33,9 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 3,59 (4H, s), 3,63 - 3,68 (4H, m), 4,29 (2H, s), 6,97 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$339 = ; HPLC tR = 1,87 min.

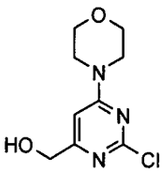
(2-Cloro-6-morfolin-4-ilpirimidin-4-il)metil metanosulfonato



Se agregó gota a gota cloruro de metanosulfonilo (10,57 mL, 136 mmol) a (2-cloro-6-morfolin-4-ilpirimidin-4-il)metanol (20,83 g, 90,70 mmol) y DIPEA (23,70 mL, 136 mmol) en DCM (375 mL) a 0°C durante un período de 15 minutos, bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 1 hora. La mezcla de reacción se diluyó con agua (100 mL) y la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un aceite marrón (27,9 g).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 308; HPLC tR = 1,58 min.

(2-Cloro-6-morfolin-4-ilpirimidin-4-il)metanol

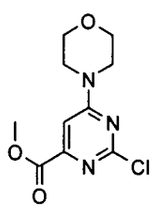


A una suspensión de metil 2-cloro-6-morfolin-4-ilpirimidina-4-carboxilato (60 g, 232,85 mmol) en THF (1200 mL) a -5°C se agregó borohidruro de litio (2M en THF, 0,122 L, 244,50 mmol) gota a gota durante 30 minutos. La mezcla de reacción se entibió hasta alcanzar TA y se agitó durante 1 hora. A esto se agregó agua (600 mL), la mezcla se agitó durante 2 horas y luego se filtró. Se agregó más agua (600 mL) y la solución se extrajo tres veces con acetato de etilo (600 mL). Los orgánicos combinados se lavaron con salmuera acuosa al 50% (900 mL), se secaron ($MgSO_4$) y el disolvente luego se eliminó bajo presión reducida para proporcionar el producto deseado como un sólido blanco (49,8 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 3,59 - 3,68 (8H, m), 4,35 (2H, dd), 5,50 (1H, t), 6,77 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 230; HPLC tR = 1,08 min

Metil 2-cloro-6-morfolin-4-ilpirimidina-4-carboxilato



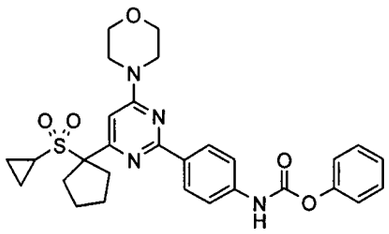
A una solución de 2,6-dicloropirimidina-4-carboxilato (60 g, 289,84 mmol) en DCM (400 mL) a -5°C se agregó trietilamina (44,4 mL, 318,82 mmol) y se lavó con DCM (80 mL). A la solución resultante se agregó morfolina (26,6 mL, 304,33 mmol) en DCM (120 mL) gota a gota durante 2 horas, manteniendo la temperatura por debajo de 5°C. La mezcla de reacción se agitó a 0°C durante 2 horas y luego se entibió hasta alcanzar TA. Se agregó agua (600 mL) y las capas se separaron. La capa orgánica se lavó dos veces con agua (180 mL) y las fracciones acuosas combinadas se extrajeron dos veces con DCM (180 mL). Los orgánicos combinados se lavaron dos veces con salmuera acuosa al 75% (180 mL), se secaron ($MgSO_4$) y el disolvente se retiró bajo presión reducida para proporcionar el producto bruto. Esto se purificó mediante cristalización a partir acetato de etilo/isohexano para proporcionar el producto deseado como un sólido blanco (65,4g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 3,72 - 3,82 (8H, m), 3,99 (3H, s), 7,20 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 258; HPLC tR = 1,38 min

La preparación de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato

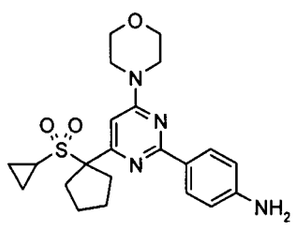


Se agregó gota a gota fenil cloroformiato (0,455 mL, 3,62 mmol) a 4-[4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]anilina (1,55 g, 3,62 mmol) y bicarbonato de sodio (0,456 g, 5,43 mmol) en dioxano (50 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 3 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (100 mL) y se lavó con agua (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un sólido amarillo (2,31 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,71 - 0,75 (2H, m), 0,84 - 0,89 (2H, m), 1,56 (2H, t), 1,78 - 1,83 (2H, m), 2,45 (1H, t), 2,57 - 2,63 (2H, m), 2,81 - 2,84 (2H, m), 3,73 (8H, s), 6,90 (1H, s), 7,23 - 7,30 (3H, m), 7,43 - 7,47 (2H, m), 7,63 (2H, d), 8,33 - 8,36 (2H, m), 10,42 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 549; HPLC tR = 3,02 min.

4-[4-(1-Ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidin-2-il]anilina

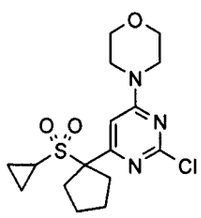


Se agregó diclorobis(trifenilfosfina)paladio(II) (0,170 g, 0,24 mmol) a una solución desgasificada de 2-cloro-4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidina (1,80 g, 4,84 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,326 g, 6,05 mmol) y una solución acuosa de carbonato de sodio (12,10 mL, 24,20 mmol) en una mezcla de disolventes de 18% DMF en 7:3:2 DME:agua:etanol (40 mL). La solución resultante se agitó a 85°C durante 1 hora. La mezcla de reacción se concentró, se diluyó con DCM (100 mL) y se lavó con agua (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 70% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (1,55 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,73 - 0,75 (2H, m), 0,83 - 0,88 (2H, m), 1,55 (2H, t), 1,78 (1H, s), 1,81 (1H, t), 2,41 (1H, d), 2,45 - 2,47 (1H, m), 2,54 - 2,58 (1H, m), 2,79 (1H, t), 2,82 (1H, s), 3,70 (8H, d), 5,53 (2H, s), 6,59 - 6,62 (2H, m), 6,77 (1H, s), 8,07 - 8,09 (2H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 429; HPLC tR = 2,36 min.

2-Cloro-4-(1-ciclopropilsulfonilciclopentil)-6-morfolin-4-ilpirimidina



Se agregó solución de hidróxido de sodio 10N (5,70 mL, 56,96 mmol) a 2-cloro-4-(ciclopropilsulfonilmetil)-6-morfolin-4-ilpirimidina (1,81 g, 5,70 mmol), 1,4-dibromobutano (0,674 mL, 5,70 mmol) y bromuro de tetrabutilamonio (0,367 g, 1,14 mmol) en tolueno (100 mL) a TA. La solución resultante se agitó a 60°C durante 3 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (75 mL) y se lavó con agua (75 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (1,8 g).

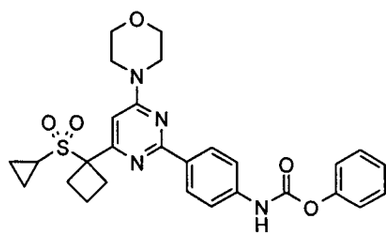
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,71 - 0,75 (2H, m), 0,90 - 0,94 (2H, m), 1,50 - 1,59 (2H, m), 1,77 - 1,80 (2H, m), 2,36 - 2,44 (2H, m), 2,57 - 2,68 (3H, m), 3,67 (8H, s), 6,97 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 372; HPLC tR = 2,26 min.

La preparación de 2-cloro-4-(ciclopropilsulfonilmetil)-6-morfolin-4-ilpirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato

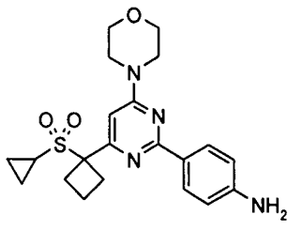


Se agregó gota a gota fenil cloroformiato (0,106 mL, 0,84 mmol) a 4-[4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]anilina (350 mg, 0,84 mmol) y bicarbonato de sodio (106 mg, 1,27 mmol) en dioxano (20 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (50 mL) y se lavó con agua (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un sólido crema (453 mg).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,75 - 0,77 (2H, m), 0,85 - 0,88 (2H, m), 1,90 (1H, d), 2,07 (1H, d), 2,54(1H, m), 2,86 - 2,90 (2H, m), 2,93 - 2,98 (2H, s), 3,73 (8H, s), 6,80 (1H, s), 7,24 - 7,30 (3H, m), 7,43 - 7,47 (2H, m), 7,63 (2H, d), 8,33 - 8,35 (2H, m), 10,42 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 535; HPLC tR = 2,91 min.

4-[4-(1-Ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidin-2-il]anilina

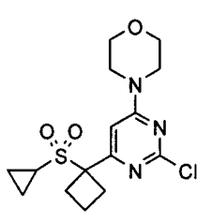


Se suspendieron 2-cloro-4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidina (430 mg, 1,20 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (329 mg, 1,50 mmol), diclorobis(trifenilfosfina)paladio(II) (42,2 mg, 0,06 mmol) y una solución acuosa de carbonato de sodio (3,00 mL, 6,01 mmol) en una mezcla de disolventes de 18% DMF en 7:3:2 DME:agua:etanol (8 mL) y se sellaron en un tubo de microondas. La reacción se calentó hasta alcanzar 100°C durante 30 minutos en el reactor de microondas y se enfrió hasta alcanzar TA. El producto bruto se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, el producto deseado se eluyó de la columna utilizando amoníaco 7M en metanol. El material aislado se purificó adicionalmente mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (350 mg).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,74 - 0,78 (2H, m), 0,83 - 0,88 (2H, m), 1,85 - 1,91 (1H, m), 2,03 - 2,07 (1H, m), 2,44 - 2,48 (1H, m), 2,83 - 2,87 (2H, m), 2,90-2,97 (2H, m), 3,70 - 3,71 (8H, m), 5,52 (2H, d), 6,58 - 6,62 (2H, m), 6,67 (1H, s), 8,06 - 8,09 (2H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 415; HPLC tR = 2,19 min.

2-Cloro-4-(1-ciclopropilsulfonilciclobutil)-6-morfolin-4-ilpirimidina



Se agregó solución de hidróxido de sodio 10N (9,60 mL, 95,97 mmol) a 1,3-dibromopropano (0,979 mL, 9,60 mmol), 2-cloro-4-(ciclopropilsulfonilmetil)-6-morfolin-4-ilpirimidina (2,80 g, 9,60 mmol) y bromuro de tetrabutilamonio (0,619 g, 1,92 mmol) en tolueno (120 mL) a TA. La solución resultante se agitó a 60°C durante 18 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (200 mL) y se lavó

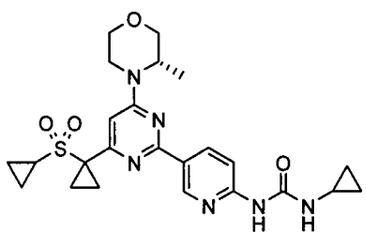
secuencialmente con agua (200 mL) y solución de salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (0,795 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,73 - 0,77 (2H, m), 0,89 - 0,94 (2H, m), 1,85 - 1,92 (1H, m), 2,04 - 2,08 (1H, m), 2,53 - 2,57 (1H, m), 2,70 - 2,78 (2H, m), 2,85 - 2,93 (2H, m), 3,66 (8H, d), 6,88 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 358; HPLC 1,95 tR = min.

La preparación de 2-cloro-4-(ciclopropilsulfonilmetil)-6-morfolin-4-ilpirimidina se describió anteriormente.

Ejemplo 14: 3-Ciclopropil-1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]urea



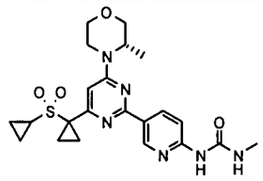
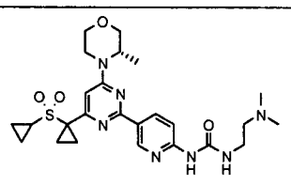
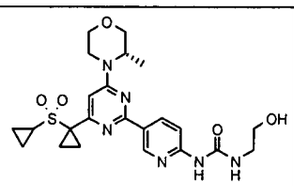
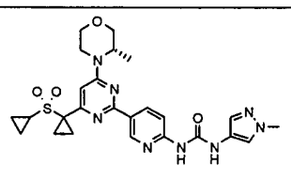
Se agregó trietilamina (0,208 mL, 1,5 mmol) a una solución de fenil *N*-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]carbamato (200 mg, 0,37 mmol) y ciclopropilamina (1,48 mmol) en NMP (2 mL). La reacción se calentó a 75°C durante 4 horas y luego se purificó mediante HPLC prep, utilizando una mezcla de agua (conteniendo 1% NH_3) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido (40 mg).

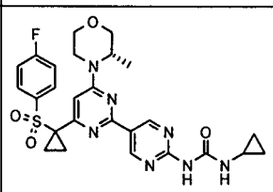
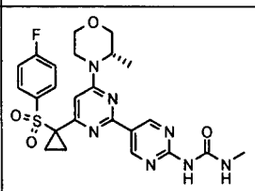
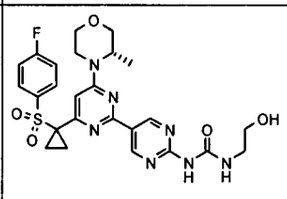
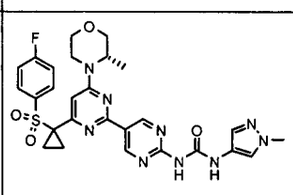
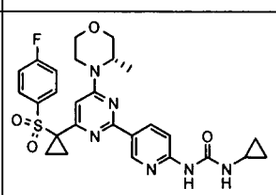
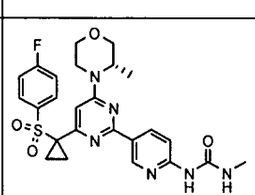
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,44 - 0,50 (2H, m), 0,64 - 0,72 (2H, m), 0,89 - 0,96 (2H, m), 1,00 - 1,06 (2H, m), 1,23 (3H, d), 1,54 - 1,60 (2H, m), 1,59 - 1,68 (2H, m), 2,59 - 2,66 (1H, m), 2,96 - 3,01 (1H, m), 3,16 - 3,25 (1H, m), 3,44 - 3,52 (1H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,20 (1H, s), 4,54 (1H, s), 6,90 (1H, s), 7,50 (1H, d), 8,18 (1H, s), 8,50 (1H, d), 9,09 (1H, s), 9,37 (1H, s)

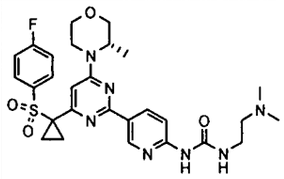
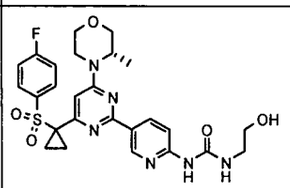
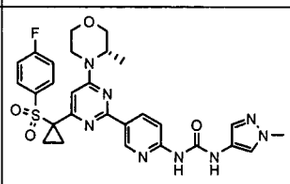
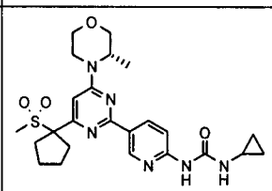
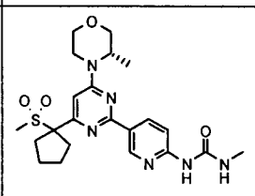
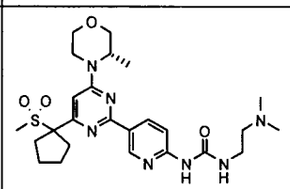
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 499; HPLC tR = 2,15 min.

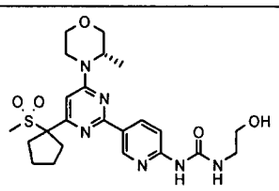
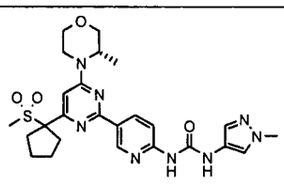
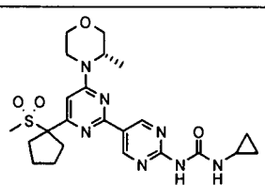
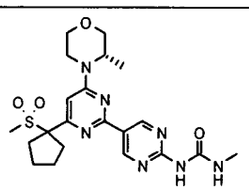
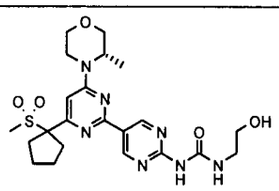
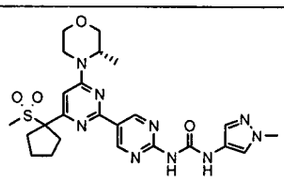
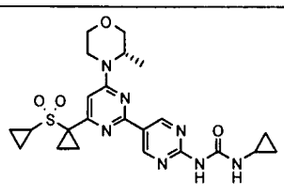
Ensayo de mTOR Quinasa (Echo): 0,0465μM

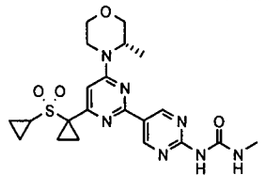
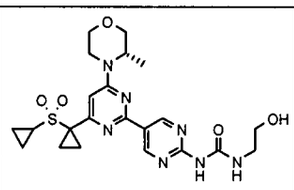
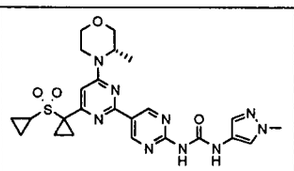
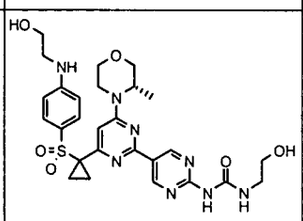
Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]carbamato, fenil *N*-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]carbamato, fenil *N*-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]carbamato, fenil *N*-[5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]carbamato, fenil *N*-[5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-il]carbamato o fenil *N*-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]carbamato utilizando la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
14a		1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-metilurea	473	2,03
14b		1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-(2-dimetilaminoetil)urea	530	1,97
14c		1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-(2-hidroxietil)urea	503	1,73
14d		1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-(1-metilpirazol-4-il)urea	539	2,01

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
14e		3-ciclopropil-1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]urea	554	2,37
14f		1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-metilurea	528	2,16
14g		1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-(2-hidroxietil)urea	558	1,91
14h		1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-(1-metilpirazol-4-il)urea	594	2,19
14i		3-ciclopropil-1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]urea	553	2,26
14j		1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-metilurea	527	2,20

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
14k		3-(2-dimetilaminoetil)-1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]urea	584	2,22
14l		1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-(2-hidroxietil)urea	557	1,92
14m		1-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-3-(1-metilpirazol-4-il)urea	593	2,13
14n		3-ciclopropil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]urea	501	2,18
14o		3-metil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]urea	475	2,01
14p		3-(2-dimetilaminoetil)-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]urea	532	2,01

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
14q		3-(2-hidroxietil)-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]urea	505	1,78
14r		1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]-3-(1-metilpirazol-4-il)urea	541	2,01
14s		3-ciclopropil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-il]urea	502	2,15
14t		3-metil-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-il]urea	476	1,99
14u		3-(2-hidroxietil)-1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-il]urea	506	1,70
14v		1-[5-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-il]-3-(1-metilpirazol-4-il)urea	542	1,95
14w		3-ciclopropil-1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-	500	2,0

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		il]urea		
14x		1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-metilurea	474	1,79
14y		1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-(2-hidroxietil)urea	504	1,54
14z		1-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]-3-(1-metilpirazol-4-il)urea	540	1,82
14aa*		3-(2-hidroxietil)-1-[5-[4-[1-[4-(2-hidroxietilamino)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]urea	599	1,63

* Aislado como un producto derivado de la reacción para generar **14g**

Ejemplo 14a: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,90 - 0,96 (2H, m), 1,01 - 1,06 (2H, m), 1,24 (3H, d), 1,55 - 1,60 (2H, m), 1,62 - 1,68 (2H, m), 2,78 (3H, s), 3,18 - 3,27 (1H, m), 3,44 - 3,54 (1H, m), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,20 (1H, d), 4,56 (1H, s), 6,91 (1H, s), 7,43 (1H, d), 8,15 (1H, s), 8,49 (1H, d), 9,12 (1H, s), 9,48 (1H, s), 9,49 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0136μM

Ejemplo 14b: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,91 - 0,95 (2H, m), 1,00 - 1,05 (2H, m), 1,23 (3H, d), 1,56 - 1,60 (2H, m), 1,63 - 1,66 (2H, m), 2,18 (6H, s), 2,36 (2H, t), 2,98 - 3,04 (1H, m), 3,17 - 3,29 (3H, m), 3,48 (1H, td), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,20 (1H, s), 4,54 (1H, s), 6,90 (1H, s), 7,53 (1H, d), 8,05 (1H, s), 8,49 (1H, d), 9,09 (1H, d), 9,48 (1H, s).

Ensayo de mTOR Quinasa (Echo): 1,39μM

Ejemplo 14c: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,90 - 0,94 (2H, m), 1,01 - 1,05 (2H, m), 1,23 (3H, d), 1,55 - 1,60 (2H, m), 1,63 - 1,67 (2H, m), 2,96 - 3,03 (1H, m), 3,16 - 3,28 (3H, m), 3,43 - 3,52 (2H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,20 (1H, s), 4,54 (1H, s), 4,80 (1H, t), 6,90 (1H, s), 7,47 (1H, d), 8,29 (1H, s), 8,50 (1H, d), 9,10 (1H, s), 9,51 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0401μM

Ejemplo 14d: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,89 - 0,96 (2H, m), 1,00 - 1,05 (2H, m), 1,24 (3H, d), 1,58 - 1,61 (2H, m), 1,64 - 1,70 (2H, m), 2,97 - 3,04 (1H, m), 3,22 (1H, td), 3,43 - 3,55 (1H, m), 3,64 (1H, dd), 3,75 - 3,82 (4H, m), 3,98 (1H, dd), 4,23 (1H, s), 4,55 (1H, s), 6,92 (1H, s), 7,49 (1H, d), 7,87 (1H, s), 8,55 (1H, d), 9,18 (1H, s), 9,73 (1H, s), 10,36 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0143μM

Ejemplo 14e: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,53 - 0,55 (2H, m), 0,69 - 0,74 (2H, m), 1,19 (3H, d), 1,60 - 1,63 (2H, m), 1,88 - 1,92 (2H, m), 3,12 - 3,21 (1H, m), 3,44 (1H, d), 3,60 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,14 - 4,24 (1H, m), 4,40 - 4,54 (1H, m), 6,77 (1H, s), 7,44 (2H, t), 7,85 (2H, dd), 8,88 (2, s), 9,11 (1H, d), 10,11 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,11μM

Ejemplo 14f: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,59 - 1,65 (2H, m), 1,89 - 1,92 (2H, m), 2,79(3H,d), 3,17 (1H, t), 3,46 - 3,63 (2H, m), 3,74 (1H, d), 3,95 (1H, d), 4,18 (1H, s), 4,46 (1H, s), 6,77 (1H, s), 7,43 (2H, t), 7,85 (2H, dd), 8,94 (2H, s), 10,08 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,189μM

Ejemplo 14g: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,59 - 1,66 (2H, m), 1,88 - 1,92 (2H, m), 3,18 (1H, d), 3,30 (2H, q), 3,44 (1H, d), 3,49 - 3,54 (2H, m), 3,60 (1H, d), 3,72 - 3,98 (4H, m), 4,18(1H,s), 4,45(1H,s), 6,77 (1H, s), 7,43 (2H, t), 7,79 - 7,89 (2H, m), 8,91(2H,s), 9,13 - 9,20 (1H, m), 10,08 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0857μM

Ejemplo 14h: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,61 - 1,65 (2H, m), 1,89 - 1,94 (2H, m), 3,19 (1H, d), 3,41 - 3,50 (1H, m), 3,61 (1H, d), 3,75 (1H, d), 3,82 (3H, s), 3,96 (1H, d), 4,22 (1H, s), 4,48 (1H, s), 6,78 (1H, s), 7,46 (2H, t), 7,54 (1H, s), 7,86 (2H, dd), 7,90

(1H, s), 8,97 (2H, s), 10,47 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,14μM

Ejemplo 14i: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,46 - 0,51 (2H, m), 0,65 - 0,70 (2H, m), 1,18 (3H, d), 1,57 - 1,64 (2H, m), 1,86 - 1,92 (2H, m), 2,60 - 2,65 (1H, m), 3,14 - 3,19 (1H, m), 3,45 (1H, dd), 3,60 (1H, dd), 3,74 (1H, d), 3,92 - 3,99 (1H, m), 4,45 (1H, s), 6,73 (1H, s), 7,38 - 7,48 (2H, m), 7,84 (2H, dd), 8,05 - 8,16 (3H, m), 8,62 (1H, s), 9,37 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0339μM

Ejemplo 14j: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,57 - 1,64 (2H, m), 1,88 - 1,91 (2H, m), 2,74 (3H, d), 3,11 - 3,21 (1H, m), 3,42 - 3,50 (1H, m), 3,60 (1H, d), 3,74 (1H, d), 3,93 - 3,98 (1H, m), 4,13 - 4,19 (1H, m), 4,40 - 4,47 (1H, m), 6,71 (1H, s), 7,35 (1H, d), 7,43 (2H, t), 7,84 (2H, dd), 7,98 - 8,07 (2H, m), 8,67 (1H, s), 9,50 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0129μM

Ejemplo 14k: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,58 - 1,62 (2H, m), 1,88 - 1,91 (2H, m), 2,19 (6H, s), 2,32 - 2,35 (2H, m), 3,17 (1H, d), 3,24 - 3,29 (2H, m), 3,44 (1H, d), 3,60 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,13 - 4,21 (1H, m), 4,41 - 4,49 (1H, m), 6,71 (1H, s), 7,39 - 7,46 (3H, m), 7,84 (2H, dd), 7,98 (1H, s), 8,06 (1H, d), 8,65 (1H, s), 9,48 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,275μM

Ejemplo 14l: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,59 - 1,65 (2H, m), 1,85 - 1,92 (2H, m), 3,12 - 3,21 (1H, m), 3,22 - 3,27 (2H, m), 3,43 - 3,50 (3H, m), 3,60 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,17 (1H, s), 4,44 (1H, s), 4,79 (1H, t), 6,71 (1H, s), 7,37 - 7,46 (3H, m), 7,80 - 7,89 (2H, m), 7,84 (3H, dd), 8,04 (1H, d), 8,16 (1H, s), 8,70 (1H, s), 9,49 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0137μM

Ejemplo 14m: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,58 - 1,65 (2H, m), 1,88 - 1,92 (2H, m), 3,13 - 3,22 (1H, m), 3,42 - 3,49 (1H, m), 3,61 (1H, d), 3,75 (1H, d), 3,81 (3H, s), 3,96 (1H, d), 4,14 - 4,24 (1H, m), 4,43 - 4,51 (1H, m), 6,73 (1H, s), 7,42 - 7,50 (3H, m), 7,82 - 7,90 (2H, m), 8,07 - 8,20 (1H, m), 8,71 (1H, s), 9,72 (1H, s), 10,28 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0143μM

Ejemplo 14n: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,44 - 0,51 (2H, m), 0,66 - 0,71 (2H, m), 1,22 (3H, d), 1,50 - 1,61 (2H, m), 1,78 - 1,85 (2H, m), 2,40 - 2,47 (2H, m), 2,60 - 2,66 (1H, m), 2,69 - 2,78 (2H, m), 2,90 (3H,s), 3,15 - 3,27 (1H, m), 3,44 - 3,54 (1H, m), 3,64 (1H, d), 3,76 (1H, d), 3,98 (1H, d), 4,29 (1H, s), 4,58 (1H, s), 6,84 (1H, s), 7,51 (1H, d), 8,20 (1H, s), 8,53 (1H, d), 9,12 (1H, s), 9,37 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0363μM

Ejemplo 14o: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,51 - 1,60 (2H, m), 1,75 - 1,86 (2H, m), 2,40 - 2,47 (2H, m), 2,71 - 2,79 (5H, m), 2,90(3H,s), 3,22 (1H, d), 3,48 (1H, d), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,21 - 4,32 (1H, m), 4,58 (1H, s), 6,84 (1H, s), 7,42 (1H, d), 8,18 (1H, s), 8,52 (1H, d), 9,14 (1H, s), 9,52 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0217μM

Ejemplo 14p: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,54 - 1,61 (2H, m), 1,78 - 1,84 (2H, m), 2,18 (6H, s), 2,32 - 2,38 (2H, m), 2,38 - 2,47 (2H, m), 2,69 - 2,79 (2H, m), 2,90 (3H,s), 3,14 - 3,29 (3H, m), 3,43 - 3,55 (1H, m), 3,64 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,26 (1H, s), 4,58 (1H, s), 6,84 (1H, s), 7,54 (1H, d), 8,03 (1H, s), 8,52 (1H, d), 9,12 (1H, s), 9,48 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,537μM

Ejemplo 14q: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,51 - 1,61 (2H, m), 1,76 - 1,86 (2H, m), 2,37 - 2,46 (2H, m), 2,69 - 2,78 (2H, m), 2,90 (3H, s), 3,17 - 3,29 (3H, m), 3,42 - 3,54 (3H, m), 3,64 (1H, dd), 3,76 (1H, d), 3,92 - 4,01 (1H, m), 4,26 (1H, s), 4,57 (1H, s), 4,80 (1H, t), 6,84 (1H, s), 7,47 (1H, d), 8,31 (1H, s), 8,53 (1H, d), 9,12 (1H, s), 9,50 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0265μM

Ejemplo 14r: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,60 (2H, m), 1,79 - 1,85 (2H, m), 2,39 - 2,47 (2H, m), 2,71 - 2,81 (2H, m), 2,90 (3H, s), 3,17 - 3,26 (1H, m), 3,46 - 3,55 (1H, m), 3,65 (2H, d), 3,78 (4H, d), 3,98 (1H, d), 4,28 (1H, s), 4,59 (1H, s), 6,86 (1H, s), 7,50 (2H, d), 7,87 (1H, s), 8,58 (1H, d), 9,20 (1H, s), 9,73 (1H, s), 10,34 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0103μM

Ejemplo 14s: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,51 - 0,58 (2H, m), 0,67 - 0,76 (2H, m), 1,23 (3H, d), 1,50 - 1,62 (2H, m), 1,76 - 1,88 (2H, m), 2,31 - 2,49 (2H, m), 2,64 - 2,79 (2H, m), 2,90 (3H, s), 3,15 - 3,26 (1H, m), 3,49 (1H, t), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,29 (1H, s), 4,59 (1H, s), 6,88 (1H, s), 9,15 (1H, s), 9,36 (2H, s), 10,13 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,122μM

Ejemplo 14t: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,56 (2H,m), 1,77 - 1,87 (2H, m), 2,34 (3H, d), 2,38 - 2,46 (2H, m), 2,68 - 2,76 (2H, m), 2,80 (3H, d), 3,16 - 3,23 (1H, m), 3,46 - 3,51 (1H, m), 3,64 (1H, d), 3,76 (1H, d), 3,96 (1H, d), 4,22 - 4,35 (1H, m), 4,54 - 4,68 (1H, m), 6,89 (1H, s), 8,97 - 9,07 (1H, m), 9,36 (2H, s), 10,11 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,197μM

Ejemplo 14u: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,52 - 1,59 (2H, m), 1,78 -

1,85 (2H, m), 2,38 - 2,52 (4H, m), 2,69 - 2,79 (2H, m), 3,20 (1H, d), 3,32 (3H, s), 3,42 - 3,47 (1H, m), 3,49 - 3,55 (2H, m), 3,61 - 3,67 (1H, m), 3,76 (1H, d), 3,97 (1H, d), 4,30 (1H, s), 4,61 (1H, s), 4,83 (1H, t), 6,89 (1H, s), 9,15 - 9,26 (1H, m), 9,36 (2H, s), 10,11 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,123μM

Ejemplo 14v: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,54 - 1,60 (2H, m), 1,79 - 1,86 (2H, m), 2,38 - 2,47 (2H, m), 2,65 - 2,81 (5H, m), 3,11 - 3,27 (1H, m), 3,46 - 3,53 (1H, m), 3,65 (1H, d), 3,76 (1H, d), 3,81 (3H, s), 3,98 (1H, d), 4,27 - 4,35 (1H, m), 4,57 - 4,65 (1H, m), 6,91 (1H, s), 7,55 (1H, s), 7,92 (1H, s), 9,08 (1H, s), 9,44 (2H, s), 10,49 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0823μM

Ejemplo 14w: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,52 - 0,57 (2H, m), 0,68 - 0,74 (2H, m), 0,91 - 0,95 (2H, m), 0,99 - 1,04 (2H, m), 1,23 (3H, d), 1,56 - 1,61 (2H, m), 1,63 - 1,68 (2H, m), 2,65 - 2,73 (1H, m), 2,95 - 3,03 (1H, m), 3,22 (1H, dd), 3,43 - 3,53 (1H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,23 (1H, s), 4,56 (1H, s), 6,95 (1H, s), 9,15 (1H, s), 9,33 (2H, s), 10,13 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,208μM

Ejemplo 14x: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,89 - 0,96 (2H, m), 1,00 - 1,06 (2H, m), 1,24 (3H, d), 1,56 - 1,61 (2H, m), 1,63 - 1,67 (2H, m), 2,80 (3H, d), 2,98 - 3,05 (1H, m), 3,19 - 3,25 (1H, m), 3,48 (1H, dd), 3,57 - 3,66 (1H, m), 3,70 - 3,80 (1H, m), 3,90 - 4,00 (1H, m), 4,21 (1H, s), 4,56 (1H, s), 6,94 (1H, s), 8,98 (1H, d), 9,33 (2H, s), 10,10 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,63μM

Ejemplo 14y: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,89 - 0,95 (2H, m), 1,00 - 1,05 (2H, m), 1,24 (3H, d), 1,57 - 1,61 (2H, m), 1,64 - 1,69 (2H, m), 2,98 - 3,04 (1H, m), 3,18 - 3,27 (1H, m), 3,29 - 3,34 (2H, m), 3,44 - 3,55 (3H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,23 (1H, s), 4,56 (1H, s), 4,83 (1H, t), 6,95 (1H, s), 9,20 (1H, t), 9,35 (2H, s), 10,11 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,152μM

Ejemplo 14z: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,92 - 0,95 (2H, m), 0,98 - 1,07 (2H, m), 1,23 (3H, d), 1,58 - 1,61 (2H, m), 1,62 - 1,68 (2H, m), 2,97 - 3,03 (1H, m), 3,23 (1H, td), 3,49 (1H, td), 3,64 (1H, d), 3,76 - 3,85 (4H, m), 3,98 (1H, dd), 4,24 (1H, s), 4,57 (1H, s), 6,96 (1H, s), 7,56 (1H, s), 7,91 (1H, s), 9,41 (2H, s), 10,49 (1H, s), 11,15 (1H, s).

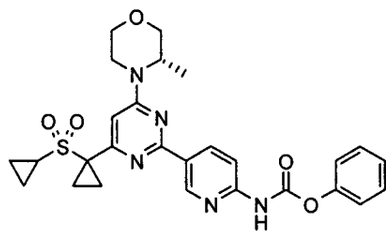
Ensayo de mTOR Quinasa (Echo): 0,171μM

Ejemplo 14aa: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,53 - 1,61 (2H, m), 1,74 - 1,79 (2H, m), 3,10 - 3,19 (2H, m), 3,28 - 3,36 (4H, m), 3,45 (1H, t), 3,48 - 3,56 (2H, m), 3,60 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,10 (1H, s), 4,34 (1H, s), 4,75 (1H, t), 4,85 (1H, t), 6,62

(2H, d), 6,65 - 6,70 (2H, m), 7,41 (2H, d), 9,11 (2H, s), 9,20 (1H, t), 10,04 (1H, s).
Ensayo de mTOR Quinasa (Echo): 0,0186μM

La preparación de fenil *N*-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]carbamato se describe a continuación.

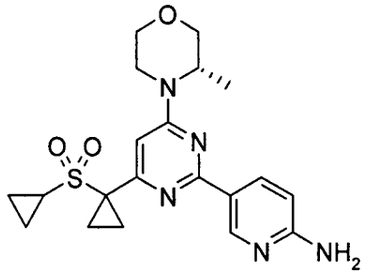
Fenil *N*-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]carbamato



Se agregó fenil cloroformiato (0,543 mL, 4,33 mmol) a una mezcla de 5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-amina (1,2 g, 2,89 mmol) e hidrogenocarbonato de sodio (0,364 g, 4,33 mmol) en dioxano (30 mL) a 5°C bajo nitrógeno. La mezcla resultante se agitó a TA durante 1 hora, luego a 40°C durante 3 horas y nuevamente a TA durante toda la noche. Se agregó más fenil cloroformiato (1 mL) y la mezcla se calentó a 40°C hasta completarse. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto que luego se purificó cromatografía en sílice, eluyendo con 10 a 80% acetato de etilo en isohexano, para proporcionar una mezcla del material deseado y material en donde estaba presente un grupo carbamato adicional (fenil *N*-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]-*N*-fenoxicarbonilcarbamato). Este material (1 g) se utilizó en la siguiente etapa sin intentos adicionales de purificación.

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 536; HPLC tR = 2,65 min.

5-[4-(1-Ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-amina



Se agregó cloruro de bis(trifenilfosfina)paladio(II) (118 mg, 0,17 mmol) a 2-cloro-4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (900 mg, 2,51 mmol), 2-amino-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina (830 mg, 3,77 mmol) y carbonato de sodio (5,03 mL, 10,06 mmol) en una mezcla de DMF (6 mL), DME (8 mL), agua (2 mL) y etanol (1,5 mL) a TA. La mezcla resultante se agitó a 90°C durante 18 horas luego la mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía en sílice, eluyendo con 0 a 5% metanol en acetato de etilo. El material se purificó adicionalmente mediante cromatografía de intercambio iónico utilizando una columna SCX con el material deseado eluyó utilizando amoníaco 7M en metanol, para proporcionar el material deseado puro como un sólido blanco (1,2 g).

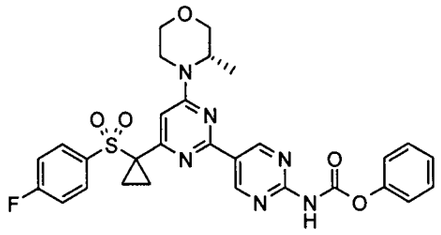
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,92 - 0,95 (2H, m), 1,00 - 1,04 (2H, m), 1,22 (3H, d), 1,53 - 1,59 (2H, m), 1,62 - 1,65 (2H, m), 2,94 - 3,02 (1H, m), 3,19 (1H, td), 3,48 (1H, td), 3,63 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,17 (1H, d), 4,53 (1H, s), 6,39 (2H, s), 6,50 (1H, d), 6,81 (1H, s), 8,23 (1H, d), 8,89 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 416; HPLC tR = 1,81 min.

La preparación de 2-cloro-4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

La preparación de fenil *N*-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]carbamato se describe a continuación.

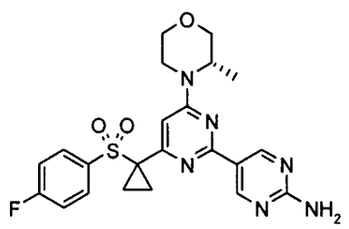
Fenil *N*-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]carbamato



Se agregó fenil cloroformiato (0,306 mL, 2,44 mmol) a una mezcla de 5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-amina (765 mg, 1,63 mmol) e hidrogenocarbonato de sodio (205 mg, 2,44 mmol) en dioxano (10 mL) a 5°C bajo nitrógeno. La mezcla resultante se agitó a TA durante toda la noche. Se agregó más fenil cloroformiato (0,2 mL) y la reacción se dejó agitar durante toda la noche. La mezcla de reacción se diluyó con acetato de etilo (100 mL), se lavó con agua (2 x 100 mL) y una solución de salmuera saturada (50 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar una goma. La goma bruta se trituró con éter dietílico para proporcionar un sólido que se recogió mediante filtración y se secó al vacío para proporcionar el material deseado como un sólido amarillo (1,0 g). No se llevó a cabo ninguna purificación adicional en esta etapa.

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 591; HPLC tR = 2,61 min.

5-[4-[1-(4-Fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-amina



Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,143 g, 0,20 mmol) a 2-cloro-4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,25 g, 3,03 mmol), 2-amino-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina (0,868 g, 3,95 mmol) y carbonato de sodio (3 mL, 6,00 mmol) en una mezcla de DMF (3 mL), DME (8 mL), agua (2 mL) y etanol (1,5 mL) a TA y la atmósfera se reemplazó con nitrógeno. La mezcla se agitó a 90°C durante 5 horas y luego se dejó agitar a TA durante toda la noche. La mezcla de reacción se diluyó con acetato de etilo (200 mL), se lavó con agua (2 x 100 mL) y la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se

trituró con DCM para proporcionar un sólido que se recogió mediante filtración y se secó al vacío para proporcionar el material deseado como un sólido beige (1,1 g).

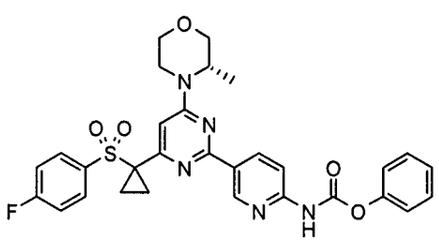
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,56 - 1,61 (2H, m), 1,86 - 1,90 (2H, m), 3,15 (1H, td), 3,45 (1H, td), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,14 (1H, d), 4,46 (1H, s), 6,69 (1H, s), 7,13 (2H, s), 7,41 (2H, t), 7,80 - 7,85 (2H, m), 8,65 (2H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 471; HPLC tR = 1,94 min.

La preparación de 2-cloro-4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

La preparación de fenil *N*-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]carbamato se describe a continuación.

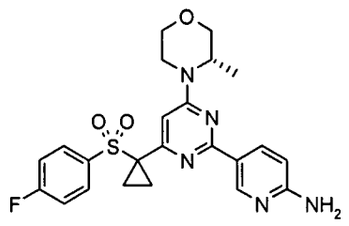
Fenil *N*-[5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-il]carbamato



Se agregó fenil cloroformiato (0,962 mL, 7,67 mmol) a una mezcla de 5-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-amina (900 mg, 1,92 mmol) e hidrogenocarbonato de sodio (242 mg, 2,88 mmol) en dioxano (50 mL) a 5°C bajo nitrógeno. La mezcla resultante se agitó a TA durante 3 días, se agregó más fenil cloroformiato (2 mL) y la reacción se agitó a TA durante 16 horas más. La mezcla de reacción se diluyó con acetato de etilo (200 mL), se lavó con agua (100 mL) y la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se trituró con éter dietílico para proporcionar un sólido que se recogió mediante filtración y se secó al vacío para proporcionar el material deseado como un sólido crema (900 mg).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 591; HPLC tR = 2,63 min.

5-[4-[1-(4-Fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]piridin-2-amina



Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,143 g, 0,20 mmol) a (2-cloro-4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,25 g, 3,03 mmol), 2-amino-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina (0,868 g, 3,95 mmol) y carbonato de sodio (3 mL, 6,00 mmol) en una mezcla de DMF (3 mL), DME (8 mL), agua (2 mL) y etanol (1,5 mL) a TA bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 90°C durante 5 horas luego a TA durante 16 horas. La mezcla de reacción se diluyó con acetato de etilo (200 mL), se lavó con agua (2 x 100 mL) y la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 20 a 80% acetato de etilo en isohexano. El material aislado se purificó adicionalmente mediante cromatografía de intercambio iónico utilizando una columna SCX y el material deseado eluyó de la columna utilizando amoníaco 7M en metanol. El material deseado se aisló como un sólido blanco (0,94 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,57 - 1,61 (2H, m), 1,86 - 1,89 (2H, m), 3,09 - 3,17 (1H, m), 3,41 - 3,49 (1H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,96 (1H, d), 4,11 (1H, d), 4,43 (1H, s), 6,35 - 6,41 (3H, m), 6,63 (1H, s), 7,38 - 7,45 (2H, m), 7,78 - 7,85 (3H, m), 8,51 (1H, d)

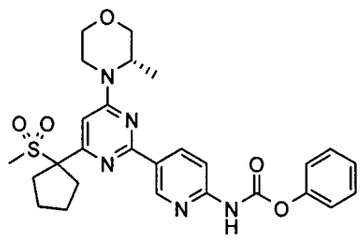
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 470; HPLC tR = 2,06 min.

La preparación de 2-cloro-4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

La preparación de fenil *N*-[5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-il]carbamato se describe a continuación.

Fenil *N*-[5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-

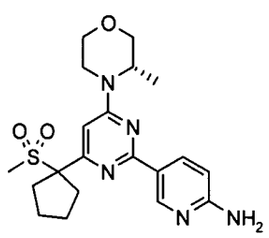
2-il]carbamato



Se agregó fenil cloroformiato (1,23 mL, 9,82 mmol) a 5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-amina (1,025 g, 2,45 mmol) e hidrogenocarbonato de sodio (0,309 g, 3,68 mmol) en dioxano (50 mL) a 5°C bajo nitrógeno. La mezcla resultante se agitó a TA durante 3 días luego se agregó más fenil cloroformiato (2 mL) y la reacción se dejó agitar a 35°C durante 3 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL), se lavó con agua (2 x 100 mL) y la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El líquido bruto se trituró con éter dietílico para proporcionar un sólido que se recogió mediante filtración y se secó al vacío para proporcionar el material deseado como un sólido crema (1,2 g).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 538; HPLC tR = 2,89 min.

5-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]piridin-2-amina



Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,261 g, 0,37 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidina (2 g, 5,56 mmol), 2-amino-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina (1,835 g, 8,34 mmol) y solución de carbonato de sodio acuoso (11,12 mL, 22,23 mmol) en una mezcla de DMF (6 mL), DME (8 mL), agua (2 mL) y etanol (1,5 mL) a TA bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 90°C durante 18 horas. La mezcla de reacción se diluyó con acetato de etilo (200 mL), se lavó con agua (2 x 100 mL) y la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 10 a 100% acetato de etilo en isohexano. El

material aislado se disolvió en metanol, el sólido se eliminó y el filtrado se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX y el producto deseado eluyó de la columna utilizando amoníaco 7M en metanol. El material deseado se aisló como un sólido blanco (2,2 g).

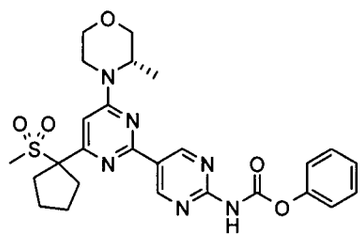
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,54 - 1,60 (2H, m), 1,78 - 1,85 (2H, m), 2,37 - 2,46 (2H, m), 2,65 - 2,78 (2H, m), 2,90 (3H, s), 3,18 (1H, dd), 3,49 (1H, td), 3,64 (1H, dd), 3,75 (1H, d), 3,97 (1H, dd), 4,22 (1H, d), 4,56 (1H, s), 6,39 (2H, s), 6,50 (1H, d), 6,75 (1H, s), 8,25 (1H, d), 8,92 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 418; HPLC tR = 2,05 min.

La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidina se describió anteriormente.

La preparación de fenil *N*-[5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-il]carbamato se describe a continuación.

Fenil *N*-[5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-il]carbamato

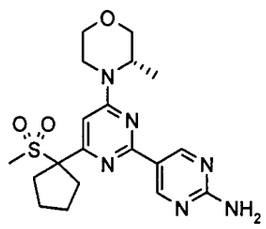


Se agregó fenil cloroformiato (0,315 mL, 2,51 mmol) a 5-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-amina (700 mg, 1,67 mmol), hidrogenocarbonato de sodio (211 mg, 2,51 mmol) en dioxano (20 mL) a 5°C bajo nitrógeno. La mezcla resultante se agitó a TA durante 48 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto que se trituró con éter dietílico para proporcionar el material deseado como un sólido amarillo (790 mg).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 539; HPLC tR = 2,52 min.

5-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidin-2-il]pirimidin-2-

amina



Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,261 g, 0,37 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidina (2 g, 5,56 mmol), 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-pirimidin-2-ilamina (1,843 g, 8,34 mmol) y solución de carbonato de sodio acuoso (11,12 mL, 22,23 mmol) en una mezcla de DMF (6 mL), DME (8 mL), agua (2 mL) y etanol (1,5 mL) a TA. La mezcla resultante se agitó a 90°C durante 18 horas bajo una atmósfera de nitrógeno. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 3% metanol en acetato de etilo. El material aislado se trituró con una mezcla de éter dietílico e isohexano y se filtró para proporcionar el material deseado como un sólido crema (2,0 g).

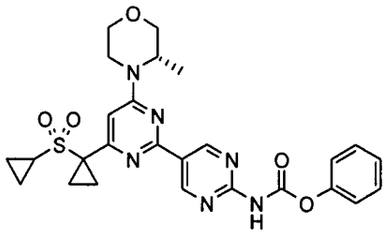
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,53 - 1,60 (2H, m), 1,76 - 1,83 (2H, m), 2,37 - 2,47 (2H, m), 2,64 - 2,76 (2H, m), 2,91 (3H, s), 3,15 - 3,23 (1H, m), 3,49 (1H, td), 3,63 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,24 (1H, d), 4,59 (1H, s), 6,82 (1H, s), 7,14 (2H, s), 9,09 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 419; HPLC tR = 1,83 min.

La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopentil)pirimidina se describió anteriormente.

La preparación de fenil *N*-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]carbamato se describe a continuación.

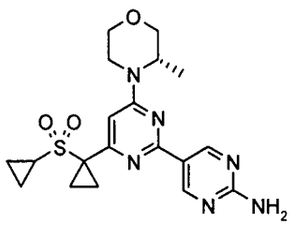
Fenil *N*-[5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-il]carbamato



Se agregó gota a gota fenil cloroformiato (0,976 mL, 7,78 mmol) a 5-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-amina (2,16 g, 5,19 mmol), hidrogenocarbonato de sodio (0,654 g, 7,78 mmol) en dioxano (30 mL) enfriado hasta alcanzar 10°C bajo nitrógeno. La mezcla resultante se agitó a TA durante 48 horas. La mezcla de reacción se diluyó con acetato de etilo (150 mL) y se lavó con agua (150 mL seguido por 125 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto que se purificó mediante trituración con éter dietílico para proporcionar el material deseado como un sólido amarillo (2,5 g).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 537; HPLC tR = 2,33 min.

5-[4-(1-Ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]pirimidin-2-amina



Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,381 g, 0,54 mmol) a 2-cloro-4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,9 g, 8,10 mmol), 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-pirimidin-2-ilamina (2,69 g, 12,16 mmol) y solución de carbonato de sodio acuoso (4 mL, 8,00 mmol) en una mezcla de DMF (18 mL), DME (8 mL), agua (2 mL) y etanol (1,5 mL) a TA. La mezcla resultante se agitó a 90°C durante 18 horas bajo una atmósfera de nitrógeno. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 7% metanol en acetato de etilo. El material aislado se purificó adicionalmente mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con metanol y luego amoníaco 7M

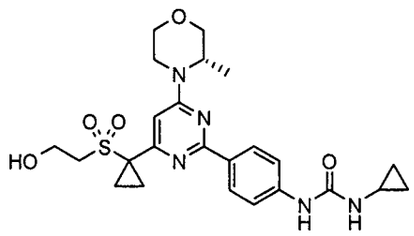
en metanol, para proporcionar el material deseado como un sólido blanco (2,16 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,90 - 0,94 (2H, m), 0,99 - 1,04 (2H, m), 1,22 (3H, d), 1,54 - 1,58 (2H, m), 1,60 - 1,65 (2H, m), 2,95 - 3,02 (1H, m), 3,16 - 3,23 (1H, m), 3,47 (1H, td), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,18 (1H, s), 4,50 (1H, s), 6,85 (1H, s), 7,16 (2H, s), 9,05 (2H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 417; HPLC tR = 1,70 min.

La preparación de 2-cloro-4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 15: 3-Ciclopropil-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



Se agregó cloruro de bis(trifenilfosfina)paladio (II) (6,84 mg, 0,00975 mmol) a 2-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletoxi-tri(propan-2-il)silano (0,101 g, 0,19 mmol), 1-ciclopropil-3-(4- (4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)urea (0,088 g, 0,29 mmol) y carbonato de sodio (0,487 mL, 0,97 mmol) en una mezcla de disolventes (18% DMF, 82% de una mezcla 7:3:2 de DME:agua:etanol) a TA bajo nitrógeno. La suspensión resultante se agitó a 80°C durante 17 horas. El disolvente se retiró y el residuo se repartió entre DCM y agua. La capa orgánica se secó ($MgSO_4$), se filtró y se agregó fluoruro de tetrabutilamonio (0,975 mL, 0,97 mmol) al filtrado y se agitó durante 2 horas. La mezcla se lavó con agua, la capa orgánica se concentró al vacío y se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes, para proporcionar el material deseado como un sólido blanco (0,057 g).

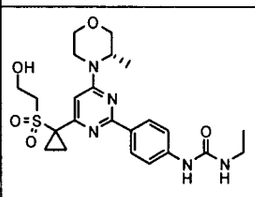
Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 0,41-0,44 (2H, m), 0,63-0,68 (2H, m), 1,23-1,25 (3H, d), 1,53-1,56 (2H, m), 1,65-1,66 (2H, m), 2,55-2,59 (1H, m), 3,17-3,25 (1H, td), 3,56-3,52 (1H, td), 3,62-3,66 (3H, m), 3,75-3,78 (1H, d), 3,88-3,89 (2H, m), 3,96-4,00 (1H, dd), 4,20-4,23 (1H, d), 4,56 (1H, bs), 5,03 (1H, bs), 6,45-6,46 (1H, d), 6,78 (1H, s), 7,50-

7,52 (2H, d), 8,20-8,22 (2H, d), 8,56 (1H, s).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 502; HPLC tR = 1,86min.

Ensayo de mTOR Quinasa (Echo): 0,00154μM

El compuesto a continuación se preparó en forma análoga utilizando el boronato apropiado.

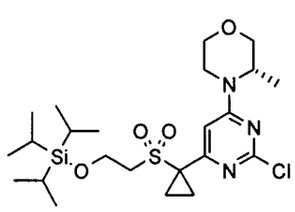
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
15a		3-etil-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	490	1,82

Ejemplo 15a: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,05-1,09 (3H, t), 1,23-1,24 (3H, d), 1,53-1,56 (2H, m), 1,64-1,67 (2H, m), 3,10-3,17 (2H, m), 3,17-3,25 (1H, td), 3,45-3,52 (1H, td), 3,62-3,66 (3H, m), 3,75-3,78 (1H, d), 3,87-3,91 (2H, t), 3,96-3,99 (1H, dd), 4,19-4,22 (1H, d), 4,55 (1H, bs), 5,03 (1H, bs), 6,17-6,20 (1H, t), 6,77 (1H, s), 7,49-7,51 (2H, q), 8,19-8,21 (2H, q), 8,68 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000591μM

La preparación de 2-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletoxi-tri(propan-2-il)silano se describe a continuación.

2-[1-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletoxi-tri(propan-2-il)silano



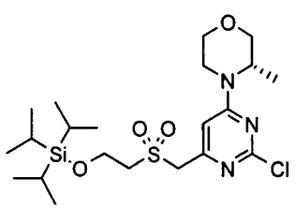
Una solución acuosa de hidróxido de sodio 50% v/v (35 mL, 5,20 mmol) se agregó a 2-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]etoxi-tri(propan-2-il)silano

(2,56 g, 5,20 mmol), 1,2-bibromoetano (1,345 mL, 15,61 mmol) y bromuro de tetrabutilamonio (0,168 g, 0,52 mmol) en tolueno (100 mL) a TA. La suspensión resultante se agitó a 60°C durante 3 horas luego la mezcla de reacción se diluyó con agua y se extrajo secuencialmente con tolueno y DCM. Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 10% acetato de etilo en DCM, para proporcionar el material deseado como un aceite incoloro que solidificó en reposo (0,304 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,01-1,11 (21H, m), 1,30-1,32 (3H, d), 1,47-1,50 (2H, q), 1,77-1,80 (2H, q), 3,24-3,31 (1H, td), 3,40-3,44 (2H, t), 3,48-3,55 (1H, td), 3,64-3,68 (1H, td), 3,75-3,78 (1H, d), 3,97-4,01 (2H, m), 4,10-4,14 (2H, t), 4,32 (1H, bs), 6,86 (1H, s).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 518; HPLC tR = 3,86min.

2-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]etoxi-tri(propan-2-il)silano

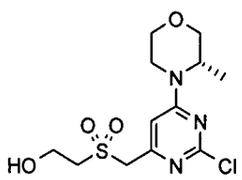


Se agregó 2-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]etanol (4,21 g, 12,53 mmol) a cloruro de triisopropilsililo (3,22 mL, 15,03 mmol) e imidazol (2,046 g, 30,06 mmol) en DMF a TA. La solución resultante se agitó a TA durante toda la noche bajo una atmósfera de nitrógeno. El DMF se retiró al vacío y se agregó acetato de etilo. Los sólidos se retiraron mediante filtración y el filtrado se concentró al vacío y se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 4% metanol en DCM. El material aislado nuevamente se purificó mediante cromatografía en sílice, eluyendo con 0 - 10% acetato de etilo en DCM, para proporcionar el material deseado como una goma clara (4,15 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,03-1,15 (21H, m), 1,27-1,29 (3H, d), 3,20-3,28 (1H, td), 3,37-3,40 (2H, m), 3,45-3,52 (1H, td), 3,61-3,65 (1H, dd), 3,71-3,74 (1H, d), 3,93-4,04 (2H, m), 4,15-4,18 (2H, t), 4,28 (3H, s), 6,50 (1H, s).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 492; HPLC tR = 3,72min.

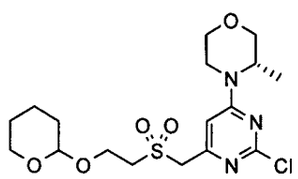
2-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]etanol



Una solución de peróxido de hidrógeno (30% solución acuosa, 0,225 mL, 7,29 mmol) se agregó a una solución agitada de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[2-(oxan-2-iloxi)etilsulfonilmetil]pirimidina (0,141 g, 0,36 mmol), tungstato de sodio dihidrato (2,4 mg, 0,0073 mmol) en agua (0,2 mL) y ácido sulfúrico 2N (0,011 mL) en 1,4-dioxano (1,4 mL) y metanol (1,4 mL) y la reacción se agitó a 55°C durante 4 horas. Se agregó agua (50 mL) y la reacción se enfrió. Se agregó solución acuosa de metabisulfito de sodio y la mezcla se extrajo con DCM. Los orgánicos se secaron ($MgSO_4$), se filtraron y se concentraron al vacío para proporcionar el material deseado como un aceite opaco (0,198 g).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 336; HPLC tR = 1,18 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[2-(oxan-2-iloxi)etilsulfonilmetil]pirimidina



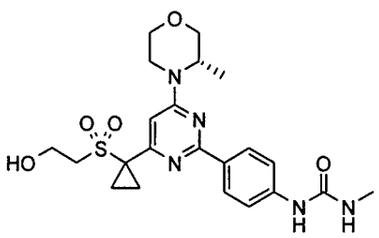
Se agregó gota a gota DIPEA (0,211 g, 1,63 mmol) a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (0,231 g, 0,65 mmol) y 2-(tetrahidro-2H-piran-2-iloxi)etanotiol (0,133 g, 0,82 mmol) en acetonitrilo a TA. La solución resultante se agitó a TA durante 1 hora. El disolvente se retiró y el residuo se repartió entre DCM y agua. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 2% metanol en DCM, para proporcionar el material deseado como un aceite incoloro (0,141 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,24-1,26 (3H, d), 1,40-1,55 (4H, m), 1,60-1,67 (1H, m), 1,69-1,77 (1H, m), 2,68-2,71 (2H, t), 3,17-3,24 (1H, td), 3,41-3,47 (2H, m), 3,50-3,58 (1H, m), 3,59 (2H, s), 3,62-3,63 (1H, d), 3,69-3,72 (1H, d), 3,76-3,86 (2H, m),

3,91-3,95 (1H, dd), 3,97 (1H, bs), 4,25 (1H, bs), 4,52-4,54 (1H, t), 6,44 (1H, s).
Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 386; HPLC tR = 2,11 min.

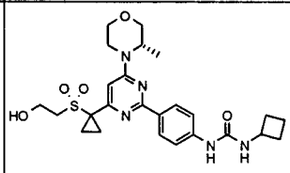
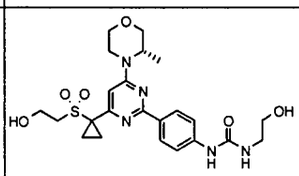
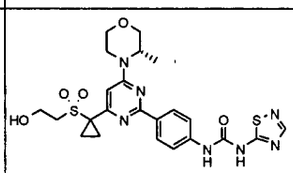
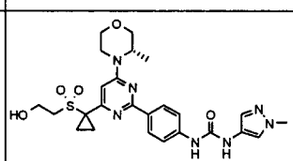
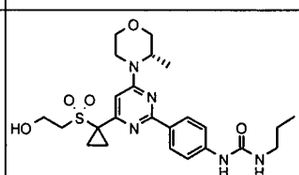
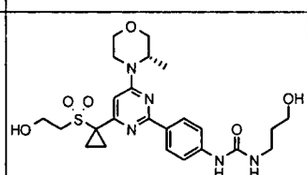
La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente

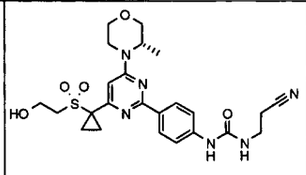
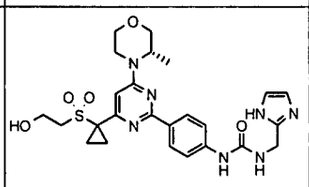
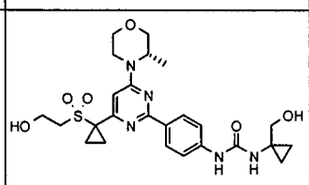
Ejemplo 16: 1-[4-[4-[1-(2-Hidroxietilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea



Se agregó metilamina (0,542 mL, 1,08 mmol) a (S)-fenil 4-(4- (1-(2-hidroxietilsulfonil)ciclopropil)-6-(3-metilmorfolino)pirimidin-2-il)fenilcarbamato (0,117 g, 0,22 mmol) y trietilamina (0,091 mL, 0,65 mmol) en DMF (3 mL) y la solución se agitó a TA durante 5 minutos. El producto bruto se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes, para proporcionar el material deseado como un sólido blanco (0,08 g).
Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,22-1,24 (3H, d), 1,53-1,56 (2H, m), 1,64-1,66 (2H, m), 2,66-2,67 (3H, d), 3,16-3,24 (1H, td), 3,45-3,51 (1H, td), 3,61-3,67 (3H, m), 3,75-3,78 (1H, d), 3,86-3,91 (2H, q), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,56 (1H, bs), 5,06-5,09 (1H, t), 6,08-6,11 (1H, q), 6,77 (1H, s), 7,50-7,52 (2H, d), 8,18-8,21 (2H, d), 8,79 (1H, s).
Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 476; HPLC tR = 1,69 min.
Ensayo de mTOR Quinasa (Echo): 0,00142μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
16a		3-ciclobutil-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	516	2,11
16b		3-(2-hidroxietil)-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	506	1,59
16c		1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	546	1,24
16d		1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	542	1,79
16e		3-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea	504	1,99
16f		1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	520	1,61

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
16g		3-(2-cianoetil)-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	515	1,77
16h		1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea	542	1,64
16i		1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[1-(hidroximetil)ciclopropil]urea	532	1,66

Ejemplo 16a: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,23-1,24 (3H, d), 1,53-1,69 (7H, m), 1,82-1,92 (2H, m), 2,18-2,25 (2H, m), 3,17-3,24 (1H, td), 3,45-3,52 (1H, td), 3,63-3,66 (3H, m), 3,75-3,78 (1H, d), 3,86-3,91 (2H, m), 3,96-3,99 (1H, dd), 4,20-4,22 (1H, d), 4,56 (1H, bs), 5,01-5,04 (1H, t), 6,46-6,48 (1H, d), 6,78 (1H, s), 7,47-7,49 (2H, d), 8,19-8,21 (2H, d), 8,57 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0101μM

Ejemplo 16b: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,23-1,24 (3H, d), 1,53-1,56 (2H, m), 1,64-1,67 (2H, m), 3,16-3,24 (3H, m), 3,45-3,52 (3H, m), 3,62-3,66 (3H, m), 3,75-3,78 (1H, d), 3,87-3,91 (2H, q), 3,96-3,99 (1H, dd), 4,19-4,23 (1H, d), 4,56 (1H, bs), 4,72-4,75 (1H, t), 5,01-5,04 (1H, t), 6,25-6,27 (1H, t), 6,77 (1H, s), 7,48-7,51 (2H, d), 8,20-8,22 (2H, d), 8,81 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00577μM

Ejemplo 16c: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,55-1,58 (2H, m), 1,66-1,68 (2H, m), 3,19-3,26 (1H, td), 3,47-3,53 (1H, td), 3,63-3,67 (3H, m), 3,77-3,79 (1H, d), 3,88-3,93 (2H, m), 3,97-4,01 (1H, dd), 4,22-4,24 (1H, d), 4,58 (1H, bs), 5,02-5,05 (1H, t),

6,83 (1H, s), 7,62-7,65 (2H, d), 8,31-8,33 (2H, d), 8,38 (1H, s), 9,43 (1H, s), 11,37 (1H, bs).

Ensayo de mTOR Quinasa (Echo): 0,0016μM

Ejemplo 16d: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,54-1,57 (2H, m), 1,65-1,67 (2H, m), 3,17-3,25 (1H, td), 3,46-3,53 (1H, td), 3,62-3,67 (3H, m), 3,76-3,79 (1H, d), 3,79 (3H, s), 3,87-3,92 (2H, m), 3,97-4,00 (1H, dd), 4,20-4,23 (1H, d), 4,56 (1H, bs), 5,02-5,05 (1H, t), 6,79 (1H, s), 7,39-7,40 (1H, s), 7,54-7,56 (2H, d), 7,76 (1H, s), 8,23-8,25 (2H, d), 8,39 (1H, s), 8,84 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00364μM

Ejemplo 16e: ^{1}H NMR (400 MHz, DMSO-D_6) δ 0,87-0,91 (3H, t), 1,23-1,25 (3H, d), 1,42-1,51 (2H, m), 1,53-1,56 (2H, m), 1,64-1,67 (2H, m), 3,05-3,09 (2H, q), 3,17-3,25 (1H, td), 3,46-3,52 (1H, td), 3,62-3,66 (3H, m), 3,75-3,78 (1H, d), 3,87-3,91 (2H, q), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,56 (1H, bs), 5,01-5,04 (1H, t), 6,19-6,22 (1H, t), 6,78 (1H, s), 7,49-7,51 (2H, d), 8,19-8,21 (2H, d), 8,65 (1H, s)

Ejemplo 16f: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,53-1,57 (2H, m), 1,59-1,62 (2H, t), 1,64-1,67 (2H, m), 3,15-3,24 (3H, m), 3,46-3,50 (3H, m), 3,63-3,66 (3H, m), 3,75-3,78 (1H, d), 3,87-3,91 (2H, q), 3,96-3,99 (1H, dd), 4,19-4,23 (1H, d), 4,47-4,49 (1H, t), 4,55 (1H, bs), 5,01-5,04 (1H, t), 6,20-6,23 (1H, t), 6,77 (1H, s), 7,49-7,51 (2H, d), 8,19-8,21 (2H, d), 8,72 (1H, s).

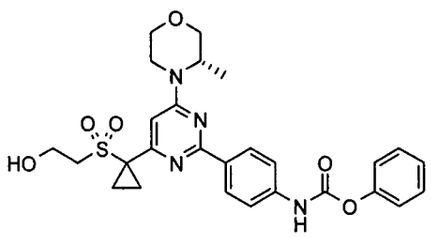
Ejemplo 16g: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,54-1,56 (2H, m), 1,65-1,67 (2H, m), 2,69-2,72 (2H, t), 3,17-3,25 (1H, td), 3,35-3,40 (2H, q), 3,46-3,52 (1H, td), 3,62-3,66 (3H, m), 3,75-3,78 (1H, d), 3,87-3,91 (2H, q), 3,96-4,00 (1H, dd), 4,20-4,23 (1H, d), 4,56 (1H, bs), 5,01-5,04 (1H, t), 6,52-6,55 (1H, t), 6,78 (1H, s), 7,51-7,53 (2H, d), 8,21-8,23 (2H, d), 8,93 (1H, s).

Ejemplo 16h: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,54-1,56 (2H, m), 1,64-1,67 (2H, m), 3,17-3,25 (1H, td), 3,46-3,52 (1H, td), 3,62-3,66 (3H, m), 3,75-3,78 (1H, d), 3,87-3,91 (2H, q), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,32-4,34 (2H, d), 4,56 (1H, bs), 5,01-5,04 (1H, t), 6,62-6,64 (1H, t), 6,78 (1H, s), 6,93-6,96 (2H, bs), 7,51-7,53 (2H, d), 8,21-8,23 (2H, d), 8,94 (1H, s), 11,84 (1H, s).

Ejemplo 16i: ^{1}H NMR (400 MHz, DMSO-D_6) δ 0,64-0,67 (2H, m), 0,70-0,73 (2H, m), 1,23-1,24 (3H, d), 1,53-1,56 (2H, m), 1,64-1,67 (2H, m), 3,17-3,25 (1H, td), 3,44-3,52 (3H, m), 3,62-3,66 (3H, m), 3,75-3,78 (1H, d), 3,87-3,91 (2H, q), 3,96-4,00 (1H, dd), 4,19-4,23 (1H, d), 4,55 (1H, bs), 4,84 (1H, bs), 5,01-5,04 (1H, t), 6,58 (1H, s), 6,78 (1H, s), 7,47-7,49 (2H, d), 8,20-8,22 (2H, d), 8,68 (1H, s).

La preparación de fenil *N*-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

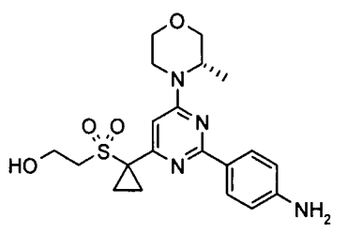
Fenil *N*-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



Se agregó fenil cloroformiato (0,043 mL, 0,34 mmol) a 2-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletanol (0,144 g, 0,34 mmol) y bicarbonato de sodio (0,043 g, 0,52 mmol) en dioxano (20 mL) y la suspensión resultante se agitó a TA durante toda la noche. La mezcla de reacción se repartió entre DCM y agua. La capa orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido beige (0,117 g).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 539; HPLC tR = 2,50 min.

2-[1-[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletanol

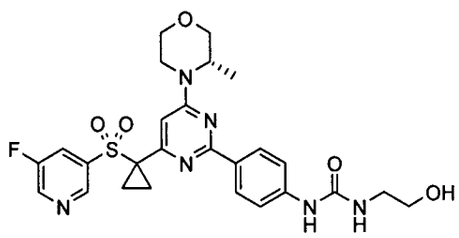


Se agregó cloruro de bis(trifenilfosfina)paladio (II) (0,012 g, 0,02 mmol) a 2-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]etoxi-tri(propan-2-il)silano (0,178 g, 0,34 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,113 g, 0,52 mmol) y una solución acuosa de carbonato de sodio (0,859 mL, 1,72 mmol) en una mezcla de disolventes (18% DMF, 82% de una mezcla 7:3:2 de DME:agua:etanol). La solución resultante se agitó a 80°C durante 4 horas, el disolvente se retiró y el residuo se repartió entre DCM y agua. La

capa orgánica se separó y se agregó fluoruro de tetrabutilamonio (1,718 mL, 1,72 mmol). La reacción se dejó agitar durante varias horas y luego se agregó más fluoruro de tetrabutilamonio (2 mL) y la reacción se dejó agitar durante 2 días. La mezcla se lavó con una solución saturada acuosa de cloruro de amonio, se secó ($MgSO_4$), se filtró y se concentró al vacío para proporcionar el material deseado que se utilizó sin purificación adicional.

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 419; HPLC tR = 1,83 min.

Ejemplo 17: 1-[4-[4-[1-(5-Fluoropiridin-3-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea



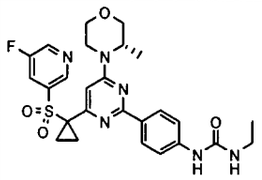
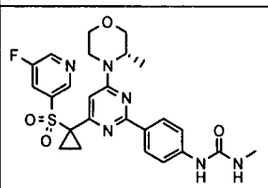
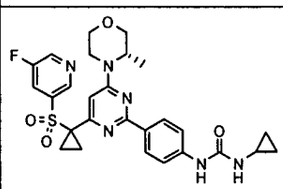
A una solución de fenil *N*-[4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (140 mg, 0,24 mmol) en DMF (2 mL) se agregó trietilamina (0,099 mL, 0,71 mmol) seguido por etanolamina (72mg, 1,19 mmol) y la reacción se calentó a 50°C durante 2 horas. El producto bruto se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes, para proporcionar el material deseado como un sólido blanco (55 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,64 - 1,67 (2H, m), 1,99 - 2,02 (2H, m), 3,15 - 3,20 (3H, m), 3,44 - 3,49 (2H, m), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,18 (1H, d), 4,50 (1H, s), 4,73 (1H, t), 6,29 (1H, t), 6,70 (1H, s), 7,38 (2H, d), 7,74 (2H, d), 8,18 - 8,21 (1H, m), 8,81 (2H, d), 8,95 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 557; HPLC tR = 1,82 min.

Ensayo de mTOR Quinasa (Echo): 0,00116μM

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
17a		3-etil-1-[4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	541	1,78
17b		1-[4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	527	1,99
17c		3-ciclopropil-1-[4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	553	2,13

Ejemplo 17a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,20 (3H, d), 1,64 - 1,67 (2H, m), 1,99 - 2,02 (2H, m), 3,09 - 3,21 (3H, m), 3,47 (1H, dt), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,18 (1H, d), 4,50 (1H, s), 6,19 (1H, t), 6,70 (1H, s), 7,38 (2H, d), 7,74 (2H, d), 8,18 - 8,19 (1H, m), 8,20 - 8,21 (1H, m), 8,68 (1H, s), 8,81 (1H, s), 8,95 (1H, d).
Ensayo de mTOR Quinasa (Echo): 0,000942μM

Ejemplo 17b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,64 - 1,67 (2H, m), 1,99 - 2,02 (2H, m), 2,66 (3H, d), 3,14 - 3,21 (1H, m), 3,47 (1H, dt), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,18 (1H, d), 4,50 (1H, s), 6,09 - 6,12 (1H, m), 6,70 (1H, s), 7,39 (2H, d), 7,74 (2H, d), 8,18 - 8,22 (1H, m), 8,79 (2H, d), 8,94 (1H, d).
Ensayo de mTOR Quinasa (Echo): 0,000584μM

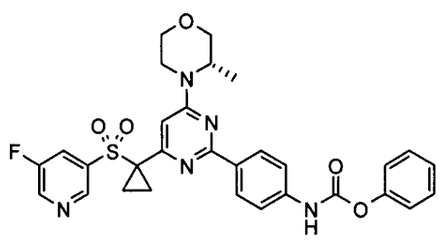
Ejemplo 17c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,41 - 0,44 (2H, m), 0,60 - 0,67 (2H, m), 1,20 (3H, d), 1,65 - 1,66 (2H, m), 1,99 - 2,02 (2H, m), 3,15 - 3,21 (2H, m), 3,42 - 3,49 (1H, m), 3,61 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,18 (1H, d), 4,50 (1H, s), 6,60 (1H, s), 6,70 (1H, s), 7,40 (2H, d), 7,74 (2H, d), 8,18 - 8,22 (1H, m), 8,69 (1H, s), 8,81 (1H, s), 8,95 (1H,

d).

Ensayo de mTOR Quinasa (Echo): 0,00179μM

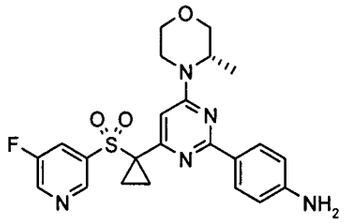
La preparación de fenil *N*-[4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



A una solución de 4-[4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (220 mg, 0,47 mmol) en 1,4-dioxano (5 mL) se agregó bicarbonato de sodio (59 mg, 0,70 mmol) y fenil cloroformiato (0,059 mL, 0,47 mmol) y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con DCM (10 mL) y se lavó con agua (10 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El sólido bruto se trituró con éter dietílico para proporcionar un sólido que se recogió mediante filtración y se secó al vacío para proporcionar el producto deseado como un sólido blanco (280 mg).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,65 - 1,69 (2H, m), 2,00 - 2,03 (2H, m), 3,15 - 3,22 (1H, m), 3,44 - 3,52 (1H, m), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,21 (1H, d), 4,51 (1H, s), 6,75 (1H, s), 7,24 - 7,27 (3H, m), 7,45 (2H, t), 7,53 (2H, d), 7,85 (2H, d), 8,20 - 8,23 (1H, m), 8,81 (1H, s), 8,94 (1H, d), 10,40 (1H, s)
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 590; HPLC tR = 2,96 min.

4-[4-[1-(5-Fluoropiridin-3-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

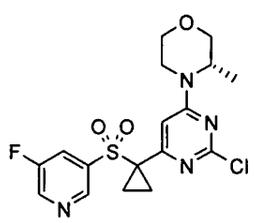


A una solución de 2-cloro-4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (700 mg, 1,70 mmol) en DMF (0,48 mL), DME (9,33 mL), agua (4,0 mL) y etanol (2,67 mL) se agregó 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (483mg, 2,2 mmol), carbonato de sodio (2,5 mL, 5,09 mmol) y diclorobis(trifenilfosfina)paladio(II) (59,5 mg, 0,08 mmol) y la suspensión se calentó a 95°C durante 2 horas. La mezcla de reacción se enfrió hasta alcanzar TA, se diluyó con acetato de etilo (10 mL) y se lavó con agua (2 x 10 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 5 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido crema (160 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,61 - 1,65 (2H, m), 1,96 - 2,00 (2H, m), 3,11 - 3,18 (1H, m), 3,42 - 3,49 (1H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,14 (1H, d), 4,46 (1H, s), 5,53 (2H, s), 6,49 (2H, d), 6,60 (1H, s), 7,57 (2H, d), 8,16 - 8,20 (1H, m), 8,80 - 8,80 (1H, m), 8,93 (1H, d)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 470; HPLC tR = 2,30 min.

2-Cloro-4-[1-(5-fluoropiridin-3-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



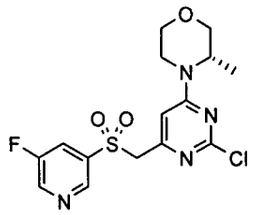
Se disolvió 2-cloro-4-[(5-fluoropiridin-3-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (950 mg, 2,40 mmol) en tolueno (15 mL) y se agregó solución de hidróxido de sodio 10N (2,45 mL, 24,5 mmol), seguido por 1,2-dibromoetano (0,42 mL, 4,91 mmol). La reacción se agitó a 60°C durante 3 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (200 mL) y se lavó secuencialmente con agua (200 mL) y solución de salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y

se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el producto deseado como un sólido blanco (700 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,61 - 1,63 (2H, m), 1,94 - 1,97 (2H, m), 3,16 (1H, dt), 3,40 (1H, dt), 3,55 (1H, dd), 3,70 (1H, d), 3,91 (1H, dd), 4,00 (1H, s), 4,33 (1H, s), 6,78 (1H, s), 8,21 (1H, dt), 8,79 (1H, t), 8,96 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 413, HPLC tR = 2,14 min

2-Cloro-4-[(5-fluoropiridin-3-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

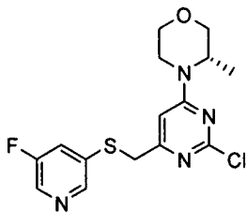


Se agregó ácido 3-cloroperoxibenzoico (2,107 g, 9,16 mmol) en porciones a 2-cloro-4-[(5-fluoropiridin-3-il)sulfanilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,3 g, 3,66 mmol), en DCM (18,32 mL) y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se lavó con una solución saturada acuosa de hidrogenocarbonato de sodio (50 mL) y la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 60% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (0,940 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 3,16 - 3,23 (1H, m), 3,44 (1H, dt), 3,59 (1H, dd), 3,72 (1H, d), 3,93 (1H, dd), 3,97 (1H, s), 4,22 (1H, s), 4,84 (2H, s), 6,84 (1H, s), 8,21 (1H, dt), 8,80 (1H, t), 8,99 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 387, HPLC tR = 1,86 min

2-Cloro-4-[(5-fluoropiridin-3-il)sulfanilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

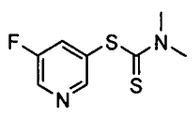


Se agregó hidróxido de potasio (1,235 g, 22,01 mmol) a (5-fluoropiridin-3-il) dimetilaminometanoditioato (1,19 g, 5,50 mmol) en etanol (27,5 mL) a TA. La solución resultante se calentó a 65°C durante 4 horas. La reacción se enfrió y se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,72 g, 7,70 mmol). La mezcla de reacción luego se agitó a TA durante 4 horas. Se agregó agua (50 mL) y la mezcla de reacción se extrajo con DCM (2 x 100 mL). Los orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido ceroso blanco (1,5 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 (3H, d), 3,11 - 3,18 (1H, m), 3,37 - 3,44 (1H, m), 3,56 (1H, dd), 3,70 (1H, d), 3,91 (1H, dd), 3,95 (1H, s), 4,21 (3H, $mult$), 6,81 (1H, s), 7,89 (1H, dt), 8,40 - 8,42 (2H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 355, HPLC tR = 2,12 min

(5-Fluoropiridin-3-il) dimetilaminometanoditioato



3-Bromo-5-fluoropiridina (2,26g, 12,84 mmol) se agregó en porciones a cloruro de isopropilmagnesio - complejo de cloruro de litio (14% en THF, 13,32 mL, 12,84 mmol) a 0°C durante un período de 2 minutos bajo una atmósfera de nitrógeno. La solución resultante se entibió hasta alcanzar TA durante un período de 2 horas y luego se enfrió hasta alcanzar 0°C y se agregó disulfuro de tetrametiltiurano (3,09 g, 12,84 mmol) en DCM (12,84 mL). La reacción se entibió hasta alcanzar TA y se agitó durante 3 horas. La reacción se vertió en una solución saturada acuosa de cloruro de amonio (50 mL) y la capa acuosa se extrajo con DCM (2 x 100mL). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron al vacío. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 60% acetato de etilo en DCM, para proporcionar el

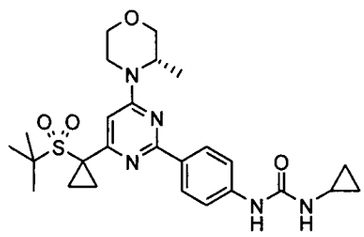
material deseado como un sólido ceroso crema (1,69 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 3,48 (3H, s), 3,52 (3H, s), 7,89 (1H, ddd), 8,41 (1H, t), 8,71 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 217, HPLC tR = 1,80 min

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 18: 1-[4-[4-(1-*terc*-Butilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea



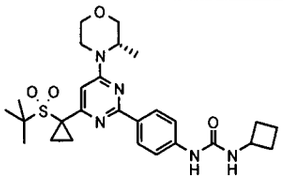
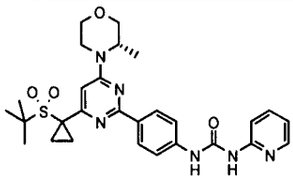
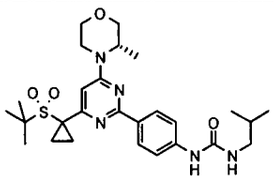
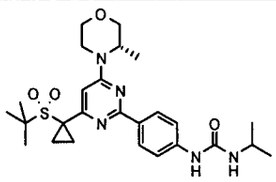
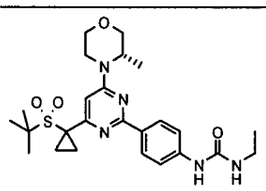
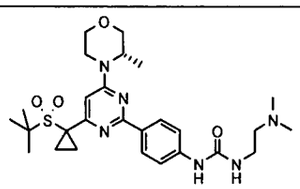
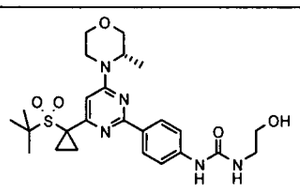
Se agregó ciclopropilamina (57 mg, 1,0 mmol) a fenil *N*-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (120 mg, 0,22 mmol) y trietilamina (0,20 mL, 1,4 mmol) en DMF (1 mL). La mezcla de reacción se dejó reposar a TA durante 4 días. El producto bruto se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido incoloro (63 mg).

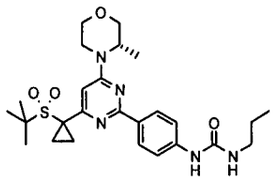
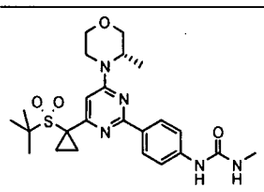
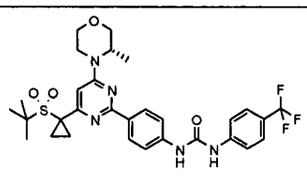
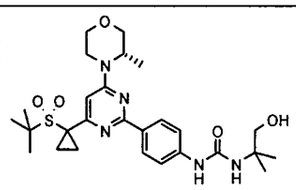
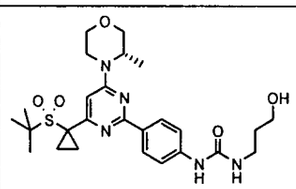
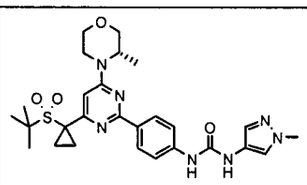
Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,63 - 0,68 (2H, m), 1,21 –1,27 (12H, m), 1,47 - 1,53 (1H, m), 1,62 - 1,69 (3H, m), 2,54 – 2,60 (1H, m), 3,15 – 3,24 (1H, m), 3,46 – 4,54 (1H, m), 3,63 - 3,67 (1H, m), 3,77 (1H, d), 3,95 - 4,02 (1H, d), 4,18 (1H, d), 4,43 (1H, br, s), 6,44 (1H, d), 6,97 (1H, s), 7,51 (2H, d), 8,23 (2H, d), 8,56 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 514; HPLC tR = 2,39 min.

Ensayo de mTOR Quinasa (Echo): 0,00135μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
18a		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclobutilurea	528	2,62
18b		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-ilurea	551	2,83
18c		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea	530	2,72
18d		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-ilurea	516	2,54
18e		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea	502	2,38
18f		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	545	2,33
18g		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	518	1,98

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
18h		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propilurea	516	2,56
18i		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	488	2,2
18j		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	618	3,29
18k		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	546	2,32
18l		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	532	2,05
18m		1-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	554	2,22

Ejemplo 18a: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,21 – 1,27 (12H, m), 1,47 – 1,53 (1H, m), 1,59 - 1,68 (3H, m), 1,81 – 1,91 (2H, m), 2,17 – 2,26 (2H, m), 3,15 – 3,23 (1H, m), 3,45 –

3,54 (1H, m), 3,62 – 3,68 (1H, m), 3,77 (1H, d), 3,95 – 4,02 (1H, m), 4,10 - 4,24 (2H, m), 4,42 (1H, br, s), 6,47 (1H, d), 6,97 (1H, s), 7,48 (2H, d), 8,22 (2H, d), 8,57 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00967μM

Ejemplo 18b: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,25 (12H, m), 1,49 - 1,54 (1H, m), 1,63 - 1,73 (3H, m), 3,16 - 3,25 (1H, m), 3,48 - 3,54 (1H, m), 3,64 - 3,68 (1H, m), 3,78 (1H, d), 3,98 - 4,01 (1H, m), 4,20 (1H, d), 4,43 (1H, br, s), 7,00 (1H, s), 7,03 - 7,06 (1H, m), 7,58 (1H, d), 7,65 (2H, d), 7,78 (1H, t), 8,29 – 8,34 (3H, m), 9,45 (1H, s), 10,57 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0147μM

Ejemplo 18c: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,90 (6H, d), 1,22 - 1,25 (12H, m), 1,47 - 1,53 (1H, m), 1,62 - 1,75 (4H, m), 2,95 (2H, t), 3,16 - 3,23 (1H, m), 3,47 - 3,53 (1H, m), 3,63 - 3,67 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,18 (1H, d), 4,42 (1H, br, s), 6,25 (1H, t), 6,97 (1H, s), 7,50 (2H, d), 8,23 (2H, d), 8,66 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,032μM

Ejemplo 18d: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,12 (6H, d), 1,21 - 1,26 (12H, m), 1,45 – 1,53 (1H, m), 1,62 - 1,71 (3H, m), 3,13 - 3,25 (1H, m), 3,44 - 3,53 (1H, m), 3,62 - 3,67 (1H, m), 3,73 - 3,82 (2H, m), 3,95 - 4,02 (1H, m), 4,18 (1H, d), 4,42 (1H, br, s), 6,07 (1H, d), 6,97 (1H, s), 7,48 (2H, d), 8,23 (2H, d), 8,55 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0151μM

Ejemplo 18e: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,23 (3H, d), 1,25 (9H, s), 1,44 – 1,53 (1H, m), 1,60 – 1,71 (3H, m), 3,08 – 3,25 (3H, m), 3,49 (1H, t), 3,65 (1H, d), 3,77 (1H, d), 3,96 - 3,99 (1H, m), 4,18 (1H, d), 4,43 (1H, br, s), 6,17 (1H, t), 6,97 (1H, s), 7,50 (2H, d), 8,23 (2H, d), 8,68 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000654μM

Ejemplo 18f: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 - 1,28 (12H, m), 1,47 - 1,54 (1H, m), 1,62 - 1,69 (3H, m), 2,19 (6H, s), 2,34 (2H, t), 3,14 - 3,24 (3H, m), 3,45 - 3,53 (1H, m), 3,62 - 3,67 (1H, m), 3,77 (1H, d), 3,95 - 4,00 (1H, m), 4,18 (1H, d), 4,42 (1H, br, s), 6,17 (1H, t), 6,97 (1H, s), 7,49 (2H, d), 8,23 (2H, d), 8,91 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,12μM

Ejemplo 18g: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,22 - 1,25 (12H, m), 1,48 - 1,52 (1H, m), 1,62 - 1,69 (3H, m), 3,16 - 3,23 (3H, m), 3,45 - 3,53 (3H, m), 3,63 - 3,67 (1H, m), 3,77 (1H, d), 3,97 - 4,00 (1H, m), 4,18 (1H, d), 4,43 (1H, br, s), 4,74 (1H, t), 6,26 (1H, t), 6,97 (1H, s), 7,49 (2H, d), 8,23 (2H, d), 8,82 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00123μM

Ejemplo 18h: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,90 (3H, t), 1,19 – 1,28 (12H, m), 1,42 – 1,54 (3H, m), 1,61 - 1,69 (3H, m), 3,07 (2H, q), 3,13 - 3,23 (1H, m), 3,45 - 3,53 (1H, m), 3,61 - 3,68 (1H, m), 3,77 (1H, d), 3,94 – 4,01 (1H, m), 4,18 (1H, d), 4,42 (1H, br, s), 6,21 (1H, t), 6,97 (1H, s), 7,50 (2H, d), 8,23 (2H, d), 8,67 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00664μM

Ejemplo 18i: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,25 (9H, s), 1,45 – 1,55 (1H, m), 1,60 – 1,69 (3H, m), 2,67 (3H, d), 3,14 - 3,23 (1H, m), 3,50 (1H, t), 3,65 (1H, d), 3,77 (1H, d), 3,94 - 3,99 (1H, m), 4,18 (1H, d), 4,43 (1H, br, s), 6,08 (1H, d), 6,97 (1H, s), 7,51 (2H, d), 8,23 (2H, d), 8,76 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00555μM

Ejemplo 18j: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,35 (9H, s), 1,50 – 1,71 (2H, m), 1,81 - 1,91 (2H, m), 3,23 - 3,33 (1H, m), 3,53 - 3,62 (1H, m), 3,68 - 3,74 (1H, m), 3,81 (1H, d), 3,98 - 4,05 (1H, m), 4,17 (1H, d), 4,42 (1H, br, s), 7,03 (1H, s), 7,23 (1H, s), 7,28 (1H, s), 7,48 (2H, d), 7,52 - 7,55 (4H, m), 8,38 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,0303μM

Ejemplo 18k: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 – 1,27 (18H, m), 1,48 - 1,52 (1H, m), 1,62 - 1,69 (3H, m), 3,14 - 3,23 (1H, m), 3,40 (2H, d), 3,45 - 3,53 (1H, m), 3,63 - 3,67 (1H, m), 3,77 (1H, d), 3,95 - 4,01 (1H, m), 4,18 (1H, d), 4,41 (1H, br, s), 4,96 (1H, t), 6,01 (1H, s), 6,97 (1H, s), 7,46 (2H, d), 8,22 (2H, d), 8,75 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0113μM

Ejemplo 18l: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,22 - 1,25 (12H, m), 1,48 - 1,52 (1H, m), 1,57 - 1,68 (5H, m), 3,15 - 3,23 (3H, m), 3,43 – 3,54 (3H, m), 3,63 - 3,67 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,18 (1H, d), 4,43 (1H, br, s), 4,49 (1H, t), 6,21 (1H, t), 6,97 (1H, s), 7,50 (2H, d), 8,23 (2H, d), 8,73 (1H, s).

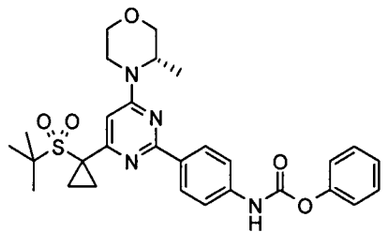
Ensayo de mTOR Quinasa (Echo): 0,0102μM

Ejemplo 18m: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,21 – 1,29 (12H, m), 1,48 – 1,55 (1H, m), 1,61 – 1,71 (3H, m), 3,16 - 3,25 (1H, m), 3,49 (1H, t), 3,66 (1H, d), 3,74 – 3,83 (4H, m), 3,99 (1H, d), 4,19 (1H, d), 4,43 (1H, br, s), 6,99 (1H, s), 7,39 (1H, s), 7,55 (2H, d), 7,77 (1H, s), 8,27 (2H, d), 8,39 (1H, s), 8,85 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00315μM

La preparación de fenil *N*-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

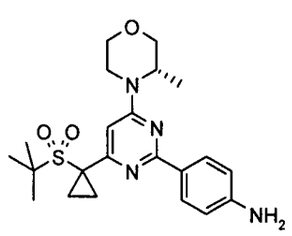


Se agregó fenil cloroformiato (0,809 mL, 6,44 mmol) a 4-[4-(1-*terc*-butilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (2,52g, 5,85 mmol) e hidrogenocarbonato de sodio (0,738 g, 8,78 mmol) en dioxano (45 mL) a TA. La mezcla se agitó a TA durante 2 horas. La mezcla se repartió entre acetato de etilo y agua. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 10% – 100% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido casi incoloro (2,99 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,31 - 1,34 (12H, m), 1,48 - 4,58 (1H, m), 1,62 - 1,70 (1H, m), 1,80 - 1,89 (2H, m), 3,31 (1H, dt), 3,60 (1H, dt), 3,75 (1H, dd), 3,82 (1H, d), 4,04 (1H, dd), 4,20 (1H, d), 4,45 (1H, br), 7,06 - 7,11 (2H, m), 7,19 - 7,28 (3H, m), 7,41 (2H, t), 7,54 (2H, d), 8,40 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 551; HPLC tR = 3,06 min.

4-[4-(1-*terc*-Butilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



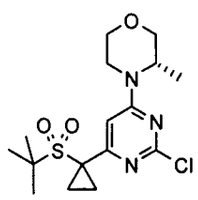
Se agregó diclorobis(trifenilfosfina)-paladio(II) (0,185 g, 0,26 mmol) a 4-(1-*terc*-butilsulfonilciclopropil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,97 g, 5,27 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,501 g, 6,85 mmol) y carbonato de sodio acuoso 2M (9,48 mL, 18,97 mmol) en DMF (11 mL), DME (11 mL), etanol (11 mL) y agua (27,5 mL) a TA bajo nitrógeno. La reacción se purgó con nitrógeno durante 15 minutos

y la mezcla resultante se agitó a 80°C durante 16 horas. La mezcla de reacción se repartió entre acetato de etilo y agua. La solución orgánica se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 25% - 100% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (2,24 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,32 (9H, s), 1,44 - 1,55 (1H, m), 1,60 - 1,68 (1H, m), 1,77 - 1,86 (2H, m), 3,28 (1H, dt), 3,59 (1H, dt), 3,74 (1H, dd), 3,81 (1H, d), 3,90 (2H, s), 4,03 (1H, dd), 4,18 (1H, d), 4,44 (1H, br), 6,71 (2H, d), 6,99 (1H, s), 8,24 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 431; HPLC tR = 2,43 min.

4-(1-*terc*-Butilsulfonilciclopropil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

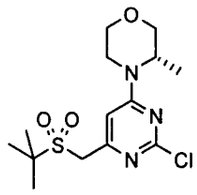


Se agregó 1,2-dibromoetano (0,349 mL, 15,40 mmol) a 4-(*terc*-butilsulfonilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,68 g, 7,7 mmol) en tolueno (40 mL) seguido por bromuro de tetrabutilamonio (0,248 g, 0,77 mmol) e hidróxido de sodio concentrado (7,70 mL, 77 mmol). La mezcla de reacción se agitó vigorosamente y se calentó a 60°C durante 1 hora. La mezcla de reacción se enfrió y se diluyó con acetato de etilo y se lavó con agua. La solución orgánica se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido incoloro (1,97 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,20 - 1,35 (12H, m), 1,46 - 1,50 (1H, m), 1,52 - 1,61 (1H, m), 1,77 - 1,86 (2H, m), 3,26 (1H, dt), 3,54 (1H, dt), 3,68 (1H, dd), 3,78 (1H, d), 3,98 - 4,08 (2H, m), 4,29 (1H, br, s), 7,14 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 374; HPLC tR = 2,34 min.

4-(*terc*-Butilsulfonilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

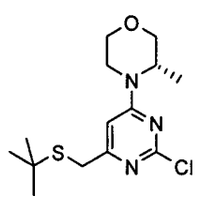


Una solución de peróxido de hidrógeno (35% solución acuosa, 9,48 mL, 107,30 mmol) se agregó gota a gota a una solución agitada de 4-(*terc*-butilsulfanilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (9,82 g, 31,1 mmol), tungstato de sodio dihidrato (0,205 g, 0,62 mmol) y ácido sulfúrico (0,6 mL, 1M, 0,6 mmol) en dioxano (80 mL). La mezcla se calentó a 55°C durante 1 hora y luego se diluyó con agua y se enfrió. Se agregó una solución de metabisulfito de sodio (10% p/v) para destruir el peróxido remanente. La solución se extrajo con DCM, se secó ($MgSO_4$), se filtró y se concentró al vacío para proporcionar el material deseado como una goma casi incolora (9,34 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,33 (3H, d), 1,44 (9H, s), 3,29 (1H, dt), 3,54 (1H, dt), 3,69 (1H, dd), 3,78 (1H, d), 3,97 - 4,13 (2H, m), 4,21 (2H, s), 4,30 (1H, br, s), 6,71 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 348; HPLC tR = 1,82 min.

4-(*terc*-Butilsulfanilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó DIPEA (8,61 mL, 49,78 mmol) a 2-metil-2-propanotiol (4,21 mL, 37,33 mmol), en DMF (55 mL) a TA bajo nitrógeno. La solución resultante se agitó a TA durante 20 minutos. Se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (11,00 g, 31,11 mmol) a la mezcla de reacción en una porción. La mezcla se agitó durante 4 horas a TA luego a 60°C durante 1,5 horas antes de repartirse entre acetato de etilo y agua. La capa orgánica se lavó con agua adicional y luego se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como una goma amarilla (10,02 g). El material se utilizó sin purificación adicional.

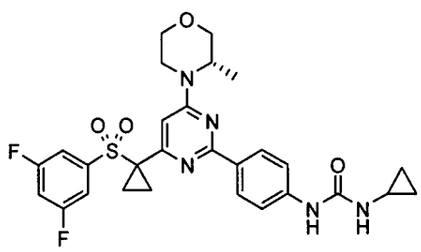
Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,34 (9H, s), 3,27 (1H, dt), 3,54 (1H, dt), 3,66 - 3,71 (3H, m), 3,78 (1H, d), 3,97 - 4,07 (2H, m), 4,31 (1H, br, s), 6,56

(1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 316, 318; HPLC tR = 2,61 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 19: 3-Ciclopropil-1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



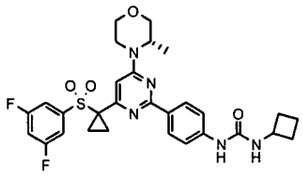
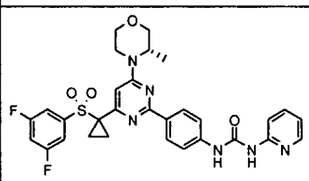
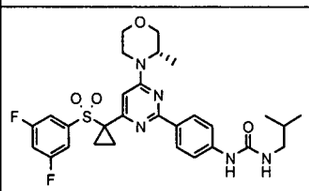
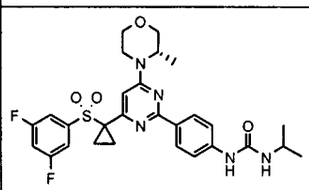
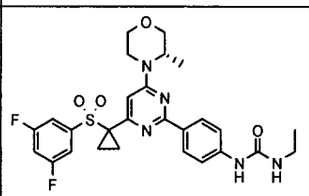
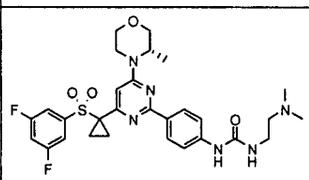
Se agregó fenil *N*-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (120 mg, 0,22 mmol) a una mezcla de ciclopropilamina (59 mg, 1,03 mmol) y trietilamina (0,2 mL, 1,49 mmol) en DMF (1 mL) a TA. La mezcla de reacción se dejó reposar a TA durante 65 horas. El producto bruto se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido incoloro (55 mg).

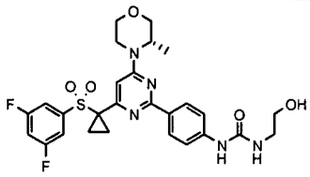
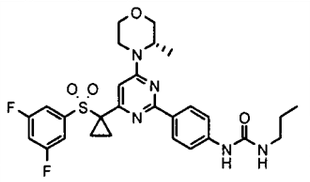
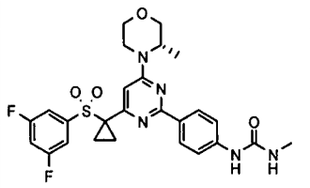
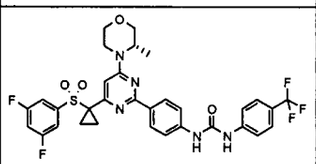
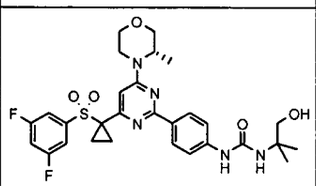
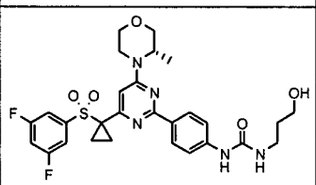
Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,41 - 0,44 (2H, m), 0,63 - 0,68 (2H, m), 1,20 (3H, d), 1,62 -1,69 (2H, m), 1,96 - 2,00 (2H, m), 2,53 - 2,59 (1H, m), 3,13 - 3,23 (1H, m), 3,42 - 3,50 (1H, m), 3,59 - 3,63 (1H, m), 3,75 (1H, d), 3,94 - 4,00 (1H, m), 4,18 (1H, d), 4,48 (1H, br, s), 6,42 (1H, d), 6,67 (1H, s), 7,42 (2H, d), 7,54 - 7,59 (2H, m), 7,70 - 7,76 (1H, m), 7,82 (2H, d), 8,53 (1H, s)

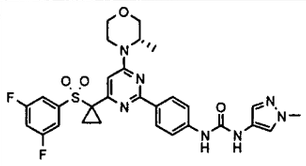
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 572; HPLC tR = 2,72 min.

Ensayo de mTOR Quinasa (Echo): 0,00131μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
19a		3-ciclobutil-1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	584	2,86
19b		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-ilurea	607	3,03
19c		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea	586	2,94
19d		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-ilurea	572	2,79
19e		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea	558	2,53
19f		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	601	2,5

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
19g		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	574	2,17
19h		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propilurea	572	2,72
19i		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	544	2,37
19j		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	674	3,27
19k		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	602	2,48
19l		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	588	2,23

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
19m		1-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	610	2,39

Ejemplo 19a: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,58 - 1,70 (4H, m), 1,80 - 1,90 (2H, m), 1,95 - 2,02 (2H, m), 2,16 - 2,25 (2H, m), 3,10 - 3,20 (1H, m), 3,40 - 3,48 (1H, m), 3,58 - 3,62 (1H, m), 3,75 (1H, d), 3,92 - 3,98 (1H, m), 4,10 - 4,20 (2H, m), 4,48 (1H, br, s), 6,45 (1H, d), 6,67 (1H, s), 7,39 (2H, d), 7,55 - 7,57 (2H, m), 7,71 - 7,75 (1H, m), 7,82 (2H, d), 8,55 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00425μM

Ejemplo 19b: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,62 - 1,71 (2H, m), 1,96 - 2,03 (2H, m), 3,13 - 3,23 (1H, m), 3,42 - 3,51 (1H, m), 3,60 - 3,65 (1H, m), 3,76 (1H, d), 3,93 - 3,99 (1H, m), 4,19 (1H, d), 4,50 (1H, br, s), 6,71 (1H, s), 7,03 - 7,06 (1H, m), 7,51 - 7,59 (5H, m), 7,70 - 7,80 (2H, m), 7,92 (2H, d), 8,31 (1H, d), 9,44 (1H, s), 10,55 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00119μM

Ejemplo 19c: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,89 (3H, s), 0,90 (3H, s), 1,20 (3H, d), 1,63 - 1,75 (3H, m), 1,94 - 2,00 (2H, m), 2,95 (2H, t), 3,11 - 3,21 (1H, m), 3,41 - 3,50 (1H, m), 3,57 - 3,63 (1H, m), 3,75 (1H, d), 3,92 - 3,98 (1H, m), 4,17 (1H, d), 4,48 (1H, br, s), 6,23 (1H, t), 6,67 (1H, s), 7,40 (2H, d), 7,52 - 7,59 (2H, m), 7,68 - 7,76 (1H, m), 7,83 (2H, d), 8,64 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0214μM

Ejemplo 19d: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,11 (3H, s), 1,13 (3H, s), 1,20 (3H, d), 1,62 - 1,69 (2H, m), 1,95 - 2,00 (2H, m), 3,11 - 3,20 (1H, m), 3,42 - 3,50 (1H, m), 3,57 - 3,63 (1H, m), 3,72 - 3,82 (2H, m), 3,92 - 3,98 (1H, m), 4,17 (1H, d), 4,48 (1H, br, s), 6,05 (1H, d), 6,67 (1H, s), 7,39 (2H, d), 7,52 - 7,59 (2H, m), 7,69 - 7,76 (1H, m), 7,82 (2H, d), 8,53 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00318μM

Ejemplo 19e: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,20 (3H, d), 1,63 - 1,68 (2H, m), 1,95 - 2,00 (2H, m), 3,09 - 3,22 (3H, m), 3,37 (1H, d), 3,42 - 3,49 (1H, m), 3,58 - 3,63

(1H, m), 3,75 (1H, d), 3,93 - 3,98 (1H, m), 4,17 (1H, d), 4,49 (1H, br, s), 6,15 (1H, t), 6,67 (1H, s), 7,40 (2H, d), 7,54 - 7,57 (2H, m), 7,69 - 7,76 (1H, m), 7,82 (2H, d), 8,65 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00135μM

Ejemplo 19f: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,63 - 1,70 (2H, m), 1,95 - 2,00 (2H, m), 2,19 (6H, s), 2,34 (2H, t), 3,11 - 3,23 (3H, m), 3,41 - 3,50 (1H, m), 3,58 - 3,63 (1H, m), 3,75 (1H, d), 3,92 - 3,98 (1H, m), 4,17 (1H, d), 4,49 (1H, br, s), 6,16 (1H, t), 6,67 (1H, s), 7,40 (2H, d), 7,51 - 7,58 (2H, m), 7,68 - 7,76 (1H, m), 7,83 (2H, d), 8,88 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0804μM

Ejemplo 19g: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,66 (2H, s), 1,92 - 2,01 (2H, m), 3,11 - 3,20 (3H, m), 3,40 - 3,51 (3H, m), 3,57 - 3,64 (1H, m), 3,75 (1H, d), 3,92 - 3,99 (1H, m), 4,17 (1H, d), 4,48 (1H, br, s), 4,74 (1H, t), 6,24 (1H, t), 6,67 (1H, s), 7,40 (2H, d), 7,50 - 7,59 (2H, m), 7,68 - 7,74 (1H, t), 7,83 (2H, d), 8,79 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000274μM

Ejemplo 19h: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,20 (3H, d), 1,41 - 1,51 (2H, m), 1,66 (2H, s), 1,94 - 2,00 (2H, m), 3,07 (2H, q), 3,12 - 3,17 (1H, m), 3,42 - 3,49 (1H, m), 3,58 - 3,64 (1H, m), 3,75 (1H, d), 3,92 - 3,98 (1H, m), 4,17 (1H, d), 4,48 (1H, br, s), 6,20 (1H, t), 6,67 (1H, s), 7,40 (2H, d), 7,52 - 7,61 (2H, m), 7,68 - 7,76 (1H, m), 7,82 (2H, d), 8,64 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00246μM

Ejemplo 19i: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,61 - 1,70 (2H, m), 1,94 - 2,01 (2H, m), 2,67 (3H, d), 3,10 - 3,20 (1H, m), 3,40 - 3,49 (1H, m), 3,58 - 3,63 (1H, m), 3,75 (1H, d), 3,92 - 3,98 (1H, m), 4,17 (1H, d), 4,48 (1H, br, s), 6,02 - 6,08 (1H, m), 6,67 (1H, s), 7,41 (2H, d), 7,53 - 7,58 (2H, m), 7,68 - 7,75 (1H, m), 7,82 (2H, d), 8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00152μM

Ejemplo 91j: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,67 (2H, s), 1,94 - 2,03 (2H, m), 3,13 - 3,22 (1H, m), 3,42 - 3,50 (1H, m), 3,59 - 3,64 (1H, m), 3,76 (1H, d), 3,93 - 3,98 (1H, m), 4,19 (1H, d), 4,49 (1H, br, s), 6,70 (1H, s), 7,50 (2H, d), 7,54 - 7,61 (2H, m), 7,62 - 7,78 (5H, m), 7,91 (2H, d), 9,04 (1H, s), 9,12 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0199μM

Ejemplo 19k: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,23 (6H, s), 1,62 – 1,68 (2H, m), 1,94 – 1,98 (2H, m), 3,13 - 3,20 (1H, m), 3,38 (2H, d), 3,42 - 3,50 (1H, m), 3,58 - 3,64 (1H, m), 3,75 (1H, d), 3,93 - 3,98 (1H, m), 4,17 (1H, d), 4,48 (1H, br, s), 4,94 (1H, t), 5,97 (1H, s), 7,35 (2H, d), 7,52 - 7,58 (2H, m), 7,69 - 7,77 (1H, m), 7,81 (2H, d), 8,71 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00415μM

Ejemplo 19l: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,55 – 1,70 (4H, m), 1,95 - 2,01 (2H, m), 3,13 - 3,21 (3H, m), 3,42 - 3,50 (3H, m), 3,58 - 3,65 (1H, m), 3,75 (1H, d), 3,93 - 3,99 (1H, m), 4,18 (1H, d), 4,43 – 4,52 (2H, m), 6,19 (1H, t), 6,67 (1H, s), 7,39 (2H, d), 7,52 - 7,61 (2H, m), 7,69 - 7,78 (1H, m), 7,83 (2H, d), 8,69 (1H, s).

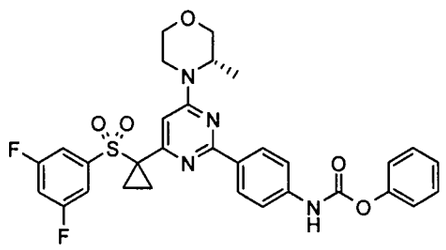
Ensayo de mTOR Quinasa (Echo): 0,00152μM

Ejemplo 19m: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,60 – 1,69 (2H, m), 1,94 - 2,01 (2H, m), 3,13 - 3,21 (1H, m), 3,42 - 3,50 (3H, m), 3,58 - 3,64 (1H, m), 3,73 – 3,81 (4H, m), 3,93 - 3,98 (1H, m), 4,18 (1H, d), 4,49 (1H, br, s), 6,67 (1H, s), 7,37 (1H, s), 7,43 (2H, d), 7,51 - 7,60 (2H, m), 7,68 - 7,78 (2H, m), 7,76 (2H, d), 8,35 (1H, s), 8,81 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000944μM

La preparación de fenil *N*-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



Se agregó fenil cloroformiato (0,764 mL, 6,08 mmol) a 4-[4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (2,69 g, 5,53 mmol) e hidrogenocarbonato de sodio (0,697 g, 8,29 mmol) en dioxano (40 mL) a TA. La suspensión resultante se agitó a TA durante 1 hora. La mezcla se repartió entre acetato de etilo y agua. La solución orgánica se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 25% - 80% acetato de etilo en isohexano, para proporcionar el material deseado como una película amarilla seca (3,07 g).

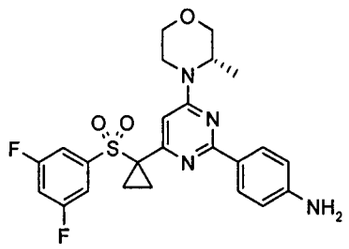
Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,32 (3H, d), 1,61 - 1,66 (1H, m), 1,68 - 1,73 (1H, m), 1,94 - 2,05 (2H, m), 3,30 (1H, dt), 3,61 (1H, dt), 3,75 (1H, dd), 3,84 (1H, d), 4,05 (1H, dd), 4,16 (1H, d), 4,43 (1H, br, s), 6,79 (1H, s), 6,94 - 7,03 (2H, m), 7,18 - 7,28

1432

(3H, m), 7,30 - 7,35 (2H, m), 7,37 - 7,47 (4H, m), 8,10 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 607; HPLC tR = 3,12 min.

4-[4-[1-(3,5-Difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

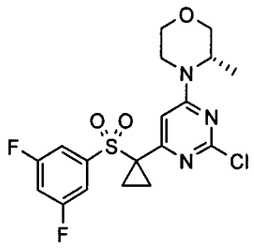


Una corriente de nitrógeno se hizo pasar a través de una mezcla de 2-cloro-4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,5 g, 5,82 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,656 g, 7,56 mmol) y carbonato de sodio acuoso 2M (10,47 mL, 20,94 mmol) en DMF (11 mL), DME (11 mL), etanol (11 mL) y agua (27,5 mL) a TA durante 15 minutos. Se agregó diclorobis(trifenilfosfina)-paladio(II) (0,204 g, 0,29 mmol) en una porción y la mezcla de reacción se agitó a 80°C bajo nitrógeno durante 1 hora. La mezcla de reacción se repartió entre acetato de etilo y agua. La solución orgánica se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 25% - 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido casi incoloro (2,76 g).

Espectro de NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,62 - 1,66 (1H, m), 1,70 - 1,74 (1H, m), 1,93 - 2,03 (2H, m), 3,28 (1H, dt), 3,59 (1H, dt), 3,72 - 3,74 (1H, dd), 3,79 - 3,89 (3H, m), 4,03 (1H, dd), 4,10 - 4,18 (1H, m), 4,37 - 4,45 (1H, m), 6,61 - 6,65 (2H, m), 6,73 (1H, s), 6,98 (1H, tt), 7,31 - 7,36 (2H, m), 7,93 - 7,96 (2H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 487; HPLC tR = 2,86 min.

2-Cloro-4-[1-(3,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

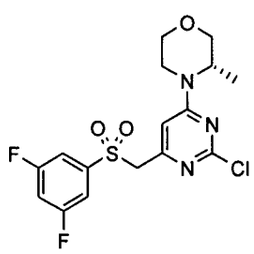


Se agregó 1,2-dibromoetano (1,0 mL, 11,6 mmol) a 2-cloro-4-[(3,5-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,68 g, 9,11 mmol) en tolueno (55 mL) seguido por bromuro de tetrabutilamonio (0,294 g, 0,91 mmol) e hidróxido de sodio concentrado (9,00 mL, 90 mmol). La mezcla de reacción se agitó a TA durante toda la noche. La mezcla luego se calentó hasta alcanzar 80°C y se continuó agitando vigorosamente durante 3 horas. Se agregó una cantidad adicional de 1,2-dibromoetano (1 mL, 11,6 mmol) y se continuó calentando durante otras 2 horas. La mezcla de reacción se diluyó con acetato de etilo y se lavó con agua. La solución orgánica se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 10 a 40% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido incoloro (3,0 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,32 (3H, d), 1,56 - 1,60 (1H, m), 1,63 - 1,68 (1H, m), 1,92 - 2,01 (2H, m), 3,28 (1H, dt), 3,55 (1H, dt), 3,70 (1H, dd), 3,80 (1H, d), 4,00 - 4,09 (2H, m), 4,28 (1H, br, s), 6,87 (1H, s), 7,07 (1H, tt), 7,24 - 7,29 (2H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 430, 432; HPLC tR = 2,55 min.

2-Cloro-4-[(3,5-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



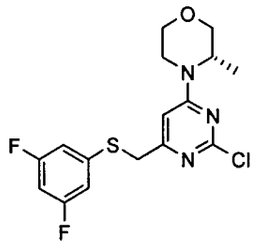
Una solución de tungstato de sodio dihidrato (199 mg, 0,60 mmol) en agua (2 mL) se agregó a una solución agitada de 2-cloro-4-[(3,5-difluorofenil)sulfanilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidina (11,23 g, 30,2 mmol) y ácido sulfúrico (0,302 mL, 2M, 0,60 mmol) en dioxano (40 mL). Se agregó peróxido de hidrógeno (3,22 mL, 104,19 mmol) y la mezcla se agitó a TA durante toda la noche. Un precipitado se recogió mediante filtración y se secó al

vacío, para proporcionar el material deseado como un sólido casi incoloro (3,61 g). El filtrado se repartió entre acetato de etilo y agua. La solución orgánica se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 5% - 20% acetato de etilo en DCM, para proporcionar el material deseado como un sólido casi incoloro (7,66 g).

Espectro de NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,34 (3H, s), 3,31 (1H, dt), 3,56 (1H, dt), 3,71 (1H, dd), 3,80 (1H, d), 3,98 - 4,10 (2H, m), 4,31 (2H, s), 6,55 (1H, s), 7,12 (1H, tt), 7,30 - 7,36 (2H, m).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 404, 406; HPLC tR = 2,32 min.

2-Cloro-4-[(3,5-difluorofenil)sulfanilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



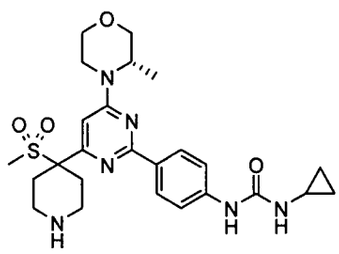
Se agregó DIPEA (8,07 mL, 46,67 mmol) a 3,5-difluorobencenotiol (5,00 g, 34,22 mmol), en DMF (55 mL) a TA bajo nitrógeno. La solución resultante se agitó a TA durante 20 minutos. Se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (11,00 g, 31,11 mmol) a la mezcla de reacción en una porción. La mezcla se agitó durante 4 horas a TA. La mezcla de reacción se calentó en un baño de agua a 60°C durante 1,5 horas antes de repartirse entre acetato de etilo y agua. La solución orgánica se lavó con más agua y luego se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como una goma (12,24 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,27 (3H, d), 3,24 (1H, dt), 3,52 (1H, dt), 3,66 (1H, dd), 3,76 (1H, d), 3,96 - 4,04 (4H, m), 4,21 (1H, br, s), 6,41 (1H, s), 6,59 - 6,66 (1H, m), 6,80 - 6,86 (2H, m).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 372, 374; HPLC tR = 2,66 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 20: 3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(4-metilsulfonilpiperidin-4-il)pirimidin-2-il]fenil]urea



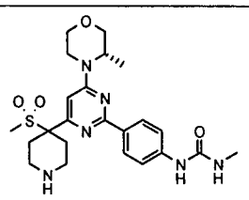
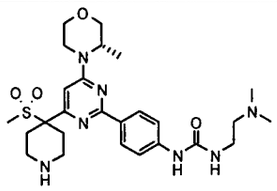
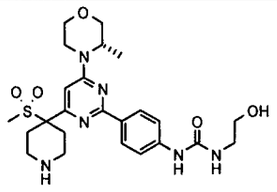
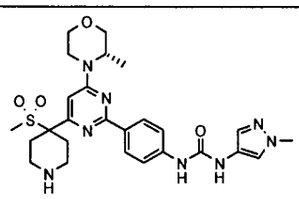
Se agregó ciclopropilamina (0,055 mL, 0,76 mmol) a *terc*-butil 4-[6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]-4-metilsulfonilpiperidina-1-carboxilato (115 mg, 0,17 mmol) y trietilamina (0,153 mL, 1,10 mmol) en DMF (1 mL) a TA y la reacción se dejó reposar durante toda la noche a TA. La mezcla se repartió entre acetato de etilo y agua. La capa orgánica se lavó dos veces con agua y luego se concentró bajo presión reducida. El residuo se disolvió en DCM (1 mL) y se trató con TFA (2 mL). La solución resultante se agitó durante 30 minutos a TA antes de concentrarse bajo presión reducida. La muestra se disolvió en DMF (1,5 mL) y se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido incoloro (26,7 mg).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,38 - 0,44 (2H, m), 0,61 - 0,68 (2H, m), 1,24 (3H, d), 1,97 - 2,10 (2H, m), 2,30 - 2,45 (2H, m), 2,57 (1H, oscurecido por señal de DMSO), 2,73 - 2,86 (5H, m), 2,90 - 3,00 (2H, m), 3,15 - 3,25 (1H, m), 3,47 - 3,55 (1H, m), 3,63 - 3,69 (1H, m), 3,77 (1H, d), 3,95 - 4,01 (1H, m), 4,29 (1H, d), 4,56 (1H, br, s), 6,45 (1H, s), 6,79 (1H, s), 7,51 (2H, d), 8,23 (2H, d), 8,57 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 515; HPLC tR = 1,50 min.

Ensayo de mTOR Quinasa (Echo): 0,0128μM

Los siguientes compuestos se prepararon en forma análoga a partir de *terc*-butil 4-[6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]-4-metilsulfonilpiperidina-1-carboxilato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
20a		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfonilpiperidin-4-il)pirimidin-2-il]fenil]urea	489,5	1,34
20b		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfonilpiperidin-4-il)pirimidin-2-il]fenil]urea	546,5	1,44
20c		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfonilpiperidin-4-il)pirimidin-2-il]fenil]urea	519,5	1,24
20d		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfonilpiperidin-4-il)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	555,5	1,41

Ejemplo 20a: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,97 - 2,09 (2H, m), 2,30 - 2,45 (2H, m), 2,67 (3H, d), 2,70 - 2,85 (5H, m), 2,90 - 3,02 (2H, m), 3,15 - 3,25 (1H, m), 3,45 - 3,55 (1H, m), 3,67 (1H, d), 3,77 (1H, d), 3,99 (1H, d), 4,28 (1H, d), 4,56 (1H, br, s), 6,05 – 6,12 (1H, m), 6,79 (1H, s), 7,51 (2H, d), 8,22 (2H, d), 8,76 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0163μM

Ejemplo 20b: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,98 - 2,09 (2H, m), 2,19 (6H, s), 2,30 – 2,47 (4H, m), 2,72 – 2,83 (5H, m), 2,92 – 3,02 (2H, m), 3,16 – 3,27 (3H, m, oscurecido por señal de agua), 3,45 - 3,57 (1H, m), 3,63 - 3,69 (1H, m), 3,77 (1H, d), 3,95 - 4,00 (1H, m), 4,28 (1H, d), 4,57 (1H, br, s), 6,17 (1H, t), 6,79 (1H, s), 7,49 (2H, d), 8,22 (2H, d), 8,91 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,874μM

Ejemplo 20c: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,97 – 2,10 (2H, m), 2,32 –

2,46 (2H, m), 2,74 – 2,83 (5H, m), 2,92 – 3,02 (2H, m), 3,14 - 3,26 (3H, m), 3,41 - 3,55 (4H, m), 3,63 - 3,69 (1H, m), 3,77 (1H, d), 3,95 - 4,01 (1H, m), 4,28 (1H, d), 4,57 (1H, br, s), 4,74 (1H, t), 6,25 (1H, t), 6,79 (1H, s), 7,49 (2H, d), 8,23 (2H, d), 8,82 (1H, s).

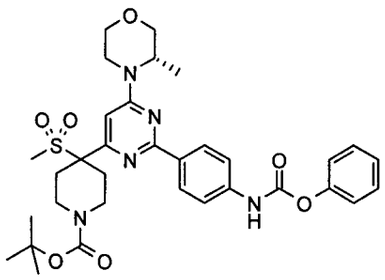
Ensayo de mTOR Quinasa (Echo): 0,00559μM

Ejemplo 20d: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,24 (3H, d), 2,00 – 2,09 (2H, m), 2,32 – 2,47 (2H, m), 2,75 - 2,84 (5H, m), 2,92 – 3,02 (1H, m), 3,17 - 3,26 (1H, m), 3,47 - 3,55 (1H, m), 3,64 - 3,70 (1H, m), 3,75 – 3,82 (4H, m), 3,95 - 4,03 (1H, m), 4,29 (1H, d), 4,57 (1H, br, s), 6,80 (1H, s), 7,38 (1H, d), 7,55 (2H, d), 7,77 (1H, s), 8,26 (2H, d), 8,44 (1H, s), 8,89 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0133μM

La preparación de *terc*-butil 4-[6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]-4-metilsulfonilpiperidina-1-carboxilato se describe a continuación.

terc-butil 4-[6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]-4-metilsulfonilpiperidina-1-carboxilato



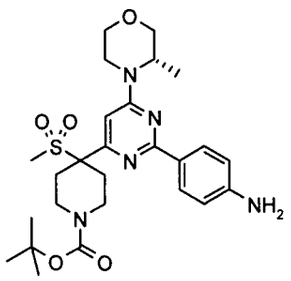
Se agregó fenil cloroformiato (0,150 mL, 1,20 mmol) a *terc*-butil 4-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]-4-metilsulfonilpiperidina-1-carboxilato (530 mg, 1,00 mmol) e hidrogenocarbonato de sodio (126 mg, 1,50 mmol) en dioxano (7 mL) a TA. La suspensión resultante se agitó a TA durante 3 horas. La mezcla se repartió entre acetato de etilo y agua. La solución orgánica se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 10% - 60% acetato de etilo en DCM, para proporcionar una goma incolora que a continuación se trituró con éter dietílico para proporcionar el material deseado como un sólido incoloro (576 mg).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,36 (3H, d), 1,44 (9H, s), 2,29 - 2,41 (2H, m), 2,72 (3H, s), 2,73 - 2,85 (4H, m), 3,33 (1H, dt), 3,61 (1H, dt), 3,76 (1H, dd), 3,84

(1H, d), 4,06 (1H, dd), 4,10 - 4,32 (3H, m), 4,46 (1H, br, s), 6,65 (1H, s), 7,12 (1H, br, s), 7,17 - 7,28 (3H, m), 7,36 - 7,44 (2H, m), 7,54 (2H, d), 8,35 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 652; HPLC tR = 3,11 min.

terc-butil 4-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]-4-metilsulfonilpiperidina-1-carboxilato

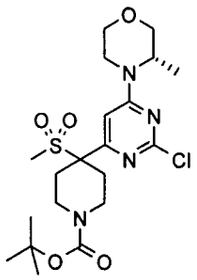


Una corriente de nitrógeno se hizo pasar a través de *terc*-butil 4-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]-4-metilsulfonilpiperidina-1-carboxilato (500 mg, 1,05 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (300 mg, 1,37 mmol) y carbonato de sodio acuoso 2M (1,895 mL, 3,79 mmol) en DMF (2 mL), DME (2 mL), etanol (2 mL) y agua (5 mL) a TA durante 15 minutos. La mezcla de reacción se trató con diclorobis(trifenilfosfina)-paladio(II) (36,9 mg, 0,05 mmol) y la mezcla se agitó a 80°C durante 30 minutos. La mezcla se repartió entre acetato de etilo y agua. La solución orgánica se secó ($MgSO_4$), se filtró y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 10% - 50% acetato de etilo en DCM. El material aislado se trituró con éter dietílico para proporcionar el material deseado como un sólido naranja claro (544 mg).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,34 (3H, d), 1,44 (9H, s), 2,30 - 2,36 (2H, m), 2,71 (3H, s), 2,69 - 2,85 (4H, m), 3,30 (1H, dt), 3,60 (1H, dt), 3,74 (1H, dd), 3,83 (1H, d), 3,93 (2H, s), 4,04 (1H, dd), 4,09 - 4,29 (3H, m), 4,45 (1H, br, s), 6,58 (1H, s), 6,71 (2H, d), 8,18 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 532; HPLC tR = 2,52 min.

terc-Butil 4-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]-4-metilsulfonilpiperidina-1-carboxilato

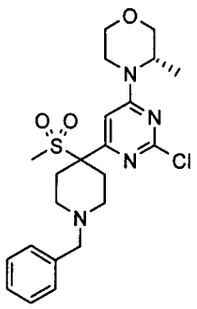


Se agregó 1-cloroetil cloroformiato (0,315 mL, 2,92 mmol) a una solución de 4-(1-bencil-4-metilsulfonilpiperidin-4-il)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (679 mg, 1,46 mmol) en DCM (10 mL). La solución se calentó a reflujo durante 3 horas. La mezcla se enfrió, se diluyó con metanol (10 mL) y se dejó reposar durante toda la noche. La mezcla se trató con di-*terc*-butil dicarbonato (0,738 mL, 3,21 mmol) y DIPEA (0,505 mL, 2,92 mmol) y esta solución se agitó a TA durante 1,5 horas. La solución se repartió entre DCM y agua y la fase orgánica se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 10% - 30% acetato de etilo en DCM, para proporcionar el material deseado como una película seca incolora (519 mg).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,33 (3H, d), 1,45 (9H, s), 2,23 - 2,34 (2H, m), 2,59 - 2,78 (7H, m), 3,30 (1H, dt), 3,55 (1H, dt), 3,70 (1H, dd), 3,80 (1H, d), 3,98 - 4,40 (5H, m), 6,61 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 475, 477; HPLC tR = 2,53 min.

4-(1-Bencil-4-metilsulfonilpiperidin-4-il)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Una solución de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina (750 mg, 2,45 mmol) en NMP (8 mL) se trató con hidruro de sodio (324 mg, 8,10 mmol). La mezcla se agitó a TA durante 10 minutos antes de tratarse con bromuro de tetrabutilamonio (979 mg, 3,04 mmol) y *N*-bencil-2-cloro-*N*-(2-cloroetil)etanamina clorhidrato (692 mg, 2,58 mmol). La mezcla de reacción se agitó durante 5 minutos, se entibió hasta alcanzar 50°C

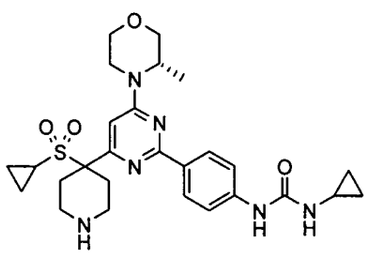
durante 1 hora y luego se entibió hasta alcanzar 80°C durante 2,5 horas. La mezcla se dejó enfriar y se agitó durante 65 horas a TA. La mezcla de reacción se aplacó mediante la adición de solución de cloruro de amonio saturado acuoso y luego se extrajo con acetato de etilo. La solución orgánica se secó ($MgSO_4$), se filtró y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 10% - 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido incoloro (710 mg).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,33 (3H, d), 1,89 - 1,99 (2H, m), 2,40 - 2,50 (2H, m), 2,57 - 2,64 (2H, m), 2,75 (3H, s), 2,87 - 2,95 (2H, m), 3,29 (1H, dt), 3,41 (2H, s), 3,55 (1H, dt), 3,69 (1H, dd), 3,79 (1H, d), 3,95 - 4,08 (2H, m), 4,29 (1H, br, s), 6,59 (1H, s), 7,21 - 7,32 (5H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 465, 467; HPLC tR = 2,59 min.

La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina se describió anteriormente.

Ejemplo 21: 3-Ciclopropil-1-[4-[4-(4-ciclopropilsulfonilpiperidin-4-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



Se agregó ciclopropilamina (0,055 mL, 0,76 mmol) a *terc*-butil 4-ciclopropilsulfonil-4-[6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]piperidina-1-carboxilato (120 mg, 0,18 mmol) y trietilamina (0,16 mL, 1,15 mmol) en DMF (1 mL) a TA y la reacción se dejó reposar durante toda la noche a TA. La mezcla se repartió entre acetato de etilo y agua. La capa orgánica se lavó dos veces con agua y luego se concentró bajo presión reducida. El residuo se disolvió en DCM (1 mL) y se trató con TFA (2 mL). La solución resultante se agitó durante 30 minutos a TA antes de concentrarse bajo presión reducida. La muestra se disolvió en DMF (1,5 mL). El producto bruto se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco conc.) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido

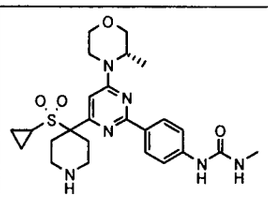
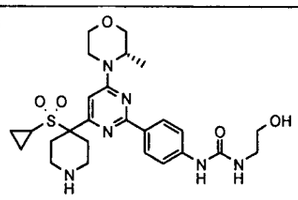
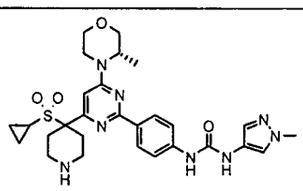
incoloro (53 mg).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,38 - 0,44 (2H, m), 0,63 - 0,68 (2H, m), 0,70 - 0,74 (2H, m), 0,83 - 0,87 (2H, m), 1,23 (3H, d), 1,98 - 2,12 (2H, m), 2,32 - 2,60 (4H, m), 2,82 – 2,98 (4H, m), 3,15 - 3,24 (1H, m), 3,47 - 3,56 (1H, m), 3,64 - 3,69 (1H, m), 3,77 (1H, d), 3,95 - 4,01 (1H, m), 4,26 (1H, d), 4,50 – 4,60 (1H, m), 6,44 (1H, s), 6,81 (1H, s), 7,51 (2H, d), 8,23 (2H, d), 8,54 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 541; HPLC tR = 1,85 min.

Ensayo de mTOR Quinasa (Echo): 0,0253μM

Los siguientes compuestos se prepararon en forma análoga a partir de *terc*-butil 4-ciclopropilsulfonil-4-[6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]piperidina-1-carboxilato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
21a		1-[4-[4-(4-ciclopropilsulfonilpiperidin-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	515,6	1,71
21b		1-[4-[4-(4-ciclopropilsulfonilpiperidin-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	545,7	1,56
21c		1-[4-[4-(4-ciclopropilsulfonilpiperidin-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	581,7	1,83

Ejemplo 21a: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,68 - 0,74 (2H, m), 0,83 - 0,87 (2H, m),

1,23 (3H, d), 1,98 - 2,10 (2H, m), 2,32 - 2,49 (3H, m), 2,67 (3H, d), 2,82 – 2,97 (4H, m), 3,15 - 3,24 (1H, m), 3,47 – 3,57 (1H, m), 3,64 - 3,69 (1H, m), 3,77 (1H, d), 3,95 - 4,01 (1H, m), 4,26 (1H, d), 4,50 – 4,59 (1H, m), 6,07 (1H, q), 6,81 (1H, s), 7,50 (2H, d), 8,22 (2H, d), 8,74 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0378μM

Ejemplo 21b: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,69 – 0,76 (2H, m), 0,82 - 0,89 (2H, m), 1,23 (3H, d), 1,95 – 2,10 (2H, m), 2,31 - 2,49 (3H, m), 2,83 – 2,97 (4H, m), 3,15 – 3,26 (3H, m), 3,43 - 3,58 (3H, m), 3,64 - 3,69 (1H, m), 3,77 (1H, d), 3,95 - 4,01 (1H, m), 4,26 (1H, d), 4,50 – 4,59 (1H, m), 4,74 (1H, t), 6,26 (1H, t), 6,81 (1H, s), 7,49 (2H, d), 8,23 (2H, d), 8,81 (1H, s).

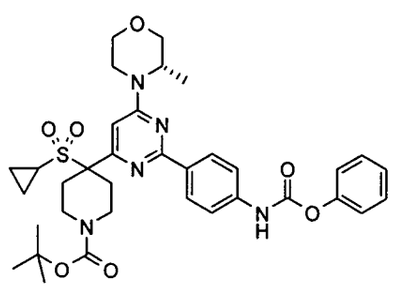
Ensayo de mTOR Quinasa (Echo): 0,0133μM

Ejemplo 21c: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,73 (2H, br, s), 0,87 (2H, d), 1,23 (3H, d), 1,99 – 2,11 (2H, m), 2,33 - 2,48 (3H, m), 2,83 – 2,98 (4H, m), 3,15 – 3,20 (1H, m), 3,45 – 3,56 (1H, m), 3,68 (1H, d), 3,74 – 3,83 (4H, m), 3,99 (1H, d), 4,27 (1H, d), 4,55 (1H, br, s), 6,82 (1H, s), 7,38 (1H, s), 7,55 (2H, d), 7,76 (1H, s), 8,26 (2H, d), 8,42 (1H, s), 8,86 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0234μM

La preparación de *terc*-butil 4-ciclopropilsulfonil-4-[6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]piperidina-1-carboxilato se describe a continuación.

terc-Butil 4-ciclopropilsulfonil-4-[6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]piperidina-1-carboxilato



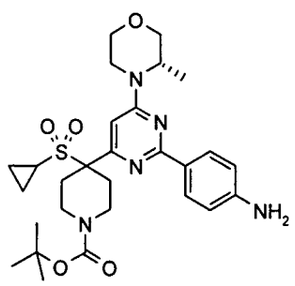
Se agregó fenil cloroformiato (0,235 mL, 1,87 mmol) a *terc*-butil 4-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]-4-ciclopropilsulfonilpiperidina-1-carboxilato (950 mg, 1,70 mmol) e hidrogenocarbonato de sodio (215 mg, 2,56 mmol) en dioxano (15 mL) a TA. La suspensión resultante se agitó a TA durante 1 hora. La mezcla se repartió entre acetato de etilo y agua. La solución orgánica se secó ($MgSO_4$) y se concentró bajo presión reducida. El

residuo se purificó mediante cromatografía en sílice, eluyendo con 25% - 80% acetato de etilo en isohexano. El material aislado se trituró con éter dietílico para proporcionar el material deseado como una película seca casi incolora (1,06 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 0,80 - 0,85 (2H, m), 0,94 - 1,06 (2H, m), 1,35 (3H, d), 1,44 (9H, s), 2,14 - 2,22 (1H, m), 2,25 - 2,39 (2H, m), 2,69 - 2,95 (4H, m), 3,33 (1H, dt), 3,62 (1H, dt), 3,76 (1H, dd), 3,84 (1H, d), 4,03 - 4,31 (4H, m), 4,39 - 4,49 (1H, m), 6,68 (1H, s), 7,11 (1H, br, s), 7,19 - 7,28 (3H, m), 7,41 (2H, t), 7,54 (2H, d), 8,37 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 678; HPLC tR = 3,18 min.

terc-Butil 4-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]-4-ciclopropilsulfonilpiperidina-1-carboxilato

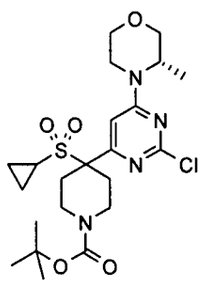


Una corriente de nitrógeno se hizo pasar a través de *terc*-butil 4-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]-4-ciclopropilsulfonilpiperidina-1-carboxilato (0,94 g, 1,88 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,534 g, 2,44 mmol) y carbonato de sodio acuoso 2M (3,38 mL, 6,75 mmol) en DMF (3,75 mL), DME (5 mL), etanol (5 mL) y agua (12,5 mL) a TA durante 15 minutos. La mezcla de reacción se trató con diclorobis(trifenilfosfina)-paladio(II) (0,066 g, 0,09 mmol) y la mezcla se agitó a 80°C durante 1 hora. La mezcla se repartió entre acetato de etilo y agua. La solución orgánica se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 10% - 50% acetato de etilo en DCM. El material aislado se trituró con éter dietílico para proporcionar el material deseado como un sólido marrón claro (0,990 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 0,77 - 0,85 (2H, m), 0,95 - 1,04 (2H, m), 1,32 (3H, d), 1,42 (9H, s), 2,14 - 2,21 (1H, m), 2,24 - 2,37 (2H, m), 2,69 - 2,93 (4H, m), 3,29 (1H, dt), 3,60 (1H, dt), 3,75 (1H, dd), 3,81 (1H, d), 3,90 (2H, s), 4,04 (1H, dd), 4,07 - 4,30 (3H, m), 4,39 - 4,48 (1H, m), 6,61 (1H, s), 6,61 (2H, d), 8,20 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 558; HPLC tR = 2,64 min.

terc-butil 4-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]-4-ciclopropilsulfonilpiperidina-1-carboxilato

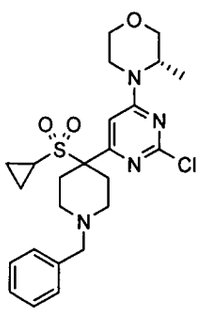


Se agregó 1-cloroetil cloroformiato (0,971 mL, 9,00 mmol) a una solución de 4-(1-bencil-4-ciclopropilsulfonilpiperidin-4-il)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,21 g, 4,50 mmol) en DCM (15 mL). La solución se calentó a reflujo durante 1,5 horas. La mezcla se diluyó con metanol (15 mL) y se continuó calentando durante 2 horas. La mezcla se trató con di-*terc*-butil dicarbonato (2,16 g, 9,90 mmol) y DIPEA (1,6 mL, 9,0 mmol) y esta solución se agitó a TA durante 1 hora. La solución se repartió entre DCM y agua. La fase orgánica se concentró bajo presión reducida y el residuo se purificó mediante cromatografía en sílice, eluyendo con 10% - 30% acetato de etilo en DCM, para proporcionar el material deseado como un sólido incoloro (1,9 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 0,93 - 1,00 (4H, m), 1,32 (3H, d), 1,44 (9H, s), 2,19 - 2,30 (3H, m), 2,62 - 2,80 (4H, m), 3,29 (1H, dt), 3,55 (1H, dt), 3,69 (1H, dd), 3,79 (1H, d), 3,95 - 4,37 (5H, m), 6,65 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 501, 503; HPLC tR = 2,70 min.

4-(1-Bencil-4-ciclopropilsulfonilpiperidin-4-il)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



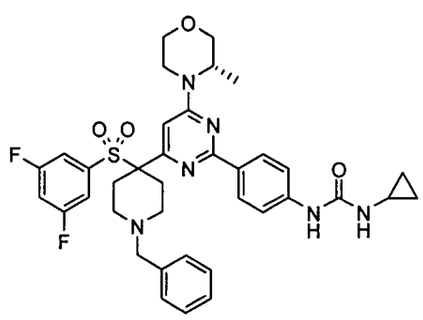
Una solución de 2-cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2 g, 6,03 mmol) en NMP (18 mL) se trató con hidruro de sodio (0,796 g, 19,89 mmol). La mezcla se agitó a TA durante 10 minutos antes de tratarse con bromuro de tetrabutilamonio (2,91 g, 9,04 mmol) y *N*-bencil-2-cloro-*N*-(2-cloroetil)etanamina clorhidrato (1,781 g, 6,63 mmol). La mezcla de reacción se agitó durante 5 minutos, se entibió hasta alcanzar 50°C durante 1 hora y luego se entibió hasta alcanzar 80°C durante 1,5 horas. La mezcla luego se dejó enfriar hasta alcanzar TA. La mezcla de reacción se aplacó mediante la adición de solución de cloruro de amonio saturado acuoso y luego se extrajo con acetato de etilo. La solución orgánica se lavó tres veces con agua y luego se secó ($MgSO_4$), se filtró y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 10% - 70% acetato de etilo en DCM, para proporcionar el material deseado como una espuma incolora (2,23 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 0,92 - 0,96 (2H, m), 0,97 - 1,02 (2H, m), 1,32 (3H, d), 1,92 - 2,00 (2H, m), 2,24 - 2,31 (1H, m), 2,40 - 2,49 (2H, m), 2,68 - 2,74 (2H, m), 2,88 - 2,92 (2H, m), 3,29 (1H, dt), 3,40 (2H, s), 3,55 (1H, dt), 3,70 (1H, dd), 3,79 (1H, d), 3,98 - 4,09 (2H, m), 4,28 (1H,br, s), 6,63 (1H, s), 7,21 - 7,33 (5H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 491, 493; HPLC tR = 2,71 min.

La preparación de 2-cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 22: 1-[4-[4-[1-Bencil-4-(3,5-difluorofenil)sulfonilpiperidin-4-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea



Una corriente de nitrógeno se hizo pasar a través de ácido [4-(3-ciclopropilureido)fenilborónico, pinacol éster (121 mg, 0,40 mmol), 4-[1-bencil-4-(3,5-difluorofenil)sulfonilpiperidin-4-il]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (225 mg,

0,40 mmol) y carbonato de sodio acuoso 2M (0,719 mL, 1,44 mmol) en DMF (0,8 mL), DME (5 mL), etanol (5 mL) y agua (12,5 mL) a 25°C durante 15 minutos. La mezcla de reacción se trató con diclorobis(trifenilfosfina)-paladio(II) (14,02 mg, 0,02 mmol) y la mezcla se agitó a 80°C durante 2 horas. La mezcla se repartió entre DCM y agua. La solución orgánica se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 2M en metanol. El material aislado se purificó adicionalmente mediante cromatografía en sílice, eluyendo con 10% - 60% acetato de etilo en DCM, para proporcionar el material deseado como una película seca incolora (125 mg).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 0,67 - 0,71 (2H, m), 0,85 - 0,90 (2H, m), 1,36 (3H, d), 1,77 - 1,98 (2H, m), 2,47 - 2,67 (3H, m), 2,74 (2H, t), 2,85 - 2,96 (2H, m), 3,30 - 3,38 (3H, m), 3,64 (1H, dt), 3,76 - 3,87 (2H, m), 4,08 (1H, dd), 4,16 (1H, d), 4,40 - 4,51 (1H, m), 4,92 (1H, s), 6,63 (1H, s), 6,80 - 6,86 (1H, m), 6,95 - 7,03 (3H, m), 7,20 - 7,31 (5H, m), 7,39 (2H, d), 7,93 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 703,6; HPLC tR = 2,97 min.

Ensayo de mTOR Quinasa (Echo): 0,503μM

La preparación de 4-[1-bencil-4-(3,5-difluorofenil)sulfonilpiperidin-4-il]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describe a continuación.

4-[1-Bencil-4-(3,5-difluorofenil)sulfonilpiperidin-4-il]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Una mezcla de 2-cloro-4-[(3,5-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (874 mg, 2,16 mmol) en NMP (10 mL) se trató con hidruro de sodio (299 mg, 7,47 mmol) y se agitó durante 5 minutos a TA. Se agregaron bromuro de tetrabutilamonio (698 mg, 2,16 mmol) y *N*-bencil-2-cloro-*N*-(2-cloroetil)etanamina clorhidrato (669 mg, 2,49

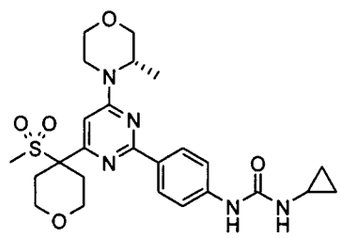
mmol) y la mezcla se calentó a 80°C durante 2 horas. La mezcla de reacción se aplacó mediante la adición de solución de cloruro de amonio saturado acuoso y luego se extrajo con acetato de etilo. La solución orgánica se secó ($MgSO_4$), se filtró y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 10% -50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido incoloro (582 mg).

Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 1,35 (3H, d), 1,85 - 1,93 (2H, m), 2,41 - 2,49 (2H, m), 2,55 (2H, d), 2,88 - 2,93 (2H, m), 3,32 (1H, dt), 3,38 (2H, s), 3,59 (1H, dt), 3,74 (1H, dd), 3,81 (1H, d), 3,98 - 4,08 (2H, m), 4,31 (1H, br, s), 6,64 (1H, s), 6,97 - 7,11 (3H, m), 7,22 - 7,33 (5H, m).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 563, 565; HPLC tR = 3,18 min.

La preparación de 2-cloro-4-[(3,5-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 23: 3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]urea



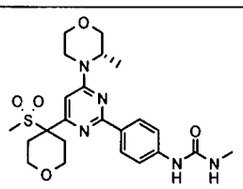
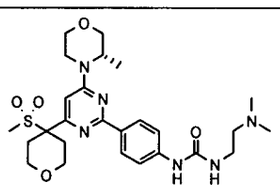
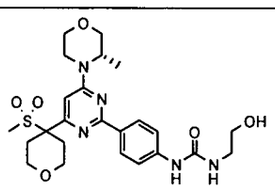
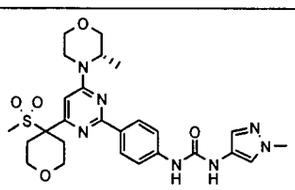
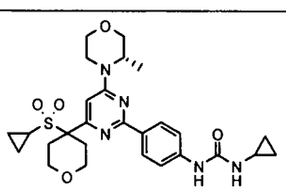
Se agregó ciclopropilamina (0,100 mL, 1,45 mmol) a fenil *N*-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]carbamato (100 mg, 0,18 mmol) en DMF (2 mL). La solución resultante se agitó a 60°C durante 4 horas. La mezcla se evaporó hasta secarse y el residuo se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (67 mg).

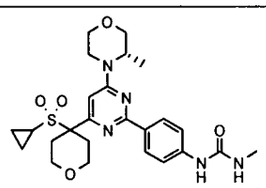
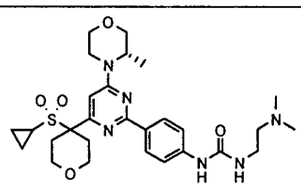
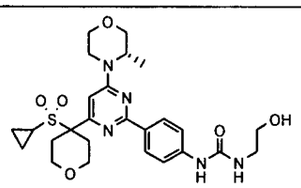
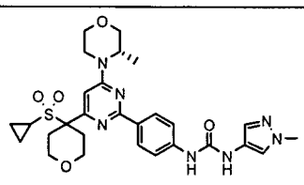
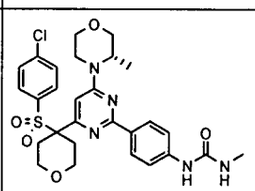
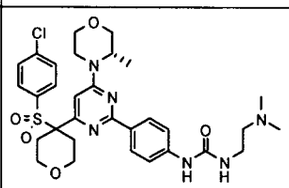
Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 0,71 (2H, ddd), 0,89 (2H, ddd), 1,35 (3H, d), 2,54 (3H, ddd), 2,64 (1H, m), 2,71 (3H, s), 2,72 (2H, br.d), 3,34 (1H, ddd), 3,42 (1H, ddd), 3,62 (1H, ddd), 3,77 (1H, dd), 3,84 (1H, d), 4,05 (3H, m), 4,20 (1H, d), 4,46 (1H, br.d), 4,89 (1H, s), 6,64 (1H, s), 7,00 (1H, s), 7,51 (2H, d), 8,31 (2H, d).

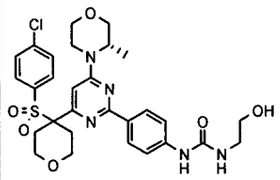
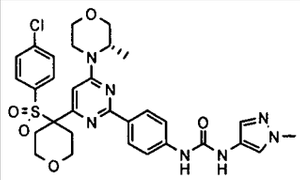
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 516; HPLC tR = 1,92 min.

Ensayo de mTOR Quinasa (Echo): 0,00492μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]carbamato, fenil *N*-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
23a		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]urea	490	1,77
23b		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]urea	547	1,84
23c		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]urea	520	1,61
23d		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	554 (M-H)-	1,83
23e		3-ciclopropil-1-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	542	2,07

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
23f		1-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	516	1,89
23g		1-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	573	1,96
23h		1-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	546	1,72
23i		1-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	580 (M-H)-	1,93
23j		1-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	586	2,26
23k		1-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	643	2,31

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
23l		1-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	616	2,05
23m		1-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	652	2,26

Ejemplo 23a: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,35 (3H, d), 2,54 (2H, ddd), 2,71 (3H, s), 2,72 (2H, d), 2,89 (3H, d), 3,35 (1H, ddd), 3,41 (2H, dd), 3,62 (1H, ddd), 3,76 (1H, dd), 3,84 (1H, d), 4,0-4,1 (3H, m), 4,19 (1H, d), 4,46 (1H, br.d), 4,62 (1H, br.q), 6,32 (1H, s), 6,64 (1H, s), 7,40 (2H, d), 8,31 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00459μM

Ejemplo 23b: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,35 (3H, d), 2,32 (6H, s), 2,5-2,6 (4H, m), 2,71 (3H, s), 2,72 (2H, d), 3,3-3,4 (3H, m), 3,41 (2H, ddd), 3,62 (1H, ddd), 3,76 (1H, dd), 3,84 (1H, d), 4,0-4,1 (3H, m), 4,19 (1H, d), 4,46 (1H, br.d), 5,22 (1H, br.t), 6,62 (1H, s), 7,44 (2H, d), 8,28 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,197μM

Ejemplo 23c: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,35 (3H, d), 2,5-2,6 (3H, m), 2,71 (3H, s), 2,72 (2H, d), 3,34 (1H, ddd), 3,41 (2H, dd), 3,45 (4H, dt), 3,62 (1H, ddd), 3,76 (1H, dd), 3,78 (2H, m), 3,84 (1H, d), 4,0-4,1 (3H, m), 4,19 (1H, d), 4,45 (1H, br.d), 5,25 (1H, t), 6,64 (1H, s), 6,86 (1H, s), 7,41 (2H, d), 8,30 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,000831μM

Ejemplo 23d: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,35 (3H, d), 2,54 (2H, ddd), 2,72 (3H, s), 2,72 (2H, m), 3,33 (1H, ddd), 3,41 (2H, dd), 3,61 (1H, ddd), 3,75 (1H, dd), 3,83 (1H, d), 3,90 (3H, s), 4,0-4,1 (3H, m), 4,18 (1H, d), 4,45 (1H, br.d), 6,25 (1H, br.s), 6,64 (1H, s), 6,78 (1H, s), 7,41 (1H, s), 7,44 (2H, d), 7,61 (1H, s), 8,29 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00534μM

Ejemplo 23e: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 0,71 (2H, ddd), 0,83 (2H, m), 0,89 (2H, ddd), 1,02 (2H, m), 1,34 (3H, d), 2,18 (1H, tt), 2,53 (2H, ddd), 2,64 (1H, tt), 2,82 (2H, br.d), 3,34 (2H, ddd), 3,43 (3H, ddd), 3,63 (1H, ddd), 3,77 (1H, dd), 3,84 (1H, d), 4,02 (2H, m), 4,06 (1H, dd), 4,19 (1H, d), 4,46 (1H, br.d), 4,86 (1H, s), 6,67 (1H, s), 6,97 (1H, s), 7,51 (2H, d), 8,33 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00876μM

Ejemplo 23f: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 0,83 (2H, m), 1,02 (2H, m), 1,34 (3H, d), 2,18 (1H, tt), 2,52 (2H, m), 2,82 (2H, br.d), 2,86 (3H, d), 3,33 (1H, ddd), 3,42 (2H, ddd), 3,62 (1H, ddd), 3,76 (1H, dd), 3,83 (1H, d), 4,01 (2H, m), 4,05 (1H, dd), 4,18 (1H, d), 4,45 (1H, br.d), 4,83 (1H, q), 6,63 (1H, s), 6,67 (1H, s), 7,40 (2H, d), 8,31 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,0199μM

Ejemplo 23g: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 0,82 (2H, m), 1,01 (2H, m), 1,34 (3H, d), 2,18 (1H, tt), 2,32 (6H, s), 2,52 (4H, m), 2,82 (2H, d), 3,32 (3H, m), 3,43 (2H, ddd), 3,62 (1H, ddd), 3,76 (1H, dd), 3,83 (1H, d), 4,01 (2H, m), 4,05 (2H, dd), 4,18 (1H, d), 4,46 (1H, br.d), 5,30 (1H, br.t), 6,66 (1H, s), 7,44 (2H, d), 8,30 (2H, d).

Ensayo de mTOR Quinasa (Echo): 1,21μM

Ejemplo 23h: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 0,83 (2H, m), 1,02 (2H, m), 1,34 (3H, d), 2,18 (1H, tt), 2,53 (3H, m), 2,82 (2H, br.d), 3,33 (1H, ddd), 3,43 (2H, dd), 3,46 (2H, t), 3,62 (1H, ddd), 3,76 (1H, dd), 3,78 (2H, t), 3,83 (1H, d), 4,01 (2H, m), 4,05 (1H, dd), 4,18 (1H, d), 4,45 (1H, br.d), 5,26 (1H, t), 6,67 (1H, s), 6,85 (1H, s), 7,40 (2H, d), 8,32 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00808μM

Ejemplo 23i: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 0,84 (2H, m), 1,03 (2H, m), 1,34 (3H, d), 2,19 (1H, tt), 2,53 (2H, m), 2,82 (2H, br.d), 3,33 (1H, ddd), 3,42 (2H, ddd), 3,61 (1H, ddd), 3,76 (1H, dd), 3,83 (1H, d), 3,92 (3H, s), 4,02 (2H, m), 4,05 (1H, dd), 4,17 (1H, d), 4,45 (1H, br.d), 6,03 (1H, s), 6,60 (1H, s), 6,67 (1H, s), 7,42 (2H, d), 7,43 (1H, s), 7,60 (1H, s), 8,31 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,0254μM

Ejemplo 23j: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,36 (3H, d), 2,55 (2H, td), 2,64 (2H, br.d), 2,87 (3H, d), 3,30 (1H, ddd), 3,34 (1H, ddd), 3,65 (1H, ddd), 3,79 (1H, dd), 3,86 (1H, d), 3,99 (2H, m), 4,08 (1H, dd), 4,16 (1H, d), 4,45 (1H, br.d), 4,64 (1H, br.q), 6,29 (1H, s), 6,62 (1H, s), 7,27 (4H, m), 7,39 (2H, d), 7,83 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,0314μM

Ejemplo 23k: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,36 (3H, d), 2,32 (6H, s), 2,52 (2H, t), 2,55 (2H, ddd), 2,63 (2H, d), 3,26 - 3,37 (5H, m), 3,64 (1H, ddd), 3,79 (1H, dd), 3,85 (1H, d), 3,98 (2H, m), 4,07 (1H, dd), 4,17 (1H, d), 4,45 (1H, br.d), 5,18 (1H, br.t), 6,61 (1H, s), 7,27 (2H, d), 7,32 (2H, d), 7,39 (2H, d), 7,80 (2H, d).

Ensayo de mTOR Quinasa (Echo): 1,14μM

Ejemplo 23l: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,36 (3H, d), 2,37 (1H, t), 2,55 (4H, ddd), 2,64 (2H, br.d), 3,26 - 3,37 (3H, m), 3,46 (2H, dt), 3,64 (1H, ddd), 3,77 - 3,81 (3H, m), 3,86 (1H, d), 3,99 (2H, m), 4,08 (1H, dd), 4,16 (1H, d), 4,45 (1H, br.d), 5,07 (1H, t), 6,49 (1H, s), 6,63 (1H, s), 7,26 (2H, d), 7,28 (2H, d), 7,39 (2H, d), 7,84 (2H, d).

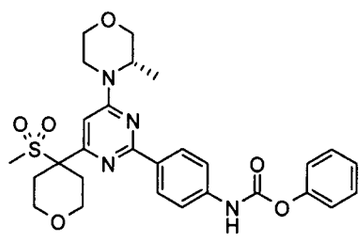
Ensayo de mTOR Quinasa (Echo): 0,00888μM

Ejemplo 23m: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,35 (3H, d), 2,53 (3H, ddd), 2,64 (2H, br.d), 3,26 - 3,37 (3H, m), 3,64 (1H, ddd), 3,78 (21H, dd), 3,85 (1H, d), 3,91 (3H, s), 3,99 (2H, m), 4,07 (1H, dd), 4,15 (1H, d), 4,44 (1H, br.d), 6,11 (1H, s), 6,61 (1H, s), 6,63 (1H, s), 7,28 (2H, d), 7,32 (2H, d), 7,41 (2H, d), 7,42 (1H, s), 7,61 (1H, s), 7,84 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,0577μM

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]fenil]carbamato



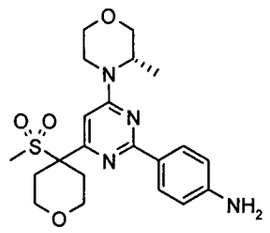
Se agregó gota a gota fenil cloroformiato (0,196 mL, 1,56 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]anilina (615 mg, 1,42 mmol) e hidrogenocarbonato de sodio (179 mg, 2,13 mmol) en dioxano (50 mL) a TA. La suspensión resultante se agitó a TA durante 2 horas. La mezcla de reacción se concentró, se diluyó con acetato de etilo (100 mL) y se lavó secuencialmente con agua (2 x 100 mL) y salmuera saturada (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 40 a 80%

acetato de etilo en *iso*-hexano, para proporcionar el material deseado como un sólido blanco (714 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,36 (3H, d), 2,55 (2H, m), 2,71 (3H, s), 2,73 (2H, d), 3,35 (1H, ddd), 3,42 (2H, ddd), 3,62 (1H, ddd), 3,77 (1H, dd), 3,84 (1H, d), 4,02 - 4,08 (3H, m), 4,20 (1H, d), 4,47 (1H, br.d), 6,66 (1H, s), 7,11 (1H, s), 7,21 (2H, d), 7,26 (1H, dd), 7,41 (2H, dd), 7,54 (2H, d), 8,35 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 553; HPLC tR = 2,57 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidin-2-il]anilina

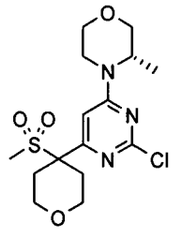


Se agregó carbonato de sodio (2M en agua, 5,75 mL, 11,49 mmol) a 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,839 g, 3,83 mmol) y 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidina (1,200 g, 3,19 mmol) en una mezcla de éter dietílico de etilenglicol (10 mL), etanol (10 mL), DMF (10 mL) y agua (20 mL) a TA bajo nitrógeno. La mezcla se desgasificó y se purgó con nitrógeno. Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,112 g, 0,16 mmol) y la mezcla se desgasificó y se purgó con nitrógeno. La suspensión resultante se agitó bajo nitrógeno a 80°C durante 90 minutos. La mezcla de reacción se concentró y se diluyó con acetato de etilo (150 mL) y se lavó secuencialmente con agua (2 x 150 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 40 a 100% acetato de etilo en *iso*-hexano, para proporcionar el material deseado como un sólido blanco (690 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,34 (3H, d), 2,53 (2H, ddd), 2,70 (3H, s), 2,72 (2H, br.d), 3,33 (1H, ddd), 3,41 (2H, ddd), 3,61 (1H, ddd), 3,76 (1H, dd), 3,83 (1H, d), 3,93 (2H, s), 4,03 (3H, m), 4,18 (1H, d), 4,45 (1H, br.d), 6,58 (1H, s), 6,71 (2H, d), 8,18 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 433; HPLC tR = 1,98 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(4-metilsulfoniloxan-4-il)pirimidina



Se agregó *terc*-butóxido de sodio (1,38 g, 14,39 mmol) en porciones a una mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina (2,00 g, 6,54 mmol) y bis(2-bromoetil) éter (2,055 mL, 16,35 mmol) en DMF (75 mL) a 0°C durante un período de 10 minutos bajo nitrógeno. La solución resultante se dejó entibiar hasta alcanzar TA y se agitó durante 7 horas. Se agregó más *terc*-butóxido de sodio (629 mg, 6,54 mmol) en porciones y la solución se agitó a TA durante otras 45 horas. La mezcla de reacción se concentró, se diluyó con acetato de etilo (200 mL) y se lavó secuencialmente con agua (2 x 200 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 40 a 100% acetato de etilo en *iso*-hexano. Las fracciones puras se evaporaron hasta secarse y el residuo se cristalizó a partir de acetato de etilo / *iso*-hexano para proporcionar el material deseado como un sólido cristalino blanco (1,42 g).

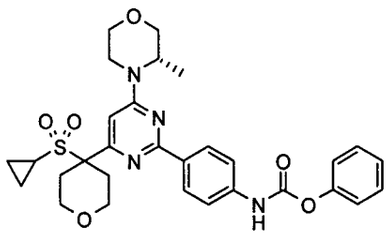
Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,34 (3H, d), 2,50 (2H, m), 2,55 (2H, m), 2,73 (3H, s), 3,33 (3H, m), 3,56 (1H, ddd), 3,71 (1H, dd), 3,80 (1H, d), 4,01 (4H, m), 4,31 (1H, br.s), 6,62 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 376, 378; HPLC tR = 1,85 min.

La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

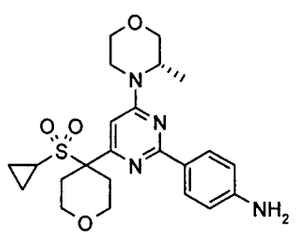


Se agregó fenil cloroformiato (0,211 mL, 1,68 mmol) a 4-[4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (700 mg, 1,53 mmol) e hidrogenocarbonato de sodio (192 mg, 2,29 mmol) en 1,4-dioxano (50 mL) a TA. La suspensión resultante se agitó a TA durante 16 horas. La mezcla de reacción se concentró y se diluyó con acetato de etilo (75 mL) y se lavó secuencialmente con agua (75 mL) y salmuera saturada (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 70% acetato de etilo en *iso*-hexano, para proporcionar el material deseado como un sólido blanco (850 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 0,83 (2H, m), 1,02 (2H, m), 1,35 (3H, d), 2,18 (1H, tt), 2,54 (2H, m), 2,83 (2H, d), 3,34 (2H, ddd), 3,43 (2H, dd), 3,63 (1H, ddd), 3,77 (1H, dd), 3,84 (1H, d), 4,02 (2H, m), 4,06 (1H, dd), 4,20 (1H, d), 4,47 (1H, br.d), 6,69 (1H, s), 7,08 (1H, s), 7,21 (2H, d), 7,26 (1H, dd), 7,41 (2H, dd), 7,54 (2H, d), 8,37 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 579,5; HPLC tR = 2,72 min.

4-[4-(4-Ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



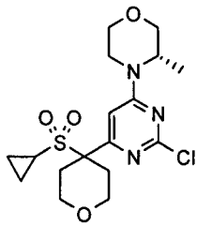
Carbonato de sodio (2M en agua, 7,48 mL, 14,96 mmol) se agregó a 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,092 g, 4,99 mmol) y 2-cloro-4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidina (1,67 g, 4,16 mmol) en una mezcla de éter dietílico de etilenglicol (10 mL), etanol (10 mL), DMF (10 mL) y agua (20 mL) a TA bajo nitrógeno. La mezcla se desgasificó y se purgó con nitrógeno. Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,146 g, 0,21 mmol) y la mezcla se desgasificó y se purgó con nitrógeno. La suspensión resultante se agitó bajo nitrógeno a 80°C durante 90 minutos. La

mezcla de reacción se concentró y se diluyó con acetato de etilo (150 mL) y se lavó secuencialmente con agua (2 x 150 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 40 a 70% acetato de etilo en *iso*-hexano, para proporcionar el material deseado como un sólido blanco (740 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 0,82 (2H, m), 1,01 (2H, m), 1,33 (3H, d), 2,17 (1H, tt), 2,51 (2H, m), 2,82 (2H, br.d), 3,32 (1H, ddd), 3,43 (2H, ddd), 3,62 (1H, ddd), 3,76 (1H, dd), 3,83 (1H, d), 3,91 (2H, s), 3,98 (2H, m), 4,05 (1H, dd), 4,17 (1H, d), 4,45 (1H, br.d), 6,62 (1H, s), 6,71 (2H, d), 8,21 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 459; HPLC tR = 2,05 min.

2-Cloro-4-(4-ciclopropilsulfoniloxan-4-il)-6-[(3S)-3-metilmorfolin-4-il]pirimidina



Se agregó *terc*-butóxido de sodio (1,738 g, 18,08 mmol) en porciones a 2-cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,00 g, 6,03 mmol) y bis(2-bromoetil) éter (2,273 mL, 18,08 mmol) en DMF (75 mL) a TA durante un período de 5 minutos bajo nitrógeno. La solución resultante se agitó a TA durante 5 horas. Se agregaron más bis(2-bromoetil) éter (0,758 mL, 6,03 mmol) y *terc*-butóxido de sodio (0,579 g, 6,03 mmol) y la solución se agitó a TA durante otras 20 horas. La mezcla de reacción se aplacó con solución de cloruro de amonio saturado acuoso (0,5 mL), se concentró, se diluyó con acetato de etilo (200 mL) y se lavó secuencialmente con agua (2 x 200 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 40 a 60% acetato de etilo en *iso*-hexano, para proporcionar el material deseado como un aceite incoloro que cristalizó en reposo (1,734 g).

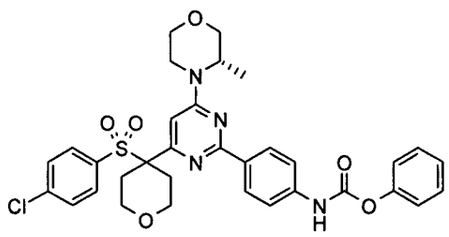
Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,01 (2H, m), 1,01 (2H, m), 1,33 (3H, d), 2,22 (1H, tt), 2,47 (2H, ddd), 2,64 (2H, br.d), 3,30 (1H, ddd), 3,36 (2H, dd), 3,56 (1H, ddd), 3,71 (1H, dd), 3,80 (1H, d), 3,97 - 4,04 (4H, m), 4,30 (1H, br.d), 6,66 (1H, s).

Espectro de LCMS: m/z (ESI-)$(M-H)^-$ = 400,4; HPLC tR = 2,04 min.

La preparación de 2-cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

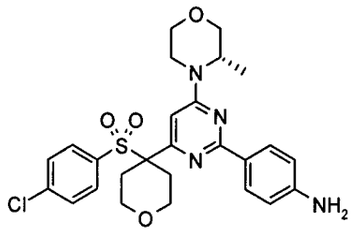


Se agregó fenil cloroformiato (0,198 mL, 1,58 mmol) a 4-[4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (759 mg, 1,43 mmol) e hidrogenocarbonato de sodio (181 mg, 2,15 mmol) en 1,4-dioxano (50 mL) a TA. La suspensión resultante se agitó a TA durante 16 horas. La mezcla de reacción se concentró y se diluyó con acetato de etilo (75 mL) y se lavó secuencialmente con agua (75 mL) y salmuera saturada (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 70% acetato de etilo en *iso*-hexano, para proporcionar el material deseado como una película seca blanca (780 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,36 (3H, d), 2,56 (2H, ddd), 2,64 (2H, br.d), 3,31 (2H, ddd), 3,35 (1H, ddd), 3,65 (1H, ddd), 3,80 (1H, dd), 3,86 (1H, d), 4,00 (2H, m), 4,08 (1H, dd), 4,18 (1H, d), 4,45 (1H, br.d), 6,64 (1H, s), 7,04 (1H, s), 7,21 (2H, d), 7,22 (1H, dd), 7,27 (2H, d), 7,39 (2H, d), 7,40 (2H, dd), 7,43 (2H, d), 7,87 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 649, 651; HPLC tR = 3,02 min.

4-[4-[4-(4-Clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

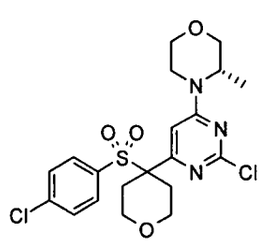


Se agregó carbonato de sodio (2M en agua, 4,02 mL, 8,05 mmol) a 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (490 mg, 2,24 mmol) y 2-cloro-4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidina (1056 mg, 2,24 mmol) en una mezcla de etanol (10 mL), agua (20 mL), DMF (10 mL) y éter dietílico de etilenglicol (10 mL) a TA bajo nitrógeno. La mezcla se desgasificó y se purgó con nitrógeno. Se agregó cloruro de bis(trifenilfosfina)paladio(II) (78 mg, 0,11 mmol) y la mezcla se desgasificó y se purgó con nitrógeno. La suspensión resultante se agitó a 80°C durante 2 horas. La mezcla de reacción se concentró y se diluyó con acetato de etilo (100 mL) y agua (100 mL). El precipitado resultante se retiró mediante la filtración. La capa orgánica se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL), se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 50% acetato de etilo en *iso*-hexano, para proporcionar el material deseado como una película seca blanca (790 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,35 (3H, d), 2,54 (2H, ddd), 2,63 (2H, d), 3,27 - 3,35 (3H, m), 3,64 (1H, ddd), 3,79 (1H, dd), 3,85 (1H, d), 3,87 (2H, s), 3,98 (2H, m), 4,06 (1H, dd), 4,16 (1H, d), 4,44 (1H, br.d), 6,56 (1H, s), 6,60 (2H, d), 7,27 (2H, d), 7,39 (2H, d), 7,69 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 529,5, 531,5; HPLC tR = 2,49 min.

2-Cloro-4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidina



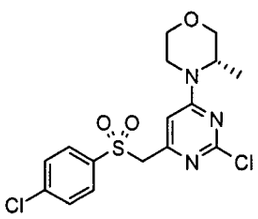
Se agregó *terc*-butóxido de sodio (1,566 g, 16,30 mmol) en porciones a 2-cloro-4-[(4-clorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,873 g, 4,66 mmol) y bis(2-bromoetil) éter (1,463 mL, 11,64 mmol) en DMF (75 mL) a TA durante un período de 5

minutos bajo nitrógeno. La solución resultante se agitó a TA durante 6 horas. Se agregó más *terc*-butóxido de sodio (0,895 g, 9,31 mmol) y la solución se agitó a TA durante otros 4 días. La mezcla de reacción se concentró y se diluyó con acetato de etilo (200 mL) y se lavó secuencialmente con agua (2 x 200 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 40 a 50% acetato de etilo en *iso*-hexano, para proporcionar el material deseado como una película seca blanca (1,0 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,35 (3H, d), 2,45 - 2,49 (4H, m), 3,22 - 3,35 (3H, m), 3,59 (1H, ddd), 3,73 (1H, dd), 3,82 (1H, d), 3,95 - 4,00 (3H, m), 4,04 (1H, dd), 4,31 (1H, br.s), 6,67 (1H, s), 7,39 (2H, d), 7,45 (2H, d).

Espectro de LCMS: m/z (ESI-)(M-H)- = 470, 472; HPLC tR = 2,62 min.

2-Cloro-4-[(4-clorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



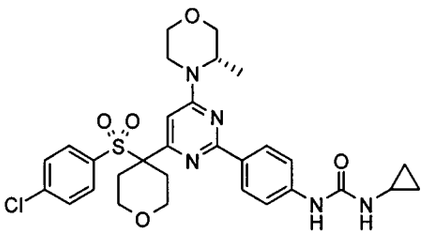
Se agregó sal de sodio de ácido 4-clorobencenosulfínico (5,39 g, 27,15 mmol) en una porción a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (8,00 g, 22,63 mmol) en acetonitrilo (400 mL) a TA. La suspensión resultante se agitó a 85°C bajo reflujo durante 5 horas. La mezcla de reacción se concentró y se diluyó con DCM (400 mL) y se lavó con agua (400 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 25 a 40% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blanco (6,90 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,33 (3H, d), 3,30 (1H, ddd), 3,55 (1H, ddd), 3,70 (1H, dd), 3,80 (1H, d), 4,02 (2H, m), 4,28 (1H, br.s), 4,29 (2H, s), 6,55 (1H, s), 7,51 (2H, d), 7,70 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 402, 404; HPLC tR = 2,26 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 24: 1-[4-[4-[4-(4-Clorofenil)sulfoniloxan-4-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea



Se agregó carbonato de sodio (0,381 mL, 0,76 mmol) a 2-cloro-4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidina (100 mg, 0,21 mmol) y ácido 4-(3-ciclopropilureido)fenilborónico (47 mg, 0,21 mmol) en DME (2 mL), etanol (2 mL), DMF (2 mL) y agua (4 mL) a TA bajo nitrógeno. La mezcla se desgasificó y se purgó con nitrógeno luego se agregó cloruro de bis(trifenilfosfina)paladio(II) (7,4 mg, 0,011 mmol) y la mezcla se agitó a 85°C durante 2 horas. La mezcla de reacción se concentró, se diluyó con acetato de etilo (25 mL) y se lavó secuencialmente con agua (2 x 25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 50% acetato de etilo en isohexano. El material aislado se purificó adicionalmente trituración con éter dietílico para proporcionar el material deseado como un sólido blanco (26 mg).

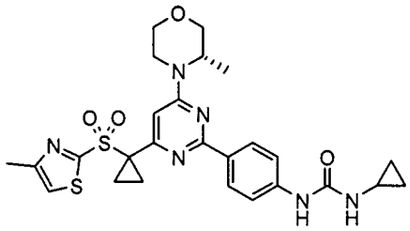
Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 0,70 (2H, m), 0,88 (2H, m), 1,36 (3H, d), 2,58 (5H, m), 3,31 (2H, m), 3,34 (1H, ddd), 3,65 (1H, ddd), 3,79 (1H, dd), 3,86 (1H, d), 3,99 (2H, m), 4,08 (1H, dd), 4,17 (1H, d), 4,45 (1H, d), 4,88 (1H, s), 6,63 (1H, s), 6,94 (1H, s), 7,27 (2H, d), 7,39 (2H, d), 7,39 (2H, d), 7,84 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 612, 6144; HPLC tR = 2,48 min.

Ensayo de mTOR Quinasa (Echo): 0,00517μM

La preparación de 2-cloro-4-[4-(4-clorofenil)sulfoniloxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 25: 3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea



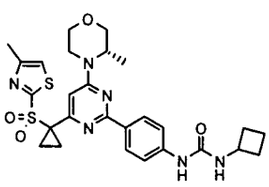
A ciclopropilamina (57 mg, 1 mmol) se agregó una solución de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]carbamato (100 mg, 0,17 mmol) en DMF (1,5 mL). Luego se agregó trietilamina (0,082 mL, 0,59 mmol) y la mezcla resultante se calentó hasta alcanzar 50°C y se agitó durante toda la noche (~18 horas). La mezcla de reacción se enfrió y luego se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) en acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (50 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,21 (3H, d), 1,75 - 1,80 (2H, m), 1,93 - 1,97 (2H, m), 2,47 - 2,49 (3H, m), 2,51 - 2,58 (1H, m), 3,17 (1H, td), 3,47 (1H, td), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,10 - 4,20 (1H, m), 4,41 - 4,48 (1H, m), 6,41 (1H, d), 6,77 (1H, s), 7,41 - 7,44 (2H, m), 7,83 (1H, d), 7,87 - 7,90 (2H, m), 8,52 (1H, s).

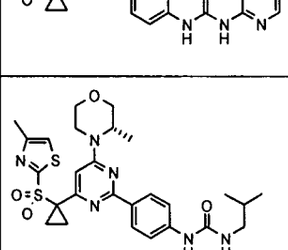
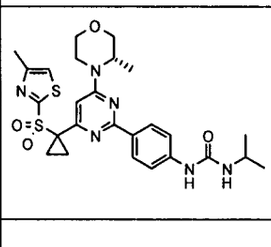
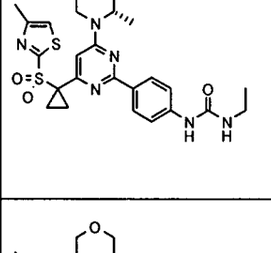
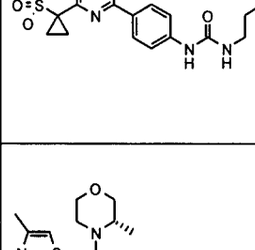
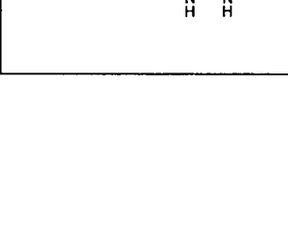
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 555; HPLC tR = 2,13 min.

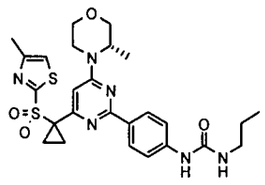
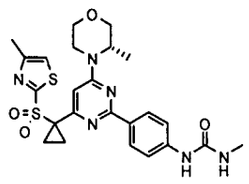
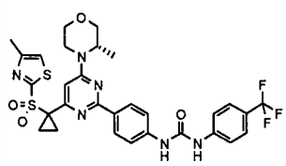
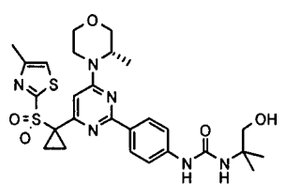
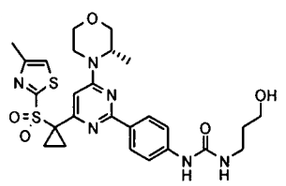
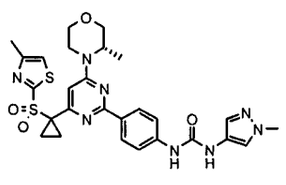
Ensayo de mTOR Quinasa (Echo): 0,00155μM

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
25a		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	569,6	1,90

1162.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
25b		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-piridin-2-ilurea	592,4	2,51
25c		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-(2-metilpropil)urea	571,4	2,42
25d		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-propan-2-ilurea	557,4	2,26
25e		1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	543,4	2,08
25f		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	586,4	1,98
25g		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	559,3	1,78

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
25h		3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-1-propilurea	557,4	2,26
25i		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	529,3	1,94
25j		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	659,3	2,9
25k		3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	587,4	2,05
25l		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	573,4	1,82
25m		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	595,4	1,99

Ejemplo 25a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,56 - 1,67 (2H, m), 1,75 - 1,79 (2H, m), 1,82 - 1,88 (2H, m), 1,93 - 1,95 (2H, m), 2,16 - 2,24 (2H, m), 2,48 (3H, s), 3,17 (1H, td), 3,46 (1H, td), 3,61 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,08 - 4,20 (2H, m), 4,41 - 4,49 (1H, m), 6,45 (1H, d), 6,77 (1H, s), 7,39 (2H, d), 7,83 - 7,88 (3H, m), 8,57 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00224μM

Ejemplo 25b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,78 - 1,82 (2H, m), 1,95 - 1,99 (2H, m), 2,49 - 2,50 (3H, m), 3,20 (1H, td), 3,48 (1H, td), 3,63 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,13 - 4,21 (1H, m), 4,43 - 4,50 (1H, m), 6,81 (1H, s), 7,02 - 7,05 (1H, m), 7,53 - 7,62 (3H, m), 7,75 - 7,79 (1H, m), 7,85 - 7,87 (1H, m), 7,96 - 7,99 (2H, m), 8,29 - 8,31 (1H, m), 9,42 (1H, s), 10,53 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000817μM

Ejemplo 25c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (6H, d), 1,21 (3H, d), 1,65 - 1,75 (1H, m), 1,75 - 1,80 (2H, m), 1,93 - 1,98 (2H, m), 2,48 - 2,49 (3H, m), 2,94 (2H, t), 3,18 (1H, td), 3,47 (1H, td), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,12 - 4,20 (1H, m), 4,41 - 4,49 (1H, m), 6,22 (1H, t), 6,77 (1H, s), 7,39 - 7,42 (2H, m), 7,83 - 7,84 (1H, m), 7,87 - 7,90 (2H, m), 8,62 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00385μM

Ejemplo 25d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11 (6H, d), 1,21 (3H, d), 1,76 - 1,80 (2H, m), 1,93 - 1,97 (2H, m), 2,48 - 2,49 (3H, m), 3,18 (1H, td), 3,47 (1H, td), 3,62 (1H, dd), 3,73 - 3,81 (2H, m), 3,97 (1H, dd), 4,12 - 4,19 (1H, m), 4,41 - 4,48 (1H, m), 6,03 (1H, d), 6,77 (1H, s), 7,38 - 7,41 (2H, m), 7,84 - 7,84 (1H, m), 7,87 - 7,90 (2H, m), 8,51 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00157μM

Ejemplo 25e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,21 (3H, d), 1,76 - 1,80 (2H, m), 1,94 - 1,97 (2H, m), 2,48 - 2,49 (3H, m), 3,09 - 3,21 (3H, m), 3,47 (1H, td), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,12 - 4,19 (1H, m), 4,41 - 4,49 (1H, m), 6,15 (1H, t), 6,77 (1H, s), 7,39 - 7,43 (2H, m), 7,83 - 7,84 (1H, m), 7,86 - 7,90 (2H, m), 8,65 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000277μM

Ejemplo 25f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,26 (3H, d), 1,81 - 1,85 (2H, m), 1,99 - 2,02 (2H, m), 2,23 (6H, s), 2,39 (2H, t), 2,53 - 2,54 (3H, m), 3,19 - 3,27 (3H, m), 3,52 (1H, td), 3,67 (1H, dd), 3,81 (1H, d), 4,02 (1H, dd), 4,17 - 4,24 (1H, m), 4,47 - 4,53 (1H, m), 6,20 (1H, t), 6,82 (1H, s), 7,44 - 7,47 (2H, m), 7,88 - 7,90 (1H, m), 7,92 - 7,95 (2H, m), 8,92 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0547μM

Ejemplo 25g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,76 - 1,80 (2H, m), 1,93 - 1,97 (2H, m), 2,47 - 2,48 (3H, m), 3,13 - 3,21 (3H, m), 3,43 - 3,50 (3H, m), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,12 - 4,19 (1H, m), 4,41 - 4,49 (1H, m), 4,73 (1H, t), 6,23 (1H, t), 6,77 (1H, s), 7,39 - 7,42 (2H, m), 7,83 - 7,84 (1H, m), 7,87 - 7,90 (2H, m), 8,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00119μM

Ejemplo 25h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,21 (3H, d), 1,46 (2H, sexteto), 1,76 - 1,80 (2H, m), 1,94 - 1,97 (2H, m), 2,48 - 2,49 (3H, m), 3,06 (2H, q), 3,14 - 3,21 (1H, m), 3,47 (1H, td), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,12 - 4,19 (1H, m), 4,41 - 4,49 (1H, m), 6,19 (1H, t), 6,77 (1H, s), 7,39 - 7,43 (2H, m), 7,83 - 7,84 (1H, m), 7,86 - 7,90 (2H, m), 8,63 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000993μM

Ejemplo 25i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,76 - 1,80 (2H, m), 1,94 - 1,97 (2H, m), 2,48 – 2,49(3H, m), 2,66 (3H, d), 3,18 (1H, td), 3,47 (1H, td), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,11 - 4,20 (1H, m), 4,40 - 4,50 (1H, m), 6,05 (1H, q), 6,77 (1H, s), 7,40 - 7,44 (2H, m), 7,83 - 7,84 (1H, m), 7,86 - 7,90 (2H, m), 8,72 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,001μM

Ejemplo 25j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,77 - 1,81 (2H, m), 1,95 - 1,99 (2H, m), 2,48 - 2,49 (3H, m), 3,19 (1H, td), 3,48 (1H, td), 3,63 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,13 - 4,21 (1H, m), 4,42 - 4,51 (1H, m), 6,80 (1H, s), 7,49 - 7,52 (2H, m), 7,63 - 7,70 (4H, m), 7,85 - 7,86 (1H, m), 7,95 - 7,98 (2H, m), 9,03 (1H, s), 9,12 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00576μM

Ejemplo 25k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,24 (6H, s), 1,76 - 1,79 (2H, m), 1,94 - 1,97 (2H, m), 2,48 - 2,49 (3H, m), 3,18 (1H, td), 3,39 (2H, d), 3,47 (1H, td), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,12 - 4,19 (1H, m), 4,41 - 4,48 (1H, m), 4,95 (1H, t), 5,98 (1H, s), 6,76 (1H, s), 7,34 - 7,39 (2H, m), 7,84 - 7,89 (3H, m), 8,72 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00292μM

Ejemplo 25l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,60 (2H, quinteto), 1,76 - 1,80 (2H, m), 1,94 - 1,97 (2H, m), 2,48 - 2,49 (3H, m), 3,14 - 3,21 (3H, m), 3,44 - 3,50 (3H, m), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,12 - 4,19 (1H, m), 4,42 - 4,49 (2H, m), 6,18 (1H, t), 6,77 (1H, s), 7,39 - 7,43 (2H, m), 7,83 - 7,84 (1H, m), 7,86 - 7,90 (2H, m), 8,69 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000956μM

Ejemplo 25m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,77 - 1,80 (2H, m), 1,94

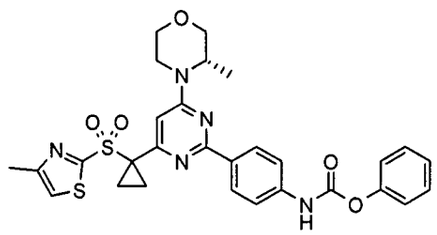
1466

- 1,98 (2H, m), 2,48 - 2,49 (3H, m), 3,15 - 3,22 (1H, m), 3,48 (1H, td), 3,62 (1H, dd), 3,75 - 3,79 (4H, m), 3,97 (1H, dd), 4,13 - 4,20 (1H, m), 4,42 - 4,49 (1H, m), 6,79 (1H, s), 7,38 - 7,39 (1H, m), 7,44 - 7,49 (2H, m), 7,77 (1H, s), 7,84 - 7,85 (1H, m), 7,90 - 7,94 (2H, m), 8,38 (1H, s), 8,83 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00025μM

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]carbamato

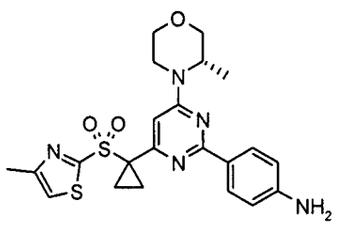


Una solución de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]anilina (1,56 g, 3,31 mmol) en 1,4-dioxano (18 mL) se trató con bicarbonato de sodio (0,445 g, 5,29 mmol). Luego se agregó gota a gota fenil cloroformiato (0,5 mL, 3,99 mmol) y la suspensión resultante se agitó a TA, bajo nitrógeno durante 150 minutos. La mezcla de reacción se evaporó hasta secarse y el residuo se repartió entre DCM (100 mL) y agua (50 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), se filtró y se evaporó hasta proporcionar una goma/espuma ámbar que se trituró bajo isohexano / éter dietílico (~1:1 v/v,~100 mL) con sonicación y el sólido resultante se recogió mediante filtración por succión y se secó, al vacío, a 50°C, para proporcionar el material deseado como un sólido beige (1,72 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15 (3H, d), 1,71 - 1,75 (2H, m), 1,87 - 1,91 (2H, m), 2,40 - 2,41 (3H, m), 3,12 (1H, td), 3,40 (1H, td), 3,55 (1H, dd), 3,69 (1H, d), 3,90 (1H, dd), 4,07 - 4,14 (1H, m), 4,35 - 4,44 (1H, m), 6,75 (1H, s), 7,16 - 7,23 (3H, m), 7,35 - 7,40 (2H, m), 7,47 - 7,50 (2H, m), 7,76 - 7,77 (1H, m), 7,90 - 7,93 (2H, m), 10,32 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 592,1; HPLC tR = 2,87 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]anilina

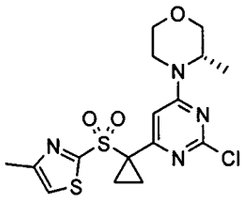


Una mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidina (1,9 g, 4,58 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,36 g, 6,21 mmol) y solución de carbonato de sodio acuoso 2M (5,72 mL, 11,45 mmol) en una mezcla de etanol (5,50 mL), DME (11 mL), agua (5,50 mL) y DMF (0,7 mL) se purgó con nitrógeno durante 10 minutos antes de agregar cloruro de bis(trifenilfosfina)paladio(II) (0,161 g, 0,23 mmol). La mezcla de reacción luego se calentó hasta alcanzar 85°C y se agitó durante 3 horas. La mezcla de reacción se enfrió y se repartió entre acetato de etilo (150 mL) y agua (250 mL), la capa orgánica se separó y lo acuoso se extrajo nuevamente con acetato de etilo (100 mL). Los orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se evaporaron hasta secarse para proporcionar el producto bruto, que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 25 a 75% acetato de etilo en isohexano. El material aislado se purificó adicionalmente mediante trituración con isohexano caliente y éter dietílico para proporcionar el material deseado como un sólido beige (1,6 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,73 - 1,77 (2H, m), 1,92 - 1,95 (2H, m), 2,48 - 2,49 (3H, m), 3,15 (1H, td), 3,46 (1H, td), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,08 - 4,16 (1H, m), 4,37 - 4,45 (1H, m), 5,52 (2H, s), 6,50 - 6,54 (2H, m), 6,67 (1H, s), 7,70 - 7,74 (2H, m), 7,82 - 7,84 (1H, m).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 472,1; HPLC tR = 2,24 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidina

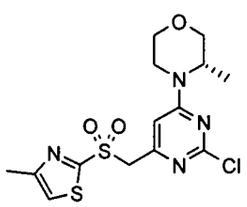


Una solución de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina (3,29 g, 8,46 mmol) en tolueno (45 mL) se trató con 1,2-dibromoetano (1,4 mL, 16,25 mmol). Luego se agregó bromuro de tetrabutilamonio (0,273 g, 0,85 mmol) seguido por una solución de hidróxido de sodio (3,4 g, 85,01 mmol) en agua (3,4 mL). La mezcla resultante se calentó hasta alcanzar 65°C, bajo una atmósfera de nitrógeno, durante 1 hora luego a 75°C durante 2,5 horas. La mezcla se dejó enfriar y se repartió entre acetato de etilo (60 mL) y agua (30 mL). La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$), se filtró y se evaporó hasta proporcionar una goma marrón. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 25 a 75% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (2,76 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,12 (3H, d), 1,63 - 1,66 (2H, m), 1,81 - 1,85 (2H, m), 2,39 - 2,41 (3H, m), 3,11 (1H, td), 3,32 - 3,38 (1H, m), 3,49 (1H, dd), 3,65 (1H, d), 3,82 - 3,92 (2H, m), 4,16 - 4,27 (1H, m), 6,83 (1H, s), 7,81 - 7,84 (1H, m).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 415,10; HPLC tR = 2,12 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina



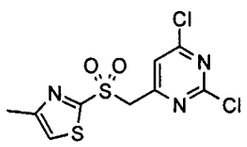
Una solución de 2,4-dicloro-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina (8,35 g, 25,76 mmol) en DCM (100 mL) se enfrió hasta alcanzar 4°C. Luego se agregó trietilamina (4,3 mL, 30,85 mmol) y la mezcla se agitó durante 5 minutos antes de la adición gota a gota, durante 10 minutos, de una solución de (S)-3-metilmorfolina (2,9 g, 28,67 mmol) en DCM (25 mL). La mezcla de reacción luego se agitó en un baño de enfriamiento durante 45 minutos luego a TA durante toda la noche. Se agregó agua (200 mL) a la mezcla de reacción y se agitó durante 10 minutos antes de que la capa orgánica se separara y la capa acuosa se extrajo con DCM (50

mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el producto bruto, que se purificó mediante cromatografía de sílice instantánea, eluyendo con 50% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (5,80 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 2,49 - 2,50 (3H, m), 3,18 (1H, td), 3,43 (1H, td), 3,58 (1H, dd), 3,72 (1H, d), 3,88 - 3,96 (2H, m), 4,15 - 4,29 (1H, m), 4,82 (2H, s), 6,80 (1H, s), 7,89 - 7,90 (1H, m).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 389,2; HPLC tR = 1,87min.

2,4-Dicloro-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina

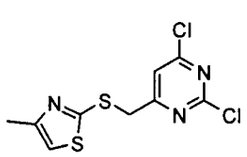


Una solución de 2,4-dicloro-6-[(4-metil-1,3-tiazol-2-il)sulfanilmetil]pirimidina (7,39 g, 25,29 mmol) en DCM (130 ml) se enfrió hasta alcanzar 4°C y se trató en porciones, durante 15 minutos con ácido 3-cloroperoxibenzoico (13,60 g, 60,70 mmol). La suspensión resultante se agitó en un baño de enfriamiento durante 15 minutos luego a TA durante 24 horas. Una solución saturada acuosa de bicarbonato de sodio (200 mL) se agregó a la mezcla de reacción y se agitó durante 30 minutos. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un aceite que solidificó en reposo (8,40 g). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 2,47 - 2,49 (3H, m), 5,19 (2H, s), 7,84 (1H, s), 7,93 - 7,95 (1H, m).

Espectro de LCMS: m/z (ESI-) (M-H)- = 322,0; HPLC tR = 1,53 min.

2,4-Dicloro-6-[(4-metil-1,3-tiazol-2-il)sulfanilmetil]pirimidina



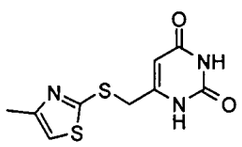
Una suspensión de 6-[(4-metil-1,3-tiazol-2-il)sulfanilmetil]-1*H*-pirimidina-2,4-diona (14,4 g, 56,40 mmol) en oxicloruro de fósforo (60 mL, 643,70 mmol) se entibió hasta alcanzar 100°C

y se agitó durante 6 horas. La mezcla de reacción se enfrió antes de evaporarse hasta proporcionar un aceite marrón y repartirse entre DCM (100 mL) y agua (100 mL). Luego se agregó cuidadosamente con agitación hidrogenocarbonato de sodio sólido para ajustar la mezcla a pH8; durante este tiempo se agregaron alícuotas adicionales de agua (100 mL) y DCM (100 mL). Se agregaron más DCM (100 mL) y agua (100 mL) y la capa orgánica se separó y la capa acuosa se extrajo nuevamente con DCM (2 x 100 mL). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se evaporaron hasta secarse para proporcionar el material deseado como un sólido tostado (15,76 g). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 2,30 - 2,32 (3H, m), 4,55 (2H, s), 7,22 - 7,24 (1H, m), 7,84 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 292,1; HPLC tR = 2,36min.

6-[(4-Metil-1,3-tiazol-2-il)sulfanilmetil]-1*H*-pirimidina-2,4-diona

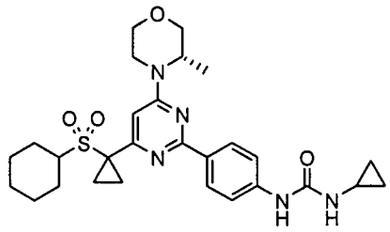


A una solución de 4-metiltiazol-2-tiol (10 g, 76,21 mmol) en DMF (150 mL) a TA se agregó DBU (14 mL, 93,80 mmol) gota a gota durante 5 minutos. La solución resultante se agitó a TA durante 30 minutos. Luego se agregó en porciones 6-(clorometil)-1*H*-pirimidina-2,4-diona (10 g, 62,28 mmol) durante un período de 20 minutos bajo nitrógeno. La solución resultante se agitó a TA durante 19 horas y luego la mezcla de reacción se evaporó hasta secarse y el residuo se repartió entre DCM (150 mL) y agua (150 mL). El precipitado sólido se recogió mediante filtración para proporcionar el material deseado como un sólido crema (11,1 g). El material deseado adicional (4,3 g) se obtuvo después de que el filtrado se acidificó con ácido clorhídrico 2M y el precipitado resultante se recogió mediante filtración.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 2,34 (3H, s), 4,08 (2H, s), 5,43 (1H, s), 7,27 (1H, s), 10,98 (2H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 256,2; HPLC tR = 0,58 min.

Ejemplo 26: 1-[4-[4-(1-Ciclohexilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea



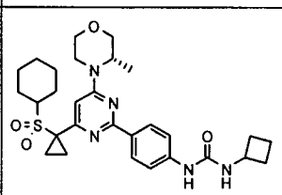
A ciclopropilamina (56 mg, 0,98 mmol) se agregó una solución de fenil *N*-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (79,5 mg, 0,14 mmol) en DMF (2 mL). Luego se agregó trietilamina (0,067 mL, 0,48 mmol) y la mezcla resultante se calentó hasta alcanzar 50°C y se agitó durante 2 horas. La mezcla de reacción se enfrió y se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% TFA) y acetonitrilo como eluyentes, seguido por purificación mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) en acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (28 mg).

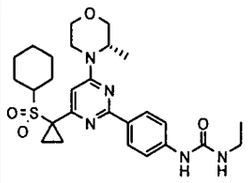
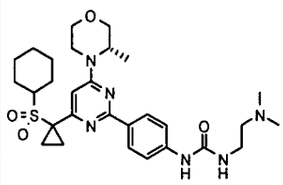
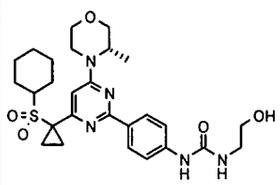
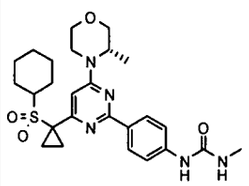
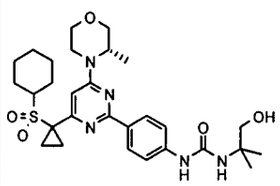
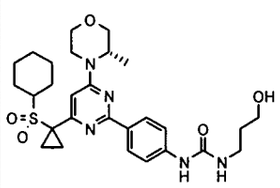
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,63 - 0,67 (2H, m), 1,13 - 1,29 (6H, m), 1,37 - 1,66 (7H, m), 1,82 - 1,88 (2H, m), 2,26 - 2,34 (2H, m), 2,53 - 2,59 (1H, m), 3,16 - 3,25 (1H, m), 3,44 - 3,53 (2H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 - 4,26 (1H, m), 4,49 - 4,59 (1H, m), 6,47 (1H, d), 6,76 (1H, s), 7,50 - 7,54 (2H, m), 8,19 - 8,23 (2H, m), 8,58 (1H, s).

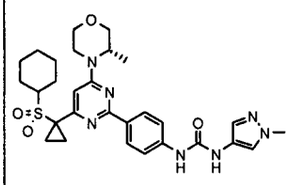
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 540; HPLC tR = 2,57 min.

Ensayo de mTOR Quinasa (Echo): 0,00605μM

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
26a		3-ciclobutil-1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	554	2,81

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
26b		3-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	528	2,56
26c		1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	571	2,53
26d		1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	544	2,15
26e		1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	514	2,39
26f		1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	572	2,27
26g		1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	558	2,21

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
26h		1-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	580	2,40

Ejemplo 26a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 - 1,28 (6H, m), 1,37 - 1,69 (9H, m), 1,81 - 1,92 (4H, m), 2,17 - 2,25 (2H, m), 2,26 - 2,34 (2H, m), 3,20 (1H, td), 3,44 - 3,52 (2H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,09 - 4,25 (2H, m), 4,50 - 4,58 (1H, m), 6,49 (1H, d), 6,76 (1H, s), 7,47 - 7,50 (2H, m), 8,19 - 8,22 (2H, m), 8,60 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00672μM

Ejemplo 26b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,13 - 1,29 (6H, m), 1,36 - 1,66 (7H, m), 1,81 - 1,89 (2H, m), 2,26 - 2,35 (2H, m), 3,09 - 3,16 (2H, m), 3,20 (1H, td), 3,45 - 3,53 (2H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 - 4,25 (1H, m), 4,50 - 4,58 (1H, m), 6,20 (1H, t), 6,76 (1H, s), 7,48 - 7,52 (2H, m), 8,18 - 8,23 (2H, m), 8,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0039μM

Ejemplo 26c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,12 - 1,29 (6H, m), 1,36 - 1,66 (7H, m), 1,82 - 1,88 (2H, m), 2,18 (6H, s), 2,27 - 2,35 (4H, m), 3,16 - 3,24 (3H, m), 3,44 - 3,52 (2H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 - 4,25 (1H, m), 4,50 - 4,58 (1H, m), 6,17 (1H, t), 6,76 (1H, s), 7,47 - 7,51 (2H, m), 8,19 - 8,23 (2H, m), 8,90 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,119μM

Ejemplo 26d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11 - 1,28 (6H, m), 1,38 - 1,65 (7H, m), 1,81 - 1,88 (2H, m), 2,27 - 2,34 (2H, m), 3,16 - 3,24 (3H, m), 3,44 - 3,52 (4H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 - 4,25 (1H, m), 4,50 - 4,58 (1H, m), 4,73 (1H, t), 6,27 (1H, t), 6,76 (1H, s), 7,48 - 7,51 (2H, m), 8,19 - 8,23 (2H, m), 8,83 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0012μM

Ejemplo 26e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 - 1,29 (6H, m), 1,37 - 1,66 (7H, m), 1,82 - 1,88 (2H, m), 2,27 - 2,34 (2H, m), 2,66 (3H, d), 3,20 (1H, td), 3,45 - 3,53 (2H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 - 4,25 (1H, m), 4,50 - 4,59 (1H, m), 6,09 (1H, q), 6,76 (1H, s), 7,49 - 7,53 (2H, m), 8,19 - 8,22 (2H, m), 8,77 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00395μM

Ejemplo 26f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,12 - 1,29 (12H, m), 1,37 - 1,67 (7H, m), 1,82 - 1,88 (2H, m), 2,27 - 2,34 (2H, m), 3,20 (1H, td), 3,39 (2H, d), 3,45 - 3,53 (2H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 - 4,25 (1H, m), 4,49 - 4,59 (1H, m), 4,95 (1H, t), 6,01 (1H, s), 6,75 (1H, s), 7,44 - 7,47 (2H, m), 8,18 - 8,22 (2H, m), 8,77 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00457μM

Ejemplo 26g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 - 1,29 (6H, m), 1,37 - 1,66 (9H, m), 1,81 - 1,88 (2H, m), 2,27 - 2,34 (2H, m), 3,14 - 3,24 (3H, m), 3,44 - 3,52 (4H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,18 - 4,24 (1H, m), 4,47 (1H, t), 4,50 - 4,58 (1H, m), 6,23 (1H, t), 6,76 (1H, s), 7,48 - 7,52 (2H, m), 8,19 - 8,22 (2H, m), 8,74 (1H, s).

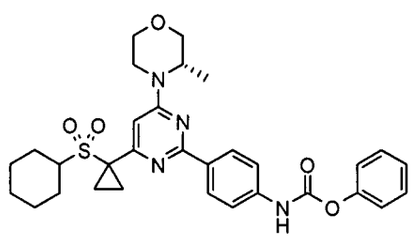
Ensayo de mTOR Quinasa (Echo): 0,00746μM

Ejemplo 26h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 - 1,30 (6H, m), 1,37 - 1,67 (7H, m), 1,82 - 1,89 (2H, m), 2,28 - 2,34 (2H, m), 3,21 (1H, td), 3,45 - 3,53 (2H, m), 3,64 (1H, dd), 3,74 - 3,79 (4H, m), 3,98 (1H, dd), 4,18 - 4,26 (1H, m), 4,51 - 4,59 (1H, m), 6,77 (1H, s), 7,39 (1H, d), 7,54 - 7,57 (2H, m), 7,77 (1H, s), 8,23 - 8,26 (2H, m), 8,42 (1H, s), 8,87 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,004μM

La preparación de fenil *N*-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



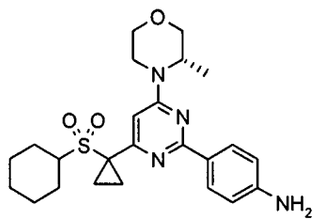
Una suspensión de 4-[4-(1-ciclohexilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (615 mg, 1,35 mmol) en 1,4-dioxano (7 mL) se trató con bicarbonato de sodio (182 mg, 2,17 mmol). Luego se agregó gota a gota fenil cloroformiato (0,20 mL, 1,59 mmol) y la mezcla resultante se dejó agitando bajo nitrógeno a TA durante toda la noche (~16 horas). La mezcla de reacción se evaporó hasta secarse y el residuo se repartió entre DCM (10 mL) y agua (10 mL). La capa orgánica se separó y se evaporó hasta proporcionar

una goma ámbar que se sometió a azeotropía con éter dietílico para proporcionar el material deseado como un sólido beige (726 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 - 1,29 (6H, m), 1,37 - 1,48 (2H, m), 1,50 - 1,65 (5H, m), 1,81 - 1,87 (2H, m), 2,26 - 2,34 (2H, m), 3,22 (1H, td), 3,44 - 3,52 (2H, m), 3,64 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,20 - 4,29 (1H, m), 4,52 - 4,60 (1H, m), 6,83 (1H, s), 7,23 - 7,30 (3H, m), 7,42 - 7,47 (2H, m), 7,63 - 7,67 (2H, m), 8,28 - 8,32 (2H, m), 10,45 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 577,1; HPLC tR = 3,12min.

4-[4-(1-Ciclohexilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

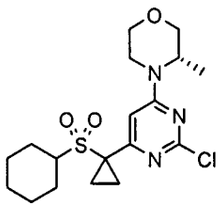


Una mezcla de 2-cloro-4-(1-ciclohexilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,78 g, 4,45 mmol) y 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,474 g, 6,73 mmol) en una mezcla de DMF (8 mL), etanol (8 mL), DME (8 mL) y agua (20 mL) se trató con solución de carbonato de sodio acuoso 2M (11 mL, 22,00 mmol). La mezcla resultante se purgó con nitrógeno durante 10 minutos antes de agregar cloruro de bis(trifenilfosfina)paladio(II) (0,156 g, 0,22 mmol). La mezcla se calentó hasta alcanzar 85°C y se agitó, bajo nitrógeno durante 4 horas antes de enfriarse y se repartió entre acetato de etilo (100 mL) y agua (100 mL). La mezcla bifásica se filtró y la capa orgánica se separó. La capa acuosa se extrajo nuevamente con acetato de etilo (2 x 50 mL) y los orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$) y se evaporaron para proporcionar el producto bruto, que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 25 a 75% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido beige (0,627 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 - 1,21 (6H, m), 1,31 - 1,49 (6H, m), 1,53 - 1,58 (1H, m), 1,74 - 1,82 (2H, m), 2,19 - 2,26 (2H, m), 3,07 - 3,14 (1H, m), 3,37 - 3,47 (2H, m), 3,55 (1H, dd), 3,68 (1H, d), 3,89 (1H, dd), 4,07 - 4,14 (1H, m), 4,40 - 4,48 (1H, m), 5,50 (2H, s), 6,54 (2H, d), 6,58 (1H, s), 7,98 (2H, d).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 457,3; HPLC tR = 2,55 min.

2-Cloro-4-(1-ciclohexilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

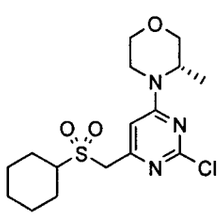


Una solución de 2-cloro-4-(ciclohexilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,8 g, 7,49 mmol) en tolueno (40 mL) se trató con 1,2-dibromoetano (1,3 mL, 15,09 mmol). Luego se agregó bromuro de tetrabutilamonio (0,241 g, 0,75 mmol) seguido por una solución de hidróxido de sodio (3,00 g, 74,89 mmol) en agua (3 mL). La mezcla resultante se calentó hasta alcanzar 64°C y se agitó durante 90 minutos. La mezcla de reacción se enfrió antes de agregar acetato de etilo (50 mL) y agua (20 mL). La mezcla se agitó durante 5 minutos luego la capa orgánica se separó, se lavó con salmuera (30 mL) y se evaporó para proporcionar el producto bruto, que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 25 a 75% acetato de etilo en isohexano, para proporcionar el compuesto deseado como un aceite amarillo claro que cristalizó en reposo (1,785 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,10 - 1,41 (8H, m), 1,48 - 1,55 (4H, m), 1,60 - 1,66 (1H, m), 1,77 - 1,84 (2H, m), 2,14 - 2,20 (2H, m), 3,16 - 3,24 (1H, m), 3,32 - 3,47 (2H, m), 3,58 (1H, dd), 3,72 (1H, d), 3,93 (1H, dd), 3,99 - 4,07 (1H, m), 4,32 - 4,43 (1H, m), 6,93 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 400,3; HPLC tR = 2,56 min.

2-Cloro-4-(ciclohexilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



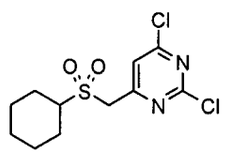
A una solución de 2,4-dicloro-6-(ciclohexilsulfonilmetil)pirimidina (1,7g, 5,50 mmol) en DCM (25 ml), enfriada con un baño de agua / hielo, se agregó trietilamina (0,85 mL, 6,10 mmol). La solución resultante se trató, gota a gota durante 5 minutos, con una solución de (S)-

3-metilmorfolina (0,658 g, 6,51 mmol) en DCM (5 mL). La mezcla se agitó en un baño de enfriamiento durante 30 minutos luego a TA durante 3 horas. Se agregó agua (25 mL) a la mezcla de reacción y se agitó durante 15 minutos. La capa orgánica se separó, se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto bruto, que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 25 a 75% acetato de etilo en isohexano, para proporcionar el material deseado como un aceite amarillo que cristalizó en reposo (1,3 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 - 1,45 (8H, m), 1,63 - 1,69 (1H, m), 1,81 - 1,87 (2H, m), 2,11 - 2,17 (2H, m), 3,16 - 3,25 (2H, m), 3,45 (1H, td), 3,60 (1H, dd), 3,73 (1H, d), 3,92 - 4,05 (2H, m), 4,26 - 4,34 (1H, m), 4,40 (2H, s), 6,90 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 374,3; HPLC tR = 2,22 min.

2,4-Dicloro-6-(ciclohexilsulfonilmetil)pirimidina

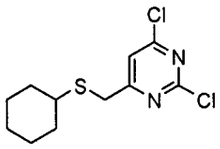


A una solución de 2,4-dicloro-6-(ciclohexilsulfanilmetil)pirimidina (4,23 g, 15,26 mmol) en DCM (90 mL), enfriada en un baño de agua / hielo, se agregó ácido 3-cloroperoxibenzoico (8,55 g, 38,15 mmol) durante un período de 30 minutos bajo nitrógeno, para mantener la temperatura por debajo de 10°C. La suspensión resultante se agitó a TA durante 3 horas. Una solución de hidrogenocarbonato de sodio acuoso saturado (120 mL) luego se agregó cuidadosamente en porciones y la mezcla de reacción se agitó durante 30 minutos antes de separarse la capa orgánica, secarse ($MgSO_4$) y evaporarse para proporcionar el material deseado como un sólido blancuzco (4,90 g). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 - 1,46 (5H, m), 1,62 - 1,68 (1H, m), 1,81 - 1,87 (2H, m), 2,10 - 2,16 (2H, m), 3,22 (1H, tt), 4,74 (2H, s), 7,85 (1H, s).

Espectro de LCMS: m/z (ESI-) (M-H)- = 307,2; HPLC tR = 2,22 min.

2,4-Dicloro-6-(ciclohexilsulfanilmetil)pirimidina

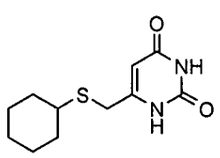


Una suspensión de 6-(ciclohexilsulfanilmetil)-1*H*-pirimidina-2,4-diona (6,4 g, 26,63 mmol) en oxicloruro de fósforo (25 mL, 268,2 mmol) se entibió hasta alcanzar 100°C, durante un período de 15 minutos. La solución naranja oscura resultante se agitó a 100°C durante 7 horas antes de enfriarse y se evaporó hasta proporcionar un aceite marrón. El aceite se repartió entre DCM (150 mL) y agua (150 mL). Luego se agregó cuidadosamente hidrogenocarbonato de sodio sólido con agitación para ajustar la mezcla a pH8 y durante la adición se agregaron alícuotas de agua (100 mL) y DCM (50 mL). La capa orgánica se separó, la capa acuosa se extrajo nuevamente con más DCM (2 x 75 mL) y las capas orgánicas combinadas se lavaron con salmuera (200 mL), se secaron ($MgSO_4$) y se evaporaron para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 15% acetato de etilo en isohexano, para proporcionar el material deseado como un líquido naranja (4,24 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 - 1,31 (5H, m), 1,51 - 1,57 (1H, m), 1,64 - 1,72 (2H, m), 1,86 - 1,92 (2H, m), 2,71 - 2,77 (1H, m), 3,85 (2H, s), 7,82 (1H, s).

Espectro de LCMS: m/z (ESI-) (M-H)- = 275,2 & 277,2 HPLC tR = 3,01 min.

6-(Ciclohexilsulfanilmetil)-1*H*-pirimidina-2,4-diona



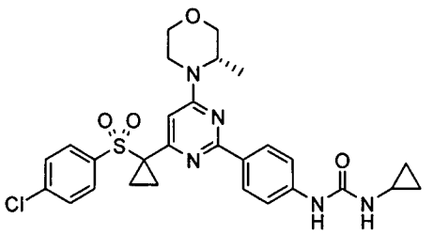
Una solución de ciclohexanotiol (10 mL, 81,74 mmol) en DMF (150 mL) a TA se trató con DBU (14 mL, 93,80 mmol). La solución resultante se agitó a TA durante 20 minutos luego 6-(clorometil)-1*H*-pirimidina-2,4-diona (10 g, 62,28 mmol) se agregó en porciones durante un período de 30 minutos, bajo nitrógeno, para mantener la temperatura interna por debajo de 35°C. La solución resultante se agitó a TA durante toda la noche. La mezcla de reacción se evaporó hasta secarse y el residuo se repartió entre DCM (100 mL) y agua (150 mL). Al mezclarse se formó un precipitado, esto se retiró mediante filtración para proporcionar el material deseado como un sólido blanco (6,45 g). El material deseado adicional (3,62 g) se

obtuvo separando el filtrado, ajustando la capa acuosa a pH_2 y recogiendo el precipitado resultante mediante filtración.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 - 1,34 (5H, m), 1,51 - 1,58 (1H, m), 1,63 - 1,72 (2H, m), 1,87 - 1,96 (2H, m), 2,65 - 2,72 (1H, m), 3,41 (2H, s), 5,49 (1H, s), 10,75 - 10,96 (2H, m).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 241,3; HPLC tR = 0,99min.

Ejemplo 27: 1-[4-[4-[1-(4-Clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea



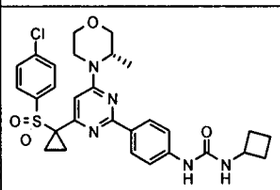
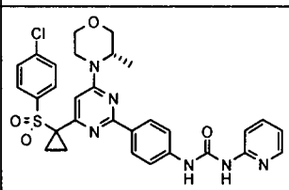
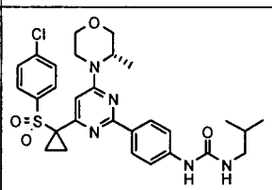
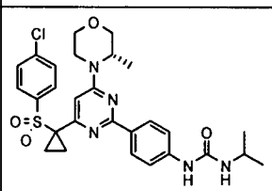
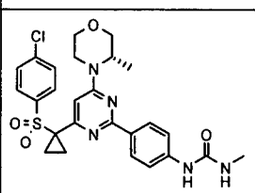
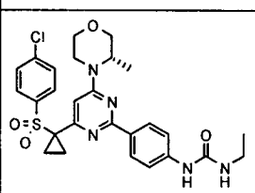
Se agregó ciclopropilamina (0,137 mL, 1,98 mmol) a fenil *N*-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (150 mg, 0,25 mmol) en DMF (2 mL). La solución resultante se agitó a 60°C durante 4 horas. La mezcla se evaporó hasta secarse y el residuo se repartió entre acetato de etilo (15 mL) y agua (15 mL). La capa orgánica se lavó con ácido cítrico acuoso 1M (15 mL) y agua (15 mL) y se evaporó hasta secarse. El residuo se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (62 mg).

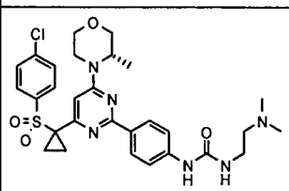
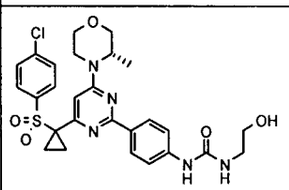
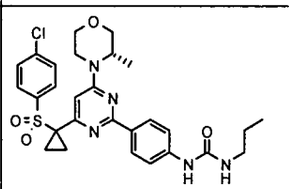
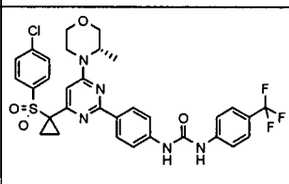
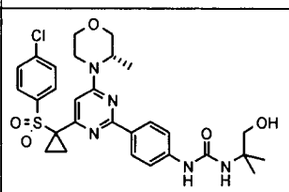
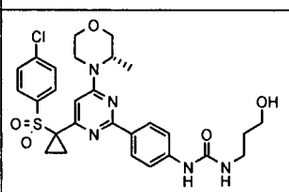
Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 0,69 (2H, m), 0,87 (2H, m), 1,32 (3H, d), 1,57 (1H, ddd), 1,64 (1H, ddd), 1,98 (2H, m), 2,63 (1H, m), 3,29 (1H, ddd), 3,59 (1H, ddd), 3,74 (1H, dd), 3,83 (1H, d), 4,04 (1H, dd), 4,14 (1H, d), 4,41 (1H, br.d), 4,87 (1H, s), 6,77 (1H, s), 6,93 (1H, s), 7,40 (2H, d), 7,42 (2H, d), 7,68 (2H, d), 7,99 (2H, d).

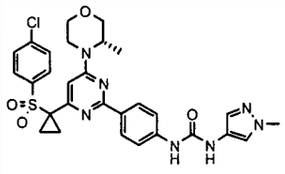
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 568, 570; HPLC tR = 2,33 min.

Ensayo de mTOR Quinasa (Echo): 0,00144μM

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
27a		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclobutilurea	582, 584	2,55
27b		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-ilurea	605, 607	2,73
27c		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea	584, 586	2,63
27d		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-ilurea	570, 572	2,47
27e		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	542, 544	2,17
27f		3-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	556, 558	2,33

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
27g		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-dimetilaminoetil)urea	599, 601	2,23
27h		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	572, 574	2,00
27i		3-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea	570, 572	2,48
27j		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	672, 674	3,09
27k		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	600, 602	2,28
27l		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	586, 588	2,04

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
27m		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	608, 610	2,38

Ejemplo 27a: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,59 (2H, m), 1,71 (2H, m), 1,84 (2H, m), 1,98 (2H, m), 2,38 (2H, m), 3,29 (1H, ddd), 3,59 (1H, ddd), 3,74 (1H, dd), 3,83 (1H, d), 4,04 (1H, dd), 4,13 (1H, d), 4,30 (1H, tt), 4,41 (1H, br.d), 4,82 (1H, d), 6,26 (1H, s), 6,76 (1H, s), 7,30 (2H, d), 7,40 (2H, d), 7,67 (2H, d), 7,98 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00388μM

Ejemplo 27b: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,32 (3H, d), 1,59 (1H, ddd), 1,66 (1H, ddd), 1,99 (2H, m), 3,30 (1H, ddd), 3,61 (1H, ddd), 3,75 (1H, dd), 3,83 (1H, d), 4,05 (1H, dd), 4,15 (1H, d), 4,42 (1H, m), 6,71 (1H, d), 6,78 (1H, s), 6,98 (1H, dd), 7,25 (1H, s), 7,41 (2H, d), 7,60 (2H, d), 7,66 (1H, ddd), 7,69 (2H, d), 8,03 (2H, d), 8,30 (1H, d), 11,92 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00425μM

Ejemplo 27c: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 0,94 (6H, d), 1,31 (3H, d), 1,56 (1H, ddd), 1,63 (1H, ddd), 1,80 (1H, m), 1,98 (2H, m), 3,10 (2H, dd), 3,29 (1H, ddd), 3,59 (1H, ddd), 3,74 (1H, dd), 3,82 (1H, d), 4,04 (1H, dd), 4,13 (1H, d), 4,41 (1H, br.d), 4,81 (1H, t), 6,41 (1H, s), 6,75 (1H, s), 7,30 (2H, d), 7,40 (2H, d), 7,67 (2H, d), 7,98 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,014μM

Ejemplo 27d: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,19 (6H, d), 1,31 (3H, d), 1,56 (1H, ddd), 1,63 (1H, ddd), 1,98 (2H, m), 3,29 (1H, ddd), 3,59 (1H, ddd), 3,74 (1H, dd), 3,82 (1H, d), 4,03 (2H, m), 4,13 (1H, d), 4,41 (1H, d), 4,54 (1H, br.d), 6,31 (1H, s), 6,75 (1H, s), 7,29 (2H, d), 7,40 (2H, d), 7,67 (2H, d), 7,97 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00307μM

Ejemplo 27e: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,32 (3H, d), 1,56 (1H, ddd), 1,62 (1H, ddd), 1,98 (2H, m), 2,87 (3H, d), 3,29 (1H, ddd), 3,59 (1H, ddd), 3,74 (1H, dd), 3,83 (1H, d), 4,04 (1H, dd), 4,13 (1H, d), 4,41 (1H, br.d), 4,65 (1H, q), 6,31 (1H, s), 6,76 (1H, s), 7,30 (2H, d), 7,40 (2H, d), 7,67 (2H, d), 7,98 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,000719μM

Ejemplo 27f: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,17 (3H, t), 1,31 (3H, d), 1,56 (1H, ddd), 1,62 (1H, ddd), 1,98 (2H, m), 3,28 (3H, ddd), 3,32 (3H, dq), 3,59 (1H, ddd), 3,74 (1H, dd), 3,82 (1H, d), 4,04 (1H, dd), 4,13 (1H, d), 4,41 (1H, br.d), 4,71 (1H, t), 6,38 (1H, s), 6,75 (1H, s), 7,30 (2H, d), 7,40 (2H, d), 7,67 (2H, d), 7,98 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,000959μM

Ejemplo 27g: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,56 (1H, ddd), 1,63 (1H, ddd), 1,97 (2H, m), 2,31 (6H, s), 2,51 (2H, t), 3,28 (3H, ddd), 3,32 (3H, dt), 3,59 (1H, ddd), 3,74 (1H, dd), 3,82 (1H, d), 4,04 (1H, dd), 4,14 (1H, d), 4,41 (1H, br.d), 5,25 (1H, br.t), 6,74 (1H, s), 7,26 (1H, s), 7,35 (2H, d), 7,40 (2H, d), 7,67 (2H, d), 7,95 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,0189μM

Ejemplo 27h: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,56 (1H, ddd), 1,62 (1H, ddd), 1,98 (2H, m), 2,64 (1H, br.s), 3,28 (1H, ddd), 3,43 (2H, dt), 3,59 (1H, ddd), 3,73 (1H, dd), 3,75 (2H, m), 3,82 (1H, d), 4,04 (1H, dd), 4,12 (1H, d), 4,40 (1H, br.d), 5,27 (1H, t), 6,73 (1H, s), 6,81 (1H, s), 7,31 (2H, d), 7,40 (2H, d), 7,67 (2H, d), 7,98 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,0000856μM

Ejemplo 27i: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 0,94 (3H, t), 1,31 (3H, d), 1,56 (2H, m), 1,56 (1H, ddd), 1,63 (1H, ddd), 1,98 (2H, m), 3,24 (2H, dt), 3,30 (1H, dd), 3,59 (1H, ddd), 3,74 (1H, dd), 3,82 (1H, d), 4,04 (1H, dd), 4,13 (1H, d), 4,41 (1H, br.d), 4,74 (1H, t), 6,36 (1H, s), 6,75 (1H, s), 7,30 (2H, d), 7,40 (2H, d), 7,67 (2H, d), 7,98 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00302μM

Ejemplo 27j: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,57 (1H, ddd), 1,63 (1H, ddd), 1,99 (2H, m), 3,29 (1H, ddd), 3,59 (1H, ddd), 3,74 (1H, dd), 3,83 (1H, d), 4,04 (1H, dd), 4,12 (1H, d), 4,40 (1H, br.d), 6,72 (1H, s), 6,77 (1H, s), 6,88 (1H, s), 7,37 (2H, d), 7,41 (2H, d), 7,50 (2H, d), 7,55 (2H, d), 7,69 (2H, d), 8,03 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00761μM

Ejemplo 27k: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,57 (1H, ddd), 1,63 (1H, ddd), 1,98 (2H, m), 3,29 (1H, ddd), 3,59 (1H, ddd), 3,64 (2H, d), 3,73 (1H, dd), 3,82 (1H, d), 4,04 (1H, dd), 4,13 (1H, d), 4,40 (1H, br.d), 4,45 (1H, t), 4,88 (1H, s), 6,54 (1H, s), 6,75 (1H, s), 7,27 (2H, d), 7,40 (2H, d), 7,67 (2H, d), 7,99 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00462μM

Ejemplo 27l: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,56 (1H, ddd), 1,62 (1H, ddd), 1,71 (2H, tt), 1,98 (2H, m), 2,94 (1H, br.s), 3,28 (1H, ddd), 3,44 (2H, dt), 3,59 (1H,

ddd), 3,72 (1H, br.s), 3,73 (1H, dd), 3,82 (1H, d), 4,04 (1H, dd), 4,12 (1H, d), 4,40 (1H, br.d), 5,13 (1H, t), 6,62 (1H, s), 6,74 (1H, s), 7,30 (2H, d), 7,40 (2H, d), 7,67 (2H, d), 7,98 (2H, d).

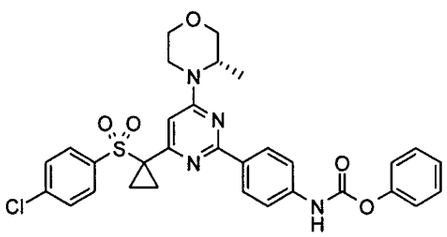
Ensayo de mTOR Quinasa (Echo): 0,00112µM

Ejemplo 27m: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,57 (1H, ddd), 1,63 (1H, ddd), 1,98 (2H, m), 3,29 (1H, ddd), 3,59 (1H, ddd), 3,74 (1H, dd), 3,83 (1H, d), 3,90 (3H, s), 4,04 (1H, dd), 4,13 (1H, d), 4,40 (1H, br.d), 6,12 (1H, s), 6,63 (1H, s), 6,76 (1H, s), 7,35 (2H, d), 7,40 (2H, d), 7,41 (1H, s), 7,60 (1H, s), 7,67 (2H, d), 7,99 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00144µM

La preparación de fenil *N*-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

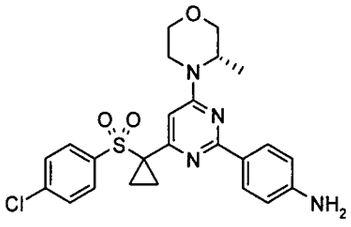


Se agregó gota a gota fenil cloroformiato (0,829 mL, 6,60 mmol) a 4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (3,20 g, 6,60 mmol) e hidrogenocarbonato de sodio (0,554 g, 6,60 mmol) en 1,4-dioxano (150 mL) a TA. La suspensión resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (400 mL) y se lavó con agua (2 x 400 mL) y salmuera saturada (200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como una película seca blanca (3,78 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,32 (3H, d), 1,57 (1H, ddd), 1,64 (1H, ddd), 1,99 (2H, m), 3,30 (1H, ddd), 3,60 (1H, ddd), 3,74 (1H, dd), 3,83 (1H, d), 4,05 (1H, dd), 4,15 (2H, br.d), 4,42 (1H, br.d), 6,78 (1H, s), 7,04 (1H, s), 7,20 (2H, d), 7,25 (2H, dd), 7,40 (2H, d), 7,40 (2H, dd), 7,45 (2H, d), 7,68 (2H, d), 8,02 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 605, 607; HPLC tR = 3,15 min.

4-[4-[1-(4-Clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

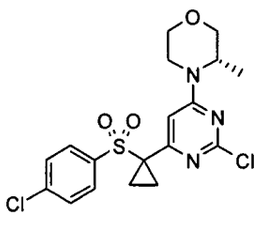


Se agregó carbonato de sodio (13,45 mL, 26,89 mmol) a 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,637 g, 7,47 mmol), 2-cloro-4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,20 g, 7,47 mmol) en una mezcla de DME (20 mL), DMF (20 mL), etanol (20 mL) y agua (40 mL) a TA bajo nitrógeno. La mezcla se desgasificó y se purgó con nitrógeno antes de que se agregara cloruro de bis(trifenilfosfina)paladio(II) (0,262 g, 0,37 mmol) y la mezcla se agitó a 80°C bajo nitrógeno durante 90 minutos. La mezcla de reacción se concentró y se diluyó con acetato de etilo (250 mL) y se lavó secuencialmente con agua (2 x 200 mL) y salmuera saturada (150 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 45% acetato de etilo en isohexano, para proporcionar el material deseado como una película beige seca (3,32 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,30 (3H, d), 1,56 (1H, ddd), 1,62 (1H, ddd), 1,96 (2H, m), 3,27 (1H, ddd), 3,59 (1H, ddd), 3,73 (1H, dd), 3,81 (1H, d), 3,86 (2H, s), 4,03 (1H, dd), 4,13 (1H, br.d), 4,41 (1H, br.d), 6,63 (2H, d), 6,70 (1H, s), 7,40 (2H, d), 7,67 (2H, d), 7,85 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 485, 487; HPLC tR = 2,70 min.

2-Cloro-4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó solución de hidróxido de sodio 10N (7,46 mL, 74,57 mmol) a 2-cloro-4-[(4-clorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,00 g, 7,46 mmol), 1,2-

1486

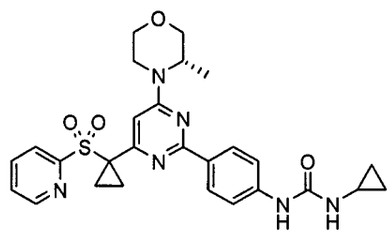
dibromoetano (1,285 mL, 14,91 mmol) y bromuro de tetrabutilamonio (0,240 g, 0,75 mmol) en tolueno (50 mL). La solución resultante se agitó a 60°C durante 1 hora. La mezcla de reacción se concentró, se diluyó con acetato de etilo (300 mL), se lavó con agua (2 x 300 mL) y salmuera saturada (200 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como una película seca blanca (2,85 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,54 (1H, ddd), 1,60 (1H, ddd), 1,95 (2H, m), 3,27 (1H, ddd), 3,54 (1H, ddd), 3,69 (1H, dd), 3,79 (1H, d), 4,01 (2H, m), 4,27 (1H, br.s), 6,87 (1H, s), 7,46 (2H, d), 7,64 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 428, 430; HPLC tR = 2,51 min.

La preparación de 2-cloro-4-[(4-clorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 28: 3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea



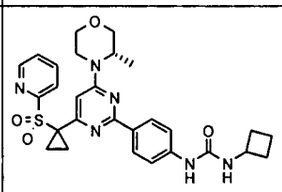
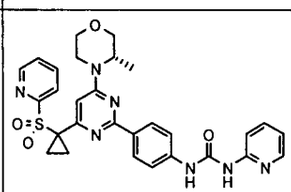
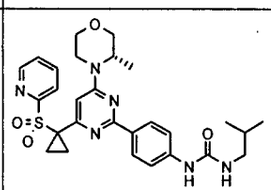
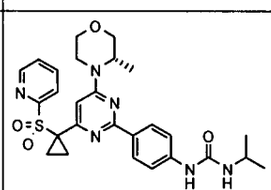
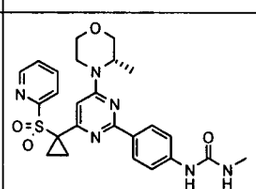
Se agregó ciclopropilamina (0,76 mmol) en una porción a fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato (104 mg, 0,19 mmol), en DMF (2 mL) a TA bajo nitrógeno. La solución resultante se agitó a TA durante 60 minutos. La mezcla de reacción se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (49 mg).

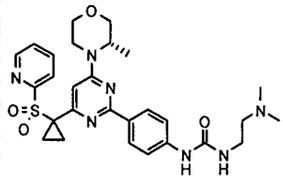
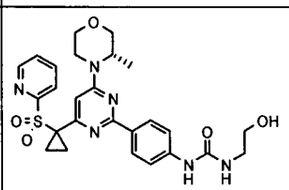
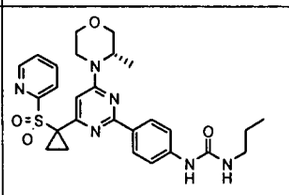
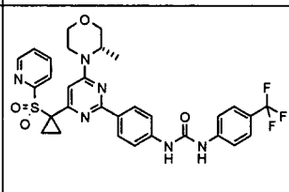
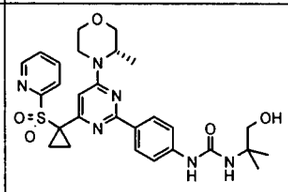
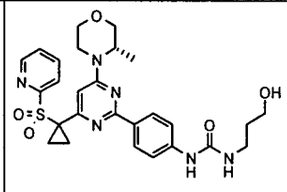
Espectro de NMR: ^{1}H NMR (399,902 DMSO-D_6) δ 0,33 (2H, s), 0,54 - 0,60 (2H, m), 1,06 - 1,10 (3H, m), 1,62 - 1,70 (2H, m), 1,92 (2H, s), 3,01 - 3,11 (1H, m), 3,37 (1H, t), 3,52 (1H, d), 3,66 (1H, d), 3,87 (1H, d), 4,00 - 4,11 (1H, m), 4,32 (1H, s), 6,33 (1H, s), 6,59 (1H, s), 7,29 (2H, d), 7,61 - 7,69 (3H, m), 7,89 - 7,93 (1H, m), 7,98 - 8,03 (1H, m), 8,41 (1H, s), 8,75 (1H, s);

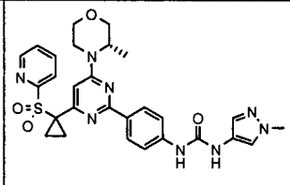
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 535,4; HPLC tR = 1,91 min.

Ensayo de mTOR Quinasa (Echo): 0,000816μM

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
28a		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	549,4	2,13
28b		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-piridin-2-ilurea	572,4	2,32
28c		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-metilpropil)urea	551,4	2,22
28d		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propan-2-ilurea	537,9	2,06
28e		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	509,4	1,73

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
28f		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	564,4	1,81
28g		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	539,4	1,6
28h		3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-1-propilurea	537,4	2,07
28i		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	639,4	2,82
28j		3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	567,4	1,87
28k		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	553,4	1,63

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
28l		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	575,4	1,8

Ejemplo 28a: ^{1}H NMR (399,902 DMSO-D_6) δ 1,16 (d, 3H), 1,57 - 1,68 (m, 2H), 1,70 - 1,78 (m, 2H), 1,80 - 1,92 (m, 2H), 1,96 - 2,04 (m, 2H), 2,17 - 2,26 (m, 2H), 3,10 - 3,18 (m, 1H), 3,41 - 3,49 (m, 1H), 3,57 - 3,63 (m, 1H), 3,75 (d, 1H), 3,93 - 3,98 (m, 1H), 4,09 - 4,19 (m, 2H), 4,40 (s, 1H), 6,44 (d, 1H), 6,67 (s, 1H), 7,34 (d, 2H), 7,72 (d, 2H), 7,73 - 7,77 (m, 1H), 7,99 (d, 1H), 8,06 - 8,11 (m, 1H), 8,52 (s, 1H), 8,81 - 8,84 (m, 1H).

Ensayo de mTOR Quinasa (Echo): 0,00253μM

Ejemplo 28b: ^{1}H NMR (399,902 DMSO-D_6) δ 1,18 (d, 3H), 1,71 - 1,82 (m, 2H), 1,98 - 2,05 (m, 2H), 3,11 - 3,21 (m, 1H), 3,42 - 3,51 (m, 1H), 3,59 - 3,64 (m, 1H), 3,76 (d, 1H), 3,94 - 4,00 (m, 1H), 4,15 (d, 1H), 4,42 (s, 1H), 6,71 (s, 1H), 7,02 - 7,07 (m, 1H), 7,50 (d, 2H), 7,56 - 7,60 (m, 1H), 7,75 - 7,80 (m, 2H), 7,81 (d, 2H), 7,99 - 8,02 (m, 1H), 8,08 - 8,13 (m, 1H), 8,29 - 8,32 (m, 1H), 8,83 - 8,85 (m, 1H), 9,42 - 9,44 (m, 1H), 10,53 (s, 1H).

Ensayo de mTOR Quinasa (Echo): 0,00149μM

Ejemplo 28c: ^{1}H NMR (399,902 DMSO-D_6) δ 0,79 (d, 6H), 1,07 (d, 3H), 1,57 - 1,68 (m, 3H), 1,88 - 1,92 (m, 2H), 2,84 (t, 2H), 3,00 - 3,09 (m, 1H), 3,31 - 3,40 (m, 1H), 3,48 - 3,53 (m, 1H), 3,65 (d, 1H), 3,84 - 3,89 (m, 1H), 4,00 - 4,07 (m, 1H), 4,30 (s, 1H), 6,13 (t, 1H), 6,57 (s, 1H), 7,24 - 7,28 (m, 2H), 7,62 (d, 2H), 7,64 - 7,67 (m, 1H), 7,88 - 7,91 (m, 1H), 7,97 - 8,02 (m, 1H), 8,51 (s, 1H), 8,72 - 8,74 (m, 1H).

Ensayo de mTOR Quinasa (Echo): 0,00847μM

Ejemplo 28d: ^{1}H NMR (399,902 DMSO-D_6) δ 1,11 (d, 6H), 1,16 (d, 3H), 1,70 - 1,79 (m, 2H), 1,96 - 2,04 (m, 2H), 3,10 - 3,18 (m, 1H), 3,41 - 3,49 (m, 1H), 3,57 - 3,63 (m, 1H), 3,72 - 3,83 (m, 2H), 3,93 - 3,99 (m, 1H), 4,13 (d, 1H), 4,40 (s, 1H), 6,04 (d, 1H), 6,67 (s, 1H), 7,34 (d, 2H), 7,72 (d, 2H), 7,74 - 7,77 (m, 1H), 7,98 - 8,01 (m, 1H), 8,06 - 8,12 (m, 1H), 8,49 (s, 1H), 8,82 - 8,84 (m, 1H).

Ensayo de mTOR Quinasa (Echo): 0,00237μM

1490

Ejemplo 28e: ^{1}H NMR (399,902 DMSO-D_6) δ 1,16 (d, 3H), 1,70 - 1,80 (m, 2H), 1,96 - 2,03 (m, 2H), 2,66 (d, 3H), 3,10 - 3,18 (m, 1H), 3,41 - 3,49 (m, 1H), 3,58 - 3,63 (m, 1H), 3,75 (d, 1H), 3,93 - 3,98 (m, 1H), 4,13 (d, 1H), 4,41 (s, 1H), 6,05 (q, 1H), 6,67 (s, 1H), 7,37 (d, 2H), 7,72 (d, 2H), 7,73 - 7,77 (m, 1H), 7,99 (d, 1H), 8,07 - 8,12 (m, 1H), 8,70 (s, 1H), 8,82 - 8,84 (m, 1H).

Ensayo de mTOR Quinasa (Echo): 0,000434μM

Ejemplo 28f: ^{1}H NMR (399,902 DMSO-D_6) δ 1,17 (d, 3H), 1,69 - 1,80 (m, 2H), 1,97 - 2,03 (m, 2H), 2,19 (s, 6H), 2,34 (t, 3H), 3,10 - 3,22 (m, 3H), 3,41 - 3,49 (m, 1H), 3,58 - 3,63 (m, 1H), 3,75 (d, 1H), 3,94 - 3,98 (m, 1H), 4,12 (d, 1H), 4,40 (s, 1H), 6,15 (t, 1H), 6,67 (s, 1H), 7,35 (d, 2H), 7,72 (d, 2H), 7,74 - 7,78 (m, 1H), 8,00 (d, 1H), 8,09 (t, 1H), 8,81 - 8,87 (m, 2H).

Ensayo de mTOR Quinasa (Echo): 0,0674μM

Ejemplo 28g: ^{1}H NMR (399,902 DMSO-D_6) δ 1,14 - 1,21 (m, 3H), 1,70 - 1,79 (m, 2H), 1,97 - 2,04 (m, 2H), 3,10 - 3,24 (m, 3H), 3,41 - 3,51 (m, 3H), 3,57 - 3,65 (m, 1H), 3,75 (d, 1H), 3,93 - 3,99 (m, 1H), 4,13 (d, 1H), 4,41 (s, 1H), 4,73 (t, 1H), 6,23 (t, 1H), 6,67 (s, 1H), 7,35 (d, 2H), 7,70 - 7,77 (m, 3H), 7,99 (d, 1H), 8,09 (t, 1H), 8,76 (s, 1H), 8,83 (d, 1H).

Ensayo de mTOR Quinasa (Echo): 0,0118μM

Ejemplo 28h: ^{1}H NMR (399,902 DMSO-D_6) δ 0,87 - 0,94 (m, 3H), 1,15 - 1,21 (m, 3H), 1,42 - 1,52 (m, 2H), 2,01 (s, 2H), 3,03 - 3,20 (m, 3H), 3,47 (t, 1H), 3,62 (d, 1H), 3,76 (d, 1H), 3,97 (d, 1H), 4,15 (d, 1H), 4,42 (s, 1H), 6,20 (s, 1H), 6,69 (s, 1H), 7,37 (d, 2H), 7,70 - 7,79 (m, 3H), 7,98 - 8,03 (m, 1H), 8,07 - 8,14 (m, 1H), 8,63 (s, 1H), 8,84 (s, 1H).

Ensayo de mTOR Quinasa (Echo): 0,00093μM

Ejemplo 28i: ^{1}H NMR (399,902 DMSO-D_6) δ 1,18 (d, 4H), 1,72 - 1,79 (m, 2H), 2,00 - 2,02 (m, 2H), 3 (d, 1H), 3,11 - 3,20 (m, 1H), 3,43 - 3,50 (m, 2H), 3,59 - 3,64 (m, 1H), 3,75 (d, 1H), 3,94 - 3,99 (m, 2H), 4,14 (d, 1H), 4,42 (s, 1H), 6,70 (s, 1H), 7,45 (d, 2H), 7,67 (q, 4H), 7,74 - 7,82 (m, 3H), 8,08 - 8,13 (m, 1H), 8,82 - 8,85 (m, 1H), 9,01 (s, 1H), 9,11 (s, 1H).

Ensayo de mTOR Quinasa (Echo): 0,00153μM

Ejemplo 28j: ^{1}H NMR (399,902 DMSO-D_6) δ 1,16 (d, 3H), 1,24 (s, 6H), 1,68 - 1,80 (m, 2H), 1,96 - 2,04 (m, 2H), 3,09 - 3,18 (m, 1H), 3,39 (d, 2H), 3,41 - 3,49 (m, 1H), 3,58 - 3,63 (m, 1H), 3,75 (d, 1H), 3,93 - 3,98 (m, 1H), 4,13 (d, 1H), 4,40 (s, 1H), 4,96 (t, 1H), 5,98 (s, 1H), 6,67 (s, 1H), 7,32 (d, 2H), 7,71 (d, 2H), 7,74 - 7,78 (m, 1H), 7,99 (d, 1H), 8,09 (t, 1H), 8,70 (s, 1H), 8,82 - 8,85 (m, 1H).

Ensayo de mTOR Quinasa (Echo): 0,00557μM

Ejemplo 28k: ^{1}H NMR (399,902 DMSO-D_6) δ 1,17 (d, 3H), 1,56 - 1,64 (m, 2H), 1,69 - 1,80

(m, 2H), 1,96 - 2,04 (m, 2H), 3,10 - 3,20 (m, 3H), 3,41 - 3,51 (m, 3H), 3,58 - 3,63 (m, 1H), 3,74 (d, 1H), 3,93 - 3,98 (m, 1H), 4,13 (d, 1H), 4,40 (s, 1H), 4,48 (t, 1H), 6,19 (t, 1H), 6,67 (s, 1H), 7,36 (d, 2H), 7,72 (d, 2H), 7,73 - 7,77 (m, 1H), 7,99 (d, 1H), 8,09 (t, 1H), 8,67 (s, 1H), 8,82 - 8,84 (m, 1H).

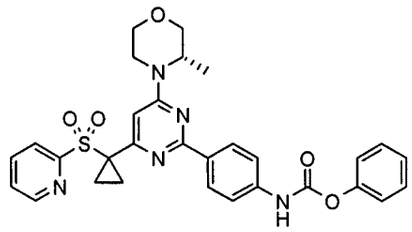
Ensayo de mTOR Quinasa (Echo): 0,000954μM

Ejemplo 28l: ^{1}H NMR (399,902 DMSO-D_6) δ 1,17 (d, 3H), 1,69 - 1,81 (m, 2H), 1,96 - 2,05 (m, 2H), 3,10 - 3,19 (m, 1H), 3,42 - 3,50 (m, 1H), 3,58 - 3,64 (m, 1H), 3,75 (d, 1H), 3,79 (s, 3H), 3,93 - 3,99 (m, 1H), 4,14 (d, 1H), 4,41 (s, 1H), 6,68 (s, 1H), 7,38 - 7,44 (m, 3H), 7,73 - 7,78 (m, 4H), 8,00 (d, 1H), 8,07 - 8,12 (m, 1H), 8,37 (s, 1H), 8,80 (s, 1H), 8,82 - 8,85 (m, 1H).

Ensayo de mTOR Quinasa (Echo): 0,000442μM

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato

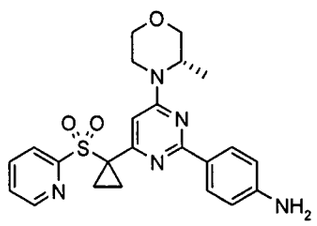


Se agregó gota a gota fenil cloroformiato (0,693 g, 4,43 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]anilina (2,0 g, 4,43 mmol) e hidrogenocarbonato de sodio (0,744 g, 8,86 mmol) en dioxano (40 mL) a TA. La suspensión resultante se agitó a TA durante 1 hora. La mezcla se repartió entre acetato de etilo y agua. La solución orgánica se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en sílice, eluyendo con 0% - 20% acetato de etilo en DCM, para proporcionar el material deseado como una goma amarilla (2,07 g).

Espectro de NMR: ^{1}H NMR (399,902 $CDCl_3$) δ 1,23 (5H, d), 1,61 - 1,71 (2H, m), 2,06 - 2,15 (2H, m), 3,17 - 3,24 (1H, m), 3,47 - 3,54 (1H, m), 3,75 (1H, d), 4,05 - 4,11 (2H, m), 4,35 (1H, s), 6,82 (1H, s), 6,95 (1H, s), 7,13 (2H, m), 7,16 - 7,21 (1H, m), 7,31 - 7,37 (4H, m), 7,38 - 7,43 (1H, m), 7,73 - 7,77 (1H, m), 7,86 (1H, d), 7,93 - 7,97 (2H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 572,6; HPLC tR = 2,81 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]anilina

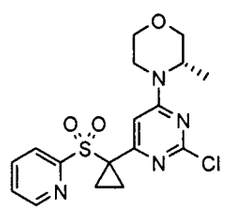


Se agregó carbonato de sodio (20,51 mL, 41,03 mmol) a 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (2,498 g, 11,4 mmol) y 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidina (4,5 g, 11,40 mmol) en una mezcla de DME (20 mL), etanol (20 mL), DMF (20 mL) y agua (40 mL). La mezcla se purgó con nitrógeno y luego se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,4 g, 0,57 mmol) y la suspensión resultante se agitó a 80°C durante 90 minutos. La mezcla de reacción se concentró, se diluyó con acetato de etilo (150 mL) y se lavó secuencialmente con agua (2 x 150 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 45% acetato de etilo en DCM, para proporcionar el material deseado como un sólido beige (3,64 g).

Espectro de NMR: ^{1}H NMR (399,902 $CDCl_3$) δ 1,20 (3H, d), 1,60 - 1,72 (2H, m), 2,04 - 2,12 (2H, m), 3,14 - 3,22 (1H, m), 3,46 - 3,53 (1H, m), 3,71 - 3,78 (3H, m), 3,92 - 3,96 (1H, m), 4,02 - 4,08 (1H, m), 4,33 (1H, s), 6,53 (2H, d), 6,76 (1H, s), 7,37 - 7,41 (1H, m), 7,72 - 7,77 (1H, m), 7,78 - 7,86 (3H, m), 8,64 - 8,66 (1H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 452,6; HPLC tR = 1,40 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidina



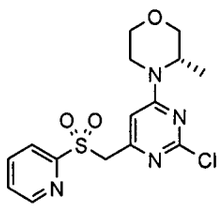
Se agregó 1,2-dibromoetano (5,61 mL, 65,08 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-

6-(piridin-2-ilsulfonilmetil)pirimidina (6 g, 16,27 mmol), solución de hidróxido de sodio 10N (32,5 mL, 325,35 mmol) y bromuro de tetrabutilamonio (0,524 g, 1,63 mmol) en tolueno (400 mL). La solución resultante se agitó a 60°C durante 3 horas. La mezcla de reacción se concentró y se diluyó con acetato de etilo (150 mL), luego se lavó con agua (2 x 100 mL) y salmuera saturada (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 5 a 20% acetato de etilo en DCM, para proporcionar el material deseado como una película seca blanca (3,02 g).

Espectro de NMR: ^{1}H NMR (399,902 $CDCl_3$) δ 1,22 (3H, d), 1,56 - 1,67 (2H, m), 1,97 - 2,07 (2H, m), 3,14 - 3,22 (1H, m), 3,41 - 3,49 (1H, m), 3,58 - 3,62 (1H, m), 3,70 (1H, d), 3,89 - 3,99 (2H, m), 4,21 (1H, s), 7,02 (1H, s), 7,44 - 7,48 (1H, m), 7,81 - 7,89 (2H, m), 8,62 - 8,64 (1H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 395,4; HPLC tR = 1,98 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-2-ilsulfonilmetil)pirimidina

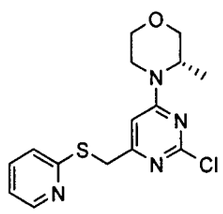


Una solución acuosa de peróxido de hidrógeno 35% (8,26 mL, 93,53 mmol) se agregó gota a gota a una solución agitada de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-2-ilsulfanilmetil)pirimidina (10,5g, 31,17 mmol), tungstato de sodio dihidrato (0,206 g, 0,62 mmol) y ácido sulfúrico 2N (0,6 mL) en dioxano (300 mL) y luego la solución se entibió hasta alcanzar 55°C. La solución se agitó a 55°C durante 4 horas. Se agregó más peróxido de hidrógeno (8,26 mL) y la mezcla se agitó a 50°C durante 18 horas. Se agregó ácido 3-cloroperoxibenzoico (5,38 g, 31,17 mmol) y la mezcla se agitó a TA durante 2 horas. La solución se diluyó con agua (500 mL) y se enfrió hasta alcanzar 20°C. Una solución de metabisulfito de sodio 10% se agregó para eliminar cualquier resto de peróxido y la solución se extrajo con acetato de etilo. La capa orgánica se secó ($MgSO_4$) y se filtró. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado como una goma amarilla (10,5 g,).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,24 (d, 3H), 3,20 (m, 1H), 3,46 (m, 1H), 3,61 (d, 1H), 3,71 (d, 1H), 3,90 - 3,98 (m, 2H), 4,21 (s, 1H), 4,51 (s, 2H), 6,50 (s, 1H), 7,51 - 7,53 (m, 1H), 7,86 - 7,95 (m, 2H), 8,72 - 8,74 (m, 1H)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 369,4; HPLC tR = 1,73 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-2-ilsulfanilmetil)pirimidina



DIPEA (8,77 ml, 50,71 mmol) se agregó a 2-mercaptopiridina (3,80 g, 34,22 mmol), en DMF (300 mL) a TA en una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 15 minutos. Se agregó en porciones 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (11 g, 31,11 mmol) durante 5 minutos y la mezcla se agitó a TA durante 3 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (200 mL) y se lavó secuencialmente con solución saturada de hidrogenocarbonato de sodio (100 mL) y salmuera saturada (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como un aceite tostado (10,50 g). La NMR muestra la presencia de 0,6 eq. de ácido 3-clorobenzoico. Este material se utilizó en la siguiente etapa sin purificación adicional.

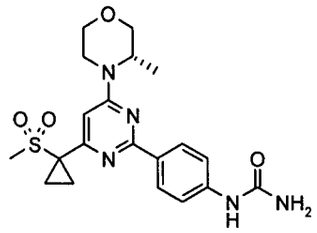
Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,23 (d, 3H), 3,17 - 3,25 (m, 1H), 3,46 - 3,54 (m, 1H), 3,62 - 3,67 (m, 1H), 3,74 (d, 1H), 3,93 - 4,01 (m, 2H), 4,20 (s, 1H), 4,29 - 4,38 (m, 2H), 6,60 (s, 1H), 6,99 - 7,02 (m, 1H), 7,20 (d, 1H), 7,47 - 7,51 (m, 1H), 8,40 - 8,42 (m, 1H).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 337,5; HPLC tR = 2,19 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 29: [4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-

il]fenil]urea



Se agregó sal clorhidrato de 6-aminopiridin-2(1*H*)-ona (0,218 g, 1,49 mmol) a fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato (0,151 g, 0,30 mmol) y trietilamina (0,249 mL, 1,78 mmol) en DMF (2 mL) a TA. La solución resultante se agitó a 50°C durante 1 día. La solución se enfrió y se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (0,094 g).

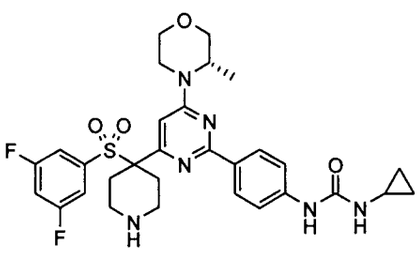
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22-1,25 (3H, d), 1,55-1,58 (2H, q), 1,66-1,69 (2H, q), 3,17-3,26 (1H, td), 3,30 (3H, s), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,57 (1H, bs), 5,91 (2H, s), 6,77 (1H, s), 7,50-7,52 (2H, q), 8,19-8,21 (2H, q), 8,76 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 432; HPLC tR = 1,66 min.

Ensayo de mTOR Quinasa (Echo): 0,0042μM

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato se describió anteriormente.

Ejemplo 30: 3-Ciclopropil-1-[4-[4-[4-(3,5-difluorofenil)sulfonilpiperidin-4-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



1-Cloroetil cloroformiato (0,015 mL, 0,14 mmol) y 1-[4-[4-[1-bencil-4-(3,5-

difluorofenil)sulfonilpiperidin-4-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea (50 mg, 0,07 mmol) se disolvió en DCM (1 mL) y se sellaron en un tubo de microondas. La reacción se calentó hasta alcanzar 110°C durante 5 minutos en un reactor de microondas y luego se enfrió hasta alcanzar TA. Se agregó metanol (1 mL) y la mezcla se calentó hasta alcanzar 110°C durante 5 minutos en un reactor de microondas y luego se enfrió hasta alcanzar TA. La mezcla se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con metanol y luego amoníaco 2M en metanol. El material aislado se purificó adicionalmente mediante cromatografía en sílice, eluyendo con 2% metanol en DCM a 20% metanol en DCM conteniendo 1% amoníaco. El material aislado se trituró con éter dietílico para proporcionar el material deseado como un sólido incoloro (26 mg).

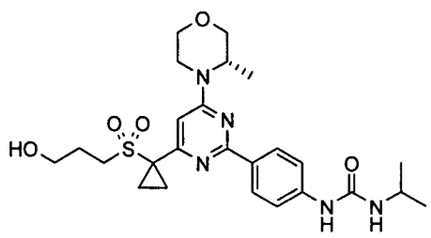
Espectro de NMR: ^{1}H NMR (399,9 MHz, $CDCl_3$) δ 0,68 - 0,72 (2H, m), 0,86 - 0,90 (2H, m), 1,36 (3H, d), 2,27 - 2,36 (2H, m), 2,52 - 2,65 (3H, m), 2,70 - 2,79 (2H, m), 3,10 - 3,15 (2H, m), 3,34 (1H, dt), 3,64 (1H, dt), 3,77 - 3,87 (2H, m), 4,05 - 4,18 (2H, m), 4,43 - 4,52 (1H, m), 4,91 (1H, s), 6,65 (1H, s), 6,81 - 6,87 (1H, m), 6,95 - 7,02 (3H, m), 7,39 (2H, d), 7,93 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 613,5; HPLC tR = 2,16 min.

Ensayo de mTOR Quinasa (Echo): 0,025μM

La preparación de 1-[4-[4-[1-bencil-4-(3,5-difluorofenil)sulfonilpiperidin-4-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea se describió anteriormente.

Ejemplo 31: 1-[4-[4-[1-(3-Hidroxipropilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-ilurea



Se agregó trietilamina (0,126 mL, 0,90 mmol) a fenil *N*-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (100 mg, 0,18 mmol) y propan-2-amina (0,078 mL, 0,90 mmol) en NMP (2 mL) a TA al aire. La solución resultante se agitó a TA durante 1 hora. El producto bruto se purificó mediante preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y

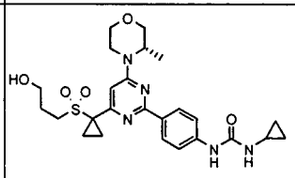
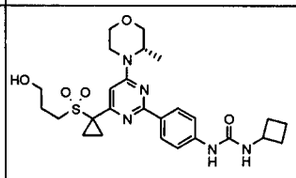
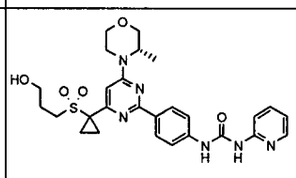
acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (65 mg).

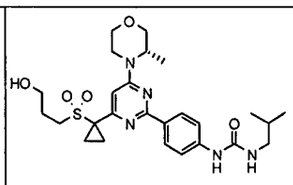
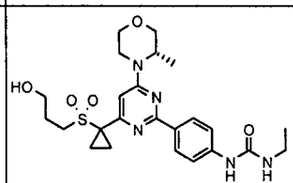
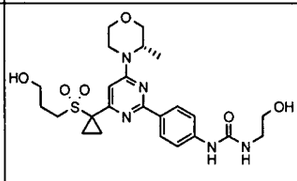
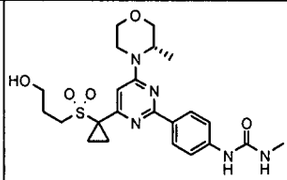
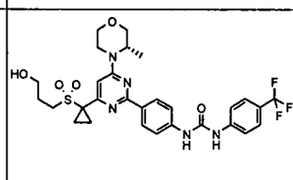
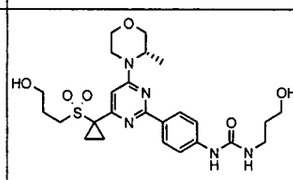
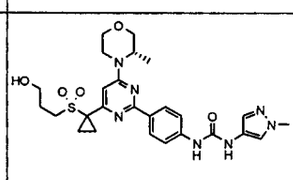
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11 (6H, d), 1,22 (3H, d), 1,54 - 1,58 (2H, m), 1,60 - 1,64 (2H, m), 1,90 - 1,97 (2H, m), 3,16 - 3,23 (1H, m), 3,31 - 3,34 (1H, m), 3,44 - 3,55 (4H, m), 3,61 - 3,64 (1H, m), 3,73 - 3,81 (2H, m), 3,95 - 3,99 (1H, m), 4,16 - 4,26 (1H, m), 4,52 - 4,59 (1H, m), 4,73 (1H, t), 6,08 (1H, d), 6,77 (1H, s), 7,47 (2H, d), 8,20 (2H, d), 8,57 (1H, s)

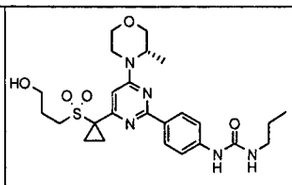
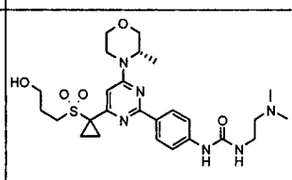
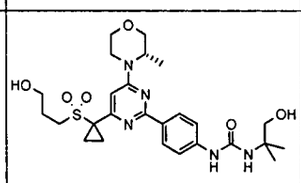
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 518; HPLC tR = 2,04min.

Ensayo de mTOR Quinasa (Echo): 0,00452μM

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
31a		3-ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	516	1,74
31b		3-ciclobutil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	530	1,94
31c		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-piridin-2-ilurea	553	2,10

31d		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilpropil)urea	532	2,02
31e		1-etil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	504	1,71
31f		3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	520	1,49
31g		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	490	1,59
31h		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[4-(trifluorometil)fenil]urea	620	2,54
31i		3-(3-hidroxipropil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	534	1,52
31j		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	556	1,66

31k		3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea	518	1,86
31l		3-(2-dimetilaminoetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	547	1,66
31m		3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	548	1,72

Ejemplo 31a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,22 (3H, d), 1,54 - 1,58 (2H, m), 1,60 - 1,64 (2H, m), 1,90 - 1,97 (2H, m), 2,53 - 2,58 (1H, m), 3,16 - 3,22 (1H, m), 3,44 - 3,55 (5H, m), 3,61 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,98 (1H, m), 4,17 - 4,25 (1H, m), 4,53 - 4,59 (1H, m), 4,73 (1H, t), 6,46 (1H, s), 6,77 (1H, s), 7,50 (2H, d), 8,21 (2H, d), 8,58 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00265μM

Ejemplo 31b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,54 - 1,63 (6H, m), 1,81 - 1,97 (4H, m), 2,17 - 2,23 (2H, m), 3,17 - 3,22 (1H, m), 3,45 - 3,54 (5H, m), 3,61 - 3,63 (1H, m), 3,76 (1H, d), 3,96 - 3,98 (1H, m), 4,10 - 4,24 (2H, m), 4,51 - 4,58 (1H, m), 4,73 (1H, t), 6,48 (1H, d), 6,77 (1H, s), 7,47 (2H, d), 8,20 (2H, d), 8,60 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00497μM

Ejemplo 31c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,58 (2H, m), 1,62 - 1,66 (2H, m), 1,91 - 1,98 (2H, m), 3,18 - 3,25 (1H, m), 3,46 - 3,57 (5H, m), 3,62 - 3,65 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,20 - 4,27 (1H, m), 4,52 - 4,61 (1H, m), 4,75 (1H, t), 6,80 (1H, s), 7,02 - 7,05 (1H, m), 7,55 - 7,58 (1H, m), 7,64 (2H, d), 7,75 - 7,79 (1H, m), 8,29 - 8,31 (1H, m), 8,30 (2H, d), 9,49 (1H, s), 10,63 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00131μM

Ejemplo 31d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,88 (6H, d), 1,22 (3H, d), 1,54 - 1,56 (2H, m), 1,60 - 1,64 (2H, m), 1,90 - 1,97 (2H, m), 2,94 (2H, t), 3,16 - 3,23 (1H, m), 3,45 - 3,55 (6H, m), 3,61 - 3,64 (1H, m), 3,76 (1H, d), 3,96 - 3,98 (1H, m), 4,16 - 4,26 (1H, m), 4,52 - 4,59 (1H, m), 4,73 (1H, t), 6,26 (1H, t), 6,77 (1H, s), 7,48 (2H, d), 8,21 (2H, d), 8,68 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00955μM

Ejemplo 31e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06 (3H, t), 1,22 (3H, d), 1,54 - 1,58 (2H, m), 1,60 - 1,64 (2H, m), 1,90 - 1,97 (2H, m), 3,09 - 3,23 (3H, m), 3,44 - 3,55 (5H, m), 3,61 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,18 - 4,24 (1H, m), 4,53 - 4,59 (1H, m), 4,73 (1H, t), 6,18 (1H, t), 6,77 (1H, s), 7,49 (2H, d), 8,20 (2H, d), 8,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00107μM

Ejemplo 31f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,54 - 1,64 (4H, m), 1,90 - 1,97 (2H, m), 3,15 - 3,19 (2H, m), 3,43 - 3,54 (8H, m), 3,61 - 3,63 (1H, m), 3,76 (1H, d), 3,95 - 3,98 (1H, m), 4,17 - 4,24 (1H, m), 4,51 - 4,59 (1H, m), 4,73 - 4,79 (2H, m), 6,28 (1H, t), 6,76 (1H, s), 7,48 (2H, d), 8,21 (2H, d), 8,84 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0016μM

Ejemplo 31g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,54 - 1,58 (2H, m), 1,60 - 1,64 (2H, m), 1,90 - 1,97 (2H, m), 2,66 (3H, d), 3,16 - 3,23 (1H, m), 3,44 - 3,55 (5H, m), 3,61 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,17 - 4,23 (1H, m), 4,52 - 4,59 (1H, m), 4,73 (1H, t), 6,07 - 6,10 (1H, m), 6,77 (1H, s), 7,50 (2H, d), 8,20 (2H, d), 8,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00323μM

Ejemplo 31h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,59 (2H, m), 1,62 - 1,65 (2H, m), 1,91 - 1,98 (2H, m), 3,17 - 3,25 (1H, m), 3,45 - 3,56 (5H, m), 3,62 - 3,65 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,18 - 4,26 (1H, m), 4,53 - 4,61 (1H, m), 4,75 (1H, t), 6,80 (1H, s), 7,58 (2H, d), 7,64 - 7,70 (4H, m), 8,29 (2H, d), 9,09 (1H, s), 9,17 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000209μM

Ejemplo 31i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,54 - 1,64 (6H, m), 1,90 - 1,97 (2H, m), 3,14 - 3,23 (3H, m), 3,44 - 3,55 (7H, m), 3,61 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,17 - 4,25 (1H, m), 4,52 (1H, t), 4,53 - 4,59 (1H, m), 4,73 (1H, t), 6,22 (1H, t), 6,77 (1H, s), 7,49 (2H, d), 8,20 (2H, d), 8,75 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00326μM

Ejemplo 31j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,54 - 1,58 (2H, m), 1,61 - 1,64 (2H, m), 1,90 - 1,98 (2H, m), 3,16 - 3,24 (1H, m), 3,46 - 3,56 (4H, m), 3,61 - 3,65 (1H, m), 3,79 (3H, s), 3,96 - 3,99 (1H, m), 4,18 - 4,25 (1H, m), 4,53 - 4,58 (1H, m), 4,74 (1H, t),

1501

6,78 (1H, s), 7,39 (1H, s), 7,54 (2H, d), 7,77 (1H, s), 8,24 (2H, d), 8,43 (1H, s), 8,89 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00103μM

Ejemplo 31k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,88 (3H, t), 1,22 (3H, d), 1,41 - 1,50 (2H, m), 1,54 - 1,58 (2H, m), 1,60 - 1,64 (2H, m), 1,88 - 1,97 (2H, m), 3,03 - 3,08 (2H, m), 3,16 - 3,23 (1H, m), 3,44 - 3,55 (5H, m), 3,61 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,17 - 4,24 (1H, m), 4,51 - 4,59 (1H, m), 4,73 (1H, t), 6,22 (1H, t), 6,77 (1H, s), 7,49 (2H, d), 8,20 (2H, d), 8,69 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00191μM

Ejemplo 31l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,54 - 1,58 (2H, m), 1,60 - 1,64 (2H, m), 1,90 - 1,97 (2H, m), 2,18 (6H, s), 2,33 (2H, t), 3,17 - 3,23 (3H, m), 3,44 - 3,55 (5H, m), 3,61 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,17 - 4,25 (1H, m), 4,50 - 4,60 (1H, m), 4,73 (1H, t), 6,17 (1H, t), 6,77 (1H, s), 7,48 (2H, d), 8,20 (2H, d), 8,92 (1H, s).

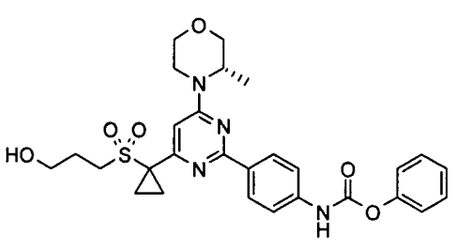
Ensayo de mTOR Quinasa (Echo): 0,214μM

Ejemplo 31m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (6H, s), 1,54 - 1,58 (2H, m), 1,60 - 1,64 (2H, m), 1,90 - 1,97 (2H, m), 3,16 - 3,23 (1H, m), 3,38 (2H, d), 3,44 - 3,55 (5H, m), 3,61 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,17 - 4,25 (1H, m), 4,51 - 4,59 (1H, m), 4,74 (1H, t), 4,99 (1H, t), 6,01 (1H, s), 6,76 (1H, s), 7,45 (2H, d), 8,19 (2H, d), 8,77 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00591μM

La preparación de fenil *N*-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



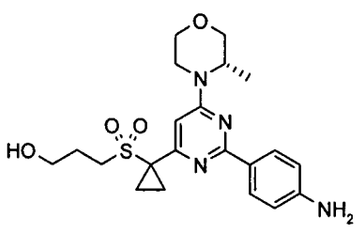
Se agregó fenil cloroformiato (0,581 mL, 4,63 mmol) a 3-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropan-1-ol (1,82 g, 4,21 mmol) y bicarbonato de sodio (0,530 g, 6,31 mmol) en dioxano (100 mL) a 5°C bajo una atmósfera de

nitrógeno. La suspensión resultante se agitó durante toda la noche y se dejó llegar a TA. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el producto deseado como una goma. La goma se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido blanco (2,32 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,48 - 1,52 (2H, m), 1,55 - 1,61 (2H, m), 1,83 - 1,90 (2H, m), 3,11 - 3,18 (1H, m), 3,38 - 3,46 (4H, m), 3,54 - 3,58 (1H, m), 3,69 (1H, d), 3,75 - 3,94 (2H, m), 3,88 - 3,92 (1H, m), 4,14 - 4,18 (1H, m), 4,47 - 4,53 (1H, m), 6,75 (1H, s), 7,17 - 7,23 (3H, m), 7,36 - 7,39 (2H, m), 7,56 (2H, d), 8,23 (2H, d), 10,37 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 553; HPLC tR = 2,51min.

3-[1-[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropan-1-ol



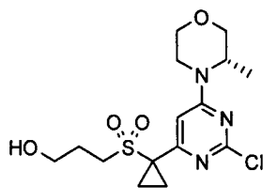
Se agregó diclorobis(trifenilfosfina)paladio (II) (0,218 g, 0,31 mmol) a 3-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropan-1-ol (2,33 g, 6,20 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,766 g, 8,06 mmol) y solución de carbonato de sodio acuoso 2M (11,16 mL, 22,32 mmol) en DMF (15 mL), agua (37,5 mL), etanol (15 mL) y DME (15 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a 80°C durante 17 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto como un sólido marrón. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 75% acetato de etilo en DCM, para proporcionar el material deseado como un sólido crema (1,82 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,52 - 1,54 (2H, m), 1,60 - 1,62 (2H, m), 1,90 - 1,97 (2H, m), 3,14 - 3,21 (1H, m), 3,44 - 3,52 (5H, m), 3,60 - 3,64

(1H, m), 3,75 (1H, d), 3,94 - 3,98 (1H, m), 4,16 - 4,19 (1H, m), 4,48 - 4,55 (1H, m), 4,67 (1H, t), 5,56 (2H, s), 6,60 (2H, d), 6,67 (1H, s), 8,04 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 433; HPLC tR = 1,81min.

3-[1-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropan-1-ol

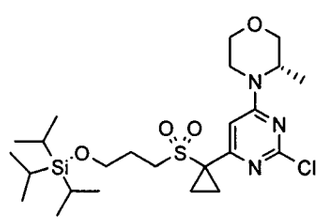


Se agregó fluoruro de tetrabutilamonio (1M en THF, 31 mL, 31 mmol) a 3-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropoxi-tri(propan-2-il)silano (3,28 g, 6,16 mmol) en THF (30 mL) a TA. La solución resultante se agitó a TA durante 1 hora y luego se concentró al vacío y se diluyó con cloruro de amonio saturado (10 mL) y agua. La mezcla se extrajo dos veces con acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, se secó ($MgSO_4$), se filtraron y se evaporaron para proporcionar el material deseado como una goma (2,33 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,33 (3H, d), 1,42 - 1,51 (4H, m), 2,07 - 2,14 (2H, m), 2,40 (1H, s), 3,28 - 3,32 (2H, m), 3,37 - 3,42 (3H, m), 3,51 - 3,57 (1H, m), 3,66 - 3,70 (1H, m), 3,77 - 3,80 (2H, m), 3,99 - 4,02 (1H, m), 4,28 - 4,38 (1H, m), 6,84 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 376; HPLC tR = 1,58min.

3-[1-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropoxi-tri(propan-2-il)silano



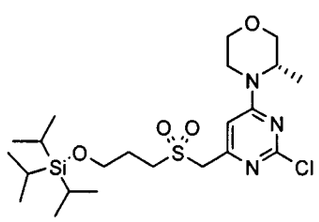
Se agregó 1,2-dibromoetano (1,723 mL, 20 mmol) a 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]propoxi-tri(propan-2-il)silano (5,0 g, 9,88 mmol), solución de hidróxido de sodio al 40% (10 mL, 98,78 mmol) y bromuro de tetrabutilamonio (0,645 g, 2 mmol) en tolueno (50 mL) a TA al aire. La mezcla resultante se agitó a 60°C durante 4 horas.

La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetato de etilo (100 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como una goma incolora (2,86 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,00 - 1,05 (21H, m), 1,32 (3H, d), 1,49 - 1,52 (2H, m), 1,78 - 1,81 (2H, m), 2,02 - 2,09 (2H, m), 3,21 - 3,32 (3H, m), 3,50 - 3,56 (1H, m), 3,65 - 3,69 (1H, m), 3,77 - 3,80 (3H, m), 3,98 - 4,02 (2H, m), 4,28 - 4,36 (1H, m), 6,90 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 532; HPLC tR = 3,37min.

3-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]propoxi-tri(propan-2-il)silano

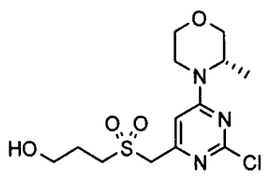


Se agregó 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]propan-1-ol (5,04 g, 14,41 mmol) en DMF (25 mL) a clorotrisopropilsilano (3,70 mL, 17,29 mmol) e imidazol (2,354 g, 34,58 mmol) en DMF (25 mL) a TA durante un período de 5 minutos bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 18 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (200 mL), luego se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como un aceite (7,29 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 0,99 - 1,07 (21H, m), 1,33 (3H, d), 2,06 - 2,13 (2H, m), 3,20 - 3,24 (2H, m), 3,26 - 3,34 (1H, m), 3,50 - 3,57 (1H, m), 3,66 - 3,70 (1H, m), 3,77 - 3,83 (3H, m), 3,99 - 4,03 (2H, m), 4,16 (2H, s), 4,25 - 4,37 (1H, m), 6,54 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 506; HPLC tR = 3,42min.

3-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]propan-1-ol

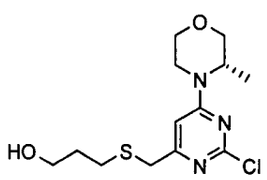


Se agregó ácido 3-clorobenzoperoxoico (4,00 g, 23,16 mmol) a 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]propan-1-ol (3,68 g, 11,58 mmol) en DCM (100 mL) a TA durante un período de 5 minutos. La solución resultante se agitó a TA durante 3 horas. Se agregó una porción adicional de ácido 3-clorobenzoperoxoico (2,00 g, 11,58 mmol) y la solución resultante se agitó a TA durante 1 hora más. La mezcla de reacción se lavó secuencialmente con solución de metabisulfito de sodio acuoso al 10% (2 x 100 mL), una solución saturada acuosa de hidrogenocarbonato de sodio (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como una goma (4,05 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,34 (3H, d), 2,12 - 2,18 (2H, m), 3,27 (2H, t), 3,31 - 3,35 (1H, m), 3,51 - 3,57 (1H, m), 3,67 - 3,70 (1H, m), 3,77 - 3,82 (3H, m), 3,99 - 4,03 (1H, m), 4,18 (2H, s), 4,26 - 4,37 (1H, m), 6,51 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 350; HPLC tR = 1,30min.

3-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]propan-1-ol



Una solución de 2-cloro-4-(yodometil)-6-[(3S)-3-metilmorfolin-4-il]pirimidina (12,4 g, 35,07 mmol) en DCM (50 mL) se agregó a una solución agitada de 3-mercapto-1-propanol (3,64 mL, 42,08 mmol) y DIPEA (9,77 mL, 56,11 mmol) en DCM (100 mL) a TA, durante un período de 40 minutos bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 18 horas. La mezcla de reacción se lavó secuencialmente con una solución saturada acuosa de hidrogenocarbonato de sodio (2 x 50 mL) y salmuera saturada (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto como un aceite marrón oscuro. El producto bruto se purificó mediante cromatografía de sílice

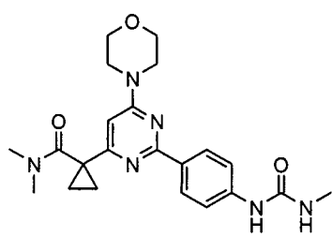
instantánea, eluyendo con 0 a 75% acetato de etilo en DCM, para proporcionar el material deseado como una goma amarilla (5,86 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,32 (3H, d), 1,84 - 1,90 (2H, m), 1,94 (1H, s), 2,69 (2H, t), 3,24 - 3,32 (1H, m), 3,51 - 3,58 (1H, m), 3,61 (2H, s), 3,67 - 3,71 (1H, m), 3,73 - 3,80 (3H, m), 3,98 - 4,04 (2H, m), 4,28 - 4,34 (1H, m), 6,45 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 318; HPLC tR = 1,55min.

La preparación de 2-cloro-4-(yodometil)-6-[(3S)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 32: *N,N*-Dimetil-1-[2-[4-(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxamida



Se agregó DIPEA (0,127 mL, 0,72 mmol) a una suspensión de ácido 1-[2-[4-(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico (96 mg, 0,24 mmol), dimetilamina (2,0M en THF, 0,36 mL, 0,72 mmol) y HBTU (138 mg, 0,36 mmol) en DMF (3 mL). Las reacciones se agitaron a TA durante 3 horas. La mezcla de reacción se hizo pasar por una columna de intercambio iónico SCX-2, eluyendo con metanol y luego amoníaco 7N en metanol. El material aislado se purificó adicionalmente mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (54 mg).

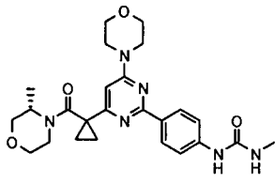
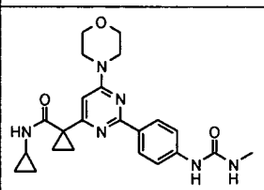
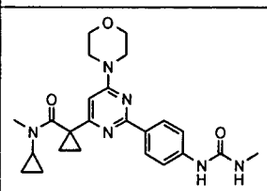
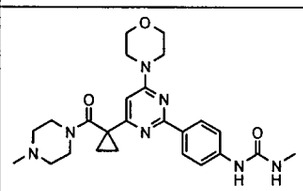
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,28 - 1,31 (2H, m), 1,51 - 1,54 (2H, m), 2,65 (3H, d), 2,87 - 2,89 (3H, s), 2,94 (3H, s), 3,64 (4H, m), 3,69 - 3,71 (4H, m), 6,08 (1H, d), 6,22 (1H, s), 7,46 - 7,49 (2H, m), 8,16 - 8,18 (2H, m), 8,76 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 425; HPLC tR = 1,45 min.

Ensayo de mTOR Quinasa (Echo): 0,00315μM

Los siguientes compuestos se prepararon en forma análoga a partir de 1-[2-[4-

(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico ácido y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
32a		3-metil-1-[4-[4-[1-[(3S)-3-metilmorfolina-4-carbonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	481,4	1,53
32b		N-ciclopropil-1-[2-[4-(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxamida	437,4	1,5
32c		N-ciclopropil-N-metil-1-[2-[4-(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxamida	451,4	1,62
32d		3-metil-1-[4-[4-[1-(4-metilpiperazina-1-carbonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	480,4	1,35

Ejemplo 32a: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,31 (2H, d), 1,62 (2H, d), 2,65 - 2,66 (3H, m), 3,17 (1H, d), 3,48 (1H, d), 3,50 (1H, m), 3,66 (4H, s), 3,70 (4H, s), 3,70 (1H, s), 3,85 (1H, m), 4,23 (1H, d), 4,47 - 4,49 (1H, m), 6,07 (1H, q), 6,23 (1H, d), 7,48 (2H, d), 8,19 (2H, d), 8,76 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0425μM

Ejemplo 32b: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,42 - 0,46 (2H, m), 0,60 - 0,65 (2H, m), 1,30 - 1,37 (4H, m), 2,66 (3H, d), 2,67 - 2,68 (1H, m), 3,67 (8H, s), 6,08 (1H, d), 6,46 (1H, s), 7,48 - 7,50 (2H, m), 8,14 - 8,17 (2H, m), 8,37 (1H, d), 8,77 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00829μM

Ejemplo 32c: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,64 (2H, s), 0,69 (2H, s), 1,32 (2H, s),

1,49 (2H, t), 2,33 (1H, t), 2,65 - 2,66 (3H, m), 2,73 - 2,76 (3H, m), 3,64 (4H, s), 3,69 - 3,71 (4H, m), 6,07 (1H, q), 6,30 (1H, s), 7,46 - 7,49 (2H, m), 8,16 - 8,18 (2H, m), 8,75 (1H, s).

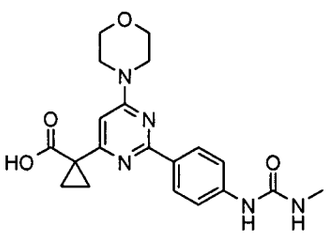
Ensayo de mTOR Quinasa (Echo): 0,00288μM

Ejemplo 32d: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,29 - 1,32 (2H, m), 1,50 - 1,53 (2H, m), 2,11 - 2,11 (3H, m), 2,14 (2H, s), 2,33 (2H, t), 2,65 - 2,66 (3H, m), 3,30 (2H, s), 3,57 (2H, s), 3,67 - 3,70 (8H, m) 6,08 (1H, q), 6,26 (1H, s), 7,46 - 7,50 (2H, m), 8,17 - 8,20 (2H, m), 8,76 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0131μM

La preparación de 1-[2-[4-(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico ácido se describe a continuación:

Ácido 1-[2-[4-(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico

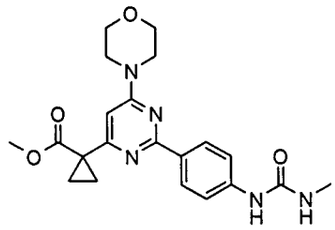


Se agregó hidróxido-1-hidrato de litio (59,5 mg, 1,42 mmol) en una porción a metil 1-[2-[4-(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxilato (583 mg, 1,42 mmol) en metanol (8 mL) y agua (8 mL). La suspensión resultante se agitó a 60°C durante 5 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en agua (25 mL) y se lavó con éter dietílico (25 mL). La capa acuosa se acidificó con ácido clorhídrico 2M y el precipitado se recogió mediante filtración, se lavó con éter dietílico y se secó al vacío para proporcionar el material deseado como un sólido marrón (486 mg).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,51 - 1,58 (4H, m), 2,65 - 2,66 (3H, m), 3,70 (8H, s), 6,09 (1H, q), 6,73 (1H, s), 7,49 - 7,52 (2H, m), 8,13 - 8,15 (2H, m), 8,80 (1H, s), 14,09 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 398; HPLC tR = 1,21 min.

Metil 1-[2-[4-(metilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxilato

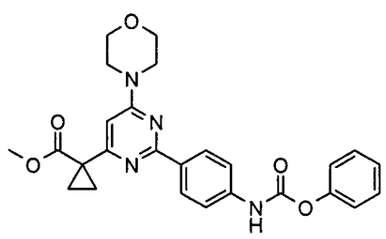


Se agregó metilamina (1,97 mL, 3,94 mmol) en una porción a metil 1-[6-morfolin-4-il-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]ciclopropano-1-carboxilato (934 mg, 1,97 mmol) en DMF (20 mL). La solución resultante se agitó a TA durante 4 horas. La mezcla de reacción se evaporó hasta secarse y el residuo se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con metanol y luego amoníaco 7M en metanol, para proporcionar el material deseado como un sólido amarillo (713 mg).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,49 - 1,55 (4H, m), 2,66 (3H, d), 3,65 (3H, s), 3,69 (8H, s), 6,05 (1H, t), 6,83 (1H, s), 7,46 - 7,49 (2H, m), 8,16 - 8,19 (2H, m), 8,71 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 412; HPLC tR = 1,93 min.

Metil 1-[6-morfolin-4-il-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]ciclopropano-1-carboxilato



Se agregó gota a gota fenil cloroformiato (0,53 mL, 4,20 mmol) a metil 1-[2-(4-aminofenil)-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxilato (1,49 g, 4,20 mmol) y bicarbonato de sodio (0,53 g, 6,31 mmol) en dioxano (50 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (60 mL) y se lavó con agua (60 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío para proporcionar el material deseado como un sólido amarillo (2,1 g).

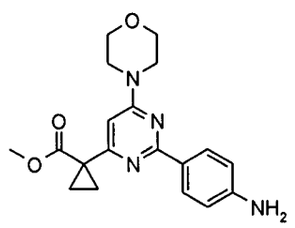
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,52 - 1,54 (4H, m), 3,57 (3H, s), 3,71 (8H, s), 6,89 (1H, s), 7,24 - 7,30 (3H, m), 7,43 - 7,47 (2H, m), 7,62 (2H, d), 8,27 (2H, d),

1510

10,46 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 475; HPLC tR = 2,83 min.

Metil 1-[2-(4-aminofenil)-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxilato

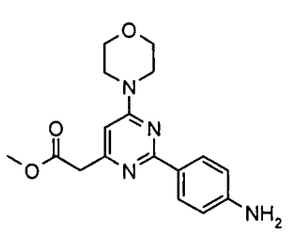


Se agregó en una porción hidruro de sodio (434 mg, 10,84 mmol) a metil 2-[2-(4-aminofenil)-6-morfolin-4-ilpirimidin-4-il]acetato (3,56 g, 10,84 mmol) en DMF (75 mL) se enfrió hasta alcanzar 0°C bajo nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos, luego se agregó 1,2-dibromoetano (0,981 mL, 11,38 mmol) y la reacción se agitó a 0°C durante 5 minutos. Se agregó más hidruro de sodio (434 mg, 10,84 mmol) en una porción y la reacción se agitó a 0°C durante 1 hora. La mezcla de reacción se aplacó con una solución saturada acuosa de cloruro de amonio (10 mL). La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (100 mL) y se lavó secuencialmente con agua (100 mL) y solución de salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío. El residuo bruto se trituró con éter dietílico para proporcionar el material deseado como un sólido amarillo (2,23 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,47 - 1,53 (4H, m), 3,64 (8H, t), 3,69 - 3,71 (3H, m), 5,50-5,60 (2H, s), 6,57 - 6,60 (2H, m), 6,73 (1H, s), 7,99 - 8,03 (2H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 355; HPLC tR = 2,06 min.

Metil 2-[2-(4-aminofenil)-6-morfolin-4-ilpirimidin-4-il]acetato



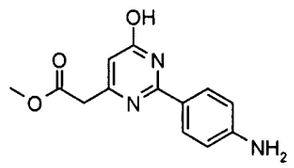
Se agregó DBU (2,2 mL, 14,68 mmol) a metil 2-[2-(4-aminofenil)-6-hidroxipirimidin-4-il]acetato (3,46 g, 13,35 mmol) y *N*-feniltrifluorometanosulfonimida (5,24 g, 14,68 mmol) en DCM (120 mL). La solución resultante se agitó a TA durante 2 horas. Se agregó morfolina

(2,91 mL, 33,36 mmol) y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con DCM (20 mL) y se lavó con una solución saturada acuosa de hidrogenocarbonato de sodio (100 mL). La capa orgánica se secó ($MgSO_4$) se filtró y se concentró al vacío. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido amarillo (3,65 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 3,62 (2H, d), 3,66 (8H,m), 3,72 - 3,73 (3H, m), 6,27 (1H, s), 6,61 - 6,64 (2H, m), 7,17 - 7,23 (2H, m), 8,12 - 8,16 (2H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 329; HPLC tR = 1,74 min.

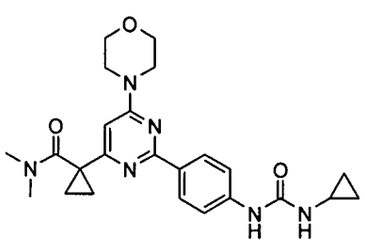
Metil 2-[2-(4-aminofenil)-6-hidroxipirimidin-4-il]acetato



A una solución agitada de dimetil 3-oxopentanodioato (15,06g, 86,50 mmol) en metanol (125 mL) se agregó 4-aminobenzimidamida diclorhidrato (12 g, 57,67 mmol) y carbonato de potasio (19,93 g, 144,17 mmol) y la mezcla de reacción se calentó a 90°C durante 5 horas y luego se dejó enfriar hasta alcanzar TA. La mezcla se concentró al vacío, se disolvió nuevamente en agua (150 mL) y se extrajo con DCM (150 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío. La capa acuosa se ajustó hasta alcanzar pH5 utilizando ácido acético y el precipitado formado se filtró y se secó en un horno de vacío para proporcionar el material deseado como un sólido amarillo (3,49g).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 260; HPLC tR = 1,06 min.

Ejemplo 33: 1-[2-[4-(Ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]-N,N-dimetilciclopropano-1-carboxamida



Se agregó DIPEA (0,142 mL, 0,81 mmol) a una suspensión de ácido 1-[2-[4-

1512

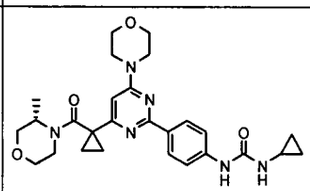
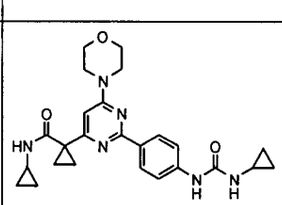
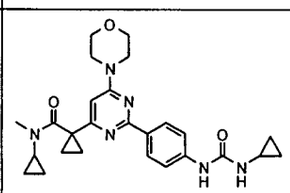
(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico (115 mg, 0,27 mmol), dimetilamina (2,0M en THF, 0,405 mL, 0,81 mmol) y HBTU (155 mg, 0,36 mmol) en DMF (3 mL). Las reacciones se agitaron a TA durante 3 horas, luego se purificaron en una columna de intercambio iónico SCX-2, eluyendo con metanol y luego amoníaco 7N en metanol. El residuo se purificó adicionalmente mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (20 mg).

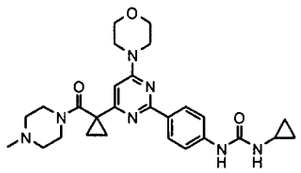
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,39 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,28 - 1,31 (2H, m), 1,51 - 1,54 (2H, m), 2,54 - 2,56 (1H, m), 2,87 (3H, s), 2,94 (3H, s), 3,64 (4H, d), 3,69 - 3,71 (4H, m), 6,22 (1H, s), 6,44 (1H, d), 7,47 - 7,49 (2H, m), 8,16 - 8,19 (2H, m), 8,55 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 451; HPLC tR = 1,83 min.

Ensayo de mTOR Quinasa (Echo): 0,00929μM

Los siguientes compuestos se prepararon en forma análoga a partir de ácido 1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
33a		3-ciclopropil-1-[4-[4-[1-[(3S)-3-metilmorfolina-4-carbonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	507	1,90
33b		N-ciclopropil-1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxamida	463	1,88
33c		N-ciclopropil-1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]-N-metilciclopropano-1-	477	2,00

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		carboxamida		
33d		3-ciclopropil-1-[4-[4-[1-(4-metilpiperazina-1-carbonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	506	1,72

Ejemplo 33a: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,39 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,16 (1H, s), 1,23 (2H, d), 1,32 - 1,36 (2H, m), 1,40 (1H, d), 1,61 - 1,64 (2H, m), 2,52 - 2,57 (1H, m), 3,17 (1H, q), 3,15 - 3,21 (1H, m), 3,46 - 3,49 (1H, m), 3,66 - 3,66 (4H, m), 3,69 (4H, d), 3,71 (1H, s), 4,20 (1H, d), 4,48 (1H, d), 6,24 (1H, s), 6,45 (1H, d), 7,48 (2H, d), 8,19 (2H, d), 8,55 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0584μM

Ejemplo 33b: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,41 - 0,45 (4H, m), 0,61 - 0,66 (4H, m), 1,31 - 1,35 (4H, m), 2,54 - 2,56 (1H, m), 2,71 (1H, d), 3,67 - 3,72 (8H, m), 6,45 (2H, d), 7,50 (2H, d), 8,15 - 8,17 (2H, m), 8,36 (1H, d), 8,56 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,012μM

Ejemplo 33c: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,39 - 0,43 (2H, m), 0,50 (2H, m), 0,63 - 0,65 (2H, m), 0,68 (2H, d), 1,32 -1,40 (2H, m), 1,49 (2H, t), 2,54 - 2,57 (1H, m), 2,75 (3H, d), 2,89 (1H, s), 3,64 (4H, d), 3,69 (4H, d), 6,31 (1H, s), 6,45 (1H, d), 7,48 (2H, d), 8,18 (2H, d), 8,54 (1H, s).

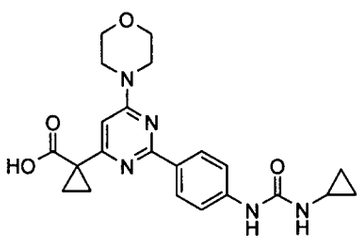
Ensayo de mTOR Quinasa (Echo): 0,00258μM

Ejemplo 33d: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,39 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,30 - 1,32 (2H, m), 1,51 (2H, t), 2,12 (4H, s), 2,33 (3H, s), 2,53 - 2,56 (1H, m), 3,58 (4H, s), 3,67 - 3,71 (8H, d), 6,27 (1H, s), 6,45 (1H, d), 7,47 - 7,50 (2H, m), 8,18 - 8,20 (2H, m), 8,55 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,133μM

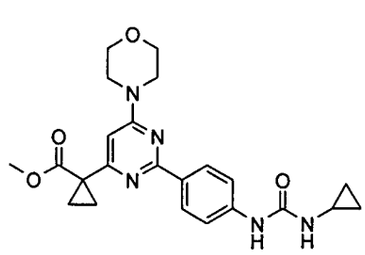
La preparación de ácido 1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico se describe a continuación:

Ácido 1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico



Se agregó en una porción hidróxido-1-hidrato de litio (67 mg, 1,59 mmol) a metil 1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxilato (697 mg, 1,59 mmol) en metanol (8 mL) y agua (8 mL). La suspensión resultante se agitó a 80°C durante 1 hora. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en agua (25 mL) y se lavó con éter dietílico (25 mL). La capa acuosa se acidificó con ácido clorhídrico 2M, el precipitado se recogió mediante filtración, se lavó con éter dietílico y se secó al vacío para proporcionar el material deseado como un sólido marrón (580 mg).
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,40 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,51 - 1,58 (4H, m), 2,53 - 2,57 (1H, m), 3,71 (8H, s), 6,48 (1H, d), 6,75 (1H, s), 7,51 (2H, d), 8,15 (2H, d), 8,63 (1H, s), 14,02 (1H, s)
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 424; HPLC tR = 1,09 min.

Metil 1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxilato



Se agregó en una porción Ciclopropanamina (0,219 mL, 3,15 mmol) a metil 1-[6-morfolin-4-il-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]ciclopropano-1-carboxilato (998 mg, 2,10 mmol) en DMF (20 mL). La solución resultante se agitó a TA durante 4 horas y la mezcla de reacción se evaporó hasta secarse. El producto bruto se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con metanol y luego amoníaco 7M

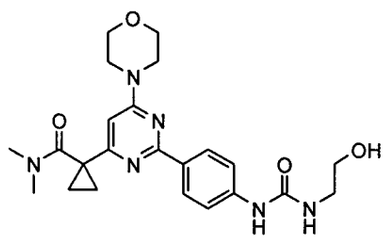
en metanol, para proporcionar el material deseado como un sólido amarillo (757 mg).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,39 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,50 - 1,53 (4H, m), 2,52 - 2,56 (1H, m), 3,64 (3H, s), 3,69 (8H, d), 6,43 (1H, d), 6,84 (1H, s), 7,47 - 7,49 (2H, m), 8,18 (2H, d), 8,55 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 438; HPLC tR = 2,10 min.

La preparación de metil 1-[6-morfolin-4-il-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]ciclopropano-1-carboxilato se describió anteriormente.

Ejemplo 34: 1-[2-[4-(2-Hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]-N,N-dimetilciclopropano-1-carboxamida



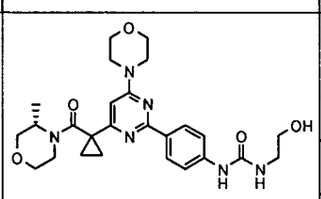
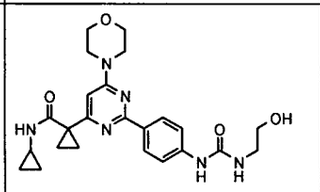
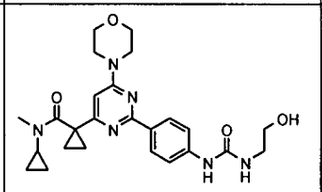
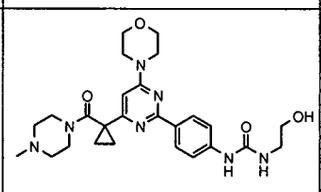
Se agregó DIPEA (0,106 mL, 0,60 mmol) a una suspensión de ácido 1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico (86 mg, 0,20 mmol), dimetilamina (2,0M en THF, 0,30 mL, 0,60 mmol) y HBTU (115 mg, 0,30 mmol) en DMF (3 mL). Las reacciones se agitaron a TA durante 1 hora y luego se purificó utilizando una columna de intercambio iónico SCX-2, eluyendo con metanol y luego amoníaco 7N en metanol. El material aislado se purificó adicionalmente mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (56 mg).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,30 - 1,31 (2H, m), 1,53 (2H, d), 2,89 (3H, s), 2,94 (3H, s), 3,17 - 3,19 (2H, m), 3,47 (2H, d), 3,65 (4H, d), 3,70 -3,71 (4H, d), 4,74 (1H, s), 6,23 (2H, m), 7,47 (2H, d), 8,18 (2H, d), 8,79 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 455; HPLC tR = 1,52 min.

Ensayo de mTOR Quinasa (Echo): 0,00405μM

Los siguientes compuestos se prepararon en forma análoga a partir de ácido 1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
34a		3-(2-hidroxietil)-1-[4-[4-[1-[(3S)-3-metilmorfolina-4-carbonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	511	1,59
34b		N-ciclopropil-1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxamida	467	1,56
34c		N-ciclopropil-1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]-N-metilciclopropano-1-carboxamida	481	1,67
34d		3-(2-hidroxietil)-1-[4-[4-[1-(4-metilpiperazina-1-carbonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	510	1,44

Ejemplo 34a: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,22 - 1,25 (3H, m), 1,33 (2H, d), 1,63 (2H, d), 3,16 - 3,20 (1H, m), 3,17 - 3,19 (3H, m), 3,46 (3H, m), 3,67 (4H, s), 3,71 (4H, d), 3,71 (2H, s), 4,20 (1H, d), 4,50(1H, s), 4,74 (1H, t), 6,25 (2H, m), 7,47 (2H, d), 8,20 (2H, d), 8,79 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0387μM

Ejemplo 34b: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,44 - 0,46 (2H, m), 0,62 - 0,65 (2H, m), 1,32 - 1,37 (4H, m), 2,73 (1H, d), 3,18 (2H, d), 3,46 (2H, t), 3,68 (4H, d), 3,71 - 3,71 (4H, d), 4,74 (1H, t), 6,25 (1H, s), 6,46 (1H, s), 7,47 - 7,50 (2H, m), 8,15 - 8,18 (2H, m), 8,35 (1H, s), 8,80 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0109μM

Ejemplo 34c: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,69 (4H, s), 1,50 (4H, m), 2,40 (1H, s),

1517

2,80 (3H, m), 3,16 - 3,19 (2H, m), 3,47 (2H, q), 3,65 (4H, d), 3,70 - 3,72 (4H, m), 4,74 (1H, t), 6,25 (2H, m), 7,46 - 7,48 (2H, m), 8,17 - 8,19 (2H, m), 8,78 (1H, s).

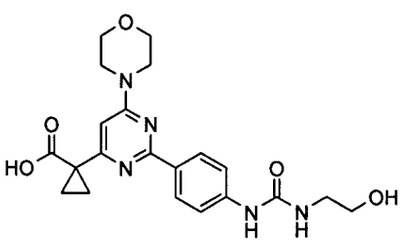
Ensayo de mTOR Quinasa (Echo): 0,00345µM

Ejemplo 34d: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,30 - 1,33 (2H, m), 1,51 - 1,54 (2H, m), 2,10 - 2,15 (5H, m), 2,33 - 2,34 (1H, t), 3,18 - 3,19 (3H, m), 3,36 (1H, d), 3,47 (2H, q), 3,58 (3H, s), 3,66 - 3,71 (4H, m), 3,71 (4H, d), 4,74 (1H, t), 6,25 (1H, t), 6,27 (1H, s), 7,46 - 7,49 (2H, m), 8,18 - 8,21 (2H, m), 8,79 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0863µM

La preparación de ácido 1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico se describe a continuación:

Ácido 1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxílico

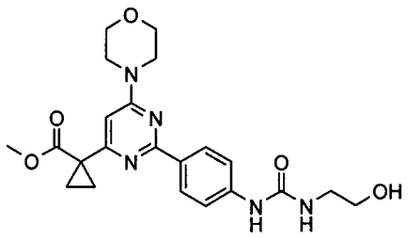


Se agregó en una porción hidróxido-1-hidrato de litio (67,2 mg, 1,60 mmol) a metil 1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxilato (707 mg, 1,60 mmol) en metanol (8 mL) y agua (8 mL). La suspensión resultante se agitó a 80°C durante 1 hora. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en agua (25 mL) y se lavó con éter dietílico (25 mL). La capa acuosa se acidificó con ácido clorhídrico 2M, el precipitado se recogió mediante filtración, se lavó con éter dietílico y se secó al vacío para proporcionar el material deseado como un sólido beige (439 mg).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,51 - 1,58 (4H, m), 3,17 (2H, q), 3,45 (2H, t), 3,70 (8H, s), 4,77 (1H, s), 6,28 (1H, t), 6,74 (1H, s), 7,48 - 7,50 (2H, m), 8,14 - 8,16 (2H, m), 8,86 (1H, s), 14,06 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 428; HPLC tR = 0,92 min.

Metil 1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropano-1-carboxilato



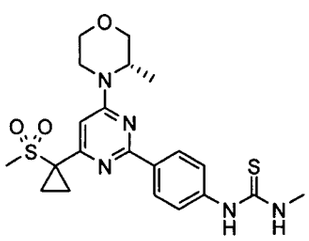
Se agregó en una porción 2-aminoetanol (0,127 mL, 2,10 mmol) a metil 1-[6-morfolin-4-il-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]ciclopropano-1-carboxilato (998 mg, 2,10 mmol) en DMF (20 mL). La solución resultante se agitó a TA durante 16 horas. La mezcla de reacción se evaporó hasta secarse y el producto bruto se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con metanol y luego amoníaco 7N en metanol, para proporcionar el material deseado como un sólido amarillo (767 mg).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,50 - 1,52 (4H, m), 3,17 (2H, q), 3,45 (2H, q), 3,64 (3H, s), 3,70 (8H, s), 4,77 (1H, t), 6,25 (1H, t), 6,83 (1H, s), 7,45 - 7,47 (2H, m), 8,16 - 8,19 (2H, m), 8,81 (1H, s)

Espectro de LCMS. m/z (ESI+) $(M+H)^+$ = 442; HPLC tR = 1,71 min.

La preparación de metil 1-[6-morfolin-4-il-2-[4-(fenoxicarbonilamino)fenil]pirimidin-4-il]ciclopropano-1-carboxilato se describió anteriormente.

Ejemplo 35: 3-Metil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea



A una solución de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina (60mg, 0,16 mmol) en DCM (2 mL) y THF (1 mL) se agregó una solución de di(imidazol-1-il)metanotione (37 mg, 0,21 mmol) en DCM (1 mL) y la solución resultante se agitó a TA durante 3 horas. Se agregó metilamina (2M en THF, 0,4 mL, 0,80 mmol) y luego trietilamina (0,022 mL, 0,16mmol) y la solución se agitó durante 1 hora a TA. El disolvente se evaporó y el producto bruto se purificó mediante HPLC preparativa, utilizando mezclas

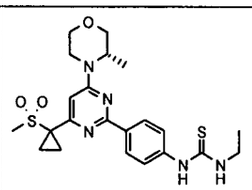
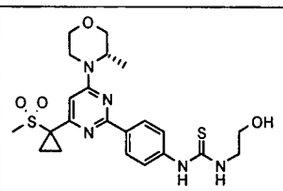
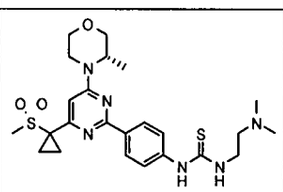
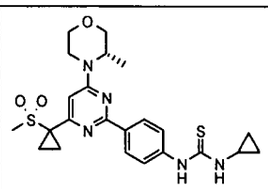
cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes, para proporcionar el material deseado como un sólido blanco (19 mg).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 – 1,58 (2H, m), 1,66 – 1,69 (2H, m), 2,95 (3H, d), 3,16 (3H, s), 3,21 – 3,26 (1H, m), 3,45 – 3,52 (1H, m), 3,61 – 3,65 (1H, m), 3,76 (1H, d), 3,95 – 3,99 (1H, m), 4,20 – 4,23 (1H, m), 4,55 – 4,63 (1H, m), 6,80 (1H, s), 7,55 (2H, d), 7,84 (1H, s), 8,26 (2H, d), 9,73 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 462; HPLC tR = 1,86min.

Ensayo de mTOR Quinasa (Echo): 0,00531μM

Los compuestos a continuación se prepararon en forma análoga a partir de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina utilizando la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
35a		3-etil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea	476	1,94
35b		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea	492	1,68
35c		3-(2-dimetilaminoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea	519	1,99
35d		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea	488	1,89

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Ejemplo 35a: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,14 (3H, t), 1,24 (3H, d), 1,55 – 1,58 (2H, m), 1,66 – 1,69 (2H, m), 3,17 – 3,25 (1H, m), 3,29 (3H, s), 3,45 – 3,51 (3H, m), 3,61 – 3,65 (1H, m), 3,76 (1H, d), 3,95 – 3,99 (1H, m), 4,20 – 4,23 (1H, m), 4,55 – 4,62 (1H, m), 6,80 (1H, s), 7,57 (2H, d), 7,88 (1H, s), 8,25 (2H, d), 9,63 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00552μM

Ejemplo 35b: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,58 (2H, m), 1,66 - 1,69 (2H, m), 3,17 - 3,25 (1H, m), 3,29 (3H, s), 3,45 - 3,52 (1H, m), 3,57 (4H, s), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,20 - 4,23 (1H, m), 4,55 - 4,62 (1H, m), 4,77 - 4,85 (1H, m), 6,80 (1H, s), 7,63 (2H, d), 7,86 (1H, s), 8,26 (2H, d), 9,81 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000577μM

Ejemplo 35c: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,58 (2H, m), 1,66 - 1,69 (2H, m), 2,20 (6H, s), 2,45 (2H, t), 3,18 - 3,25 (1H, m), 3,26 (3H, s), 3,45 - 3,52 (1H, m), 3,56 (2H, s), 3,61 - 3,65 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,21 (1H, d), 4,56 - 4,61 (1H, m), 6,80 (1H, s), 7,65 (2H, d), 7,77 (1H, s), 8,25 (2H, d), 9,90 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,108μM

Ejemplo 35d: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,58 - 0,62 (2H, m), 0,74 - 0,79 (2H, m), 1,24 (3H, d), 1,55 - 1,59 (2H, m), 1,67 - 1,69 (2H, m), 2,89 - 2,97 (1H, m), 3,17 - 3,27 (1H, m), 3,30 (3H, s), 3,46 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,77 (1H, d), 3,96 - 3,99 (1H, m), 4,21 - 4,24 (1H, m), 4,60 (1H, s), 6,81 (1H, s), 7,62 (2H, d), 8,14 (1H, s), 8,25 (2H, d), 9,51 (1H, s).

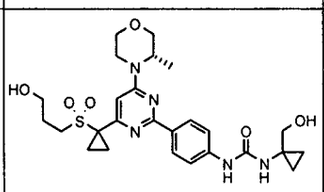
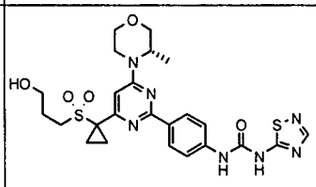
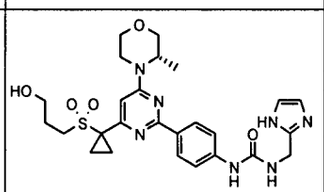
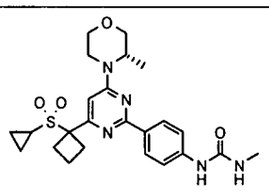
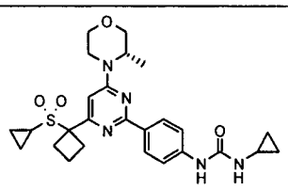
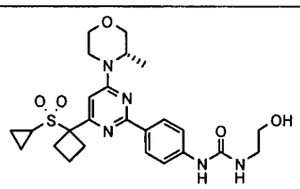
Ensayo de mTOR Quinasa (Echo): 0,00411μM

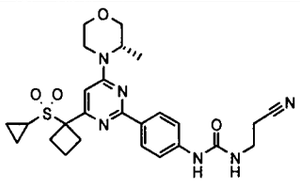
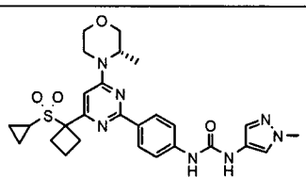
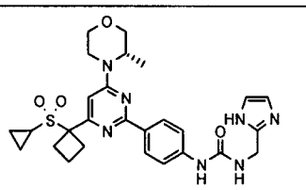
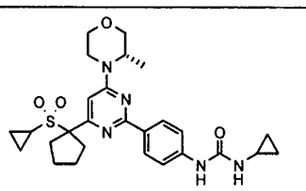
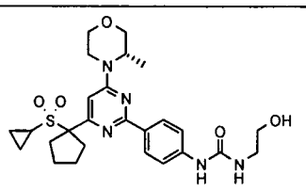
La preparación de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina se describió anteriormente.

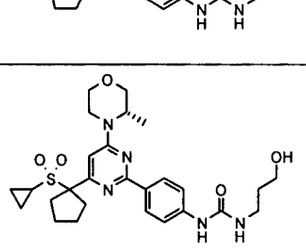
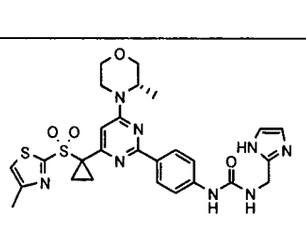
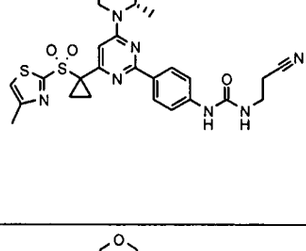
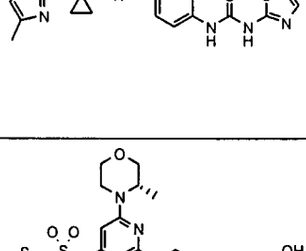
Ejemplo 36

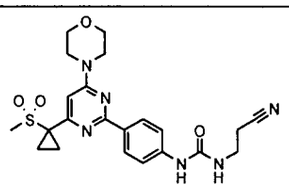
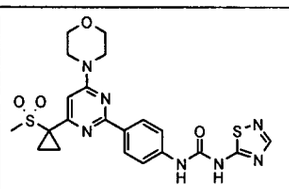
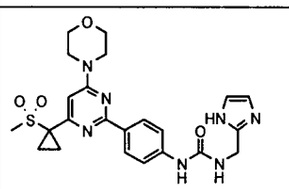
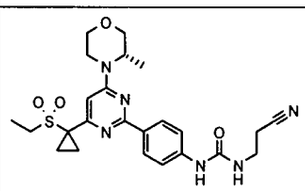
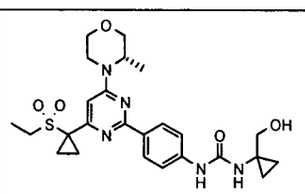
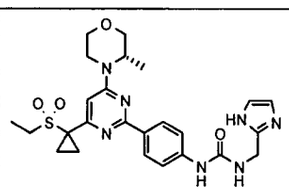
Los siguientes compuestos se prepararon de acuerdo con el siguiente Procedimiento General:

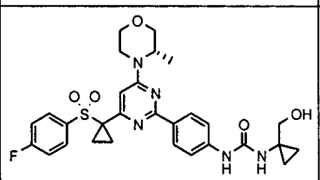
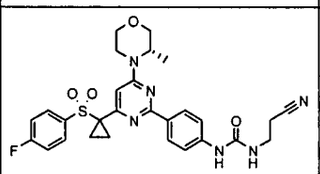
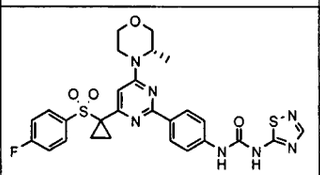
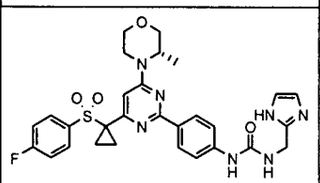
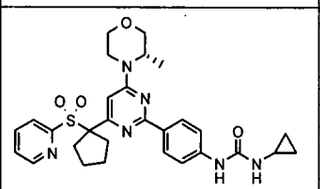
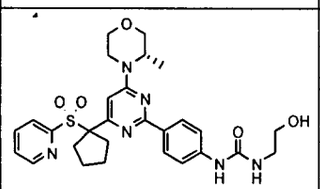
El fenilcarbamato apropiado y un exceso de trietilamina y la amina apropiada se disolvieron en DMF, NMP o DMA y se agitaron a 50°C – 70°C durante 2 – 18 horas (a menos que se indique de otra forma). Los materiales se purificaron mediante HPLC preparativa excepto donde se indique lo contrario.

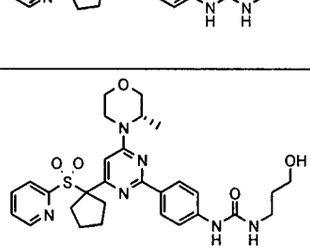
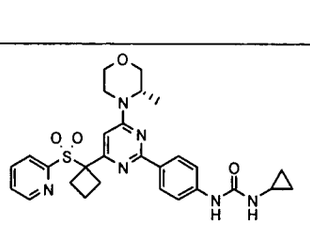
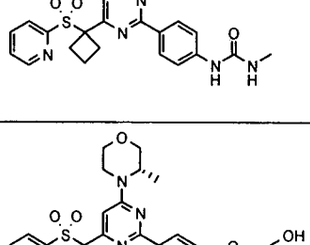
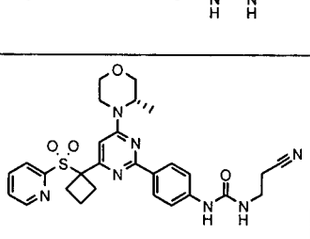
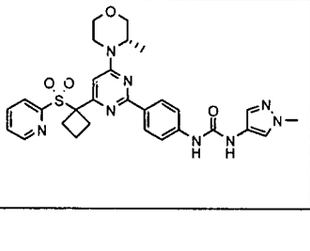
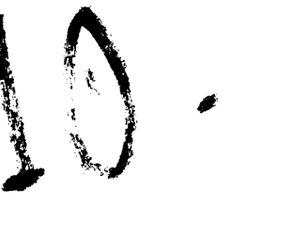
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36a		3-[1-(hidroximetil)ciclopropil]-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	546	1,67
36b		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	560	1,41
36c		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea	556	1,65
36d		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	486	1,92
36e		3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	512	2,16
36f		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-	516	1,84

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		hidroxietil)urea		
36g		3-(2-cianoetil)-1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	525	2,07
36h		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	552	2,04
36i		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea	552	1,99
36j		3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	526	2,34
36k		1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	530	1,97

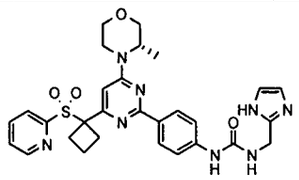
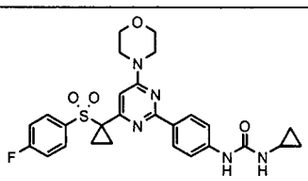
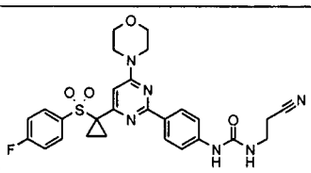
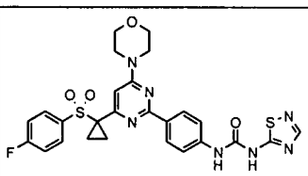
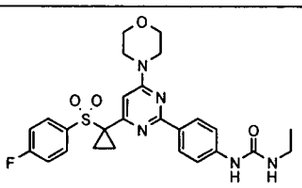
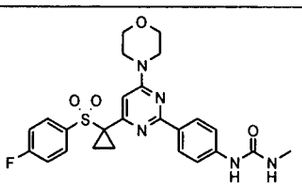
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36l		3-(2-cianoetil)-1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	539	2,19
36m		1-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	544	1,99
36n		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	595	2,07
36o		3-(2-cianoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	568	2,25
36p		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	599	1,81
36q		3-[1-(hidroximetil)ciclopropil]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	585	2,09

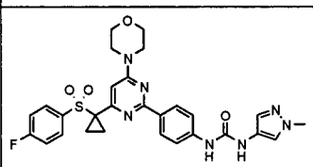
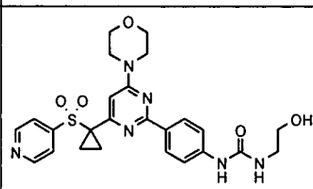
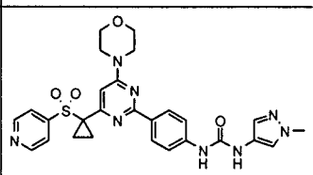
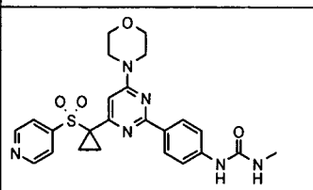
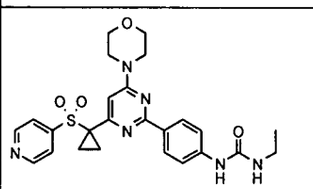
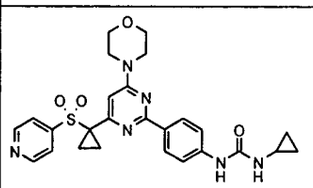
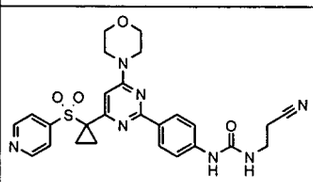
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36r		3-(2-cianoetil)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	471,5	1,66
36s*		1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	502	1,61
36t		3-(1H-imidazol-2-ilmetil)-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea	498,6	2,02
36u		3-(2-cianoetil)-1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	499,1	2,10
36v		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[1-(hidroximetil)ciclopropil]urea	516,1	1,97
36w		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea	526,1	1,94

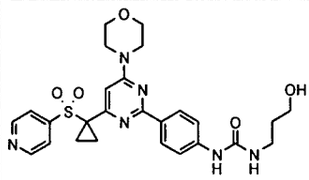
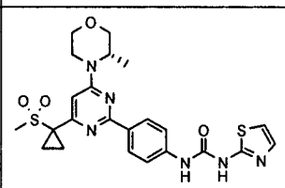
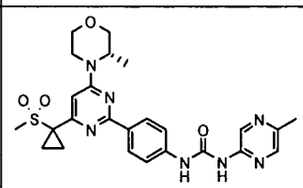
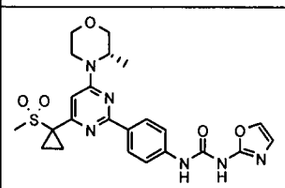
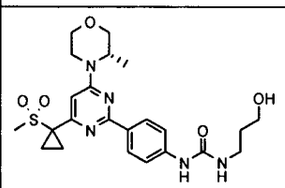
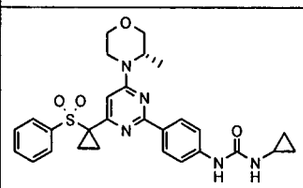
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36x		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[1-(hidroximetil)ciclopropil]urea	582	2,17
36y		3-(2-cianoetil)-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	565	2,40
36z		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	596	1,49
36aa		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea	592	2,07
36ab		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]fenil]urea	563	2,38
36ac		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]fenil]urea	567	2,01

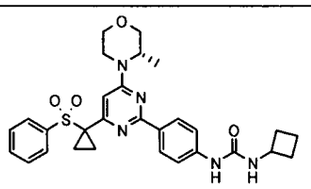
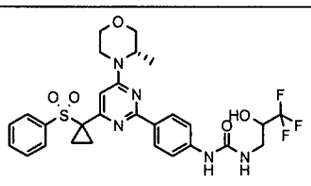
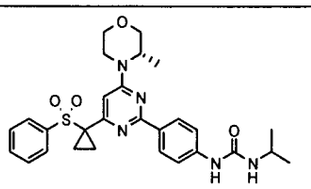
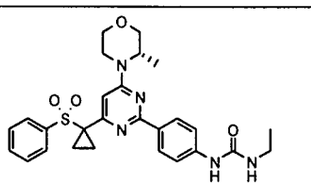
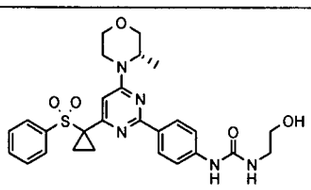
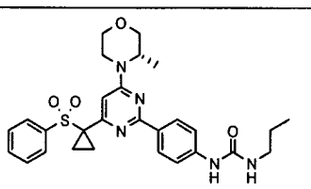
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36ad		3-(2-cianoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]fenil]urea	576	2,28
36ae		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]fenil]urea	581	2,05
36af		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea	549	2,25
36ag		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea	523	2,08
36ah		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea	553	1,89
36ai		3-(2-cianoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea	562	2,15
36aj		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-	589	2,11

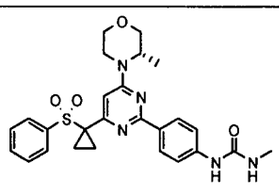
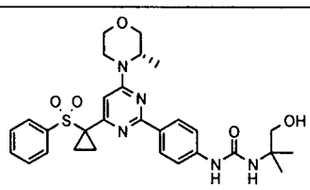
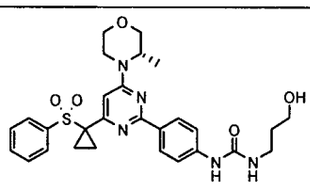
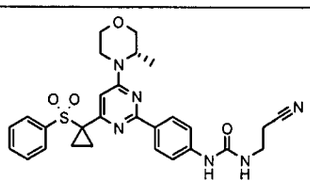
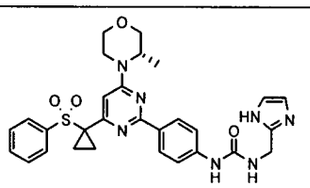
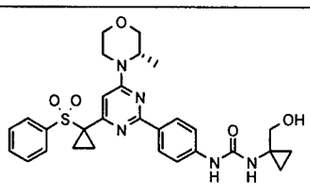
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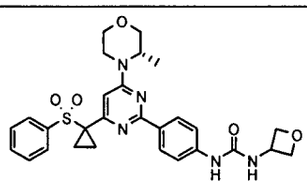
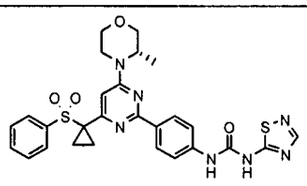
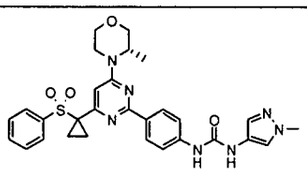
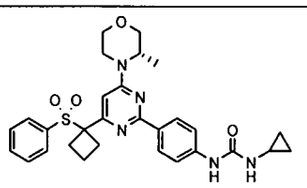
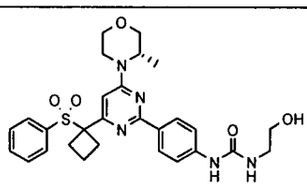
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		il)urea		
36ak		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea	589	2,34
36al**		3-ciclopropil-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	538	2,36
36am**		3-(2-cianoetil)-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	551	2,27
36an		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	542	1,41
36ao		1-etil-3-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	526	2,14
36ap		3-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-metilurea	512	1,99

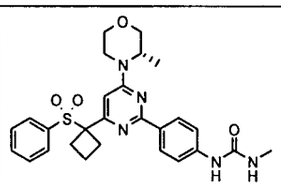
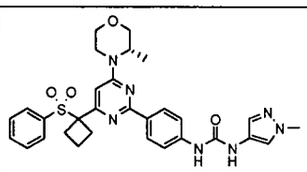
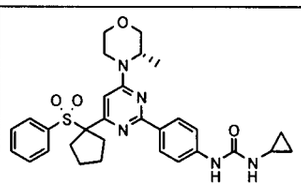
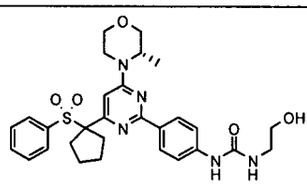
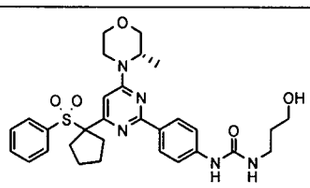
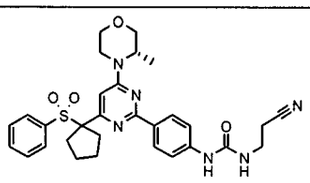
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36aq		3-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-(1-metilpirazol-4-il)urea	578	2,04
36ar		3-(2-hidroxietil)-1-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	525	1,66
36as		1-(1-metilpirazol-4-il)-3-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	561	1,81
36at		1-metil-3-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	495	1,81
36au		1-etil-3-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	509	1,99
36av		3-ciclopropil-1-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	521	1,95
36aw		3-(2-cianoetil)-1-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	534	1,89

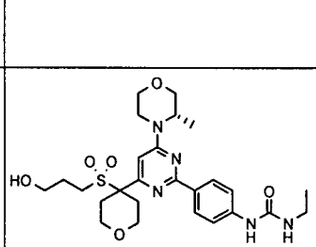
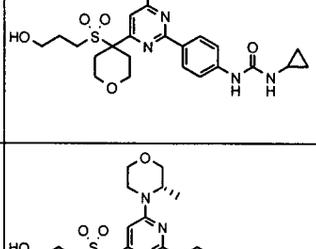
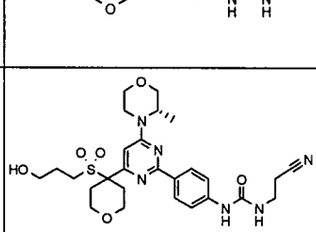
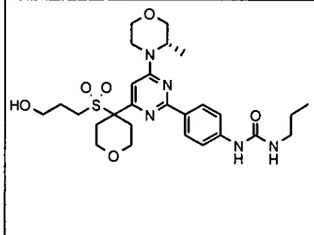
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36ax		3-(3-hidroxipropil)-1-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	539	1,72
36ay		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,3-tiazol-2-il)urea	515	2,19
36az		3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-1-(5-metilpirazin-2-il)urea	524	2,35
36ba		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,3-oxazol-2-il)urea	499	1,99
36bb		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	490	1,75
36bc		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea	534	2,39

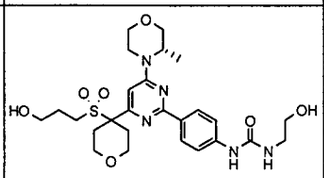
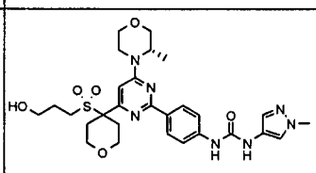
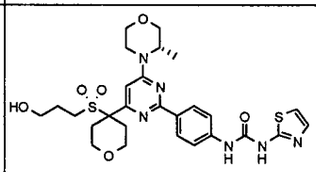
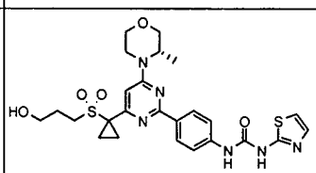
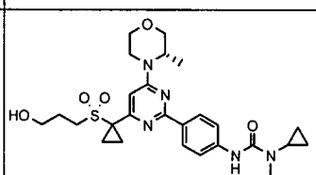
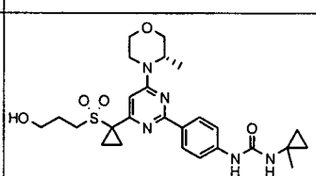
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36bd		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclobutilurea	548	2,61
36be		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3,3,3-trifluoro-2-hidroxipropil)urea	606	2,45
36bf		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-propan-2-ilurea	536	2,51
36bg		3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	522	2,32
36bh		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	538	1,98
36bi		3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea	536	2,49

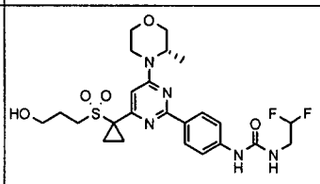
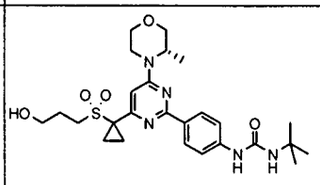
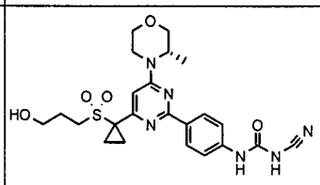
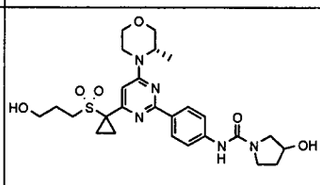
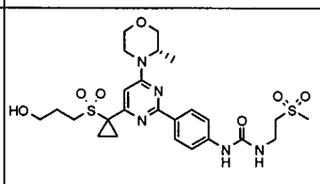
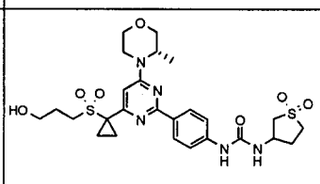
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36bj		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	508	2,16
36bk		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	566	2,28
36bl		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	552	2,03
36bm		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-cianoetil)urea	547	2,24
36bn		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea	574	2,12
36bo		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[1-	564	2,11

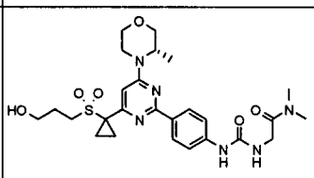
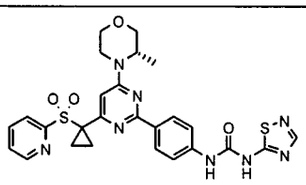
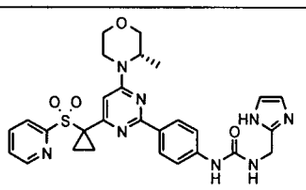
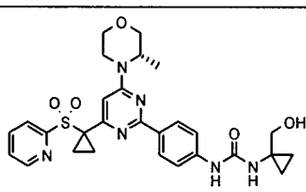
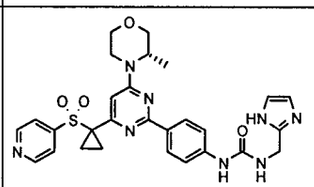
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		(hidroximetil)ciclopropil]urea		
36bp		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(oxetan-3-il)urea	550	2,13
36bq		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	578	1,35
36br		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	574	2,21
36bs		1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea	548	2,53
36bt		1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	552	2,14

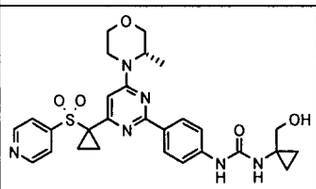
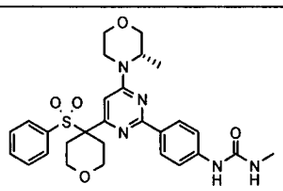
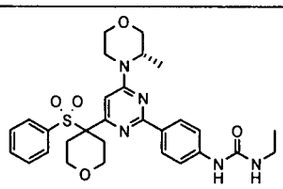
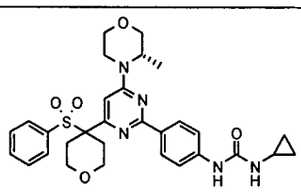
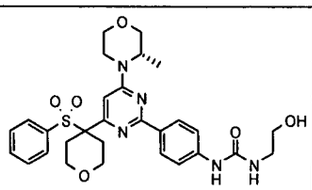
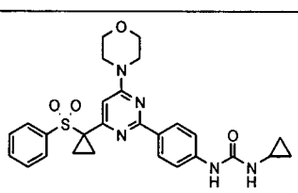
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36bu		1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	522	2,35
36bv		1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	588	2,37
36bw		1-[4-[4-[1-(bencenosulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea	562	2,75
36bx		1-[4-[4-[1-(bencenosulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	566	2,30
36by		1-[4-[4-[1-(bencenosulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	580	2,31
36bz		1-[4-[4-[1-(bencenosulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-	575	2,55

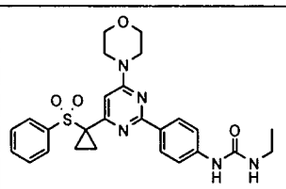
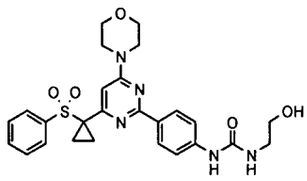
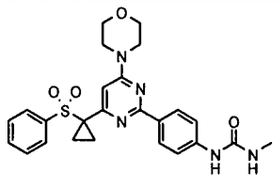
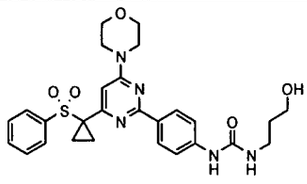
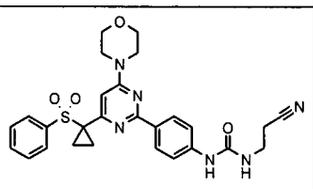
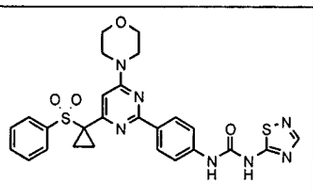
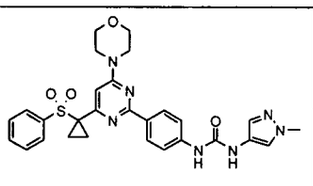
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		cianoetil)urea		
36ca***		1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	534	1,56
36cb***		1-etil-3-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	548	1,67
36cc***		3-ciclopropil-1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	560	1,71
36cd***		3-ciclobutil-1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	574	1,89
36ce***		3-(2-cianoetil)-1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	573	1,62
36cf***		3-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea	562	1,83

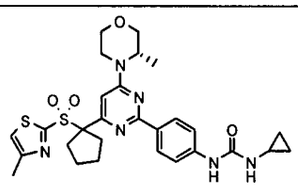
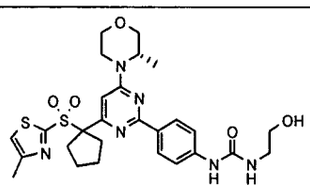
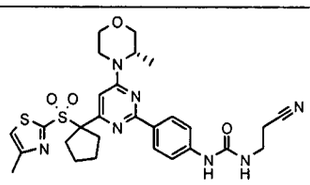
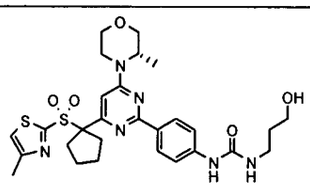
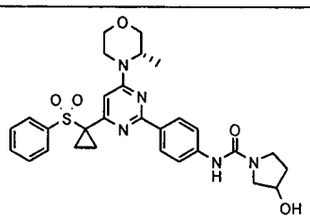
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36cg***		3-(2-hidroxietil)-1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	564	1,46
36ch***		1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	600	1,62
36ci***		1-[4-[4-[4-(3-hidroxipropilsulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,3-tiazol-2-il)urea	603	1,87
36cj***		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,3-tiazol-2-il)urea	559	1,94
36ck***		1-ciclopropil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-metilurea	530	1,96
36cl***		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilciclopropil)urea	530	1,88

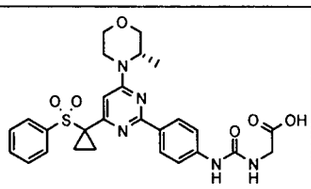
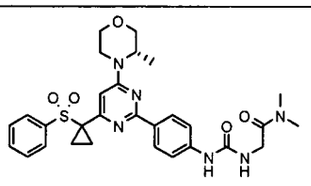
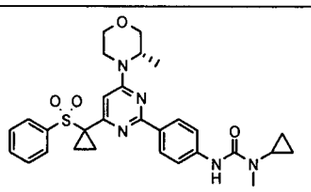
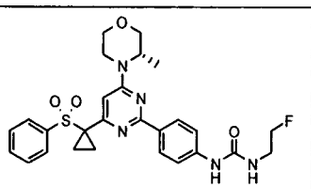
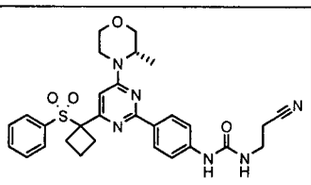
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36cm***		3-(2,2-difluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	540	1,85
36cn***		3-*terc*-butil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	532	2,10
36co***		3-ciano-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	501	1,12
36cp***		3-hidroxi-N-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]pirrolidina-1-carboxamida	546	1,52
36cq***		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-metilsulfoniletil)urea	582	1,61
36cr***		3-(1,1-dioxotiolan-3-il)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	594	1,66

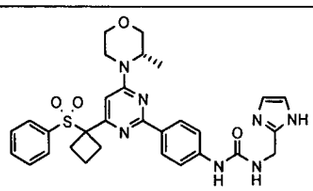
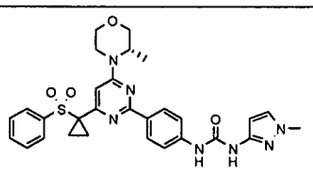
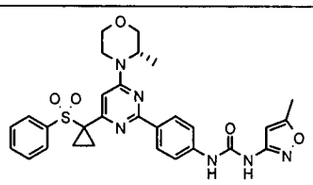
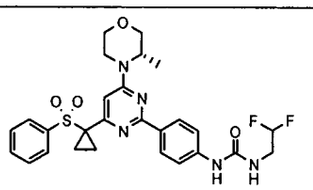
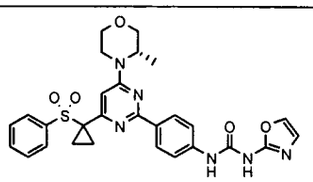
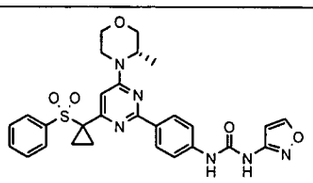
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36cs**		2-[[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamoilamino]-N,N-dimetilacetamida	561	1,59
36ct		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	579	1,37
36cu		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	575	1,76
36cv		3-[1-(hidroximetil)ciclopropil]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	565	1,77
36cw		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	576	1,77

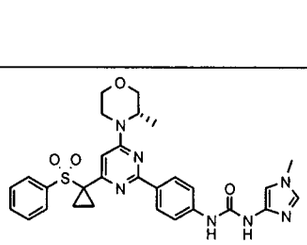
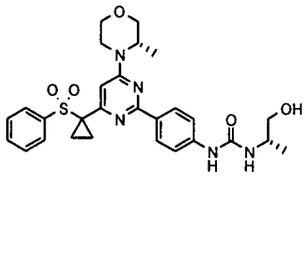
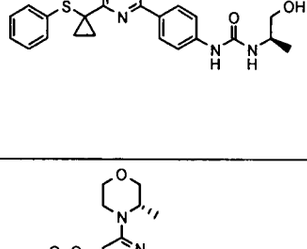
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36cx		3-[1-(hidroximetil)ciclopropil]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	566	1,78
36cy		1-[4-[4-[4-(bencenosulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	553	2,14
36cz		3-[4-[4-[4-(bencenosulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	567	2,29
36da		1-[4-[4-[4-(bencenosulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea	579	2,29
36db		1-[4-[4-[4-(bencenosulfonil)oxan-4-il]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	583	1,93
36dc		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-ciclopropilurea	520	2,24

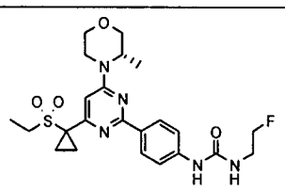
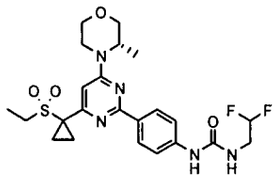
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36dd		3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-etilurea	508	2,24
36de		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-hidroxietil)urea	524	1,89
36df		3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-metilurea	494	2,08
36dg		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	538	1,95
36dh		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(2-cianoetil)urea	533	2,16
36di		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	564	1,41
36dj		3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-(1-metilpirazol-4-	560	2,11

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		il)urea		
36dk**		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]fenil]urea	583	2,62
36dl**		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]fenil]urea	588	2,24
36dm**		3-(2-cianoetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]fenil]urea	596	2,50
36dn**		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]fenil]urea	601	2,28
36do		N-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-hidroxipirrolidina-1-carboxamida	564	2,02

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36dp		2-[[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamoilamino]ácido acético	552	1,21
36dq		2-[[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamoilamino]-N,N-dimetilacetamida	579	2,11
36dr		3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-ciclopropil-1-metilurea	548	2,61
36ds		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	540	2,33
36dt		1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-cianoetil)urea	561	2,41

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36du		1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea	588	2,31
36dv		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-3-il)urea	574	2,76
36dw		3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-(5-metil-1,2-oxazol-3-il)urea	575	2,97
36dx		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea	558	2,81
36dy		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,3-oxazol-2-il)urea	561	2,51
36dz		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2-	561	2,85

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		oxazol-3-il)urea		
36ea		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2,2-trifluoroetil)urea	576	2,94
36eb		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilimidazol-4-il)urea	574	2,61
36ec		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea	552	2,47
36ed		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea	552	2,47
36ee		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-cloroetil)urea	590	2,84

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
36ef**		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	493	2,46
36eg**		3-(2,2-difluoroetil)-1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	511	2,60

* Siguiendo las condiciones de reacción iniciales la mezcla se colocó en un tubo sellado y se calentó a 100°C en un reactor de microondas durante 10 minutos.

** El material se purificó mediante trituración con éter dietílico

*** Siguiendo las condiciones de reacción iniciales la mezcla se dejó enfriar, se agregó fluoruro de tetrabutilamonio (1 equivalente) y la reacción se agitó a TA durante 1 hora. La reacción se purificó mediante HPLC prep.

**** La mezcla se agitó a TA durante 16 horas

Ejemplo 36a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,63 - 0,68 (2H, m), 0,68 - 0,73 (2H, m), 1,23 (3H, d), 1,53 - 1,58 (2H, m), 1,60 - 1,66 (2H, m), 1,88 - 1,98 (2H, m), 3,16 - 3,25 (1H, m), 3,28 - 3,35 (4H, m), 3,47 - 3,54 (3H, m), 3,63 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,23 (1H, d), 4,56 (1H, s), 4,69 (1H, t), 6,57 (1H, s), 6,77 (1H, s), 7,47 (2H, d), 8,21 (2H, d), 8,68 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,142μM

Ejemplo 36b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,54 - 1,60 (2H, m), 1,62 - 1,68 (2H, m), 1,92 - 1,99 (2H, m), 3,23 - 3,31 (3H, m), 3,47 - 3,58 (3H, m), 3,64 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,21 (1H, d), 4,57 (1H, s), 4,71 (1H, t), 6,80 (1H, s), 7,64 (2H, d), 8,30 (2H, d), 9,46 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00179μM

Ejemplo 36c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,52 - 1,58 (2H, m), 1,62 -

1,65 (2H, m), 1,89 - 1,97 (2H, m), 3,22 - 3,34 (3H, m), 3,44 - 3,56 (3H, m), 3,63 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,16 - 4,24 (1H, m), 4,35 (2H, d), 4,55 (1H, s), 4,69 (1H, s), 6,67 (1H, t), 6,77 (1H, s), 6,99 (2H, s), 7,52 (2H, d), 8,21 (2H, d), 8,99 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,114μM

Ejemplo 36d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,70 - 0,78 (2H, m), 0,81 - 0,88 (2H, m), 1,23 (3H, d), 1,88 - 1,96 (1H, m), 2,01 - 2,14 (1H, m), 2,67 (3H, d), 2,81 - 2,99 (4H, m), 3,15 - 3,26 (2H, m), 3,50 (1H, dd), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,21 (1H, d), 4,55 (1H, s), 6,06 (1H, t), 6,70 (1H, s), 7,50 (2H, d), 8,23 (2H, d), 8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00317μM

Ejemplo 36e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,39 - 0,44 (2H, m), 0,61 - 0,68 (2H, m), 0,72 - 0,78 (2H, m), 0,82 - 0,88 (2H, m), 1,23 (3H, d), 1,84 - 1,96 (1H, m), 2,02 - 2,12 (1H, m), 2,50 - 2,59 (2H, m), 2,81 - 3,01 (4H, m), 3,17 - 3,24 (1H, m), 3,50 (1H, dd), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,22 (1H, d), 4,55 (1H, s), 6,42 (1H, t), 6,71 (1H, s), 7,48 (2H, d), 8,24 (2H, d), 8,53 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00667μM

Ejemplo 36f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,68 - 0,80 (2H, m), 0,81 - 0,89 (2H, m), 1,23 (3H, d), 1,84 - 1,95 (1H, m), 2,02 - 2,13 (1H, m), 2,76 - 3,00 (4H, m), 3,11 - 3,27 (3H, m), 3,43 - 3,56 (3H, m), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,21 (1H, d), 4,54 (1H, s), 4,72 (1H, t), 6,24 (1H, t), 6,70 (1H, s), 7,48 (2H, d), 8,24 (2H, d), 8,79 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00278μM

Ejemplo 36g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,69 - 0,79 (2H, m), 0,81 - 0,89 (2H, m), 1,23 (3H, d), 1,84 - 1,96 (1H, m), 2,02 - 2,12 (1H, m), 2,63 - 2,73 (2H, m), 2,83 - 3,03 (4H, m), 3,14 - 3,23 (1H, m), 3,33 - 3,43 (2H, m), 3,51 (1H, dd), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,22 (1H, d), 4,55 (1H, s), 6,51 (1H, t), 6,71 (1H, s), 7,51 (2H, d), 8,25 (2H, d), 8,90 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00841μM

Ejemplo 36h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,70 - 0,80 (2H, m), 0,82 - 0,91 (2H, m), 1,23 (3H, d), 1,86 - 1,97 (1H, m), 2,02 - 2,12 (1H, m), 2,77 - 3,03 (4H, m), 3,15 - 3,29 (5H, m), 3,51 (1H, d), 3,66 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,22 (1H, d), 4,55 (1H, s), 6,72 (1H, s), 7,38 (1H, s), 7,54 (2H, d), 7,76 (1H, s), 8,27 (2H, d), 8,37 (1H, s), 8,83 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00314μM

Ejemplo 36i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,74 - 0,84 (2H, m), 0,87 - 0,94 (2H, m), 1,28 (3H, d), 1,91 - 2,01 (1H, m), 2,08 - 2,19 (1H, m), 2,84 - 3,09 (4H, m), 3,25 - 3,32 (2H,

m), 3,56 (1H, d), 3,71 (1H, d), 3,82 (1H, d), 4,03 (1H, d), 4,27 (1H, d), 4,38 (2H, d), 4,61 (1H, s), 6,68 (1H, t), 6,76 (1H, s), 7,00 (1H, s), 7,56 (2H, d), 8,31 (2H, d), 8,98 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0518μM

Ejemplo 36j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,39 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 0,68 - 0,75 (2H, m), 0,80 - 0,87 (2H, m), 1,22 (3H, d), 1,52 - 1,61 (2H, m), 1,76 - 1,86 (2H, m), 2,50 - 2,61 (4H, m), 2,74 - 2,90 (2H, m), 3,14 - 3,24 (1H, m), 3,50 (2H, dd), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,22 (1H, d), 4,54 (1H, s), 6,42 (1H, s), 6,81 (1H, s), 7,50 (2H, d), 8,24 (2H, d), 8,53 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,018μM

Ejemplo 36k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,66 - 0,77 (2H, m), 0,80 - 0,89 (2H, m), 1,22 (3H, d), 1,52 - 1,61 (2H, m), 1,76 - 1,86 (2H, m), 2,43 - 2,61 (3H, m), 2,75 - 2,89 (2H, m), 3,16 - 3,22 (3H, m), 3,43 - 3,55 (3H, m), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,22 (1H, d), 4,54 (1H, s), 4,73 (1H, t), 6,25 (1H, t), 6,81 (1H, s), 7,49 (2H, d), 8,24 (2H, d), 8,79 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0131μM

Ejemplo 36l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,66 - 0,76 (2H, m), 0,82 - 0,87 (2H, m), 1,22 (3H, d), 1,53 - 1,60 (2H, m), 1,74 - 1,85 (2H, m), 2,49 - 2,61 (3H, m), 2,65 - 2,72 (2H, m), 2,74 - 2,88 (2H, m), 3,16 - 3,25 (1H, m), 3,33 - 3,40 (2H, m), 3,50 (1H, d), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,23 (1H, d), 4,55 (1H, s), 6,52 (1H, t), 6,81 (1H, s), 7,51 (2H, d), 8,26 (2H, d), 8,91 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0428μM

Ejemplo 36m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,67 - 0,77 (2H, m), 0,81 - 0,89 (2H, m), 1,22 (3H, d), 1,52 - 1,64 (4H, m), 1,78 - 1,85 (2H, m), 2,41 - 2,56 (3H, m), 2,74 - 2,93 (2H, m), 3,13 - 3,25 (3H, m), 3,42 - 3,56 (3H, m), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,16 - 4,26 (1H, m), 4,47 (1H, t), 4,54 (1H, s), 6,19 (1H, t), 6,81 (1H, s), 7,49 (2H, d), 8,24 (2H, d), 8,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0347μM

Ejemplo 36n: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,76 - 1,80 (2H, m), 1,93 - 1,97 (2H, m), 2,48 (3H, s), 3,14 - 3,21 (1H, m), 3,47 (1H, t), 3,62 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,14 - 4,17 (1H, m), 4,32 (2H, d), 4,42 - 4,49 (1H, m), 6,61 (1H, t), 6,78 (1H, s), 6,93 (2H, bs), 7,43 (2H, d), 7,84 (1H, s), 7,90 (2H, d), 8,90 (1H, s), 11,85 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0248μM

Ejemplo 36o: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,77 - 1,79 (2H, m), 1,94 -

1,97 (2H, m), 2,48 (3H, s), 2,70 (2H, t), 3,14 - 3,22 (1H, m), 3,35 - 3,39 (2H, m), 3,44 - 3,50 (1H, m), 3,60 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,15 - 4,18 (1H, m), 4,42 - 4,48 (1H, m), 6,51 (1H, t), 6,78 (1H, s), 7,43 (2H, d), 7,84 (1H, s), 7,90 (2H, d), 8,90 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00358μM

Ejemplo 36p: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,77 - 1,81 (2H, m), 1,95 - 1,99 (2H, m), 2,51 (3H, s), 3,16 - 3,24 (1H, m), 3,45 - 3,51 (1H, m), 3,61 - 3,65 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,16 - 4,20 (1H, m), 4,43 - 4,49 (1H, m), 6,82 (1H, s), 7,55 (2H, d), 7,87 (1H, s), 8,00 (2H, d), 8,37 (1H, s), 9,45 (1H, s), 11,32 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00161μM

Ejemplo 36q: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,63 - 0,66 (2H, m), 0,69 - 0,73 (2H, m), 1,21 (3H, d), 1,77 - 1,80 (2H, m), 1,94 - 1,97 (2H, m), 2,48 (3H, s), 3,14 - 3,21 (1H, m), 3,44 (2H, d), 3,47 - 3,50 (1H, m), 3,60 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,98 (1H, m), 4,14 - 4,17 (1H, m), 4,42 - 4,48 (1H, m), 4,83 (1H, s), 6,54 (1H, s), 6,77 (1H, s), 7,40 (2H, d), 7,84 (1H, s), 7,89 (2H, d), 8,65 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0889μM

Ejemplo 36r: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,54 - 1,57 (2H, m), 1,65 - 1,68 (2H, m), 2,70 (2H, t), 3,27 (3H, s), 3,35 - 3,40 (2H, m), 3,72 (8H, s), 6,53 (1H, t), 6,81 (1H, s), 7,50 - 7,54 (2H, m), 8,20 - 8,24 (2H, m), 8,93 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00733μM

Ejemplo 36s: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,55 - 1,59 (2H, m), 1,67 - 1,70 (2H, m), 3,27 (3H, s), 3,73 (8H, s), 6,86 (1H, s), 7,61 - 7,65 (2H, m), 8,30 - 8,33 (2H, m), 8,37 (1H, s), 9,44 (1H, s), 11,40 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00475μM

Ejemplo 36t: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,54 - 1,57 (2H, m), 1,65 - 1,68 (2H, m), 3,27 (3H, s), 3,72 (8H, s), 4,32 (2H, d), 6,62 (1H, t), 6,81 - 6,83 (2H, m), 7,03 (1H, s), 7,50 - 7,54 (2H, m), 8,20 - 8,23 (2H, m), 8,94 (1H, s), 11,83 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,194μM

Ejemplo 36u: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,32 (3H, t), 1,53 - 1,56 (2H, m), 1,62 - 1,65 (2H, m), 2,70 (2H, t), 3,17 - 3,24 (1H, m), 3,35 - 3,52 (5H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 - 4,24 (1H, m), 4,52 - 4,58 (1H, m), 6,53 (1H, t), 6,78 (1H, s), 7,50 - 7,54 (2H, m), 8,18 - 8,22 (2H, m), 8,92 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00922μM

Ejemplo 36v: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,63 - 0,67 (2H, m), 0,69 - 0,73 (2H,

m), 1,23 (3H, d), 1,32 (3H, t), 1,53 - 1,58 (2H, m), 1,60 - 1,65 (2H, m), 3,17 - 3,24 (1H, m), 3,40 - 3,52 (5H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 - 4,24 (1H, m), 4,52 - 4,58 (1H, m), 4,81 - 4,86 (1H, m), 6,57 (1H, s), 6,78 (1H, s), 7,46 - 7,50 (2H, m), 8,17 - 8,21 (2H, m), 8,68 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,467μM

Ejemplo 36w: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,32 (3H, t), 1,53 - 1,56 (2H, m), 1,62 - 1,65 (2H, m), 3,17 - 3,24 (1H, m), 3,40 - 3,52 (3H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,18 - 4,24 (1H, m), 4,32 (2H, d), 4,53 - 4,58 (1H, m), 6,63 (1H, t), 6,78 (1H, s), 6,84 (1H, s), 7,03 (1H, s), 7,50 - 7,54 (2H, m), 8,18 - 8,22 (2H, m), 8,93 (1H, s), 11,84 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,11μM

Ejemplo 36x: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,63 - 0,66 (2H, m), 1,18 (2H, d), 1,59 - 1,62 (3H, m), 1,88 - 1,90 (2H, m), 2,09 (2H, s), 3,15 (1H, dt), 3,30 (2H, s), 3,44 - 3,49 (1H, m), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,14 (1H, d), 4,41 (1H, s), 4,83 (1H, s), 6,53 (1H, s), 6,65 (1H, s), 7,36 - 7,44 (4H, m), 7,80 - 7,86 (4H, m), 8,64 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,182μM

Ejemplo 36y: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,59 - 1,62 (2H, m), 1,88 - 1,91 (2H, m), 2,70 (2H, t), 3,13 - 3,18 (1H, m), 3,33 - 3,39 (2H, m), 3,46 (1H, t), 3,61 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,14 (1H, d), 4,43 (1H, s), 6,49 (1H, t), 6,65 (1H, s), 7,40 - 7,44 (4H, m), 7,81 - 7,86 (4H, m), 8,89 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00131μM

Ejemplo 36z: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,62 - 1,64 (2H, m), 1,90 - 1,94 (2H, m), 3,17 - 3,18 (1H, m), 3,42 - 3,51 (1H, m), 3,62 (1H, d), 3,76 (1H, d), 3,94 - 3,98 (1H, m), 4,16 (1H, d), 4,44 (1H, s), 6,69 (1H, s), 7,43 (2H, t), 7,52 (2H, d), 7,83 - 7,87 (2H, m), 7,92 (2H, d), 8,37 (1H, s), 9,39 (1H, s), 11,34 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00208μM

Ejemplo 36aa: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,59 - 1,62 (2H, m), 1,88 - 1,91 (2H, m), 3,12 - 3,19 (1H, m), 3,43 - 3,49 (1H, m), 3,59 - 3,63 (1H, m), 3,75 (1H, d), 3,96 (1H, dd), 4,14 (1H, d), 4,32 (2H, d), 4,42 (1H, s), 6,60 (1H, t), 6,65 (1H, s), 6,94 (2H, s), 7,42 (4H, t), 7,81 - 7,86 (4H, m), 8,91 (1H, s), 11,89 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0749μM

Ejemplo 36ab: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,19 (3H, d), 1,51 - 1,60 (2H, m), 1,80 - 1,89 (2H, m), 2,53 - 2,58 (1H, m), 2,70 - 2,80

(4H, m), 3,12 (1H, dt), 3,47 (1H, dt), 3,63 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,10 (1H, d), 4,46 (1H, d), 6,41 (1H, d), 6,59 (1H, s), 7,37 (2H, d), 7,54 - 7,56 (1H, m), 7,57 - 7,59 (1H, m), 7,76 (2H, d), 7,85 (1H, dt), 8,48 (1H, s), 8,73 - 8,75 (1H, m).

Ensayo de mTOR Quinasa (Echo): 0,011μM

Ejemplo 36ac: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,52 - 1,58 (2H, m), 1,81 - 1,89 (2H, m), 2,68 - 2,80 (4H, m), 3,08 - 3,15 (2H, m), 3,27 (1H, s), 3,44 - 3,50 (3H, m), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,10 (1H, d), 4,47 (1H, s), 4,72 (1H, t), 6,23 (1H, t), 6,59 (1H, s), 7,36 (2H, d), 7,54 - 7,59 (2H, m), 7,76 (2H, d), 7,85 (1H, dt), 8,73 - 8,75 (2H, m).

Ensayo de mTOR Quinasa (Echo): 0,00441μM

Ejemplo 36ad: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 8,87 (1H, s), 8,74 (1H, d), 7,85 (1H, td), 7,77 (2H, d), 7,54 - 7,59 (2H, m), 7,38 (2H, d), 6,60 (1H, s), 6,51 (1H, t), 4,48 (1H, s), 4,10 (1H, d), 3,96 (1H, dd), 3,75 (1H, d), 3,63 (1H, dd), 3,47 (1H, td), 3,37 (2H, q), 3,12 (1H, td), 2,72 - 2,81 (4H, m), 2,70 (2H, t), 1,80 - 1,89 (2H, m), 1,55 - 1,58 (2H, m), 1,19 (3H, d).

Ensayo de mTOR Quinasa (Echo): 0,0323μM

Ejemplo 36ae: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,55 - 1,63 (4H, m), 1,81 - 1,89 (2H, m), 2,68 - 2,80 (4H, m), 3,08 - 3,19 (3H, m), 3,45 - 3,49 (3H, m), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,10 (1H, d), 4,48 (2H, t), 6,18 (1H, t), 6,59 (1H, s), 7,36 (2H, d), 7,53 - 7,59 (2H, m), 7,75 (2H, d), 7,85 (1H, dt), 8,65 (1H, s), 8,74 (1H, d).

Ensayo de mTOR Quinasa (Echo): 0,0151μM

Ejemplo 36af: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,18 (3H, d), 1,88 - 1,95 (1H, m), 2,11 - 2,17 (1H, m), 2,53 - 2,57 (2H, m), 2,79 - 2,87 (2H, m), 3,12 (1H, dt), 3,23 - 3,28 (3H, m), 3,46 (1H, dt), 3,62 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,09 (1H, d), 4,44 (1H, s), 6,40 (1H, d), 6,48 (1H, s), 7,37 (2H, d), 7,58 - 7,61 (2H, m), 7,87 (1H, ddt), 8,48 (1H, s), 8,74 - 8,75 (1H, m).

Ensayo de mTOR Quinasa (Echo): 0,00275μM

Ejemplo 36ag: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,86 - 1,97 (1H, m), 2,09 - 2,18 (1H, m), 2,65 (3H, s), 2,79 - 2,87 (2H, m), 3,12 (1H, dt), 3,22 - 3,28 (2H, m), 3,46 (1H, dt), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,08 (1H, d), 4,44 (1H, s), 6,04 - 6,07 (1H, m), 6,48 (1H, s), 7,37 (2H, d), 7,58 - 7,61 (2H, m), 7,74 (2H, d), 7,87 (1H, dt), 8,68 (1H, s), 8,75 (1H, d).

Ensayo de mTOR Quinasa (Echo): 0,0013μM

Ejemplo 36ah: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,88 - 1,95 (1H, m), 2,10

- 2,17 (1H, m), 2,81 - 2,87 (2H, m), 3,08 - 3,19 (2H, m), 3,22 - 3,27 (3H, m), 3,44 - 3,50 (3H, m), 3,62 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,08 (1H, d), 4,45 (1H, s), 4,72 (1H, t), 6,23 (1H, t), 6,48 (1H, s), 7,35 (2H, d), 7,60 (2H, t), 7,74 (2H, d), 7,87 (1H, t), 8,75 (2H, s).

Ensayo de mTOR Quinasa (Echo): 0,00247μM

Ejemplo 36ai: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,88 - 1,95 (1H, m), 2,09 - 2,16 (1H, m), 2,69 (2H, t), 2,78 - 2,87 (2H, m), 3,10 - 3,16 (1H, m), 3,23 - 3,25 (3H, m), 3,35 - 3,39 (2H, m), 3,47 (1H, t), 3,62 (1H, dd), 3,74 (1H, d), 3,95 (1H, d), 4,09 (1H, d), 4,45 (1H, s), 6,49 (1H, s), 7,38 (2H, d), 7,58 - 7,61 (2H, m), 7,76 (2H, d), 7,87 (1H, dt), 8,74 - 8,75 (1H, m), 8,86 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00561μM

Ejemplo 36aj: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,89 - 1,97 (1H, m), 2,11 - 2,18 (1H, m), 2,79 - 2,87 (2H, m), 3,13 (1H, dt), 3,23 - 3,29 (2H, m), 3,47 (1H, dt), 3,62 (1H, dd), 3,75 (1H, d), 3,79 (3H, s), 3,96 (1H, dd), 4,10 (1H, d), 4,45 (1H, s), 6,50 (1H, s), 7,38 (1H, s), 7,41 (2H, d), 7,59 - 7,62 (1H, m), 7,76 (1H, s), 7,77 (2H, d), 7,86 - 7,90 (1H, m), 7,88 (1H, dt), 8,38 (1H, s), 8,75 - 8,76 (1H, m), 8,80 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00258μM

Ejemplo 36ak: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,89 - 1,98 (1H, m), 2,10 - 2,19 (1H, m), 2,79 - 2,87 (2H, m), 3,13 (1H, dt), 3,23 - 3,28 (2H, m), 3,47 (1H, dt), 3,62 (1H, dd), 3,74 (2H, s), 3,75 (1H, d), 3,96 (1H, dd), 4,10 (1H, d), 4,45 (1H, s), 6,25 (1H, d), 6,51 (1H, s), 7,43 (2H, d), 7,54 (1H, d), 7,59 - 7,63 (1H, m), 7,60 (1H, d), 7,79 (2H, d), 7,88 (1H, dt), 8,75 - 8,76 (1H, m), 8,91 (1H, s), 9,11 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00245μM

Ejemplo 36al: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,41 (2H, m), 0,63 - 0,66 (2H, m), 1,59 (2H, m), 1,88 (2H, m), 2,57 - 2,61 (1H, m), 3,66 (4H, s), 3,68 (4H, s), 6,39 (1H, s), 6,71 (1H, s), 7,38 - 7,43 (4H, m), 7,78 (2H, d), 7,85 (2H, t), 8,52 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0187μM

Ejemplo 36am: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,58 - 1,61 (2H, m), 1,87 - 1,90 (2H, m), 2,70 (2H, t), 3,37 (2H, q), 3,67 (4H, s), 3,69 (4H, s), 6,49 (1H, t), 6,72 (1H, s), 7,39 - 7,44 (4H, m), 7,79 - 7,86 (4H, m), 8,90 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0277μM

Ejemplo 36an: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,59 - 1,62 (2H, m), 1,89 - 1,92 (2H, m), 3,68 (4H, s), 3,70 (4H, s), 6,76 (1H, s), 7,43 (2H, t), 7,51 (2H, d), 7,83 - 7,96 (4H, m), 8,37 (1H, s), 9,39 (1H, s), 11,33 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0104μM

Ejemplo 36ao: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06 (3H, t), 1,57 - 1,61 (2H, m), 1,87 - 1,90 (2H, m), 3,09 - 3,16 (2H, m), 3,65 - 3,66 (4H, m), 3,69 - 3,70 (4H, m), 6,12 (1H, t), 6,71 (1H, s), 7,37 - 7,44 (4H, m), 7,78 (2H, d), 7,82 - 7,86 (2H, m), 8,64 (1H, s)

Ejemplo 36ap: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,57 - 1,61 (2H, m), 1,87 - 1,90 (2H, m), 2,66 (3H, d), 3,66 (4H, s), 3,69 - 3,70 (4H, m), 6,01 - 6,05 (1H, m), 6,71 (1H, s), 7,38 - 7,43 (4H, m), 7,78 (2H, d), 7,82 - 7,86 (2H, m), 8,72 (1H, s)

Ejemplo 36aq: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,58 - 1,61 (2H, m), 1,88 - 1,91 (2H, m), 3,63 - 3,67 (4H, m), 3,69 - 3,73 (4H, m), 3,79 (3H, s), 6,73 (1H, s), 7,38 - 7,45 (5H, m), 7,77 - 7,86 (5H, m), 8,34 (1H, s), 8,82 (1H, s)

Ejemplo 36ar: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,66 - 1,69 (2H, m), 1,95 - 1,98 (2H, m), 3,15 - 3,19 (2H, m), 3,44 - 3,48 (2H, m), 3,69 (8H, s), 4,72 (1H, t), 6,22 (1H, t), 6,73 (1H, s), 7,34 (2H, d), 7,63 (2H, d), 7,77 (2H, d), 8,77 (1H, s), 8,86 (2H, d)

Ejemplo 36as: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,66 - 1,70 (2H, m), 1,96 - 1,99 (2H, m), 3,69 (8H, s), 3,79 (3H, s), 6,74 (1H, s), 7,40 (3H, d), 7,66 (2H, d), 7,77 - 7,78 (3H, m), 8,35 (1H, s), 8,80 (1H, s), 8,87 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00911μM

Ejemplo 36at: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,66 - 1,69 (2H, m), 1,95 - 1,99 (2H, m), 2,66 (3H, d), 3,69 (8H, s), 6,02 - 6,04 (1H, m), 6,73 (1H, s), 7,35 (2H, d), 7,63 (2H, d), 7,77 (2H, d), 8,71 (1H, s), 8,86 (2H, d)

Ejemplo 36au: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,66 - 1,69 (2H, m), 1,95 - 1,98 (2H, m), 3,09 - 3,16 (2H, m), 3,69 (8H, s), 6,13 (1H, t), 6,73 (1H, s), 7,35 (2H, d), 7,63 (2H, d), 7,77 (2H, d), 8,63 (1H, s), 8,86 (2H, d)

Ejemplo 36av: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,62 - 0,67 (2H, m), 1,66 - 1,69 (2H, m), 1,95 - 1,98 (2H, m), 2,53 - 2,57 (1H, m), 3,69 (8H, s), 6,40 (1H, d), 6,73 (1H, s), 7,36 (2H, d), 7,64 (2H, d), 7,77 (2H, d), 8,50 (1H, s), 8,86 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00995μM

Ejemplo 36aw: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,66 - 1,69 (2H, m), 1,95 - 1,98 (2H, m), 2,70 (2H, t), 3,36 (2H, q), 3,69 (8H, s), 6,49 (1H, t), 6,73 (1H, s), 7,37 (2H, d), 7,64 (2H, d), 7,77 (2H, d), 8,86 (2H, d), 8,89 (1H, s)

Ejemplo 36ax: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,56 - 1,63 (2H, m), 1,66 - 1,69 (3H, m), 1,95 - 1,98 (2H, m), 3,16 (2H, q), 3,47 (2H, q), 3,69 (8H, s), 4,47 (1H, t), 6,17 (1H, t), 6,73 (1H, s), 7,34 (2H, d), 7,63 (2H, d), 7,77 (2H, d), 8,86 (2H, d)

Ejemplo 36ay: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,56-1,59 (2H, q), 1,67-1,70 (2H, q), 3,19-3,26 (1H, td), 3,30 (3H, s), 3,46-3,53 (1H, td), 3,63-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,97-4,00 (1H, dd), 4,22-4,25 (1H, bd), 4,58 (1H, bs), 6,81 (1H, s), 7,14 (1H, s), 7,39-7,40 (1H, d), 7,59-7,62 (2H, d), 8,28-8,30 (2H, d), 9,21 (1H, s), 10,50 (1H, s).
Ensayo de mTOR Quinasa (Echo): 0,00117μM

Ejemplo 36az: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,56-1,59 (2H, q), 1,67-1,70 (2H, q), 2,44 (3H, s), 3,19-3,26 (1H, td), 3,31 (3H, s), 3,46-3,52 (1H, td), 3,63-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,98-4,00 (1H, dd), 4,22-4,25 (1H, bd), 4,59 (1H, bs), 6,81 (1H, s), 7,61-7,63 (2H, d), 8,21-8,22 (1H, d), 8,28-8,30 (2H, d), 8,99-9,00 (1H, d), 9,41 (1H, s), 9,70 (1H, s).
Ensayo de mTOR Quinasa (Echo): 0,00149μM

Ejemplo 36ba: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,56-1,59 (2H, q), 1,67-1,70 (2H, q), 3,19-3,25 (1H, td), 3,30 (3H, s), 3,47-3,52 (1H, td), 3,63-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,97-4,00 (1H, dd), 4,22-4,25 (1H, d), 4,59 (1H, bs), 6,81 (1H, s), 7,16 (1H, s), 7,63-7,66 (2H, d), 7,84 (1H, bs), 8,28-8,30 (2H, d), 10,45 (1H, bs), 10,88 (1H, bs).
Ensayo de mTOR Quinasa (Echo): 0,00312μM

Ejemplo 36bb: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,24 (3H, d), 1,54-1,58 (2H, q), 1,59-1,63 (2H, m), 1,66-1,69 (2H, q), 3,15-3,25 (3H, m), 3,30 (3H, s), 3,45-3,52 (3H, m), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,20-4,23 (1H, d), 4,46-4,49 (1H, t), 4,58 (1H, bs), 6,19-6,22 (1H, t), 6,77 (1H, s), 7,49-7,51 (2H, d), 8,19-8,21 (2H, d), 8,72 (1H, s).
Ensayo de mTOR Quinasa (Echo): 0,0205μM

Ejemplo 36bc: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40-0,44 (2H, m), 0,63-0,67 (2H, m), 1,16-1,18 (3H, d), 1,60-1,68 (2H, m), 1,89-1,92 (2H, m), 3,10-3,18 (1H, td), 3,42-3,49 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,08-4,12 (1H, d), 4,38 (1H,

bs), 5,76 (1H, s), 6,40-6,41 (1H, d), 6,63 (1H, s), 7,38-7,40 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, t), 7,78-7,85 (4H, m), 8,49 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00205μM

Ejemplo 36bd: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16-1,18 (3H, d), 1,57-1,67 (4H, m), 1,81-1,92 (4H, m), 2,18-2,25 (2H, m), 3,10-3,18 (1H, td), 3,42-3,49 (1H, td), 3,59-3,62 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,97 (1H, dd), 4,08-4,19 (2H, m), 4,38 (1H, bs), 6,42-6,44 (1H, d), 6,62 (1H, s), 7,35-7,37 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,85 (4H, m), 8,52 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00258μM

Ejemplo 36be: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16-1,18 (3H, d), 1,60-1,67 (2H, m), 1,89-1,92 (2H, m), 3,10-3,20 (1H, td), 3,30 (2H, m (bajo pico de agua)) 3,42-3,55 (2H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,07-4,11 (1H, d), 4,38 (1H, bs), 6,35-6,38 (1H, t), 6,47-6,49 (1H, d), 6,63 (1H, s), 7,38-7,40 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,81 (2H, d), 7,84-7,86 (2H, d), 8,89 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00376μM

Ejemplo 36bf: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,10-1,12 (6H, d), 1,16-1,18 (3H, d), 1,60-1,67 (2H, m), 1,59-1,92 (2H, m), 3,10-3,19 (1H, td), 3,42-3,49 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,81 (2H, m), 3,94-3,97 (1H, dd), 4,09-4,12 (1H, d), 4,38 (1H, bs), 6,02-6,04 (1H, d), 6,62 (1H, s), 7,35-7,38 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,85 (4H, m), 8,49 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00457μM

Ejemplo 36bg: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,05-1,08 (3H, t), 1,16-1,18 (3H, d), 1,60-1,67 (2H, m), 1,89-1,90 (2H, m), 3,09-3,16 (3H, m), 3,42-3,49 (1H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,95-3,97 (1H, dd), 4,09-4,12 (1H, d), 4,38 (1H, bs), 6,12-6,15 (1H, t), 6,62 (1H, s), 7,37-7,39 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, t), 7,78-7,85 (4H, m), 8,62 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000922μM

Ejemplo 36bh: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16-1,18 (3H, d), 1,60-1,67 (2H, m), 1,89-1,92 (2H, m), 3,10-3,15 (1H, td), 3,17-3,19 (2H, m), 3,42-3,49 (3H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,08-4,11 (1H, d), 4,38 (1H, bs), 4,71-4,74 (1H, t), 6,22-6,24 (1H, t), 6,62 (1H, s), 7,36-7,39 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,85 (4H, m), 8,76 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00121μM

Ejemplo 36bi: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,87-0,91 (3H, t), 1,16-1,18 (3H, d), 1,41-1,50 (2H, m), 1,60-1,67 (2H, m), 1,89-1,92 (2H, m), 3,04-3,09 (2H, q), 3,10-3,17 (1H, td), 3,42-3,49 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,97 (1H, dd), 4,08-4,12 (1H, d), 4,39 (1H, bs), 6,16-6,19 (1H, t), 6,62 (1H, s), 7,37-7,39 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,85 (4H, m), 8,61 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00231μM

Ejemplo 36bj: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16-1,18 (3H, d), 1,60-1,68 (2H, m), 1,89-1,92 (2H, m), 2,65-2,66 (3H, d), 3,10-3,17 (1H, td), 3,42-3,49 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,97 (1H, dd), 4,09-4,12 (1H, d), 4,38 (1H, bs), 6,03-6,06 (1H, q), 6,62 (1H, s), 7,38-7,40 (2H, d), 7,57-7,61 (2H, t), 7,70-7,73 (1H, tt), 7,74-7,85 (4H, m), 8,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000621μM

Ejemplo 36bk: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16-1,18 (3H, d), 1,24 (6H, s), 1,60-1,67 (2H, m), 1,88-1,91 (2H, m), 3,10-3,17 (1H, td), 3,38-3,40 (2H, d), 3,42-3,49 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,08-4,12 (1H, d), 4,38 (1H, bs), 4,93-4,96 (1H, t), 5,98 (1H, s), 6,62 (1H, s), 7,33-7,35 (2H, d), 7,58-7,61 (2H, t), 7,70-7,74 (1H, m), 7,78-7,84 (4H, m), 8,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00433μM

Ejemplo 36bl: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16-1,18 (3H, d), 1,56-1,67 (4H, m), 1,89-1,92 (2H, m), 3,10-3,17 (3H, m), 3,42-3,49 (3H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,97 (1H, dd), 4,08-4,12 (1H, d), 4,38 (1H, bs), 4,46-4,49 (1H, t), 6,16-6,19 (1H, t), 6,62 (1H, s), 7,37-7,39 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,85 (4H, m), 8,67 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00208μM

Ejemplo 36bm: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17-1,18 (3H, d), 1,60-1,68 (2H, m), 1,89-1,92 (2H, m), 2,68-2,72 (2H, t), 3,11-3,18 (1H, td), 3,34-3,39 (2H, q), 3,43-3,49 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,97 (1H, dd), 4,09-4,12 (1H, d), 4,38 (1H, bs), 6,49-6,52 (1H, t), 6,63 (1H, s), 7,39-7,41 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,86 (4H, m), 8,88 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00193μM

Ejemplo 36bn: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16-1,18 (3H, d), 1,60-1,68 (2H, m), 1,88-1,93 (2H, m), 3,10-3,17 (1H, td), 3,42-3,49 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H,

d), 3,94-3,97 (1H, dd), 4,08-4,12 (1H, d), 4,31-4,33 (2H, d), 4,38 (1H, bs), 6,59-6,63 (2H, m), 6,94 (2H, bs), 7,39-7,41 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, t), 7,78-7,81 (2H, d), 7,84-7,87 (2H, d), 8,88 (1H, s), 11,84 (1H, bs).

Ensayo de mTOR Quinasa (Echo): 0,00637μM

Ejemplo 36bo: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,63-0,66 (2H, q), 0,69-0,73 (2H, q), 1,16-1,18 (3H, d), 1,60-1,67 (2H, m), 1,89-1,92 (2H, m), 3,10-3,17 (1H, td), 3,42-3,49 (3H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,09-4,12 (1H, d), 4,38 (1H, bs), 4,83 (1H, bs), 6,54 (1H, s), 6,63 (1H, s), 7,35-7,37 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,74-7,85 (4H, m), 8,63 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0176μM

Ejemplo 36bp: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16-1,18 (3H, d), 1,60-1,67 (2H, m), 1,89-1,90 (2H, m), 3,10-3,17 (1H, td), 3,42-3,49 (1H, td), 3,59-3,62 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,97 (1H, dd), 4,08-4,12 (1H, d), 4,38 (1H, bs), 4,43-4,46 (2H, t), 4,72-4,81 (3H, m), 6,63 (1H, s), 6,91-6,93 (1H, d), 7,37-7,39 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,86 (4H, m), 8,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00198μM

Ejemplo 36bq: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18-1,19 (3H, d), 1,61-1,66 (2H, m), 1,91-1,92 (2H, m), 3,12-3,18 (1H, td), 3,44-3,50 (1H, td), 3,61-3,64 (1H, dd), 3,74-3,77 (1H, d), 3,95-3,99 (1H, dd), 4,10-4,14 (1H, d), 4,40 (1H, bs), 6,66 (1H, s), 7,52-7,54 (2H, d), 7,59-7,62 (2H, t), 7,72-7,76 (1H, t), 7,79-7,81 (3H, d), 7,90-7,92 (2H, d), 8,28 (1H, s), 9,39 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00131μM

Ejemplo 36br: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17-1,18 (3H, d), 1,61-1,68 (2H, m), 1,90-1,91 (2H, m), 3,11-3,17 (1H, td), 3,43-3,50 (1H, td), 3,59-3,63 (1H, dd), 3,74-3,76 (1H, d), 3,79 (3H, s), 3,94-3,98 (1H, dd), 4,09-4,13 (1H, d), 4,39 (1H, bs), 6,64 (1H, s), 7,38 (1H, s), 7,42-7,44 (2H, d), 7,58-7,62 (2H, t), 7,71-7,73 (1H, t), 7,77-7,81 (3H, m), 7,86-7,88 (2H, d), 8,36 (1H, s), 8,80 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00188μM

Ejemplo 36bs: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,39-0,43 (2H, m), 0,62-0,67 (2H, m), 1,19-1,20 (3H, d), 1,82-1,93 (1H, m), 2,03-2,14 (1H, m), 2,54 (1H, m), 2,75-2,82 (2H, m), 3,01-3,09 (2H, m), 3,10-3,17 (1H, td), 3,44-3,51 (1H, td), 3,61-3,65 (1H, dd), 3,74-3,77 (1H, d), 3,94-3,98 (1H, dd), 4,06-4,09 (1H, d), 4,44 (1H, bs), 6,40-6,41 (1H, d), 6,46 (1H, s), 7,36-7,39 (2H, d), 7,43-7,51 (4H, m), 7,58-7,62 (1H, m), 7,78-7,80 (2H, d), 8,48 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00161μM

Ejemplo 36bt: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19-1,21 (3H, d), 1,82-1,93 (1H, m), 2,03-2,14 (1H, m), 2,74-2,82 (2H, m), 3,02-3,10 (2H, m), 3,13-3,19 (3H, m), 3,44-3,51 (3H, m), 3,62-3,65 (1H, dd), 3,74-3,77 (1H, d), 3,94-3,98 (1H, dd), 4,07-4,10 (1H, d), 4,45 (1H, bs), 4,71-4,74 (1H, t), 6,22-6,25 (1H, t), 6,47 (1H, s), 7,35-7,37 (2H, d), 7,44-7,51 (4H, m), 7,58-7,62 (1H, m), 7,78-7,81 (2H, d), 8,74 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00105μM

Ejemplo 36bu: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19-1,21 (3H, d), 1,82-1,93 (1H, m), 2,04-2,14 (1H, m), 2,65-2,66 (3H, d), 2,75-2,82 (2H, m), 3,02-3,11 (2H, m), 3,13-3,19 (1H, td), 3,45-3,51 (1H, td), 3,62-3,65 (1H, dd), 3,74-3,77 (1H, d), 3,94-3,98 (1H, dd), 4,06-4,10 (1H, d), 4,45 (1H, bs), 6,03-6,06 (1H, q), 6,46 (1H, s), 7,36-7,38 (2H, d), 7,44-7,51 (4H, m), 7,58-7,62 (1H, m), 7,78-7,80 (2H, d), 8,68 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00118μM

Ejemplo 36bv: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20-1,21 (3H, d), 1,83-1,94 (1H, m), 2,04-2,15 (1H, m), 2,76-2,83 (2H, m), 3,02-3,10 (2H, m), 3,11-3,18 (1H, td), 3,45-3,52 (1H, td), 3,62-3,66 (1H, dd), 3,75-3,77 (1H, d), 3,79 (3H, s), 3,95-3,98 (1H, dd), 4,07-4,10 (1H, d), 4,46 (1H, bs), 6,48 (1H, s), 7,38-7,51 (7H, m), 7,59-7,76 (1H, m), 7,76 (1H, s), 7,82-7,84 (2H, d), 8,36 (1H, s), 8,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00264μM

Ejemplo 36bw: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40-0,44 (2H, m), 0,63-0,67 (2H, m), 1,20-1,22 (3H, d), 1,49-1,58 (2H, m), 1,80-1,87 (2H, m), 2,53 (2H, m), 2,67-2,73 (2H, m), 3,12-3,18 (1H, td), 3,46-3,53 (1H, td), 3,63-3,67 (1H, dd), 3,75-3,78 (1H, d), 3,95-3,99 (1H, dd), 4,09-4,12 (1H, d), 4,48-4,49 (1H, bs), 6,40-6,41 (1H, d), 6,62 (1H, s), 7,37-7,39 (2H, d), 7,42-7,48 (4H, m), 7,57-7,61 (1H, m), 7,80-7,82 (2H, d), 8,48 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00909μM

Ejemplo 36bx: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20-1,22 (3H, d), 1,50-1,59 (2H, m), 1,80-1,89 (2H, m), 2,52-2,61 (2H, m), 2,66-2,74 (2H, m), 3,11-3,19 (3H, m), 3,44-3,52 (3H, m), 3,63-3,67 (1H, dd), 3,75-3,78 (1H, d), 3,95-3,99 (1H, dd), 4,08-4,12 (1H, d), 4,48 (1H, bs), 4,71-4,74 (1H, t), 6,22-6,25 (1H, t), 6,62 (1H, s), 7,35-7,38 (2H, d), 7,42-7,48 (4H, m), 7,57-7,61 (1H, m), 7,80-7,82 (2H, d), 8,74 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00269μM

Ejemplo 36by: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20-1,22 (3H, d), 1,52-1,56 (2H, m), 1,57-1,63 (2H, m), 1,79-1,88 (2H, m), 2,54-2,61 (2H, m), 2,67-2,72 (2H, m), 3,11-3,17 (3H, m), 3,45-3,52 (3H, m), 3,63-3,66 (1H, dd), 3,75-3,78 (1H, d), 3,95-3,99 (1H, dd), 4,09-4,12

(1H, d), 4,46-4,49 (2H, m), 6,17-6,19 (1H, t), 6,62 (1H, s), 7,35-7,38 (2H, d), 7,42-7,48 (4H, m), 7,57-7,61 (1H, m), 7,79-7,82 (2H, d), 8,65 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,012μM

Ejemplo 36bz: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21-1,22 (3H, d), 1,50-1,59 (2H, m), 1,81-1,88 (2H, m), 2,53-2,59 (2H, m), 2,67-2,72 (4H, m), 3,11-3,19 (1H, td), 3,34-3,39 (2H, m), 3,46-3,52 (1H, td), 3,63-3,67 (1H, dd), 3,75-3,78 (1H, d), 3,95-3,99 (1H, dd), 4,09-4,13 (1H, d), 4,49 (1H, bs), 6,49-6,52 (1H, t), 6,63 (1H, s), 7,38-7,40 (2H, d), 7,42-7,48 (4H, m), 7,57-7,61 (1H, m), 7,81-7,83 (2H, d), 8,86 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0143μM

Ejemplo 36ca: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,68-1,74 (2H, m), 2,20-2,27 (2H, td), 2,67-2,68 (3H, d), 2,82-2,87 (2H, t), 3,05-3,09 (2H, m), 3,18-3,22 (1H, m), 3,22-3,25 (2H, t), 3,37-3,40 (2H, t), 3,50-3,58 (1H, td), 3,66-3,70 (1H, dd), 3,77-3,80 (1H, d), 3,90-3,96 (2H, m), 3,98-4,01 (1H, dd), 4,39-4,32 (1H, d), 4,57 (1H, s), 6,10-6,13 (1H, q), 6,86 (1H, s), 7,50-7,53 (2H, d), 8,21-8,23 (2H, d), 8,79 (1H, s)

Ejemplo 36cb: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,68-1,75 (2H, m), 2,20-2,27 (2H, td), 2,54 (3H, d), 2,82-2,87 (2H, t), 3,06-3,11 (2H, m), 3,12-3,16 (1H, m), 3,18-3,24 (2H, m), 3,37-3,40 (2H, t), 3,50-3,57 (1H, td), 3,66-3,70 (1H, dd), 3,77-3,80 (1H, d), 3,91-3,95 (2H, m), 4,00-4,02 (1H, dd), 4,29-4,32 (1H, d), 4,58 (1H, s), 6,27-6,29 (1H, t), 6,86 (1H, s), 7,50-7,52v(2H, d), 8,21-8,23 (2H, d), 8,78 (1H, s)

Ejemplo 36cc: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (2H, d), 1,68-1,75 (2H, m), 2,20-2,27 (2H, td), 2,538-2,543 (3H, d), 2,82-2,87 (2H, t), 3,06-3,09 (2H, m), 3,16-3,21 (1H, m), 3,22-3,25 (2H, m), 3,37-3,40 (1H, td), 3,66-3,70 (1H, dd), 3,77-3,80 (1H, d), 3,90-3,96 (2H, m), 4,00-4,02 (1H, dd), 4,29-4,33 (1H, d), 4,58 (1H, s), 6,49-6,50 (1H, d), 6,86 (1H, s), 7,51-7,53 (2H, d), 8,22-8,24 (2H, d), 8,61 (1H, s)

Ejemplo 36cd: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,55-1,65 (2H, m), 1,67-1,74 (2H, m), 2,19-2,26 (4H, m), 2,537-2,541 (3H, d), 2,81-2,86 (2H, t), 3,05-3,09 (2H, m), 3,16-3,22 (2H, m), 3,24-3,26 (1H, m), 3,37-3,40 (2H, t), 3,49-3,56 (1H, td), 3,66-3,70 (1H, dd), 3,77-3,79 (1H, d), 3,90-3,96 (2H, m), 3,98-4,01 (1H, dd), 4,11-4,21 (1H, sex), 4,29-4,32 (1H, d), 4,57 (1H, s), 6,52-6,54 (1H, d), 6,86 (1H, s), 7,48-7,50 (2H, d), 7,54-7,67(1H, m), 8,21-8,23 (2H, d), 8,63 (1H, s)

Ejemplo 36ce: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,35 (3H, d), 1,67-1,74 (2H, m), 2,20-2,27 (2H, td), 2,538-2,541 (3H, d), 2,70-3,73 (2H, t), 2,82-2,87 (2H, t), 3,05-3,09 (2H, m), 3,18-3,23 (2H, m), 3,25-3,26 (1H, m), 3,18-3,23 (2H, m), 2,25-2,26 (1H, m), 3,36-3,40 (4H, m), 3,50-3,56 (1H, td), 3,66-3,70 (1H, dd), 3,77-3,80 (1H, d), 3,90-3,96 (2H, c), 3,98-4,02 (1H, dd), 4,30-4,33 (1H, d), 4,56-4,58 (1H, m), 6,54-6,57 (1H, t), 6,86 (1H, s), 7,52-7,54 (2H, d), 8,23-8,25 (2H, d), 8,95 (1H, s)

Ejemplo 36cf: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,68-1,75 (2H, m), 2,20-2,27 (2H, td), 2,82-2,87 (2H, t), 3,16-3,22 (2H, m), 3,25 (1H, m), 3,37-3,40 (2H, t), 3,50-3,56 (1H, td), 3,66-3,70 (1H, dd), 3,77-3,80 (1H, d), 3,90-3,96 (2H, m), 4,00-4,02 (1H, dd), 4,29-4,33 (1H, d), 4,58 (1H, s), 6,23-6,25 (1H, t), 6,86 (1H, t), 7,49-7,52 (2H, d), 8,21-8,23 (2H, d), 8,69 (1H, s)

Ejemplo 36cg: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,68-1,75 (2H, m), 2,20-2,27 (2H, td), 2,82-2,87 (2H, t), 3,06-3,09 (2H, m), 3,17-3,23 (4H, m), 3,25-3,26 (1H, m), 3,37-3,40(2H, t), 3,46-3,48 (2H, t), 3,50-3,56 (1H, td), 3,66-3,70 (1H, dd), 3,77-3,80 (1H, d), 3,90-3,96 (2H, c), 3,98-4,02 (1H, dd) 4,29-4,33 (1H, d), 4,57 (1H, s), 6,30-6,33 (1H, t), 6,86 (1H, s), 7,49-7,51 (2H, d), 8,22-8,24 (2H, d), 8,87 (1H, s)

Ejemplo 36ch: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,68-1,75 (2H, m), 2,20-2,28 (2H, td), 2,82-2,87 (2H, t), 3,06-3,10 (2H, m), 3,18-3,22 (2H, m), 3,23-3,25 (1H, m), 3,38-3,41 (2H, t), 3,50-3,57 (1H, td), 3,67-3,70 (1H, dd), 3,77 (1H, s), 3,80 (3H, s), 3,91-3,96 (2H, c), 3,98-4,02 (1H, dd), 4,30-4,33 (1H, d), 4,58 (1H, intercambio), 6,87 (1H, s), 7,390-7,392 (1H, d), 7,55-7,57 (2H, d), 7,77 (1H, s), 8,25-8,27 (2H, d), 8,49 (1H, intercambio), 8,93 (1H, intercambio)

Ejemplo 36ci: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,25 (3H, d), 1,68-1,75 (2H, m), 2,20-2,28 (2H, td), 2,82-2,86 (2H, t), 3,07-3,11 (2H, m), 3,16-3,20 (1H, m), 3,22-3,23 (1H, d), 3,38-3,41 (2H, t), 3,51-3,57 (2H, td), 3,68-3,69 (1H, dd), 3,77-3,80 (1H, d), 3,90-3,96 (2H, t), 3,99-4,01 (1H, d), 4,29-4,33 (1H, d), 4,57-4,58 (1H, intercambio), 6,84 (1H, s), 7,23 (1H, s), 7,57-7,59 (1H, m), 7,65-7,67 (2H, d), 8,20-8,22 (2H, d)

Ejemplo 36cj: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,63-1,66 (2H, m), 1,93-2,00 (2H, m), 3,15-3,20 (2H, m), 3,217-3,226 (1H, d), 3,47-3,51 (1H, dd), 3,53-3,57 (4H, m), 3,63-3,67 (1H, dd), 3,76-3,79 (1H, d), 3,97-4,01 (1H, dd), 4,22-4,25 (1H, d), 4,57 (1H, intercambio), 4,73 (1H, intercambio), 6,77 (1H, s), 6,84-6,85 (1H, d), 7,33-7,34 (1H, d), 7,66-7,68 (2H, d), 8,23-8,25 (2H, d)

Ejemplo 36ck: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,70-0,74 (2H, m), 0,91-0,93 (2H, dd), 1,24-1,26 (3H, d), 1,56-1,58 (2H, m), 1,64-1,66 (2H, m), 1,92-1,99 (2H, m), 2,72-2,77 (1H, sep), 2,89 (2H, s), 3,16-3,20 (2H, t), 3,22-3,23 (1H, d), 3,4703,50 (1H, dd), 3,51-3,56 (4H, m), 3,63-3,67 (1H, dd), 3,77-3,80 (1H, d), 3,97-4,01 (1H, dd), 4,22-4,25 (1H, d), 4,57 (1H, intercambio), 6,79 (1H, s), 7,64-7,67 (2H, dd), 8,22-8,24 (2H, s), 8,41 (1H, intercambio)

Ejemplo 36cl: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,56-0,59 (2H, t), 0,66-0,68 (2H, t), 1,24-1,26 (3H, d), 1,31-1,36 (3H, m), 1,56-1,60 (2H, m), 1,62-1,66 (2H, m), 1,92-2,00 (2H, m), 3,16-3,21 (2H, t), 3,47-3,50 (1H, dd), 2,52-3,55 (4H, m), 3,63-3,67 (1H, dd), 3,52-3,55 (4H, m), 3,63-3,67 (1H, dd), 3,77-3,79 (1H, d), 4,00-4,01 (1H, dd), 4,21-4,24 (1H, d), 4,56 (1H, intercambio), 6,78 (1H, s), 7,49-7,51 (2H, d), 8,21-8,23 (2H, d)

Ejemplo 36cm: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,56-1,58 (2H, m), 1,64-1,67 (2H, m), 1,92-1,99 (2H, m), 3,19-3,26 (1H, dd), 3,51-3,55 (6H, m), 3,63-3,67 (1H, dd), 3,77-3,79 (1H, d), 3,97-4,01 (1H, dd), 4,21-4,24 (1H, d), 4,57 (1H, s), 4,71 (1H, s), 5,94-6,24 (1H, tt), 6,55-6,58 (1H, t), 6,80 (1H, s), 7,51-7,54 (2H, d), 8,23-8,26 (2H, d), 8,96 (1H, s)

Ejemplo 36cn: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,32 (9H, s), 1,54-1,60 (2H, m), 1,61-1,67 (2H, m), 1,92-1,99 (2H, m), 3,18-3,26 (1H, m), 3,47-3,50 (1H, dd), 3,52-3,56 (4H, m), 3,63-3,67 (1H, dd), 3,77-3,80 (1H, d), 3,97-4,01 (1H, dd), 4,21-4,24 (1H, d), 4,57 (1H, s), 4,72 (1H, intercambio), 6,09 (1H, s), 6,78 (1H, s), 7,45-7,48 (2H, d), 8,20-8,23 (2H, d), 8,52 (1H, s)

Ejemplo 36co: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,55-1,59 (2H, m), 1,60-1,64 (2H, m), 1,91-1,98 (2H, m), 3,46-3,50 (1H, dd), 3,50-3,54 (4H, m), 3,62-3,66 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,08 (1H, s), 4,19-4,22 (1H, d), 4,55 (intercambio), 4,70 (intercambio), 6,73 (1H, s), 7,59-7,61 (2H, d), 8,10-8,12 (2H, d), 8,38 (1H, intercambio)

Ejemplo 36cp: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,25 (3H, d), 1,55-1,59 (2H, m), 1,62-1,66 (2H, m), 1,77-1,84 (2H, m), 1,91-1,99 (2H, m), 3,16-3,20 (2H, m), 3,21-3,25 (1H, dd), 3,46-3,47 (1H, d), 3,49-3,55 (6H, m), 3,62-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,96-4,00 (1H, dd), 4,21-4,25 (1H, d), 4,31-4,32 (1H, m), 4,56 (intercambio), 6,78 (1H, s), 7,64-7,66 (2H, d), 8,20-8,22 (2H, d), 8,34 (intercambio)

Ejemplo 36cq: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,55-1,59 (2H, m), 1,62-1,65 (2H, m), 1,91-1,98 (2H, m), 3,05 (3H, s), 3,16-3,25 (2H, m), 3,33-3,34 (2H, d), 3,46-3,50 (1H, dd), 3,50-3,58 (6H, m), 3,62-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,96-4,00 (1H, dd), 4,20-4,23 (1H, d), 4,56 (intercambio), 4,70 (intercambio), 6,45-6,48 (1H, t), 6,78 (1H, s), 7,51-7,53 (2H, d), 8,21-8,24 (2H, d), 9,05 (intercambio)

Ejemplo 36cr: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,56-1,60 (2H, m), 1,62-1,66 (2H, m), 1,92-1,99 (2H, m), 3,00-3,05 (1H, dd), 3,16-3,22 (6H, m), 3,42-3,47 (2H, dd), 3,51-3,55 (4H, m), 3,63-3,67 (1H, dd), 3,76-3,79 (1H, d), 3,97-4,00 (1H, dd), 4,21-4,24 (1H, d), 4,45-4,48 (intercambio, t), 4,56 (intercambio), 6,79 (1H, s), 7,11 (intercambio), 7,52-7,54 (2H, d), 8,22-8,24 (2H, d), 9,21 (intercambio)

Ejemplo 36cs: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,25 (3H, d), 1,56-1,58 (2H, m), 1,62-1,66 (2H, m), 1,91-1,98 (2H, m), 2,89 (3H, s), 2,98 (3H, s), 3,16-3,22 (2H, m), 3,46-3,50 (1H, dd), 3,50-2,54 (4H, m), 3,63-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,96-3,97 (1H, d), 3,99-4,00 (2H, d), 4,20-4,24 (1H, d), 4,57 (1H, intercambio), 6,43-6,45 (t, intercambio), 6,79 (1H, s), 7,50-7,52 (2H, d), 8,22-8,24 (2H, d), 9,19 (intercambio)

Ejemplo 36ct: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15-1,20 (3H, d), 1,70-1,79 (2H, q), 1,95-2,05 (2H, q), 3,10-3,20 (1H, td), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,10-4,20 (1H, d), 4,45 (1H, bs), 6,70 (1H, s), 7,45-7,52 (2H, d), 7,75-7,80 (1H, dd), 7,80-7,82 (2H, d), 8,00-8,05 (1H, d), 8,10-8,15 (1H, td), 8,40 (1H, s), 8,85 (1H, d), 9,40 (1H, s), 11,40 (1H, br s).

Ensayo de mTOR Quinasa (Echo): 0,00157μM

Ejemplo 36cu: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,10-1,15 (3H, d), 1,70-1,79 (2H, q), 1,95-2,00 (2H, q), 3,10-3,20 (1H, td), 3,45-3,50 (1H, td), 3,60-3,62 (1H, dd), 3,75-3,78 (1H,

d), 3,96-3,99 (1H, dd), 4,10-4,20 (1H, d), 4,30 (2H, d), 4,45 (1H, bs), 6,60 (1H, t), 6,70 (1H, s), 6,90-7,00 (2H, br d), 7,40 (2H, d), 7,75-7,80 (3H, m), 8,00-8,05 (1H, d), 8,10-8,15 (1H, td), 8,80 (1H, d), 8,90 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0686μM

Ejemplo 36cv: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,55-0,65 (2H, q), 0,65-0,75 (2H, q), 1,10-1,15 (3H, d), 1,70-1,79 (2H, q), 1,95-2,00 (2H, q), 3,10-3,20 (1H, td), 3,40-3,50 (2H, m), 3,60-3,62 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,10-4,20 (1H, d), 4,45 (1H, bs), 4,80 (1H, bs), 6,55 (1H, t), 6,65 (1H, s), 7,30 (2H, d), 7,70-7,80 (3H, m), 7,95-8,00 (1H, d), 8,05-8,10 (1H, td), 8,60 (1H, s), 8,80 (1H, d).

Ensayo de mTOR Quinasa (Echo): 0,259μM

Ejemplo 36cw: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15-1,20 (3H, d), 1,65-1,70 (2H, q), 1,95-2,00 (2H, q), 3,10-3,20 (1H, td), 3,40-3,50 (1H, td), 3,60-3,64 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,10-4,20 (1H, d), 4,35 (2H, d), 4,45 (1H, bs), 6,60 (1H, t), 6,70 (1H, s), 6,80-7,10 (2H, m), 7,40 (2H, d), 7,70 (2H, d), 7,80 (2H, dd), 8,85 (2H, dd), 8,90 (1H, s), 11,85 (1H, s).

Ejemplo 36cx: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,55-0,65 (2H, q), 0,65-0,75 (2H, q), 1,15-1,20 (3H, d), 1,70-1,75 (2H, q), 1,95-2,00 (2H, q), 3,10-3,20 (1H, td), 3,45 (2H, d), 3,50 (1H, td), 3,60-3,63 (1H, dd), 3,74-3,78 (1H, d), 3,94-3,99 (1H, dd), 4,10-4,20 (1H, d), 4,45 (1H, bs), 4,80-4,90 (1H, t), 6,55 (1H, s), 6,65 (1H, s), 7,30 (2H, d), 7,65 (2H, d), 7,80 (2H, dd), 8,70 (1H, s), 8,85 (2H, dd)

Ejemplo 36cy: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, m), 2,22-2,30 (2H, td), 2,65 (3H, d), 2,75 (2H, t), 3,13 (3H, m), 3,50 (1H, td), 3,65 (1H, dd), 3,75 (1H, d), 3,90-3,95 (2H, d), 3,98 (1H, dd), 4,15 (1H, d), 4,50 (1H, br s), 6,05 (1H, q), 6,68 (1H, s), 7,37 (2H, d), 7,44 (2H, d), 7,46 (2H, d), 7,61 (1H, tt), 7,76 (2H, d), 8,68 (1H, s)

Ejemplo 36cz: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06 (3H, t), 1,21 (3H, d), 2,26-2,31 (2H, td), 2,74 (2H, t), 3,12 (5H, dt), 3,50 (1H, td), 3,65 (1H, dd), 3,76 (1H, d), 3,90 (2H, d), 3,97 (1H, dd), 4,14 (1H, d), 4,52 (1H, m), 6,14 (1H, t), 6,68 (1H, s), 7,36 (2H, d), 7,44 (4H, q), 7,60 (1H, m), 7,76 (2H, d), 8,60 (1H, s)

Ejemplo 36da: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,41 (2H, q), 0,65 (2H, q), 1,21 (3H, d), 2,23-2,32 (2H, td), 2,55 (1H, dd), 2,75 (2H, m), 3,15 (3H, m), 3,50 (1H, td), 3,66 (1H, dd),

3,76 (1H, d), 3,91 (2H, d), 3,97 (1H, dd), 4,14 (1H, d), 4,51 (1H, br s), 6,41 (1H, d), 6,69 (1H, s), 7,37 (2H, d), 7,44 (4H, dd), 7,61 (1H, t), 7,77 (2H, d), 8,48 (1H, s)

Ejemplo 36db: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 2,26-2,31 (2H, td), 2,74-2,78 (2H, t), 3,11-3,17 (5H, m), 3,46 (2H, q), 3,56 (1H, dd), 3,66 (1H, dd), 3,76 (1H, d), 3,90 (2H, d), 3,97 (1H, dd), 4,15 (1H, d), 4,50 (1H, br s), 4,72 (1H, t), 6,24 (1H, t), 6,68 (1H, s), 7,36 (2H, d), 7,44 (4H, q), 7,60 (1H, m), 7,77 (2H, d), 8,75 (1H, s)

Ejemplo 36dc: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40-0,44 (2H, m), 0,63-0,67 (2H, m), 1,60-1,64 (2H, q), 1,88-1,91 (2H, q), 2,54-2,57 (1H, m), 3,63-3,64 (4H, m), 3,68-3,70 (4H, m), 6,40-6,41 (1H, d), 6,68 (1H, s), 7,37-7,40 (2H, d), 7,57-7,61 (2H, t), 7,71-7,74 (1H, tt), 7,78-7,83 (4H, t), 8,50 (1H, s)

Ejemplo 36dd: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,05-1,08 (3H, t), 1,60-1,64 (2H, q), 1,88-1,91 (2H, q), 3,09-3,16 (2H, m), 3,63-3,64 (4H, m), 3,68-3,70 (4H, m), 6,12-6,15 (1H, t), 6,68 (1H, s), 7,36-7,38 (2H, d), 7,57-7,61 (2H, t), 7,71-7,74 (1H, tt), 7,78-7,82 (4H, m), 8,62 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00291μM

Ejemplo 36de: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,60-1,64 (2H, q), 1,88-1,91 (2H, q), 3,15-3,19 (2H, m), 3,44-3,48 (2H, q), 3,63-3,64 (4H, m), 3,68-3,70 (4H, m), 4,71-4,74 (1H, t), 6,21-6,24 (1H, t), 6,68 (1H, s), 7,36-7,38 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,83 (4H, m), 8,76 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00389μM

Ejemplo 36df: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,60-1,64 (2H, q), 1,88-1,91 (2H, q), 2,65-2,66 (3H, d), 3,63-3,64 (4H, m), 3,68-3,69 (4H, m), 6,02-6,06 (1H, m), 6,68 (1H, s), 7,37-7,39 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,82 (4H, m), 8,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00712μM

Ejemplo 36dg: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,56-1,64 (4H, m), 1,88-1,91 (2H, q), 3,14-3,19 (2H, q), 3,45-3,49 (2H, q), 3,63-3,64 (4H, m), 3,68-3,70 (4H, m), 4,46-4,49 (1H, t), 6,16-6,19 (1H, t), 6,68 (1H, s), 7,36-7,39 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,82 (4H, m), 8,67 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0164μM

Ejemplo 36dh: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,60-1,64 (2H, q), 1,88-1,91 (2H, q),

2,68-2,72 (2H, t), 3,34-3,39 (2H, q), 3,63-3,64 (4H, m), 3,68-3,69 (4H, m), 6,49-6,52 (1H, m), 6,68 (1H, s), 7,38-7,41 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,84 (4H, m), 8,88 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0034μM

Ejemplo 36di: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,61-1,65 (2H, q), 1,89-1,92 (2H, q), 3,63-3,66 (4H, m), 3,69-3,71 (4H, m), 6,73 (1H, m), 6,95 (1H, s), 7,08 (1H, s), 7,21 (1H, s), 7,49-7,52 (2H, d), 7,59-7,63 (2H, t), 7,70-7,74 (1H, tt), 7,79-7,91 (2H, d), 7,92-7,94 (2H, d), 8,38 (1H, s), 9,40 (1H, s), 11,39 (1H, s). (sal de amonio)

Ejemplo 36dj: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,61-1,64 (2H, q), 1,89-1,92 (2H, q), 3,63-3,65 (4H, m), 3,69-3,70 (4H, m), 3,79 (3H, s), 6,69 (1H, s), 7,38-7,39 (1H, d), 7,41-7,44 (2H, d), 7,58-7,62 (2H, t), 7,71-7,75 (1H, tt), 7,77 (1H, s), 7,79-7,81 (2H, dd), 7,83-7,86 (2H, d), 8,36 (1H, s), 8,80 (1H, s)

Ejemplo 36dk: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,63 - 0,67 (2H, m), 1,21 (3H, d), 1,58 - 1,64 (2H, m), 1,86 - 1,88 (2H, m), 2,39 (3H, s), 2,54 - 2,58 (1H, m), 2,75 - 2,78 (4H, m), 3,11 - 3,18 (1H, m), 3,46 - 3,51 (1H, m), 3,62 - 3,66 (1H, m), 3,76 (1H, d), 3,95 - 3,98 (1H, m), 4,13 - 4,16 (1H, m), 4,48 - 4,54 (1H, m), 6,40 (1H, s), 6,66 (1H, s), 7,43 (2H, d), 7,64 (1H, s), 7,89 (2H, d), 8,51 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00905μM

Ejemplo 36dl: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,57 - 1,63 (2H, m), 1,84 - 1,89 (2H, m), 2,39 (3H, s), 2,74 - 2,79 (4H, m), 3,12 - 3,20 (3H, m), 3,44 - 3,51 (3H, m), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,12 - 4,16 (1H, m), 4,48 - 4,53 (1H, m), 4,72 (1H, t), 6,24 (1H, t), 6,66 (1H, s), 7,41 (2H, d), 7,64 (1H, s), 7,89 (2H, d), 8,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00399μM

Ejemplo 36dm: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,57 - 1,64 (2H, m), 1,84 - 1,90 (2H, m), 2,39 (3H, s), 2,70 (2H, t), 2,74 - 2,79 (4H, m), 3,12 - 3,18 (1H, m), 3,35 - 3,39 (2H, m), 3,46 - 3,51 (1H, m), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,15 (1H, d), 4,48 - 4,54 (1H, m), 6,51 (1H, t), 6,67 (1H, s), 7,44 (2H, d), 7,64 (1H, s), 7,90 (2H, d), 8,90 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0298μM

Ejemplo 36dn: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,57 - 1,61 (4H, m), 1,85 - 1,90 (2H, m), 2,39 (3H, s), 2,74 - 2,79 (4H, m), 3,12 - 3,19 (3H, m), 3,45 - 3,51 (3H, m), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,14 (1H, d), 4,47 - 4,54 (1H, m), 4,47 (1H, t), 6,18

(1H, t), 6,66 (1H, s), 7,41 (2H, d), 7,64 (1H, s), 7,89 (2H, d), 8,68 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0138μM

Ejemplo 36do: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17-1,19(3H, d), 1,61-1,68 (2H, m), 1,78-1,86 (1H, m), 1,88-1,98 (3H, m), 3,10-3,18 (1H, td), 3,31-3,33 (1H, d), 3,43-3,49 (4H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,10-4,13 (1H, d), 4,31 (1H, bs), 4,38 (1H, bs), 4,94-4,95 (1H, d), 6,63 (1H, s), 7,52-7,55 (2H, d), 7,58-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,79-7,84 (4H, m), 8,28 (1H, s).

Ejemplo 36dp: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17-1,18 (3H, d), 1,60-1,68 (2H, m), 1,87-1,93 (2H, m), 3,10-3,17 (1H, td), 3,43-3,49 (1H, td), 3,53-3,54 (2H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,97 (1H, dd), 4,09-4,12 (1H, d), 4,38 (1H, bs), 6,47 (1H, t), 6,63 (1H, s), 7,39-7,41 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,83 (4H, m), 9,27 (1H, s). (H del grupo OH enterrado bajo pico de agua).

Ejemplo 36dq: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16-1,18 (3H, d), 1,61-1,68 (2H, m), 1,87-1,92 (2H, m), 2,88 (3H, s), 2,97 (3H, s), 3,10-3,18 (1H, td), 3,42-3,49 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (3H, m), 4,09-4,12 (1H, d), 4,39 (1H, bs), 6,37-6,40 (1H, t), 6,63 (1H, s), 7,38-7,40 (2H, d), 7,57-7,61 (2H, t), 7,69-7,74 (1H, tt), 7,78-7,80 (2H, dd), 7,84-7,86 (2H, d), 9,12 (1H, s).

Ejemplo 36dr: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,68-0,72 (2H, m), 0,88-0,93 (2H, m), 1,17-1,19 (3H, d), 1,61-1,68 (2H, m), 1,89-1,92 (2H, m), 2,69-2,75 (1H, m), 2,87 (3H, s), 3,11-3,18 (1H, td), 3,43-3,50 (1H, td), 3,59-3,63 (1H, dd), 3,74-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,09-4,14 (1H, d), 4,39 (1H, bs), 6,64 (1H, s), 7,52-7,54 (2H, d), 7,58-7,62 (2H, t), 7,70-7,74 (1H, tt), 7,79-7,85 (4H, m), 8,34 (1H, s).

Ejemplo 36ds: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16-1,18 (3H, d), 1,60-1,68 (2H, m), 1,87-1,93 (2H, m), 3,10-3,18 (1H, td), 3,36-3,40 (1H, q), 3,42-3,49 (2H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,09-4,12 (1H, d), 4,39 (1H, bs), 4,40-4,43 (1H, t), 4,52-4,55 (1H, t), 6,40-6,43 (1H, t), 6,63 (1H, s), 7,38-7,40 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,80 (2H, dd), 7,84-7,86 (2H, d), 8,77 (1H, s).

Ejemplo 36dt: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19-1,21 (3H, d), 1,85-1,93 (1H, m), 2,04-2,14 (1H, m), 2,68-2,72 (2H, t), 2,76-2,83 (2H, m), 3,02-3,10 (2H, m), 3,13-3,19 (1H, td), 3,34-3,39 (2H, q), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,74-3,77 (1H, d), 3,94-3,98 (1H, dd), 4,07-4,10 (1H, d), 4,45 (1H, bs), 6,47 (1H, s), 6,49-6,52 (1H, t), 7,38-7,40 (2H, d), 7,44-7,51 (4H, m), 7,58-7,62 (1H, tt), 7,80-7,82 (2H, d), 8,86 (1H, s).

Ejemplo 36du: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19-1,21 (3H, d), 1,82-1,93 (1H, m),

2,05-2,13 (1H, m), 2,76-2,83 (2H, m), 3,02-3,19 (4H, m), 3,45-3,51 (1H, td), 3,62-3,65 (1H, dd), 3,74-3,77 (1H, d), 3,94-3,98 (1H, dd), 4,06-4,10 (1H, d), 4,31-4,33 (2H, d), 4,45-4,46 (1H, bs), 6,47 (1H, s), 6,59-6,62 (1H, t), 6,94 (2H, bs), 7,38-7,40 (2H, d), 7,44-7,51 (4H, m), 7,58-7,62 (1H, tt), 7,80-7,82 (2H, d), 8,87 (1H, s).

Ejemplo 36dv: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,64 (2H, m), 1,90 (2H, m), 3,15 (1H, m), 3,47 (1H, m), 3,61 (1H, m), 3,76 (4H, m), 3,95 (1H, m), 4,14 (1H, m), 4,39 (1H, m), 6,26 (1H, m), 6,65 (1H, s), 7,44 (2H, m), 7,59 (3H, m), 7,74 (1H, m), 7,80 (2H, m), 7,88 (2H, m), 8,94 (1H, s), 9,12 (1H, s)

Ejemplo 36dw: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,64 (2H, m), 1,91 (2H, m), 3,15 (1H, m), 3,34 (3H, s), 3,46 (1H, m), 3,61 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,12 (1H, m), 4,40 (1H, m), 6,58 (1H, m), 6,66 (1H, m), 7,45 (2H, m), 7,60 (2H, m), 7,77 (3H, m), 7,90 (2H, m), 9,03 (1H, s), 9,49 (1H, s)

Ejemplo 36dx: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,64 (2H, m), 1,90 (2H, m), 3,14 (1H, m), 3,52 (4H, m), 3,75 (1H, m), 3,96 (1H, m), 4,11 (1H, m), 4,38 (1H, m), 6,08 (1H, m), 6,53 (1H, m), 6,63 (1H, s), 7,40 (2H, m), 7,60 (2H, m), 7,72 (1H, m), 7,82 (4H, m), 8,92 (1H, s)

Ejemplo 36dy: No se registró el espectro.

Ejemplo 36dz: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,64 (2H, m), 1,90 (2H, m), 3,15 (1H, m), 3,47 (1H, m), 3,61 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,13 (1H, m), 4,40 (1H, m), 6,66 (1H, s), 6,88 (1H, m), 7,46 (2H, m), 7,61 (2H, m), 7,77 (3H, m), 7,90 (2H, m), 8,77 (1H, m), 9,05 (1H, s), 9,64 (1H, s)

Ejemplo 36ea: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,64 (2H, m), 1,91 (2H, m), 3,14 (1H, m), 3,46 (1H, m), 3,61 (1H, m), 3,75 (1H, m), 3,94 (3H, m), 4,12 (1H, m), 4,39 (1H, m), 6,64 (1H, s), 6,79 (1H, m), 7,40 (2H, m), 7,59 (2H, m), 7,79 (5H, m), 8,99 (1H, s)

Ejemplo 36eb: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,65 (2H, m), 1,91 (2H, m), 3,15 (1H, m), 3,46 (1H, m), 3,61 (4H, m), 3,75 (1H, m), 3,97 (1H, m), 4,12 (1H, m), 4,40 (1H, m), 6,64 (1H, s), 6,97 (1H, s), 7,41 (3H, m), 7,61 (2H, m), 7,80 (5H, m), 8,70 (1H, s), 9,07 (1H, s)

Ejemplo 36ec: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,08 (3H, d), 1,17 (3H, d), 1,64 (2H, m), 1,90 (2H, m), 3,13 (1H, m), 3,40 (3H, m), 3,67 (3H, m), 3,96 (1H, m), 4,10 (1H, m), 4,37 (1H, m), 4,83 (1H, t), 6,10 (1H, m), 6,63 (1H, s), 7,36 (2H, m), 7,60 (2H, m), 7,78 (5H, m), 8,70 (1H, s)

Ejemplo 36ed: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,08 (3H, d), 1,17 (3H, d), 1,64 (2H, m), 1,91 (2H, m), 3,14 (1H, m), 3,42 (3H, m), 3,67 (3H, m), 3,96 (1H, m), 4,11 (1H, m), 4,39 (1H, m), 4,83 (1H, t), 6,10 (1H, m), 6,62 (1H, s), 7,36 (2H, m), 7,59 (2H, m), 7,77 (5H, m), 8,71 (1H, s)

Ejemplo 36ee: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,63 (2H, m), 1,90 (2H, m), 3,13 (1H, m), 3,45 (3H, m), 3,67 (4H, m), 3,95 (1H, m), 4,12 (1H, m), 4,39 (1H, m), 6,47 (1H, m), 6,63 (1H, s), 7,39 (2H, m), 7,60 (2H, m), 7,79 (5H, m), 8,91 (1H, s)

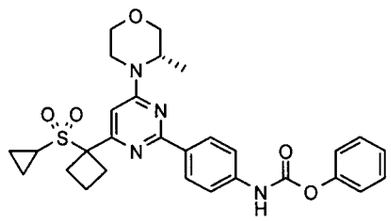
Ejemplo 36ef: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,23 (d, 3H), 1,33 (t, 3H), 1,52 - 1,58 (m, 2H), 1,60 - 1,66 (m, 2H), 3,20 (td, 1H), 3,37 - 3,53 (m, 5H), 3,63 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,14 - 4,28 (m, 1H), 4,42 (t, 1H), 4,50 - 4,62 (m, 1H), 4,54 (t, 1H), 6,47 (t, 1H), 6,79 (s, 1H), 7,51 (d, 2H), 8,20 (d, 2H), 8,85 (s, 1H)

Ejemplo 36eg: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,23 (d, 3H), 1,33 (t, 3H), 1,53 - 1,58 (m, 2H), 1,60 - 1,66 (m, 2H), 3,20 (td, 1H), 3,44 (q, 2H), 3,48 - 3,65 (m, 4H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,16 - 4,26 (m, 1H), 4,51 - 4,64 (m, 1H), 6,07 (tt, 1H), 6,56 (t, 1H), 6,79 (s, 1H), 7,52 (d, 2H), 8,21 (d, 2H), 8,97 (s, 1H)

La preparación de los fenilcarbamatos necesarios para los ejemplos **36a – 36eg** se describen más adelante o han sido descritos previamente.

La preparación de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

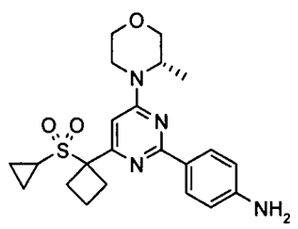


Se agregó hidrogenocarbonato de sodio (259 mg, 3,08 mmol) a 4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (880 mg, 2,05 mmol) en dioxano (20 mL) a 5°C bajo una atmósfera de nitrógeno. Luego se agregó fenil cloroformiato (0,387 mL, 3,08 mmol) y la mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con DCM (50 mL), la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. La goma bruta se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido crema que se recogió mediante filtración y se secó al vacío (1,06 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,69 - 0,80 (2H, m), 0,81 - 0,90 (2H, m), 1,23 (3H, d), 1,86 - 1,98 (1H, m), 2,02 - 2,12 (1H, m), 2,80 - 3,04 (5H, m), 3,15 - 3,28 (1H, m), 3,46 - 3,59 (1H, m), 3,66 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,23 (1H, d), 4,57 (1H, s), 6,74 (1H, s), 7,22 - 7,31 (3H, m), 7,41 - 7,49 (2H, m), 7,62 (2H, d), 8,33 (2H, d), 10,42 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 549; HPLC tR = 3,05 min.

4-[4-(1-Ciclopropilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



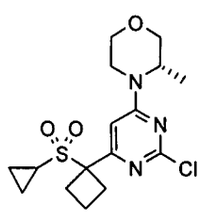
Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,164 g, 0,23 mmol) a 2-cloro-4-(1-ciclopropilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,3 g, 3,50 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,149 g, 5,24 mmol) y una solución acuosa de carbonato de sodio (1 mL, 2,00 mmol) en una mezcla de disolventes de DMF (5 mL), DME (12 mL), agua (1 mL) y etanol (1 mL) a TA. La mezcla resultante se agitó a 90°C durante 5 horas bajo una atmósfera de nitrógeno. La mezcla de reacción se diluyó con acetato

de etilo (100 mL) y se lavó con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 70% acetato de etilo en isohexano y el producto bruto se purificó adicionalmente mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7N en metanol, para proporcionar el material deseado como un sólido beige (0,88 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,70 - 0,89 (4H, m), 1,21 (3H, d), 1,84 - 1,93 (1H, m), 2,02 - 2,10 (1H, m), 2,76 - 2,98 (5H, m), 3,10 - 3,24 (1H, m), 3,45 - 3,55 (1H, m), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,18 (1H, d), 4,50 (1H, s), 5,52 (2H, d), 6,60 (2H, d), 8,07 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 429; HPLC tR = 2,41 min.

2-Cloro-4-(1-ciclopropilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó 1,3-dibromopropano (2,95 mL, 28,93 mmol) a 2-cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,2 g, 9,64 mmol), bromuro de tetrabutilamonio (0,311 g, 0,96 mmol) y una solución acuosa de hidróxido de sodio (2,89 mL, 28,93 mmol) en tolueno (24,11 mL). La reacción se agitó a TA durante 1 hora y luego se agregó agua y las capas se separaron. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como una goma incolora (1,3 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,69 - 0,78 (2H, m), 0,88 - 0,93 (2H, m), 1,20 (3H, d), 1,83 - 1,95 (1H, m), 2,02 - 2,12 (1H, m), 2,50 - 2,60 (1H, m), 2,67 - 2,80 (2H, m), 2,83 - 2,96 (2H, m), 3,13 - 3,25 (1H, m), 3,40 - 3,49 (1H, m), 3,61 (1H, d), 3,72 (1H, d), 3,93 (1H, d), 4,06 (1H, s), 4,40 (1H, s), 6,82 (1H, s)

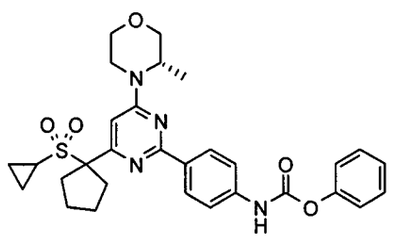
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 372; HPLC tR = 2,04 min.

La preparación de 2-cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

se describió anteriormente.

La preparación de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopentil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

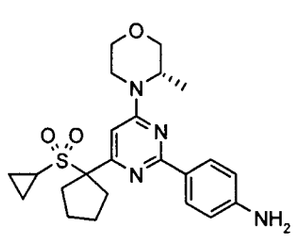


Se agregó hidrogenocarbonato de sodio (228 mg, 2,71 mmol) a 4-[4-(1-ciclopropilsulfonilciclopentil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (800 mg, 1,81 mmol) en dioxano (20 mL) a 5°C bajo una atmósfera de nitrógeno. Luego se agregó fenil cloroformiato (0,341 mL, 2,71 mmol). La mezcla resultante se agitó a TA durante 2 horas y luego se diluyó con acetato de etilo (100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto que se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido crema que se recogió mediante filtración y se secó al vacío (700 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,57 - 0,78 (2H, m), 0,79 - 0,90 (2H, m), 1,23 (3H, d), 1,53 - 1,62 (2H, m), 1,77 - 1,87 (2H, m), 2,41 - 2,50 (2H, m), 2,55 - 2,62 (1H, m), 2,76 - 2,91 (2H, m), 3,16 - 3,26 (1H, m), 3,45 - 3,56 (1H, m), 3,66 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,24 (1H, d), 4,55 (1H, s), 6,84 (1H, s), 7,20 - 7,34 (3H, m), 7,41 - 7,51 (2H, m), 7,62 (2H, d), 8,34 (2H, d), 10,42 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 563; HPLC tR = 3,15 min.

4-[4-(1-Ciclopropilsulfonilciclopentil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

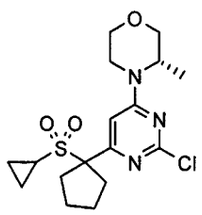


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,122 g, 0,17 mmol) a 2-cloro-4-(1-ciclopropilsulfonilciclopentil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1 g, 2,59 mmol) y una solución acuosa de carbonato de sodio (1 mL, 2,00 mmol) en una mezcla de disolventes de DMF (5 mL), DME (12 mL), agua (1 mL) y etanol (1 mL). La mezcla resultante se agitó a 90°C durante 5 horas bajo una atmósfera inerte. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 50% acetato de etilo en isohexano, seguido por cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7N en metanol, para proporcionar el material deseado como un sólido beige (0,80 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,67 - 0,79 (2H, m), 0,81 - 0,89 (2H, m), 1,22 (3H, d), 1,50 - 1,59 (2H, m), 1,75 - 1,85 (2H, m), 2,41 - 2,51 (2H, m), 2,72 - 2,90 (3H, m), 3,11 - 3,23 (1H, m), 3,45 - 3,56 (1H, m), 3,58 - 3,66 (1H, m), 3,76 (1H, d), 3,97 (1H, d), 4,18 (1H, d), 4,51 (1H, s), 5,52 (1H, d), 6,61 (2H, d), 6,71 (1H, s), 8,07 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 443; HPLC tR = 2,51 min.

2-Cloro-4-(1-ciclopropilsulfonilciclopentil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó 1,4-dibromobutano (0,322 mL, 2,71 mmol) a 2-cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (900 mg, 2,71 mmol), bromuro de tetrabutilamonio (87 mg, 0,27 mmol) y una solución acuosa de hidróxido de sodio (0,814 mL, 8,14 mmol) en tolueno (20 mL). La reacción se agitó a TA durante 1 hora y luego se agregó agua y la capa orgánica se separó, se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (1043 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,66 - 0,75 (2H, m), 0,88 - 0,94 (2H, m), 1,20 (3H, d), 1,50 - 1,57 (2H, m), 1,74 - 1,83 (2H, m), 2,36 - 2,46 (2H, m), 2,54 - 2,69 (3H, m), 3,13 - 3,25 (1H, m), 3,40 - 3,50 (1H, m), 3,59 (1H, d), 3,72 (1H, d), 3,93 (1H,

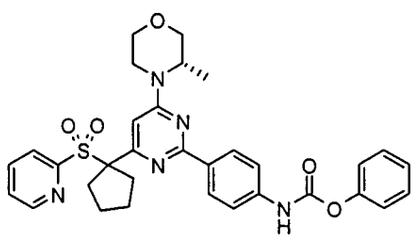
d), 4,04 (1H, d), 4,41 (1H, s), 6,92 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 386; HPLC tR = 2,47 min.

La preparación de 2-cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]fenil]carbamato

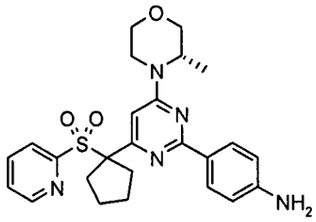


Se agregaron bicarbonato de sodio (139 mg, 1,66 mmol) y fenil cloroformiato (0,14 mL, 1,11 mmol) a una solución de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]anilina (530 mg, 1,11 mmol), en 1,4-dioxano (5,6 mL) y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (10 mL), se lavó con agua (10 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se trituró con éter dietílico para proporcionar el material deseado como un sólido crema (620 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,51 - 1,62 (2H, m), 1,80 - 1,90 (2H, m), 2,68 - 2,82 (4H, m), 3,10 - 3,17 (1H, m), 3,44 - 3,50 (1H, m), 3,61 - 3,64 (1H, m), 3,75 (1H, d), 3,94 - 3,97 (1H, m), 4,12 (1H, d), 4,49 (1H, s), 6,64 (1H, s), 7,24 - 7,30 (3H, m), 7,45 (2H, t), 7,50 (2H, d), 7,55 - 7,59 (2H, m), 7,84 - 7,86 (3H, m), 8,74 (1H, d), 10,37 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 600; HPLC tR = 3,05 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidin-2-il]anilina

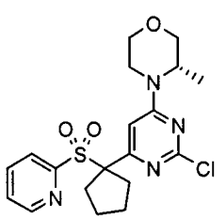


Se agregaron 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (418 mg, 1,91 mmol), una solución acuosa de carbonato de sodio (2,2 mL, 4,40 mmol) y diclorobis(trifenilfosfina)paladio(II) (51,4 mg, 0,07 mmol) a una solución de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidina (620 mg, 1,47 mmol) en una mezcla de disolventes de DMF (0,24 mL), DME (9,33 mL), agua (4,0 mL) y etanol (2,67 mL). La mezcla resultante se calentó a 90°C durante 4 horas. La mezcla de reacción se enfrió hasta alcanzar TA, se diluyó con acetato de etilo (10 mL) y se lavó con agua (10 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% metanol en DCM, para proporcionar el material deseado como un sólido crema (530 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,51 - 1,58 (2H, m), 1,80 - 1,88 (2H, m), 2,68 - 2,79 (4H, m), 3,09 (1H, dt), 3,46 (1H, dt), 3,61 (1H, dd), 3,74 (1H, d), 3,94 (1H, dd), 4,01 - 4,06 (1H, m), 4,43 (1H, d), 6,46 - 6,49 (3H, m), 7,54 (1H, d), 7,57 - 7,60 (1H, m), 7,60 (2H, d), 7,85 (1H, dt), 8,74 (1H, d)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 480; HPLC tR = 2,37 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopentil)pirimidina



1,4-dibromobutano (0,77 mL, 6,51 mmol) se agregó a 2-cloro-4-[(3S)-3-metilmorfolin-4-il]-6-(piridin-2-ilsulfonilmetil)pirimidina (600 mg, 1,63 mmol) en tolueno (4 mL) seguido por bromuro de tetrabutilamonio (52,4 mg, 0,16 mmol) y una solución acuosa de hidróxido de sodio (0,976 mL, 9,76 mmol). La reacción se agitó a 60°C durante toda la noche y luego el tolueno se eliminó bajo presión reducida y la reacción se disolvió nuevamente en DCM y se lavó con agua. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea,

gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (620 mg).

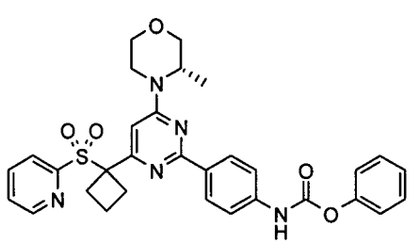
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,50 - 1,58 (2H, m), 1,75 - 1,85 (2H, m), 2,53 - 2,57 (2H, m), 2,63 - 2,71 (3H, m), 3,11 (1H, dt), 3,41 (1H, dt), 3,56 (1H, dd), 3,70 (1H, d), 3,91 (1H, dd), 4,32 (1H, s), 6,67 (1H, s), 7,65 (1H, d), 7,70 - 7,73 (1H, m), 8,03 (1H, dt), 8,74 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 423, HPLC tR = 2,26 min

La preparación de 2-cloro-4-[(3S)-3-metilmorfolin-4-il]-6-(piridin-2-ilsulfonilmetil)pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]fenil]carbamato

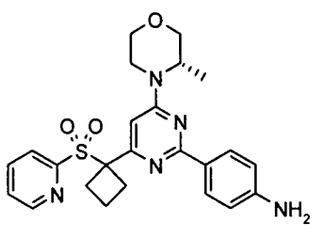


Se agregaron bicarbonato de sodio (154 mg, 1,84 mmol) y fenil cloroformiato (0,154 mL, 1,22 mmol) a una solución de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]anilina (570 mg, 1,22 mmol), en 1,4-dioxano (6,0 mL) y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (10 mL), se lavó con agua (10 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se trituró con éter dietílico para proporcionar el material deseado como un sólido crema (600 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,86 - 1,98 (1H, m), 2,07 - 2,19 (1H, m), 2,80 - 2,87 (2H, m), 3,10 - 3,17 (1H, m), 3,23 - 3,30 (2H, m), 3,47 (1H, dt), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,10 - 4,18 (1H, m), 4,46 (1H, s), 6,52 (1H, s), 6,74 - 6,78 (1H, m), 7,15 (1H, t), 7,23 - 7,30 (3H, m), 7,45 (1H, t), 7,51 (1H, d), 7,60 - 7,62 (2H, m), 7,83 - 7,90 (3H, m), 8,74 (1H, d), 10,39 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 586; HPLC tR = 3,04 min.

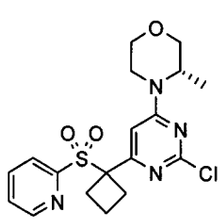
4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidin-2-il]anilina



Se agregaron 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (460 mg, 2,10 mmol), una solución acuosa de carbonato de sodio (2,42 mL, 4,84 mmol) y diclorobis(trifenilfosfina)paladio(II) (56,6 mg, 0,08 mmol) a una solución de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidina (660 mg, 1,61 mmol) en una mezcla de disolventes de DMF (0,24 mL), DME (9,33 mL), agua (4,0 mL) y etanol (2,67 mL) y la suspensión se calentó a 90°C durante 4 horas. La mezcla de reacción se enfrió hasta alcanzar TA, se diluyó con acetato de etilo (10 mL) y se lavó con agua (10 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% metanol en DCM, para proporcionar el material deseado como un sólido crema (570 mg).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 466; HPLC tR = 2,27 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclobutil)pirimidina



Se agregó 1,3-dibromopropano (1,565 mL, 15,35 mmol) a 2-cloro-4-[(3S)-3-metilmorfolin-4-il]-6-(piridin-2-ilsulfonilmetil)pirimidina (2,83 g, 7,67 mmol), en tolueno (20 mL) seguido por bromuro de tetrabutilamonio (0,247 g, 0,77 mmol) y una solución acuosa de hidróxido de sodio (2,3 mL, 23,02 mmol). La reacción se agitó a 60°C durante toda la noche. El tolueno se retiró bajo presión reducida y la reacción se disolvió nuevamente en DCM y los orgánicos se lavaron con agua y luego se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea,

gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido crema (0,66 g).

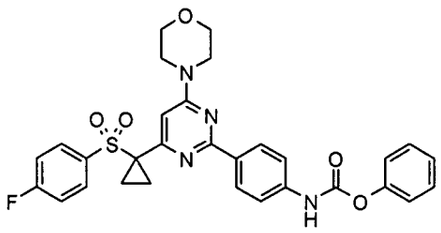
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 (3H, d), 1,86 - 1,95 (1H, m), 2,05 - 2,13 (1H, m), 2,68 - 2,76 (2H, m), 3,07 - 3,18 (3H, m), 3,37 - 3,43 (1H, m), 3,55 (1H, dd), 3,69 (1H, d), 3,90 (2H, dd), 4,28 (1H, s), 6,52 (1H, s), 7,68 - 7,73 (2H, m), 8,03 (1H, dt), 8,74 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 409, HPLC tR = 2,03 min

La preparación de 2-cloro-4-[(3S)-3-metilmorfolin-4-il]-6-(piridin-2-ilsulfonilmetil)pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato

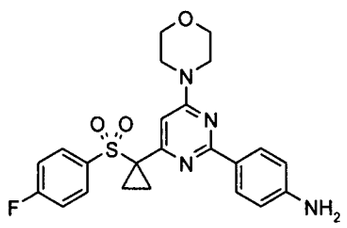


Se agregó bicarbonato de sodio (0,776 g, 9,24 mmol) a 4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]anilina (2,8 g, 6,16 mmol), en 1,4-dioxano (30,8 mL) a TA, seguido por la adición gota a gota de fenil cloroformiato (0,775 ml, 6,16 mmol) durante 2 minutos y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (20 mL) y se lavó con agua (20 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un sólido que se trituró con éter dietílico para proporcionar el material deseado como un sólido crema (3,5 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,59 - 1,62 (2H, m), 1,88 - 1,91 (2H, m), 3,57 (4H, s), 3,69 (4H, s), 6,75 (1H, s), 7,24 - 7,30 (3H, m), 7,40 - 7,47 (4H, m), 7,53 (2H, d), 7,83 - 7,89 (4H, m), 10,40 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 575; HPLC tR = 3,03 min.

4-[4-[1-(4-Fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidin-2-il]anilina

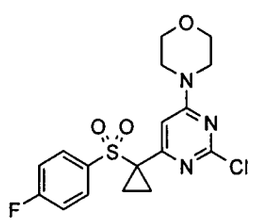


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,285 g, 0,41 mmol) a 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (2,312 g, 10,55 mmol) y 2-cloro-4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidina (3,23 g, 8,12 mmol) y una solución acuosa de carbonato de sodio (12,18 mL, 24,36 mmol) en una mezcla de disolventes de DME (20 mL), etanol (10 mL) y agua (10 mL) a TA bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 95°C durante 4 horas. La mezcla de reacción se dejó enfriar, se diluyó con acetato de etilo (20 mL) y se lavó con agua (2 x 20mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% metanol en DCM, para proporcionar el material deseado como un sólido crema (2,8 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,55 - 1,58 (2H, m), 1,85 - 1,88 (2H, m), 3,62 (4H, d), 3,67 - 3,70 (4H, m), 6,49 (2H, d), 6,61 (1H, s), 7,41 (2H, t), 7,62 (2H, d), 7,82 - 7,85 (2H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 455; HPLC tR = 2,42 min.

2-Cloro-4-[1-(4-fluorofenil)sulfonilciclopropil]-6-morfolin-4-ilpirimidina



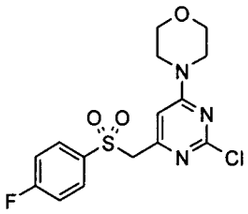
Se agregó 1,2-dibromoetano (0,695 mL, 8,07 mmol) a 2-cloro-4-[(4-fluorofenil)sulfonilmetil]-6-morfolin-4-ilpirimidina (3 g, 8,07 mmol), bromuro de tetrabutilamonio (0,260 g, 0,81 mmol) y una solución acuosa de hidróxido de sodio (2,42 mL, 24,21 mmol) en tolueno (20,17 mL). La reacción se agitó a TA durante 4 horas. El tolueno se eliminó bajo presión reducida y el residuo se disolvió nuevamente en DCM. Los orgánicos se

lavaron con agua, se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar un producto bruto. El producto bruto se trituró con éter dietílico para proporcionar el material deseado como un sólido crema (3,23 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,52 - 1,55 (2H, m), 1,81 - 1,84 (2H, m), 3,56 (4H, s), 3,63 - 3,65 (4H, m), 6,77 (1H, s), 7,80 - 7,84 (2H, m), 7,82 (2H, t)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 398, HPLC tR = 2,26 min

2-Cloro-4-[(4-fluorofenil)sulfonilmetil]-6-morfolin-4-ilpirimidina



Se agregó sal de sodio de ácido 4-fluorobencenosulfínico (3,30 g, 18,11 mmol) a 2-cloro-4-(yodometil)-6-morfolin-4-ilpirimidina (5,00 g, 14,72 mmol) en acetonitrilo (150 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a 80°C durante 20 horas. El disolvente se retiró y el residuo se disolvió nuevamente en DCM. Los orgánicos se lavaron dos veces con agua, se secaron ($MgSO_4$) y se filtraron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 30% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (3,98 g).

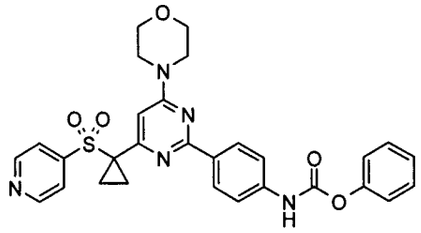
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 3,55-3,67 (8H, m), 4,65 (2H, s), 6,78 (1H, s), 7,47-7,52 (2H, m), 7,84-7,87 (2H, m).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 372; HPLC tR = 1,99 min.

La preparación de 2-cloro-4-(yodometil)-6-morfolin-4-ilpirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato

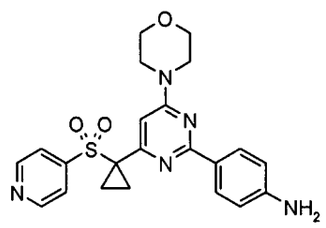


Se agregó bicarbonato de sodio (0,677 g, 8,06 mmol) a 4-[4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]anilina (2,35 g, 5,37 mmol), en 1,4-dioxano (26,9 mL) a TA, seguido por la adición gota a gota de fenil cloroformiato (0,676 mL, 5,37 mmol) durante 2 minutos y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (20 mL) y se lavó con agua (20 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un sólido que se trituró con éter dietílico para proporcionar el material deseado como un sólido crema (3,0 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,67 - 1,70 (2H, m), 1,94 - 1,99 (2H, m), 3,57 (4H, s), 3,69 (4H, s), 6,74 - 6,77 (2H, m), 7,24 - 7,26 (2H, m), 7,43 - 7,50 (3H, m), 7,73 (2H, d), 7,78 (2H, d), 8,86 (2H, d), 9,29 (1H, s), 10,39 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 558; HPLC tR = 2,71 min.

4-[4-Morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]anilina

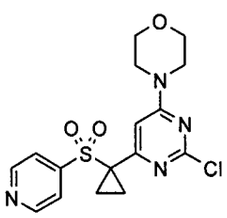


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,309 g, 0,44 mmol) a 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (2,505 g, 11,43 mmol) y 2-cloro-4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidina (3,35 g, 8,80 mmol) y una solución acuosa de carbonato de sodio (13,19 mL, 26,39 mmol) en una mezcla de disolventes de DME (20 mL), etanol (10 mL) y agua (10 mL) a TA bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 95°C durante 4 horas. La mezcla de reacción se diluyó con acetato de etilo (20 mL) y se lavó con agua (2 x 20 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% metanol en DCM, para proporcionar el material deseado como un sólido marrón (2,37 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,63 - 1,67 (2H, m), 1,93 - 1,96 (2H, m), 3,64 (4H, d), 3,67 - 3,69 (4H, m), 5,52 (2H, s), 6,45 (2H, d), 6,62 (1H, s), 7,47 (2H, d), 7,76 (2H, dd), 8,85 (2H, dd)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 438; HPLC tR = 1,94 min.

2-Cloro-4-morfolin-4-il-6-(1-piridin-4-ilsulfonilciclopropil)pirimidina

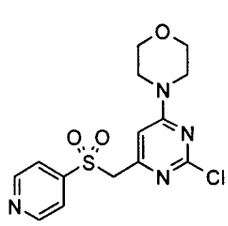


Se agregó 1,2-dibromoetano (0,510 mL, 22,55 mmol) a 2-cloro-4-morfolin-4-il-6-(piridin-4-ilsulfonilmetil)pirimidina (4 g, 11,27 mmol) en tolueno (56,4 mL) seguido por bromuro de tetrabutilamonio (0,363 g, 1,13 mmol) y una solución acuosa de hidróxido de sodio (5,64 mL, 56,37 mmol). La reacción se agitó a 60°C durante 7 horas luego el tolueno se eliminó bajo presión reducida y el residuo se disolvió nuevamente en DCM. Los orgánicos se lavaron con agua, se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar un producto bruto. El producto bruto se trituró con éter dietílico para proporcionar el material deseado como un sólido marrón (3,35 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,60 - 1,63 (2H, m), 1,89 - 1,92 (2H, m), 3,58 (4H, d), 3,63 - 3,65 (4H, m), 6,81 (1H, s), 7,74 (2H, d), 8,88 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 381, HPLC tR = 1,70 min

2-Cloro-4-morfolin-4-il-6-(piridin-4-ilsulfonilmetil)pirimidina



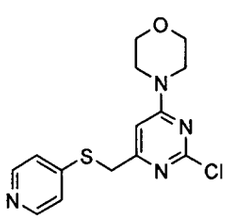
Se disolvió 2-cloro-4-morfolin-4-il-6-(piridin-4-ilsulfanilmetil)pirimidina (3,28 g, 10,16 mmol) en dioxano (45 mL) y se agregó ácido sulfúrico 2N (0,11 mL). La solución se calentó hasta alcanzar 55°C. Se agregó una solución de tungstato de sodio dihidrato (0,067 g, 0,20

mmol) en agua (1,08 mL) a la solución y se dejó agitar durante 10 minutos. Luego se agregó gota a gota peróxido de hidrógeno (6,28 mL, 203,2 mmol) durante varios minutos. La solución se calentó a 55°C durante 3 horas. Se agregó agua y la reacción se dejó enfriar. La solución acuosa se extrajo con DCM y los orgánicos se separaron, se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se trituró con éter dietílico para proporcionar el material deseado como un sólido crema (3,20 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 3,56 (4H, s), 3,65 - 3,68 (4H, m), 4,77 (2H, s), 6,84 (1H, s), 7,78 (2H, d), 8,92 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 355, HPLC tR = 1,53 min

2-Cloro-4-morfolin-4-il-6-(piridin-4-ilsulfanilmetil)pirimidina



Se agregó en porciones 2-cloro-4-(yodometil)-6-morfolin-4-ilpirimidina (5 g, 14,72 mmol) a 4-mercaptopiridina (1,8 g, 16,20 mmol) y DBU (2,344 mL, 16,20 mmol) en acetonitrilo (73,6 mL) a TA. La suspensión resultante se agitó a TA durante 30 minutos. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en DCM (50 mL) y los orgánicos se lavaron con agua (50 mL), se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 100% acetato de etilo en DCM, para proporcionar el material deseado como un sólido beige (3,3 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 3,58 (4H, s), 3,64 - 3,67 (4H, m), 4,24 (2H, s), 6,97 (1H, s), 7,35 (2H, d), 8,38 (2H, d)

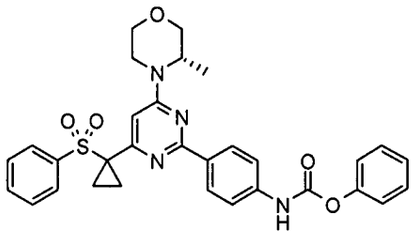
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 323, HPLC tR = 1,75 min

La preparación de 2-cloro-4-(yodometil)-6-morfolin-4-ilpirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-

il]fenil]carbamato

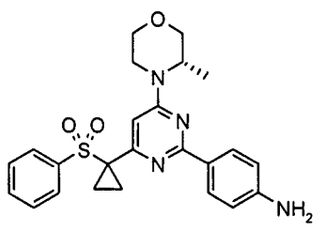


Se agregó gota a gota fenil cloroformiato (0,471 mL, 3,75 mmol) a 4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (1,690 g, 3,75 mmol) y bicarbonato de sodio (0,473 g, 5,63 mmol) en dioxano y la mezcla resultante se agitó a TA durante 18 horas. El disolvente se retiró, se agregó DCM y los orgánicos se lavaron con agua se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el material deseado como un sólido beige (2,44 g) que se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17-1,19 (3H, d), 1,62-1,69 (2H, m), 1,90-1,93 (2H, m), 3,12-3,19 (1H, td), 3,41-3,49 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,10-4,14 (1H, d), 4,39 (1H, bs), 6,66 (1H, s), 7,24-7,30 (3H, m), 7,43-7,47 (2H, t), 7,51-7,53 (2H, d), 7,58-7,61 (2H, t), 7,70-7,74 (1H, t), 7,79-7,81 (2H, d), 7,92-7,94 (2H, d), 10,38 (1H, s).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 571; HPLC tR = 3,00 min.

4-[4-[1-(Bencenosulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



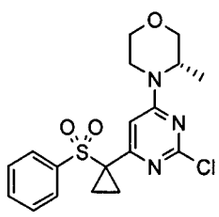
Se agregó en una porción cloruro de bis(trifenilfosfina)paladio (II) (0,246 g, 0,35 mmol) a 4-[1-(bencenosulfonil)ciclopropil]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,76 g, 7,01 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,535 g, 7,01 mmol) y una solución acuosa de carbonato de sodio (17,52 mL, 35,04 mmol) en una mezcla de disolventes de 18% DMF, 82% de una mezcla 7:3:2 de DME:agua:etanol) y la mezcla resultante se agitó a 80°C durante 3 horas bajo una atmósfera de nitrógeno. El producto bruto se disolvió en acetato de etilo y se lavó con agua. Los orgánicos se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de intercambio iónico

utilizando una columna SCX, eluyendo con amoníaco 7M en metanol, para proporcionar el material deseado como un sólido amarillo (3,35 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15-1,16 (3H, d), 1,58-1,66 (2H, m), 1,85-1,91 (2H, m), 3,07-3,14 (1H, td), 3,41-3,48 (1H, td), 3,58-3,61 (1H, dd), 3,72-3,75 (1H, d), 3,93-3,96 (1H, dd), 4,05-4,08 (1H, d), 4,33 (1H, bs), 5,50 (2H, s), 6,49-6,53 (3H, t), 7,57-7,61 (2H, t), 7,68-7,71 (3H, m), 7,78-7,81 (2H, d).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 451; HPLC tR = 2,37 min.

4-[1-(Bencenosulfonil)ciclopropil]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

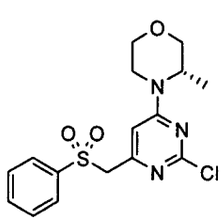


Se agregó hidróxido de sodio (solución acuosa 50% p/p, 299,03 mmol) a 4-(bencenosulfonilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,0 g, 5,44 mmol), 1,2-dibromoetano (1,406 mL, 16,31 mmol) y bromuro de tetrabutilamonio (0,175 g, 0,54 mmol) en tolueno (75 mL) y la mezcla resultante se agitó a 60°C durante 4 horas. Se agregó agua y la mezcla se extrajo con tolueno. Los orgánicos se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (2,76 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13-1,15 (3H, d), 1,55-1,57 (2H, m), 1,83-1,86 (2H, m), 3,09-3,16 (1H, td), 3,36-3,43 (1H, td), 3,52-3,56 (1H, dd), 3,68-3,71 (1H, d), 3,86-3,93 (2H, m), 4,20 (1H, bs), 6,67 (1H, s), 7,60-7,63 (2H, m), 7,72-7,77 (3H, m).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 394; HPLC tR = 2,28 min.

4-(Bencenosulfonilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



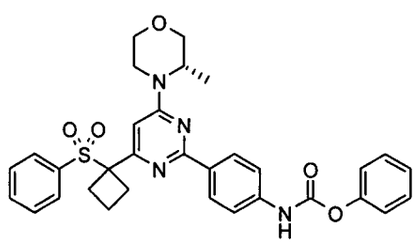
Se agregó ácido bencenosulfínico, sal de sodio (4,22 g, 25,74 mmol) a 2-cloro-4-(yodometil)-

6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (7,0 g, 19,80 mmol) en acetonitrilo (200 mL) y la mezcla resultante se agitó bajo una atmósfera de nitrógeno a 80°C durante 20 horas. La reacción se enfrió y el disolvente se retiró. Se agregó DCM y la solución se lavó con agua. El DCM se secó ($MgSO_4$), se filtró y el disolvente se retiró. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 30% acetato de etilo en DCM, para proporcionar el material deseado como un sólido crema (6,21 g).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15-1,16 (3H, d), 3,11-3,18 (1H, td), 3,38-3,45 (1H, td), 3,55-3,58 (1H, dd), 3,70-3,73 (1H, d), 3,85-3,94 (2H, m), 4,15 (1H, bs), 4,64 (2H, s), 6,67 (1H, s), 7,63-7,66 (2H, m), 7,74-7,80 (3H, m).
Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 368; HPLC tR = 2,05 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3S)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

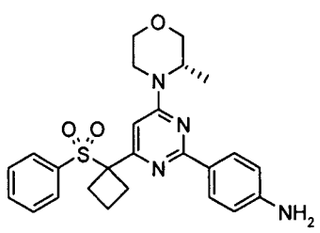


Se agregó fenil cloroformiato (0,083 mL, 0,66 mmol) a 4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (0,307 g, 0,66 mmol) e hidrogenocarbonato de sodio (0,083 g, 0,99 mmol) en dioxano y la mezcla resultante se agitó a TA durante 2 horas. El disolvente se retiró y el residuo se repartió entre DCM y agua. Los orgánicos se lavaron con agua, se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el material deseado como una goma (0,386 g) que se utilizó sin purificación adicional.
Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,31-1,33 (3H, d), 1,87-1,99 (1H, m), 2,20-2,31 (1H, m), 2,75-2,83 (2H, m), 3,17-3,32 (3H, m), 3,57-3,63 (1H, td), 3,73-3,77 (1H, dd), 3,80-3,83 (1H, d), 4,01-4,05 (1H, dd), 4,09-4,12 (1H, d), 4,44 (1H, bs), 6,55 (1H, s),

6,78-6,81 (1H, d), 7,16-7,28 (4H, m), 7,36-7,42 (5H, m), 7,49-7,51 (2H, d), 7,56 (1H, s), 7,89-7,92 (2H, d).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 585; HPLC tR = 3,30 min.

4-[4-[1-(Bencenosulfonil)ciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

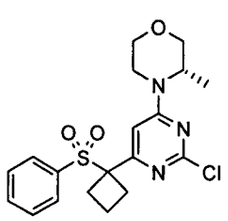


Se agregó en una porción cloruro de bis(trifenilfosfina)paladio (II) (0,023 g, 0,03 mmol) a 4-[1-(bencenosulfonil)ciclobutil]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (0,270 g, 0,66 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,145 g, 0,66 mmol) y una solución acuosa de carbonato de sodio (1,653 mL, 3,31 mmol) en una mezcla de disolventes comprendiendo 18% DMF, 82% de una mezcla 7:3:2 de DME:agua:etanol y la mezcla resultante se agitó a 80°C durante 3 horas bajo una atmósfera de nitrógeno. El producto bruto se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol, para proporcionar una muestra que se purificó adicionalmente mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar lo deseado como una goma incolora (0,395 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,30-1,32 (3H, d), 1,87-1,98 (1H, m), 2,19-2,29 (1H, m), 2,74-2,83 (2H, m), 3,14-3,22 (2H, m), 3,24-3,31 (1H, td), 3,57-3,63 (1H, td), 3,73-3,85 (4H, m), 4,01-4,04 (1H, dd), 4,08-4,12 (1H, d), 4,43-4,45 (1H, m), 6,48 (1H, s), 6,55-6,57 (2H, d), 7,26-7,31 (2H, t), 7,39-7,43 (1H, t), 7,48-7,51 (2H, dd), 7,74-7,76 (2H, d).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 465; HPLC tR = 2,49 min.

4-[1-(Bencenosulfonil)ciclobutil]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó hidróxido de sodio (solución acuosa 50% p/p, 120,21 mmol) a 4-

(bencenosulfonilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (0,804 g, 2,19 mmol), 1,3-dibromopropano (0,666 mL, 6,56 mmol) y bromuro de tetrabutilamonio (0,070 g, 0,22 mmol) en tolueno (50 mL) y la mezcla resultante se agitó a 45°C durante 1 hora. Se agregó agua, los orgánicos separaron, se lavaron con agua, se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (0,27 g).

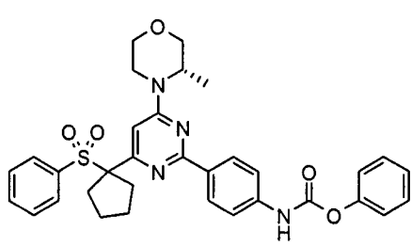
Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,29-1,31 (3H, d), 1,89-1,96 (1H, m), 2,17-2,28 (1H, m), 2,63-2,67 (2H, m), 3,07-3,16 (2H, m), 3,22-3,29 (1H, td), 3,50-3,57 (1H, td), 3,67-3,70 (1H, dd), 3,76-3,79 (1H, d), 3,95-4,01 (2H, m), 4,28 (1H, bs), 6,52 (1H, s), 7,41-7,44 (2H, t), 7,48-7,50 (2H, m), 7,57-7,61 (1H, m).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 408; HPLC tR = 2,35 min.

La preparación de 4-(bencenosulfonilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopentil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopentil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



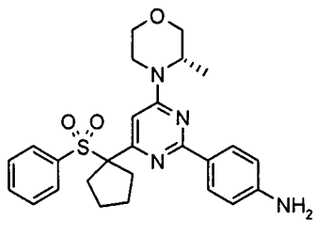
Se agregó fenil cloroformiato (0,244 mL, 1,94 mmol) a 4-[4-[1-(bencenosulfonil)ciclopentil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (0,930 g, 1,94 mmol) e hidrogenocarbonato de sodio (0,245 g, 2,91 mmol) en dioxano y la mezcla resultante se agitó a TA durante 2 horas. El disolvente se retiró y el residuo se repartió entre DCM y agua. Los orgánicos se lavaron con agua, se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el material deseado como un sólido beige (1,19 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21-1,23 (3H, d), 1,52-1,56 (2H,

m), 1,80-1,88 (2H, m), 2,55-2,60 (2H, m), 2,67-2,69 (2H, m), 3,12-3,19 (1H, td), 3,46-3,52 (1H, td), 3,63-3,67 (1H, dd), 3,75-3,78 (1H, d), 3,95-3,99 (1H, dd), 4,12-4,16 (1H, d), 4,50 (1H, bs), 6,66 (1H, s), 7,23-7,30 (3H, m), 7,42-7,51 (8H, m), 7,56-7,60 (1H, m), 7,88-7,90 (2H, d), 10,37 (1H, s).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 599; HPLC tR = 3,44 min.

4-[4-[1-(Bencenosulfonil)ciclopentil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

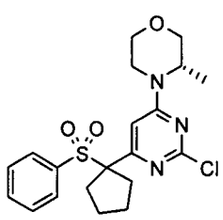


Se agregó cloruro de bis(trifenilfosfina)paladio (II) (0,072 g, 0,10 mmol) en una porción a 4-[1-(bencenosulfonil)ciclopentil]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (0,863 g, 2,05 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,448 g, 2,05 mmol) y una solución acuosa de carbonato de sodio (5,11 mL, 10,23 mmol) en una mezcla de disolventes comprendiendo 18% DMF, 82% de una mezcla 7:3:2 de DME:agua:etanol y la mezcla resultante se agitó a 80°C durante 3 horas. El producto bruto se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol, para proporcionar el material deseado como un sólido beige (0,93 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19-1,20 (3H, d), 1,52-1,55 (2H, m), 1,81-1,85 (2H, m), 2,50 (2H, m), 2,67-2,70 (2H, m), 3,07-3,15 (1H, td), 3,45-3,51 (1H, td), 3,62-3,65 (1H, dd), 3,74-3,77 (1H, d), 3,94-3,97 (1H, dd), 4,04-4,08 (1H, d), 4,43-4,45 (1H, bs), 5,47 (2H, s), 6,48-6,51 (3H, m), 7,42-7,48 (4H, m), 7,57-7,62 (1H, m), 7,65-7,67 (2H, d).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 479; HPLC tR = 2,67 min.

4-[1-(Bencenosulfonil)ciclopentil]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó hidróxido de sodio (solución acuosa 50% p/p, 112,53 mmol) a 4-(bencenosulfonilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (0,753 g, 2,05 mmol), 1,4-dibromobutano (0,733 mL, 6,14 mmol) y bromuro de tetrabutilamonio (0,066 g, 0,20 mmol) en tolueno (50 mL) y la suspensión resultante se agitó a 60°C durante 4 horas. Se agregó agua, la capa orgánica se separó y se lavó dos veces con agua. Los orgánicos se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como una goma incolora (0,904 g).

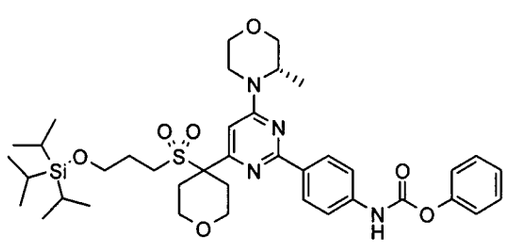
Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,28-1,30 (3H, d), 1,52-1,63 (2H, m), 1,83-1,93 (2H, m), 2,41-2,49 (2H, m), 2,56-2,66 (2H, m), 3,20-3,28 (1H, td), 3,49-3,56 (1H, td), 3,65-3,69 (1H, dd), 3,74-3,77 (1H, d), 3,95-3,99 (2H, m), 4,27 (1H, bs), 6,69 (1H, s), 7,38-7,46 (4H, m), 7,54-7,58 (1H, m).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 422; HPLC tR = 2,61 min.

La preparación de 4-(bencenosulfonilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[4-[3-tri(propan-2-il)sililoxipropilsulfonil]oxan-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[4-[3-tri(propan-2-il)sililoxipropilsulfonil]oxan-4-il]pirimidin-2-il]fenil]carbamato



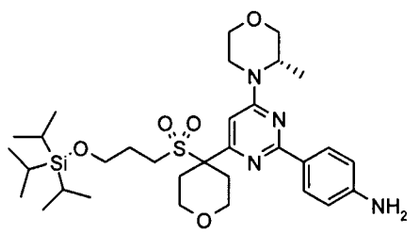
Se agregó bicarbonato de sodio (0,380 g, 4,53 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[4-[3-tri(propan-2-il)sililoxipropilsulfonil]oxan-4-il]pirimidin-2-il]anilina (1,910 g, 3,02 mmol), en 1,4-dioxano (15,09 mL) a TA. Se agregó gota a gota fenil cloroformiato (0,380 mL, 3,02 mmol) durante 2 minutos y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (40 mL) y se lavó con agua (40 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un sólido que

se trituró con éter dietílico para proporcionar el material deseado como un sólido ámbar (2,25 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,87-0,88 (18H, d), 1,09-1,13 (1H, t), 1,23-1,25 (3H, d), 1,31 (1H, s), 1,74-1,81 (2H, c), 2,20-2,27 (2H, td), 2,83-2,88 (2H, t), 3,00-3,04 (2H, td), 3,18-3,29 (3H, m), 3,49-3,51 (2H, m), 3,63-3,66 (2H, t), 3,78-3,80 (1H, d), 3,91-3,97 (2H, c), 3,99-4,03 (1H, dd), 4,30-4,33 (1H, d), 4,58 (1H, intercambio), 6,90 (1H, s), 7,25-7,27 (2H, dd), 7,29-7,31 (1H, dd), 7,44-7,47 (2H, d), 7,62-7,64 (2H, d), 8,30-8,32 (2H, d)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 753,4; HPLC tR = 3,97 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[4-[3-tri(propan-2-il)sililoxipropilsulfonil]oxan-4-il]pirimidin-2-il]anilina

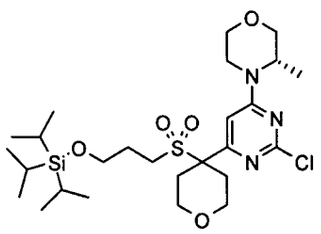


Se agregó diclorobis(trifenilfosfina)paladio (II) (0,118 g, 0,17 mmol) a 3-[4-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]oxan-4-il]sulfonilpropoxi-tri(propan-2-il)silano (1,94 g, 3,37 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,959 g, 4,38 mmol) y carbonato de sodio acuoso 2M (6,06 mL, 12,12 mmol) en agua (9,35 mL), etanol (3,74 mL) y DME (3,74 mL) y la solución resultante se agitó a 80°C durante 3 horas bajo una atmósfera de nitrógeno. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 75% acetato de etilo en DCM, para proporcionar el material deseado como un sólido ámbar (1,91 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,90-0,91 (18H, d), 1,21-1,23 (3H, d), 1,73-1,80 (2H, c), 2,17-2,25 (2H, td), 2,79-2,84 (2H, t), 2,98-3,02 (2H, td), 3,28 (2H, s), 3,31 (2H, s), 3,47-3,53 (1H, td), 3,63-3,67 (3H, m), 3,76-3,79 (1H, d), 3,90-3,96 (2H, c), 3,97-4,01 (1H, dd), 4,25-4,29 (1H, d), 4,53-4,54 (1H, m), 5,53-5,55 (1H, d), 6,59-6,61 (2H, d), 6,76 (1H, s), 8,02-8,05 (2H, d)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 633,34; HPLC tR = 3,67 min.

3-[4-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]oxan-4-il]sulfonilpropoxi-tri(propan-2-il)silano



Se agregó *terc*-butóxido de sodio (1,519 g, 15,80 mmol) en porciones a 3-[[2-cloro-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]propoxi-tri(propan-2-il)silano (2 g, 3,95 mmol) y bis(2-bromoetil) éter (1,987 mL, 15,80 mmol) en DMF (19,76 mL) a TA durante un período de 5 minutos bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 16 horas. La mezcla de reacción se aplacó con solución de cloruro de amonio saturado acuoso (0,5 mL), se concentró y se diluyó con acetato de etilo (200 mL). Los orgánicos se separaron, se lavaron secuencialmente con agua (2 x 200 mL) y salmuera saturada (100 mL), se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 40 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blancuzco (1,94 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,98-1,02 (18H, m), 1,20-1,22 (4H, q), 1,78-1,85 (2H, c), 2,13-2,20 (2H, t), 2,65-2,69 (2H, m), 2,95-3,03 (2H, m), 3,15-3,24 (3H, q), 3,28-3,31 (3H, d), 3,42-3,49 (1H, td), 3,59-3,63 (1H, dd), 3,72-3,76 (2H, q), 3,87-3,92 (2H, c), 3,94-3,98 (1H, dd), 4,11-4,14 (1H, d), 4,45 (1H, intercambio), 6,99 (1H, s)

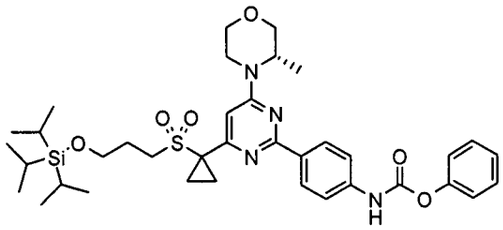
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 576,31; HPLC tR = 4,06 min

La preparación de 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]propoxi-tri(propan-2-il)silano se describió anteriormente.

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[3-tri(propan-2-il)sililoxipropilsulfonil]ciclopropil]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[3-tri(propan-2-il)sililoxipropilsulfonil]ciclopropil]pirimidin-2-il]fenil]carbamato

1590

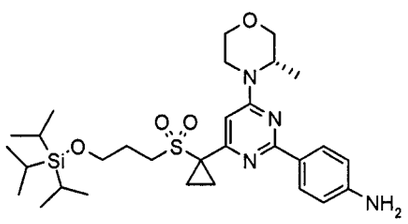


Se agregó bicarbonato de sodio (0,749 g, 8,92 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[3-tri(propan-2-il)sililoxipropilsulfonil]ciclopropil]pirimidin-2-il]anilina (3,5 g, 5,94 mmol), en 1,4-dioxano (29,7 mL) a TA. Se agregó gota a gota fenil cloroformiato (0,748 mL, 5,94 mmol) durante 2 minutos y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en DCM (100 mL) y se lavó con agua (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un sólido, que se trituró con dietilo para proporcionar el material deseado como un sólido amarillo claro (4,13 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,95-0,96 (18H, d), 1,24-1,26 (3H, d), 1,30 (2H, s), 1,58-1,60 (2H, m), 1,54-1,67 (2H, m), 1,95-2,02 (2H, sex), 3,18-3,26 (1H, td), 3,38-3,43 (2H, m), 3,46-3,49 (3H, m), 3,62-3,66 (1H, dd), 3,75-3,78 (2H, t), 3,97-4,01 (1H, dd), 4,21-4,24 (1H, d), 4,57 (1H, intercambio), 6,86 (1H, s), 7,25-7,27 (2H, d), 7,29-7,31 (1H, d), 7,44-7,46 (2H, d), 7,63-7,65 (2H, d), 8,27-8,30 (2H, d), 10,45 (1H, intercambio)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 709,41; HPLC tR = 3,82 min

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-[3-tri(propan-2-il)sililoxipropilsulfonil]ciclopropil]pirimidin-2-il]anilina



Se agregó diclorobis(trifenilfosfina)paladio (II) (0,214 g, 0,31 mmol) a 3-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropoxi-tri(propan-2-il)silano (3,25 g, 6,11 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,739 g, 7,94 mmol) y carbonato de sodio acuoso 2M (10,99 mL, 21,98 mmol) en agua (16,96 mL), etanol (6,79 mL) y DME (6,79 mL) y la solución resultante se agitó a 80°C durante 3 horas bajo una atmósfera de nitrógeno. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó

($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 75% acetato de etilo en DCM, para proporcionar el material deseado como una goma ámbar, que solidificó en reposo (3,50 g).

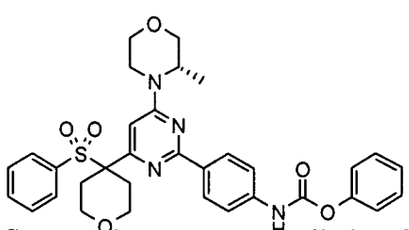
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,98-0,99 (18H, d), 1,53-1,58 (2H, m), 1,60-1,64 (2H, m), 1,96-2,03 (4H, m), 3,14-3,22 (1H, td), 3,29-3,31 (1H, d), 3,45-3,49 (3H, m), 3,61-3,64 (1H, dd), 3,75-3,78 (3H, t), 3,96-4,00 (1H, dd), 4,02-4,08 (1H, q), 4,15-4,19 (1H, d), 4,51 (1H, m), 5,55-5,57 (1H, d), 6,59-6,61 (2H, d), 6,71 (1H, s), 8,02-8,04 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 589,88; HPLC tR = 3,80 min

La preparación de 3-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropoxi-tri(propan-2-il)silano se describió anteriormente.

La preparación de fenil *N*-[4-[4-[4-(bencenosulfonil)oxan-4-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[4-(bencenosulfonil)oxan-4-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

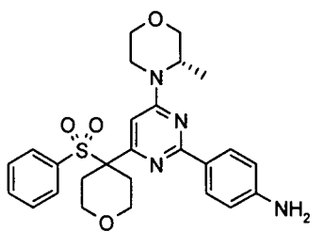


Se agregó gota a gota fenil cloroformiato (0,098 mL, 0,78 mmol) a 4-[4-[4-(bencenosulfonil)oxan-4-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (0,35 g, 0,71 mmol) y bicarbonato de sodio (0,089 g, 1,06 mmol) en dioxano (25 mL) y la suspensión resultante se agitó a TA durante 18 horas. La mezcla de reacción se diluyó con DCM (20 mL) y se lavó con agua (20 mL), la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como una goma naranja (0,45 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 2,20-2,30 (2H, td), 2,75 (2H, m), 3,23 (3H, m), 3,50 (1H, td), 3,65 (1H, dd), 3,75 (1H, d), 3,85 (2H, dd), 3,97 (1H, dd), 4,20 (1H, d), 4,55 (1H, br s), 6,70-6,80 (3H, m), 7,15 (1H, t), 7,25 (2H, dd), 7,40-7,55 (7H, m), 7,85 (2H, d), 10,40 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 615; HPLC tR = 2,93 min.

4-[4-[4-(Bencenosulfonil)oxan-4-il]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

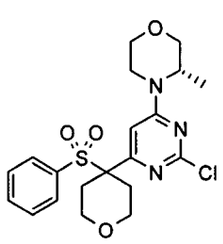


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,067 g, 0,09 mmol) en una porción a 4-[4-(bencenosulfonil)oxan-4-il]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (0,83 g, 1,90 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,498 g, 2,27 mmol) y una solución acuosa de carbonato de sodio (4,74 mL, 9,48 mmol) en una mezcla de DMF (3,60 mL), DME (9,56 mL), agua (4,1 mL) y etanol (2,72 mL). La solución resultante se agitó a 80°C durante 3 horas bajo una atmósfera de nitrógeno. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (50 mL) y se lavó secuencialmente con agua (20 mL) y salmuera saturada (20 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como un sólido beige (0,82 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 2,20-2,30 (2H, td), 2,75 (2H, m), 3,10-3,20 (3H, m), 3,50 (1H, td), 3,65 (1H, dd), 3,75 (1H, d), 3,85 (2H, dd), 3,97 (1H, dd), 4,20 (1H, d), 4,50 (1H, d), 5,47 (2H, s), 6,45 (2H, d), 6,60 (1H, s), 7,40 (4H, m), 7,60 (3H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 495; HPLC tR = 2,37 min.

4-[4-(Bencenosulfonil)oxan-4-il]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó hidróxido de sodio acuoso 50% v/v (4,49 g, 112,14 mmol) a 4-(bencenosulfonilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (0,75 g, 2,04 mmol),

bromuro de tetrabutilamonio (0,066 g, 0,20 mmol) y 1-bromo-2-(2-bromoetoxi)etano (1,419 g, 6,12 mmol) en tolueno (50 mL). La mezcla resultante se agitó a 60°C durante 6 horas. La mezcla de reacción se diluyó con agua (50 mL) y se lavó dos veces con más agua (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (0,83 g).

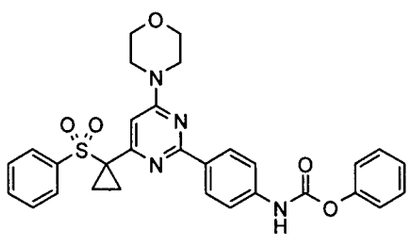
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15 (3H, d), 2,10-2,23 (2H, td), 2,60 (2H, td), 3,10-3,20 (3H, m), 3,25 (1H, d), 3,40 (1H, td), 3,60 (1H, dd), 3,70 (1H, dd), 3,80 (2H, dd), 3,90 (1H, dd), 4,40 (1H, d), 6,70 (1H, s), 7,40 (2H, d), 7,60 (2H, td), 7,75 (1H, td)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 438; HPLC tR = 2,45 min.

La preparación de 4-(bencenosulfonilmetil)-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato

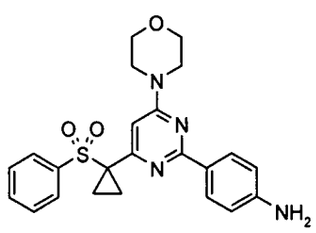


Se agregó fenil cloroformiato (0,307 mL, 2,45 mmol) a 4-[4-[1-(bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]anilina (1,069 g, 2,45 mmol) e hidrogenocarbonato de sodio (0,309 g, 3,67 mmol) en dioxano y la suspensión resultante se agitó a TA durante toda la noche. Los sólidos se filtraron y se lavaron con dioxano y agua y luego se secaron en el horno de vacío a 50°C durante toda la noche. El filtrado se concentró y los sólidos se filtraron, se enjuagaron con agua y se secaron en el horno de vacío durante toda la noche. Las dos cosechas se combinaron para proporcionar el material deseado como un sólido beige (1,132 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,62-1,65 (2H, q), 1,89-1,92 (2H, q), 3,66-3,70 (8H, m), 6,71 (1H, s), 7,24-7,31 (3H, m), 7,43-7,47 (2H, t), 7,51-7,54 (2H, d),

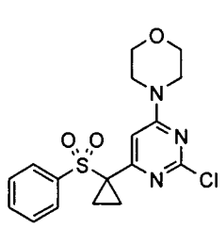
7,58-7,62 (2H, t), 7,70-7,74 (1H, tt), 7,79-7,81 (2H, d), 7,90-7,92 (2H, d), 10,40 (1H, bs).
Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 557; HPLC tR = 3,03 min.

4-[4-[1-(Bencenosulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]anilina



Se agregó cloruro de bis(trifenilfosfina)paladio (II) (0,088 g, 0,13 mmol) en una porción a 4-[1-(bencenosulfonil)ciclopropil]-2-cloro-6-morfolin-4-ilpirimidina (0,956 g, 2,52 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,552 g, 2,52 mmol) y una solución acuosa de carbonato de sodio (6,29 mL, 12,59 mmol) en una mezcla de disolventes comprendiendo 18% DMF y 82% de una mezcla 7:3:2 de DME:agua:etanol y la solución se agitó a 80°C durante 3 horas bajo una atmósfera de nitrógeno. El producto bruto se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol para proporcionar una muestra que se purificó adicionalmente mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (1,07 g).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,58-1,62 (2H, q), 1,86-1,89 (2H, q), 3,59-3,60 (4H, m), 3,67-3,69 (4H, m), 5,50 (2H, s), 6,48-6,50 (2H, d), 6,58 (1H, s), 7,57-7,61 (2H, t), 7,66-7,68 (2H, d), 7,69-7,73 (1H, tt), 7,78-7,80 (2H, m).
Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 437; HPLC tR = 2,19 min.

4-[1-(Bencenosulfonil)ciclopropil]-2-cloro-6-morfolin-4-ilpirimidina



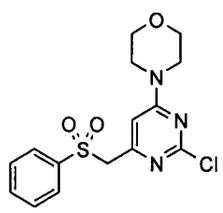
Se agregó hidróxido de sodio (solución acuosa 50% p/p, 248,52 mmol) 4-(bencenosulfonilmetil)-2-cloro-6-morfolin-4-ilpirimidina (1,599 g, 4,52 mmol), 1,2-

dibromoetano (1,168 mL, 13,56 mmol) y bromuro de tetrabutilamonio (0,146 g, 0,45 mmol) en tolueno (75 mL) y la suspensión resultante se agitó a 60°C durante 18 horas. Se agregó agua a la mezcla, los orgánicos se separaron, se lavaron dos veces con agua, se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (0,956 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,53-1,56 (2H, q), 1,82-1,85 (2H, q), 3,53 (4H, bs), 3,63-3,65 (4H, t), 6,72 (1H, s), 7,59-7,63 (2H, m), 7,73-7,77 (3H, m).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 380; HPLC tR = 2,02 min.

4-(Bencenosulfonilmetil)-2-cloro-6-morfolin-4-ilpirimidina



Se agregó bencenosulfinato de sodio (4,31 g, 26,26 mmol) a 2-cloro-4-(yodometil)-6-morfolin-4-ilpirimidina (6,86 g, 20,20 mmol) en acetonitrilo (200 mL) a 22°C bajo nitrógeno. La suspensión resultante se agitó a 80 °C durante 3 horas. La reacción se completó. El disolvente se retiró y se agregaron DCM y agua. El DCM se lavó con agua, se secó sobre $MgSO_4$, se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 30% acetato de etilo en DCM. Las fracciones puras se evaporaron hasta secarse para proporcionar 4-(2-cloro-6- (fenilsulfonilmetil)pirimidin-4-il)morfolina (4,96 g, 69,4 %) como un sólido crema.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 3,53 (4H, bs), 3,64-3,67 (4H, t), 4,61 (2H, s), 6,71 (1H, s), 7,63-7,67 (2H, m), 7,75-7,81 (3H, m).

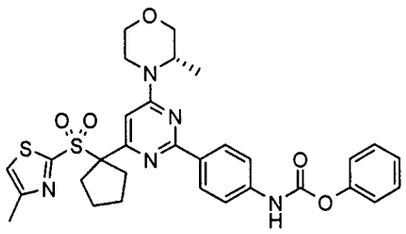
Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 354; HPLC tR = 1,79 min.

La preparación de 2-cloro-4-(yodometil)-6-morfolin-4-ilpirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]fenil]carbamato se describe a continuación:

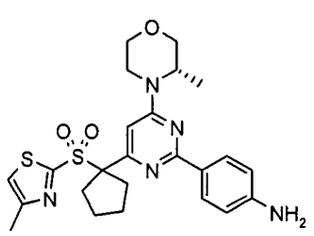
Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-

il)sulfonil]ciclopentil]pirimidin-2-il]fenil]carbamato



Se agregó fenil cloroformiato (0,232 mL, 1,85 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]anilina (840 mg, 1,68 mmol) y bicarbonato de sodio (212 mg, 2,52 mmol) en dioxano (50 mL) a 10°C bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 10°C durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar fenil *N*-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]fenil]carbamato (1,24g) como una película amarilla seca.
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,60 - 1,63 (2H, m), 1,83 - 1,92 (2H, m), 2,38 (3H, s), 2,76 - 2,80 (4H, m), 3,12 - 3,19 (1H, m), 3,49 - 3,55 (1H, m), 3,61 - 3,66 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,15 - 4,18 (1H, m), 4,49 - 4,56 (1H, m), 6,70 (1H, s), 7,24 - 7,26 (3H, m), 7,43 - 7,45 (2H, m), 7,56 (2H, d), 7,64 (1H, s), 7,99 (2H, d), 10,39 (1H, s)
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 620; HPLC tR = 3,26min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidin-2-il]anilina



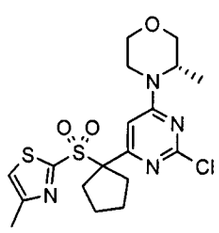
Se agregó cloruro de bis(trifenilfosfina)paladio (II) (0,162 g, 0,23 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidina (2,05g, 4,63 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,318 g, 6,02 mmol) y carbonato de sodio acuoso 2M (8,33 mL, 16,66 mmol) en DME (10 mL), etanol (10 mL) y agua (25 mL) y la mezcla resultante se agitó a 80°C durante 18 horas. La mezcla de reacción enfriada

se diluyó con acetato de etilo (100 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 75% acetato de etilo en DCM, para proporcionar el material deseado como una goma amarilla (0,84 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,57 - 1,62 (2H, m), 1,83 - 1,89 (2H, m), 2,40 (3H, s), 2,73 - 2,78 (4H, m), 3,08 - 3,15 (1H, m), 3,44 - 3,50 (1H, m), 3,61 - 3,64 (1H, m), 3,75 (1H, d), 3,94 - 3,97 (1H, m), 4,10 (1H, d), 4,43 - 4,49 (1H, m), 5,50 (2H, s), 6,53 (2H, d), 6,54 (1H, s), 7,64 (1H, s), 7,73 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 500; HPLC tR = 2,66min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopentil]pirimidina



Se agregó 1,4-dibromobutano (0,627 mL, 5,30 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina (2,06 g, 5,30 mmol), solución acuosa de hidróxido de sodio al 40% (5,30 mL, 53 mmol) y bromuro de tetrabutilamonio (0,342 g, 1,06 mmol) en tolueno (100 mL) y la solución resultante se agitó a 60°C durante 3 horas. La mezcla de reacción se concentró y se diluyó con acetato de etilo (100 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como una goma naranja (2,55g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ δ 1,18 (3H, d), 1,57 - 1,62 (2H, m), 1,78 - 1,86 (2H, m), 2,45 (3H, s), 2,55 - 2,68 (4H, m), 3,10 - 3,17 (1H, m), 3,39 - 3,46 (1H, m), 3,55 - 3,59 (1H, m), 3,71 (1H, d), 3,90 - 3,99 (2H, m), 4,32 - 4,38 (1H, m), 6,72 (1H, s), 7,87 (1H, s)

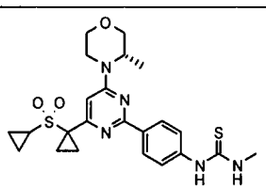
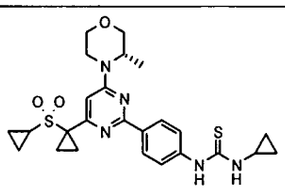
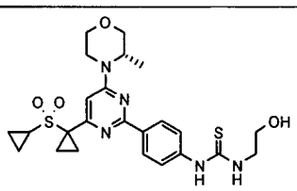
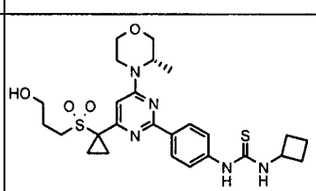
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 443; HPLC tR = 2,66min.

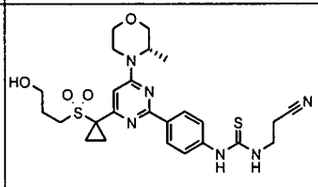
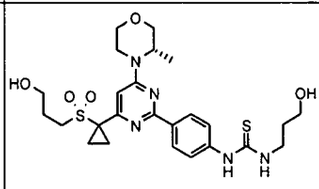
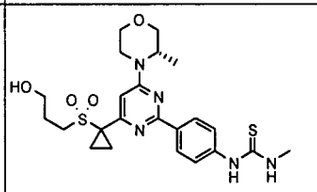
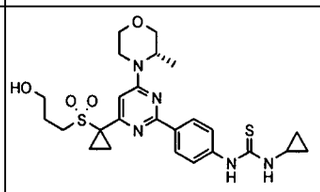
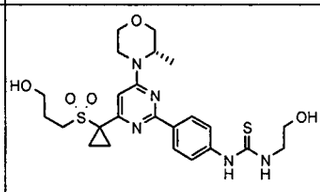
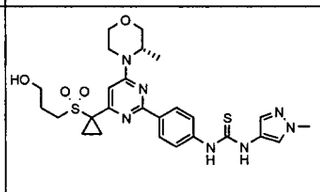
La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina se describió anteriormente.

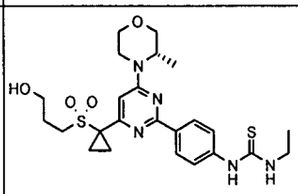
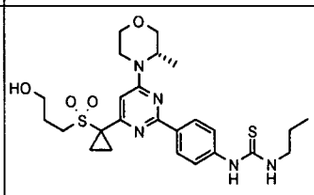
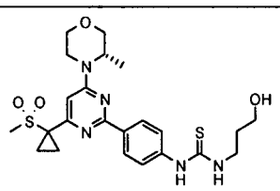
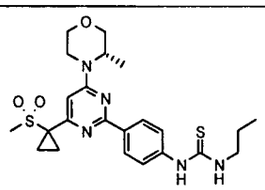
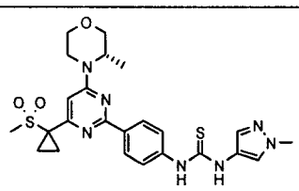
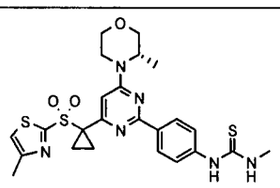
Ejemplo 37

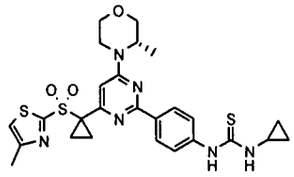
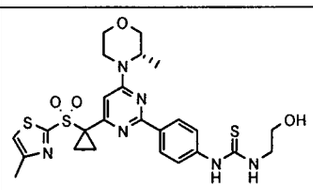
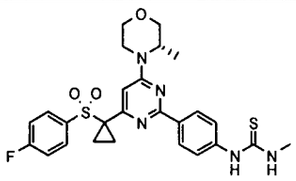
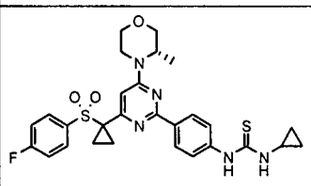
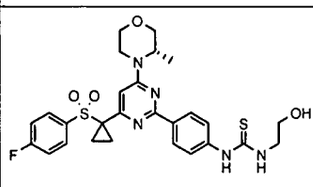
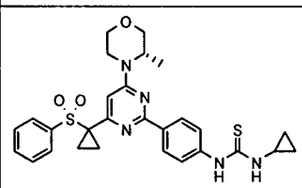
Los siguientes compuestos se prepararon de acuerdo con el siguiente Procedimiento General.

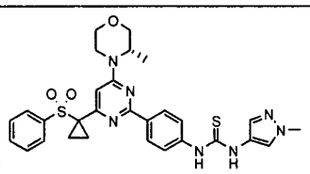
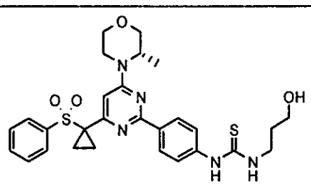
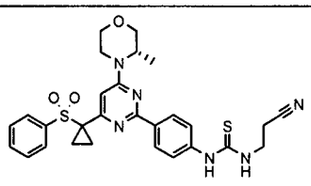
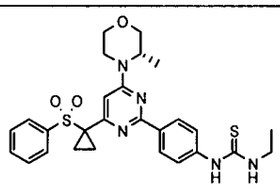
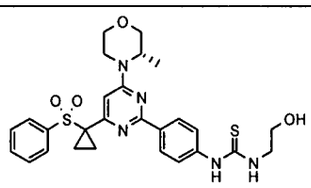
La anilina apropiada se trató con 1,1'-tiocarbonildiimidazol en una mezcla de disolventes de DCM y THF a TA durante 2 - 16 horas. Se agregaron trietilamina y la amina apropiada y las reacciones se agitaron a TA durante 1 – 16 horas adicionales (a menos que se indique de otra forma). La mezclas se purificaron mediante HPLC prep.

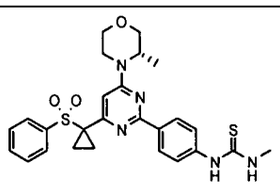
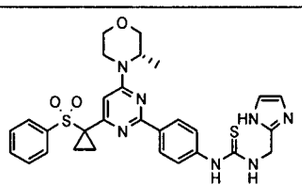
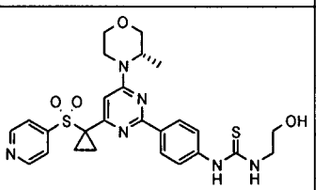
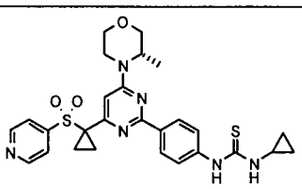
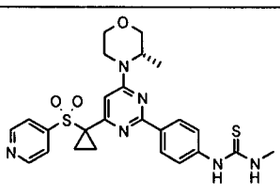
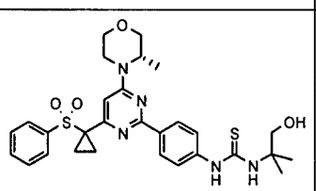
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
37a		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea	488	2,14
37b		3-ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	514	2,28
37c		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea	518	1,95
37d		3-ciclobutil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	546	2,32

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
37e		3-(2-cianoetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	545	2,0
37f		3-(3-hidroxipropil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	572	1,78
37g		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea	506	1,75
37h		3-ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	532	1,87
37i		3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	536	1,60
37j		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)tiourea	572	1,72

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
37k		1-etil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	520	1,91
37l		3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propiltiourea	534	2,07
37m		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea	506,5	1,74
37n		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-propiltiourea	490,5	2,24
37o		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)tiourea	528,5	1,84
37p		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]tiourea	545	2,38

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
37q		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]tiourea	571	2,51
37r		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]tiourea	575	2,13
37s		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea	540	2,52
37t		3-ciclopropil-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	568	2,65
37u		1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea	572	2,27
37v		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropiltiourea	550	2,59

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
37w		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)tiourea	589	2,30
37x		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)tiourea	568	2,20
37y		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-cianoetil)tiourea	563	2,49
37z		3-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etiltiourea	538	2,60
37aa		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea	554	2,18

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
37ab		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea	524	2,41
37ac		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)tiourea	590	2,40
37ad*		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea	556	1,92
37ae*		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea	552	2,22
37af*		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea	526	2,10
37ag		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)tiourea	582	2,50

* La anilina apropiada se trató con 1,1'-tiocarbonildiimidazol en una mezcla de disolventes de DCM y THF a TA durante 16 horas. Se disolvieron trietilamina y la amina apropiada en DMF, se agregaron y las reacciones se agitaron a 50°C durante 1 hora. La mezcla se purificó mediante HPLC prep.

Ejemplo 37a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,90 - 0,98 (2H, m), 0,99 - 1,08 (2H, m), 1,24 (3H, d), 1,55 - 1,62 (2H, m), 1,63 - 1,70 (2H, m), 2,91 - 3,05 (4H, m), 3,19 - 3,25 (1H, m), 3,44 - 3,55 (1H, m), 3,64 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,20 (1H, d), 4,56 (1H, s), 6,88 (1H, s), 7,55 (2H, d), 7,83 (1H, s), 8,27 (2H, d), 9,72 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,026μM

Ejemplo 37b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,57 - 0,63 (2H, m), 0,72 - 0,78 (2H, m), 0,90 - 0,96 (2H, m), 0,99 - 1,07 (2H, m), 1,24 (3H, d), 1,55 - 1,62 (2H, m), 1,63 - 1,68 (2H, m), 2,90 - 3,04 (2H, m), 3,17 - 3,27 (1H, m), 3,50 (1H, d), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,18 (1H, d), 4,56 (1H, s), 6,89 (1H, s), 7,62 (2H, d), 8,27 (2H, d), 9,50 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0124μM

Ejemplo 37c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,90 - 0,96 (2H, m), 1,00 - 1,07 (2H, m), 1,24 (3H, d), 1,55 - 1,61 (2H, m), 1,64 - 1,69 (2H, m), 2,95 - 3,05 (1H, m), 3,17 - 3,27 (3H, m), 3,44 - 3,56 (3H, m), 3,64 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,20 (1H, d), 4,55 (1H, s), 4,82 (1H, s), 6,88 (1H, s), 7,57 - 7,68 (2H, m), 7,86 (1H, s), 8,27 (2H, d), 9,81 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00344μM

Ejemplo 37d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,54 - 1,60 (2H, m), 1,62 - 1,71 (3H, m), 1,89 - 1,98 (2H, m), 2,25 - 2,34 (2H, m), 2,42 - 2,52 (2H, m), 3,14 - 3,24 (3H, m), 3,41 - 3,55 (3H, m), 3,64 (1H, d), 3,77 (1H, d), 3,97 (1H, d), 4,20 (1H, d), 4,53 - 4,68 (2H, m), 6,81 (1H, s), 7,60 (2H, d), 8,11 (1H, s), 8,26 (2H, d), 9,58 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00439μM

Ejemplo 37e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,60 (2H, m), 1,62 - 1,68 (2H, m), 1,91 - 1,98 (2H, m), 2,84 - 2,92 (2H, m), 3,13 - 3,24 (1H, m), 3,43 - 3,57 (5H, m), 3,64 (1H, d), 3,72 - 3,80 (3H, m), 3,97 (1H, d), 4,20 (1H, d), 4,57 (1H, s), 4,68 (1H, t), 6,83 (1H, s), 7,56 (2H, d), 8,16 (1H, s), 8,29 (2H, d), 9,98 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0049μM

Ejemplo 37f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,59 (2H, m), 1,62 - 1,67 (2H, m), 1,93 - 1,98 (4H, m), 2,28 - 2,36 (2H, m), 2,65 - 2,70 (2H, m), 3,13 - 3,23 (1H, m), 3,44 - 3,56 (5H, m), 3,64 (1H, d), 3,77 (1H, d), 3,97 (1H, d), 4,20 (1H, d), 4,58 (1H, s),

4,71 (2H, s), 6,82 (1H, s), 7,00 (2H, s), 7,69 (2H, d), 8,21 (0H, s), 8,29 (2H, s).

Ensayo de mTOR Quinasa (Echo): 0,12μM

Ejemplo 37g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,54 - 1,59 (2H, m), 1,62 - 1,68 (2H, m), 1,89 - 1,99 (2H, m), 2,96 (3H, s), 3,14 - 3,28 (3H, m), 3,45 - 3,55 (3H, m), 3,64 (1H, d), 3,77 (1H, d), 3,97 (1H, d), 4,21 (1H, d), 4,58 (1H, s), 4,68 (1H, t), 6,82 (1H, s), 7,55 (2H, d), 7,84 (1H, s), 8,27 (2H, d), 9,73 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0179μM

Ejemplo 37h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,56 - 0,66 (2H, m), 0,72 - 0,80 (2H, m), 1,24 (3H, d), 1,53 - 1,60 (2H, 1m), 1,62 - 1,68 (2H, m), 1,88 - 2,00 (2H, m), 2,92 (1H, s), 3,16 - 3,27 (1H, m), 3,44 - 3,58 (5H, m), 3,64 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,22 (1H, d), 4,57 (1H, s), 4,68 (1H, t), 6,82 (1H, s), 7,62 (2H, d), 8,14 (1H, s), 8,26 (2H, d), 9,50 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0132μM

Ejemplo 37i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,54 - 1,59 (2H, m), 1,63 - 1,68 (2H, m), 1,89 - 1,97 (2H, m), 3,14 - 3,29 (5H, m), 3,46 - 3,60 (5H, m), 3,64 (1H, d), 3,77 (1H, d), 3,97 (1H, d), 4,21 (1H, d), 4,57 (1H, s), 4,68 (1H, t), 4,81 (1H, s), 6,82 (1H, s), 7,63 (2H, d), 7,96 (1H, s), 8,27 (2H, d), 9,81 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00306μM

Ejemplo 37j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,54 - 1,60 (2H, m), 1,62 - 1,68 (2H, m), 1,89 - 1,99 (2H, m), 3,15 - 3,25 (1H, m), 3,41 - 3,56 (5H, m), 3,64 (1H, d), 3,82 (1H, d), 3,98 (1H, d), 4,22 (1H, d), 4,58 (1H, s), 4,69 (1H, t), 6,82 (1H, s), 7,51 (1H, s), 7,62 (2H, d), 8,05 (1H, s), 8,28 (2H, d), 9,69 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0309μM

Ejemplo 37k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 (3H, t), 1,24 (3H, d), 1,53 - 1,60 (2H, m), 1,62 - 1,67 (2H, m), 1,89 - 1,97 (2H, m), 3,14 - 3,28 (3H, m), 3,46 - 3,56 (5H, m), 3,64 (1H, d), 3,77 (1H, d), 3,97 (1H, d), 4,21 (1H, d), 4,58 (1H, s), 4,68 (1H, t), 6,82 (1H, s), 7,56 (2H, d), 7,88 (1H, s), 8,27 (2H, d), 9,62 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0114μM

Ejemplo 37l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,91 (3H, t), 1,24 (3H, d), 1,53 - 1,60 (4H, m), 1,62 - 1,67 (2H, m), 1,90 - 1,97 (2H, m), 3,16 - 3,27 (3H, m), 3,42 - 3,53 (5H, m), 3,64 (1H, d), 3,77 (1H, d), 3,97 (1H, d), 4,21 (1H, d), 4,57 (1H, s), 4,68 (1H, t), 6,82 (1H, s), 7,58 (2H, d), 7,89 (1H, s), 8,26 (2H, d), 9,63 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,032μM

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Ejemplo 37m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,58 (2H, m), 1,67 - 1,75 (4H, m), 3,17 - 3,26 (1H, m), 3,28 (3H, s), 3,45 - 3,58 (5H, m), 3,64 (1H, dd), 3,77 (1H, d), 3,97 (1H, dd), 4,18 - 4,25 (1H, m), 4,52 - 4,63 (2H, m), 6,80 (1H, s), 7,57 - 7,60 (2H, m), 7,91 (1H, s), 8,24 - 8,27 (2H, m), 9,71 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0506μM

Ejemplo 37n: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,91 (3H, t), 1,24 (3H, d), 1,53 - 1,62 (4H, m), 1,66 - 1,69 (2H, m), 3,22 (1H, td), 3,27 (3H, s), 3,43 - 3,52 (3H, m), 3,64 (1H, dd), 3,77 (1H, d), 3,97 (1H, dd), 4,18 - 4,25 (1H, m), 4,56 - 4,62 (1H, m), 6,80 (1H, s), 7,60 (2H, d), 7,91 (1H, s), 8,24 - 8,28 (2H, m), 9,65 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0393μM

Ejemplo 37o: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,56 - 1,59 (2H, m), 1,67 - 1,70 (2H, m), 3,22 (1H, td), 3,27 (3H, s), 3,49 (1H, td), 3,64 (1H, dd), 3,77 (1H, d), 3,81 (3H, s), 3,98 (1H, dd), 4,19 - 4,25 (1H, m), 4,57 - 4,63 (1H, m), 6,81 (1H, s), 7,51 (1H, s), 7,62 - 7,65 (2H, m), 8,05 (1H, s), 8,25 - 8,29 (2H, m), 9,67 - 9,76 (2H, m).

Ensayo de mTOR Quinasa (Echo): 0,033μM

Ejemplo 37p: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,78 - 1,81 (2H, m), 1,95 - 1,98 (2H, m), 2,48 (3H, s), 2,95 (3H, d), 3,16 - 3,23 (1H, m), 3,44 - 3,51 (1H, m), 3,62 (1H, d), 3,76 (1H, d), 3,96 - 3,99 (1H, m), 4,14 - 4,18 (1H, m), 4,44 - 4,50 (1H, m), 6,82 (1H, s), 7,47 (2H, d), 7,80 (1H, s), 7,84 (1H, s), 7,96 (2H, d), 9,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00534μM

Ejemplo 37q: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,58 - 0,62 (2H, m), 0,74 - 0,79 (2H, m), 1,22 (3H, d), 1,78 - 1,81 (2H, m), 1,95 - 1,98 (2H, m), 2,49 (3H, s), 2,87 - 2,97 (1H, m), 3,17 - 3,23 (1H, m), 3,44 - 3,51 (1H, m), 3,61 - 3,64 (1H, m), 3,76 (1H, d), 3,96 - 3,99 (1H, m), 4,15 - 4,18 (1H, m), 4,44 - 4,51 (1H, m), 6,83 (1H, s), 7,54 (2H, d), 7,84 (1H, s), 7,95 (2H, d), 8,15 (1H, s), 9,47 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00294μM

Ejemplo 37r: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,78 - 1,81 (2H, m), 1,94 - 1,98 (2H, m), 2,48 (3H, s), 3,16 - 3,23 (1H, m), 3,44 - 3,50 (1H, m), 3,57 (4H, s), 3,61 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,15 - 4,18 (1H, m), 4,43 - 4,52 (1H, m), 4,82 (1H, s), 6,82 (1H, s), 7,54 (2H, d), 7,84 (2H, s), 7,95 (2H, d), 9,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00162μM

Ejemplo 37s: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,59 - 1,65 (2H, m), 1,89 - 1,91 (2H, m), 2,94 (3H, d), 3,16 (1H, dt), 3,47 (1H, dt), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H,

dd), 4,14 (1H, d), 4,44 (1H, s), 6,69 (1H, s), 7,44 (4H, t), 7,80 - 7,90 (5H, m), 9,70 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00756μM

Ejemplo 37t: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,57 - 0,62 (2H, m), 0,74 - 0,79 (2H, m), 1,19 (3H, d), 1,61 - 1,63 (2H, m), 1,89 - 1,91 (2H, m), 2,90 - 2,94 (1H, m), 3,17 (1H, dt), 3,47 (1H, dt), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,14 (1H, d), 4,45 (1H, s), 6,69 (1H, s), 7,42 (2H, t), 7,52 (2H, d), 7,83 - 7,89 (4H, m), 8,13 (1H, s), 9,47 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00889μM

Ejemplo 37u: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (4H, d), 1,59 - 1,63 (3H, m), 1,89 - 1,91 (2H, m), 3,13 - 3,20 (1H, m), 3,43 - 3,50 (1H, m), 3,56 (4H, m), 3,60 - 3,63 (1H, m), 3,75 (1H, d), 3,96 (1H, dd), 4,14 (1H, d), 4,44 (1H, s), 4,81 (1H, s), 6,68 (1H, s), 7,42 (2H, t), 7,53 (2H, d), 7,83 - 7,86 (1H, m), 7,88 (2H, d), 9,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000395μM

Ejemplo 37v: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,58-0,62 (2H, m), 0,74-0,79 (2H, m), 1,17-1,19 (3H, d), 1,62-1,69 (2H, m), 1,88-1,93 (2H, m), 2,92 (1H, bs), 3,12-3,19 (1H, td), 3,43-3,50 (1H, td), 3,60-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,10-4,13 (1H, d), 4,41 (1H, bs), 6,67 (1H, s), 7,49-7,52 (2H, d), 7,58-7,62 (2H, t), 7,70-7,74 (1H, tt), 7,79-7,81 (2H, d), 7,89-7,91 (2H, d), 8,10 (1H, bs), 9,47 (1H, bs).

Ensayo de mTOR Quinasa (Echo): 0,00549μM

Ejemplo 37w: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15-1,20 (3H, d), 1,60-1,70 (2H, m), 1,90-1,95 (2H, bs), 3,12-31,7 (1H, m), 3,25-3,30 (1H, m oscurecido por disolvente peak), 3,45-3,50 (1H, m), 3,6 (1H, d), 3,7 (1H, d), 3,8 (3H, s), 4,0 (1H, m), 4,1 (1H, d), 4,40-4,45 (1H, bs), 6,7 (1H, s), 7,49-7,53 (3H, m), 7,68-7,73 (2H, m), 7,7 (1H, t), 7,8 (2H, d), 7,9 (2H, d), 8,0 (1H, bs), 9,7 (1H, bs).

Ensayo de mTOR Quinasa (Echo): 0,00137μM

Ejemplo 37x: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17-1,19 (3H, d), 1,61-1,67 (2H, m), 1,68-1,75 (2H, m), 1,88-1,93 (2H, m), 3,11-3,17 (1H, td), 3,43-3,55 (5H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,09-4,12 (1H, d), 4,40 (1H, bs), 4,53-4,54 (1H, t), 6,66 (1H, s), 7,45-7,47 (2H, d), 7,58-7,62 (2H, t), 7,70-7,75 (1H, tt), 7,79-7,81 (2H, dd), 7,86 (1H, bs), 7,89-7,92 (2H, d), 9,64 (1H, bs).

Ensayo de mTOR Quinasa (Echo): 0,00944μM

Ejemplo 37y: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17-1,19 (3H, d), 1,61-1,68 (2H, m), 1,89-1,92 (2H, m), 2,85-2,88 (2H, t), 3,11-3,19 (1H, td), 3,43-3,49 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,75 (3H, m), 3,94-3,98 (1H, dd), 4,09-4,12 (1H, d), 4,41 (1H, bs), 6,67 (1H, s),

7,42-7,45 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,81 (2H, dd), 7,90-7,93 (2H, d), 8,08-8,11 (1H, t), 9,91 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00553μM

Ejemplo 37z: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,12-1,19 (6H, m), 1,61-1,69 (2H, m), 1,89-1,92 (2H, m), 3,11-3,19 (1H, td), 3,43-3,52 (3H, m), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,09-4,12 (1H, d), 4,40 (1H, bs), 6,66 (1H, s), 7,44-7,46 (2H, d), 7,58-7,62 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,81 (2H, d), 7,84 (1H, bs), 7,90-7,92 (2H, d), 9,58 (1H, bs).

Ensayo de mTOR Quinasa (Echo): 0,00481μM

Ejemplo 37aa: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17-1,19 (3H, d), 1,61-1,69 (2H, m), 1,88-1,92 (2H, m), 3,11-3,19 (1H, td), 3,43-3,49 (1H, td), 3,51-3,63 (5H, m), 3,72-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,09-4,12 (1H, d), 4,40 (1H, bs), 4,82 (1H, bs), 6,66 (1H, s), 7,51-7,53 (2H, d), 7,58-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,81 (2H, d), 7,89-7,91 (3H, m), 9,83 (1H, bs).

Ensayo de mTOR Quinasa (Echo): 0,00567μM

Ejemplo 37ab: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17-1,19 (3H, d), 1,61-1,68 (2H, m), 1,88-1,92 (2H, m), 2,94-2,95 (3H, d), 3,11-3,17 (1H, td), 3,44-3,49 (1H, td), 3,58-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,08-4,12 (1H, d), 4,41 (1H, bs), 6,67 (1H, s), 7,43-7,45 (2H, d), 7,58-7,62 (2H, t), 7,70-7,74 (1H, tt), 7,79-7,81 (3H, m), 7,90-7,92 (2H, d), 9,70 (1H, bs).

Ensayo de mTOR Quinasa (Echo): 0,003μM

Ejemplo 37ac: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17-1,19 (3H, d), 1,62-1,69 (2H, m), 1,90-1,93 (2H, m), 3,12-3,18 (1H, td), 3,43-3,50 (1H, td), 3,59-3,63 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,09-4,13 (1H, d), 4,41 (1H, bs), 4,71-4,72 (2H, d), 6,67 (1H, s), 7,00 (2H, bs), 7,56-7,62 (4H, m), 7,70-7,74 (1H, tt), 7,79-7,81 (2H, dd), 7,91-7,93 (2H, d), 8,17 (1H, bs), 9,98 (1H, bs), 11,98 (1H, bs).

Ensayo de mTOR Quinasa (Echo): 0,0298μM

Ejemplo 37ad: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,70 (2H, q), 1,98 (2H, q), 3,10-3,20 (1H, td), 3,40-3,50 (1H, td), 3,50-3,58 (4H, m), 3,58 (1H, dd), 3,75 (1H, d), 3,95 (1H, dd), 4,15 (1H, d), 4,50 (1H, br s), 4,80 (1H, br s), 6,70 (1H, s), 7,50 (2H, d), 7,74-7,77 (4H, m), 7,82 (1H, s), 8,87 (2H, dd), 9,75 (1H, s)

Ejemplo 37ae: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ δ 0,60 (2H, q), 0,77 (2H, q), 1,20 (3H,

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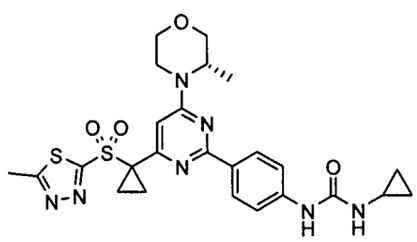
d), 1,70 (2H, q), 1,98 (2H, q), 2,85-2,95 (1H, m), 3,19 (1H, td), 3,47 (1H, td), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,17 (1H, d), 4,48 (1H, br s), 6,71 (1H, s), 7,49 (2H, d), 7,72 (2H, d), 7,78 (2H, dd), 8,15 (1H, br s), 8,87 (2H, dd), 9,46 (1H, br s)

Ejemplo 37af: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,70 (2H, q), 1,98 (2H, q), 2,94 (3H, d), 3,17 (1H, td), 3,46 (1H, td), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,10-4,20 (1H, d), 4,50 (1H, br s), 6,71 (1H, s), 7,43 (2H, d), 7,74-7,76 (2H, d), 7,77-7,79 (2H, dd), 7,82 (1H, m), 8,87 (2H, dd), 9,70 (1H, br s).

Ejemplo 37ag: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,45 (6H, s), 1,65 (2H, m), 1,90 (2H, m), 3,14 (1H, m), 3,46 (1H, m), 3,58 (3H, m), 3,75 (1H, m), 3,96 (1H, m), 4,11 (1H, m), 4,41 (1H, m), 6,67 (1H, s), 7,39 (1H, m), 7,50 (2H, m), 7,60 (2H, m), 7,75 (3H, m), 7,88 (2H, m)

Las preparaciones de las anilinas necesarias para los ejemplos **37a – 37ag** se han descrito anteriormente.

Ejemplo 38: 3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea



Se agregó ciclopropilamina (84 mg, 1,48 mmol) a fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]carbamato (175 mg, 0,30 mmol) y trietilamina (0,205 mL, 1,48 mmol) en NMP (2 mL) a TA y la reacción se dejó agitar durante 2 horas. La mezcla se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido crema (112 mg).

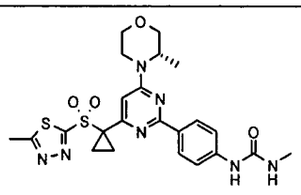
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,37 - 0,45 (2H, m), 0,61 - 0,68 (2H, m), 1,21 (3H, d), 1,78 - 1,88 (2H, m), 1,97 - 2,05 (2H, m), 2,83 (3H, s), 3,12 - 3,23 (1H, m), 3,42 - 3,52 (1H, m), 3,61 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,20 (1H, s), 4,52 (1H, s), 6,46 (1H, t), 6,77 (1H, s), 7,42 (2H, d), 7,74 (2H, d), 8,57 (1H, s)

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Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 556; HPLC tR = 2,25 min.

Ensayo de mTOR Quinasa (Echo): 0,00131μM

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]carbamato y la amina apropiada.

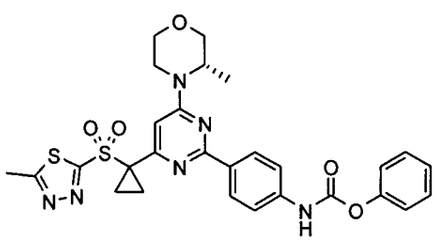
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
38a		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	530	209

Ejemplo 38a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,82 - 1,85 (2H, m), 1,98 - 2,04 (2H, m), 2,66 (3H, s), 2,82 (3H, s), 3,13 - 3,25 (1H, m), 3,40 - 3,47 (1H, m), 3,61 (1H, d), 3,76 (1H, d), 3,96 (1H, d), 4,21 (1H, s), 6,08 (1H, t), 6,77 (1H, s), 7,42 (2H, d), 7,74 (2H, d), 8,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000918μM

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]carbamato



Se agregó lentamente fenil cloroformiato (0,398 mL, 3,17 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidin-2-

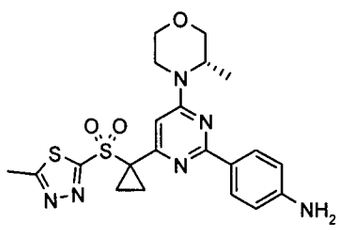
1611

il]anilina (1,25 g, 2,65 mmol) e hidrogenocarbonato de sodio (0,333 g, 3,97 mmol) en dioxano (30 mL) a 5°C bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a TA durante 18 horas luego la mezcla se diluyó con acetato de etilo (125 mL) y se lavó secuencialmente con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó. El material bruto se trituró con éter dietílico e isohexano para proporcionar un sólido que se recogió mediante filtración y se secó al vacío para proporcionar el material deseado como un sólido crema (1,24 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,82 - 1,88 (2H, m), 2,00 - 2,05 (2H, m), 2,82 (3H, s), 3,20 (1H, dd), 3,42 - 3,50 (1H, m), 3,60 (1H, d), 3,76 (1H, d), 4,00 (1H, d), 4,23 (1H, s), 4,53 (1H, s), 6,81 (1H, s), 7,22 - 7,34 (3H, m), 7,40 - 7,50 (2H, m), 7,55 (2H, d), 7,84 (2H, d), 10,46 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 593; HPLC tR = 2,81 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]anilina



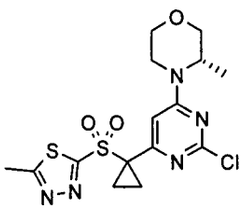
Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,164 g, 0,23 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidina (1,45 g, 3,49 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,146 g, 5,23 mmol) y solución de carbonato de sodio acuoso (3 mL, 6,00 mmol) en una mezcla de disolventes de DMF (10 mL), DME (2 mL), agua (2 mL) y etanol (2 mL). La atmósfera se reemplazó con nitrógeno y la reacción se agitó a 90°C durante 18 horas. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con salmuera saturada (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 80% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido beige (1,25 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,78 - 1,83 (2H, m), 1,98 - 2,01 (2H, m), 2,83 (3H, s), 3,10 - 3,21 (1H, m), 3,38 - 3,51 (1H, m), 3,60 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,16 (1H, s), 4,48 (1H, s), 5,59 (2H, s), 6,51 (2H, d), 6,66 (1H, s), 7,57

(2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 473; HPLC tR = 2,14 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(5-metil-1,3,4-tiadiazol-2-il)sulfonil]ciclopropil]pirimidina

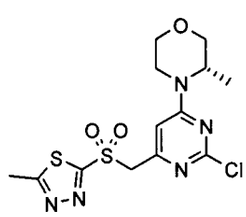


Una solución acuosa de hidróxido de sodio (20 mL, 532,5 mmol) se agregó a una mezcla agitada de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(5-metil-1,3,4-tiadiazol-2-il)sulfonilmetil]pirimidina (1,8 g, 4,62 mmol), 1,2-dibromoetano (1,99 ml, 23,08 mmol) y bromuro de tetraetilamonio (0,097 g, 0,46 mmol) en DCM (40 mL) a TA. La mezcla resultante se agitó a TA durante 24 horas luego la mezcla se diluyó con DCM (50 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto que se cromatografió sobre sílice, gradiente de elución de 10 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (1,48 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,79 - 1,84 (2H, m), 1,94 - 2,01 (2H, m), 2,87 (3H, s), 3,17 - 3,23 (1H, m), 3,37 - 3,46 (1H, m), 3,55 (1H, dd), 3,71 (1H, d), 3,92 (1H, dd), 4,06 (1H, s), 4,33 (1H, s), 6,87 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 416; HPLC tR = 1,98 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(5-metil-1,3,4-tiadiazol-2-il)sulfonilmetil]pirimidina



Se agregó ácido 3-cloroperoxibenzoico (4,77 g, 27,66 mmol) en porciones a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(5-metil-1,3,4-tiadiazol-2-il)sulfanilmetil]pirimidina (3,3 g, 9,22 mmol), en DCM (70 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 2 horas y luego se diluyó con acetato de etilo (250 mL) y se lavó

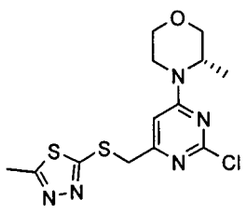
1613

secuencialmente con una solución acuosa de metabisulfito de sodio al 10% (100 mL) y carbonato de sodio 2M (100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 100% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blanco (2,22 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (4H, d), 2,87 (4H, s), 3,15 - 3,26 (1H, m), 3,44 (1H, td), 3,59 (1H, d), 3,73 (1H, d), 3,94 (2H, m), 4,22 (1H, s), 5,03 (2H, s), 6,92 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 390; HPLC tR = 1,83 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(5-metil-1,3,4-tiadiazol-2-il)sulfanilmetil]pirimidina



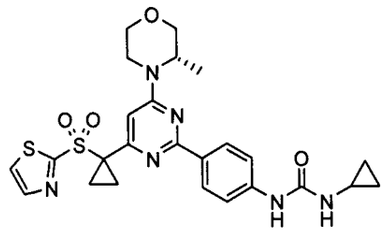
Se agregó DIPEA (2,94 mL, 16,97 mmol) a 5-metil-1,3,4-tiadiazol-2-tiol (1,645 g, 12,44 mmol), en acetonitrilo (40 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 20 minutos luego se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4 g, 11,31 mmol). La mezcla resultante se agitó a TA durante 1 hora, luego la mezcla se diluyó con acetato de etilo (300 mL) y se lavó con agua (150 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 2% metanol en acetato de etilo, para proporcionar el material deseado como un sólido blanco (3,30 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 6,90 (1H, s), 1,17 (3H, d), 2,68 (3H, s), 3,12 - 3,22 (1H, m), 3,42 (1H, td), 3,57 (1H, dd), 3,71 (1H, d), 3,86 - 4,04 (2H, m), 4,27 (1H, s), 4,42 (2H, s)

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

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Ejemplo 39: 3-Ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea

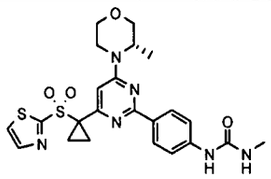


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (17,6 mg, 0,03 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidina (150 mg, 0,37 mmol), 1-ciclopropil-3-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)urea (170 mg, 0,56 mmol) y una solución acuosa de carbonato de sodio (5 mL, 10,00 mmol) en una mezcla de disolventes de DMF (2 mL), DME (16 mL), agua (2 mL) y etanol (2 mL). La atmósfera se reemplazó con nitrógeno y la mezcla se agitó a 90°C durante 18 horas. La mezcla se dejó enfriar y se diluyó con acetato de etilo (200 mL) y se lavó con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 4% metanol en acetato de etilo. El material bruto se purificó adicionalmente mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado (30 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,37 - 0,45 (2H, m), 0,60 - 0,67 (2H, m), 1,19 (3H, d), 1,76 - 1,82 (2H, m), 1,95 - 2,02 (2H, m), 3,12 - 3,21 (1H, m), 3,45 (1H, d), 3,61 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,18 (1H, s), 4,44 (1H, s), 6,45 (1H, s), 6,73 (1H, s), 7,41 (2H, d), 7,83 (2H, d), 8,24 (1H, s), 8,28 (1H, s), 8,54 (1H, s)

El siguiente compuesto se elaboró en forma análoga a partir de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidina y la amina apropiada.

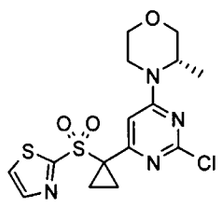
1615

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
39a		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea	515	2,05

Ejemplo 39a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,76 - 1,81 (2H, m), 1,96 - 2,01 (2H, m), 2,66 (3H, d), 3,11 - 3,22 (1H, m), 3,42 - 3,49 (1H, m), 3,61 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,17 (1H, s), 4,44 (1H, s), 6,07 (1H, q), 6,73 (1H, s), 7,40 (2H, d), 7,82 (2H, d), 8,24 (1H, d), 8,28 (1H, d), 8,75 (1H, s)

La preparación de 2-cloro-4-[(*3S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidina se describe a continuación.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidina

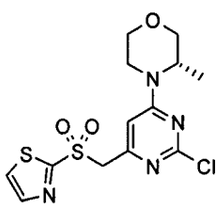


Una solución acuosa de hidróxido de sodio (0,235 mL, 6,27 mmol) se agregó a una mezcla agitada de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1,3-tiazol-2-ilsulfonilmetil)pirimidina (2,35 g, 6,27 mmol), 1,2-dibromoetano (2,70 mL, 31,34 mmol) y bromuro de tetraetilamonio (0,132 g, 0,63 mmol) en tolueno a TA. La mezcla resultante se agitó a 70°C durante 2 horas y luego se diluyó con acetato de etilo (150 mL) y se lavó con agua (100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (2,45 g).

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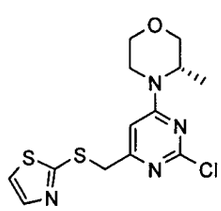
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (4H, d), 1,69 - 1,75 (2H, m), 1,91 - 1,96 (2H, m), 3,12 - 3,21 (1H, m), 3,40 (1H, d), 3,55 (1H, d), 3,70 (1H, d), 3,92 (1H, d), 4,00 (1H, s), 4,27 (1H, s), 6,84 (1H, s), 8,20 (1H, d), 8,33 (1H, d)
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 401; HPLC tR = 2,04 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1,3-tiazol-2-ilsulfonilmetil)pirimidina



Se agregó ácido 3-cloroperoxibenzoico (6,04 g, 35,00 mmol) en porciones a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1,3-tiazol-2-ilsulfanilmetil)pirimidina (4 g, 11,67 mmol), en DCM (10 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 3 horas. La mezcla de reacción se diluyó con acetato de etilo (250 mL) y se lavó con una solución acuosa de metabisulfito de sodio al 10% (100 mL) y una solución saturada acuosa de carbonato de sodio (100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 100% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blanco (2,85 g).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 8,33 (1H, d), 1,18 (4H, d), 3,14 - 3,25 (1H, m), 3,43 (1H, dd), 3,58 (1H, d), 3,72 (1H, d), 3,88 - 4,01 (2H, m), 4,20 (1H, s), 4,87 (2H, s), 6,82 (1H, s), 8,24 (1H, d)
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 375; HPLC tR = 1,86 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1,3-tiazol-2-ilsulfanilmetil)pirimidina



Se agregó DIPEA (2,94 mL, 16,97 mmol) a 2-mercaptotiazol (1,458 g, 12,44 mmol), en acetonitrilo (40 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a

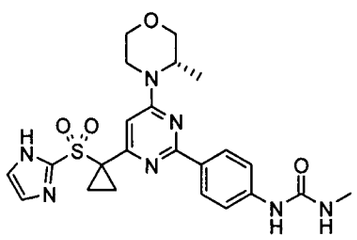
TA durante 20 minutos. Se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4 g, 11,31 mmol) y la mezcla se agitó durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo (300 mL) y se lavó con agua (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 80% acetato de etilo en isohexano, para proporcionar el material deseado como una goma incolora (3,77 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15 (5H, d), 3,15 (1H, td), 3,41 (2H, td), 3,56 (1H, dd), 3,70 (1H, d), 3,91 (2H, m), 4,25 (1H, s), 4,36 (2H, s), 6,84 (1H, s), 7,70 (1H, d), 7,76 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 343; HPLC tR = 2,07 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 40: 1-[4-[4-[1-(1*H*-Imidazol-2-ilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea



Se agregó anisol (0,159 mL, 1,46 mmol) a 1-[4-[4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea (180 mg, 0,29 mmol) en TFA (8 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a 60°C durante 90 minutos, luego el disolvente se retiró bajo presión reducida y el residuo se cromatografió en una columna SCX, eluyendo con amoníaco 7M en metanol. El material se purificó adicionalmente mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 90% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido crema (122 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,68 - 1,74 (2H, m), 1,91 - 1,98 (2H, m), 2,66 (3H, s), 3,09 - 3,19 (1H, m), 3,44 - 3,50 (1H, m), 3,61 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,13 (1H, s), 4,40 (1H, s), 6,05 (1H, s), 6,64 (1H, s), 7,35 (2H, s), 7,43

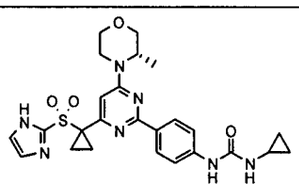
1618

(2H, d), 8,00 (2H, d), 8,71 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 493; HPLC tR = 1,33 min.

Ensayo de mTOR Quinasa (Echo): 0,00436μM

El siguiente compuesto se elaboró en forma análoga a partir de 3-ciclopropil-1-[4-[4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea.

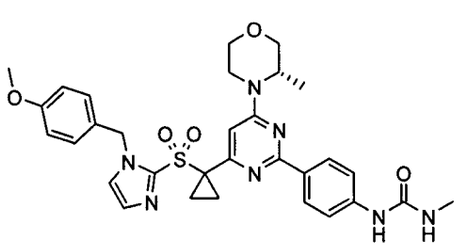
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
40a		3-ciclopropil-1-[4-[4-[1-(1H-imidazol-2-ilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	524	1,56

Ejemplo 40a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,38 - 0,44 (2H, m), 0,63 - 0,68 (2H, m), 1,19 (3H, d), 1,67 - 1,75 (2H, m), 1,89 - 1,99 (2H, m), 2,51 - 2,57 (1H, m), 3,11 - 3,22 (1H, m), 3,39 - 3,52 (1H, m), 3,61 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,11 (1H, d), 4,39 (1H, s), 6,41 (1H, s), 6,65 (1H, s), 7,36 (2H, s), 7,44 (2H, d), 8,00 (2H, d), 8,50 (1H, s) 13,5(1H,s).

Ensayo de mTOR Quinasa (Echo): 0,00649μM

La preparación de 1-[4-[4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea se describe a continuación.

1-[4-[4-[1-[1-[(4-Metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea

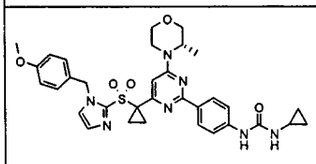


Se agregó trietilamina (0,246 mL, 1,76 mmol) a fenil *N*-[4-[4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (240 mg, 0,35 mmol) y metilamina (0,705 mL, 1,41 mmol) en DMF (3 mL) a TA. La solución resultante se agitó a 40°C durante 30 minutos luego a TA durante toda la noche. La mezcla se concentró al vacío y se cromatografió sobre sílice, gradiente de elución de 100 % acetato de etilo, para proporcionar el material deseado como un sólido crema (190 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 (3H, d), 1,68 - 1,72 (2H, m), 1,88 - 1,95 (2H, m), 2,67 (3H, d), 3,07 - 3,20 (1H, m), 3,36 - 3,51 (1H, m), 3,57 (1H, d), 3,68 - 3,79 (4H, m), 3,94 (1H, d), 4,06 (1H, s), 4,35 (1H, s), 5,21 (2H, s), 6,05 (1H, t), 6,55 (1H, s), 6,77 (2H, d), 7,05 (2H, d), 7,23 (1H, s), 7,41 - 7,48 (3H, m), 8,02 (2H, d), 8,72 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 618; HPLC tR = 2,17 min

Se elaboró 3-ciclopropil-1-[4-[4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea en forma análoga a partir de fenil *N*-[4-[4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

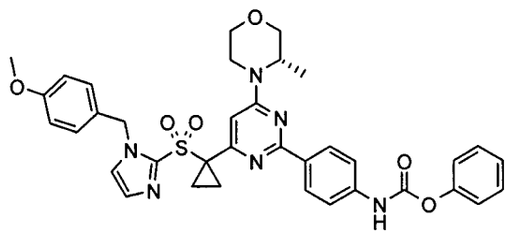
Estructura	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
	3-ciclopropil-1-[4-[4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	644	2,32

^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,38 - 0,45 (2H, m), 0,60 - 0,69 (2H, m), 1,14 (3H, d), 1,66 - 1,74 (2H, m), 1,88 - 1,94 (2H, m), 2,53 - 2,62 (1H, m), 3,09 - 3,18 (1H, m), 3,39 - 3,48 (1H, m), 3,57 (1H, d), 3,66 - 3,78 (4H, m), 3,95 (1H, d), 4,11 (1H, s), 4,35 (1H, s), 5,21 (2H, s), 6,43 (1H, s), 6,55 (1H, s), 6,77 (2H, d), 7,06 (2H, d), 7,23 (1H, s), 7,42 - 7,49 (3H, m), 8,02 (2H, d), 8,52 (1H, s)

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La preparación de fenil *N*-[4-[4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

Fenil *N*-[4-[4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

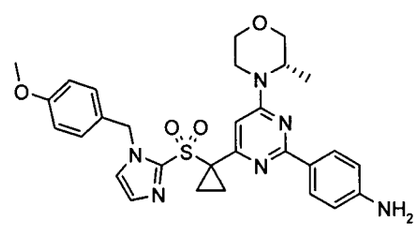


Se agregó fenil cloroformiato (0,202 mL, 1,61 mmol) a 4-[4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (600 mg, 1,07 mmol) e hidrogenocarbonato de sodio (135 mg, 1,61 mmol) en dioxano (10 mL) a 5°C bajo nitrógeno. La mezcla resultante se agitó a TA durante 90 minutos. La mezcla de reacción se diluyó con acetato de etilo (150 mL) y se lavó con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. La goma bruta se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido beige que se recogió mediante filtración y se secó al vacío (570 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 (3H, d), 1,67 - 1,74 (2H, m), 1,90 - 1,95 (2H, m), 3,03 - 3,21 (1H, m), 3,36 - 3,47 (1H, m), 3,53 - 3,62 (1H, m), 3,64 - 3,76 (4H, m), 3,95 (1H, d), 4,10 (1H, s), 4,37 (1H, s), 5,23 (2H, s), 6,60 (1H, s), 6,77 (2H, d), 7,06 (2H, d), 7,23 - 7,33 (4H, m), 7,42 - 7,50 (3H, m), 7,59 (2H, d), 8,11 (2H, d), 10,41 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 682; HPLC tR = 2,88 min

4-[4-[1-[1-[(4-Metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

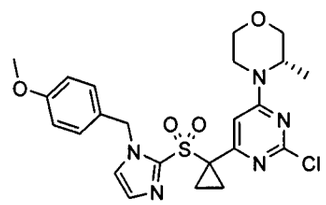


1621

Se agregó cloruro de bis(trifenilfosfina)paladio(II) (42,5 mg, 0,06 mmol) a 2-cloro-4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (610 mg, 1,21 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (530 mg, 2,42 mmol) y una solución acuosa de carbonato de sodio (2 mL, 4,00 mmol) en una mezcla de disolventes de DMF (2 mL), DME (4 mL), agua (0,5 mL) y etanol (0,5 mL) a TA. La atmósfera se reemplazó con nitrógeno y la mezcla se agitó a 90°C durante 5 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 100% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blanco (600 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11 (3H, d), 1,65 - 1,69 (2H, m), 1,88 - 1,92 (2H, m), 3,04 - 3,15 (1H, m), 3,41 (1H, td), 3,56 (1H, d), 3,67 - 3,75 (4H, m), 3,93 (1H, d), 4,06 (1H, s), 4,31 (1H, s), 5,16 (2H, s), 5,54 (2H, s), 6,44 (1H, s), 6,57 (2H, d), 6,79 (2H, d), 7,06 (2H, d), 7,22 (1H, s), 7,43 (1H, s), 7,87 (2H, d)

2-Cloro-4-[1-[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



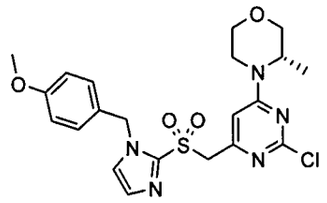
Una solución acuosa de hidróxido de sodio (10 mL, 186,4 mmol) se agregó a 2-cloro-4-[[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,1 g, 2,30 mmol), bromuro de tetraetilamonio (0,097 g, 0,46 mmol) y 1,2-dibromoetano (2,38 mL, 27,62 mmol) en DCM (20 mL) a TA bajo una atmósfera de nitrógeno. La reacción se agitó a TA durante 4 horas. La mezcla de reacción se diluyó con DCM (50 mL), las fases se separaron y la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó. El residuo se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 75% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blanco (0,77 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,10 (4H, d), 1,64 (3H, m), 1,85 - 1,89 (2H, m), 3,03 - 3,15 (1H, m), 3,33 - 3,42 (1H, m), 3,50 (1H, d), 3,68 (1H, d), 3,74 (3H,

s), 3,87 - 3,93 (2H, m), 4,06 (1H, s), 5,33 (2H, s), 6,57 (1H, s), 6,87 (2H, d), 7,17 (2H, d), 7,22 (1H, s), 7,59 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 504; HPLC tR = 2,35 min

2-Cloro-4-[[1-[(4-metoxifenil)metil]imidazol-2-il]sulfonilmetil]-6-[(3I)-3-metilmorfolin-4-il]pirimidina

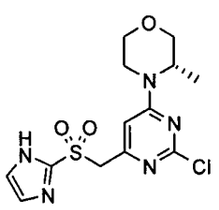


Se agregó cloruro 4-metoxibencilo (0,470 mL, 3,46 mmol) a 2-cloro-4-(1*H*-imidazol-2-ilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,18 g, 3,30 mmol) y carbonato de potasio (0,501 g, 3,63 mmol) en DMF (30 mL) a TA bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 75°C durante 1 hora y luego se dejó enfriar y se diluyó con acetato de etilo (100 mL). La mezcla se lavó con agua (2 x 50 mL), la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 70% acetato de etilo en isohexano, para proporcionar el material deseado como una goma incolora (1,27 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 (3H, d), 3,10 - 3,19 (1H, m), 3,35 - 3,45 (1H, m), 3,54 (1H, d), 3,70 (1H, d), 3,74 (3H, s), 3,87 - 3,96 (2H, m), 4,14 (1H, s), 4,68 (2H, s), 5,36 (2H, s), 6,55 (1H, s), 6,88 (2H, d), 7,15 - 7,28 (3H, m), 7,57 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 478; HPLC tR = 2,26 min

2-Cloro-4-(1*H*-imidazol-2-ilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



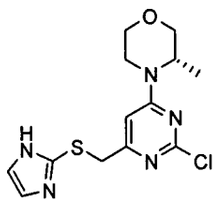
Se agregó ácido 3-cloroperoxibenzoico (2,62 g, 15,19 mmol) a 2-cloro-4-(1*H*-imidazol-2-ilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,25 g, 6,91 mmol) en DCM (100

mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con DCM (100 mL) y se lavó secuencialmente con una solución acuosa de metabisulfito de sodio al 10% (200 mL) y una solución saturada de hidrogenocarbonato de sodio (200 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido blanco que se recogió mediante filtración y se secó al vacío (1,8 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 3,06 - 3,21 (1H, m), 3,35 - 3,46 (1H, m), 3,55 (1H, d), 3,71 (1H, d), 3,83 - 3,97 (2H, m), 4,16 (1H, s), 4,66 (2H, s), 6,52 (1H, s), 7,35 (2H, s), 13,65(1H,s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 358; HPLC tR = 0,87 min

2-Cloro-4-(1*H*-imidazol-2-ilsulfanilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó DIPEA (2,94 mL, 16,97 mmol) a 1*H*-imidazol-2-tiol (1,246 g, 12,44 mmol), en acetonitrilo (50 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 20 minutos. Se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4 g, 11,31 mmol) y la mezcla se agitó durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo (300 mL) y se lavó con agua (150 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 4% metanol en acetato de etilo, para proporcionar el material deseado como un sólido blanco (2,80 g).

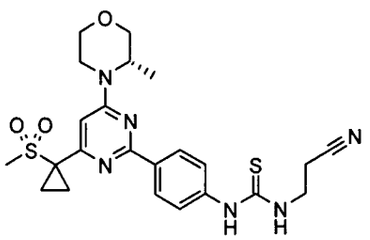
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 (3H, d), 3,11 (1H, dd), 3,34 - 3,45 (1H, m), 3,54 (1H, dd), 3,69 (1H, d), 3,87 - 3,95 (2H, m), 4,06 (2H, s), 4,17 (1H, s), 6,52 (1H, s), 6,96 (1H, s), 7,17 (1H, s), 12,35 (1H,s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 326; HPLC tR = 1,41 min

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

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Ejemplo 41: 3-(2-Cianoetil)-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea



Una solución de 1,1'-tiocarbonildiimidazol (50 mg, 0,28 mmol) en DCM (1 mL) se agregó a una suspensión de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina (75 mg, 0,19 mmol) en DCM (2 mL) y THF (1 mL). La mezcla de reacción se agitó a TA durante 1 hora antes de agregar 3-aminopropionitrilo (91 mg, 1,30 mmol) y trietilamina (0,026 mL, 0,19 mmol). Se continuó agitando a TA durante toda la noche. La reacción fue incompleta y se observó material insoluble significativo por lo que se agregó DMF (1 mL) y se continuó agitando durante 1 hora más. La reacción aún era incompleta, por lo que la mezcla de reacción se transfirió a un tubo de microondas, se selló, se calentó hasta alcanzar 100°C en el reactor de microondas y se mantuvo durante 10 minutos. La reacción aún era incompleta, de manera que se agregó más 3-aminopropionitrilo (91 mg, 1,30 mmol) y la mezcla de reacción se agitó a TA durante 2-3 horas. La mezcla de reacción se evaporó y se purificó el residuo mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo como eluyentes, para proporcionar el material deseado como un sólido blanco (29 mg).

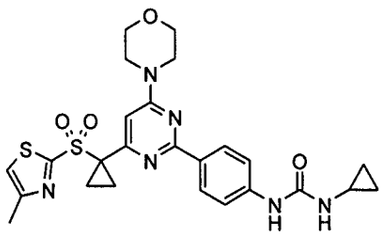
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,58 (2H, m), 1,67 - 1,69 (2H, m), 2,87 (2H, t), 3,19 - 3,26 (1H, m), 3,27 (3H, s), 3,49 (1H, td), 3,64 (1H, dd), 3,74 - 3,78 (3H, m), 3,98 (1H, dd), 4,18 - 4,25 (1H, m), 4,56 - 4,63 (1H, m), 6,82 (1H, s), 7,57 (2H, d), 8,16 (1H, s), 8,26 - 8,30 (2H, m), 9,98 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 501; HPLC tR = 1,99 min

Ensayo de mTOR Quinasa (Echo): 0,0308μM

La preparación de 4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina se describió previamente.

Ejemplo 42: 3-Ciclopropil-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea



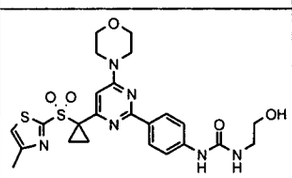
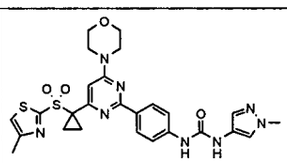
Se agregó trietilamina (0,119 mL, 0,85mmol) a una solución de fenil *N*-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato (100 mg, 0,17 mmol) y ciclopropilamina (0,059 mL, 0,85 mmol) en NMP (2 mL) y la solución resultante se agitó a temperatura ambiente durante 18 horas. El producto bruto se purificó mediante HPLC preparativa para proporcionar el material deseado como un sólido blanco (80 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,62 - 0,67 (2H, m), 1,75 - 1,78 (2H, m), 1,94 - 1,97 (2H, m), 2,49 (3H, s), 2,54 - 2,58 (1H, m), 3,70 (8H, s), 6,40 (1H, s), 6,82 (1H, s), 7,42 (2H, d), 7,84 (1H, s), 7,87 (2H, d), 8,52 (1H, s)

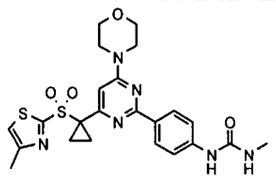
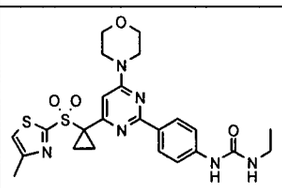
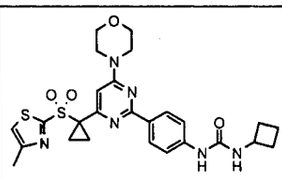
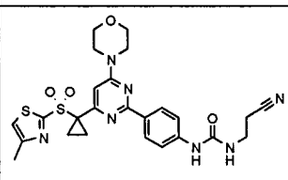
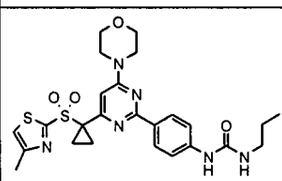
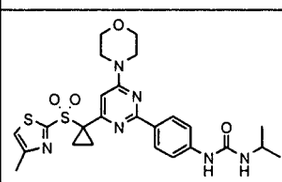
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 541; HPLC tR = 2,15min.

Ensayo de mTOR Quinasa (Echo): 0,000705μM

Los compuestos a continuación se prepararon en forma análoga utilizando la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
42a		3-(2-hidroxietil)-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	545	1,79
42b		3-(1-metilpirazol-4-il)-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	581	2,01

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Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
42c		3-metil-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	515	1,96
42d		1-etil-3-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	529	2,14
42e		3-ciclobutil-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	555	1,95
42f		3-(2-cianoetil)-1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	554	1,63
42g		3-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-1-propilurea	543	2,13
42h		1-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-propan-2-ilurea	543	2,13

Ejemplo 42a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,75 - 1,78 (2H, m), 1,94 - 1,97 (2H, m), 2,48 (3H, s), 3,15 - 3,20 (2H, m), 3,44 - 3,48 (2H, m), 3,70 (8H, s), 4,72 (1H, t), 6,23 (1H, t), 6,82 (1H, s), 7,40 (2H, d), 7,84 (1H, s), 7,87 (2H, d), 8,78 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00261μM

Ejemplo 42b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,75 - 1,79 (2H, m), 1,94 - 1,98 (2H, m), 2,50 (3H, s), 3,70 (8H, s), 3,79 (3H, s), 6,83 (1H, s), 7,38 (1H, s), 7,46 (2H, d), 7,77 (1H, s), 7,85 (1H, s), 7,90 (2H, d), 8,36 (1H, s), 8,82 (1H, s).

Ejemplo 42c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,75 - 1,78 (2H, m), 1,94 - 1,97 (2H, m), 2,49 (3H, s), 2,66 (3H, d), 3,70 (8H, s), 6,04 (1H, q), 6,82 (1H, s), 7,41 (2H, d), 7,84 (1H, s), 7,86 (2H, d), 8,72 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0036μM

Ejemplo 42d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,75 - 1,78 (2H, m), 1,94 - 1,97 (2H, m), 2,49 (3H, s), 3,09 - 3,16 (2H, m), 3,70 (8H, s), 6,14 (1H, t), 6,82 (1H, s), 7,41 (2H, d), 7,84 (1H, s), 7,86 (2H, d), 8,64 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,000425μM

Ejemplo 42e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,57 - 1,66 (2H, m), 1,75 - 1,78 (2H, m), 1,81 - 1,91 (2H, m), 1,94 - 1,97 (2H, m), 2,18 - 2,25 (2H, m), 2,48 (3H, s), 3,70 (8H, s), 4,09 - 4,19 (1H, m), 6,43 (1H, d), 6,82 (1H, s), 7,39 (2H, d), 7,84 (1H, s), 7,86 (2H, d), 8,54 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00257μM

Ejemplo 42f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,75 - 1,78 (2H, m), 1,94 - 1,97 (2H, m), 2,49 (3H, s), 2,70 (2H, t), 3,34 - 3,39 (2H, m), 3,70 (8H, s), 6,52 (1H, t), 6,83 (1H, s), 7,43 (2H, d), 7,84 (1H, s), 7,88 (2H, d), 8,92 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00264μM

Ejemplo 42g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,41 - 1,50 (2H, m), 1,75 - 1,78 (2H, m), 1,94 - 1,97 (2H, m), 2,49 (3H, s), 3,04 - 3,09 (2H, m), 3,70 (8H, s), 6,18 (1H, t), 6,82 (1H, s), 7,40 (2H, d), 7,84 (1H, s), 7,86 (2H, d), 8,63 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00401μM

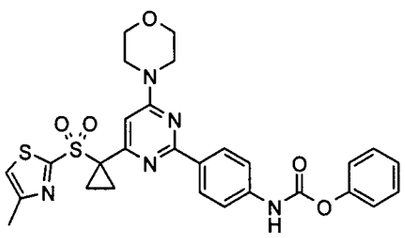
Ejemplo 42h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,11 (6H, d), 1,75 - 1,78 (2H, m), 1,94 - 1,97 (2H, m), 2,48 (3H, s), 3,70 (8H, s), 3,73 - 3,81 (1H, m), 6,03 (1H, d), 6,82 (1H, s), 7,39 (2H, d), 7,84 (1H, s), 7,86 (2H, d), 8,51 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,00412μM

La preparación de fenil *N*-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato se describe a continuación:

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Fenil *N*-[4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato

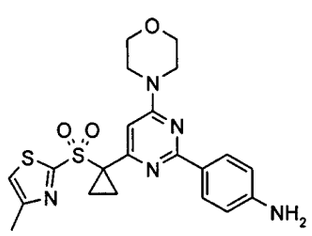


Se agregó fenil cloroformiato (0,664 mL, 5,29 mmol) a 4-[4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]anilina (2,2 g, 4,81 mmol) e hidrogenocarbonato de sodio (0,606 g, 7,21 mmol) en dioxano (100 mL) a 10°C bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 10°C durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto como una goma (2,83 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,76 - 1,80 (2H, m), 1,94 - 1,97 (2H, m), 2,48 (3H, s), 3,70 (8H, s), 6,87 (1H, s), 7,24 - 7,30 (3H, m), 7,43 - 7,47 (2H, m), 7,55 (2H, d), 7,85 (1H, s), 7,96 (2H, d), 10,45 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 578; HPLC tR = 2,88 min.

4-[4-[1-[(4-Metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]anilina



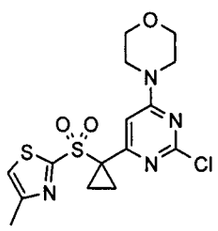
Se agregó cloruro de bis(trifenilfosfina)paladio (II) (0,256 g, 0,37 mmol) a 2-cloro-4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidina (2,93 g, 7,31 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (2,082 g, 9,50 mmol) y carbonato de sodio acuoso 2M (13,16 mL, 26,31 mmol) en una mezcla de disolventes de DMF (15 mL), agua (37,5 mL), etanol (15 mL) y DME (15 mL) a TA bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 80°C durante 16 horas. La mezcla de reacción enfriada se diluyó con acetato de etilo (100 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada

(100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 75% acetato de etilo en DCM, para proporcionar el material deseado como un sólido crema (2,2 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,72 - 1,75 (2H, m), 1,91 - 1,94 (2H, m), 2,49 (3H, s), 3,62 - 3,71 (8H, m), 5,57 (2H, s), 6,50 (2H, d), 6,71 (1H, s), 7,68 (2H, d), 7,84 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 458; HPLC tR = 2,21min.

2-Cloro-4-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-morfolin-4-ilpirimidina

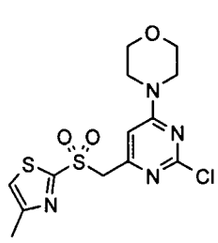


Se agregó 1,2-dibromoetano (0,230 mL, 2,67 mmol) a 2-cloro-4-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]-6-morfolin-4-ilpirimidina (500 mg, 1,33 mmol), solución de hidróxido de sodio al 40% (1,3 mL,13 mmol) y bromuro de tetrabutilamonio (86 mg, 0,27 mmol) en tolueno (10 mL) a TA. La solución resultante se agitó a 60°C durante 3 horas. La mezcla de reacción enfriada se evaporó hasta secarse y se disolvió nuevamente en acetato de etilo (50 mL) y se lavó secuencialmente con agua (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado como una goma marrón clara (528 mg).

Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,76 - 1,79 (2H, m), 2,09 - 2,12 (2H, m), 2,52 (3H, s), 3,65 - 3,71 (4H, m), 3,77 - 3,79 (4H, m), 7,29 (1H, s), 7,30 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 401; HPLC tR = 2,04 min.

2-Cloro-4-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]-6-morfolin-4-ilpirimidina



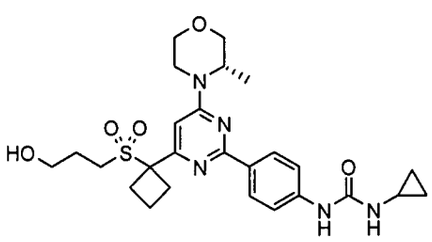
Una solución de morfolina (0,994 g, 11,41 mmol) en DCM (25 mL) se agregó gota a gota a una solución agitada de 2,4-dicloro-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina (3,7 g, 11,41 mmol) y trietilamina (1,155 g, 11,41 mmol) en DCM (50 mL). La solución resultante se agitó a TA durante 18 horas. La mezcla de reacción se lavó tres veces con agua y la capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido amarillo (2,84 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 2,57 (3H, s), 3,58 - 3,69 (8H, m), 4,56 (2H, s), 6,58 (1H, s), 7,30 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 375; HPLC tR = 2,14 min.

La preparación de 2,4-dicloro-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina se describió previamente.

Ejemplo 43: 3-Ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



Se agregó ciclopropilamina (0,122 mL, 1,76 mmol) en una porción a una solución agitada de fenil *N*-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,2 g, 0,35 mmol) y trietilamina (0,148 mL, 1,06 mmol) en DMA (35,3 mL) a TA. La solución resultante se agitó a 50°C durante 24 horas. La mezcla de reacción luego se concentró y el producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 5% metanol en DCM, para proporcionar un aceite claro que luego se trituró con éter dietílico para proporcionar el material deseado como un sólido blanco (0,126 g).

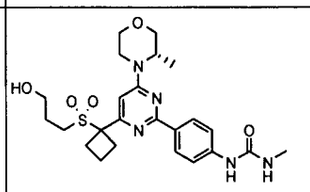
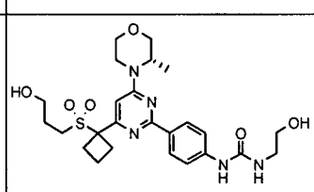
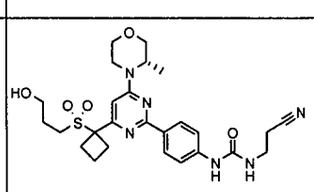
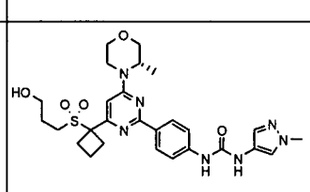
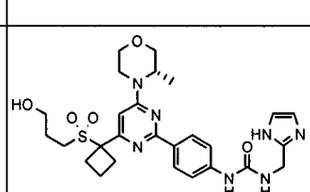
Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 0,60 - 0,67 (2H, m), 0,74 - 0,83 (2H, m), 1,33 (3H, d), 1,94 - 2,01 (3H, m), 2,16 - 2,25 (2H, m), 2,57 - 2,63 (1H, m), 2,80 - 2,88 (2H, m), 2,98 - 3,01 (2H, m), 3,09 - 3,16 (2H, m), 3,28 - 3,35 (1H, m), 3,56 - 3,62 (3H, m), 3,71 - 3,75 (1H, m), 3,81 (1H, d), 4,01 - 4,05 (1H, m), 4,16 (1H, d), 4,46 (1H, d), 5,30 (1H, s), 6,55 (1H, s), 7,31 (1H, s), 7,48 (2H, d), 8,32 (2H, d).

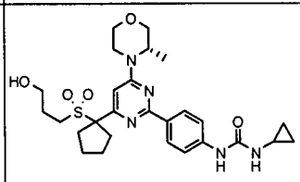
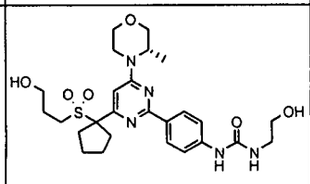
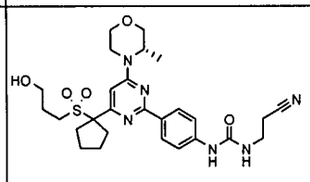
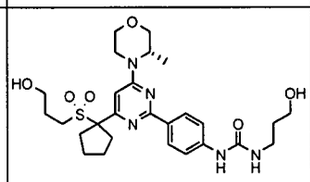
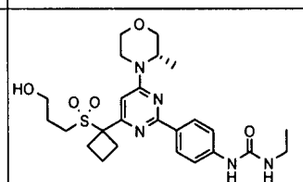
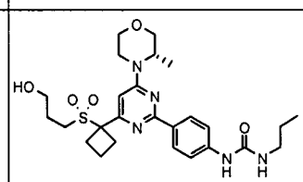
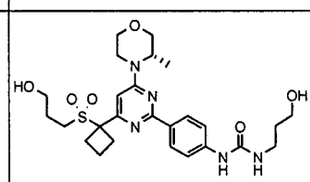
1631

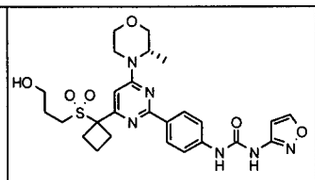
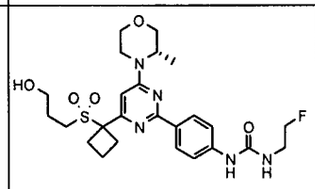
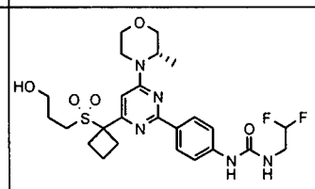
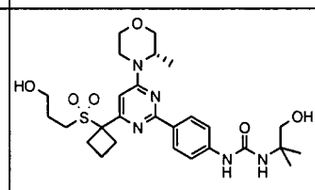
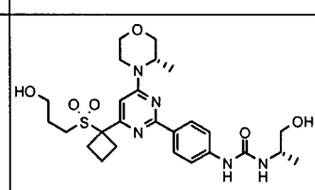
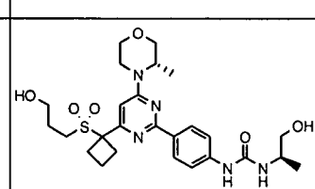
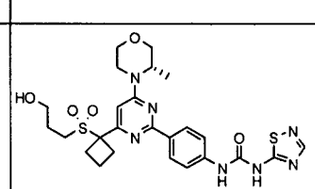
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 530; HPLC tR = 2,09 min.

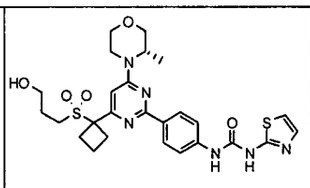
Ensayo de mTOR Quinasa (Echo): 0,00539μM

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopentil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
43a		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	504	1,93
43b		3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	534	1,83
43c		3-(2-cianoetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	543	2,00
43d		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	570	1,98
43e		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-	570	1,93

		imidazol-2-ilmetil)urea		
43f		3-ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	544	2,21
43g		3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	548	1,91
43h		3-(2-cianoetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	557	2,12
43i		3-(3-hidroxipropil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopentil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	562	1,94
43j*		1-etil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	518	1,89
43k*		3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propilurea	532	2,04
43l*		3-(3-hidroxipropil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	548	1,68

43m*		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea	557	2,04
43n*		3-(2-fluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	536	1,88
43o*		3-(2,2-difluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	554	2,00
43p*		3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	562	1,88
43q*		3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	548	1,72
43r*		3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	548	1,71
43s*		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2,4-tiadiazol-5-il)urea	574	1,28

43t*		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,3-tiazol-2-il)urea	573	2,05

* Las reacciones se agitaron en NMP a 70°C durante 2,5 horas

Ejemplo 43a: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,30 (3H, d), 1,94 - 1,99 (3H, m), 2,14 - 2,23 (1H, m), 2,73 (3H, d), 2,79 - 2,90 (3H, m), 2,96 - 3,04 (2H, m), 3,06 - 3,13 (2H, m), 3,24 - 3,32 (1H, m), 3,54 - 3,59 (3H, m), 3,68 - 3,72 (1H, m), 3,78 (1H, d), 3,98 - 4,02 (1H, m), 4,10 - 4,15 (1H, m), 4,43 (1H, s), 5,49 (1H, q), 6,52 (1H, s), 7,41 (2H, d), 7,62 (1H, s), 8,29 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00479μM

Ejemplo 43b: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,28 (3H, d), 1,90 - 2,00 (3H, m), 2,08 - 2,22 (2H, m), 2,79 - 2,88 (2H, m), 2,94 - 3,09 (4H, m), 3,24 - 3,33 (3H, m), 3,45 - 3,56 (6H, m), 3,68 (1H, d), 3,76 (1H, d), 3,98 (1H, d), 4,11 (1H, d), 4,42 (1H, s), 5,84 (1H, t), 6,50 (1H, s), 7,39 (2H, d), 7,89 (1H, s), 8,27 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00751μM

Ejemplo 43c: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,93 - 2,04 (4H, m), 2,16 - 2,25 (1H, m), 2,55 - 2,60 (2H, m), 2,79 - 2,88 (2H, m), 2,97 - 3,06 (2H, m), 3,09 - 3,15 (2H, m), 3,26 - 3,33 (1H, m), 3,43 - 3,49 (2H, m), 3,53 - 3,63 (3H, m), 3,69 - 3,73 (1H, m), 3,79 (1H, d), 3,99 - 4,03 (1H, m), 4,15 (1H, d), 4,44 (1H, s), 5,87 (1H, t), 6,55 (1H, s), 7,42 (2H, d), 7,54 (1H, s), 8,31 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,0288μM

Ejemplo 43d: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,30 (3H, d), 1,95 - 2,01 (3H, m), 2,14 - 2,26 (1H, m), 2,78 - 2,91 (2H, m), 3,03 - 3,07 (2H, m), 3,08 - 3,15 (2H, m), 3,25 - 3,32 (1H, m), 3,39 (1H, s), 3,55 - 3,59 (3H, m), 3,67 (3H, s), 3,68 - 3,71 (1H, m), 3,78 (1H, d), 3,98 - 4,02 (1H, m), 4,11 - 4,14 (1H, m), 4,42 (1H, s), 6,53 (1H, s), 7,18 (1H, s), 7,39 (2H, d), 7,44 (1H, s), 7,55 (1H, s), 7,84 (1H, s), 8,29 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,011μM

Ejemplo 43e: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,29 (3H, d), 1,92 - 1,99 (3H, m), 2,13 - 2,20 (1H, m), 2,75 - 2,84 (2H, m), 2,96 - 3,01 (2H, m), 3,05 - 3,12 (2H, m), 3,23 - 3,30 (1H, m), 3,48 - 3,55 (4H, m), 3,69 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,11 (1H, d), 4,36 - 4,41 (3H,

m), 6,51 (1H, s), 6,91 (2H, s), 7,00 (1H, t), 7,34 (2H, d), 8,23 - 8,25 (2H, m), 8,63 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,188μM

Ejemplo 43f: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 0,53 - 0,56 (2H, m), 0,73 - 0,76 (2H, m), 1,32 (3H, d), 1,63 - 1,66 (2H, m), 1,91 - 1,97 (4H, m), 2,57 - 2,65 (3H, m), 2,73 - 2,80 (3H, m), 3,05 - 3,11 (2H, m), 3,26 - 3,33 (1H, m), 3,55 - 3,62 (3H, m), 3,71 - 3,75 (1H, m), 3,81 (1H, d), 4,00 - 4,04 (1H, m), 4,17 (1H, d), 4,46 (1H, s), 5,81 (1H, s), 6,66 (1H, s), 7,49 (2H, d), 7,82 (1H, s), 8,31 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,0392μM

Ejemplo 43g: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,28 (3H, d), 1,58 - 1,64 (2H, m), 1,85 - 1,95 (4H, m), 2,53 - 2,63 (3H, m), 2,67 - 2,78 (3H, m), 3,12 - 3,16 (2H, m), 3,26 - 3,30 (3H, m), 3,52 - 3,58 (5H, m), 3,36 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,12 (1H, d), 4,41 (1H, s), 5,05 (1H, s), 5,90 (1H, t), 6,61 (1H, s), 7,41 (2H, d), 7,96 (1H, s), 8,29 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,029μM

Ejemplo 43h: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,31 (3H, d), 1,64 - 1,67 (3H, m), 1,92 - 1,99 (5H, m), 2,47 - 2,64 (4H, m), 2,74 - 2,79 (2H, m), 3,13 - 3,17 (2H, m), 3,26 - 3,33 (1H, m), 3,43 - 3,48 (2H, m), 3,53 - 3,63 (3H, m), 3,69 - 3,73 (1H, m), 3,79 (1H, d), 3,99 - 4,03 (1H, m), 4,15 (1H, d), 4,44 (1H, s), 5,89 (1H, t), 6,66 (1H, s), 7,42 (2H, d), 7,58 (1H, s), 8,32 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,133μM

Ejemplo 43i: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,29 (3H, d), 1,54 - 1,62 (4H, m), 1,89 - 1,99 (4H, m), 2,55 - 2,64 (2H, m), 2,70 - 2,80 (2H, d), 3,12 - 3,19 (2H, m), 3,24 - 3,29 (4H, m), 3,52 - 3,59 (5H, m), 3,68 - 3,83 (3H, m), 3,98 (1H, d), 4,11 - 4,14 (1H, m), 4,42 (1H, s), 5,75 (1H, t), 6,62 (1H, s), 7,42 (2H, d), 7,79 (1H, s), 8,29 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,102μM

Ejemplo 43j: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,23 (3H, d), 1,72 - 1,81 (2H, m), 1,88 - 1,96 (1H, m), 1,99 - 2,10 (1H, m), 2,75 - 2,86 (2H, m), 2,90 - 2,96 (2H, m), 2,98 - 3,04 (2H, m), 3,10 - 3,16 (2H, m), 3,19 - 3,25 (1H, m), 3,35 - 3,42 (2H, m), 3,46 - 3,55 (1H, m), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,24 (1H, d), 4,50 - 4,62 (2H, m), 6,17 (1H, s), 6,72 (1H, s), 7,49 (2H, d), 8,21 (2H, d), 8,66 (1H, s)

Ejemplo 43k: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,24 (3H, d), 1,39 - 1,50 (2H, m), 1,73 - 1,81 (2H, m), 1,86 - 1,96 (1H, m), 2,00 - 2,09 (1H, m), 2,77 - 2,87 (2H, m), 2,90 - 2,97 (2H, m), 2,97 - 3,08 (4H, m), 3,19 - 3,25 (1H, m), 3,35 - 3,41 (2H, m), 3,46 - 3,55

(1H, m), 3,65 (1H, d), 3,77 (1H, d), 3,97 (1H, d), 4,24 (1H, d), 4,53 - 4,60 (2H, m), 6,20 (1H, t), 6,71 (1H, s), 7,49 (2H, d), 8,22 (2H, d), 8,65 (1H, s)

Ejemplo 43l: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 8,21 (2H, d), 1,23 (3H, d), 1,55 - 1,64 (2H, m), 1,74 - 1,80 (2H, m), 1,88 - 1,98 (1H, m), 2,01 - 2,10 (1H, m), 2,77 - 2,87 (2H, m), 2,90 - 2,97 (2H, m), 2,98 - 3,04 (2H, m), 3,13 - 3,24 (3H, m), 3,34 - 3,42 (2H, m), 3,45 - 3,54 (3H, m), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,24 (1H, d), 4,47 (1H, t), 4,53 - 4,59 (2H, m), 6,20 (1H, t), 6,71 (1H, s), 7,49 (2H, d), 8,71 (1H, s)

Ejemplo 43m: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,74 - 1,81 (2H, m), 1,88 - 1,97 (1H, m), 2,01 - 2,11 (1H, m), 2,78 - 2,87 (2H, m), 2,90 - 2,99 (2H, m), 3,00 - 3,06 (2H, m), 3,19 - 3,26 (1H, m), 3,36 - 3,42 (2H, m), 3,47 - 3,56 (1H, m), 3,66 (1H, d), 3,77 (1H, d), 3,99 (1H, d), 4,26 (1H, d), 4,53 - 4,61 (2H, m), 6,75 (1H, s), 6,87 (1H, s), 7,57 (2H, d), 8,30 (2H, d), 8,76 (1H, s), 9,08 (1H, s), 9,62 (1H, s)

Ejemplo 43n: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,73 - 1,81 (2H, m), 1,86 - 1,96 (1H, m), 2,01 - 2,10 (1H, m), 2,78 - 2,86 (2H, m), 2,90 - 2,98 (2H, m), 2,97 - 3,05 (2H, m), 3,13 - 3,26 (1H, m), 3,34 - 3,41 (2H, m), 3,44 - 3,55 (3H, m), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,24 (1H, d), 4,42 (1H, t), 4,51 - 4,59 (2H, m), 6,43 (1H, t), 6,72 (1H, s), 7,50 (2H, d), 8,23 (2H, d), 8,81 (1H, s)

Ejemplo 43o: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,72 - 1,81 (2H, m), 1,88 - 1,96 (1H, m), 2,02 - 2,10 (1H, m), 2,78 - 2,87 (2H, m), 2,91 - 2,98 (2H, m), 2,98 - 3,05 (2H, m), 3,17 - 3,26 (1H, m), 3,35 - 3,43 (2H, m), 3,47 - 3,60 (3H, m), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,24 (1H, d), 4,53 - 4,60 (2H, m), 5,91 - 6,27 (1H, m), 6,54 (1H, t), 6,73 (1H, s), 7,51 (2H, d), 8,24 (2H, d), 8,93 (1H, s)

Ejemplo 43p: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,71 - 1,81 (2H, m), 1,86 - 1,96 (1H, m), 2,02 - 2,11 (1H, m), 2,75 - 2,88 (2H, m), 2,91 - 2,98 (2H, m), 2,99 - 3,05 (2H, m), 3,17 - 3,26 (1H, m), 3,27 - 3,31 (2H, m), 3,35 - 3,42 (2H, m), 3,47 - 3,54 (1H, m), 3,65 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,24 (1H, d), 4,51 - 4,60 (2H, m), 4,95 (1H, t), 6,00 (1H, s), 6,71 (1H, s), 7,45 (2H, d), 8,20 (2H, d), 8,73 (1H, s)

Ejemplo 43q: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,08 (3H, d), 1,23 (3H, d), 1,72 - 1,82 (2H, m), 1,89 - 1,95 (1H, m), 2,02 - 2,09 (1H, m), 2,75 - 2,85 (2H, m), 2,90 - 2,97 (2H, m), 2,97 - 3,06 (2H, m), 3,17 - 3,25 (1H, m), 3,33 - 3,41 (2H, m), 3,48 - 3,56 (1H, m), 3,63 - 3,79 (4H, m), 3,98 (1H, d), 4,24 (1H, d), 4,51 - 4,59 (2H, m), 4,78 (1H, t), 6,10 (1H, t), 6,72 (1H, s), 7,47 (2H, d), 8,22 (2H, d), 8,71 (1H, s)

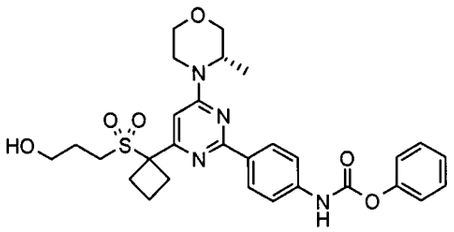
Ejemplo 43r: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,14 (3H, d), 1,29 (3H, d), 1,78 - 1,88 (2H, m), 1,94 - 2,03 (1H, m), 2,07 - 2,16 (1H, m), 2,81 - 2,93 (2H, m), 2,96 - 3,03 (2H, m), 3,03 - 3,10 (2H, m), 3,23 - 3,32 (1H, m), 3,38 - 3,48 (3H, m), 3,53 - 3,61 (1H, m), 3,68 - 3,84 (4H, m), 4,03 (1H, d), 4,30 (1H, d), 4,58 - 4,65 (2H, m), 4,83 (1H, t), 6,15 (1H, t), 6,77 (1H, s), 7,53 (2H, d), 8,27 (2H, d), 8,77 (1H, s)

Ejemplo 43s: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,25 (3H, d), 1,74 - 1,82 (2H, m), 1,89 - 1,98 (1H, m), 2,03 - 2,10 (1H, m), 2,77 - 2,90 (2H, m), 2,92 - 3,00 (2H, m), 3,02 - 3,07 (2H, m), 3,20 - 3,26 (1H, m), 3,36 - 3,44 (2H, m), 3,46 - 3,56 (1H, m), 3,66 (1H, d), 3,78 (1H, d), 3,99 (1H, d), 4,27 (1H, d), 4,51 - 4,63 (2H, m), 6,77 (1H, s), 7,63 (2H, d), 8,28 - 8,39 (3H, m), 9,46 (1H, s)

Ejemplo 43t: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,25 (3H, d), 1,74 - 1,83 (2H, m), 1,88 - 1,96 (1H, m), 2,00 - 2,09 (1H, m), 2,77 - 2,88 (2H, m), 2,91 - 2,98 (2H, m), 3,00 - 3,07 (2H, m), 3,20 - 3,25 (1H, m), 3,37 - 3,43 (2H, m), 3,46 - 3,56 (1H, m), 3,66 (1H, d), 3,78 (1H, d), 3,99 (1H, d), 4,26 (1H, d), 4,53 - 4,62 (2H, m), 6,76 (1H, s), 7,14 (1H, s), 7,40 (1H, s), 7,59 (2H, d), 8,31 (2H, d), 9,20 (1H, s)

La preparación de fenil *N*-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

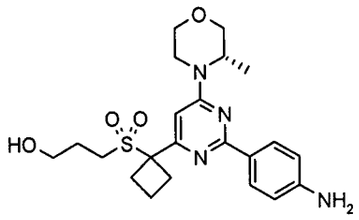
Fenil *N*-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



Se agregó gota a gota fenil cloroformiato (0,632 mL, 5,04 mmol) a 3-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclobutil]sulfonilpropan-1-ol (1,5 g, 3,36 mmol) e hidrogenocarbonato de sodio (0,423 g, 5,04 mmol) en dioxano (33,6 mL), se enfrió hasta alcanzar 10°C bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (300 mL) y se lavó con agua (150 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto como una goma amarilla. Este material se utilizó directamente en la siguiente etapa sin purificación adicional.

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 565; HPLC tR = 2,71 min.

3-[1-[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclobutil]sulfonilpropan-1-ol

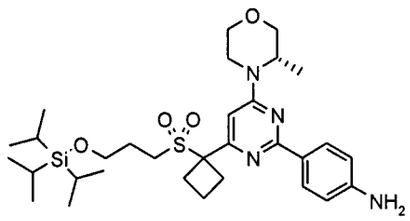


Una solución de fluoruro de tetrabutilamonio (18,25 mL, 18,25 mmol) en THF se agregó a una solución agitada de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[3-tri(propan-2-il)sililoxipropilsulfonil]ciclobutil]pirimidin-2-il]anilina (2,2 g, 3,65 mmol) en THF (24,33 mL) a TA. La solución resultante se agitó a TA durante 2 horas. La mezcla de reacción se concentró y se diluyó con acetato de etilo (150 mL) y se lavó con agua (100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 100% acetato de etilo en isohexano, para proporcionar el material deseado como un aceite amarillo claro que solidificó en reposo (1,50 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,33 (3H, d), 1,57 (1H, t), 1,94 - 2,04 (3H, m), 2,18 - 2,25 (1H, m), 2,82 - 2,88 (2H, m), 2,98 (2H, t), 3,09 - 3,16 (2H, m), 3,28 - 3,35 (1H, m), 3,63 (3H, q), 3,73 - 3,76 (1H, m), 3,82 (1H, d), 3,90 (2H, s), 4,01 - 4,05 (1H,

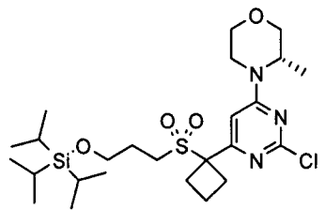
m), 4,16 (1H, d), 4,47 (1H, d), 6,51 (1H, s), 6,70 - 6,72 (2H, m), 8,22 - 8,24 (2H, m).
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 447; HPLC tR = 2,09 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-[3-tri(propan-2-il)sililoxipropilsulfonil]ciclobutil]pirimidin-2-il]anilina



Se agregó diclorobis(trifenilfosfina)paladio(II) (0,132 g, 0,19 mmol) en una porción a una solución cuidadosamente desgasificada de 3-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclobutil]sulfonilpropoxi-tri(propan-2-il)silano (2,05 g, 3,75 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,233 g, 5,63 mmol) y solución de carbonato de sodio acuoso 2M (6,57 mL, 13,14 mmol) en una mezcla de disolventes de DMF (6,82 mL), agua (17,06 mL), etanol (6,82 mL) y DME (6,82 mL). La mezcla resultante se agitó a 80°C durante 4 horas. La mezcla de reacción enfriada se diluyó con acetato de etilo (200 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 75% acetato de etilo en isohexano, para proporcionar el material deseado como una espuma amarilla clara que solidificó al vacío (2,2 g).
Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 0,89 - 0,98 (21H, m), 1,32 (3H, s), 1,92 - 1,99 (3H, m), 2,15 - 2,25 (1H, m), 2,84 - 2,87 (2H, m), 2,91 - 2,95 (2H, m), 3,07 - 3,13 (2H, m), 3,26 - 3,34 (1H, m), 3,57 - 3,62 (1H, m), 3,65 (2H, t), 3,74 (1H, dd), 3,81 (1H, d), 3,88 (2H, s), 4,03 (1H, dd), 4,15 (1H, d), 4,47 (1H, s), 6,52 (1H, s), 6,68 - 6,70 (2H, m), 8,21 - 8,23 (2H, m).
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 603; HPLC tR = 3,82 min.

3-[1-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclobutil]sulfonilpropoxi-tri(propan-2-il)silano



Se agregó solución acuosa de hidróxido de sodio (50% p/p, 48,7 mL) a 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]propoxi-tri(propan-2-il)silano (5,6 g, 11,06 mmol), 1,3-dibromopropano (3,37 mL, 33,19 mmol) y bromuro de tetrabutilamonio (0,357 g, 1,11 mmol) en tolueno (221 mL) a TA. La suspensión resultante se agitó a 45°C durante 1 hora. Se agregó agua a la solución. El tolueno se lavó con agua dos veces se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como una goma incolora (2,05 g).

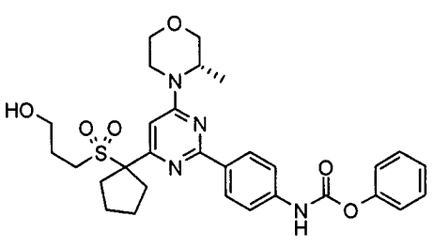
Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 0,97 - 1,08 (21H, m), 1,32 (3H, d), 1,94 - 2,01 (3H, m), 2,21 - 2,23 (1H, m), 2,70 - 2,76 (2H, m), 2,93 (2H, q), 3,03 - 3,08 (2H, m), 3,28 - 3,32 (1H, m), 3,51 - 3,57 (1H, m), 3,66 - 3,70 (1H, m), 3,76 (3H, t), 3,98 - 4,02 (2H, m), 4,32 (1H, s), 6,55 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 546; HPLC tR = 4,05 min.

La preparación de 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]propoxi-tri(propan-2-il)silano se describió anteriormente.

La preparación de fenil *N*-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopentil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

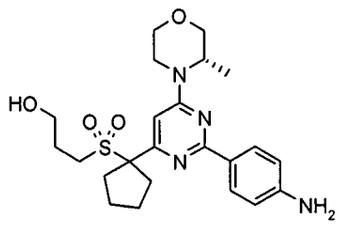
Fenil *N*-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopentil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



Se agregó gota a gota fenil cloroformiato (1,512 mL, 12,05 mmol) a 3-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopentil]sulfonilpropan-1-ol (3,7 g, 8,03 mmol) e

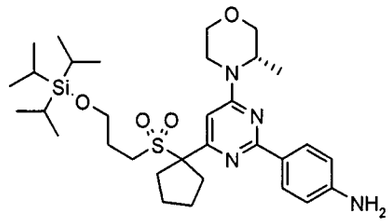
hidrogenocarbonato de sodio (1,012 g, 12,05 mmol) en dioxano (80 mL) se enfrió hasta alcanzar 10°C bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (300 mL) y se lavó con agua (150 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido amarillo que se utilizó sin purificación adicional (3,60 g).
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 581; HPLC tR = 2,83 min.

3-[1-[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopentil]sulfonilpropan-1-ol



Una solución de fluoruro de tetrabutilamonio (46,2 mL, 46,20 mmol) en THF se agregó a una solución agitada de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[3-tri(propan-2-il)sililoxipropilsulfonil]ciclopentil]pirimidin-2-il]anilina (5,7 g, 9,24 mmol) en THF (61,6 mL) a TA. La solución resultante se agitó a TA durante 2 horas. La mezcla de reacción se concentró y se diluyó con acetato de etilo (250 mL) y se lavó con agua (150 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 100% acetato de etilo en isohexano, para proporcionar el material deseado como un aceite amarillo claro que solidificó en reposo (3,70 g).
Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,32 (3H, d), 1,59 (1H, t), 1,61 - 1,70 (2H, m), 1,92 - 1,98 (4H, m), 2,57 - 2,66 (2H, m), 2,74 - 2,83 (2H, m), 3,07 (2H, t), 3,27 - 3,34 (1H, m), 3,57 - 3,65 (3H, m), 3,73 - 3,77 (1H, m), 3,82 (1H, d), 3,90 (2H, s), 4,01 - 4,05 (1H, m), 4,11 - 4,18 (1H, m), 4,46 (1H, d), 6,63 (1H, s), 6,71 (2H, d), 8,23 (2H, d).
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 461; HPLC tR = 2,18 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-[3-tri(propan-2-il)sililoxipropilsulfonil]ciclopentil]pirimidin-2-il]anilina

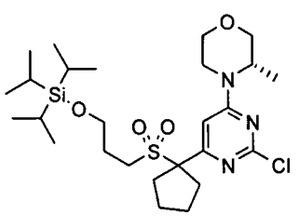


Se agregó diclorobis(trifenilfosfina)paladio(II) (0,345 g, 0,49 mmol) en una porción a una solución cuidadosamente desgasificada de 3-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopentil]sulfonilpropoxi-tri(propan-2-il)silano (5,5 g, 9,82 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (3,23 g, 14,73 mmol) y solución de carbonato de sodio acuoso 2M (17,18 mL, 34,36 mmol) en una mezcla de disolventes de DMF (17,85 mL), agua (44,6 mL), etanol (17,85 mL) y DME (17,85 mL). La mezcla resultante se agitó a 80°C durante 4 horas. La mezcla de reacción enfriada se diluyó con acetato de etilo (200 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 75% acetato de etilo en DCM, para proporcionar el material deseado como una espuma amarilla clara que solidificó al vacío (5,70 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 0,90 - 0,98 (21H, m), 1,32 (4H, t), 1,63 - 1,66 (2H, m), 1,89 - 1,96 (4H, m), 2,59 - 2,64 (2H, m), 2,77 - 2,81 (2H, m), 2,98 - 3,02 (2H, m), 3,29 - 3,32 (1H, m), 3,57 - 3,63 (1H, m), 3,66 (2H, t), 3,72 - 3,76 (1H, m), 3,81 (1H, d), 3,88 (2H, s), 4,01 - 4,05 (1H, m), 4,15 (1H, d), 4,45 (1H, s), 6,66 (1H, s), 6,69 (2H, d), 8,22 (2H, d).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 617; HPLC tR = 3,91 min.

3-[1-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopentil]sulfonilpropoxi-tri(propan-2-il)silano



Se agregó solución acuosa de hidróxido de sodio (50% p/p ac, 48,7 mL) a 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]propoxi-tri(propan-2-il)silano (5,6 g, 11,06 mmol), 1,4-dibromobutano (3,93 mL, 33,19 mmol) y bromuro de tetrabutilamonio (0,357 g,

1645

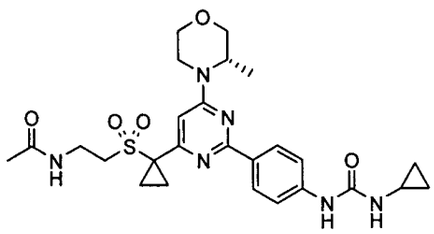
1,11 mmol) en tolueno (221 mL) a TA. La suspensión resultante se agitó a 45°C durante 1 hora y el tolueno se lavó con agua dos veces, se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (5,57 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 0,98 - 1,08 (21H, m), 1,31 (3H, d), 1,60 - 1,65 (2H, m), 1,88 - 1,99 (4H, m), 2,56 - 2,61 (4H, m), 2,97 - 3,00 (2H, m), 3,28 - 3,32 (1H, m), 3,51 - 3,58 (1H, m), 3,67 - 3,71 (1H, m), 3,76 (3H, t), 3,98 - 4,02 (2H, m), 4,31, (1H, s), 6,71 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 560; HPLC tR = 3,86 min.

La preparación de 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]propoxi-tri(propan-2-il)silano se describió anteriormente.

Ejemplo 44: *N*-[2-[1-[2-[4-(Ciclopropilcarbamoilamino)fenil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletil]acetamida



Se agregó ciclopropilamina (0,120 mL, 1,73 mmol) en una porción a una solución agitada de fenil *N*-[4-[4-[1-(2-acetamidoetilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,2 g, 0,35 mmol) en THF (34,5 mL) a TA. La solución resultante se agitó a 40°C durante 24 horas. La mezcla de reacción luego se concentró y el producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 5% metanol en DCM, para proporcionar el material deseado como un sólido blanco (0,135 g).

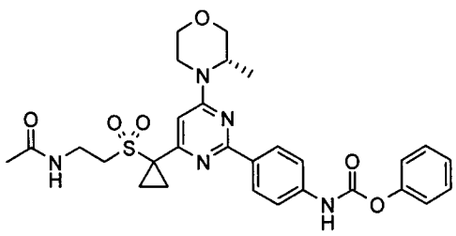
Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 0,66 - 0,70 (2H, m), 0,84 - 0,89 (2H, m), 1,34 (3H, d), 1,49 - 1,58 (2H, m), 1,82 - 1,85 (2H, m), 1,93 (3H, s), 2,61 - 2,66 (1H, m), 3,29 - 3,36 (1H, m), 3,48 - 3,51 (2H, m), 3,56 - 3,63 (1H, m), 3,72 - 3,75 (1H, m), 3,79 - 3,84 (3H, m), 4,03 - 4,06 (1H, m), 4,15 (1H, d), 4,48 (1H, s), 5,05 (1H, s), 6,67 (1H, s), 6,74 (1H, d), 7,13 (1H, s), 7,51 (2H, d), 8,26 (2H, d).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 543; HPLC tR = 1,86 min.

Ensayo de mTOR Quinasa (Echo): 0,0234μM

La preparación de fenil *N*-[4-[4-[1-(2-acetamidoetilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

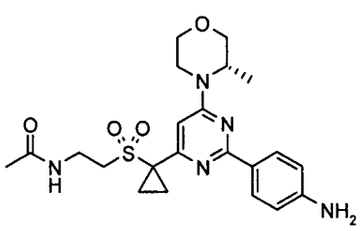
Fenil *N*-[4-[4-[1-(2-acetamidoetilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



Se agregó gota a gota fenil cloroformiato (0,328 mL, 2,61 mmol) a *N*-[2-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletil]acetamida (800 mg, 1,74 mmol) e hidrogenocarbonato de sodio (219 mg, 2,61 mmol) en dioxano (174 mL) se enfrió hasta alcanzar 10°C bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (300 mL) y se lavó con agua (150 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido amarillo (741 mg). Este material se utilizó directamente sin purificación adicional.

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 580; HPLC tR = 2,44 min.

N-[2-[1-[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletil]acetamida



Se agregó diclorobis(trifenilfosfina)paladio(II) (0,174 g, 0,25 mmol) en una porción a una solución cuidadosamente desgasificada de *N*-[2-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-

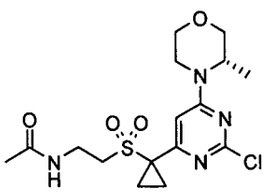
1645

il]pirimidin-4-il]ciclopropil]sulfoniletil]acetamida (2 g, 4,96 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,414 g, 6,45 mmol) y solución de carbonato de sodio acuoso 2M (8,69 mL, 17,37 mmol) en una mezcla de disolventes de DMF (9,03 mL), agua (22,56 mL), etanol (9,03 mL) y DME (9,03 mL). La mezcla resultante se agitó a 80°C durante 4 horas. La mezcla de reacción enfriada se diluyó con acetato de etilo (200 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 75% acetato de etilo en DCM, para proporcionar el material deseado como una espuma amarilla clara que solidificó al vacío (1,805 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,33 (3H, d), 1,49 - 1,51 (2H, m), 1,80 - 1,84 (2H, m), 1,93 (3H, s), 3,28 - 3,35 (1H, m), 3,47 - 3,50 (2H, m), 3,55 - 3,62 (1H, m), 3,71 - 3,75 (1H, m), 3,79 - 3,83 (3H, m), 3,92 (2H, s), 4,01 - 4,05 (1H, m), 4,10 - 4,17 (1H, m), 4,47 (1H, s), 6,61 (1H, s), 6,69 - 6,72 (2H, m), 6,81 (1H, s), 8,13 - 8,16 (2H, m).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 460; HPLC tR = 1,79 min.

N-[2-[1-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletil]acetamida

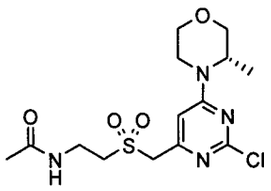


Se agregó solución acuosa de hidróxido de sodio (50% ac, 8,52 mL) a *N*-[2-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]etil]acetamida (3,21 g, 8,52 mmol), 1,2-dibromoetano (1,468 mL, 17,03 mmol) y bromuro de tetrabutilamonio (0,549 g, 1,70 mmol) en tolueno (122 mL) a TA. La solución resultante se agitó a 60°C durante 3 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetato de etilo (200 mL) y se lavó secuencialmente con agua (200 mL) y salmuera saturada (100 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (2,04 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,34 (3H, d), 1,44 - 1,47 (2H, m), 1,80 - 1,84 (2H, m), 2,02 (3H, s), 3,27 - 3,34 (1H, m), 3,35 - 3,38 (2H, m), 3,51 - 3,57 (1H, m), 3,66 - 3,70 (1H, m), 3,75 - 3,80 (3H, m), 3,99 - 4,03 (2H, m), 4,34 (1H, s), 6,73 (1H, s), 6,88 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 403; HPLC tR = 1,51 min.

N-[2-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]etil]acetamida

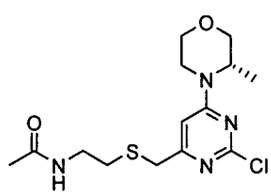


Se disolvió *N*-[2-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]etil]acetamida (3,24 g, 9,40 mmol) en dioxano (28,2 mL) y se agregó ácido sulfúrico 2N (0,282 mL). La solución se calentó hasta alcanzar 55°C. Se agregó tungstato de sodio dihidrato (0,062 g, 0,19 mmol) disuelto en agua (2,82 mL) a la solución y se dejó agitar durante 5 minutos. Luego se agregó peróxido de hidrógeno (5,42 mL, 56,37 mmol) gota a gota durante varios minutos. La solución se calentó a 55°C durante 2,5 horas. El calor se retiró y se agregó agua (300 mL). La suspensión resultante se agitó durante 30 minutos. Los sólidos se filtraron, se enjuagaron con agua y se secaron en un horno de vacío a 50°C durante toda la noche, para proporcionar el material deseado como un sólido blanco (3,30 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,82 (3H, s), 3,19 - 3,26 (1H, m), 3,36 - 3,43 (2H, m), 3,45 - 3,51 (3H, m), 3,58 - 3,62 (1H, m), 3,73 (1H, d), 3,92 - 3,96 (2H, m), 4,30 (1H, s), 4,49 (2H, s), 6,92 (1H, s), 8,11 (1H, t).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 377; HPLC tR = 1,37 min.

N-[2-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]etil]acetamida



Se agregó *N*-Acetilcisteamina (1,804 mL, 16,97 mmol) a 2-cloro-4-(yodometil)-6-[(3*S*)-3-

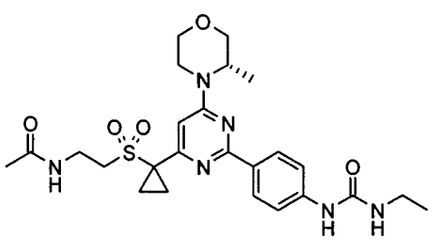
metilmorfolin-4-il]pirimidina (4 g, 11,31 mmol) y DIPEA (4,93 mL, 28,28 mmol) en acetonitrilo (226 mL) a TA. La solución resultante se agitó a TA durante 3 horas. El disolvente se retiró al vacío y el material bruto luego se purificó mediante cromatografía de sílice instantánea, eluyendo con acetato de etilo, para proporcionar el material deseado como un sólido blanco (3,24 g).

Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,33 (3H, d), 2,01 (3H, s), 2,71 (2H, t), 3,25 - 3,33 (1H, m), 3,48 - 3,58 (3H, m), 3,59 (2H, s), 3,67 - 3,71 (1H, m), 3,79 (1H, d), 3,99 - 4,03 (2H, m), 4,33 (1H, s), 6,40 (1H, s), 6,55 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 345; HPLC tR = 1,54 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 45: *N*-[2-[1-[2-[4-(Etilcarbamoilamino)fenil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletil]acetamida



Una solución de etilamina (2M en THF, 0,863 mL, 1,73 mmol) se agregó en una porción a una solución agitada de fenil *N*-[4-[4-[1-(2-acetamidoetilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,2 g, 0,35 mmol) en THF (34,5 mL) a TA. La solución resultante se agitó a 50°C durante 2 horas. El producto se concentró al vacío, luego se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% metanol en DCM, para proporcionar al residuo que se trituró con acetonitrilo para proporcionar el material deseado como un sólido blanco (0,147 g).

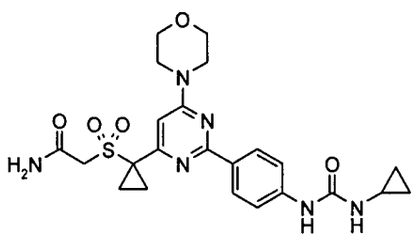
Espectro de NMR: ^{1}H NMR (400,13 MHz, $CDCl_3$) δ 1,16 (3H, t), 1,33 (3H, d), 1,48 - 1,51 (2H, m), 1,81 - 1,84 (2H, m), 1,93 (3H, s), 3,27 - 3,34 (3H, m), 3,49 - 3,52 (2H, m), 3,55 - 3,60 (1H, m), 3,70 - 3,74 (1H, m), 3,78 - 3,83 (3H, m), 4,01 - 4,05 (1H, m), 4,10 - 4,16 (1H, m), 4,46 (1H, s), 5,18 (1H, t), 6,64 (1H, s), 6,89 (1H, t), 7,15 (1H, s), 7,42 (2H, d), 8,23 (2H, d).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 531; HPLC tR = 1,87 min.

Ensayo de mTOR Quinasa (Echo): 0,0219μM

La preparación de fenil *N*-[4-[4-[1-(2-acetamidoetilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describió anteriormente.

Ejemplo 46: 2-[1-[2-[4-(Ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropil]sulfonilacetamida

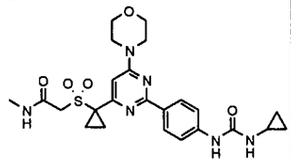


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (19,03 mg, 0,03 mmol) a 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonilacetamida (146 mg, 0,40 mmol), 1-ciclopropil-3-(4-(4,4,5,5-tetrametil-1,3-dioxolan-2-il)fenil)urea (185 mg, 0,61 mmol) y carbonato de sodio (0,809 mL, 1,62 mmol) en una mezcla de disolventes de DMF (3 mL), DME (8 mL), agua (2 mL) y etanol (1,5 mL) a TA. La mezcla resultante se agitó a 90°C durante 18 horas bajo una atmósfera inerte. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó con agua (100 mL seguido por 75 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. La goma bruta se trituró con una mezcla de metanol y DCM y el sólido se eliminó mediante filtración. El filtrado se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 7% metanol en acetato de etilo, para proporcionar una goma que se purificó adicionalmente mediante cromatografía de intercambio iónico en una columna SCX, eluyendo con amoníaco 7N en metanol, para proporcionar un sólido beige que se purificó adicionalmente mediante HPLC prep para proporcionar el material deseado (7 mg).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 499; HPLC tR = 1,67 min.

Ensayo de mTOR Quinasa (Echo): 0,00456μM

El siguiente compuesto se preparó en forma análoga a partir de 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonil-*N*-metilacetamida.

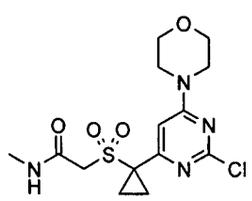
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
46a		2-[1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-morfolin-4-ilpirimidin-4-il]ciclopropil]sulfonil-N-metilacetamida	515	1,74

Ejemplo 46a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,39 - 0,43 (2H, m), 0,61 - 0,67 (2H, m), 1,57 - 1,61 (2H, m), 1,66 - 1,71 (2H, m), 2,63 (3H, d), 3,72 (8H, s), 4,39 (2H, s), 6,46 (1H, s), 6,87 (1H, s), 7,51 (2H, d), 8,20 (2H, d), 8,29 (1H, d), 8,58 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0126μM

La preparación de 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonil-*N*-metilacetamida se describe a continuación.

2-[1-(2-Cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonil-*N*-metilacetamida



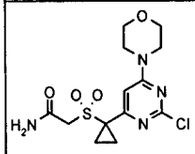
Se agregó hATU (252 mg, 0,66 mmol) a ácido 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonilacético (200 mg, 0,55 mmol) y trietilamina (0,077 mL, 0,55 mmol) en DCM (10 mL) a TA bajo una atmósfera de nitrógeno y se agitó durante 15 minutos. Se agregó metilamina (2M en THF, 2 mL) y la reacción se agitó durante 18 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó con una solución saturada de hidrogenocarbonato de sodio (100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 50 a 90% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (156 mg)

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,51 - 1,54 (2H, m), 1,62 - 1,67

(2H, m), 2,62 (3H, d), 3,66 (8H, m), 4,27 (2H, s), 7,06 (1H, s), 8,22 (1H, s)

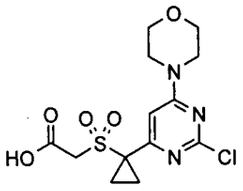
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 375; HPLC tR = 1,35 min.

Se elaboró 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonilacetamida mediante un procedimiento análogo al descrito anteriormente (se cromatografió utilizando 0 – 4% metanol en acetato de etilo).

Estructura	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
	2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonilacetamida	361	1,31

La preparación de ácido 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonilacético se describe a continuación.

Ácido 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonilacético



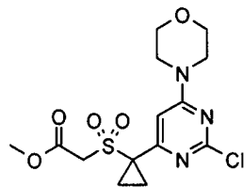
Se agregó hidróxido de litio (0,812 g, 33,93 mmol) a metil 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonilacetato (2,55 g, 6,79 mmol), en una mezcla de THF (40 mL) y agua (8 mL). La mezcla resultante se agitó a TA durante 2 horas y luego se acidificó con ácido clorhídrico 2M. La mezcla de reacción se extrajo con acetato de etilo (400 mL) y la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido blanco (1,96 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,53 - 1,58 (2H, m), 1,69 - 1,72 (2H, m), 3,66 (8H, s), 4,55 (2H, s), 6,98 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 362; HPLC tR = 0,69 min.

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Metil 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonilacetato



Se agregó gota a gota diisopropilamida de litio (8,92 mL, 16,05 mmol) a 2-cloro-4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidina (4,25 g, 13,37 mmol), en THF (80 mL) a -78°C bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a -78°C durante 15 minutos. Se agregó dimetil carbonato (5,63 mL, 66,87 mmol) y la mezcla resultante se agitó a -78 °C durante 10 minutos, luego se dejó entibiar hasta alcanzar TA. La mezcla se enfrió nuevamente hasta alcanzar -78C y se agregó más diisopropilamida de litio (8,92 mL, 16,05 mmol). La mezcla se agitó a -78°C durante 10 minutos, luego se agregó dimetil carbonato (5,63 mL, 66,87 mmol) y la mezcla se dejó llegar a TA y el pH se ajustó hasta alcanzar 7 con ácido clorhídrico 2M. La mezcla de reacción se diluyó con acetato de etilo (350 mL) y se lavó con agua (150 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 70% acetato de etilo en isohexano, para proporcionar un sólido amarillo que se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido blanco (3,10 g).

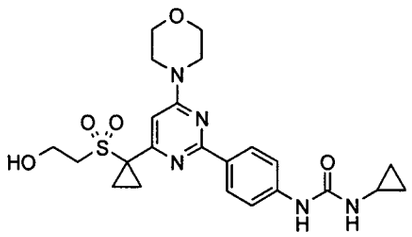
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,56 - 1,60 (2H, m), 1,68 - 1,72 (2H, m), 3,63 - 3,70 (11H, m), 4,71 (2H, s), 6,97 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 376; HPLC tR = 1,76 min.

La preparación de 2-cloro-4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidina se describió anteriormente.

Ejemplo 47: 3-Ciclopropil-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea

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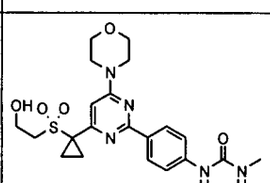
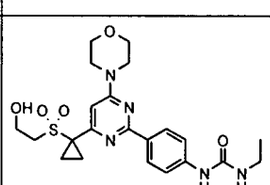


Una solución de fenil *N*-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato (50 mg, 0,09 mmol), ciclopropilamina (0,48 mmol) y trietilamina (0,066 mL, 0,048 mmol) en NMP (1 mL) se agitó a TA hasta que la reacción se completó. La mezcla de reacción bruta se purificó mediante HPLC prep para proporcionar el material deseado como un sólido (31 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,45 (2H, m), 0,61 - 0,67 (2H, m), 1,50 - 1,59 (2H, m), 1,59 - 1,69 (2H, m), 2,54 - 2,61 (1H, m), 3,62 - 3,69 (2H, m), 3,69 - 3,76 (8H, m), 3,86 - 3,92 (2H, m), 5,03 (1H, t), 6,44 (1H, s), 6,81 (1H, s), 7,51 (2H, d), 8,21 (2H, d), 8,54 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 488; HPLC tR = 1,61 min.

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
47a		1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]-3-metilurea	462	1,45
47b		3-etil-1-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea	476	1,58

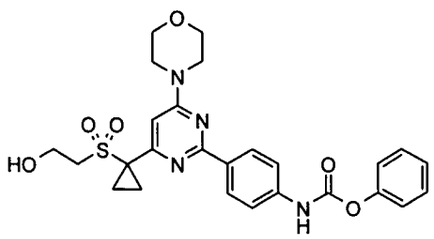
Ejemplo 47a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,48 - 1,58 (2H, m), 1,62 - 1,69 (2H,

m), 2,67 (3H, d), 3,61 - 3,68 (2H, m), 3,69 - 3,76 (8H, m), 3,85 - 3,92 (2H, m), 5,03 (1H, s), 6,09 (1H, t), 6,81 (1H, s), 7,50 (2H, d), 8,20 (2H, d), 8,76 (1H, s).

Ejemplo 47b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,51 - 1,57 (2H, m), 1,62 - 1,68 (2H, m), 3,14 (2H, q), 3,60 - 3,69 (2H, m), 3,69 - 3,77 (8H, m), 3,85 - 3,92 (2H, m), 5,03 (1H, t), 6,16 (1H, t), 6,81 (1H, s), 7,47 (2H, d), 8,20 (2H, d), 8,67 (1H, s).

La preparación de fenil *N*-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(2-hidroxietilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato

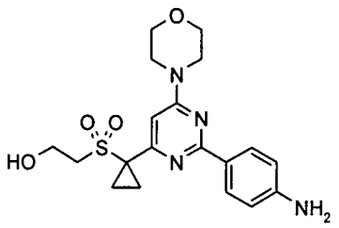


Se agregó hidrogenocarbonato de sodio (65,4 mg, 0,78 mmol) a 2-[1-[2-(4-aminofenil)-6-morfolin-4-ilpirimidin-4-il]ciclopropil]sulfoniletanol (210 mg, 0,52 mmol) en dioxano (8 mL) a 5°C bajo una atmósfera de nitrógeno. Se agregó fenil cloroformiato (0,072 mL, 0,57 mmol) y la mezcla se agitó a TA durante 18 horas. La mezcla de reacción se diluyó con acetato de etilo (50 mL), la capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. La goma bruta se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido beige (170 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,52 - 1,60 (2H, m), 1,61 - 1,70 (2H, m), 3,61 - 3,79 (10H, m), 3,82 - 3,96 (2H, m), 6,85 (1H, s), 7,21 - 7,34 (3H, m), 7,45 (2H, d), 7,64 (2H, d), 8,31 (2H, d), 10,45 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 525; HPLC tR = 2,40 min.

2-[1-[2-(4-Aminofenil)-6-morfolin-4-ilpirimidin-4-il]ciclopropil]sulfoniletanol

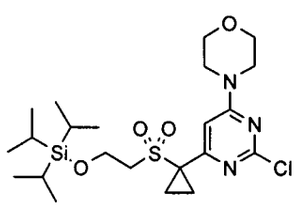


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (48,5 mg, 0,07 mmol) a 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfoniletoxi-tri(propan-2-il)silano (520 mg, 1,03 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (339 mg, 1,55 mmol) y una solución acuosa de carbonato de sodio (1 mL, 2,00 mmol) en una mezcla de disolventes de DMF (5 mL), DME (12 mL), agua (1 mL) y etanol (1 mL) a TA. La atmósfera se reemplazó con nitrógeno y la mezcla se agitó a 90°C durante 18 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó con agua (2 x 100 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se disolvió en DCM, luego se agregó fluoruro de tetrabutilamonio (5,16 mL, 5,16 mmol) y la mezcla se dejó agitando durante 1 hora. Se agregó una solución saturada de cloruro de amonio, las capas se separaron y los orgánicos se secaron (Na_2SO_4), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 50% acetato de etilo en isohexano y el sólido resultante se purificó adicionalmente mediante cromatografía de intercambio iónico en una columna SCX, eluyendo con amoníaco 7N en metanol. El sólido bruto se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido beige (210mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,47 - 1,54 (2H, m), 1,59 - 1,67 (2H, m), 3,59 - 3,77 (10H, m), 3,81 - 3,94 (2H, m), 5,02 (1H, t), 5,57 (2H, s), 6,60 (2H, d), 6,71 (1H, s), 8,04 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 405; HPLC tR = 1,65 min.

2-[1-(2-Cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfoniletoxi-tri(propan-2-il)silano



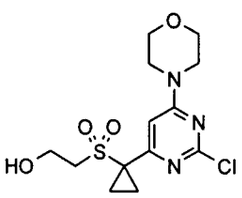
Se agregó 2-[1-(2-Cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfoniletanol (550 mg,

1,58 mmol) a cloruro de triisopropilsililo (0,406 mL, 1,90 mmol) e imidazol (258 mg, 3,80 mmol) en DMF (10 mL) a TA. La solución resultante se agitó bajo una atmósfera de nitrógeno durante toda la noche. El DMF se retiró al vacío y se agregó acetato de etilo. Los sólidos se retiraron mediante filtración y se descartaron. El filtrado se concentró al vacío y se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 4% metanol en DCM, para proporcionar material que se purificó adicionalmente mediante cromatografía de sílice instantánea, gradiente de elución de 0-10% acetato de etilo en DCM para proporcionar el material deseado como una goma clara (700 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,02 (18H, d), 1,49 - 1,53 (2H, m), 1,62 - 1,66 (2H, m), 2,00 (2H, s), 3,33 (2H, s), 3,62 - 3,69 (8H, m), 4,03 - 4,09 (3H, m), 6,95 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 504; HPLC tR = 3,63 min.

2-[1-(2-Cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfoniletanol



Se agregó DIPEA (1,052 mL, 6,08 mmol) a ácido 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonilacético (1,1 g, 3,04 mmol), en THF (50 mL) a 0°C bajo una atmósfera de nitrógeno. La solución resultante se agitó a 0°C durante 5 minutos. Se agregó etil cloroformiato (0,349 mL, 3,65 mmol) y la reacción se agitó a 0°C durante 1 hora. La mezcla de reacción se filtró y el filtrado se enfrió nuevamente hasta alcanzar 0°C. Se agregó borohidruro de litio (13,68 mL, 27,36 mmol) y la mezcla se entibió hasta alcanzar se dejó llegar a TA. La mezcla se enfrió nuevamente hasta alcanzar 0°C y se agregó más borohidruro de litio (13,68 mL, 27,36 mmol) y la reacción se dejó llegar a TA. La mezcla se enfrió nuevamente hasta alcanzar 0°C y se agregó más borohidruro de litio (13,68 mL, 27,36 mmol) y la reacción se dejó llegar a TA y se agitó durante 72 horas. La mezcla de reacción se ajustó hasta alcanzar pH7 con ácido clorhídrico 2M y se extrajo con acetato de etilo (100 mL). La capa orgánica se lavó con agua (100 mL), se secó (Na_2SO_4), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 100% acetato de etilo en isohexano, para

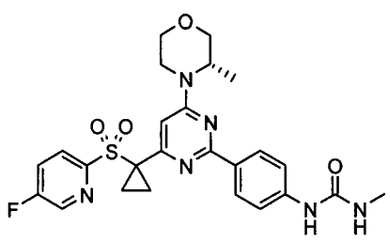
proporcionar el material deseado como un sólido blanco (500 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,47 - 1,52 (2H, m), 1,59 - 1,67 (2H, m), 3,49 - 3,57 (2H, m), 3,60 - 3,70 (8H, m), 3,76 - 3,86 (2H, m), 4,99 (1H, t), 6,98 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 348; HPLC tR = 1,38 min.

La preparación de ácido 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfonilacético se describió anteriormente.

Ejemplo 48: 1-[4-[4-[1-(5-Fluoropiridin-2-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea



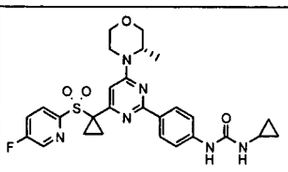
Se agregó metilamina (0,509 mL, 1,02 mmol) a fenil *N*-[4-[4-[1-(5-fluoropiridin-2-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (200 mg, 0,34 mmol) y trietilamina (0,141 mL, 1,02 mmol) en DMF (1,7 mL) y la reacción se agitó a 50°C durante 2 horas. El producto bruto se purificó mediante HPLC prep para proporcionar el material deseado como un sólido blanco (70,0 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,69 - 1,72 (2H, m), 1,96 - 1,99 (2H, m), 2,66 (3H, d), 3,12 - 3,18 (1H, m), 3,43 - 3,48 (1H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, d), 4,15 (1H, d), 4,45 (1H, s), 6,02 - 6,04 (1H, m), 6,68 (1H, s), 7,37 (2H, d), 7,68 (2H, d), 7,95 - 8,00 (1H, m), 8,03 - 8,06 (1H, m), 8,72 (1H, s), 8,87 (1H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 527; HPLC tR = 1,61 min.

Ensayo de mTOR Quinasa (Echo): 0,00252μM

El siguiente compuesto se preparó en forma análoga a partir de fenil *N*-[4-[4-[1-(5-fluoropiridin-2-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

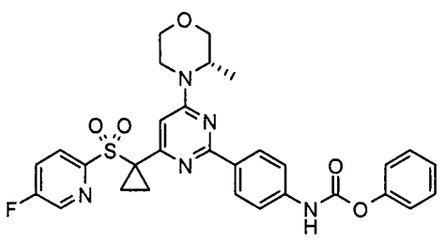
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
48a		3-ciclopropil-1-[4-[4-[1-(5-fluoropiridin-2-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	553	2,43

Ejemplo 48a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,66 - 1,70 (2H, m), 1,96 - 1,99 (2H, m), 3,69 (8H, s), 3,79 (3H, s), 6,74 (1H, s), 7,40 (3H, d), 7,66 (2H, d), 7,77 - 7,78 (3H, m), 8,35 (1H, s), 8,80 (1H, s), 8,87 (2H, d).

Ensayo de mTOR Quinasa (Echo): 0,00103μM

La preparación de fenil *N*-[4-[4-[1-(5-fluoropiridin-2-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[1-(5-fluoropiridin-2-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



Se agregó bicarbonato de sodio (0,403 g, 4,79 mmol) a 4-[4-[1-(5-fluoropiridin-2-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (1,5 g, 3,19 mmol), en 1,4-dioxano (15,97 mL), seguido por la adición gota a gota de fenil cloroformiato (0,402 mL, 3,19 mmol) durante 2 minutos y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en DCM (20 mL), los orgánicos se lavaron con agua (20 mL), se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado (2,0 g) que se utilizó sin purificación adicional.

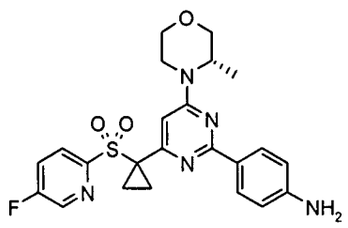
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,71 - 1,76 (2H, m), 1,96 - 1,99 (2H, m), 3,14 - 3,22 (1H, m), 3,42 - 3,49 (1H, m), 3,58 - 3,62 (1H, m), 3,75 (1H,

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d), 3,94 - 3,98 (1H, m), 4,19 (1H, s), 4,48 (1H, s), 6,74 (1H, s), 7,24 - 7,26 (2H, m), 7,45 (2H, t), 7,54 (2H, d), 7,80 (2H, d), 7,99 (1H, dt), 8,07 (1H, dd), 8,89 (1H, d), 10,48 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 590; HPLC tR = 2,95 min.

4-[4-[1-(5-Fluoropiridin-2-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

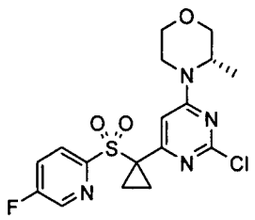


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,136 g, 0,19 mmol) a 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,104 g, 5,04 mmol) y 2-cloro-4-[1-(5-fluoropiridin-2-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,6 g, 3,88 mmol) y una solución acuosa de carbonato de sodio (5,81 mL, 11,63 mmol) en una mezcla de disolventes de DMF (0,564 mL), etanol (4,70 mL) y agua (4,70 mL) a TA bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 85°C durante 4 horas. La mezcla de reacción se diluyó con acetato de etilo (20 mL) y los orgánicos se lavaron con agua (2 x 20 mL), se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% amoníaco metanólico 3,5N en DCM, para proporcionar el material deseado como un sólido crema (1,5 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,65 - 1,70 (2H, m), 1,94 - 1,97 (2H, m), 3,12 (1H, dt), 3,44 (1H, dt), 3,59 (1H, dd), 3,73 (1H, d), 3,93 (1H, dd), 4,11 - 4,13 (1H, m), 4,41 (1H, s), 6,46 (2H, d), 6,58 (1H, s), 7,49 (2H, d), 7,98 (2H, dt), 8,04 (2H, dd), 8,89 (1H, d)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 470; HPLC tR = 2,30 min.

2-Cloro-4-[1-(5-fluoropiridin-2-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

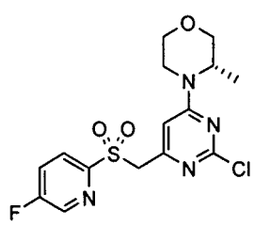


Se agregó 1,2-dibromoetano (1,025 mL, 11,89 mmol) a 2-cloro-4-[(5-fluoropiridin-2-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,3 g, 5,95 mmol), una solución acuosa de hidróxido de sodio (2,97 mL, 29,73 mmol) y bromuro de tetrabutilamonio (0,383 g, 1,19 mmol) en tolueno (29,7 mL) y la solución resultante se agitó a 60ºC durante 3 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en acetato de etilo (50 mL) y los orgánicos se lavaron secuencialmente con agua (50 mL) y salmuera saturada (50 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 5 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (1,8 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 (3H, d), 1,63 - 1,66 (2H, m), 1,88 - 1,93 (2H, m), 3,11 - 3,17 (1H, m), 3,39 (1H, dt), 3,54 (1H, dd), 3,69 (1H, d), 3,91 (2H, dd), 4,27 (1H, s), 6,81 (1H, s), 8,02 - 8,11 (2H, m), 8,83 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 413, HPLC tR = 2,10 min

2-Cloro-4-[(5-fluoropiridin-2-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



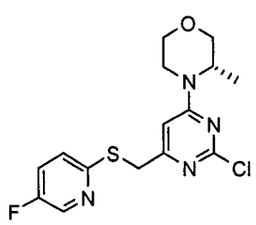
Se agregó ácido 3-cloroperoxibenzoico (5,79 g, 25,15 mmol) en porciones a 2-cloro-4-[(5-fluoropiridin-2-il)sulfanilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,57 g, 10,06 mmol), en DCM (50,3 mL) y la reacción se agitó a TA durante 2 horas. La mezcla de reacción se lavó con una solución saturada de hidrogenocarbonato de sodio (50 mL), la capa orgánica se separó, se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 60% acetato de etilo en DCM, para proporcionar el material deseado como un sólido

blanco (2,3 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 3,17 (1H, t), 3,42 (1H, dt), 3,57 (1H, dd), 3,71 (1H, d), 3,92 (2H, dd), 4,17 (1H, s), 4,74 (2H, d), 6,82 (1H, s), 8,01 - 8,09 (2H, m), 8,89 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 387, HPLC tR = 1,88 min

2-Cloro-4-[(5-fluoropiridin-2-il)sulfanilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

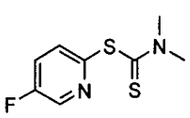


Se agregó hidróxido de potasio (3,22 g, 57,33 mmol) a (5-fluoropiridin-2-il) dimetilaminometanoditioato (3,1 g, 14,33 mmol) en etanol (71,7 mL) y la solución resultante se calentó a 65°C durante 4 horas. La reacción se enfrió, se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (7,09 g, 20,06 mmol) y la reacción se agitó a TA durante 4 horas. Se agregó agua (50 mL) y la reacción se extrajo con DCM (2 x 100 mL). Los orgánicos se secaron ($MgSO_4$), se filtraron y se concentraron para proporcionar un producto bruto que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado as a beige gum (3,57 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 (3H, d), 3,11 - 3,17 (1H, m), 3,41 (1H, dt), 3,54 - 3,57 (1H, m), 3,69 (1H, d), 3,90 (2H, dd), 4,24 - 4,26 (1H, m), 4,29 (2H, d), 6,84 (1H, s), 7,45 (1H, dd), 7,68 (1H, dt), 8,50 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 355, HPLC tR = 2,38 min

(5-Fluoropiridin-2-il) dimetilaminometanoditioato



2-Bromo-5-fluoropiridina (4 g, 22,73 mmol) se agregó en porciones a cloruro de isopropilmagnesio - complejo de cloruro de litio (14% en THF, 23 mL, 22,73 mmol), a 0°C,

1661

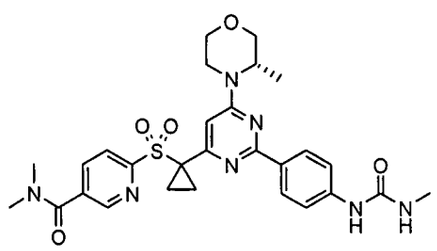
durante un período de 2 minutos bajo una atmósfera de nitrógeno. La solución resultante se entibió hasta alcanzar TA durante un período de 2 horas y luego se enfrió nuevamente hasta alcanzar 0°C y se agregó disulfuro de tetrametiltiurano (5,46 g, 22,73 mmol) en DCM (22,73 mL). La reacción se entibió hasta alcanzar TA y se agitó durante 6 horas. La reacción se vertió en una solución saturada acuosa de cloruro de amonio (100 mL) y la capa acuosa se extrajo con DCM (2 x 100 mL). Los orgánicos se secaron ($MgSO_4$), se concentraron al vacío y el producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 60% acetato de etilo en DCM, para proporcionar el material deseado como un aceite marrón que solidificó en reposo (3,10 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 3,45 (3H, s), 3,46 (3H, s), 7,70 (1H, dd), 7,86 (1H, dt), 8,65 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ 217, HPLC tR = 1,70 min

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 49: *N,N*-Dimetil-6-[1-[2-[4-(metilcarbamoilamino)fenil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpiridina-3-carboxamida



Se agregó metilamina (0,250 mL, 0,50 mmol) a fenil *N*-[4-[4-[1-[5-(dimetilcarbamoil)piridin-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,064 g, 0,10 mmol) y trietilamina (0,042 mL, 0,30 mmol) en DMF (2 mL) y la solución resultante se agitó a 50°C durante 18 horas. La reacción se enfrió y la mezcla se purificó mediante HPLC preparativa para proporcionar el material deseado como un sólido blanco (0,03 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ δ 1,16-1,18 (3H, d), 1,73-1,76 (2H, m), 1,99-2,02 (2H, m), 2,65-2,66 (3H, d), 2,88 (3H, s), 3,05 (3H, s), 3,05-3,17 (1H, td), 3,41-3,48 (1H, td), 3,58-3,62 (1H, dd), 3,73-3,76 (1H, d), 3,93-3,97 (1H, dd), 4,15 (1H, bs), 4,44 (1H, bs), 6,07-6,10 (1H, q), 6,65 (1H, s), 7,37-7,39 (2H, d), 7,67-7,69 (2H, d), 8,00-8,01 (1H,

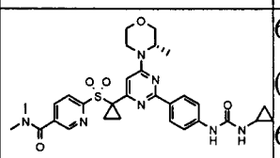
162

d), 8,11-8,13 (1H, dd), 8,72 (1H, s), 8,87-8,88 (1H, dd).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 580; HPLC tR = 1,88min.

Ensayo de mTOR Quinasa (Echo): 0,00187μM

El compuesto que figura en la tabla a continuación se preparó en forma análoga a partir de fenil *N*-[4-[4-[1-[5-(dimetilcarbamoil)piridin-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

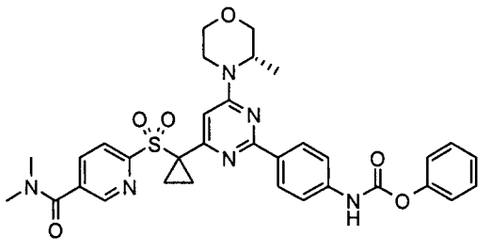
Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
49a		6-[1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-N,N-dimetilpiridina-3-carboxamida	606	2,00

Ejemplo 49a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,39-0,43 (2H, m), 0,62-0,67 (2H, m), 1,16-1,18 (3H, d), 1,73-1,76 (2H, m), 2,00-2,02 (2H, m), 2,88 (3H, s), 3,05 (3H, s), 3,11-3,18 (1H, td), 3,42-3,48 (1H, td), 3,58-3,62 (1H, dd), 3,73-3,76 (1H, d), 3,93-3,97 (1H, dd), 4,13 (1H, bs), 4,44 (1H, bs), 6,44-6,45 (1H, d), 6,66 (1H, s), 7,37-7,39 (2H, d), 7,67-7,69 (2H, d), 8,00-8,03 (1H, d), 8,11-8,13 (1H, dd), 8,51 (1H, s), 8,87-8,88 (1H, dd).

Ensayo de mTOR Quinasa (Echo): 0,00267μM

La preparación de fenil *N*-[4-[4-[1-[5-(dimetilcarbamoil)piridin-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-[5-(dimetilcarbamoil)piridin-2-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

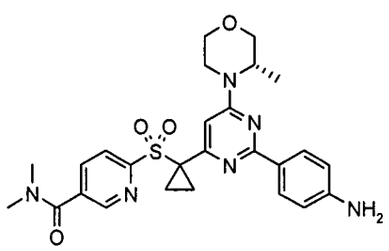


Se agregó gota a gota fenil cloroformiato (0,015 mL, 0,12 mmol) a 6-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-*N,N*-dimetilpiridina-3-carboxamida (0,064 g, 0,12 mmol) e hidrogenocarbonato de sodio (0,015 g, 0,18 mmol) en dioxano (7,5 mL) y la solución resultante se agitó a TA durante 1 hora. El material se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado .

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,29-1,31 (3H, d), 1,66-1,74 (2H, m), 2,17-2,19 (2H, m), 2,88 (3H, s), 3,12 (3H, s), 3,24-3,31 (1H, td), 3,54-3,61 (1H, td), 3,70-3,74 (1H, dd), 3,80-3,83 (1H, d), 4,01-4,05 (1H, dd), 4,16-4,17 (1H, bs), 4,42 (1H, bs), 6,79 (1H, s),,16-7,26 (2H, d), 7,22-7,26 (1H, t), 7,37-7,41 (2H, t), 7,47-7,49 (2H, d), 7,64-7,69 (1H, m), 7,84-7,87 (1H, dd), 7,95-7,97 (3H, m), 8,75-8,76 (1H, d).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 643; HPLC tR = 2,62min.

6-[1-[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-*N,N*-dimetilpiridina-3-carboxamida

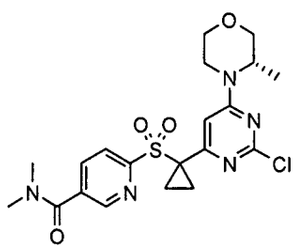


Se agregó cloruro de bis(trifenilfosfina)paladio (II) (0,015 g, 0,02 mmol) a 6-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-*N,N*-dimetilpiridina-3-carboxamida (0,203 g, 0,44 mmol), 4- (4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,096 g, 0,44 mmol) y una solución acuosa de carbonato de sodio (1,09 mL, 2,18 mmol) en una mezcla de disolventes (2 mL) (la mezcla de disolventes comprendía 18% DMF, 82% de una mezcla 7:3:2 de DME:agua:etanol) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a 80°C durante 3 horas. La reacción se enfrió, se agregó agua y los sólidos

se eliminaron mediante filtración. El filtrado se extrajo dos veces con acetato de etilo y los orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron. Los sólidos de la filtración se combinaron con los de la extracción para proporcionar el material deseado que se utilizó sin purificación adicional.

Espectro de LCMS: m/z (ES+) $(M+H)^+ = 523$; HPLC tR = 1,98min.

6-[1-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-*N*,*N*-dimetilpiridina-3-carboxamida

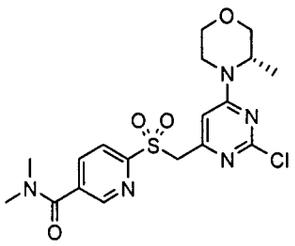


Se agregó hidróxido de sodio (3,36 g, 83,96 mmol) en agua (3,6 mL) a 6-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]-*N*,*N*-dimetilpiridina-3-carboxamida (0,666 g, 1,51 mmol), 1,2-dibromoetano (0,652 mL, 7,56 mmol) y bromuro de tetrabutilamonio (0,049 g, 0,15 mmol) en DCM (20 mL) y la solución resultante se agitó a TA durante 18 horas. La mezcla de reacción se diluyó con agua y se extrajo con DCM. Los orgánicos se lavaron con salmuera saturada, se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 7% metanol (conteniendo 0,1% amoníaco) en DCM, para proporcionar el material deseado como una goma marrón (0,406 g).

Espectro de NMR: ^1H NMR (400,132 MHz, $CDCl_3$) δ 1,27-1,29 (3H, d), 1,61-1,68 (2H, m), 2,07-2,10 (2H, m), 3,00 (3H, s), 3,14 (3H, s), 3,20-3,28 (1H, td), 3,48-3,54 (1H, td), 3,64-3,67 (1H, dd), 3,75-3,78 (1H, d), 3,96-4,02 (2H, m), 4,26 (1H, bs), 6,95 (1H, s), 7,93-7,99 (2H, m), 8,71-8,72 (1H, d).

Espectro de LCMS: m/z (ES+) $(M+H)^+ = 466$; HPLC tR = 1,71min.

6-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]-*N*,*N*-dimetilpiridina-3-carboxamida

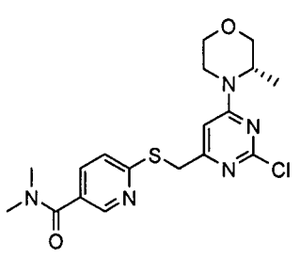


6-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]-*N,N*-dimetilpiridina-3-carboxamida (1,47 g, 3,60 mmol) se disolvió en dioxano (45 mL) y se agregó ácido sulfúrico 2N (0,11 mL). La solución se calentó hasta alcanzar 55°C, una solución de tungstato de sodio dihidrato (0,024 g, 0,07 mmol) en agua (1,08 mL) se agregó y la solución se dejó agitar durante 10 minutos. Luego se agregó peróxido de hidrógeno (2,229 mL, 72,07 mmol) gota a gota durante varios minutos y la solución se calentó a 55°C durante 3 horas. Se agregó agua y la reacción se dejó enfriar. La solución acuosa se extrajo con DCM, los orgánicos se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido crema (1,45 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,31-1,33 (3H, d), 3,04 (3H, s), 3,17 (3H, s), 3,24-3,32 (1H, td), 3,50-3,57 (1H, td), 3,66-3,70 (1H, dd), 3,78-3,80 (1H, d), 3,99-4,03 (2H, m), 4,26 (1H, bs), 4,58 (2H, s), 6,52 (1H, s), 7,97-8,03 (2H, m), 8,82-8,83 (1H, m).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 440; HPLC tR = 1,59min.

6-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]-*N,N*-dimetilpiridina-3-carboxamida

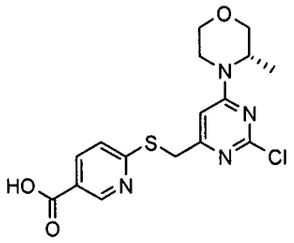


Se agregó DIPEA (1,043 mL, 5,99 mmol) a 6-[[2-cloro-6-[(3*S*)-3- metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]piridina-3-carboxílico ácido (1,369 g, 3,59 mmol) y HATU (1,366 g, 3,59 mmol) en DMA (10 mL) y la solución resultante se agitó a TA durante 15 minutos. Se agregó dimetilamina (1,497 mL, 2,99 mmol) y la reacción se dejó agitar durante 2,5 horas. Se agregó agua a la solución y la solución se extrajo con acetato de etilo. El acetato

de etilo se lavó con una solución saturada acuosa de bicarbonato de sodio, se secó ($MgSO_4$), se filtró y se evaporó para proporcionar el material deseado que se utilizó sin purificación adicional.

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 408; HPLC tR = 1,83min.

6-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]piridina-3-carboxílico ácido



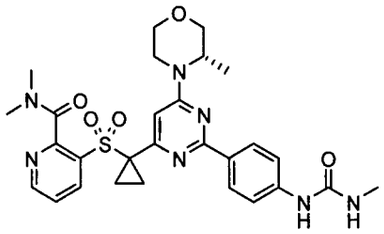
Se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,0 g, 5,66 mmol) a ácido 6-mercaptonicotínico (1,317 g, 8,48 mmol) y DIPEA (2,463 mL, 14,14 mmol) en acetonitrilo (100 mL) y la solución resultante se agitó a TA durante 2 horas. El disolvente se retiró al vacío y el residuo se disolvió en DCM. Los orgánicos se lavaron secuencialmente con agua y salmuera saturada, se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% metanol (conteniendo 0,1% amoníaco) en DCM, para proporcionar el material deseado como un sólido marrón (1,79 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,19-1,20 (3H, d), 3,16-3,21 (1H, t), 3,40-3,47 (1H, m), 3,58-3,61 (2H, dd), 3,91-3,94 (2H, d), 4,25 (3H, bs), 6,08 (1H, bs), 6,52 (1H, s), 7,01 (1H, bs), 7,89 (1H, bs), 8,89 (1H, bs).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 381; HPLC tR = 0,83min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 50: *N,N*-Dimetil-3-[1-[2-[4-(metilcarbamoilamino)fenil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpiridina-2-carboxamida



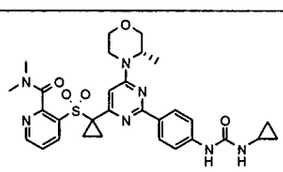
Se agregó metilamina (0,441 mL, 0,88 mmol) a fenil *N*-[4-[4-[1-[2-(dimetilcarbamoil)piridin-3-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,113 g, 0,18 mmol) y trietilamina (0,074 mL, 0,53 mmol) en DMF (2 mL) y la solución resultante se agitó a 50°C durante 2 horas. La reacción se enfrió y se purificó mediante HPLC preparativa, para proporcionar el material deseado como una goma incolora (11 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16-1,18 (3H, d), 1,62 (2H, bs), 1,98 (2H, bs), 2,55 (3H, s), 2,66 (3H, s), 2,96 (3H, s), 3,13-3,19 (1H, td), 3,41-3,47 (1H, td), 3,58-3,61 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,98 (1H, dd), 4,16 (1H, bs), 4,47 (1H, bs), 6,12 (1H, bs), 6,73 (1H, s), 7,43-7,46 (2H, d), 7,59-7,62 (1H, q), 7,85-7,87 (2H, d), 8,16-8,18 (1H, d), 8,82 (1H, bs), 8,85-8,86 (1H, dd).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 580; HPLC tR = 1,76min.

Ensayo de mTOR Quinasa (Echo): 0,0104μM

El siguiente compuesto se preparó en forma análoga a partir de fenil *N*-[4-[4-[1-[2-(dimetilcarbamoil)piridin-3-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
50a		3-[1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-N,N-dimetilpiridina-2-carboxamida	606	1,92

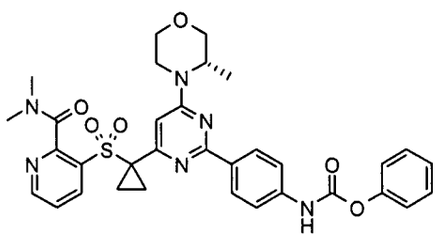
Ejemplo 50a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40-0,44 (2H, m), 0,63-0,67 (2H, m),

1,16-1,17 (3H, d), 1,60 (2H, bs), 1,96 (2H, bs), 2,55 (3H, s), 2,97 (3H, s), 3,10-3,17 (1H, td), 3,42-3,48 (1H, td), 3,58-3,62 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,97 (1H, dd), 4,15 (1H, bs), 4,45 (1H, bs), 6,45-6,46 (1H, d), 6,72 (1H, s), 7,41-7,43 (2H, d), 7,57-7,60 (1H, q), 7,84-7,86 (2H, d), 8,11-8,14 (1H, dd), 8,55 (1H, s), 8,84-8,85 (1H, dd).

Ensayo de mTOR Quinasa (Echo): 0,00794μM

La preparación de fenil *N*-[4-[4-[1-[2-(dimetilcarbamoil)piridin-3-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-[2-(dimetilcarbamoil)piridin-3-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

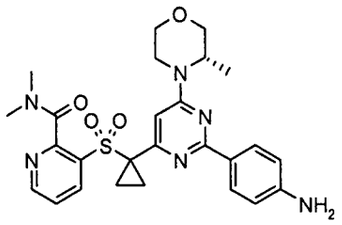


Se agregó gota a gota fenil cloroformiato (0,071 mL, 0,57 mmol) a 3-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-*N,N*-dimetilpiridina-2-carboxamida (0,296 g, 0,57 mmol) e hidrogenocarbonato de sodio (0,071 g, 0,85 mmol) en dioxano (18 mL) y la solución resultante se agitó a TA durante 3 horas. Los sólidos se retiraron mediante filtración y el filtrado se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 100% acetato de etilo en DCM, para proporcionar el material deseado adicional como una goma amarilla (0,227 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,22-1,24 (3H, d), 1,53-1,60 (2H, m), 2,13-2,17 (2H, m), 2,77 (3H, s), 3,14 (3H, s), 3,18-3,25 (1H, td), 3,50-3,57 (1H, td), 3,66-3,70 (1H, dd), 3,77-3,80 (1H, d), 3,98-3,99 (1H, dd), 4,08 (1H, bs), 4,38 (1H, bs), 6,69 (1H, s), 7,16-7,18 (2H, d), 7,21-7,25 (2H, m), 7,36-7,40 (2H, t), 7,48-7,50 (2H, d), 7,67 (1H, bs), 7,94-7,96 (1H, dd), 8,15-8,17 (2H, d), 8,70-8,72 (1H, dd).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 643; HPLC tR = 3,09min.

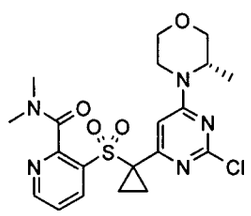
3-[1-[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-*N,N*-dimetilpiridina-2-carboxamida



Se agregó cloruro de bis(trifenilfosfina)paladio (II) (0,038 g, 0,05 mmol) a 3-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-*N,N*-dimetilpiridina-2-carboxamida (0,503 g, 1,08 mmol), 4- (4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,237 g, 1,08 mmol) y una solución acuosa de carbonato de sodio (2,70 mL, 5,40 mmol) en una mezcla de disolventes (2 mL) (la mezcla de disolventes comprendía 18% DMF, 82% de una mezcla 7:3:2 de DME:agua:etanol) y la solución resultante se agitó a 80°C durante 15 horas. La reacción se enfrió hasta alcanzar TA y se agregó agua. Los sólidos se filtraron para proporcionar el material deseado. El filtrado se extrajo con acetato de etilo y los orgánicos se secaron ($MgSO_4$), se filtraron y se evaporaron hasta secarse para proporcionar una muestra adicional del material deseado. Ambas cosechas del material deseado se combinaron y se utilizaron sin purificación adicional.

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 523; HPLC tR = 1,85min.

3-[1-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-*N,N*-dimetilpiridina-2-carboxamida

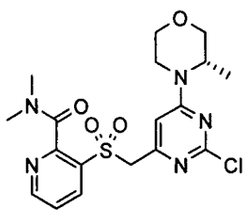


Se agregó hidróxido de sodio (2,373 g, 59,32 mmol) en agua (2,373 mL) a 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]-*N,N*-dimetilpiridina-2-carboxamida (0,475 g, 1,08 mmol), 1,2-dibromoetano (0,465 mL, 5,39 mmol) y bromuro de tetrabutilamonio (0,035 g, 0,11 mmol) en DCM y la solución resultante se agitó a TA durante 18 horas. Se agregó agua y la solución se extrajo con DCM. La capa orgánica se secó ($MgSO_4$) y se filtró para proporcionar el material deseado (0,539 g).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 466; HPLC tR = 1,64min.

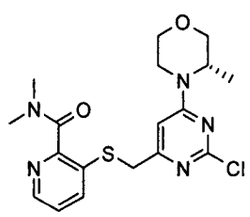
1620

3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]-*N,N*-dimetilpiridina-2-carboxamida



Se disolvió 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]-*N,N*-dimetilpiridina-2-carboxamida (0,533 g, 1,31 mmol) en dioxano (15 mL) y se agregó ácido sulfúrico 2N (0,041 mL). La solución se calentó hasta alcanzar 55°C y una solución de tungstato de sodio dihidrato (8,62 mg, 0,03 mmol) en agua (0,4 mL) se agregó y la solución se dejó agitar durante 10 minutos. Luego se agregó gota a gota peróxido de hidrógeno (0,808 mL, 26,13 mmol) durante varios minutos. La solución se calentó a 55°C durante 5,5 horas. El calor se retiró y la reacción se dejó agitar a TA durante toda la noche. Se agregó agua y la reacción se dejó enfriar. La solución acuosa se extrajo con DCM. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 7% metanil (conteniendo 0,1% amoníaco) en DCM, para proporcionar el material deseado como una goma amarilla (0,475 g).
Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 440; HPLC tR = 1,62min.

3-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]-*N,N*-dimetilpiridina-2-carboxamida

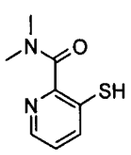


Se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,009 g, 2,85 mmol) a *N,N*-dimetil-3-sulfanilpiridina-2-carboxamida (0,520 g, 2,85 mmol) y DIPEA (0,746 mL, 4,28 mmol) en acetonitrilo (20 mL) y la solución resultante se agitó a TA durante 2 horas. Se agregó más DIPEA (0,746 mL, 4,28 mmol) y la reacción se dejó agitar durante

varios un fin de semana. La reacción se calentó a 40°C durante 7 días. El disolvente se retiró y el residuo se disolvió en DCM y se lavó con agua. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol, para proporcionar material que se purificó adicionalmente mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 7% metanol en DCM, para proporcionar el material deseado como una goma marrón (0,533 g).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 408; HPLC tR = 1,57min.

N,N-Dimetil-3-sulfanilpiridina-2-carboxamida

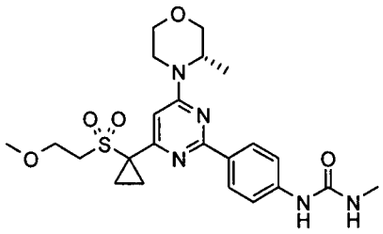


Se agregó DIPEA (2,164 mL, 12,42 mmol) a ácido 3-mercaptopicolínico (1,156 g, 7,45 mmol) y HATU (2,83 g, 7,45 mmol) en DMA (30 mL) y la solución resultante se agitó a TA durante 15 minutos. Se agregó dimetilamina (3,11 mL, 6,21 mmol) y la reacción se dejó agitar durante toda la noche. Se agregó agua a la solución y la solución se extrajo con DCM. Los orgánicos se lavaron con una solución saturada acuosa de bicarbonato de sodio, se secaron ($MgSO_4$) y se filtraron. La mayor parte del disolvente se retiró y se agregó éter dietílico. El sólido se retiró mediante filtración y se descartó. Se agregó agua al filtrado y el producto se extrajo con acetato de etilo. Los orgánicos se secaron ($MgSO_4$), se filtraron y se evaporaron para proporcionar el material deseado (0,52 g).

Espectro de LCMS: m/z (ES-) (M-H)- = 181; HPLC tR = 1,17min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 51: 1-[4-[4-[1-(2-Metoxietilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea



Se agregó cloruro de bis(trifenilfosfina)paladio(II) (5,8 mg, 0,827 mmol) a 2-cloro-4-[1-(2-metoxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidina (0,062 g, 0,17 mmol), 1-metil-3-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)urea (0,046 g, 0,17 mmol) y una solución acuosa de carbonato de sodio (0,414 mL, 0,83 mmol) en una mezcla de disolventes (2 mL) (la mezcla de disolventes comprendía 18% DMF, 82% de una mezcla 7:3:2 de DME:agua:etanol) a TA bajo una atmósfera de nitrógeno. La suspensión resultante se agitó a 80°C durante 6 horas. La mezcla de reacción bruta se hizo pasar a través de una columna SCX, eluyendo con amoníaco 7M en metanol, para proporcionar una muestra que se concentró al vacío y se disolvió nuevamente en DMF (2 mL). La mezcla se purificó mediante HPLC preparativa para proporcionar el material deseado como un sólido blanco (17 mg).

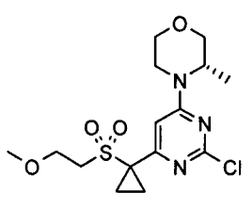
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22-1,23 (3H, d), 1,54-1,57 (2H, m), 1,64-1,66 (2H, m), 2,65-2,66 (3H, d), 3,16-3,23 (1H, td), 3,27 (3H, s), 3,44-3,51 (1H, td), 3,61-3,64 (1H, dd), 3,75-3,78 (1H, d), 3,80-3,81 (4H, t), 3,95-3,99 (1H, dd), 4,21 (1H, bs), 4,57 (1H, bs), 6,07-6,10 (1H, q), 6,76 (1H, s), 7,49-7,51 (2H, d), 8,17-8,19 (2H, d), 8,79 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 490; HPLC tR = 1,93min.

Ensayo de mTOR Quinasa (Echo): 0,00332μM

La preparación de 2-cloro-4-[1-(2-metoxietilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidina se describe a continuación.

2-Cloro-4-[1-(2-metoxietilsulfonil)ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



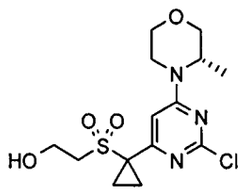
Se agregó hidruro de sodio (0,026 g, 1,07 mmol) a (S)-2-(1-(2-cloro-6-(3-

metilmorfolino)pirimidin-4-il)ciclopropilsulfonil)etanol (0,231 g, 0,64 mmol) en THF (20 mL) se enfrió hasta alcanzar 0°C bajo una atmósfera de nitrógeno. La solución resultante se agitó a 0°C durante 10 minutos. A esta solución, se agregó yoduro de metil (0,040 mL, 0,64 mmol) y la reacción lentamente se dejó entibiar hasta alcanzar TA. Se agregó agua cuidadosamente y la reacción se extrajo con DCM. Los orgánicos se secaron ($MgSO_4$), se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 60% acetato de etilo en DCM, para proporcionar el material deseado como una película seca incolora (0,062 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,31-1,32 (3H, d), 1,47-1,50 (2H, q), 1,79-1,82 (2H, q), 3,25-3,32 (1H, td), 3,35 (3H, s), 3,44-3,47 (2H, t), 3,49-3,56 (1H, td), 3,65-3,69 (1H, dd), 3,76-3,79 (1H, d), 3,79-3,85 (2H, m), 3,98-4,03 (2H, m), 4,33 (1H, bs), 6,84 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 376; HPLC tR = 1,87min.

2-[1-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfoniletanol

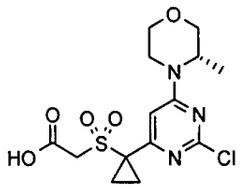


Se agregó DIPEA (3,70 mL, 21,23 mmol) a ácido 2-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilacético (3,99 g, 10,62 mmol) en THF se enfrió hasta alcanzar 0°C bajo una atmósfera de nitrógeno. La solución resultante se agitó a 0°C durante 5 minutos; luego se agregó gota a gota etil cloroformiato (1,117 mL, 11,68 mmol). La solución se dejó agitar durante 1 hora, los sólidos se eliminaron mediante filtración y el filtrado se enfrió nuevamente hasta alcanzar 0°C. se agregó borohidruro de litio (17,52 mL, 35,03 mmol) y la reacción lentamente se dejó entibiar hasta alcanzar TA. Se agregó más borohidruro de litio (10,62 mmol) y la mezcla se agitó durante varias horas. La reacción se aplacó con una solución saturada acuosa de cloruro de amonio y luego se extrajo con DCM. La capa orgánica se separó, se lavó con salmuera saturada, se secó ($MgSO_4$), se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 60% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (1,96 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21-1,22 (3H, d), 1,49-1,52 (2H, m), 1,62-1,65 (2H, m), 3,17-3,25 (1H, td), 3,40-3,47 (1H, td), 3,52-3,55 (2H, t), 3,56-3,60 (1H, dd), 3,71-3,74 (1H, d), 3,79-3,84 (2H, q), 3,92-3,95 (1H, dd), 4,04 (1H, bs), 4,40 (1H, bs), 4,98-5,01 (1H, t), 6,95 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 362; HPLC tR = 1,67 min.

Ácido 2-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilacético

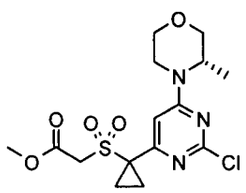


Se agregó solución de hidróxido de sodio 2 M (13,85 mL, 27,70 mmol) a metil 2-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilacetato (3,60 g, 9,23 mmol) en THF (100 mL) y la solución resultante se agitó a TA durante 6 horas. La solución se ajustó hasta alcanzar pH7 con ácido clorhídrico 2M y se agregó sal para concentrar la solución. La solución acuosa se extrajo con DCM, la capa orgánica se separó, se secó ($MgSO_4$), se filtró y se evaporó hasta proporcionar el material deseado como un sólido blanco (3,45 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20-1,22 (3H, d), 1,55-1,58 (2H, q), 1,69-1,72 (2H, q), 3,18-3,24 (1H, m), 3,40-3,46 (1H, td), 3,56-3,59 (1H, dd), 3,71-3,74 (1H, d), 3,92-3,95 (1H, dd), 4,04 (1H, bs), 4,41 (1H, bs), 4,55 (2H, s), 6,95 (1H, s), 13,36 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 376; HPLC tR = 0,71 min.

Metil 2-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilacetato

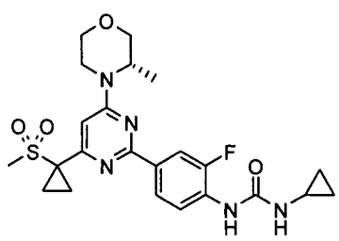


Una solución de diisopropilamida de litio (solución 2M en THF/n-heptano, 5,46 mL, 9,84 mmol) en THF (60 mL) se agregó a una solución agitada de 2-cloro-4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina (2,720 g, 8,20 mmol), y dimetil carbonato (6,97

mL, 81,97 mmol) en THF (60 mL), se enfrió hasta alcanzar -78°C, durante un período de 5 minutos bajo una atmósfera de nitrógeno. La solución resultante muy lentamente se dejó llegar a TA con agitación durante 18 horas. La reacción se enfrió nuevamente hasta alcanzar – 78°C y se agregó más diisopropilamida de litio (2,73 mL, 4,92 mmol), y dimetil carbonato (6,97 mL, 81,97 mmol). Nuevamente la mezcla se dejó entibiar lentamente hasta alcanzar TA con agitación durante 24 horas. La mezcla de reacción se diluyó con acetato de etilo (150 mL), se lavó con ácido cítrico 1M (150 mL) y salmuera saturada (150 mL). La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó para proporcionar un producto bruto que se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla.
Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,33 (3H, d), 1,55 (2H, q), 1,91 (2H, q), 3,30 (1H, m), 3,50 (1H, s), 3,68 (1H, q), 3,79 (4H, t), 4,01 (2H, q), 4,28 (2H, s), 4,41 (1H, s), 6,78 (1H, s).
Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 390; HPLC tR = 2,01 min.

La preparación de 2-cloro-4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina se describió anteriormente.

Ejemplo 52: 3-Ciclopropil-1-[2-fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea



Se agregaron ciclopropilamina (0,055 mL, 0,80 mmol) y luego trietilamina (0,067 mL, 0,48 mmol) a una solución de fenil *N*-[2-fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato (85,4mg, 0,16 mmol) en DMF (2 mL) y la reacción se calentó a 50°C durante toda la noche. El producto bruto se purificó mediante HPLC preparativa para proporcionar el material deseado como un sólido blanco (62 mg).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40-0,44 (2H, m), 0,64-0,69 (2H, m), 1,23-1,25 (3H, d), 1,55-1,58 (2H, q), 1,66-1,69 (2H, q), 2,55-2,61 (1H, m), 3,18-3,25 (1H, td), 3,28 (3H, s), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd),

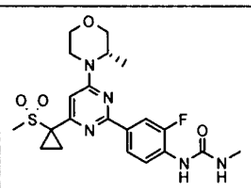
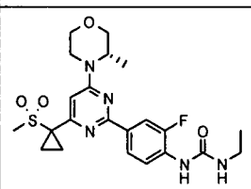
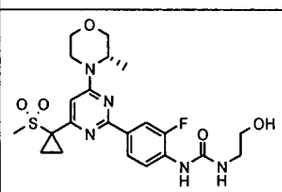
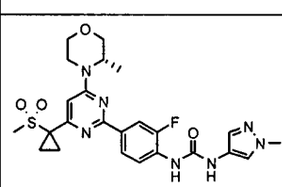
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4,21-4,24 (1H, d), 4,58 (1H, bs), 6,81 (1H, s), 6,88-6,89 (1H, d), 8,01-8,04 (1H, dd), 8,06-8,09 (1H, dd), 8,27-8,31 (1H, t), 8,36-8,37 (1H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$490 = HPLC tR = 2,28 min.

Ensayo de mTOR Quinasa (Echo): 0,0184μM

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[2-fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
52a		1-[2-fluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-metilurea	4,64	2,04
52b		3-etil-1-[2-fluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	478	2,21
52c		1-[2-fluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	4,94	1,80
52d		1-[2-fluoro-4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	530	2,07

Ejemplo 52a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,55-1,58 (2H, q), 1,66-1,69 (2H, q), 2,68-2,69 (3H, d), 3,18-3,25 (1H, td), 3,28 (3H, s), 3,45-3,52 (1H, td), 3,62-

3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,21-4,24 (1H, d), 4,57 (1H, bs), 6,55-6,58 (1H, q), 6,81 (1H, s), 8,00-8,04 (1H, dd), 8,05-8,08 (1H, dd), 8,26-8,31 (1H, t), 8,54-8,55 (1H, d).

Ensayo de mTOR Quinasa (Echo): 0,0103μM

Ejemplo 52b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06-1,10 (3H, t), 1,23-1,25 (3H, d), 1,55-1,58 (2H, q), 1,66-1,69 (2H, q), 3,11-3,18 (2H, m), 3,18-3,25 (1H, td), 3,28 (3H, s), 3,45-3,52 (1H, td), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, d), 3,96-3,99 (1H, dd), 4,21-4,24 (1H, d), 4,57 (1H, bs), 6,67-6,69 (1H, t), 6,81 (1H, s), 8,01-8,04 (1H, dd), 8,05-8,08 (1H, dd), 8,27-8,31 (1H, t), 8,47-8,48 (1H, d).

Ensayo de mTOR Quinasa (Echo): 0,0307μM

Ejemplo 52c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23-1,25 (3H, d), 1,55-1,58 (2H, q), 1,66-1,69 (2H, q), 3,17-3,25 (3H, m), 3,28 (3H, s), 3,45-3,65 (3H, m), 3,62-3,65 (1H, dd), 3,75-3,78 (1H, dd), 3,96-3,99 (1H, dd), 4,21-4,24 (1H, d), 4,58 (1H, bs), 4,73-7,76 (1H, t), 6,81 (1H, s), 6,84-6,87 (1H, t), 8,00-8,04 (1H, dd), 8,05-8,08 (1H, dd), 8,27-8,32 (1H, t), 8,63-8,64 (1H, d).

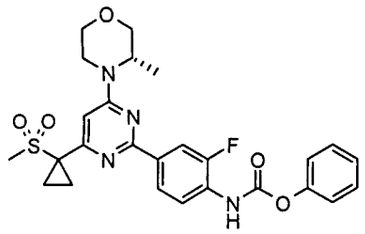
Ensayo de mTOR Quinasa (Echo): 0,0296μM

Ejemplo 52d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,25 (3H, d), 1,56-1,59 (2H, q), 1,67-1,70 (2H, q), 3,19-3,26 (1H, td), 3,29 (3H, s), 3,46-3,53 (1H, td), 3,62-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,80 (3H, s), 3,96-3,99 (1H, dd), 4,22-4,25 (1H, d), 4,58 (1H, bs), 6,83 (1H, s), 7,40 (1H, s), 7,79 (1H, s), 8,04-8,08 (1H, dd), 8,09-8,12 (1H, dd), 8,28-8,33 (1H, t), 8,67-8,68 (1H, d), 8,81 (1H, s).

Ensayo de mTOR Quinasa (Echo): 0,0107μM

La preparación de fenil *N*-[2-fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[2-fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato

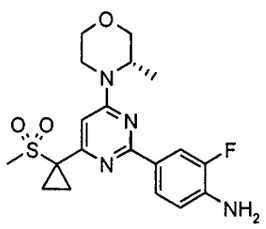


Se agregó fenil cloroformiato (0,116 mL, 0,93 mmol) a 2-fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina (0,376 g, 0,93 mmol) e hidrogenocarbonato de sodio (0,117 g, 1,39 mmol) en dioxano (10 mL) y la solución resultante se agitó a TA durante 2 horas. Se agregó agua y la solución se extrajo con DCM. Los orgánicos se secaron ($MgSO_4$), se filtraron y se evaporaron. El residuo se trituró con éter dietílico para proporcionar el material deseado como un sólido blanco (0,427 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24-1,26 (3H, d), 1,27-1,60 (2H, q), 1,68-1,70 (2H, q), 3,19-3,27 (1H, td), 3,28 (3H, s), 3,46-3,53 (1H, td), 3,62-3,66 (1H, dd), 3,76-3,79 (1H, d), 3,96-4,00 (1H, dd), 4,23-4,26 (1H, d), 4,59 (1H, bs), 6,87 (1H, s), 7,24-7,30 (3H, m), 7,43-7,47 (2H, t), 7,87-7,91 (1H, t), 8,08-8,18 (2H, dd), 10,15 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 527; HPLC tR = 2,93 min.

2-Fluoro-4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina



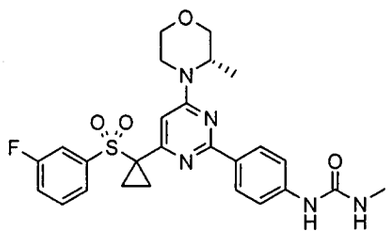
Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,031 g, 0,04 mmol) en una porción a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina (0,297 g, 0,90 mmol), 2-fluoro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,319 g, 1,34 mmol) y una solución acuosa de carbonato de sodio (2,24 mL, 4,48 mmol) en una mezcla de disolventes de 18% DMF, 82% de una mezcla 7:3:2 de DME:agua:etanol. La solución resultante se agitó a 80°C bajo una atmósfera de nitrógeno durante 30 minutos. El disolvente se retiró y el residuo se repartió entre agua y acetato de etilo. La capa orgánica se secó ($MgSO_4$), se filtró y se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 30% acetato de etilo en DCM, para proporcionar el material deseado como una goma marrón (0,376 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,31-1,33 (3H, d), 1,52-1,55 (2H, q), 1,81-1,84 (2H, q), 3,08 (3H, s), 3,26-3,33 (1H, td), 3,54-3,60 (1H, td), 3,70-3,73 (1H, dd), 3,79-3,80 (1H, d), 4,00-4,03 (3H, m), 4,13 (1H, bs), 4,46-4,47 (1H, bs), 6,72 (1H, s), 6,76-6,80 (1H, t), 7,99-8,02 (2H, m).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 407; HPLC tR = 2,29 min.

La prepa[redacted] 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina se describió anteriormente.

Ejemplo 53: 1-[4-[4-[1-(3-Fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea

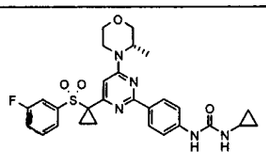
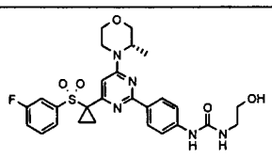
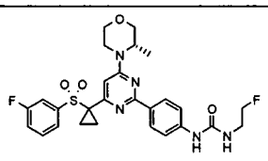
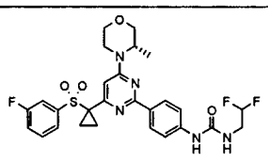
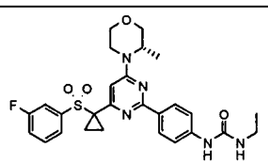
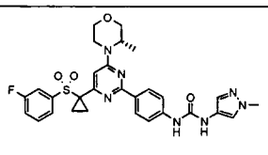


Se agregó metilamina (26,4 mg, 0,85 mmol) a fenil *N*-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (100 mg, 0,17 mmol) en NMP (2 mL). La solución resultante se calentó a 50°C durante 2 días. El producto bruto se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes, para proporcionar el material deseado como un sólido blanco (41 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,65 (2H, m), 1,94 (2H, m), 2,67 (4H, m), 3,46 (1H, m), 3,61 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,14 (1H, m), 4,44 (1H, m), 6,05 (1H, m), 6,65 (1H, s), 7,40 (2H, m), 7,63 (4H, m), 7,82 (2H, m), 8,72 (1H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 526; HPLC tR = 2,07 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
53a		3-ciclopropil-1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	552	2,28
53b		1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	556	1,97
53c		3-(2-fluoroetil)-1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	558	2,27
53d		3-(2,2-difluoroetil)-1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	576	2,39
53e		1-etil-3-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	540	2,27
53f		1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	592	2,20

Ejemplo 53a: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 0,43 (2H, m), 0,66 (2H, m), 1,19 (3H, d), 1,65 (2H, m), 1,94 (2H, m), 2,56 (1H, m), 3,16 (1H, m), 3,46 (1H, m), 3,61 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,14 (1H, m), 4,44 (1H, m), 6,41 (1H, m), 6,65 (1H, s), 7,40 (2H, m), 7,62 (4H, m), 7,82 (2H, m), 8,52 (1H, s)

Ejemplo 53b: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,65 (2H, m), 1,93 (2H, m), 3,18 (3H, m), 3,46 (3H, m), 3,62 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,15 (1H, m), 4,43 (1H, m), 4,74 (1H, m), 6,23 (1H, m), 6,65 (1H, s), 7,39 (2H, m), 7,63 (4H, m), 7,83 (2H, m), 8,78 (1H, s)

Ejemplo 53c: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,65 (2H, m), 1,93 (2H, m), 3,16 (1H, m), 3,43 (3H, m), 3,62 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,16 (1H, m), 4,43 (2H, m), 4,54 (1H, m), 6,42 (1H, m), 6,66 (1H, s), 7,40 (2H, m), 7,63 (4H, m), 7,83 (2H, m), 8,79 (1H, s)

Ejemplo 53d: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,65 (2H, m), 1,94 (2H, m), 3,16 (1H, m), 3,53 (4H, m), 3,75 (1H, m), 3,96 (1H, m), 4,15 (1H, m), 4,45 (1H, m), 6,07 (1H, m), 6,53 (1H, m), 6,66 (1H, s), 7,41 (2H, m), 7,63 (4H, m), 7,84 (2H, m), 8,91 (1H, s)

Ejemplo 53e: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,19 (3H, d), 1,65 (2H, m), 1,94 (2H, m), 3,13 (3H, m), 3,47 (1H, m), 3,62 (1H, m), 3,74 (1H, m), 3,96 (1H, m), 4,13 (1H, m), 4,44 (1H, m), 6,14 (1H, m), 6,65 (1H, s), 7,39 (2H, m), 7,63 (4H, m), 7,82 (2H, m), 8,64 (1H, s)

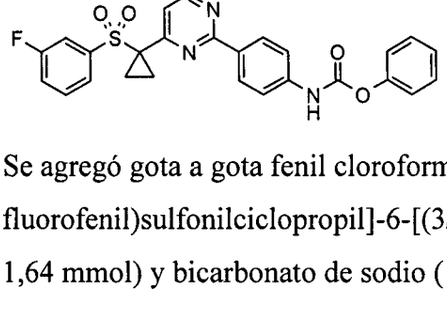
Ejemplo 53f: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,65 (2H, m), 1,95 (2H, m), 3,17 (1H, m), 3,47 (1H, m), 3,62 (1H, m), 3,78 (4H, m), 3,97 (1H, m), 4,15 (1H, m), 4,45 (1H, m), 6,66 (1H, s), 7,42 (3H, m), 7,65 (4H, m), 7,77 (1H, s), 7,86 (2H, d), 8,38 (1H, s), 8,81 (1H, s)

La preparación de fenil *N*-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-

1682

il]fenil]carbamato

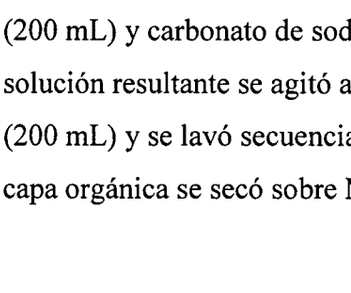


Se agregó gota a gota fenil cloroformiato (0,206 mL, 1,64 mmol) a 4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (770 mg, 1,64 mmol) y bicarbonato de sodio (138 mg, 1,64 mmol) en dioxano (30 mL). La solución resultante se agitó a TA durante 3 horas. La mezcla de reacción se filtró y el precipitado se recogió y se disolvió nuevamente en DCM (100 mL). Esto se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como una goma amarilla (722 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,65 (2H, m), 1,95 (2H, m), 3,17 (1H, m), 3,46 (1H, m), 3,61 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,16 (1H, m), 4,46 (1H, m), 6,70 (1H, s), 7,27 (3H, m), 7,55 (8H, m), 7,92 (2H, m), 10,40 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 589; HPLC tR = 3,02 min.

4-[4-[1-(3-Fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



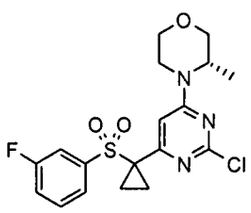
Se agregó 1,1'-bis(difenilfosfino)ferrocenodicloropaladio(II) (0,747 g, 1,03 mmol) a 2-cloro-4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4,25 g, 10,32 mmol) y 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (2,487 g, 11,35 mmol) en DME (200 mL) y carbonato de sodio (5,47 g, 51,59 mmol) en agua (25 mL) bajo nitrógeno. La solución resultante se agitó a 80°C durante 5 horas. La mezcla de reacción se diluyó con DCM (200 mL) y se lavó secuencialmente con agua (200 mL) y salmuera saturada (200 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto

bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar un producto bruto como una goma amarilla. El producto bruto se purificó adicionalmente mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 5% acetato de etilo en DCM, para proporcionar el material deseado como una goma amarilla (2,86 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,63 (2H, m), 1,92 (2H, m), 3,12 (1H, m), 3,45 (1H, m), 3,60 (1H, m), 3,74 (1H, m), 3,95 (1H, m), 4,11 (1H, m), 4,40 (1H, s), 5,52 (2H, s), 6,50 (2H, m), 6,57 (1H, m), 7,63 (6H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 469; HPLC tR = 2,35 min.

2-Cloro-4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

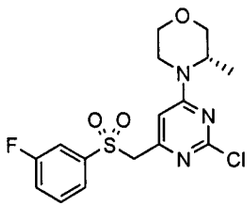


Se agregó hidróxido de sodio (24,80 g, 620,07 mmol) en agua (24,8 mL) a 2-cloro-4-[(3-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4,35 g, 11,27 mmol), 1,2-dibromoetano (2,91 mL, 33,82 mmol) y bromuro de tetrabutilamonio (0,363 g, 1,13 mmol) en tolueno (200 mL). La solución resultante se agitó a 60°C durante 3 horas. La mezcla de reacción se diluyó con DCM (200 mL) y se lavó dos veces con agua (200 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (4,25 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,63 (2H, m), 1,94 (2H, m), 3,18 (1H, m), 3,45 (1H, m), 3,60 (1H, m), 3,74 (1H, m), 3,97 (2H, m), 4,32 (1H, m), 6,76 (1H, s), 7,69 (4H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 412; HPLC tR = 2,27 min.

2-Cloro-4-[(3-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



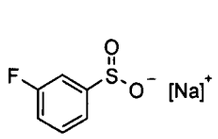
Se agregó 2-Cloro-4-(yodometil)-6-[(3S)-3-metilmorfolin-4-il]pirimidina (7 g, 19,80 mmol) a de 3-fluorobencenosulfinato sodio (5,41 g, 29,70 mmol) en acetonitrilo (100 mL) bajo nitrógeno. La suspensión resultante se agitó a 80°C durante 3 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (200 mL) y se lavó secuencialmente con agua (200 mL) y salmuera saturada (200 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 5% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (6,38 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,17 (3H, d), 3,16 (1H, m), 3,43 (1H, m), 3,58 (1H, m), 3,73 (1H, m), 3,93 (2H, m), 4,18 (1H, m), 4,71 (2H, s), 6,74 (1H, s), 7,68 (4H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 386; HPLC tR = 2,06 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3S)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

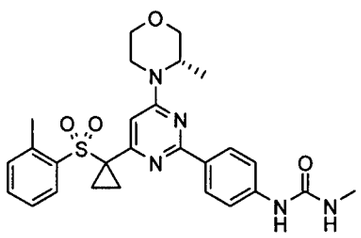
3-Fluorobencenosulfinato de sodio



Una solución de sulfito de sodio (7,77 g, 61,66 mmol) en agua (60 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (10,36 g, 123,32 mmol) y la solución resultante se agitó a 50°C durante 1 hora. Se agregó gota a gota cloruro de 3-fluorobenceno-1-sulfonilo (8,20 mL, 61,66 mmol) y la solución resultante se agitó a 50°C durante 20 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en MeOH. La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar el material deseado (12,60 g) como un sólido blanco, que se secó al aire durante toda la noche al vacío y se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 7,03 (1H, m), 7,21 (1H, m), 7,29 (1H, m), 7,36 (1H, m)

Ejemplo 54: 3-Metil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea

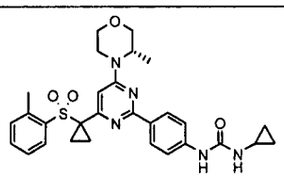
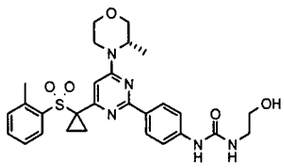
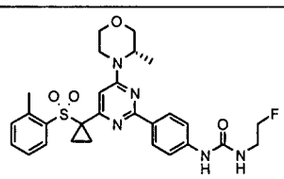
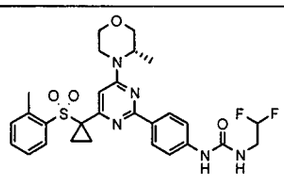
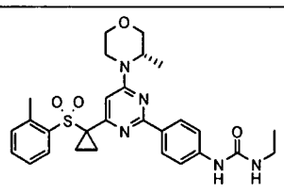
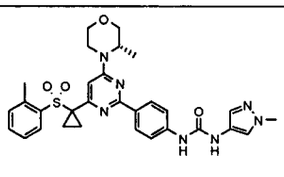


Se agregó metilamina (37,27 mg, 1,2 mmol) a fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]carbamato (140 mg, 0,24 mmol) y trietilamina (0,2 mL, 0,72 mmol) en NMP (2 mL). La solución resultante se calentó a 50°C durante 2 días. El producto bruto se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes, para proporcionar el material deseado (87 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (3H, d), 1,66 (2H, m), 1,86 (2H, m), 2,45 (3H, s), 2,66 (3H, m), 3,12 (1H, m), 3,45 (1H, m), 3,60 (1H, m), 3,74 (1H, m), 3,94 (1H, m), 4,06 (1H, m), 4,39 (1H, m), 6,05 (1H, m), 6,60 (1H, s), 7,37 (4H, m), 7,51 (1H, m), 7,85 (3H, m), 8,71 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 522; HPLC tR = 2,29 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
54a		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea	548	2,47
54b		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea	552	2,09
54c		3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea	554	2,42
54d		3-(2,2-difluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea	572	2,56
54e		1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea	536	2,45
54f		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-	588	2,31

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea		

Ejemplo 54a: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 0,42 (2H, m), 0,65 (2H, m), 1,15 (3H, d), 1,66 (2H, m), 1,86 (2H, m), 2,46 (3H, s), 2,56 (1H, m), 3,13 (1H, m), 3,44 (1H, m), 3,59 (1H, m), 3,74 (1H, m), 3,95 (1H, m), 4,07 (1H, m), 4,39 (1H, m), 6,42 (1H, m), 6,60 (1H, s), 7,37 (4H, m), 7,51 (1H, m), 7,84 (3H, m), 8,51 (1H, s)

Ejemplo 54b: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (3H, d), 1,66 (2H, m), 1,86 (2H, m), 2,46 (3H, s), 3,14 (3H, m), 3,45 (3H, m), 3,59 (1H, m), 3,74 (1H, m), 3,95 (1H, m), 4,07 (1H, m), 4,38 (1H, m), 4,74 (1H, t), 6,24 (1H, m), 6,60 (1H, s), 7,36 (4H, m), 7,51 (1H, m), 7,84 (3H, m), 8,77 (1H, s)

Ejemplo 54c: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (3H, d), 1,66 (2H, m), 1,86 (2H, m), 2,45 (3H, s), 3,12 (1H, m), 3,43 (3H, m), 3,60 (1H, m), 3,74 (1H, m), 3,95 (1H, m), 4,07 (1H, m), 4,40 (2H, m), 4,54 (1H, m), 6,42 (1H, m), 6,61 (1H, s), 7,37 (4H, m), 7,51 (1H, m), 7,85 (3H, m), 8,78 (1H, s)

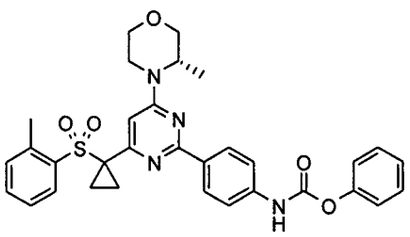
Ejemplo 54d: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (3H, d), 1,66 (2H, m), 1,86 (2H, m), 2,46 (3H, s), 3,11 (1H, m), 3,51 (4H, m), 3,75 (1H, m), 3,95 (1H, m), 4,07 (1H, m), 4,39 (1H, m), 6,08 (1H, m), 6,52 (1H, m), 6,61 (1H, s), 7,38 (4H, m), 7,51 (1H, m), 7,85 (3H, m), 8,89 (1H, s)

Ejemplo 54e: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,15 (3H, d), 1,66 (2H, m), 1,85 (2H, m), 2,45 (3H, s), 3,12 (3H, m), 3,44 (1H, m), 3,60 (1H, m), 3,74 (1H, m), 3,95 (1H, m), 4,06 (1H, m), 4,39 (1H, m), 6,15 (1H, m), 6,60 (1H, s), 7,37 (4H, m), 7,51 (1H, m), 7,84 (3H, m), 8,63 (1H, s)

Ejemplo 54f: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,66 (2H, m), 1,86 (2H, m), 2,46 (3H, s), 3,12 (1H, m), 3,45 (1H, m), 3,60 (1H, m), 3,74 (1H, m), 3,80 (3H, s), 3,95 (1H, m), 4,07 (1H, m), 4,39 (1H, m), 6,61 (1H, s), 7,43 (6H, m), 7,80 (2H, m), 7,90 (2H, m), 8,37 (1H, s), 8,80 (1H, s)

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]carbamato

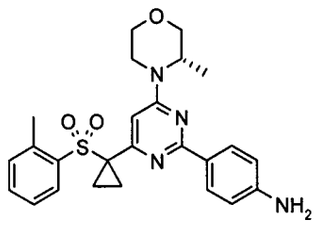


Se agregó gota a gota fenil cloroformiato (0,205 mL, 1,64 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]anilina (760 mg, 1,64 mmol) y bicarbonato de sodio (151 mg, 1,80 mmol) en dioxano (30 mL). La suspensión resultante se agitó a TA durante 3 horas. La mezcla de reacción se filtró y el precipitado se disolvió nuevamente en DCM (50 mL) y se lavó secuencialmente con agua (50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como una goma amarilla (985 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,67 (2H, m), 1,87 (2H, m), 2,47 (3H, s), 3,12 (1H, m), 3,45 (1H, m), 3,61 (1H, m), 3,74 (1H, m), 3,95 (1H, m), 4,08 (1H, m), 4,40 (1H, m), 6,64 (1H, s), 7,30 (5H, m), 7,49 (5H, m), 7,81 (1H, m), 7,95 (2H, m), 10,39 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 585; HPLC tR = 3,08 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]anilina

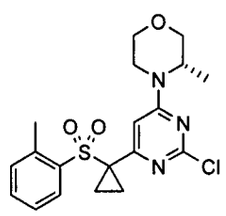


Una solución de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidina (2,04 g, 5,00 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,205 g, 5,50 mmol) y carbonato de sodio (2,120 g, 20,00 mmol) en DME (60 mL) y agua (15,00 mL) se agitó bajo nitrógeno durante 5 minutos. Se agregó diclorobis(trifenilfosfina)paladio(II) (0,351 g, 0,50 mmol) y la solución resultante se agitó a 80°C durante 2 horas. La mezcla de reacción se diluyó con DCM (200 mL) y se lavó con agua (200 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un aceite amarillo que solidificó en reposo (2,14 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,69 (2H, m), 1,87 (2H, m), 2,51 (3H, s), 3,12 (1H, m), 3,47 (1H, m), 3,63 (1H, m), 3,77 (1H, m), 3,98 (1H, m), 4,08 (1H, m), 4,39 (1H, m), 5,56 (2H, s), 6,54 (3H, m), 7,39 (2H, m), 7,56 (1H, m), 7,77 (2H, m), 7,87 (1H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 465; HPLC tR = 2,41 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidina

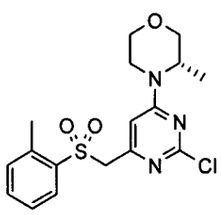


Se agregó hidróxido de sodio (12,67 g, 317 mmol) en agua (12,7 mL) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(2-metilfenil)sulfonilmetil]pirimidina (2,2 g, 5,76 mmol), 1,2-dibromoetano (1,489 mL, 17,28 mmol) y bromuro de tetrabutilamonio (0,186 g, 0,58 mmol) en tolueno (80 mL). La solución resultante se agitó a 60°C durante 1 hora. La mezcla de reacción se diluyó con DCM (200 mL) y se lavó secuencialmente con agua (200 mL) y salmuera saturada (200 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de

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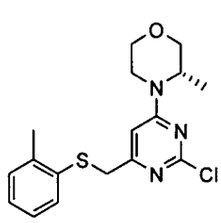
sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como una goma incolora que solidificó en reposo (2,04 g).
Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,63 (2H, m), 1,86 (2H, m), 2,48 (3H, s), 3,14 (1H, m), 3,42 (1H, m), 3,58 (1H, m), 3,74 (1H, m), 3,95 (2H, m), 4,25 (1H, m), 6,70 (1H, s), 7,43 (2H, m), 7,63 (1H, m), 7,79 (1H, m)
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 408; HPLC tR = 2,44 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(2-metilfenil)sulfonilmetil]pirimidina



Se agregó ácido sulfúrico 2N (0,352 mL) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(2-metilfenil)sulfanilmetil]pirimidina (4,37 g, 12,49 mmol) en dioxano (110 mL) y la solución se calentó hasta alcanzar 55°C. Se agregó tungstato de sodio dihidrato (0,082 g, 0,25 mmol) en agua (3,5 mL) y la solución se dejó agitar durante 5 minutos. Se agregó peróxido de hidrógeno (7,65 mL, 74,94 mmol) gota a gota a la solución. La solución resultante se agitó a 55°C durante 5 horas. La reacción se enfrió hasta alcanzar TA luego se agregó agua hasta que cesó la precipitación. El precipitado se recogió mediante filtración, se lavó con agua y se secó al vacío para proporcionar el material deseado como un sólido blanco (3,70 g).
Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,16 (3H, d), 2,63 (3H, s), 3,14 (1H, m), 3,42 (1H, m), 3,56 (1H, m), 3,72 (1H, m), 3,93 (2H, m), 4,18 (1H, s), 4,59 (2H, s), 6,67 (1H, s), 7,44 (2H, m), 7,65 (2H, m)
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 382; HPLC tR = 2,23 min.

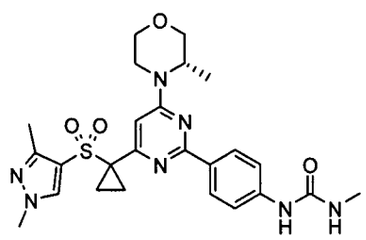
2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(2-metilfenil)sulfanilmetil]pirimidina



Se agregó DIPEA (3,70 mL, 21,21 mmol) a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (5 g, 14,14 mmol) y 2-metilbencenotiol (2,5 mL, 21,21 mmol) en THF (80 mL). La suspensión resultante se agitó a TA durante 18 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (100 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 5% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (4,37 g).
Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,13 (3H, d), 2,28 (3H, s), 3,11 (1H, m), 3,40 (1H, m), 3,55 (1H, m), 3,69 (1H, m), 3,90 (2H, m), 4,04 (2H, m), 4,21 (1H, m), 6,65 (1H, s), 7,18 (3H, m), 7,37 (1H, m)
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 350; HPLC tR = 2,71 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 55: 1-[4-[4-[1-(1,3-Dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea



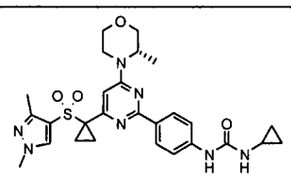
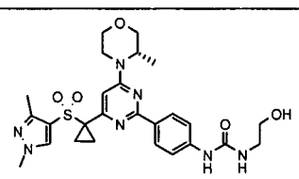
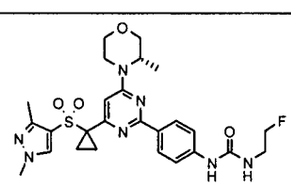
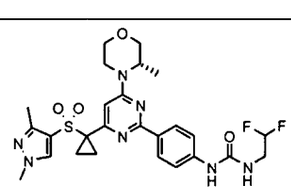
Se agregó metilamina (26,4 mg, 0,85 mmol) a fenil *N*-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (100 mg, 0,17 mmol) y trietilamina (0,2 mL, 0,72 mmol) en NMP (2 mL). La solución resultante se calentó a 50°C durante 2 días. El producto bruto se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes, para proporcionar el material deseado (77 mg).
Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,54 (2H, m), 1,74 (2H, m), 2,03 (3H, s), 2,67 (3H, m), 3,20 (1H, m), 3,48 (1H, m), 3,63 (1H, m), 3,77 (4H, m), 3,98 (1H, m), 4,13 (1H, m), 4,46 (1H, m), 6,06 (1H, m), 6,70 (1H, s), 7,45 (2H, d), 7,98 (2H,

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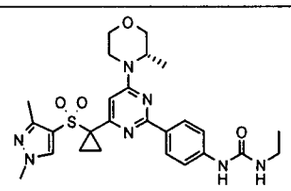
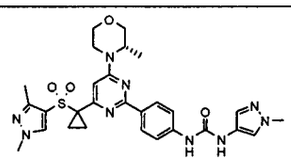
d), 8,18 (1H, s), 8,72 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 526; HPLC tR = 1,87 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
55a		3-ciclopropil-1-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	552	2,02
55b		1-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	556	1,71
55c		1-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	558	2,00
55d		3-(2,2-difluoroetil)-1-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	576	2,13

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Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
55e		3-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	540	2,00
55f		1-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	592	1,92

Ejemplo 55a: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 0,42 (2H, m), 0,65 (2H, m), 1,20 (3H, d), 1,54 (2H, m), 1,74 (2H, m), 2,03 (3H, s), 2,56 (1H, m), 3,18 (1H, m), 3,48 (1H, m), 3,63 (1H, m), 3,76 (4H, m), 3,98 (1H, m), 4,14 (1H, m), 4,45 (1H, m), 6,42 (1H, m), 6,70 (1H, s), 7,46 (2H, m), 7,99 (2H, m), 8,19 (1H, s), 8,53 (1H, s)

Ejemplo 55b: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,54 (2H, m), 1,73 (2H, m), 2,03 (3H, s), 3,18 (3H, m), 3,47 (3H, m), 3,63 (1H, m), 3,76 (4H, m), 3,98 (1H, m), 4,14 (1H, m), 4,46 (1H, m), 4,74 (1H, t), 6,25 (1H, m), 6,70 (1H, s), 7,44 (2H, d), 7,98 (2H, d), 8,19 (1H, s), 8,79 (1H, s)

Ejemplo 55c: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,54 (2H, m), 1,74 (2H, m), 2,03 (3H, s), 3,18 (2H, m), 3,39 (1H, m), 3,46 (2H, m), 3,63 (1H, m), 3,76 (4H, m), 3,98 (1H, m), 4,14 (1H, m), 4,49 (2H, m), 6,43 (1H, m), 6,70 (1H, s), 7,46 (2H, d), 7,99 (2H, d), 8,18 (1H, s), 8,80 (1H, s)

Ejemplo 55d: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,55 (2H, m), 1,74 (2H,

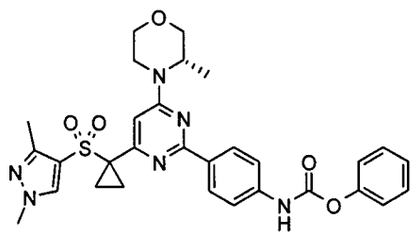
m), 2,02 (3H, s), 3,17 (1H, m), 3,54 (4H, m), 3,76 (4H, m), 3,97 (1H, m), 4,14 (1H, m), 4,47 (1H, m), 6,08 (1H, m), 6,52 (1H, m), 6,71 (1H, s), 7,46 (2H, m), 8,01 (2H, m), 8,19 (1H, s), 8,90 (1H, s)

Ejemplo 55e: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,20 (3H, d), 1,54 (2H, m), 1,74 (2H, m), 2,03 (3H, s), 3,15 (3H, m), 3,48 (1H, m), 3,63 (1H, m), 3,76 (4H, m), 3,98 (1H, m), 4,13 (1H, m), 4,46 (1H, m), 6,16 (1H, m), 6,70 (1H, s), 7,45 (2H, d), 7,98 (2H, d), 8,19 (1H, s), 8,65 (1H, s)

Ejemplo 55f: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,54 (2H, m), 1,74 (2H, m), 2,04 (3H, s), 3,18 (1H, m), 3,49 (1H, m), 3,63 (1H, m), 3,77 (7H, m), 3,98 (1H, m), 4,15 (1H, m), 4,47 (1H, m), 6,71 (1H, s), 7,39 (1H, s), 7,50 (2H, d), 7,77 (1H, s), 8,02 (2H, d), 8,19 (1H, s), 8,38 (1H, s), 8,82 (1H, s)

La preparación de fenil *N*-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



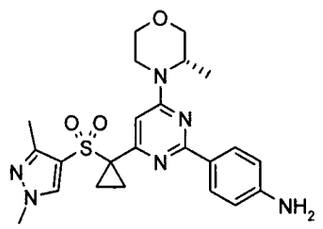
Se agregó gota a gota fenil cloroformiato (0,201 mL, 1,60 mmol) a 4-[4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (750mg, 1,60 mmol) y bicarbonato de sodio (148 mg, 1,76 mmol) en dioxano (30 mL). La suspensión resultante se agitó a TA durante 3 horas. La mezcla de reacción se filtró y el precipitado se disolvió nuevamente en DCM (50 mL) y se lavó secuencialmente con agua (50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como una goma naranja que formó una espuma sólida al calentarse en el desecador (1,030 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,55 (2H, m), 1,75

(2H, m), 2,04 (3H, s), 3,20 (1H, m), 3,49 (1H, m), 3,63 (1H, m), 3,76 (4H, m), 3,98 (1H, m), 4,16 (1H, m), 4,48 (1H, m), 6,75 (1H, s), 7,28 (3H, m), 7,45 (2H, m), 7,59 (2H, m), 8,07 (2H, m), 8,20 (1H, s), 10,43 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 589; HPLC tR = 2,63 min.

4-[4-[1-(1,3-Dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



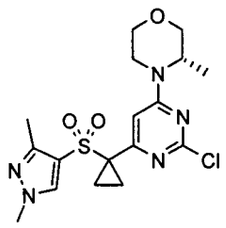
Una solución de 2-cloro-4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,44 g, 5,92 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,428 g, 6,52 mmol) y carbonato de sodio (2,51 g, 23,69 mmol) en DME (60 mL) y agua (15 mL) se agitó bajo nitrógeno durante 5 minutos. Se agregó diclorobis(trifenilfosfina)paladio(II) (0,416 g, 0,59 mmol) y la solución resultante se agitó a 80°C durante 5 horas. La mezcla de reacción se diluyó con DCM (200 mL) y se lavó secuencialmente con agua (200 mL) y salmuera saturada (200 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 1% MeOH en DCM, para proporcionar un producto bruto. El producto bruto se purificó adicionalmente mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco en metanol 2M, para proporcionar el material deseado as a orange solid (1,25 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,52 (2H, m), 1,72 (2H, m), 2,04 (3H, s), 3,15 (1H, m), 3,47 (1H, m), 3,61 (1H, m), 3,75 (4H, m), 3,97 (1H, m), 4,09 (1H, m), 4,42 (1H, m), 5,52 (2H, s), 6,57 (3H, m), 7,82 (2H, m), 8,17 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 469; HPLC tR = 1,87 min.

2-Cloro-4-[1-(1,3-dimetilpirazol-4-il)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

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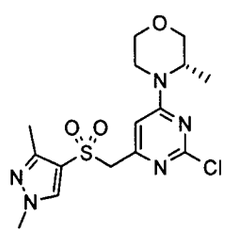


Se agregó hidróxido de sodio (14,54 g, 363,47 mmol) en agua (14,5 mL) a una solución agitada de 2-cloro-4-[(1,3-dimetilpirazol-4-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,55 g, 6,61 mmol), 1,2-dibromoetano (1,708 mL, 19,83 mmol) y bromuro de tetrabutilamonio (0,213 g, 0,66 mmol) en tolueno (100 mL). La solución resultante se agitó a 60°C durante 3 horas. La mezcla de reacción se diluyó con DCM (200 mL) y se lavó secuencialmente con agua (200 mL) y salmuera saturada (200 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 30% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (2,44 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,48 (2H, m), 1,70 (2H, m), 2,05 (3H, s), 3,17 (1H, m), 3,42 (1H, m), 3,57 (1H, m), 3,72 (1H, m), 3,80 (3H, s), 3,93 (2H, m), 4,30 (1H, m), 6,77 (1H, s), 8,20 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 412; HPLC tR = 1,69 min.

2-Cloro-4-[(1,3-dimetilpirazol-4-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



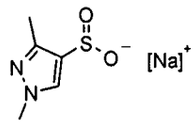
Se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (5 g, 14,14 mmol) a sodio 1,3-dimetil-1*H*-pirazol-4-sulfinato (4,79 g, 26,29 mmol) en DMF (80 mL). La solución resultante se agitó a TA durante 18 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (100 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (4,55 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,19 (3H, d), 2,13 (3H, s), 3,18 (1H, m), 3,44 (1H, m), 3,58 (1H, m), 3,73 (1H, m), 3,80 (3H, s), 3,94 (2H, m), 4,22 (1H, s), 4,46 (2H, s), 6,72 (1H, s), 8,14 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 386; HPLC tR = 1,63 min.

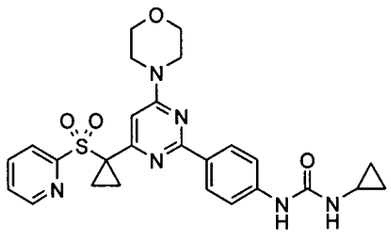
La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

1,3-dimetil-1*H*-pirazol-4-sulfinato de sodio



Una solución de sulfito de sodio (2,82 g, 22,35 mmol) en agua (30 mL) se agitó durante 10 minutos a TA. Se agregó bicarbonato de sodio (3,75 g, 44,70 mmol) y la solución se agitó durante 1 hora a 50°C. 1,3-Dimetil-1*H*-pirazol-4-sulfonilo cloruro (4,35 g, 22,35 mmol) se agregó en porciones y la solución resultante se agitó a 50°C durante 18 horas. La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar el material deseado como un sólido blanco, que se secó al aire durante toda la noche al vacío y se utilizó sin purificación adicional (4,79 g).

Ejemplo 56: 3-Ciclopropil-1-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea



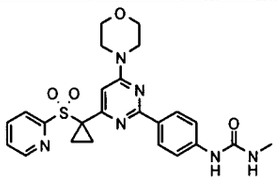
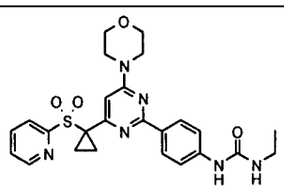
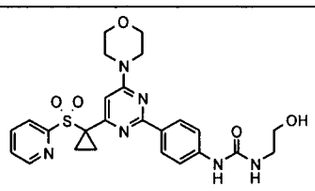
Una solución de fenil *N*-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato (0,100g, 0,18mmol), ciclopropilamina (0,90 mmol) y trietilamina (0,076 mL, 0,54 mmol) en NMP (2 mL) se calentó a 50°C durante 16 horas. El producto bruto se purificó mediante HPLC preparativa, utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes, para proporcionar el material deseado como

un sólido (75 mg).

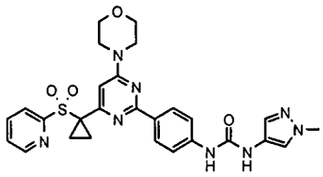
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40-0,44 (2H, m), 0,63-0,67 (2H, m), 1,71-1,74 (2H, q), 1,98-2,01 (2H, q), 2,54-2,58 (1H, m), 3,63-3,65 (4H, m), 3,68-3,70 (4H, m), 6,40-6,41 (1H, d), 6,71 (1H, s), 7,35-7,37 (2H, d), 7,68-7,70 (2H, d), 7,73-7,76 (1H, m), 7,96-7,99 (1H, dt), 8,06-8,10 (1H, td), 8,49 (1H, s), 8,82-8,83 (1H, m).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 521; HPLC tR = 1,99min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato utilizando la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
56a		3-metil-1-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	495	1,82
56b		3-etil-1-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	509	1,96
56c		3-(2-hidroxietil)-1-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	525	1,65

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Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
56d		3-(1-metilpirazol-4-il)-1-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	561	1,88

Ejemplo 56a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,70-1,74 (2H, q), 1,98-2,01 (2H, q), 2,65-2,66 (3H, d), 3,63-3,65 (4H, m), 3,68-3,70 (4H, m), 6,02-6,06 (1H, q), 6,71 (1H, s), 7,34-7,37 (2H, d), 7,67-7,70 (2H, d), 7,73-7,76 (1H, m), 7,96-7,98 (1H, dt), 8,06-8,10 (1H, td), 8,69 (1H, s), 8,82-8,84 (1H, m).

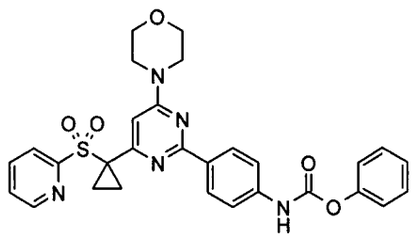
Ejemplo 56b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,05-1,08 (3H, t), 1,70-1,73 (2H, q), 1,98-2,01 (2H, q), 3,09-3,16 (2H, m), 3,63-3,64 (4H, m), 3,68-3,69 (4H, m), 6,12-6,15 (1H, t), 6,71 (1H, s), 7,33-7,36 (2H, d), 7,67-7,70 (2H, d), 7,73-7,76 (1H, m), 7,96-7,99 (1H, dt), 8,06-8,10 (1H, td), 8,61 (1H, s), 8,82-8,83 (1H, m).

Ejemplo 56c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,70-1,74 (2H, q), 1,98-2,01 (2H, q), 3,15-3,19 (2H, m), 3,44-3,48 (2H, m), 3,63-3,65 (4H, m), 3,68-3,69 (4H, m), 4,71-4,74 (1H, t), 6,23-6,24 (1H, t), 6,71 (1H, s), 7,33-7,35 (2H, d), 7,68-7,70 (2H, d), 7,73-7,76 (1H, m), 7,96-7,99 (1H, dt), 8,06-8,10 (1H, td), 8,76 (1H, s), 8,82-8,84 (1H, m).

Ejemplo 56d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,71-1,74 (2H, q), 1,99-2,02 (2H, q), 3,64-3,66 (4H, m), 3,68-3,71 (4H, m), 3,79 (3H, s), 6,73 (1H, s), 7,38-7,41(3H m), 7,71-7,76 (4H, m), 7,97-7,99 (1H, dt), 8,07-8,11 (1H, td), 8,36 (1H, s), 8,79 (1H, s), 8,83-8,84 (1H, m).

La preparación de fenil *N*-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato

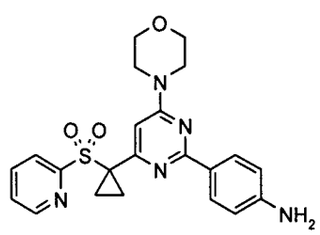


Se agregó fenil cloroformiato (0,363 mL, 2,89 mmol) a 4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]anilina (1,265 g, 2,89 mmol) e hidrogenocarbonato de sodio (0,364 g, 4,34 mmol) en DCM (50 mL) a TA y la suspensión resultante se agitó durante 2 horas. La mezcla se lavó con agua, se secó sobre $MgSO_4$, se filtró y se evaporó y la goma resultante se secó en el horno de vacío a 50°C durante toda la noche para proporcionar el material deseado as a colorles gum (1,86 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,73-1,77 (2H, q), 1,99-2,03 (2H, q), 3,68-3,69(8H, m), 6,77 (1H, s), 7,24-7,32 (3H, m), 7,44-7,52 (4H, m), 7,74-7,77 (1H, m), 7,80-7,82 (2H, d), 7,98-8,01 (1H, dt), 8,07-8,11 (1H, td), 8,83-8,85 (1H, dq), 10,4 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 558; HPLC tR = 2,75 min.

4-[4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]anilina



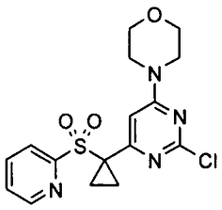
Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,131 g, 0,19 mmol) en una porción a 2-cloro-4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidina (1,42 g, 3,73 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,817 g, 3,73 mmol) y solución de carbonato de sodio acuoso 2M (9,32 mL, 18,64 mmol) en una solución de DMF (18% DMF, 82% de una mezcla 7:3:2 de DME:agua:etanol) a 22°C bajo nitrógeno. La solución resultante se agitó a 80°C durante 3 horas. El disolvente se retiró, acetato de etilo se agregó y los orgánicos se lavaron con agua. Se observó el precipitado en la capa acuosa y se aisló mediante filtración para proporcionar un producto bruto. Este material se disolvió en DCM y insoluble material se eliminó mediante filtración y se descartó. El filtrado se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol, para proporcionar material que se purificó adicionalmente mediante

cromatografía de sílice instantánea, gradiente de elución de 0 a 60% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (1,265 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,68-1,71 (2H, q), 1,96-2,00 (2H, q), 3,59-3,61 (4H, m), 3,66-3,69 (4H, m), 5,48-5,50 (1H, d (NH_2), 6,45-6,47 (2H, d), 6,61 (1H, s), 7,52-7,54 (2H, d), 7,72-7,75 (1H, m), 7,96-7,98 (1H, dt), 8,05-8,10 (1H, td), 8,81-8,83 (1H, dq).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 438; HPLC tR = 1,93 min.

2-Cloro-4-morfolin-4-il-6-(1-piridin-2-ilsulfonilciclopropil)pirimidina

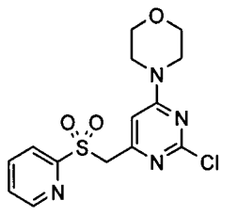


Se agregó hidróxido de sodio (solución 50% p/p) (12,71 g, 317,77 mmol) a 2-cloro-4-morfolin-4-il-6-(piridin-2-ilsulfonilmetil)pirimidina (2,050 g, 5,78 mmol), 1,2-dibromoetano (1,494 mL, 17,33 mmol) y bromuro de tetrabutilamonio (0,186 g, 0,58 mmol) en tolueno (50 mL) a TA. La suspensión resultante se agitó a 60°C durante toda la noche. Se agregó agua y las capas se separaron. La capa orgánica se lavó dos veces con agua, se secó sobre $MgSO_4$, se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (1,42 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,63-1,66 (2H, q), 1,91-1,95 (2H, q), 3,55 (4H, bs), 3,63-3,65 (4H, t), 6,84 (1H, s), 7,73-7,76 (1H, m), 7,98-8,00 (1H, dt), 8,10-8,14 (1H, td), 8,77-8,79 (1H, dt).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 381; HPLC tR = 1,71 min.

2-Cloro-4-morfolin-4-il-6-(piridin-2-ilsulfonilmetil)pirimidina

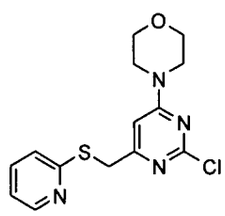


Se disolvió 2-cloro-4-morfolin-4-il-6-(piridin-2-ilsulfanilmetil)pirimidina (4,96 g, 15,36 mmol) en dioxano (70 mL) y se agregó ácido sulfúrico 2N (0,362 mL). La solución se calentó hasta alcanzar 55°C. Se disolvió tungstato de sodio dihidrato (0,101 g, 0,31 mmol) en agua (3,54 mL) se agregó a la solución y se dejó agitar durante 10 minutos. Luego se agregó peróxido de hidrógeno (9,50 mL, 307,30 mmol) gota a gota durante varios minutos. La solución se calentó a 55°C durante 4 horas. Se agregó agua (300mL) y la reacción se dejó enfriar. La mezcla de reacción se extrajo con DCM, la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto deseado como un sólido amarillo claro (5,09g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 3,64 (3H, bs), 3,75-3,77(5H, t), 4,56 (2H, s), 6,60 (1H, s), 7,57-7,61 (1H, m), 7,97-7,97 (2H, m), 8,78-8,80 (1H, dt).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 355; HPLC tR = 1,51 min.

2-Cloro-4-morfolin-4-il-6-(piridin-2-ilsulfanilmetil)pirimidina



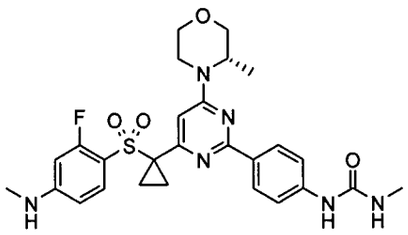
Se agregó 2-cloro-4-(yodometil)-6-morfolin-4-ilpirimidina (6,60 g, 19,44 mmol) a 2-mercaptopiridina (3,24 g, 29,16 mmol) y DIPEA (5,08 mL, 29,16 mmol) en acetonitrilo (140 mL) a TA. La solución resultante se agitó a TA durante 2 horas y luego se evaporó hasta secarse, se disolvió nuevamente en DCM y se lavó secuencialmente con agua y salmuera saturada. La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 30% acetato de etilo en DCM, para proporcionar el material deseado as a beige aceite que solidificó en reposo (4,96 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 3,52 (4H, bs), 3,64-3,67 (4H, t), 4,27 (2H, s), 6,58 (1H, s), 6,93-6,96 (1H, q), 7,11-7,13 (1H, dd), 7,41-7,45 (1H, td), 8,34-8,36 (1H, dt).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 323; HPLC tR = 1,98 min.

La preparación de 2-cloro-4-(yodometil)-6-morfolin-4-ilpirimidina se describió anteriormente.

Ejemplo 57: 1-[4-[4-[1-(2-Fluoro-4-metilaminofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea

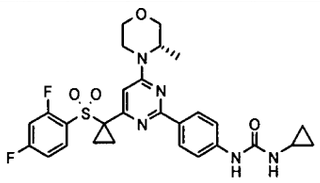
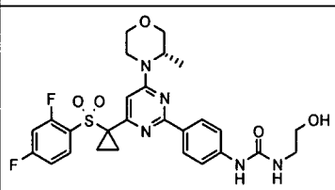
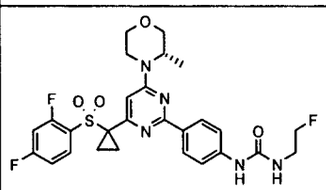
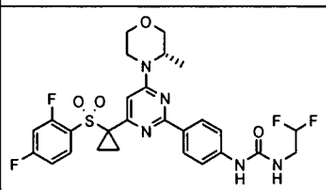
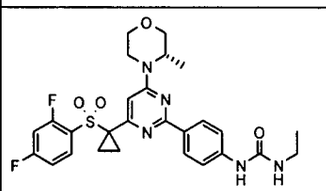
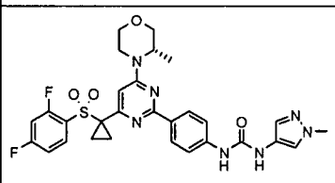


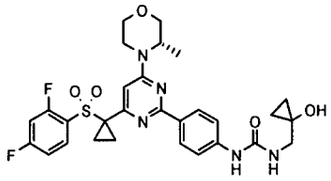
Se agregaron fenil *N*-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,15 g, 0,25 mmol), trietilamina (0,103 mL, 0,74 mmol) y solución de metilamina (2M en THF, 1,236 mL, 2,47 mmol) a dioxano (10 mL) y se calentó a 50°C durante el fin de semana. La reacción se evaporó hasta secarse y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (0,074 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,51 - 1,48 (2H, m), 1,82 - 1,78 (2H, m), 2,66 (3H, d), 3,14 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,06 (1H, d), 4,43 (1H, s), 6,04 (1H, q), 6,33 - 6,32 (1H, m), 6,38 (1H, dd), 6,43 (1H, ddd), 6,54 (1H, s), 7,47 (3H, m), 7,95 (2H, d), 8,72 (1H, s);

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 555; HPLC tR = 2,40 min.

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
57a		3-ciclopropil-1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	570	2,51
57b		1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	573	1,96
57c		1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	576	2,47
57d		3-(2,2-difluoroetil)-1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	595	2,60
57e		3-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	558	2,48
57f		1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	610	2,35

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
57g		1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-hidroxiciclopropil)metil]urea	600	2,31

Ejemplo 57a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,43 - 0,40 (2H, m), 0,67 - 0,62 (2H, m), 1,19 (3H, d), 1,67 - 1,64 (2H, m), 1,91 - 1,89 (2H, m), 2,57 - 2,54 (1H, m), 3,16 (1H, ddd), 3,46 (1H, ddd), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,16 (1H, d), 4,46 (1H, s), 6,39 (1H, s), 6,69 (1H, s), 7,20 (1H, ddd), 7,38 (2H, d), 7,65 - 7,59 (1H, m), 7,77 - 7,72 (3H, m), 8,51 (1H, s).

Ejemplo 57b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,67 - 1,63 (2H, m), 1,91 - 1,87 (2H, m), 3,17 (3H, m), 3,48 - 3,42 (3H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, d), 4,15 (1H, d), 4,46 (1H, s), 4,72 (1H, t), 6,22 (1H, t), 6,68 (1H, s), 7,20 (1H, ddd), 7,36 (2H, d), 7,65 - 7,60 (1H, m), 7,77 - 7,72 (3H, m), 8,78 (1H, s).

Ejemplo 57c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,67 - 1,64 (2H, m), 1,91 - 1,89 (2H, m), 3,16 (1H, ddd), 3,38 (1H, q), 3,49 - 3,43 (2H, m), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,16 (1H, d), 4,41 (1H, t), 4,47 (1H, s), 4,53 (1H, t), 6,40 (1H, t), 6,69 (1H, s), 7,20 (1H, ddd), 7,38 (2H, d), 7,65 - 7,60 (1H, m), 7,77 - 7,71 (3H, m), 8,79 (1H, s).

Ejemplo 57d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,67 - 1,64 (2H, m), 1,92 - 1,87 (2H, m), 3,16 (1H, ddd), 3,63 - 3,43 (4H, m), 3,74 (1H, d), 3,95 (1H, dd), 4,16 (1H, d), 4,47 (1H, s), 6,07 (1H, ddt), 6,49 (1H, t), 6,69 (1H, s), 7,20 (1H, t), 7,39 (1H, d), 7,65 - 7,60 (1H, m), 7,76 - 7,71 (4H, m), 8,90 (1H, s).

Ejemplo 57e: No se registró el espectro.

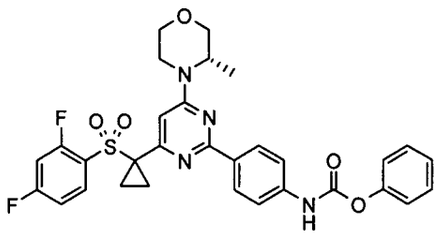
Ejemplo 57f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,67 - 1,64 (2H, m), 1,92 - 1,90 (2H, m), 3,16 (1H, ddd), 3,46 (1H, ddd), 3,61 (1H, dd), 3,75 (1H, d), 3,79 (3H, s), 3,96 (1H, d), 4,16 (1H, d), 4,48 (1H, s), 6,70 (1H, s), 7,20 (1H, ddd), 7,38 (1H, s), 7,42 (2H, d), 7,66 - 7,61 (1H, m), 7,78 - 7,71 (4H, m), 8,34 (1H, s), 8,82 (1H, s).

Ejemplo 57g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,51 - 0,48 (2H, m), 0,60 - 0,57 (2H,

m), 1,19 (3H, d), 1,67 - 1,62 (2H, m), 1,91 - 1,87 (2H, m), 3,22 (2H, d), 3,29 - 3,27 (1H, m), 3,46 (1H, ddd), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,17 - 4,14 (1H, m), 4,47 (1H, s), 6,29 (1H, t), 6,68 (1H, s), 7,20 (1H, t), 7,36 (2H, d), 7,63 (1H, t), 7,73 (3H, d), 8,78 (1H, s).

La preparación de fenil *N*-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

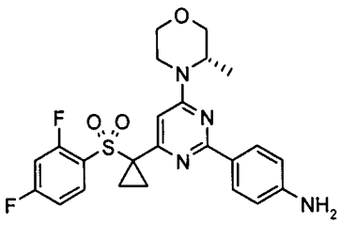


Se agregaron 4-[4-[1-(2,4-Difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (2,1 g, 4,32 mmol) y bicarbonato de sodio (0,725 g, 8,63 mmol) a dioxano (50 mL) y se agitó durante 10 minutos. Se agregó lentamente fenil cloroformiato (0,704 mL, 5,61 mmol) y la reacción se agitó durante 1 hora. La mezcla de reacción se aplacó con ácido cítrico 1,0 N (50 mL), se extrajo con acetato de etilo (3 x 75 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido naranja. Esto se disolvió en DCM, el disolvente lentamente se eliminó hasta que no se observó ningún sólido. Luego se agregó éter dietílico a la solución agitando rápidamente para proporcionar el material deseado como un sólido blanco (1,65 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,69 - 1,66 (2H, m), 1,92 - 1,89 (2H, m), 3,18 (1H, ddd), 3,46 (1H, ddd), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,36 - 4,10 (1H, m), 4,55 - 4,44 (1H, m), 6,75 (1H, s), 7,30 - 7,18 (4H, m), 7,47 - 7,43 (2H, m), 7,54 (2H, d), 7,64 (1H, t), 7,78 - 7,72 (1H, m), 7,85 (2H, d), 10,43 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 607; HPLC tR = 2,97 min

4-[4-[1-(2,4-Difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

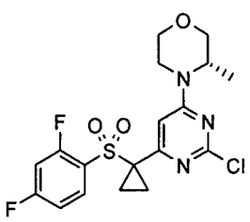


Se agregaron 2-cloro-4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,61 g, 8,40 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (2,208 g, 10,08 mmol), carbonato de sodio (4,45 g, 41,99 mmol) y 1,1'-bis(difenilfosfino)ferrocenodicloropaladio(II) (0,608 g, 0,84 mmol) a DME (60,0 mL) y agua (15 mL) y se calentaron hasta alcanzar 90°C durante un período de 2 horas bajo nitrógeno. El disolvente se evaporó y el residuo se aplacó agua (100 mL), se extrajo con acetato de etilo (3 x 75 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma negra. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 40 a 100% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (2,2 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,29 (3H, d), 1,58 - 1,55 (1H, m), 1,66 - 1,62 (1H, m), 2,11 - 2,04 (2H, m), 3,26 (1H, ddd), 3,57 (1H, ddd), 3,72 (1H, dd), 3,80 (1H, d), 3,86 (2H, s), 4,02 (1H, dd), 4,11 (1H, m), 4,43 - 4,36 (1H, m), 6,60 (2H, d), 6,65 (1H, s), 6,86 - 6,82 (1H, m), 6,91 (1H, ddd), 7,75 - 7,69 (1H, m), 7,85 (2H, d).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 487; HPLC tR = 2,56 min.

2-Cloro-4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



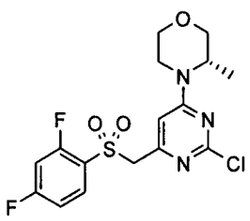
Se agregó hidróxido de sodio (solución 50% p/p) (32,7 g, 817,17 mmol) a 2-cloro-4-[(2,4-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (6,0 g, 14,86 mmol), 1,2-dibromoetano (3,84 mL, 44,57 mmol) y bromuro de tetrabutilamonio (0,479 g, 1,49 mmol) en tolueno (75 mL) a TA. La suspensión resultante se agitó a 60°C durante toda la noche. Se agregó agua (100 mL) y la mezcla se extrajo con acetato de etilo (3 x 100 mL), se secó sobre $MgSO_4$, se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice

instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar un material bruto que se disolvió en éter dietílico caliente y luego se agitó durante 2 horas para proporcionar el material deseado como un sólido blanco (3,61 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,30 (3H, d), 1,56 - 1,52 (1H, m), 1,62 - 1,59 (1H, m), 2,10-2,00 (2H, m), 3,26 (1H, ddd), 3,53 (1H, ddd), 3,68 (1H, dd), 3,78 (1H, d), 4,00 (2H, dd), 4,26 (1H, s), 6,81 (1H, s), 6,99 - 6,90 (2H, m), 7,77 - 7,71 (1H, m).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 430; HPLC tR = 2,48 min

2-Cloro-4-[(2,4-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



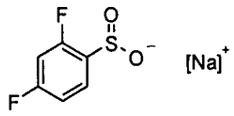
Se disolvió ácido 2,4-difluorobencenosulfínico, sal de sodio (3,98 g, 19,80 mmol) y 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (7 g, 19,80 mmol) en DMF (50 mL) y se agitó durante 1 hora a TA. El disolvente se evaporó para proporcionar una goma marrón, esto se aplacó con solución de cloruro de amonio saturado acuoso (50 mL), se extrajo con éter dietílico (3 x 75 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido marrón. El material bruto se hizo pasar a través de un lecho de sílice, eluyendo con 80% acetato de etilo en isohexano, para proporcionar el material bruto que se trituró con éter dietílico para proporcionar el material deseado como un sólido blanco (7,04 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, $CDCl_3$) δ 1,32 (3H, d), 3,28 (1H, ddd), 3,54 (1H, ddd), 3,69 (1H, dd), 3,79 (1H, d), 4,03 - 3,99 (2H, m), 4,28 (1H, s), 4,43 (2H, s), 6,55 (1H, s), 7,03 - 6,98 (2H, m), 7,78 - 7,72 (1H, m).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 404; HPLC tR = 2,30 min;

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

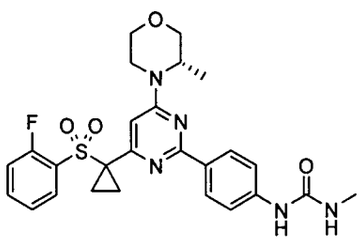
Ácido 2,4-difluorobencenosulfínico, sal de sodio



Una solución de sulfito de sodio (29,6 g, 235,18 mmol) en agua (200 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (39,5 g, 470,36 mmol) a la solución agitada. La solución resultante se agitó a 50°C durante 10 minutos. Se agregó cloruro 2,4-difluorobenceno-1-sulfonilo (50 g, 235,18 mmol) en porciones a la solución y se agitó a 50°C durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en metanol (200 mL). La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar un sólido blanco, esto se agitó con acetonitrilo (50 mL) y luego se filtró para proporcionar el material deseado como un sólido blanco (41,6 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 7,10 - 7,04 (2H, m), 7,74 - 7,68 (1H, m);

Ejemplo 58: 1-[4-[4-[1-(2-Fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea



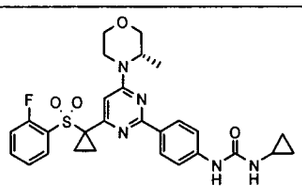
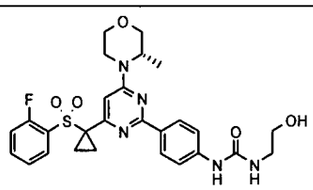
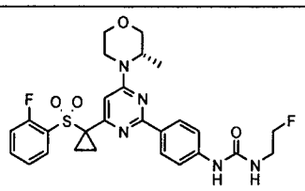
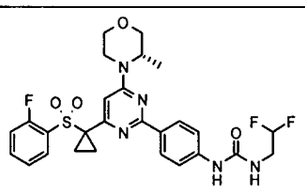
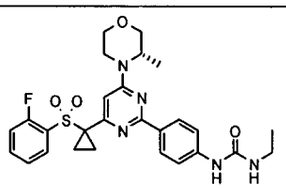
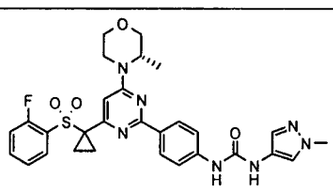
Se agregaron fenil *N*-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,2 g, 0,34 mmol) y solución de metilamina (2M en THF, 1,699 mL, 3,40 mmol) a dioxano (10 mL) y se agitaron durante toda la noche. La reacción se evaporó hasta secarse y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (0,119 g).

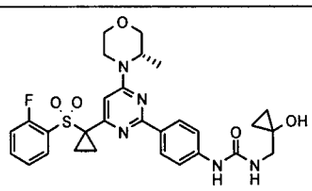
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,71 - 1,65 (2H, m), 1,94 - 1,89 (2H, m), 2,66 (3H, d), 3,14 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,12 (1H, d), 4,42 (1H, s), 6,04 (1H, q), 6,66 (1H, s), 7,37 - 7,31 (3H, m), 7,52 - 7,48 (1H, m), 7,78 - 7,70 (4H, m), 8,69 (1H, s);

m/z (ESI+) $(M+H)^+$ = 526; HPLC tR = 2,34 min;

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(2-

fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
58a		3-ciclopropil-1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	552	2,45
58b		1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	556	2,09
58c		3-(2-fluoroetil)-1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	558	2,41
58d		3-(2,2-difluoroetil)-1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	576	2,53
58e		1-etil-3-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	540	2,41
58f		1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	591	2,31

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
58g		1-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-hidroxiciclopropil)metil]urea	582	2,26

Ejemplo 58a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,43 - 0,40 (2H, m), 0,67 - 0,62 (2H, m), 1,17 (3H, d), 1,71 - 1,65 (2H, m), 1,95 - 1,87 (2H, m), 2,58 - 2,51 (1H, m), 3,14 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,12 (1H, d), 4,43 (1H, s), 6,40 (1H, d), 6,66 (1H, s), 7,37 - 7,31 (3H, m), 7,52 - 7,48 (1H, m), 7,79 - 7,70 (4H, m), 8,48 (1H, s);

Ejemplo 58b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,71 - 1,65 (2H, m), 1,93 - 1,89 (2H, m), 3,19 - 3,10 (3H, m), 3,48 - 3,42 (3H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,12 (1H, d), 4,43 (1H, s), 4,72 (1H, t), 6,23 (1H, t), 6,66 (1H, s), 7,35 - 7,31 (3H, m), 7,52 - 7,48 (1H, m), 7,78 - 7,70 (4H, m), 8,75 (1H, s);

Ejemplo 58c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,71 - 1,65 (2H, m), 1,94 - 1,88 (2H, m), 3,14 (1H, ddd), 3,48 - 3,36 (3H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,12 (1H, d), 4,46 - 4,40 (2H, m), 4,53 (1H, t), 6,41 (1H, t), 6,66 (1H, s), 7,37 - 7,31 (3H, m), 7,52 - 7,48 (1H, m), 7,78 - 7,69 (4H, m), 8,76 (1H, s);

Ejemplo 58d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,71 - 1,67 (2H, m), 1,94 - 1,89 (2H, m), 3,14 (1H, ddd), 3,55 - 3,42 (3H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,13 (1H, d), 4,42 (1H, s), 6,07 (1H, ddt), 6,51 (1H, t), 6,67 (1H, s), 7,38 - 7,31 (3H, m), 7,52 - 7,48 (1H, m), 7,78 - 7,70 (4H, m), 8,87 (1H, s);

Ejemplo 58e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06 (3H, t), 1,17 (3H, d), 1,71 - 1,65 (2H, m), 1,94 - 1,88 (2H, m), 3,17 - 3,09 (3H, m), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, ddd), 4,12 (1H, d), 4,42 (1H, s), 6,13 (1H, t), 6,66 (1H, s), 7,36 - 7,31 (3H, m), 7,52 - 7,48 (1H, m), 7,78 - 7,71 (4H, m), 8,60 (1H, s);

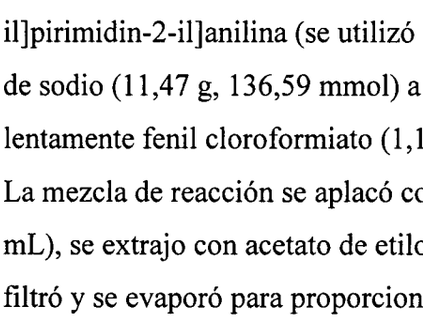
Ejemplo 58f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,72 - 1,65 (2H, m), 1,94 - 1,89 (2H, m), 3,15 (1H, ddd), 3,46 (1H, ddd), 3,61 (1H, dd), 3,74 (1H, d), 3,79 (3H, s), 3,95

(1H, dd), 4,13 (1H, d), 4,43 (1H, s), 6,67 (1H, s), 7,34 (1H, t), 7,41 - 7,38 (3H, m), 7,53 - 7,49 (1H, m), 7,79 - 7,70 (5H, m), 8,35 (1H, s), 8,78 (1H, s).

Ejemplo 58g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,51 - 0,48 (2H, m), 0,59 - 0,57 (2H, m), 1,17 (3H, d), 1,71 - 1,65 (2H, m), 1,94 - 1,90 (2H, m), 3,14 (1H, ddd), 3,22 (2H, d), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,12 (1H, d), 4,42 (1H, s), 5,36 (1H, s), 6,29 (1H, t), 6,66 (1H, s), 7,35 - 7,31 (3H, m), 7,52 - 7,48 (1H, m), 7,78 - 7,70 (4H, m), 8,76 (1H, s).

La preparación de fenil *N*-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

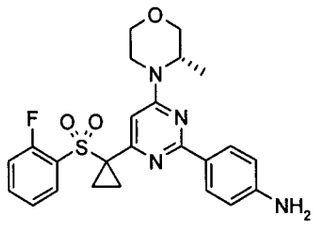


Se agregaron 4-[4-[1-(2-Fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (se utilizó como la sal clorhidrato) (3,2 g, 6,83 mmol) y bicarbonato de sodio (11,47 g, 136,59 mmol) a DCM (75 mL) y se agitaron durante 10 minutos. Se agregó lentamente fenil cloroformiato (1,114 mL, 8,88 mmol) y la reacción se agitó durante 1 hora. La mezcla de reacción se aplacó con una solución saturada acuosa de cloruro de amonio (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido naranja. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como una espuma amarilla (3,5 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,72 - 1,66 (2H, m), 1,97 - 1,88 (2H, m), 3,15 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,14 (1H, d), 4,44 (1H, s), 6,70 (1H, s), 7,35 - 7,23 (4H, m), 7,53 - 7,42 (5H, m), 7,77 - 7,71 (2H, m), 7,83 (2H, d), 10,37 (1H, s).

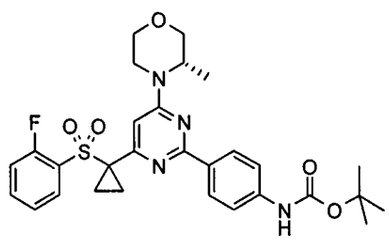
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 589; HPLC tR = 3,04 min;

4-[4-[1-(2-Fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



Se agregó *terc*-butil *N*-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (3,6 g, 6,33 mmol) a cloruro de hidrógeno 6N en propan-2-ol (60 mL) y se agitó a TA durante 5 horas. El disolvente se retiró hasta proporcionar 80% del volumen inicial luego se agregó éter dietílico rápidamente para proporcionar el material deseado (como una sal clorhidrato) como un sólido amarillo (3,20 g). Esto se utilizó en la siguiente etapa sin purificación adicional.

terc-butil *N*-[4-[4-[1-(2-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

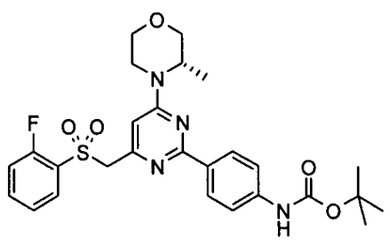


terc-butil *N*-[4-[4-[(2-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (5,75 g, 10,60 mmol) se agregó a hidruro de sodio (1,526 g, 31,79 mmol) y 1,2-dibromoetano (1,826 mL, 21,19 mmol) en DMF (30 mL) a TA. La suspensión resultante se agitó a 45°C durante 1 hora. Se agregaron más hidruro de sodio (1,526 g, 31,79 mmol) y 1,2-dibromoetano (1,826 mL, 21,19 mmol) y la reacción se agitó a 45°C durante toda la noche. La mezcla de reacción se aplacó con agua (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma marrón. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como una espuma amarilla(3,60 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,49 (9H, s), 1,71 - 1,65 (2H, m), 1,94 - 1,90 (2H, m), 3,14 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, ddd), 4,13 (1H, d), 4,42 (1H, s), 6,68 (1H, s), 7,33 (1H, t), 7,42 (2H, d), 7,53 - 7,48 (1H, m), 7,78 - 7,70 (4H, m), 9,48 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 569; HPLC tR = 3,13 min;

terc-butil *N*-[4-[4-[(2-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

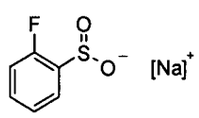


Se agregaron [6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-[(2-metilpropan-2-il)oxicarbonilamino]fenil]pirimidin-4-il]metil metanosulfonato (4,74 g, 9,90 mmol) y yoduro de litio(3,98 g, 29,71 mmol) a dioxano (70 mL) y se calentaron a 97°C durante 30 minutos. A esto se agregó 2-fluorobencenosulfinato de sodio (2,71 g, 14,86 mmol) y DMF (5 mL), la reacción se agitó a 97°C durante toda la noche. La mezcla de reacción se aplacó con agua (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma naranja. Se agregó éter dietílico (100 mL) con agitación vigorosa para proporcionar el material deseado como un sólido blanco (4,0 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,49 (9H, s), 3,17 (1H, ddd), 3,48 (1H, ddd), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,12 (1H, d), 4,39 (1H, s), 4,76 (2H, s), 6,75 (1H, s), 7,34 (1H, t), 7,41 (2H, d), 7,65 - 7,57 (2H, m), 7,71 (2H, d), 7,83 - 7,77 (1H, m), 9,48 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 543; HPLC tR = 2,92 min;

2-Fluorobencenosulfinato de sodio

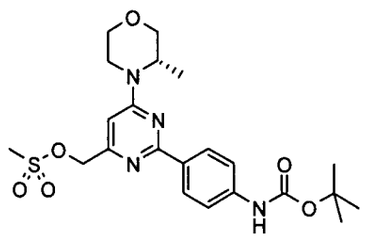


Una solución de sulfito de sodio (32,4 g, 256,92 mmol) en agua (200 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (43,2 g, 513,85 mmol) a la solución agitada. La solución resultante se agitó a 50°C durante 10 minutos. Se agregó en porciones cloruro 2-fluorobenceno-1-sulfonilo (50 g, 256,92 mmol) a la solución y se agitó a 50°C durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en metanol (200 mL). La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar un sólido blanco, esto se agitó con acetonitrilo

(50 mL) y luego se filtró para proporcionar el material deseado como un sólido blanco (41,0 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 6,99 (1H, t), 7,16 (1H, t), 7,28 - 7,22 (1H, m), 7,61 (1H, t).

[6-[(3*S*)-3-Metilmorfolin-4-il]-2-[4-[(2-metilpropan-2-il)oxicarbonilamino]fenil]pirimidin-4-il]metil metanosulfonato

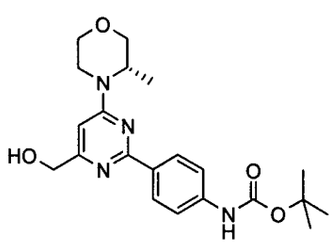


Se agregaron *terc*-butil *N*-[4-[4-(hidroximetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (23 g, 57,43 mmol) y DIPEA (12,04 mL, 68,92 mmol) a DCM (80 mL), a esto se agregó lentamente cloruro de metanosulfonilo (4,48 mL, 57,43 mmol) y la reacción se agitó durante 30 minutos. La mezcla de reacción se aplacó con una solución saturada acuosa de cloruro de amonio (100 mL), se extrajo con DCM (2 x 100 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como una goma marrón (27,0 g). Esto se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,50 (9H, s), 3,22 (1H, ddd), 3,34 (3H, s), 3,50 (1H, ddd), 3,65 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,19 (1H, d), 4,53 (1H, s), 5,19 (2H, s), 6,71 (1H, s), 7,56 (2H, d), 8,23 (2H, d), 9,55 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 479; HPLC tR = 2,74 min;

terc-butil *N*-[4-[4-(hidroximetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



Se agregaron [2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metanol (18,00 g, 73,86 mmol), *terc*-butil 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenilcarbamato (23,58 g, 73,86 mmol), carbonato de sodio (39,1 g, 369,32 mmol) y 1,1'-

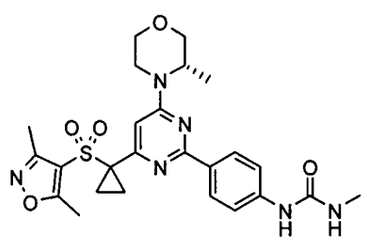
bis(difenilfosfino)ferrocenodicloropaladio(II) (5,35 g, 7,39 mmol) a DME (300 mL) y agua (75 mL) y se calentaron hasta alcanzar 90°C durante toda la noche bajo nitrógeno. El disolvente se evaporó y el residuo se aplacó con agua (100 mL), se extrajo con acetato de etilo (3 x 100 mL), la capa acuosa se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma marrón. El residuo se filtró a través de un lecho de sílice eluyendo con acetato de etilo para proporcionar una goma naranja clara. Esto se trituró con éter dietílico para proporcionar el material deseado como un sólido blanco (24,4 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,49 (9H, s), 3,19 (1H, ddd), 3,49 (1H, ddd), 3,64 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 (1H, d), 4,50 - 4,46 (3H, m), 5,39 (1H, s), 6,67 (1H, s), 7,54 (2H, d), 8,22 (2H, d), 9,50 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 401; HPLC tR = 2,30 min;

La preparación de [2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metanol se describió anteriormente.

Ejemplo 59: 1-[4-[4-[1-[(3,5-Dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea

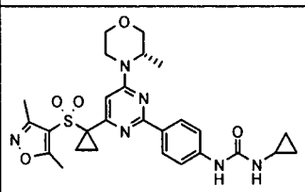
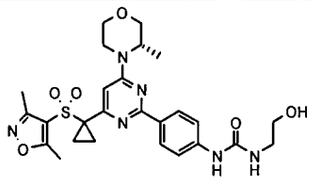
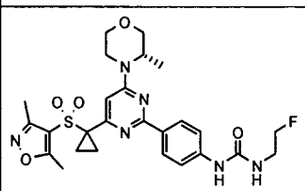
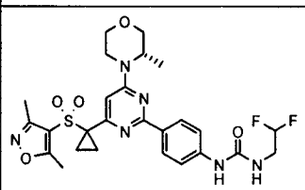
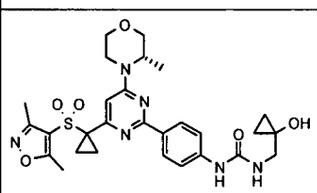


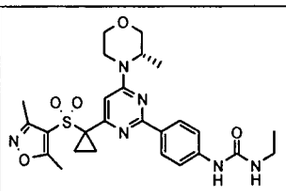
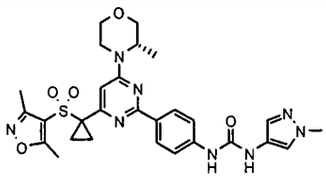
Se agregaron fenil *N*-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,15 g, 0,25 mmol) y metilamina (2M en THF, 1,272 mL, 2,54 mmol) a dioxano (10 mL) y se agitaron durante toda la noche a 50°C. La reacción se evaporó hasta secarse y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (0,098 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,59 - 1,52 (2H, m), 1,80 - 1,77 (2H, m), 2,11 (3H, s), 2,33 (3H, s), 2,66 (3H, d), 3,18 (1H, ddd), 3,47 (1H, ddd), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 (1H, d), 4,52 (1H, s), 6,07 (1H, q), 6,75 (1H, s), 7,45 (2H, d), 7,96 (2H, d), 8,72 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 527; HPLC tR = 2,18 min

Las siguientes muestras se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
59a		3-ciclopropil-1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	553	2,31
59b		1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	557	2,00
59c		1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	559	2,33
59d		3-(2,2-difluoroetil)-1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	577	2,44
59e		1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-hidroxiciclopropil)metil]urea	583	2,16

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
59f		3-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	541	2,34
59g		1-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	593	2,21

Ejemplo 59a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,44 - 0,40 (2H, m), 0,67 - 0,63 (2H, m), 1,21 (3H, d), 1,59 - 1,52 (2H, m), 1,80 - 1,77 (2H, m), 2,11 (3H, s), 2,32 (3H, s), 2,59 - 2,54 (1H, m), 3,18 (1H, ddd), 3,47 (1H, ddd), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 (1H, d), 4,52 (1H, s), 6,44 (1H, d), 6,76 (1H, s), 7,45 (2H, d), 7,96 (2H, d), 8,52 (1H, s).

Ejemplo 59b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,59 - 1,52 (2H, m), 1,80 - 1,75 (2H, m), 2,11 (3H, s), 2,32 (3H, s), 3,22 - 3,14 (3H, m), 3,51 - 3,45 (3H, m), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 (1H, d), 4,52 (1H, s), 4,73 (1H, t), 6,26 (1H, t), 6,75 (1H, s), 7,43 (2H, d), 7,96 (2H, d), 8,79 (1H, s).

Ejemplo 59c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,59 - 1,53 (2H, m), 1,80 - 1,75 (2H, m), 2,11 (3H, s), 2,33 (3H, s), 3,22 - 3,14 (1H, m), 3,39 (1H, q), 3,51 - 3,44 (1H, m), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 (1H, d), 4,42 (1H, t), 4,55 - 4,49 (2H, m), 5,75 (1H, s), 6,44 (1H, t), 6,76 (1H, s), 7,45 (2H, d), 7,97 (2H, d), 8,79 (1H, s);

Ejemplo 59d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,60 - 1,52 (2H, m), 1,81 - 1,75 (2H, m), 2,11 (3H, s), 2,33 (3H, s), 3,18 (1H, ddd), 3,64 - 3,44 (4H, m), 3,76 (1H, d), 3,97 (1H, dd), 4,18 (1H, d), 4,52 (1H, s), 6,07 (1H, ddt), 6,54 (1H, t), 6,77 (1H, s), 7,46 (2H, d), 7,98 (2H, d), 8,91 (1H, s).

Ejemplo 59e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,53 - 0,49 (2H, m), 0,60 - 0,56 (2H, m), 1,20 (3H, d), 1,59 - 1,52 (2H, m), 1,80 - 1,77 (2H, m), 2,11 (3H, s), 2,32 (3H, s), 3,18 - 3,14 (1H, m), 3,22 (2H, d), 3,47 (1H, ddd), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17

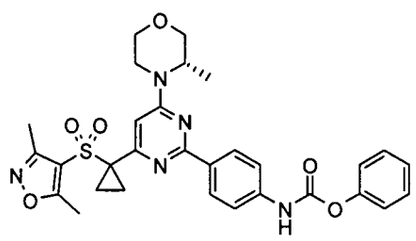
(1H, d), 4,52 (1H, s), 5,37 (1H, s), 6,33 (1H, t), 6,76 (1H, s), 7,43 (2H, d), 7,96 (2H, d), 8,80 (1H, s);

Ejemplo 59f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,21 (3H, d), 1,59 - 1,52 (2H, m), 1,80 - 1,77 (2H, m), 2,11 (3H, s), 2,32 (3H, s), 3,22 - 3,09 (3H, m), 3,47 (1H, ddd), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,17 (1H, d), 4,53 (1H, s), 6,17 (1H, t), 6,75 (1H, s), 7,44 (2H, d), 7,95 (2H, d), 8,64 (1H, s);

Ejemplo 59g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,59 - 1,53 (2H, m), 1,81 - 1,78 (2H, m), 2,12 (3H, s), 2,33 (3H, s), 3,23 - 3,15 (1H, m), 3,48 (1H, ddd), 3,63 (1H, dd), 3,76 (1H, d), 3,79 (3H, s), 3,97 (1H, dd), 4,18 (1H, d), 4,53 (1H, s), 6,77 (1H, s), 7,39 (1H, s), 7,49 (2H, d), 7,77 (1H, s), 7,99 (2H, d), 8,40 (1H, s), 8,82 (1H, s).

La preparación de fenil *N*-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

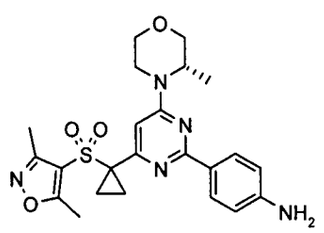


Se agregaron 4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (como la sal clorhidrato) (1,94 g, 3,83 mmol) y bicarbonato de sodio (1,610 g, 19,17 mmol) a DCM (60 mL) y se agitaron durante 10 minutos. Se agregó fenil cloroformiato (0,625 mL, 4,98 mmol) lentamente y la reacción se agitó durante 1 hora. La mezcla de reacción se aplacó con una solución saturada acuosa de cloruro de amonio (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido naranja. Se agregaron DCM y luego éter dietílico y el disolvente lentamente se eliminó hasta que se obtuvo un sólido. El sólido se recogió mediante filtración y se secó al vacío para proporcionar el material deseado como un sólido blanco (1,89 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,60 - 1,52 (2H, m), 1,81 - 1,78 (2H, m), 2,11 (3H, s), 2,33 (3H, s), 3,19 (1H, ddd), 3,48 (1H, ddd), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,19 (1H, d), 4,54 (1H, s), 6,80 (1H, s), 7,30 - 7,24 (3H, m), 7,45 (2H, t), 7,57 (2H, d), 8,04 (2H, d), 10,42 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 590; HPLC tR = 2,86 min

4-[4-[1-[(3,5-Dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

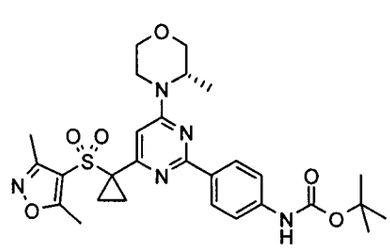


Se agregaron *terc*-butil *N*-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (2,6 g, 4,56 mmol) a cloruro de hidrógeno 6N en propan-2-ol (40 mL) y se agitaron durante 2 horas a TA. La solución bruta se trituró con éter dietílico para proporcionar el material deseado (como la sal clorhidrato) como un sólido amarillo (1,96 g). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,69 - 1,58 (2H, m), 1,84 - 1,82 (2H, m), 2,09 (3H, s), 2,38 (3H, s), 3,30 - 3,24 (1H, m), 3,50 - 3,45 (1H, m), 3,62 (1H, dd), 3,81 - 3,75 (1H, m), 3,99 (1H, dd), 4,28 (1H, s), 4,60 (1H, s), 6,93 (1H, s), 7,23 - 7,13 (2H, m), 8,05 (2H, d).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 470; HPLC tR = 1,88 min

terc-butil *N*-[4-[4-[1-[(3,5-dimetil-1,2-oxazol-4-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



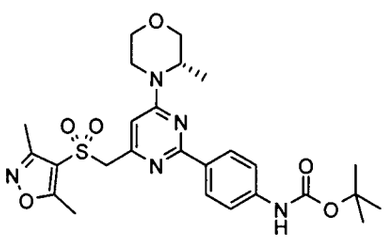
Se agregaron hidruro de sodio (2,177 g, 45,36 mmol) y 1,2-dibromoetano (2,61 mL, 30,24 mmol) en DMF (70 mL) rápidamente a una solución de *terc*-butil *N*-[4-[4-[(3,5-dimetil-1,2-oxazol-4-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (4,11 g, 7,56 mmol) en DMF (70 mL) a TA. La suspensión resultante se agitó a TA durante 1 hora. Se agregaron más hidruro de sodio (1,1 g, 22,68 mmol) y 1,2-dibromoetano (1,305 mL, 15,12

mmol) y la reacción se agitó a TA durante 30 minutos. La mezcla de reacción se aplacó con agua (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma marrón. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano, para proporcionar una espuma amarilla. Esto se disolvió en 40% acetato de etilo en isohexano y se agitó para proporcionar el material deseado como un sólido blanco que se recogió mediante filtración (2,60 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,50 (9H, s), 1,59 - 1,53 (2H, m), 1,81 - 1,77 (2H, m), 2,11 (3H, s), 2,32 (3H, s), 3,18 (1H, ddd), 3,47 (1H, ddd), 3,62 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,18 (1H, d), 4,53 (1H, s), 6,78 (1H, s), 7,51 (2H, d), 7,97 (2H, d), 9,54 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 570; HPLC tR = 2,99 min

terc-butil *N*-[4-[4-[(3,5-dimetil-1,2-oxazol-4-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



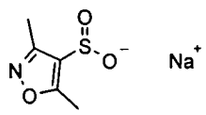
Se disolvieron ácido 3,5-dimetilisoxazol-4-sulfínico, sal de sodio (1,443 g, 7,84 mmol) y *terc*-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (4 g, 7,84 mmol) en DMF (50 mL) y se agitaron durante 1 hora a TA. El disolvente se evaporó para proporcionar un sólido amarillo, esto se aplacó con agua (50 mL) y se extrajo con DCM (2 x 75 mL), se secó y el disolvente se evaporó para proporcionar una goma naranja que se agitó rápidamente con éter dietílico (100 mL) para proporcionar un sólido que se recogió mediante filtración y se secó al vacío para proporcionar el material deseado como un sólido blancuzco (4,11 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,50 (9H, s), 2,19 (3H, s), 2,33 (3H, s), 3,20 (1H, ddd), 3,50 (1H, ddd), 3,65 (1H, dd), 3,78 (1H, d), 3,98 (1H, dd), 4,15 (1H, d), 4,44 (1H, s), 4,69 (2H, s), 6,79 (1H, s), 7,51 (2H, d), 7,97 (2H, d), 9,55 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 544; HPLC tR = 2,76 min

1922

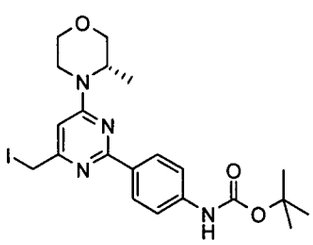
Ácido 3,5-Dimetilisoxazol-4-sulfínico, sal de sodio



Una solución de sulfito de sodio (5,03 g, 39,87 mmol) en agua (50 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (6,70 g, 79,74 mmol) y la solución resultante se agitó a 50°C durante 10 minutos. Se agregó en porciones cloruro de 3,5-dimetilisoxazol-4-sulfonilo (7,8 g, 39,87 mmol) a la solución y se agitó a 50°C durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en metanol (200 mL). La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar un sólido blanco, esto se agitó con acetonitrilo (50 mL) y luego se filtró para proporcionar el material deseado como un sólido blanco (7,16 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 2,24 (3H, s), 2,39 (3H, s).

terc-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



[6-[(3*S*)-3-Metilmorfolin-4-il]-2-[4-[(2-metilpropan-2-il)oxicarbonilamino]fenil]pirimidin-4-il]metil metanosulfonato (27 g, 56,42 mmol) y yoduro de litio(4,33 mL, 112,84 mmol) se agregaron a dioxano (250 mL) y se calentó a 60°C durante 1 hora y luego a TA durante toda la noche. El disolvente se evaporó hasta secarse, la mezcla de reacción se aplacó con una solución saturada acuosa de cloruro de amonio (100 mL) y se extrajo con DCM (3 x 75 mL). Luego los extractos orgánicos se lavaron a través de un lecho de sílice de dos pulgadas, eluyendo con acetato de etilo, para proporcionar una espuma marrón. Esto rápidamente se disolvió en éter dietílico y se agitó para proporcionar el material deseado como un sólido blanco (25,2 g).

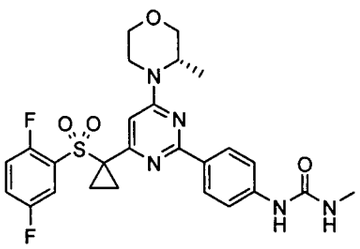
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,50 (9H, s), 3,19 (1H, ddd), 3,49 (1H, ddd), 3,64 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,16 (1H, d), 4,39 (2H,

s), 4,48 (1H, s), 6,80 (1H, s), 7,55 (2H, d), 8,22 (2H, d), 9,53 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 511; HPLC tR = 2,85 min

La preparación de [6-[(3*S*)-3-metilmorfolin-4-il]-2-[4-[(2-metilpropan-2-il)oxicarbonilamino]fenil]pirimidin-4-il]metil metanosulfonato se describió anteriormente.

Ejemplo 60: 1-[4-[4-[1-(2,5-Difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea

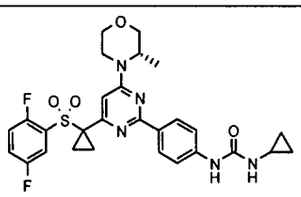
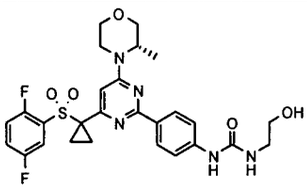
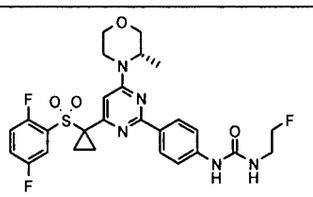
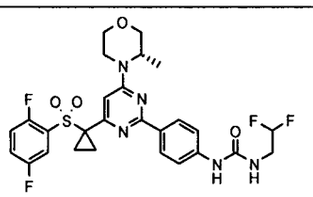
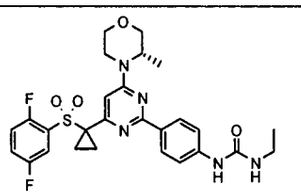
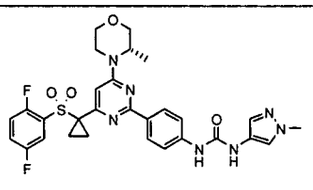


Se agregaron fenil *N*-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,15 g, 0,25 mmol) y metilamina (2M en THF, 1,236 mL, 2,47 mmol) a dioxano (10 mL) y se agitaron durante toda la noche. La reacción se evaporó hasta secarse y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (0,113 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,72 - 1,70 (2H, m), 1,96 - 1,91 (2H, m), 2,66 (3H, d), 3,16 (1H, ddd), 3,46 (1H, ddd), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,16 (1H, d), 4,48 (1H, s), 6,05 (1H, q), 6,68 (1H, s), 7,37 (2H, d), 7,54 - 7,50 (1H, m), 7,69 - 7,57 (2H, m), 7,73 (2H, d), 8,70 (1H, s);

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 544; HPLC tR = 2,30 min

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
60a		3-ciclopropil-1-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	570	2,51
60b		1-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	574	2,11
60c		1-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	576	2,48
60d		3-(2,2-difluoroetil)-1-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	594	2,61
60e		3-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	558	2,48
60f		1-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	610	2,46

Ejemplo 60a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,44 - 0,40 (2H, m), 0,67 - 0,62 (2H, m), 1,19 (3H, d), 1,74 - 1,68 (2H, m), 1,96 - 1,90 (2H, m), 2,58 - 2,53 (1H, m), 3,16 (1H, ddd), 3,46 (1H, ddd), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,16 (1H, d), 4,48 (1H, s),

6,41 (1H, s), 6,68 (1H, s), 7,38 (2H, d), 7,54 - 7,50 (1H, m), 7,69 - 7,57 (2H, m), 7,73 (2H, d), 8,50 (1H, s);

Ejemplo 60b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,74 - 1,68 (2H, m), 1,98 - 1,89 (2H, m), 2,09 (3H, s), 3,20 - 3,12 (3H, m), 3,49 - 3,42 (3H, m), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,16 (1H, d), 4,48 (1H, s), 4,73 (1H, t), 6,24 (1H, t), 6,68 (1H, s), 7,36 (2H, d), 7,54 - 7,50 (1H, m), 7,69 - 7,57 (2H, m), 7,73 (2H, d), 8,77 (1H, s);

Ejemplo 60c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,74 - 1,68 (2H, m), 1,96 - 1,90 (2H, m), 3,16 (1H, ddd), 3,48 - 3,36 (3H, m), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,16 (1H, d), 4,47 (2H, dt), 4,48 (1H, s), 6,41 (1H, t), 6,68 (1H, s), 7,37 (2H, d), 7,54 - 7,50 (1H, m), 7,69 - 7,57 (2H, m), 7,74 (2H, d), 8,77 (1H, s);

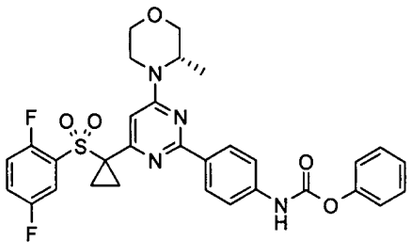
Ejemplo 60d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,74 - 1,68 (2H, m), 1,96 - 1,91 (2H, m), 3,16 (1H, ddd), 3,63 - 3,43 (4H, m), 3,74 (1H, d), 3,96 (1H, dd), 4,16 (1H, d), 4,48 (1H, s), 6,07 (1H, ddt), 6,51 (1H, t), 6,69 (1H, s), 7,38 (2H, d), 7,54 - 7,50 (1H, m), 7,69 - 7,57 (2H, m), 7,75 (2H, d), 8,89 (1H, s);

Ejemplo 60e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,19 (3H, d), 1,72 - 1,69 (2H, m), 1,95 - 1,91 (2H, m), 3,19 - 3,09 (3H, m), 3,45 (1H, ddd), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,16 (1H, d), 4,48 (1H, s), 6,14 (1H, t), 6,68 (1H, s), 7,36 (2H, d), 7,54 - 7,50 (1H, m), 7,69 - 7,57 (2H, m), 7,72 (2H, d), 8,62 (1H, s);

Ejemplo 60f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,74 - 1,68 (2H, m), 1,96 - 1,92 (2H, m), 3,17 (1H, ddd), 3,46 (1H, ddd), 3,61 (1H, dd), 3,75 (1H, d), 3,79 (3H, s), 3,96 (1H, dd), 4,17 (1H, d), 4,48 (1H, s), 6,69 (1H, s), 7,38 (1H, s), 7,42 (2H, d), 7,55 - 7,51 (1H, m), 7,70 - 7,58 (2H, m), 7,78 - 7,75 (3H, m), 8,36 (1H, s), 8,80 (1H, s);

La preparación de fenil *N*-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

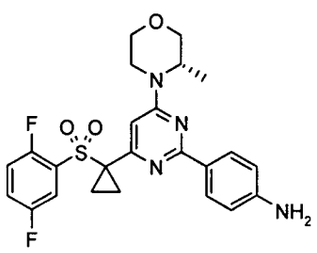


Se agregaron 4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (como la sal clorhidrato) (2,54 g, 4,86 mmol) y bicarbonato de sodio (2,04 g, 24,28 mmol) a DCM (60 mL) y se agitaron durante 10 minutos. Se agregó lentamente fenil cloroformiato (0,792 mL, 6,31 mmol) y la reacción se agitó durante 1 hora. La mezcla de reacción se aplacó con una solución saturada acuosa de cloruro de amonio (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido naranja. El sólido se hizo pasar a través de un lecho de sílice, eluyendo con acetato de etilo, para proporcionar un sólido que se purificó adicionalmente mediante trituración con éter dietílico para proporcionar el material deseado como un sólido blanco (2,20 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,73 - 1,69 (2H, m), 1,98 - 1,91 (2H, m), 3,17 (1H, ddd), 3,51 - 3,44 (1H, m), 3,61 (1H, dd), 3,75 (1H, d), 3,95 (1H, d), 4,18 (1H, d), 4,49 (1H, s), 6,72 (1H, s), 7,30 - 7,24 (3H, m), 7,45 (2H, t), 7,55 - 7,50 (3H, m), 7,69 - 7,57 (2H, m), 7,83 (2H, d), 10,39 (1H, s);

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 607; HPLC tR = 3,15 min

4-[4-[1-(2,5-Difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



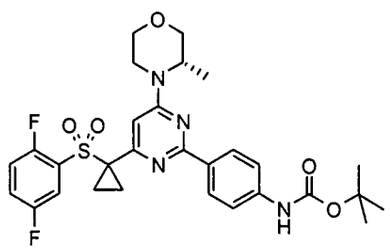
Se agregó *terc*-butil *N*-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (2,85 g, 4,86 mmol) a cloruro de hidrógeno 6N en propan-2-ol (30 mL) y se agitó durante 2 horas a TA. La solución bruta se trituró con éter dietílico para proporcionar el material deseado (como una sal clorhidrato) como un sólido

amarillo (2,4 g, 94 %). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,78 - 1,71 (2H, m), 1,97 - 1,93 (2H, m), 3,23 (1H, ddd), 3,45 (1H, ddd), 3,59 (1H, dd), 3,82 - 3,73 (1H, m), 3,96 (1H, dd), 4,29 - 4,18 (1H, m), 4,59 - 4,47 (1H, m), 6,81 (1H, s), 7,25 (2H, d), 7,63 - 7,54 (2H, m), 7,72 - 7,66 (1H, m), 7,95 (2H, d);

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 487; HPLC tR = 2,52 min

terc-butil *N*-[4-[4-[1-(2,5-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

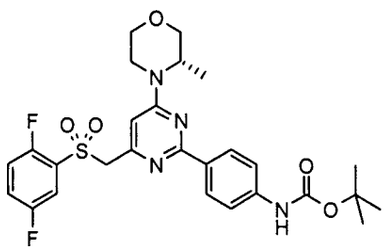


Se agregó rápidamente hidruro de sodio (1,38 g, 28,56 mmol) a una solución de *terc*-butil *N*-[4-[4-[(2,5-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (4,0 g, 7,14 mmol) en DMF (70 mL) y la mezcla se agitó a 40°C durante 10 minutos antes de la adición lenta de 1,2-dibromoetano (2,459 mL, 28,54 mmol) en DMF (70 mL) a TA. La suspensión resultante se agitó a 40°C durante 1 hora. Se agregaron más hidruro de sodio (0,69 g, 14,26) y 1,2-dibromoetano (1,23 mL, 14,26 mmol) y la reacción se agitó a TA durante 30 minutos. La mezcla de reacción se aplacó con agua (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma marrón. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano, para proporcionar una espuma amarilla. Esto se disolvió en 40% acetato de etilo en isohexano y al agitar el material deseado se precipitó como un sólido blanco (2,85 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,49 (9H, s), 1,74 - 1,68 (2H, m), 1,96 - 1,92 (2H, m), 3,16 (1H, ddd), 3,46 (1H, ddd), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,17 (1H, d), 4,48 (1H, s), 6,70 (1H, s), 7,44 (2H, d), 7,54 - 7,50 (1H, m), 7,69 - 7,57 (2H, m), 7,76 (2H, d), 9,50 (1H, s);

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 587; HPLC tR = 2,94 min

terc-butil *N*-[4-[4-[(2,5-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

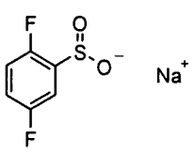


Se disolvieron 2,5-difluorobencenosulfonato de sodio (2,117 g, 9,80 mmol) y *terc*-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (5 g, 9,80 mmol) en DMF (50 mL) y se agitaron durante 1 hora a TA. El disolvente se evaporó y el residuo se repartió entre agua (50 mL) y DCM (75 mL). Las capas se separaron, la capa acuosa se extrajo adicionalmente con DCM (75 mL) y los orgánicos combinados se hicieron pasar a través de un lecho de sílice, eluyendo con acetato de etilo, para proporcionar un sólido amarillo. Este material se trituró con éter dietílico para proporcionar el material deseado como un sólido blanco (4,90 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,49 (9H, s), 3,19 (1H, ddd), 3,48 (1H, ddd), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,13 (1H, d), 4,41 (1H, s), 4,82 (2H, s), 6,78 (1H, s), 7,44 - 7,42 (3H, m), 7,75 - 7,68 (4H, m), 9,50 (1H, s);

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 561; HPLC tR = 2,95 min

Ácido 2,5-difluorobencenosulfínico, sal de sodio



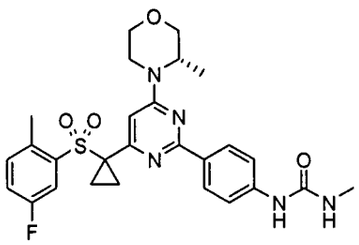
Una solución de sulfito de sodio (29,6 g, 235,18 mmol) en agua (200 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (39,5 g, 470,36 mmol) a la solución agitada. La solución resultante se agitó a 50°C durante 10 minutos. Se agregó en porciones cloruro 2,5-difluorobenceno-1-sulfonilo (50 g, 235 mmol) y la solución se agitó a 50°C durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en etanol (200 mL). La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar un sólido blanco, esto se agitó con acetonitrilo (50 mL) y luego se filtró para proporcionar el material deseado como un sólido blanco (43,0

g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 7,09 - 7,05 (2H, m), 7,36 - 7,32 (1H, m).

La preparación de *terc*-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describió anteriormente.

Ejemplo 61: 1-[4-[4-[1-(5-Fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea

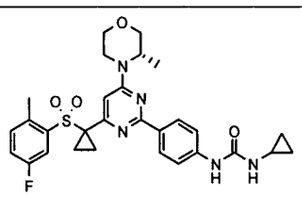
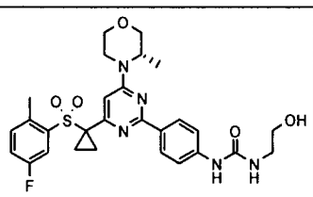
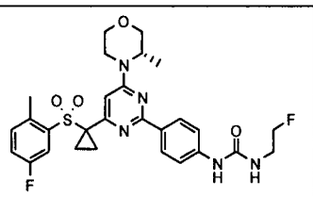
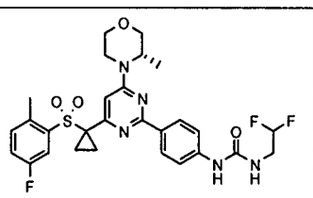
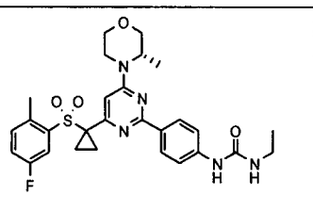
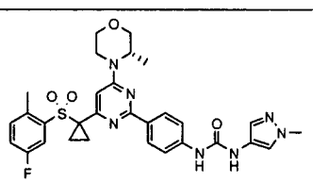


Se agregaron fenil *N*-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,15 g, 0,25 mmol) y metilamina (2M en THF, 1,244 mL, 2,49 mmol) a dioxano (10 mL) y se agitaron durante toda la noche. La reacción se evaporó hasta secarse y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (0,130 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,70 - 1,64 (2H, m), 1,90 - 1,87 (2H, m), 2,41 (3H, s), 2,66 (3H, d), 3,12 (1H, ddd), 3,44 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,43 (1H, s), 6,05 (1H, q), 6,64 (1H, s), 7,42 - 7,38 (4H, m), 7,62 (1H, d), 7,86 (2H, d), 8,71 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 540; HPLC tR = 2,46 min

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
61a		3-ciclopropil-1-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	566	2,65
61b		1-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	570	2,28
61c		3-(2-fluoroetil)-1-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	572	2,48
61d		3-(2,2-difluoroetil)-1-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	590	2,74
61e		1-etil-3-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	554	2,54
61f		1-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	606	2,40

Ejemplo 61a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,44 - 0,40 (2H, m), 0,67 - 0,63 (2H, m), 1,16 (3H, d), 1,73 - 1,64 (2H, m), 1,90 - 1,87 (2H, m), 2,41 (3H, s), 2,59 - 2,53 (1H, m), 3,12 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,43

(1H, s), 6,42 (1H, s), 6,64 (1H, s), 7,42 - 7,38 (4H, m), 7,63 - 7,61 (1H, m), 7,86 (2H, d), 8,50 (1H, s).

Ejemplo 61b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,70 - 1,64 (2H, m), 1,90 - 1,87 (2H, m), 2,41 (3H, s), 3,20 - 3,09 (3H, m), 3,48 - 3,41 (3H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,43 (1H, s), 4,73 (1H, t), 6,24 (1H, t), 6,64 (1H, s), 7,40 - 7,38 (4H, m), 7,63 - 7,60 (1H, m), 7,86 (2H, d), 8,77 (1H, s);

Ejemplo 61c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,70 - 1,64 (2H, m), 1,91 - 1,87 (2H, m), 2,41 (3H, s), 3,13 (1H, ddd), 3,47 - 3,37 (3H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,47 - 4,40 (1H, m), 4,47 (2H, dt), 6,42 (1H, t), 6,64 (1H, s), 7,41 - 7,38 (4H, m), 7,61 (1H, d), 7,87 (2H, d), 8,78 (1H, s).

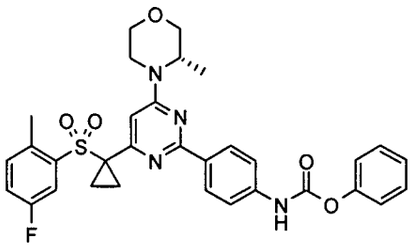
Ejemplo 61d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,70 - 1,64 (2H, m), 1,90 - 1,87 (2H, m), 2,41 (3H, s), 3,12 (1H, ddd), 3,62 - 3,41 (4H, m), 3,74 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,44 (1H, s), 6,08 (1H, ddt), 6,52 (1H, t), 6,65 (1H, s), 7,42 - 7,38 (4H, m), 7,62 - 7,60 (1H, m), 7,88 (2H, d), 8,89 (1H, s).

Ejemplo 61e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,16 (3H, d), 1,70 - 1,65 (2H, m), 1,90 - 1,85 (2H, m), 2,4 (S, 3H), 3,15 - 3,09 (3H, m), 3,44 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,43 (1H, s), 6,14 (1H, t), 6,64 (1H, s), 7,39 (4H, d), 7,62 (1H, d), 7,86 (2H, d), 8,63 (1H, s).

Ejemplo 61f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,71 - 1,65 (2H, m), 1,90 - 1,88 (2H, m), 2,41 (3H, s), 3,13 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,77 (3H, s), 3,95 (1H, ddd), 4,43 (1H, s), 6,65 (1H, s), 7,41 - 7,39 (4H, m), 7,45 (2H, d), 7,62 (1H, d), 7,77 (1H, s), 7,89 (2H, d), 8,37 (1H, s), 8,80 (1H, s).

La preparación de fenil *N*-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

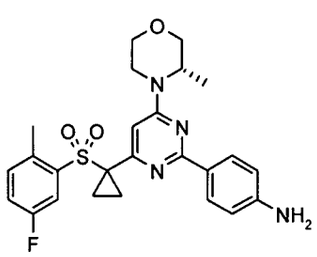


Se agregaron 4-[4-[1-(5-Fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (como la sal clorhidrato) (2,4 g, 4,62 mmol) y bicarbonato de sodio (1,942 g, 23,12 mmol) a DCM (60 mL) y se agitaron durante 10 minutos. Se agregó lentamente fenil cloroformiato (0,754 mL, 6,01 mmol) y la reacción se agitó durante 1 hora. La mezcla de reacción se aplacó con una solución saturada acuosa de cloruro de amonio (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido naranja. A esto se agregó DCM y luego éter dietílico, el disolvente lentamente se eliminó hasta que el material deseado se precipitó de la mezcla como un sólido blanco (2,05 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,72 - 1,66 (2H, m), 1,91 - 1,87 (2H, m), 2,41 (3H, s), 3,14 (1H, ddd), 3,47 - 3,38 (1H, m), 3,60 (1H, d), 3,74 (1H, d), 3,95 (1H, dd), 4,12 (1H, d), 4,45 (1H, s), 6,68 (1H, s), 7,30 - 7,24 (3H, m), 7,40 (2H, d), 7,45 (2H, t), 7,54 (2H, d), 7,62 (1H, d), 7,95 (2H, d), 10,39 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 603; HPLC tR = 3,02 min

4-[4-[1-(5-Fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

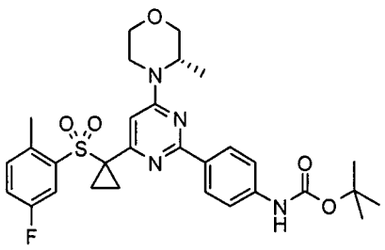


Se agregó *terc*-butil *N*-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (2,7 g, 4,63 mmol) a cloruro de hidrógeno 6N en propan-2-ol (30 mL) y se agitó durante 2 horas a TA. La solución bruta se trituró con éter dietílico para proporcionar el material deseado (como la sal clorhidrato) como un sólido amarillo (2,40 g). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,73 - 1,69 (2H, m), 1,93 - 1,90 (2H, m), 2,38 (3H, s), 3,20 (1H, ddd), 3,44 (1H, ddd), 3,58 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,26 - 4,12 (1H, m), 4,51 (1H, s), 6,71 (1H, s), 7,17 - 7,13 (2H, m), 7,45 (2H, d), 7,60 (1H, d), 7,97 (2H, d).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 483; HPLC tR = 2,57 min

terc-butil *N*-[4-[4-[1-(5-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

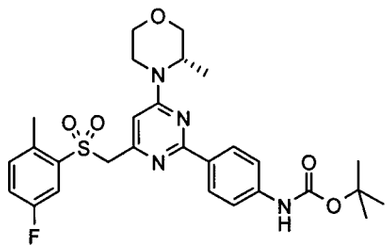


Se agregó rápidamente hidruro de sodio (1,987 g, 41,39 mmol) a una solución de *terc*-butil *N*-[4-[4-[(5-fluoro-2-metilfenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (3,84 g, 6,90 mmol) en DMF (70 mL) y la mezcla se agitó a TA durante 10 minutos antes de la adición lenta de 1,2-dibromoetano (2,38 mL, 27,59 mmol) en DMF (70 mL). La suspensión resultante se agitó a TA durante 30 minutos. Se agregaron más hidruro de sodio (0,95 g, 20,70 mmol) y 1,2 dibromoetano (1,19 g, 20,70 mmol) y la reacción se agitó durante otros 30 minutos. La mezcla de reacción se aplacó con agua (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma marrón. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano, para proporcionar un material que se purificó adicionalmente mediante trituración con 40% acetato de etilo en isohexano para proporcionar el material deseado como un sólido blanco (2,70 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,49 (9H, s), 1,70 - 1,64 (2H, m), 1,90 - 1,87 (2H, m), 2,41 (3H, s), 3,13 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,11 (1H, d), 4,43 (1H, s), 6,66 (1H, s), 7,41 - 7,38 (2H, m), 7,46 (2H, d), 7,62 - 7,60 (1H, m), 7,88 (2H, d), 9,50 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 583; HPLC tR = 3,19 min

terc-butil *N*-[4-[4-[(5-fluoro-2-metilfenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

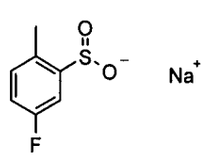


Se disolvieron ácido 5-fluoro-2-metilbencenosulfínico, sal de sodio (2,079 g, 9,80 mmol) y *terc*-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (5 g, 9,80 mmol) en DMF (50 mL) y se agitó durante 1 hora a TA. El disolvente se evaporó y el residuo se repartió entre agua (50 mL) y DCM (75 mL). Las capas se separaron, la capa acuosa se extrajo adicionalmente con DCM (75 mL) y los orgánicos combinados se secaron y el disolvente se evaporó para proporcionar una goma naranja que se purificó adicionalmente mediante trituración con éter dietílico para proporcionar el material deseado como un sólido blancuzco (4,75 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,50 (9H, s), 2,61 (3H, s), 3,17 (1H, ddd), 3,48 (1H, ddd), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,11 (1H, d), 4,40 (1H, s), 4,75 (2H, s), 6,69 (1H, s), 7,50 - 7,41 (4H, m), 7,56 - 7,53 (1H, m), 7,82 (2H, d), 9,50 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 557; HPLC tR = 2,91 min

Ácido 5-fluoro-2-metilbencenosulfínico, sal de sodio

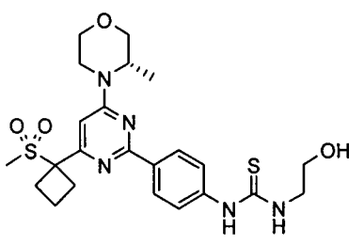


Una solución de sulfito de sodio (30,2 g, 239,65 mmol) en agua (200 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (40,3 g, 479,30 mmol) a la solución agitada. La solución resultante se agitó a 50°C durante 10 minutos. Se agregó cloruro de 5-fluoro-2-metilsulfonilo en porciones y la solución se agitó a 50°C durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en etanol (200 mL). La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar un sólido blanco, esto se agitó con acetonitrilo (50 mL) y luego se filtró para proporcionar el material deseado como un sólido blanco (27,0 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 2,41 (3H, s), 6,90 (1H, ddd), 7,05 (1H, dd), 7,36 (1H, dd).

La preparación de *terc*-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describió anteriormente.

Ejemplo 62: 3-(2-Hidroxietil)-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea

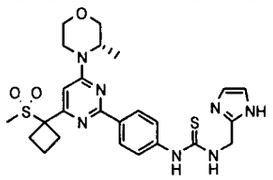
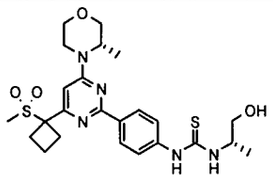
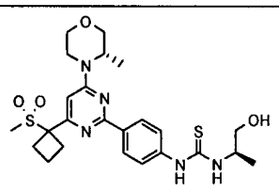
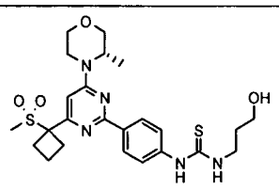


Se agregó 1,1'-tiocarbonildiimidazol (57,6 mg, 0,32 mmol) a una solución agitada de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]anilina (100 mg, 0,25 mmol) en THF (1,0 mL) y DCM (2,0 mL) a TA. La solución resultante se agitó durante 2 horas. Se agregaron trietilamina (0,035 mL, 0,25 mmol) y etanolamina (15,18 mg, 0,25 mmol) a la mezcla de reacción y luego se agitó a TA durante 1 hora más. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetonitrilo (2,0 mL), se filtró y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (73 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,25 (3H, d), 1,92 (1H, d), 2,07 - 2,09 (1H, m), 2,79 - 2,86 (2H, m), 2,88 (3H, s), 2,87 - 2,95 (2H, m), 3,18 - 3,26 (1H, m), 3,47 - 3,54 (1H, m), 3,57 (3H, s), 3,64 - 3,67 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,30 (1H, d), 4,63 (1H, d), 4,85 (1H, s), 6,75 (1H, s), 7,61 - 7,64 (2H, m), 7,90 (1H, s), 8,27 - 8,30 (2H, m), 9,85 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 506,55; HPLC tR = 2,35 min.

Los compuestos a continuación se prepararon en forma análoga a partir de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]anilina utilizando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
62a		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea	542,6	2,41
62b		3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea	520,6	2,47
62c		3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea	520,6	2,47
62d		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea	520,6	2,39

Ejemplo 62a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,25 (3H, d), 1,90 - 1,93 (1H, m), 2,07 - 2,09 (1H, m), 2,79 - 2,86 (2H, m), 2,88 (3H, s), 2,89 - 2,95 (2H, m), 3,20 - 3,26 (1H, m), 3,47 - 3,54 (1H, m), 3,64 - 3,67 (1H, m), 3,77 (1H, d), 3,97 - 4,00 (1H, m), 4,27 (1H, d), 4,60 (1H, s), 4,71 (2H, s), 6,76 (1H, s), 6,88 (1H, s), 7,09 (1H, s), 7,68 (2H, d), 8,24 (1H, s), 8,28 - 8,32 (2H, m), 10,06 (1H, s).

Ejemplo 62b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 - 1,16 (3H, m), 1,24 (3H, s), 1,90 - 1,94 (1H, m), 2,07 - 2,09 (1H, m), 2,79 - 2,84 (2H, m), 2,88 (3H, s), 2,91 - 2,95 (2H, m), 3,20 - 3,26 (1H, m), 3,44 - 3,54 (3H, m), 3,64 - 3,67 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m),

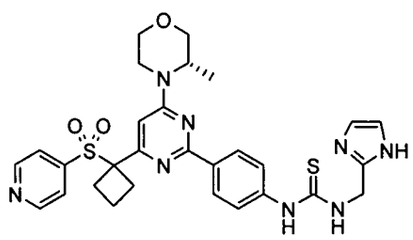
4,26 (1H, d), 4,38 (1H, s), 4,60 (1H, s), 4,92 (1H, s), 6,75 (1H, s), 7,63 - 7,66 (2H, m), 7,73 - 7,75 (1H, m), 8,28 (2H, d), 9,75 (1H, s).

Ejemplo 62c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 - 1,16 (3H, m), 1,24 (3H, s), 1,90 - 1,94 (1H, m), 2,07 - 2,09 (1H, m), 2,79 - 2,84 (2H, m), 2,88 (3H, s), 2,91 - 2,95 (2H, m), 3,20 - 3,26 (1H, m), 3,44 - 3,54 (3H, m), 3,64 - 3,67 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,26 (1H, d), 4,38 (1H, s), 4,60 (1H, s), 4,92 (1H, s), 6,75 (1H, s), 7,63 - 7,66 (2H, m), 7,73 - 7,75 (1H, m), 8,28 (2H, d), 9,75 (1H, s).

Ejemplo 62d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 - 1,25 (3H, m), 1,68 - 1,75 (2H, m), 1,90 - 1,93 (1H, m), 2,07 - 2,09 (1H, m), 2,79 - 2,86 (2H, m), 2,88 (3H, s), 2,89 - 2,95 (2H, m), 3,18 - 3,25 (1H, m), 3,47 - 3,54 (5H, m), 3,64 - 3,67 (1H, m), 3,77 (1H, d), 3,96 - 4,00 (1H, m), 4,26 (1H, d), 4,58 (2H, s), 6,75 (1H, s), 7,55 - 7,59 (2H, m), 7,93 (1H, s), 8,27 - 8,30 (2H, m), 9,74 (1H, s).

La preparación de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclobutil)pirimidin-2-il]anilina se describió anteriormente.

Ejemplo 63: 3-(1*H*-Imidazol-2-ilmetil)-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]tiourea



Se agregó 1,1'-tiocarbonildiimidazol (49,8 mg, 0,28 mmol) a una solución agitada de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]anilina (100 mg, 0,21 mmol) en THF (1,0 mL) y DCM (2,0 mL) a TA. La solución resultante se agitó durante 2 horas. Luego se agregaron trietilamina (0,030 mL, 0,21 mmol) y (1H-imidazol-2-il)metanamina (20,86 mg, 0,21 mmol) a la mezcla de reacción y se agitaron a TA durante 1 hora. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetonitrilo (2,0 mL), se filtró y luego se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (85mg).

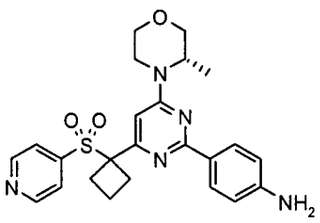
Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,21 - 1,23 (3H, d), 1,94 (1H, m), 2,15 (1H, m), 2,82 (2H, m), 3,14 (2H, m), 3,51 (1H, t), 3,63 (1H, d), 3,68 (1H, d), 3,77 (1H,

d), 3,97 (1H, dd), 4,17 (1H, d), 4,55 (1H, s), 4,73 (2H, s), 6,57 (1H, s), 6,89 (1H, s), 7,08 (1H, s), 7,48 (2H, d), 7,56 (2H, d), 7,79 (2H, d), 8,20 (1H, s), 8,73 (2H, d), 10,00 (1H, s), 11,94 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 605,51; HPLC tR = 2,03 min.

La preparación de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]anilina se describe a continuación:

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]anilina

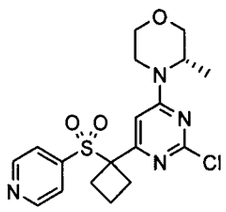


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (79 mg, 0,11 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidina (920 mg, 2,25 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (641 mg, 2,92 mmol) y solución de carbonato de sodio acuoso 2M (5 mL, 10,0 mmol) en DMF (10 mL), DME (40 mL), etanol (10 mL) y agua (10 mL) a TA bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 80°C durante 2 horas. La mezcla de reacción luego se diluyó con acetato de etilo (400 mL) y se lavó secuencialmente con agua (200 mL) y luego salmuera (250 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, con un gradiente de elución de 0% a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco cremoso (1,01 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,19 - 1,21 (3H, m), 1,88 - 1,95 (1H, m), 2,10 - 2,15 (1H, m), 2,76 - 2,83 (2H, m), 3,05 - 3,18 (3H, m), 3,45 - 3,52 (1H, m), 3,62 - 3,65 (1H, m), 3,75 (1H, d), 3,94 - 3,98 (1H, m), 4,13 (1H, d), 4,47 (1H, d), 5,50 (2H, d), 6,45 - 6,48 (2H, m), 6,52 (1H, s), 7,44 - 7,46 (2H, m), 7,52 - 7,66 (2H, d), 8,70 - 8,72 (2H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 466,20; HPLC tR = 2,06 min

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidina



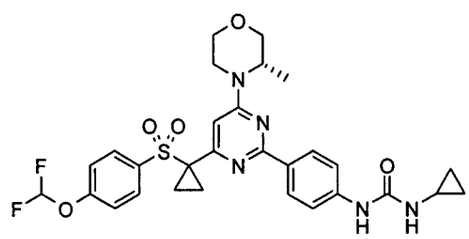
Se agregó hidróxido de sodio (solución 50% p/p) (24,39 g, 609,89 mmol) a una mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfonilmetil)pirimidina (4,09 g, 11,09 mmol), 1,3-dibromopropano (3,38 mL, 33,27 mmol) y bromuro de tetrabutilamonio (0,357 g, 1,11 mmol) en tolueno (200 mL) a TA al aire. La mezcla resultante se entibió hasta alcanzar 45°C durante 3 horas. Se agregó agua (100 mL) a la solución y la capa de tolueno se lavó con más agua, salmuera y luego se secó sobre $MgSO_4$. La mezcla se filtró y el filtrado se evaporó hasta secarse. El producto bruto se purificó mediante cromatografía de sílice instantánea, eluyendo con un gradiente de 30 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido (936 mg).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,17 - 1,19 (3H, m), 1,89 - 1,94 (1H, m), 2,07 - 2,13 (1H, m), 2,68 - 2,75 (2H, m), 2,96 - 3,06 (2H, m), 3,11 - 3,19 (1H, m), 3,39 - 3,46 (1H, m), 3,56 - 3,59 (1H, m), 3,71 (1H, d), 3,91 - 3,94 (2H, m), 4,34 (1H, s), 6,65 (1H, s), 7,47 - 7,49 (2H, m), 8,83 - 8,85 (2H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 409; HPLC tR = 2,04 min.

La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(piridin-4-ilsulfonilmetil)pirimidina se describió anteriormente.

Ejemplo 64: 3-Ciclopropil-1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea

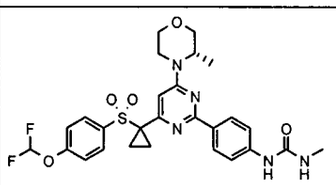
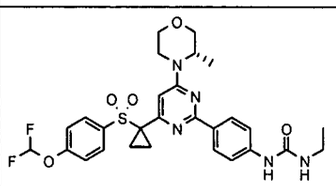
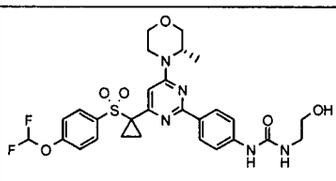
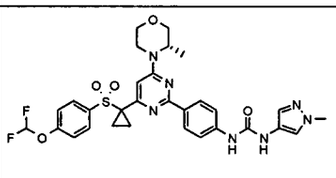


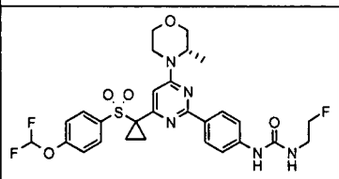
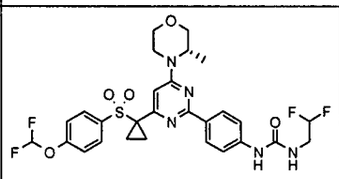
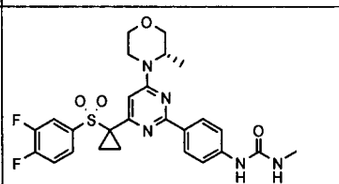
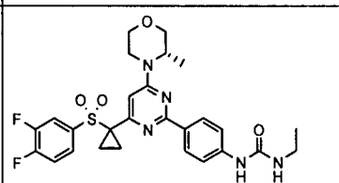
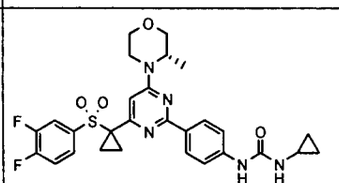
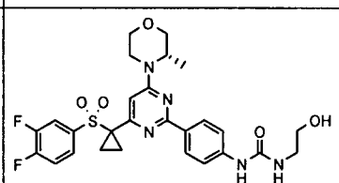
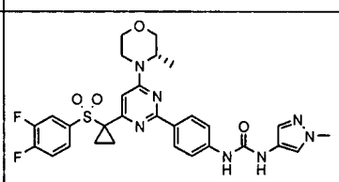
Se agregó ciclopropilamina (0,136 mL, 0,80 mmol) a una solución de fenil *N*-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (100 mg, 0,16 mmol) y trietilamina (0,066 mL, 0,48 mmol) en DMA (1 mL). La reacción se agitó a TA durante 18 horas. El producto bruto se purificó mediante

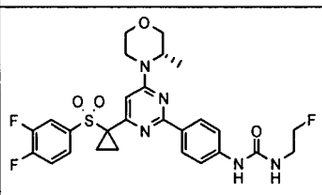
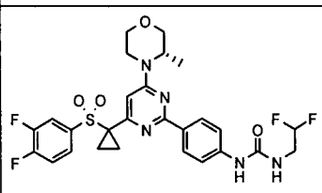
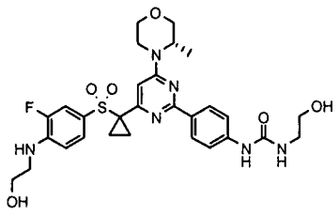
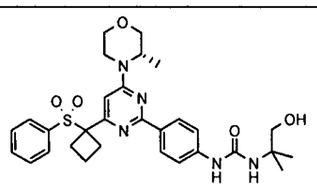
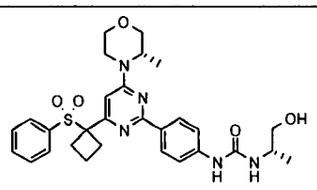
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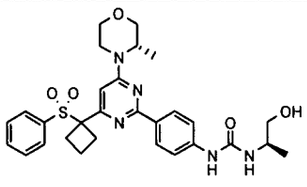
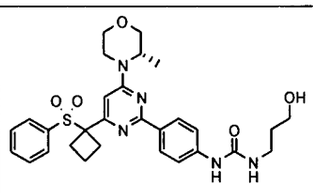
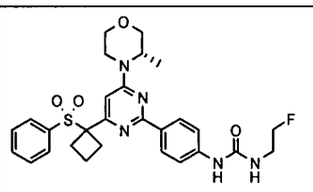
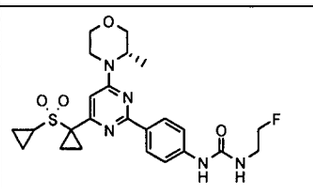
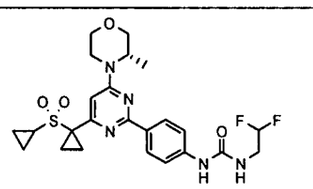
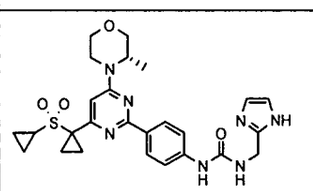
HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo para proporcionar el producto deseado como un sólido (66 mg).
Espectro de NMR: ^{1}H NMR (400,13 MHz, DMSO-D_6) δ 0,41 (2H, m), 0,64 (2H, m), 1,18 (3H, d), 1,61 (2H, m), 1,87 (2H, m), 2,55 (1H, dd), 3,14 (1H, m), 3,46 (1H, td), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,14 (1H, s), 4,40 (1H, s), 6,40 (1H, d), 6,63 (1H, s), 7,37 – 7,58 (5H, m), 7,84 (4H, m), 8,50 (1H, s)
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 600; HPLC tR = 2,36 min.

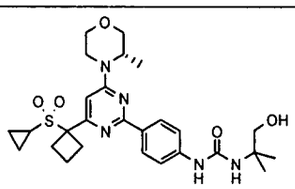
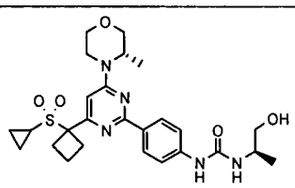
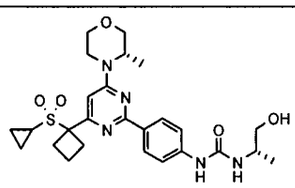
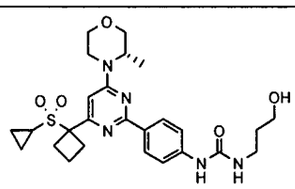
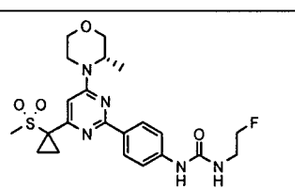
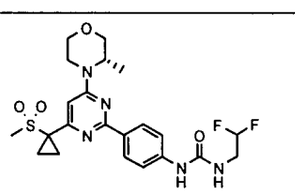
Los compuestos a continuación se prepararon en forma análoga utilizando el carbamato apropiado y la amina apropiada.

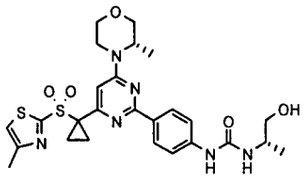
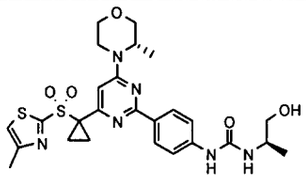
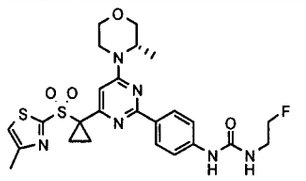
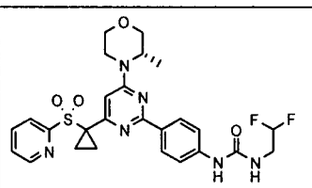
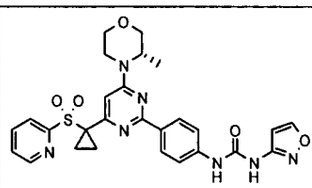
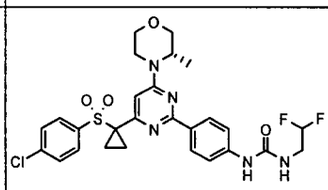
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
64a*		1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	574	2,21
64b*		3-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	588	2,35
64c*		1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	604	2,05
64d**		1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	640	2,22

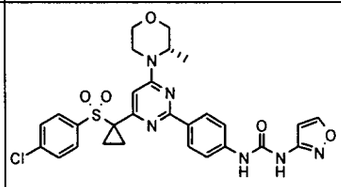
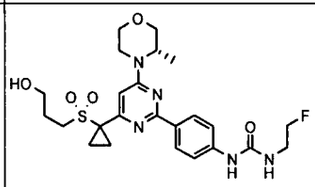
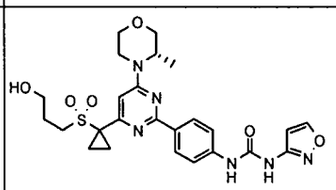
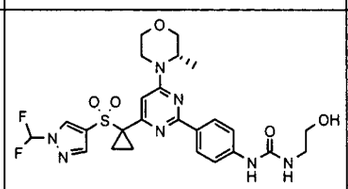
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
64e**		1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	606	2,33
64f**		3-(2,2-difluoroetil)-1-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	624	2,45
64g*		1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	544	2,21
64h*		3-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	558	2,40
64i		3-ciclopropil-1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	570	2,47
64j		1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	574	2,06
64k**		1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-	610	2,22

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		metilpirazol-4-il)urea		
64l**		1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	576	2,34
64m**		3-(2,2-difluoroetil)-1-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	594	2,45
64n***		1-[4-[4-[1-[3-fluoro-4-(2-hidroxietilamino)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	615	1,72
64o		1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	580	2,30
64p		1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea	566	2,11

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
64q		1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea	566	2,11
64r		1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	566	2,05
64s**		1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	554	2,32
64t**		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	504	1,95
64u**		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea	522	2,10
64v		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea	538	1,77

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
64w		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	544	2,11
64x		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea	530	1,91
64y		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea	530	1,91
64z		1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	530	1,86
64aa**		3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	478	1,84
64ab**		3-(2,2-difluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	496	2,03

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
64ac		3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	573	1,92
64ad		3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	573	1,92
64ae**		3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea	561	2,14
64af**		3-(2,2-difluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea	559	2,07
64ag		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea	562	2,12
64ah**		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea	592	2,48

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
64ai		1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea	595	2,51
64aj**		3-(2-fluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	522	1,72
64ak		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1,2-oxazol-3-il)urea	543	1,77
64al*		1-[4-[4-[1-[1-(difluorometil)pirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	578	2,00

* Se utilizaron 1,2 equivalentes de amina

** La reacción se calentó a 50°C durante 3 horas

*** Producto derivado formado y aislado cuando se preparó el **Ejemplo 64j**

Ejemplo 64a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,60 (2H, m), 1,89 (2H, m), 2,66 (3H, d), 3,14 (1H, td), 3,46 (1H, td), 3,62 (1H, dd), 3,74 (1H, d), 3,94 (1H, dd), 4,15 (1H, d), 4,40 (1H, s), 6,04 (1H, q), 6,63 (1H, s), 7,36 – 7,61 (5H, m), 7,84 (4H, m), 8,70 (1H, s)

Ejemplo 64b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06 (3H, t), 1,18 (3H, d), 1,61 (2H, m), 1,88 (2H, m), 3,13 (3H, m), 3,46 (1H, td), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,15 (1H, d), 4,40 (1H, s), 6,13 (1H, t), 6,63 (1H, s), 7,37 – 7,59 (5H, m), 7,84 (4H, m), 8,62 (1H,

s)

Ejemplo 64c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,60 (2H, m), 1,87 (2H, m), 3,16 - 3,18 (3H, m), 3,46 (3H, m), 3,61 (1H, dd), 3,75 (1H, d), 3,95 (1H, dd), 4,15 (1H, d), 4,40 (1H, s), 4,72 (1H, t), 6,24 (1H, t), 6,63 (1H, s), 7,37 – 7,60 (5H, m), 7,84 (4H, m), 8,76 (1H, s)

Ejemplo 64d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,61 (2H, m), 1,89 (2H, m), 3,17 (1H, td), 3,46 (1H, td), 3,61 (1H, dd), 3,75 (1H, d), 3,79 (3H, s), 3,96 (1H, dd), 4,15 (1H, d), 4,40 (1H, s), 6,65 (1H, s), 7,36 – 7,60 (6H, m), 7,76 (1H, s), 7,84 - 7,86 (4H, dd), 8,35 (1H, s), 8,80 (1H, s)

Ejemplo 64e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,61 (2H, m), 1,89 (2H, m), 3,16 (1H, td), 3,38 (1H, m), 3,45 (2H, m), 3,61 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,15 (1H, d), 4,41 (2H, t), 4,53 (1H, t), 6,41 (1H, t), 6,64 (1H, s), 7,37-7,60 (5H, m), 7,84 (4H, m), 8,77 (1H, s)

Ejemplo 64f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,60 (2H, m), 1,89 (2H, m), 3,16 (1H, td), 3,48 -3,54 (3H, m), 3,61 (1H, dd), 3,74 (1H, d), 3,96 (1H, dd), 4,14 (1H, d), 4,40 (1H, s), 5,90 - 6,40 (1H, m), 6,50 (1H, t), 6,64 (1H, s), 7,38 - 7,60 (5H, m), 7,85 (4H, m), 8,88 (1H, s)

Ejemplo 64g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, m), 1,61 (2H, dd), 1,93 (2H, dd), 2,67 (3H, t), 3,17 (1H, m), 3,46 (1H, td), 3,62 (1H, dd), 3,75 (1H, m), 3,92 (1H, dd), 4,20 (1H, d), 4,45 (1H br s), 6,04 (1H, q), 6,67 (1H, s), 7,40 (2H, m), 7,67 (2H, m), 7,79 (2H, m), 7,91 (1H, m), 8,73 (1H, s)

Ejemplo 64h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,19 (3H, d), 1,61 (2H, dd), 1,93 (2H, dd), 3,12 (2H, m), 3,16 (1H, m), 3,45 (1H, td), 3,62 (1H, dd), 3,75 (1H, d), 3,95 (1H, dd), 4,15 (1H, d), 4,45 (1H, br s), 6,13 (1H, t), 6,67 (1H, s), 7,39 (2H, m), 7,65 (1H, d), 7,67 (1H, t), 7,79 (2H, m), 7,91 (1H, m), 8,65 (1H, s)

Ejemplo 64i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,42 (2H, dt), 0,65 (2H, td), 1,19 (3H, d), 1,61 (2H, dd), 1,93 (2H, dd), 2,56 (1H, m), 3,18 (1H, td), 3,46 (1H, td), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,15 (1H, d), 4,47 (1H, br s), 6,30 (1H, s), 6,67 (1H, s), 7,40 (2H, m), 7,66 (2H, m), 7,80 (2H, m), 7,90 (1H, td), 8,53 (1H, s)

Ejemplo 64j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,61 (2H, dd), 1,93 (2H, m), 3,17 (3H, q), 3,45 (3H, m), 3,61 (1H, dd), 3,73 (1H, d), 3,91 (1H, dd), 4,15 (1H, d), 4,50 (1H, br s), 4,72 (1H, t), 6,22 (1H, s), 6,67 (1H, s), 7,38 (2H, m), 7,66 (1H, t), 7,67 (1H, s), 7,79 (2H, m), 7,90 (1H, m), 8,79 (1H, s)

Ejemplo 64k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,62 (2H, dd), 1,94 (2H, dd), 3,17 (1H, td), 3,47 (1H, td), 3,62 (1H, dd), 3,74 (1H, d), 3,79 (3H, s), 3,96 (1H, dd), 4,17 (1H, d), 4,47 (1H, br s), 6,68 (1H, s), 7,38 (1H, d), 7,45 (2H, m), 7,67 (2H, m), 7,77 (1H, d), 7,83 (2H, d), 7,91 (1H, t), 8,35 (1H, s), 8,84 (1H, s)

Ejemplo 64l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, m), 1,61 (2H, dd), 1,93 (2H, dd), 3,17 (1H, td), 3,39 (1H, t), 3,45 (2H, q), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,15 (1H, d), 4,42 (1H, t), 4,50 (1H, br s), 4,53 (1H, t), 6,40 (1H, t), 6,67 (1H, s), 7,40 (2H, m), 7,66 (1H, d), 7,67 (1H, t), 7,80 (2H, d), 7,90 (1H, m), 8,80 (1H, s)

Ejemplo 64m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,61 (2H, dd), 1,94 (2H, dd), 3,17 (1H, td), 3,45 (1H, td), 3,54 (2H, m), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,17 (1H, d), 4,47 (1H, br s), 5,90-6,20 (1H, tt), 6,50 (1H, t), 6,68 (1H, s), 7,41 (2H, m), 7,67 (2H, m), 7,82 (2H, m), 7,90 (1H, m), 8,92 (1H, s)

E**jemplo 64n:** ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,56 (2H, m), 1,81 (2H, m), 3,15 (1H, m), 3,17 (2H, m), 3,46 (3H, q), 3,57 (2H, q), 3,62 (1H, m), 3,75 (1H, d), 3,96 (1H, dd), 4,06 (1H, m), 4,37 (1H, br s), 4,73 (2H, q), 6,25 (1H, t), 6,36 (1H, m), 6,58 (1H, s), 6,82 (1H, t), 7,33 (1H, m), 7,41 (3H, m), 7,96 (2H, m), 8,76 (1H, s)

E**jemplo 64o:** ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,22 (6H, s), 1,87 (1H, m), 2,08 (1H, m), 2,78 (2H, m), 3,04-3,20 (3H, m), 3,38 (2H, d), 3,48 (1H, td), 3,63 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,08 (1H, d), 4,44 (1H, br s), 4,95 (1H, t), 5,97 (1H, s), 6,46 (1H, s), 7,32 (2H, m), 7,47 (4H, m), 7,60 (1H, m), 7,78 (2H, d), 8,67 (1H, s)

E**jemplo 64p:** ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,08 (3H, d), 1,20 (3H, d), 1,87 (1H, m), 2,08 (1H, m), 2,79 (2H, m), 3,04-3,20 (3H, m), 3,36 (2H, m), 3,48 (1H, td), 3,63 (1H, dd), 3,71 (2H, m), 3,96 (1H, dd), 4,07 (1H, d), 4,45 (1H, br s), 4,78 (1H, t), 6,07 (1H, m), 6,46 (1H, s), 7,35 (2H, m), 7,47 (4H, m), 7,60 (1H, m), 7,79 (2H, d), 8,65 (1H, s)

E**jemplo 64q:** ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,08 (3H, d), 1,20 (3H, d), 1,87 (1H, m), 2,08 (1H, m), 2,79 (2H, m), 3,04 -3,20 (3H, m), 3,36 (2H, m), 3,48 (1H, td), 3,63 (1H, dd), 3,71 (1H, m), 3,73 (1H, m), 3,96 (1H, dd), 4,07 (1H, d), 4,45 (1H, br s), 4,78 (1H, t), 6,07 (1H, d), 6,46 (1H, s), 7,35 (2H, d), 7,47 (4H, m), 7,59 (1H, td), 7,79 (2H, m), 8,65 (1H, s)

E**jemplo 64r:** ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,59 (2H, m), 1,87 (1H, m), 2,08 (1H, m), 2,79 (2H, m), 3,04 (2H, m), 3,12 (1H, m), 3,25 (2H, d), 3,46 (3H, m), 3,63 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,07 (1H, m), 4,47 (2H, m), 6,18 (1H, t), 6,46 (1H, s), 7,36 (2H, m), 7,48 (4H, m), 7,59 (1H, m), 7,79 (2H, d), 8,65 (1H, s)

E**jemplo 64s:** ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,87 (1H, m), 2,12 (1H,

m), 2,75 (2H, m), 3,00-3,20 (3H, m), 3,40 (1H, t), 3,45 (2H, m), 3,61 (1H, dd), 3,74 (1H, d), 3,92 (1H, dd), 4,15 (1H, d), 4,41 (2H, m), 4,53 (1H, t), 6,41 (1H, t), 6,47 (1H, s), 7,37 (2H, m), 7,48 (4H, m), 7,60 (1H, t), 7,80 (2H, m), 8,75 (1H, s)

Ejemplo 64t: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,94 (2H, m), 1,03 (2H, m), 1,24 (3H, d), 1,58 (2H, m), 1,65 (2H, m), 3,00 (1H, m), 3,15 (1H, td), 3,36 (1H, m), 3,46 (2H, m), 3,61 (1H, dd), 3,77 (1H, d), 3,94 (1H, dd), 4,20 (1H, d), 4,42 (1H, t), 4,53 (2H, t), 6,43 (1H, t), 6,85 (1H, s), 7,50 (2H, m), 8,22 (2H, m), 8,80 (1H, s)

Ejemplo 64u: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,94 (2H, m), 1,03 (2H, m), 1,24 (3H, d), 1,59 (2H, m), 1,65 (2H, m), 3,00 (1H, m), 3,21 (1H, td), 3,54 (3H, m), 3,64 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,20 (1H, d), 4,54 (1H, br s), 5,90-6,20 (1H, tt), 6,53 (1H, t), 6,85 (1H, s), 7,51 (2H, m), 8,23 (2H, m), 8,91 (1H, s)

Ejemplo 64v: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,94 (2H, m), 1,03 (2H, m), 1,24 (3H, d), 1,59 (2H, m), 1,65 (2H, m), 3,00 (1H, m), 3,19 (1H, td), 3,49 (1H, td), 3,64 (1H, dd), 3,77 (1H, d), 3,96 (1H, dd), 4,20 (1H, d), 4,32 (2H, d), 4,54 (1H, br s), 6,62 (1H, t), 6,85 (1H, s), 6,95 (1H, br s), 7,51 (2H, m), 8,22 (2H, m), 8,92 (1H, s)

Ejemplo 64w: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,76 (2H, m), 0,85 (2H, m), 1,24 (9H, m), 1,90 (1H, m), 2,10 (1H, m), 2,45 (1H, m), 2,80 – 3,30 (4H, m), 3,20 (1H, td), 3,39 (2H, d), 3,50 (1H, td), 3,65 (1H, dd), 3,75 (1H, d), 3,95 (1H, dd), 4,20 (1H, d), 4,50 (1H, br s), 4,95 (1H, t), 6,00 (1H, s), 6,70 (1H, s), 7,45 (2H, m), 8,22 (2H, m), 8,72 (1H, s)

Ejemplo 64x: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,70 (2H, m), 0,85 (2H, m), 1,10 (3H, d), 1,25 (3H, d), 1,90 (1H, m), 2,10 (1H, m), 2,45 (1H, m), 2,80 -3,00 (4H, m), 3,15 (1H, td), 3,35 (2H, m), 3,50 (1H, td), 3,60-3,80 (3H, m), 3,95 (1H, dd), 4,20 (1H, d), 4,55 (1H, br s), 4,75 (1H, t), 6,10 (1H, d), 6,70 (1H, s), 7,45 (2H, m), 8,20 (2H, m), 8,70 (1H, s)

Ejemplo 64y: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,70 (2H, m), 0,84 (2H, m), 1,08 (3H, d), 1,23 (3H, d), 1,89 (1H, m), 2,10 (1H, m), 2,46 (1H, m), 2,84-3,00 (4H, m), 3,15 (1H, td), 3,36 (2H, m), 3,51 (1H, td), 3,67 (1H, td), 3,77 (2H, m), 3,95 (1H, dd), 4,20 (1H, d), 4,55 (1H, br s), 4,78 (1H, t), 6,09 (1H, d), 6,70 (1H, s), 7,47 (2H, m), 8,23 (2H, m), 8,70 (1H, s)

Ejemplo 64z: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,70 (2H, m), 0,84 (2H, m), 1,20 (3H, d), 1,57 (2H, m), 1,89 (1H, m), 2,10 (1H, m), 2,46 (1H, m), 2,80-3,00 (4H, m), 3,15 (4H, m), 3,45 (2H, m), 3,55 (1H, td), 3,65 (1H, dd), 3,77 (1H, d), 3,95 (1H, dd), 4,20 (1H, d), 4,45 (1H, t), 4,55 (1H, br s), 6,20 (1H, t), 6,70 (1H, s), 7,47 (2H, m), 8,25 (2H, m), 8,70 (1H, s)

Ejemplo 64aa: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, m), 1,58 (2H, m), 1,67 (2H, m), 2,47 (3H, s), 3,20 (1H, td), 3,39 (1H, q), 3,46 (2H, m), 3,63 (1H, dd), 3,76 (1H, d), 3,97

(1H, dd), 4,21 (1H, d), 4,42 (1H, t), 4,54 (1H, br s), 4,55 (1H, t), 6,43 (1H, t), 6,77 (1H, s), 7,51 (2H, m), 8,21 (2H, m), 8,82 (1H, s)

Ejemplo 64ab: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,56 (2H, m), 1,67 (2H, m), 2,46 (3H, s), 3,15 (1H, td), 3,47 -3,63 (4H, m), 3,76 (1H, d), 3,97 (1H, dd), 4,21 (1H, d), 4,57 (1H, br s), 5,90 – 6,20 (1H, m), 6,53 (1H, t), 6,78 (1H, s), 7,52 (2H, m), 8,22 (2H, m), 8,93 (1H, s

Ejemplo 64ac: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,08 (3H, d), 1,21 (3H, d), 1,77 (2H, m), 1,94 (2H, m), 2,48 (3H, d), 3,18 (1H, td), 3,36 (2H, m), 3,40 (1H, td), 3,63 (1H, dd), 3,71 (1H, m), 3,76 (1H, d), 3,96 (1H, dd), 4,15 (1H, d), 4,45 (1H, br s), 4,78 (1H, t), 6,07 (1H, m), 6,77 (1H, s), 7,39 (2H, m), 7,84-7,90 (3H, m), 8,69 (1H, s)

Ejemplo 64ad: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,08 (3H, d), 1,21 (3H, d), 1,77 (2H, m), 1,94 (2H, m), 2,48 (3H, d), 3,18 (1H, td), 3,36 (2H, m), 3,40 (1H, td), 3,63 (1H, dd), 3,71 (1H, m), 3,76 (1H, d), 3,96 (1H, dd), 4,15 (1H, d), 4,45 (1H, br s), 4,78 (1H, t), 6,07 (1H, m), 6,77 (1H, s), 7,39 (2H, m), 7,84-7,90 (3H, m), 8,70 (1H, s)

Ejemplo 64ae: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,77 (2H, m), 1,96 (2H, m), 2,48 (3H, d), 3,18 (1H, td), 3,38 (1H, m), 3,45 (2H, m), 3,62 (1H, dd), 3,76 (1H, d), 3,96 (1H, dd), 4,15 (1H, d), 4,41 (1H, t), 4,45 (1H, br s), 4,53 (1H, t), 6,41 (1H, t), 6,78 (1H, s), 7,42 (2H, m), 7,84 (1H, s), 7,90 (2H, m), 8,79 (1H, s)

Ejemplo 64af: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,74 (2H, m), 1,97 (2H, m), 3,15 (1H, td), 3,40(1H, td), 3,50 -3,60 (3H, m), 3,74 (1H, d), 3,95 (1H, dd), 4,13 (1H, d), 4,40 (1H, br s), 5,90-6,20 (1H, m), 6,50 (1H, t), 6,70 (1H, s), 7,35 (2H, m), 7,76 (3H, m), 7,95 (1H, m), 8,09 (1H, td), 8,75 (1H, d), 8,83 (1H, s)

Ejemplo 64ag: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,74 (2H, m), 2,00 (2H, m), 3,15 (1H, td), 3,52 (1H, td), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,13 (1H, d), 4,40 (1H, br s), 6,70 (1H, s), 6,87 (1H, s), 7,43 (2H, m), 7,76-7,81 (3H, m), 7,99 (1H, m), 8,09 (1H, td), 8,75 (1H, s), 8,83 (1H, m), 9,02 (1H, s), 9,60 (1H, s)

Ejemplo 64ah: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,61 (2H, dd), 1,90 (2H, dd), 3,17 (1H, m), 3,40 - 3,64 (4H, m), 3,75 (1H, d), 3,96 (1H, dd), 4,15 (1H, d), 4,45 (1H, br s), 5,90 - 6,20(1H, t), 6,49 (1H, t), 6,64 (1H, s), 7,41 (2H, d), 7,66 (2H, m), 7,78 (4H, m), 8,90 (1H, s)

Ejemplo 64ai: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, m), 1,62 (2H, m), 1,91 (2H, m), 3,15 (1H, td), 3,45 (1H, td), 3,61 (1H, dd), 3,75 (1H, d), 3,95 (1H, dd), 4,15 (1H, d), 4,45 (1H, br s), 6,66 (1H, s), 6,87 (1H, s), 7,47 (2H, d), 7,67 (2H, d), 7,79 (2H, d), 7,84 (2H, m),

8,75 (1H, s), 9,10 (1H, s), 9,60 (1H, s)

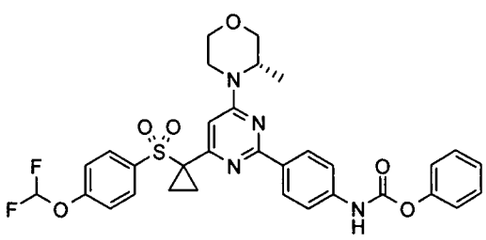
Ejemplo 64aj: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,56 (2H, m), 1,64 (2H, m), 1,94 (2H, m), 3,15-3,25 (2H, m), 3,39 (1H, m), 3,40 - 3,52 (5H, m), 3,65 (1H, dd), 3,75 (1H, d), 3,95 (1H, dd), 4,20 (1H, br s, 4,42 (1H, t), 4,54 (2H, m), 4,69 (1H, t), 6,43 (1H, t), 6,77 (1H, s), 7,50 (2H, m), 8,22 (2H, m), 8,81 (1H, s)

Ejemplo 64ak: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,57 (2H, m), 1,64 (2H, m), 1,94 (2H, m), 3,25 (1H, m), 3,51 (1H, m), 3,53 (4H, m), 3,76 (1H, dd), 3,86 (1H, d), 4,10 (1H, dd), 4,30 (1H, d), 4,65 (1H, br s), 4,70 (1H, t), 6,80 (1H, s), 6,87 (1H, s), 7,57 (2H, m), 8,29 (2H, m), 8,76 (1H, s), 9,07 (1H, s), 9,62 (1H, s)

Ejemplo 64al: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,60 (2H, m), 1,85 (2H, m), 2,78 (1H, s), 2,95 (1H, s), 3,15 (2H, m), 3,42 (2H, m), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,15 (1H, d), 4,45 (1H, s), 4,72 (1H, t), 6,23 (1H, t), 6,70 (1H, s), 7,40 (2H, m), 7,70 -8,00 (3H, m), 8,20 (1H, s), 8,80 (1H, s), 8,91 (1H, s)

La preparación de fenil *N*-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



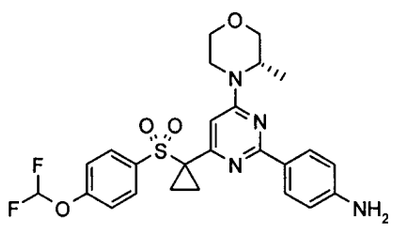
Se agregó gota a gota fenil cloroformiato (0,170 mL, 1,36 mmol) a 4-[4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (0,700 g, 1,36 mmol) e hidrogenocarbonato de sodio (0,114 g, 1,36 mmol) en dioxano y la suspensión resultante se agitó a TA durante 6 horas. La mezcla de reacción se concentró y se diluyó con DCM (50 mL) y se lavó secuencialmente con agua (10 mL), agua (10 mL) y salmuera saturada (10 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se trituró con una mezcla de éter dietílico:isohexano (20:80) para proporcionar el material deseado como un sólido blanco (0,710 g).

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Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, m), 1,62 (2H, dd), 1,90 (2H, dd), 3,16 (1H, td), 3,46 (1H, td), 3,60 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,14 (1H, d), 4,42 (1H, s), 6,67 (1H, s), 7,24 -7,27 (3H, m), 7,37 (3H, m), 7,45 (2H, m), 7,53 (2H, m), 7,84 (2H, m), 7,93 (2H, m), 10,40 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 637; HPLC tR = 3,04 min.

4-[4-[1-[4-(Difluorometoxi)fenil]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

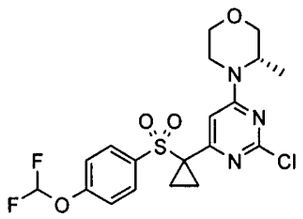


Se agregó trans-diclorobis(trifenilfosfina)paladio (II) (0,225 g, 0,32 mmol) a 2-cloro-4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,95 g, 6,41 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,476 g, 6,74 mmol) y solución acuosa de carbonato de sodio 2M (16,04 mL, 32,07 mmol) en la solución de DMF (150mL) (la solución de DMF fue 18% DMF, 82% de una mezcla 7:3:2 de DME:H_2O:etanol) a TA bajo nitrógeno. La solución resultante se agitó a 80°C durante 5 horas. La reacción se enfrió y la mezcla de reacción se diluyó con acetato de etilo y agua. La mezcla de reacción se extrajo con acetato de etilo y los orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% acetato de etilo en DCM, para proporcionar el material deseado como un sólido beige (1,35 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,59 (2H, dd), 1,87 (2H, dd), 3,26 (1H, td), 3,50 (1H, td), 3,61 (1H, dd), 3,73 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,40 (1H, br s), 5,51 (2H, br s), 6,50 (2H, m), 6,53 (1H, s), 7,21 - 7,60 (1H, m), 7,35 (2H, m), 7,68 (2H, m), 7,83 (2H, m).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 517; HPLC tR = 2,53 min.

2-Cloro-4-[1-[4-(difluorometoxi)fenil]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

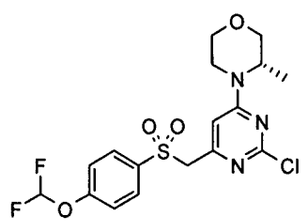


Una solución de hidróxido de sodio 50% p/v (14,2 mL, 354,96 mmol) se agregó en porciones a una solución agitada de 2-cloro-4-[[4-(difluorometoxi)fenil]sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,8 g, 6,45 mmol), bromuro de tetrabutilamonio (0,208 g, 0,65 mmol) y 1,2-dibromoetano (1,668 mL, 19,36 mmol) en tolueno (150 mL) y la suspensión resultante se agitó a 60°C durante 6 horas. La mezcla de reacción se diluyó con agua (50 mL) y luego se lavó secuencialmente con agua (2 x 50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% acetato de etilo en DCM, para proporcionar el material deseado como un aceite incoloro que solidificó en reposo (2,95 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, dd), 1,55 (2H, dd), 1,83 (2H, dd), 3,13 (1H, td), 3,40 (1H, td), 3,54 (1H, dd), 3,69 (1H, d), 3,90 (2H, dd), 4,23 (1H, br s), 6,68 (1H, s), 7,23-7,60 (1H, t), 7,37 (2H, d), 7,82 (2H, d).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 459; HPLC tR = 2,49 min.

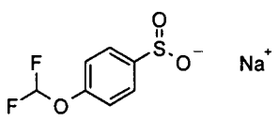
2-Cloro-4-[[4-(difluorometoxi)fenil]sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó 4-(difluorometoxi)bencenosulfinato de sodio (2,54 g, 11,03 mmol) en porciones a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,25 g, 9,19 mmol) en acetonitrilo (125 mL) y la suspensión resultante se agitó a 80°C durante 6 horas. Se agregó más 4-(difluorometoxi)bencenosulfinato de sodio (680mg, 3,39 mmol) en una porción y la suspensión se agitó a 80°C durante otras 2 horas. La mezcla de reacción se concentró y se diluyó con DCM (200 mL) y se lavó secuencialmente con solución de tiosulfato de sodio acuoso al 10% (50 mL), agua (50 mL) y salmuera saturada (50 mL). La capa orgánica se secó

sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. La goma bruta se trituró con éter dietílico para proporcionar el material deseado como un sólido beige (2,94 g).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 3,15 (1H, td), 3,42 (1H, m), 3,57 (1H, dd), 3,71 (1H, d), 3,91 (1H, br s), 3,92 (1H, dd), 4,17 (1H, br s), 4,64 (2H, s), 6,68 (1H, s), 7,25-7,60 (1H, t), 7,41 (2H, m), 7,84 (2H, m).
Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 434; HPLC tR = 2,29 min.

4-(Difluorometoxi)bencenosulfinato de sodio

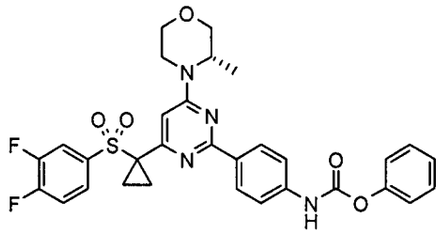


Una solución de sulfito de sodio (1,470 g, 11,66 mmol) en agua (15 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (1,960 g, 23,33 mmol) a la solución agitada. La solución resultante se agitó a 50°C durante 1 hora. Se agregó gota a gota cloruro de 4-(difluorometoxi)benceno-1-sulfonilo (2,83 g, 11,66 mmol) con cuidado a la solución y se agitó a 50°C durante 18 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en metanol (15 mL). La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar un producto bruto que se trituró con isohexano para proporcionar el material deseado como un sólido crema (2,85 g).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 7,10 (2H, dd), 7,50 (2H, dd).

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

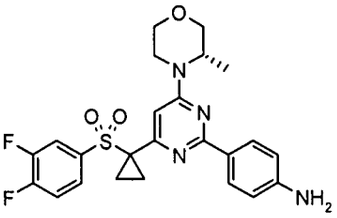


Se agregó gota a gota fenil cloroformiato (0,206 mL, 1,64 mmol) a 4-[4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (800 mg, 1,64 mmol) e hidrogenocarbonato de sodio (138 mg, 1,64 mmol) en dioxano y la suspensión resultante se agitó a TA durante 6 horas. La mezcla de reacción se concentró y se diluyó con DCM (50 mL) y se lavó secuencialmente con agua (2 x 10 mL) y salmuera saturada (10 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se trituró con acetonitrilo para proporcionar el material deseado como un sólido blanco (1,0 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,63 (2H, dd), 1,94 (2H, dd), 3,17 (1H, td), 3,47 (1H, td), 3,61 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,18 (1H, d), 4,50 (1H, br s), 6,71 (1H, s), 7,25 (2H, dt), 7,29 (1H, m), 7,45 (2H, dd), 7,54 (2H, d), 7,67 (2H, m), 7,91 (3H, dd), 10,40 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 607; HPLC tR = 3,05 min.

4-[4-[1-(3,4-Difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



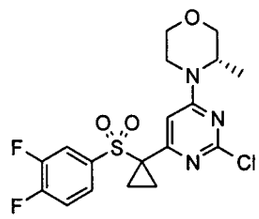
Se agregó trans-diclorobis(trifenilfosfina)paladio (II) (0,252 g, 0,36 mmol) a 2-cloro-4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,09 g, 7,19 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,575 g, 7,19 mmol) y una solución acuosa de carbonato de sodio 2M (17,97 mL, 35,94 mmol) en la solución de DMF (la solución de DMF fue 18% DMF, 82% de una mezcla 7:3:2 de DME:H_2O:etanol) (150mL) a TA bajo nitrógeno. La solución resultante se agitó a 80°C durante 5 horas. La reacción se enfrió y la mezcla se diluyó con acetato de etilo y agua. La mezcla de reacción se extrajo con acetato de etilo y los orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se

evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 5% acetato de etilo en DCM, para proporcionar un material que se purificó adicionalmente mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol, para proporcionar el material deseado como un sólido tostado (1,94 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,59 (2H, dd), 1,91 (2H, dd), 3,10 (1H, td), 3,45 (1H, td), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,13 (1H, m), 4,43 (1H, br s), 5,53 (2H, d), 6,50 (2H, m), 6,57 (1H, s), 7,64 (1H, m), 7,65 (3H, m), 7,89 (1H, m).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 487; HPLC tR = 2,55 min.

2-Cloro-4-[1-(3,4-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

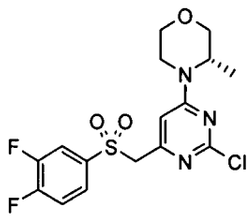


Una solución de hidróxido de sodio 50% p/v (17,32 mL, 433,10 mmol) se agregó en porciones a una solución agitada de 2-cloro-4-[(3,4-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,18 g, 7,87 mmol), bromuro de tetrabutilamonio (0,254 g, 0,79 mmol) y 1,2-dibromoetano (2,036 mL, 23,62 mmol) en tolueno (200 mL) y la suspensión resultante se agitó a 60°C durante 6 horas. La mezcla de reacción se diluyó con agua (50 mL) y se lavó secuencialmente con agua (2 x 50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (3,09 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,56 (2H, dd), 1,88 (2H, dd), 3,15 (1H, td), 3,40 (1H, td), 3,54 (1H, dd), 3,69 (1H, d), 3,91 (1H, dd), 3,97 (1H, d), 4,29 (1H, br s), 6,73 (1H, s), 7,65 (1H, m), 7,66 (1H, m), 7,92 (1H, ddd).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 430; HPLC tR = 2,41 min.

2-Cloro-4-[(3,4-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

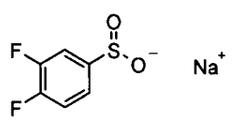


Se agregó 3,4-difluorobencenosulfinato de sodio (3,40 g, 16,97 mmol) en porciones a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (6 g, 16,97 mmol) en acetonitrilo (200 mL) y la suspensión resultante se agitó a 80°C durante 6 horas. Se agregó más 3,4-difluorobencenosulfinato de sodio (680mg, 3,39mmol) en una porción y la suspensión se agitó a 80°C durante otras 2 horas. La mezcla de reacción se concentró y se diluyó con DCM (200 mL) y se lavó secuencialmente con agua (2 x 50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% acetato de etilo en DCM, para proporcionar el material deseado como un sólido amarillo (4,58 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, m), 3,10-3,20 (1H, td), 3,40-3,45 (1H, td), 3,55-3,60 (1H, dd), 3,70 (1H, d), 3,90-4,00 (2H, dd), 4,20 (1H, br s), 4,70 (2H, s), 6,77 (1H, s), 7,66 (1H, m), 7,74 (1H, dt), 7,95 (1H, ddd).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 404; HPLC tR = 2,24 min.

3,4-difluorobencenosulfinato de sodio



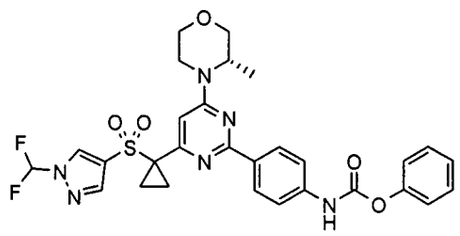
Una solución de sulfito de sodio (2,96 g, 23,52 mmol) en agua (25 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (3,95 g, 47,04 mmol) a la solución agitada. La solución resultante se agitó a 50°C durante 1 hora. Se agregó en porciones cloruro de 3,4-difluorobenceno-1-sulfonilo (5 g, 23,52 mmol) a la solución y se agitó a 50°C durante 18 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en metanol (15 mL). La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar el material deseado como un sólido blanco (5,30 g), que se secó durante toda la noche al vacío y se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 7,28 (1H, ddd), 7,37 (2H, m).

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente

La preparación de fenil *N*-[4-[4-[1-[1-(difluorometil)pirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-[1-(difluorometil)pirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

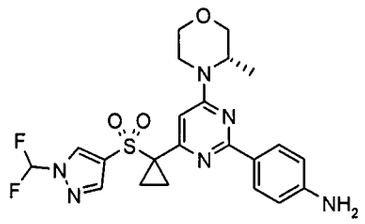


Se agregó gota a gota fenil cloroformiato (0,018 mL, 0,14 mmol) a 4-[4-[1-[1-(difluorometil)pirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (70 mg, 0,14 mmol) e hidrogenocarbonato de sodio (11,99 mg, 0,14 mmol) en dioxano y la suspensión resultante se agitó a TA durante 6 horas. La mezcla de reacción se concentró y se diluyó con DCM (50 mL) y se lavó secuencialmente con agua (2 x 10 mL) y salmuera saturada (10 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se trituró con éter dietílico:isohexano (20:80) para proporcionar el material deseado como un sólido blanco (80 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,59 (2H, m), 1,89 (2H, m), 3,15 (1H, td), 3,45 (1H, td), 3,63 (1H, dd), 3,75 (1H, d), 3,95 (1H, dd), 4,15 (1H, d), 4,50 (1H, br s), 6,75 (1H, m), 7,26 (3H, m), 7,45 (2H, m), 7,56 (2H, m), 7,70-8,00 (1H, t),8,00 (2H, m), 8,17 (1H, s), 8,93 (1H, s), 10,40 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 611; HPLC tR = 2,83 min.

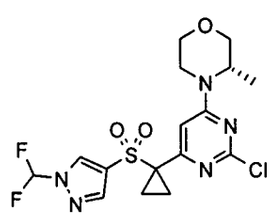
4-[4-[1-[1-(Difluorometil)pirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



Se agregó trans-diclorobis(trifenilfosfina)paladio (II) (0,197 g, 0,28 mmol) a 2-cloro-4-[1-[1-(difluorometil)pirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,44 g, 5,62 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,232 g, 5,62 mmol) y una solución acuosa de carbonato de sodio 2M (14,06 mL, 28,12 mmol) en la solución de DMF (la solución de DMF fue 18% DMF, 82% de una mezcla 7:3:2 de DME:H_2O:etanol) (150mL) y la solución resultante se agitó a 80°C durante 5 horas. La mezcla de reacción se repartió entre acetato de etilo y agua, las capas se separaron y la capa acuosa se extrajo con acetato de etilo. Los orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 5% acetato de etilo en DCM, para proporcionar el material deseado como un sólido tostado (0,070 g).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 491; HPLC tR = 2,23 min.

2-Cloro-4-[1-[1-(difluorometil)pirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



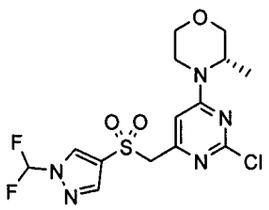
Una solución de hidróxido de sodio 50% p/v (16,18 mL, 404,59 mmol) se agregó en porciones a una solución agitada de 2-cloro-4-[[1-(difluorometil)pirazol-4-il]sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3 g, 7,36 mmol), bromuro de tetrabutilamonio (0,237 g, 0,74 mmol) y 1,2-dibromoetano (1,902 mL, 22,07 mmol) en tolueno (200 mL) y la suspensión resultante se agitó a TA durante 6 horas. La mezcla de reacción se diluyó con agua (50 mL) y se lavó secuencialmente con agua (2 x 50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de

elución de 0 a 10% acetato de etilo en DCM, para proporcionar el material deseado como un aceite amarillo (2,44 g) que solidificó en reposo.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,57 (2H, dd), 1,82 (2H, dd), 3,16 (1H, td), 3,40 (1H, td), 3,56 (1H, dd), 3,70 (1H, d), 3,92 (1H, dd), 4,04 (1H, d), 4,30 (1H, br s), 6,78 (1H, s), 7,70-8,00 (1H, t), 8,19 (1H, s), 8,93 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 434; HPLC tR = 2,15 min.

2-Cloro-4-[[1-(difluorometil)pirazol-4-il]sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

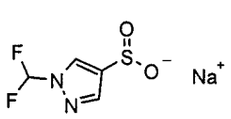


Se agregó en porciones 1-(difluorometil)-1H-pirazol-4-sulfinato de sodio (3,28 g, 16,09 mmol) a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4,74 g, 13,41 mmol) en acetonitrilo (150 mL) y la suspensión resultante se agitó a 80°C durante 6 horas. Se agregó más 1-(difluorometil)-1H-pirazol-4-sulfinato de sodio (680 mg, 3,39mmol) en una porción y la suspensión se agitó a 80°C durante otras 2 horas. La mezcla de reacción se concentró y se diluyó con DCM (200 mL) y se lavó secuencialmente con solución de tiosulfato de sodio acuoso al 10% (50 mL), agua (50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El residuo bruto se trituró con éter dietílico para proporcionar el material deseado como un sólido beige (4,50 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 3,18 (1H, td), 3,43 (1H, td), 3,58 (1H, dd), 3,72 (1H, d), 3,93 (2H, dd), 4,21 (1H, br s), 4,67 (2H, s), 6,77 (1H, s), 7,70-8,05 (1H, t), 8,13 (1H, s), 8,87 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 408; HPLC tR = 1,91 min.

1-(difluorometil)-1H-pirazol-4-sulfinato de sodio

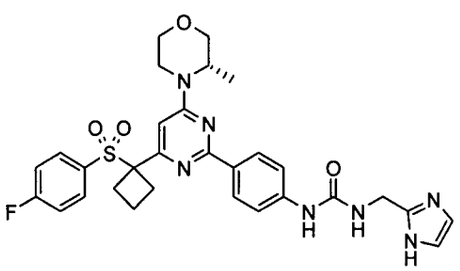


Una solución de sulfito de sodio (2,87 g, 22,81 mmol) en agua (25 mL) se agitó a TA durante

10 minutos. Se agregó bicarbonato de sodio (3,83 g, 45,62 mmol) a la solución agitada. La solución resultante se agitó a 50°C durante 1 hora. Se agregó gota a gota cloruro de 1-(difluorometil)-1H-pirazol-4-sulfonilo (4,94 g, 22,81 mmol) con cuidado a la solución y se agitó a 50°C durante 18 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en metanol (15 mL). La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar un sólido que se trituró con isohexano para proporcionar el material deseado como un sólido blanco (5,85 g).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 7,60 (1H, m), 7,74 (1H, s), 7,90 (1H, m).

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente

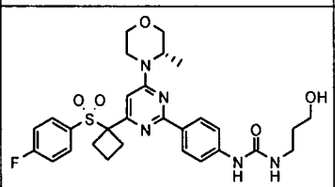
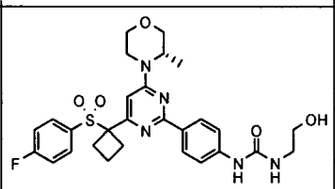
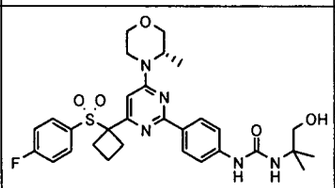
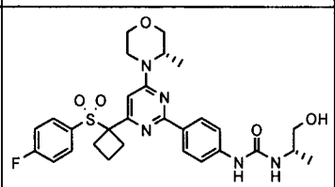
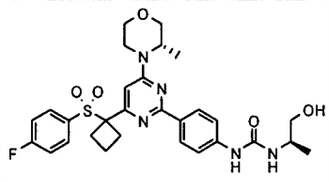
Ejemplo 65: 1-[4-[4-[1-(4-Fluorofenil)sulfonilciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea



Se agregó en una porción *C*-(1*H*-Imidazol-2-il)-metilamina (17,73 mg, 0,18 mmol) a fenil *N*-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (100 mg, 0,17 mmol) y trietilamina (0,069 mL, 0,50 mmol) en NMP (2 mL) a TA y se agitó durante un período de 16 horas al aire. El producto bruto se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido crema (42 mg).
Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (d, 3H), 1,83 - 1,93 (m, 1H), 2,04 - 2,15 (m, 1H), 2,75 - 2,82 (m, 2H), 3,02 - 3,11 (m, 2H), 3,16 (td, 1H), 3,49 (td, 1H), 3,64 (dd, 1H), 3,76 (d, 1H), 3,97 (dd, 1H), 4,15 (d, 1H), 4,32 (d, 2H), 4,44 - 4,54 (m, 1H), 6,55 (s, 1H), 6,60 (t, 1H), 6,80 - 6,90 (m, 1H), 7,00 - 7,08 (m, 1H), 7,29 (dd, 2H), 7,40 (dt, 2H), 7,55 (ddd, 2H), 7,80 (d, 2H), 8,90 (s, 1H), 11,85 (s, 1H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 606,55; HPLC tR = 2,09 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
65a		1-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	584,5	2,15
65b		1-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	570,5	2,05
65c		1-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	598,6	2,33
65d		1-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea	584,5	2,15
65e		1-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-	584,5	2,13

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		hidroxipropan-2-il]urea		

Ejemplo 65a : ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (d, 3H), 1,57 - 1,63 (m, 2H), 1,83 - 1,94 (m, 1H), 2,05 - 2,15 (m, 1H), 2,75 - 2,82 (m, 2H), 3,01 - 3,09 (m, 2H), 3,17 (dd, 3H), 3,48 (dd, 3H), 3,64 (dd, 1H), 3,76 (d, 1H), 3,97 (dd, 1H), 4,10 - 4,19 (m, 1H), 4,48 (t, 2H), 6,18 (t, 1H), 6,54 (s, 1H), 7,29 (t, 2H), 7,38 (d, 2H), 7,55 (ddd, 2H), 7,78 (d, 2H), 8,68 (s, 1H)

Ejemplo 65b: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (d, 3H), 1,83 - 1,94 (m, 1H), 2,04 - 2,15 (m, 1H), 2,75 - 2,82 (m, 2H), 3,01 - 3,09 (m, 2H), 3,16 - 3,20 (m, 3H), 3,44 - 3,50 (m, 3H), 3,64 (dd, 1H), 3,76 (d, 1H), 3,97 (dd, 1H), 4,09 - 4,19 (m, 1H), 4,43 - 4,53 (m, 1H), 4,73 (t, 1H), 6,23 (t, 1H), 6,54 (s, 1H), 7,29 (t, 2H), 7,37 (d, 2H), 7,55 (ddd, 2H), 7,78 (d, 2H), 8,77 (s, 1H)

Ejemplo 65c: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (d, 3H), 1,25 (s, 6H), 1,83 - 1,94 (m, 1H), 2,05 - 2,15 (m, 1H), 2,73 - 2,83 (m, 2H), 3,01 - 3,09 (m, 2H), 3,12 - 3,20 (m, 1H), 3,39 (d, 2H), 3,49 (td, 1H), 3,64 (dd, 1H), 3,76 (d, 1H), 3,97 (dd, 1H), 4,10 - 4,18 (m, 1H), 4,43 - 4,53 (m, 1H), 4,96 (t, 1H), 5,98 (s, 1H), 6,54 (s, 1H), 7,27 - 7,35 (m, 4H), 7,53 - 7,57 (m, 2H), 7,77 (d, 2H), 8,70 (s, 1H)

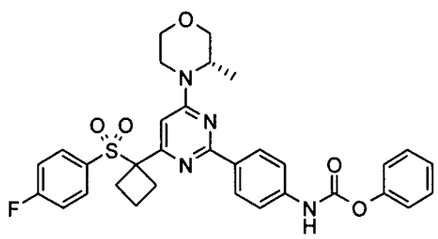
Ejemplo 65d: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,09 (d, 3H), 1,21 (d, 3H), 1,82 - 1,93 (m, 1H), 2,02 - 2,15 (m, 1H), 2,75 - 2,82 (m, 2H), 3,01 - 3,11 (m, 2H), 3,16 (td, 1H), 3,33 - 3,43 (m, 2H), 3,49 (td, 1H), 3,64 (dd, 1H), 3,69 - 3,73 (m, 1H), 3,76 (d, 1H), 3,97 (dd, 1H), 4,11 - 4,19 (m, 1H), 4,44 - 4,53 (m, 1H), 4,79 (t, 1H), 6,08 (d, 1H), 6,54 (s, 1H), 7,29 (ddd, 2H), 7,36 (d, 2H), 7,55 (ddd, 2H), 7,78 (d, 2H), 8,68 (s, 1H)

Ejemplo 65e: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,09 (d, 3H), 1,21 (d, 3H), 1,83 - 1,94 (m, 1H), 2,05 - 2,15 (m, 1H), 2,75 - 2,82 (m, 2H), 3,01 - 3,09 (m, 2H), 3,16 (td, 1H), 3,33 - 3,43 (m, 2H), 3,49 (td, 1H), 3,64 (dd, 1H), 3,69 - 3,73 (m, 1H), 3,76 (d, 1H), 3,97 (dd, 1H), 4,10 - 4,18 (m, 1H), 4,44 - 4,53 (m, 1H), 4,79 (t, 1H), 6,08 (d, 1H), 6,54 (s, 1H), 7,29 (ddd, 2H), 7,36 (d, 2H), 7,55 (ddd, 2H), 7,78 (d, 2H), 8,68 (s, 1H)

La preparación de fenil *N*-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3*S*)-3-metilmorfolin-

4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

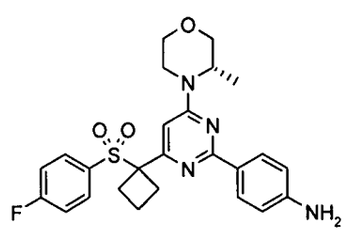


Se agregó gota a gota fenil cloroformiato (0,285 mL, 2,27 mmol) a 4-[4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (1,095 g, 2,27 mmol) e hidrogenocarbonato de sodio (0,191 g, 2,27 mmol) en dioxano (20 mL) y la suspensión resultante se agitó a TA durante 3 horas. La mezcla de reacción se evaporó y DCM (50 mL) se agregó y se lavó secuencialmente con agua (2 x 20 mL) y salmuera saturada (20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como una película seca (1,4 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,22 (d, 3H), 1,84 - 1,95 (m, 1H), 2,05 - 2,16 (m, 1H), 2,74 - 2,86 (m, 2H), 3,02 - 3,12 (m, 2H), 3,17 (td, 1H), 3,45 - 3,55 (m, 1H), 3,61 - 3,69 (m, 1H), 3,71 - 3,85 (m, 1H), 3,93 - 4,03 (m, 1H), 4,11 - 4,24 (m, 1H), 4,45 - 4,58 (m, 1H), 7,22 - 7,35 (m, 5H), 7,42 - 7,49 (m, 2H), 7,50 - 7,60 (m, 4H), 7,88 (d, 2H), 10,40 (s, 1H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 603,17; HPLC tR = 3,15 min.

4-[4-[1-(4-Fluorofenil)sulfonilciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



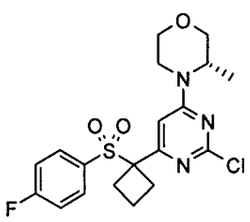
Se agregó en una porción cloruro de bis(trifenilfosfina)paladio(II) (0,086 g, 0,12 mmol) a 2-cloro-4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,046 g, 2,46 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,538 g, 2,46 mmol) y

carbonato de sodio (6,14 mL, 12,28 mmol) en una solución de DMF:DME:agua:etanol y la mezcla de reacción se desgasificó por completo y se agitó a 80°C durante 3 horas bajo una atmósfera de nitrógeno. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (50 mL) y se lavó secuencialmente con agua (50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 100% acetato de etilo en isohexano, para proporcionar el material deseado como una película seca incolora (1,1 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 (d, 3H), 1,82 - 1,95 (m, 1H), 2,03 - 2,14 (m, 1H), 2,71 - 2,82 (m, 2H), 2,98 - 3,08 (m, 2H), 3,13 (td, 1H), 3,48 (td, 1H), 3,63 (dd, 1H), 3,75 (d, 1H), 3,93 - 3,99 (m, 1H), 4,07 - 4,15 (m, 1H), 4,41 - 4,49 (m, 1H), 5,49 (d, 1H), 6,44 (s, 1H), 6,49 (d, 2H), 7,28 (ddd, 2H), 7,54 (ddd, 2H), 7,62 (d, 2H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 483,27; HPLC tR = 2,39 min.

2-Cloro-4-[1-(4-fluorofenil)sulfonilciclobutil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



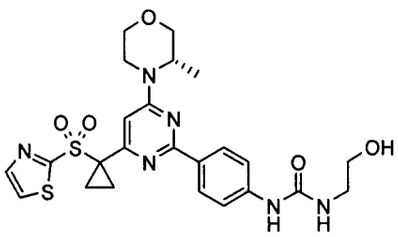
Se agregó hidróxido de sodio (solución 50% p/p) (16,91 g, 422,79 mmol) a 2-cloro-4-[(4-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,966 g, 7,69 mmol), 1,3-dibromopropano (2,341 mL, 23,06 mmol) y bromuro de tetrabutilamonio (0,248 g, 0,77 mmol) en tolueno (150 mL) y la suspensión resultante se agitó a 45°C durante 1 hora. Los orgánicos se lavaron con agua dos veces, se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 30% acetato de etilo en DCM, para proporcionar el material deseado como una película seca incolora (1,055 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,18 (d, 3H), 1,81 - 1,92 (m, 1H), 2,01 - 2,12 (m, 1H), 2,65 - 2,72 (m, 2H), 2,91 - 3,01 (m, 2H), 3,14 (td, 1H), 3,42 (td, 1H), 3,57 (dd, 1H), 3,71 (d, 1H), 3,88 - 4,00 (m, 2H), 4,23 - 4,40 (m, 1H), 6,56 (s, 1H), 7,38 - 7,44 (m, 2H), 7,54 - 7,60 (m, 2H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 426,06; HPLC tR = 2,52 min.

La preparación de 2-cloro-4-[(4-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 66: 3-(2-Hidroxietil)-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea

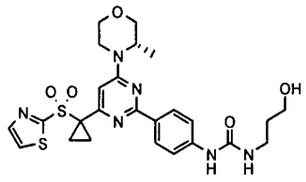
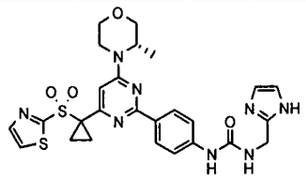


Se agregó etanolamina (0,052 mL, 0,87 mmol) en una porción a fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]carbamato (100 mg, 0,17 mmol) y trietilamina (0,072 mL, 0,52 mmol) en NMP (2 mL) y se entibió hasta alcanzar 55°C durante un período de 16 horas al aire. La mezcla de reacción bruta se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como una película seca incolora. (84 mg)

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (d, 3H), 1,77 - 1,82 (m, 2H), 1,98 - 2,02 (m, 2H), 3,14 - 3,21 (m, 3H), 3,44 - 3,50 (m, 3H), 3,62 (dd, 1H), 3,76 (d, 1H), 3,97 (dd, 1H), 4,10 - 4,21 (m, 1H), 4,40 - 4,51 (m, 1H), 4,74 (t, 1H), 6,25 (t, 1H), 6,74 (s, 1H), 7,40 (d, 2H), 7,85 (d, 2H), 8,24 (d, 1H), 8,29 (d, 1H), 8,78 (s, 1H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 545,75; HPLC tR = 1,79 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]carbamato y la amina apropiada.

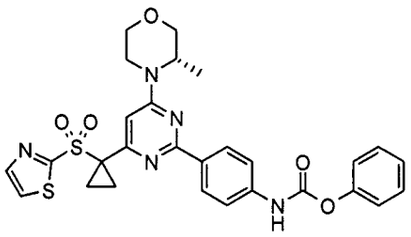
Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
66a		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea	559,8	1,84
66b		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea	581,8	1,30

Ejemplo 66a : ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21, 1,60, 1,77 - 1,82, 1,97 - 2,03, 3,14 - 3,21, 3,44 - 3,50, 3,62, 3,76, 3,97, 4,12 - 4,20, 4,40 - 4,52, 4,49, 6,19, 6,74, 7,40, 7,85, 8,23, 8,28, 8,68

Ejemplo 66b : ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (d, 3H), 1,77 - 1,82 (m, 2H), 1,97 - 2,03 (m, 2H), 3,14 - 3,21 (m, 1H), 3,47 (td, 1H), 3,62 (dd, 1H), 3,76 (d, 1H), 3,97 (dd, 1H), 4,11 - 4,21 (m, 1H), 4,32 (d, 2H), 4,39 - 4,54 (m, 1H), 6,62 (t, 1H), 6,74 (s, 1H), 6,88 - 7,01 (m, 2H), 7,43 (d, 2H), 7,87 (d, 2H), 8,23 (d, 1H), 8,28 (d, 1H), 8,90 (s, 1H), 11,85 (s, 1H)

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]carbamato

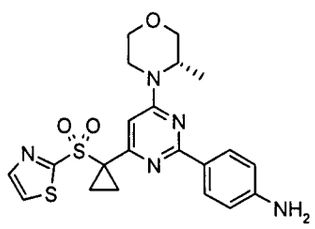


Se agregó gota a gota fenil cloroformiato (0,123 mL, 0,98 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]anilina (450 mg, 0,98 mmol) e hidrogenocarbonato de sodio (83 mg, 0,98 mmol) en dioxano y la suspensión resultante se agitó a TA durante 3 horas. La mezcla de reacción se evaporó y DCM (50 mL) se agregó y se lavó secuencialmente con agua (2 x 20 mL) y salmuera saturada (20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto deseado como una película seca (522 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,22 (d, 3H), 1,78 - 1,84 (m, 2H), 1,98 - 2,04 (m, 2H), 3,19 (td, 1H), 3,48 (td, 1H), 3,63 (dd, 1H), 3,76 (d, 1H), 3,97 (dd, 1H), 4,12 - 4,24 (m, 1H), 4,40 - 4,52 (m, 1H), 6,79 (s, 1H), 7,23 - 7,32 (m, 3H), 7,46 (t, 2H), 7,55 (d, 2H), 7,95 (d, 2H), 8,24 (d, 1H), 8,29 (d, 1H), 10,41 (s, 1H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 578,04; HPLC tR = 2,83 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]anilina



Cloruro de bis(trifenilfosfina)paladio(II) (0,139 g, 0,20 mmol) se agregó en una porción a 2-cloro-4-[(*3S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidina (1,59 g, 3,97 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,869 g, 3,97 mmol) y carbonato de sodio (9,92 mL, 19,83 mmol) una solución de DMF, DME, agua y etanol a TA bajo nitrógeno. La mezcla de reacción se desgasificó por completo y se agitó a 80°C durante 3 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (50 mL) y se lavó secuencialmente con agua (50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución

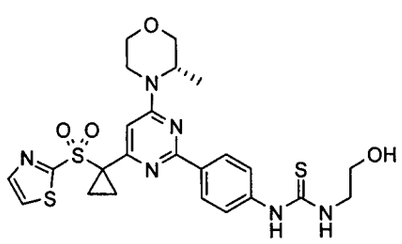
de 30 a 100 % acetato de etilo en isohexano, para proporcionar el material deseado como una película beige seca (1,430 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,16 - 1,21 (m, 3H), 1,75 - 1,79 (m, 2H), 1,96 - 2,01 (m, 2H), 3,14 (td, 1H), 3,46 (td, 1H), 3,61 (dd, 1H), 3,75 (d, 1H), 3,96 (dd, 1H), 4,07 - 4,17 (m, 1H), 4,35 - 4,48 (m, 1H), 5,50 - 5,55 (m, 1H), 6,52 (d, 2H), 6,63 (s, 1H), 7,69 (d, 2H), 8,22 (d, 1H), 8,27 (d, 1H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 458,16; HPLC tR = 1,68 min.

La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidina se describió anteriormente.

Ejemplo 67: 3-(2-Hidroxietil)-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]tiourea



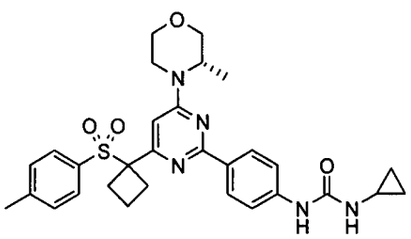
Una solución de 1,1'-tiocarbonildiimidazol (50,6 mg, 0,28 mmol) en DCM (2 mL) se agregó a una solución agitada de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]anilina (100 mg, 0,22 mmol) en THF (1 mL) y DCM (2 mL) a TA, durante un período de 2 minutos bajo nitrógeno. La solución resultante se agitó a TA durante 2 horas. Se agregaron trietilamina (0,030 mL, 0,22 mmol) y etanolamina (0,066 mL, 1,09 mmol) a la mezcla de reacción. La solución resultante se agitó a TA durante 60 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetonitrilo (2 mL), se filtró y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido beige (88 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,22 (d, 3H), 1,78 - 1,84 (m, 2H), 1,98 - 2,03 (m, 2H), 3,19 (td, 1H), 3,48 (td, 1H), 3,54 - 3,60 (m, 3H), 3,63 (dd, 1H), 3,76 (d, 1H), 3,97 (dd, 1H), 4,16 (d, 1H), 4,41 - 4,53 (m, 1H), 4,78 - 4,88 (m, 1H), 6,79 (s, 1H), 7,54 (d, 2H), 7,82 - 7,89 (m, 1H), 7,92 (dt, 2H), 8,24 (d, 1H), 8,28 (d, 1H), 9,78 (s, 1H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 561,82; HPLC tR = 2,12 min.

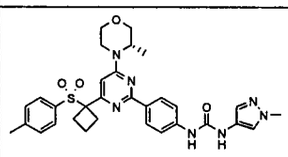
La preparación de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]anilina se describió anteriormente.

Ejemplo 68: 3-Ciclopropil-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclobutil]pirimidin-2-il]fenil]urea



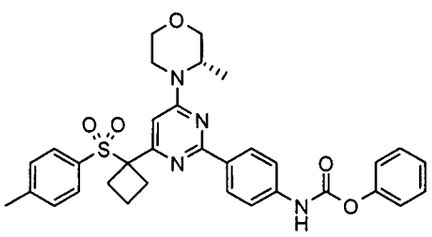
Se agregó trietilamina (0,057 mL, 0,41 mmol) a fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclobutil]pirimidin-2-il]fenil]carbamato (82 mg, 0,14 mmol) y ciclopropilamina (0,047 mL, 0,68 mmol) en NMP (2 mL) y la solución resultante se agitó a 50°C durante toda la noche. El producto bruto se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (43 mg).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40-0,44 (2H, m), 0,63-0,67 (2H, m), 1,19-1,20 (3H, d), 1,81-1,92 (1H, m), 2,02-2,13 (1H, m), 2,27 (3H, s), 2,54-2,59 (1H, m), 2,73-2,79 (2H, m), 2,99-3,07 (2H, m), 3,09-3,17 (1H, td), 3,45-3,51 (1H, td), 3,62-3,65 (1H, dd), 3,74-3,77 (1H, d), 3,95-3,98 (1H, dd), 4,07-4,10 (1H, d), 4,44 (1H, bs), 6,40-6,41 (1H, d), 6,45 (1H, s), 7,24-7,26 (2H, d), 7,35-7,40 (4H, m), 7,76-7,78 (2H, d), 8,49 (1H, s).
Espectro de LCMS: m/z (ESI+)$(M+H)^+$562 = HPLC tR = 2,60 min.

El siguiente compuesto se elaboró en forma análoga utilizando la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
68a		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclobutil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	601	2,44

Ejemplo 68a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19-1,21 (3H, d), 1,83-1,90 (1H, m), 2,04-2,12 (1H, m), 2,28 (3H, s), 2,73-2,80 (2H, m), 3,00-3,07 (2H, m), 3,10-3,15 (1H, td), 3,45-3,52 (1H, td), 3,62-3,66 (1H, dd), 3,75-3,78 (1H, d), 3,79 (3H, s), 3,95-3,99 (1H, dd), 4,08-4,11 (1H, d), 4,45 (1H, bs), 6,46 (1H, s), 7,24-7,26 (2H, d), 7,35-7,38 (3H, m), 7,42-7,44 (2H, d), 7,77 (1H, s), 7,79-7,81 (2H, d), 8,35 (1H, s), 8,79 (1H, s).

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclobutil]pirimidin-2-il]fenil]carbamato



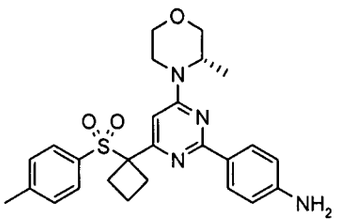
Se agregó fenil cloroformiato (0,034 mL, 0,27 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclobutil]pirimidin-2-il]anilina (129 mg, 0,27 mmol)e hidrogenocarbonato de sodio (34,0 mg, 0,40 mmol) en dioxano (10 mL). La suspensión resultante se agitó a TA durante 5 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetato de etilo (125 mL) y se lavó secuencialmente con agua (125 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado (182 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,34 (3H, d), 1,87 - 1,98 (1H, m), 2,19 - 2,30 (4H, m), 2,72 - 2,81 (2H, m), 3,15 - 3,25 (2H, m), 3,30 (1H, td), 3,63 (1H, td), 3,70

(1H, s), 3,72 - 3,82 (3H, m), 4,03 - 4,16 (3H, m), 4,46 (1H, q), 6,56 (1H, s), 7,01 (21H, s), 7,07 (2H, d), 7,19 - 7,27 (3H, m, oscurecido por pico de $CDCl_3$), 7,35 - 7,42 (6H, m), 7,91 (2H, d).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 599; HPLC tR = 3,25 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclobutil]pirimidin-2-il]anilina

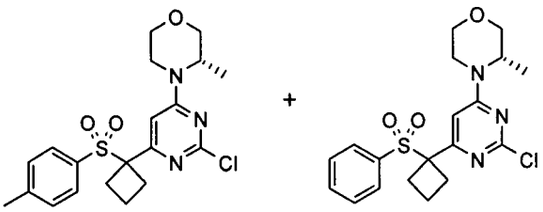


Se agregó en una porción cloruro de bis(trifenilfosfina)paladio(II) (0,131 g, 0,19 mmol) a una mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclobutil]pirimidina y 4-[1-(bencenosulfonil)ciclobutil]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,522 g), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,817 g, 3,73 mmol) y una solución de carbonato de sodio (9,33 mL, 18,66 mmol) en DMF (18 mL), DME (47,8 mL), agua (20,5 mL)y etanol (13,5 mL) y la solución resultante se agitó a 80°C durante 2 horas. La mezcla de reacción se concentró al vacío para eliminar el etanol luego la mezcla de reacción se acidificó con ácido clorhídrico 2M. La suspensión resultante se purificó mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol, seguido por HPLC preparativa, para proporcionar el material deseado como un sólido blancuzco (0,136 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,32 (3H, d), 1,85 - 1,97 (1H, m), 2,17 - 2,29 (4H, m), 2,71 - 2,81 (2H, m), 3,11 - 3,33 (3H, m), 3,61 (1H, t), 3,74 - 3,90 (4H, m), 4,03 (1H, d), 4,09 - 4,15 (1H, m), 4,44 (1H, q), 6,48 (1H, s), 6,57 (2H, d), 7,07 (2H, d), 7,36 (2H, d), 7,75 (2H, d).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 479; HPLC tR = 2,23 min.

Mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclobutil]pirimidina y 4-[1-(bencenosulfonil)ciclobutil]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

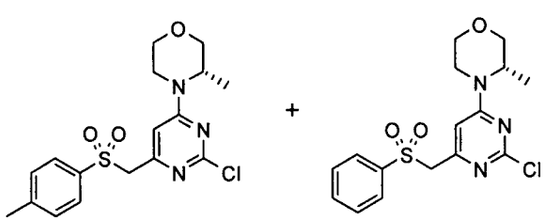


Se agregó hidróxido de sodio (solución 50% p/p) (52,4 g, 654,89 mmol) a una mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metilfenil)sulfonilmetil]pirimidina y 4-(bencenosulfonilmetil)-2-cloro-6-[(3S)-3-metilmorfolin-4-il]pirimidina (4,38 g), 1,3-dibromopropano (3,63 mL, 35,72 mmol) y bromuro de tetrabutilamonio (0,384 g, 1,19 mmol) en tolueno (270 mL). La suspensión resultante se agitó a 45°C durante 1 hora. La mezcla de reacción se diluyó con agua (300 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar un sólido blanco (1,522 g) que pareció ser una mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclobutil]pirimidina (12%) y 4-[1-(bencenosulfonil)ciclobutil]-2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (83%). La mezcla se utilizó en la siguiente etapa sin purificación adicional.

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 422; HPLC tR = 2,59 min.

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 408; HPLC tR = 2,45 min.

Mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metilfenil)sulfonilmetil]pirimidina y 4-(bencenosulfonilmetil)-2-cloro-6-[(3S)-3-metilmorfolin-4-il]pirimidina



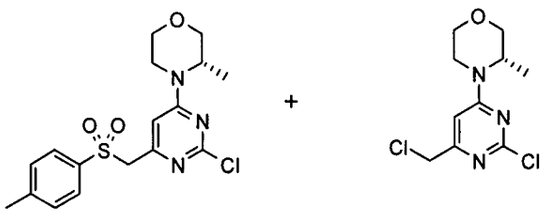
Se agregó ácido bencenosulfínico, sal de sodio (3,66 g, 22,32 mmol) a una mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metilfenil)sulfonilmetil]pirimidina y 2-cloro-4-(clorometil)-6-[(3S)-3-metilmorfolin-4-il]pirimidina (5,85 g) en acetonitrilo (200 mL) bajo argón. La suspensión resultante se agitó a reflujo durante 18 horas. Se agregaron más ácido bencenosulfínico, sal de sodio (1,2 g, 7,31 mmol) y yoduro de sodio (0,335 g, 2,23 mmol) y la suspensión se agitó a reflujo durante otras 24 horas. La mezcla de reacción se evaporó hasta

secarse, se disolvió nuevamente en DCM (500 mL) y se lavó con agua (250 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó. El material bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar un sólido blanco (4,38 g) que pareció ser una mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metilfenil)sulfonilmetil]pirimidina (7%) y 4-(bencenosulfonilmetil)-2-cloro-6-[(3S)-3-metilmorfolin-4-il]pirimidina (93%). La mezcla se utilizó en la siguiente etapa sin purificación adicional.

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 382; HPLC tR = 2,23 min.

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 368; HPLC tR = 2,06 min.

Mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metilfenil)sulfonilmetil]pirimidina y 2-cloro-4-(clorometil)-6-[(3S)-3-metilmorfolin-4-il]pirimidina



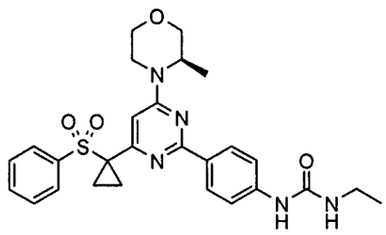
Una solución de cloruro de p-toluenosulfonilo (23,47 g, 123,11 mmol) en DCM (50 mL) se agregó gota a gota a una solución agitada de [2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metanol (20 g, 82,07 mmol) y DIPEA (21,44 mL, 123,11 mmol) en DCM (200 mL) se enfrió hasta alcanzar 5°C, durante un período de 1 hora bajo nitrógeno. La solución resultante se agitó a 5°C durante 72 horas y luego a reflujo durante 24 horas. La mezcla de reacción se lavó con agua y la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma marrón que pareció ser una mezcla de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metilfenil)sulfonilmetil]pirimidina (11%) y 2-cloro-4-(clorometil)-6-[(3S)-3-metilmorfolin-4-il]pirimidina (87%). La mezcla se utilizó en la siguiente etapa sin purificación adicional.

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 398; HPLC tR = 2,52 min.

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 262; HPLC tR = 1,97 min.

La preparación de [2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metanol se describió anteriormente.

Ejemplo 69: 1-[4-[4-[1-(Bencenosulfonil)ciclopropil]-6-[(3*R*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea

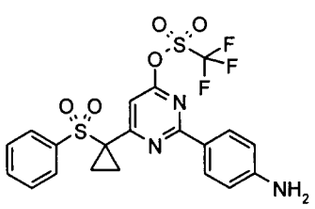


Se agregó trietilamina (0,064 mL, 0,46 mmol) a [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato (0,104 g, 0,21 mmol), (*R*)-3-metilmorfolina (0,042 g, 0,42 mmol) en dioxano (5 mL) y la solución resultante se agitó a TA durante toda la noche. Se agregó etil isocianato (0,494 mL, 6,25 mmol) y la solución se dejó agitar a TA durante toda la noche. Se agregó metanol cuidadosamente y luego se retiró el disolvente. El producto bruto se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido tostado (0,052 g).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) 1,05-1,08 (3H, t), 1,16-1,18 (3H, d), 1,60-1,67 (2H, m), 1,88-1,92 (2H, m), 3,09-3,19 (3H, m), 3,42-3,49 (1H, td), 3,59-3,62 (1H, dd), 3,73-3,76 (1H, d), 3,94-3,97 (1H, dd), 4,08-4,12 (1H, d), 4,37(1H, bs), 6,13-6,16 (1H, t), 6,62 (1H, s), 7,37-7,39 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,78-7,85 (4H, m), 8,63 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 522; HPLC tR = 2,32min.

[2-(4-Aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato



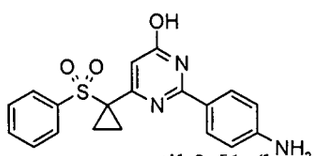
Se disolvió 2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-ol (4,0 g, 10,89 mmol), 1,1,1-trifluoro-*N*-fenil-*N*-(trifluorometilsulfonil)metanosulfonamida (4,28 g, 11,98 mmol) en DCM (75 mL), a esto se agregó DBU (1,791 mL, 11,98 mmol) y la reacción se agitó a TA durante toda la noche. El disolvente se evaporó hasta secarse y la goma se aplacó

con ácido cítrico 1,0N (100 mL) y se extrajo con éter dietílico (3 x 100 mL). Los orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se evaporaron para proporcionar un sólido naranja. El sólido se hizo pasar a través de un lecho de sílice, eluyendo con éter dietílico, para proporcionar un sólido amarillo. Este sólido se disolvió en una cantidad mínima de éter dietílico caliente, al que se agregó iso-hexano y el sistema se agitó para proporcionar el material deseado como un sólido amarillo (1,5 g).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) 1,79 (2H, q), 2,02 (2H, q), 5,43 (2H, s), 6,62 (2H, d), 7,43 (1H, s), 7,59 (2H, t), 7,68 (2H, d), 7,72 (1H, t), 7,80 (2H, d).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 500; HPLC tR = 2,96min

2-(4-Aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-ol

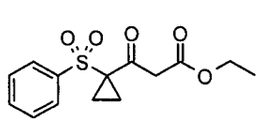


Se agregaron etil 3-[1-(bencenosulfonil)ciclopropil]-3-oxopropanoato (5,4 g, 15,12 mmol), 4-aminobenzamidina diclorhidrato (3,78 g, 18,15 mmol) y carbonato de potasio (3,83 mL, 63,52 mmol) a metanol (150 mL) y se calentaron a reflujo durante toda la noche. El disolvente se evaporó hasta secarse y el sólido remanente se acidificó con ácido cítrico 1,0N. El sólido se filtró y luego se trituró con acetonitrilo caliente para proporcionar el material deseado como un sólido amarillo (4,0 g).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) 1,58 (2H, q), 1,86 (2H, q), 5,86 (2H, s), 6,21 (1H, s), 6,50 (2H, d), 7,51 (2H, d), 7,60 (2H, t), 7,72 (1H, t), 7,82 (2H, d), 12,11 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 368; HPLC tR = 1,23min

Etil 3-[1-(bencenosulfonil)ciclopropil]-3-oxopropanoato

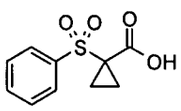


Se agregaron trietilamina (20,70 mL, 148,51 mmol) y cloruro de magnesio (9,28 g, 97,46 mmol) a una solución agitada de 3-etoxi-3-oxopropanoato de potasio (15,80 g, 92,82 mmol) en acetonitrilo (150 mL). La reacción se agitó durante 2 horas. Se disolvieron ácido 1-(Bencenosulfonil)ciclopropano-1-carboxílico (10,5 g, 46,41 mmol) y 1,1'-carbonildiimidazol (9,03 g, 55,69 mmol) en acetonitrilo (30 mL) y se agitaron durante 2 horas. Esto luego se

agregó a la reacción inicial y el sistema se agitó durante el fin de semana a TA. Se agregó ácido clorhídrico 2M (150 mL) y la mezcla se extrajo con éter dietílico (3 x 50 mL), los orgánicos se separaron y se evaporó para proporcionar un aceite naranja. Este aceite se lavó con una solución saturada de hidrogenocarbonato de sodio (100 mL) y se extrajo con éter dietílico (3 x 100 mL). Los orgánicos se secaron sobre $MgSO_4$, se filtraron y se evaporaron para proporcionar una goma amarilla. Esto se hizo pasar a través de un lecho de sílice, eluyendo con DCM, para proporcionar una goma incolora. El producto bruto se purificó adicionalmente mediante cromatografía de sílice instantánea, eluyendo con DCM, para proporcionar el material deseado como una goma incolora (5,6 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,23 (3H, t), 1,74 (2H, q), 1,99 (2H, q), 3,77 (2H, s), 4,12 (2H, q), 7,57 (2H, t), 7,67 (1H, t), 7,92 (2H, d).

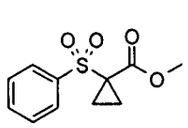
Ácido 1-(Bencenosulfonil)ciclopropano-1-carboxílico



Se agregó metil 1-(bencenosulfonil)ciclopropano-1-carboxilato (11 g, 45,78 mmol) a etanol (50 mL) y agua (50 mL), a esto se agregó hidróxido de sodio (1,904 mL, 48,07 mmol) y la reacción se agitó durante 1 hora. El etanol se evaporó cuidadosamente y la mezcla de reacción se extrajo con éter dietílico (1 x 100 mL). La capa acuosa se aplacó con ácido clorhídrico 2M (50 mL), se extrajo con éter dietílico (3 x 100 mL) y los orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se evaporaron para proporcionar un sólido blanco. El sólido bruto se trituró con acetato de etilo para proporcionar el material deseado como un sólido blanco (10,5 g).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,63 (2H, q), 1,85 (2H, q), 7,63 (2H, t), 7,73 (1H, t), 7,97 (2H, d).

Metil 1-(bencenosulfonil)ciclopropano-1-carboxilato



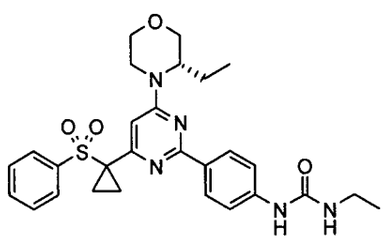
Se agregaron metil 2-(fenilsulfonil)acetato (15 g, 70,02 mmol), cloruro de benciltrietilamonio

(4,77 g, 21,00 mmol), carbonato de potasio (29,0 g, 210,05 mmol) y 1,2-dibromoetano (12,07 mL, 140,03 mmol) a tolueno (200 mL) y se calentaron a 100°C durante el fin de semana. La reacción se filtró y el disolvente se evaporó para proporcionar una goma viscosa. Esta mezcla de reacción se aplacó con agua (100 mL) y se extrajo con éter dietílico (3 x 100 mL). Los orgánicos se secaron sobre $MgSO_4$, se filtraron y se evaporaron para proporcionar un líquido naranja. Este líquido se hizo pasar a través de un lecho de sílice, eluyendo con éter dietílico, para proporcionar una goma naranja. La goma bruta se trituró con etanol para proporcionar el material deseado como un sólido blanco (11,0 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 11,70 (2H, q), 2,00 (2H, q), 3,63 (3H, s), 7,55 (2H, t), 7,64 (1H, t), 8,00 (2H, d).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 241; HPLC tR = 1,84min

Ejemplo 70: 1-[4-[4-[1-(Bencenosulfonil)ciclopropil]-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea



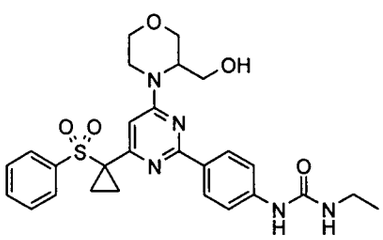
Se agregó trietilamina (0,062 mL, 0,45 mmol) a [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato (0,102 g, 0,20 mmol), (*S*)-3-etilmorfolina (0,047 g, 0,41 mmol) en dioxano (5 mL) y la solución resultante se agitó a 50°C durante toda la noche. Se agregó etil isocianato (0,564 mL, 7,12 mmol) y la solución se dejó agitar a TA durante toda la noche. Se agregó metanol y luego el disolvente se retiró. El producto bruto se purificó mediante HPLC preparativa, para proporcionar el material deseado como un sólido blanco (0,042 g).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 0,83-0,86 (3H, t), 1,05-1,08 (3H, t), 1,56-1,67 (4H, m), 1,71-1,80 (1H, m), 1,88-1,91 (2H, m), 3,09-3,16 (3H, m), 3,40-3,47 (1H, td), 3,50-3,54 (1H, dd), 3,84-3,87 (1H, d), 3,90-3,94 (1H, dd), 4,18 (1H, bs), 6,12-6,15 (1H, t), 6,61 (1H, s), 7,37-7,40 (2H, d), 7,57-7,61 (2H, t), 7,69-7,74 (1H, tt), 7,77-7,80 (2H, dd), 7,84-7,86 (2H, d), 8,61 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 536; HPLC tR = 2,43min.

La preparación de [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato se describió anteriormente.

Ejemplo 71: 1-[4-[4-[1-(Bencenosulfonil)ciclopropil]-6-[3-(hidroximetil)morfolin-4-il]pirimidin-2-il]fenil]-3-etilurea

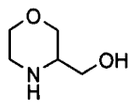


Se agregó trietilamina (0,112 mL, 0,80 mmol) a [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato (0,100 g, 0,20 mmol), morfolin-3-ilmetanol clorhidrato (0,062 g, 0,40 mmol) en dioxano (5 mL) y la solución resultante se agitó a 50°C durante toda la noche. Etil isocianato (0,555 mL, 7,01 mmol) se agregó y la solución se dejó agitar a TA durante toda la noche. El disolvente se retiró y el sedimento se recogió en metanol. Se agregó metóxido de sodio al 30% en solución de metanol y la reacción se dejó agitar durante toda la noche. Se agregó más metóxido de sodio al 30% en solución de metanol y la reacción se sometió a reflujo durante toda la noche. Aproximadamente 80% del metanol se retiró y la solución se aplacó con solución de cloruro de amonio saturado. La mezcla se extrajo con DCM, los orgánicos se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El producto bruto se purificó mediante HPLC preparativa, para proporcionar el material deseado como un sólido crema (0,019 g).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,05-1,08 (3H, t), 1,58-1,66 (2H, m), 1,86-1,92 (2H, m), 3,07-3,16 (3H, m), 3,42-3,53 (3H, m), 3,69-3,73 (1H, m), 3,92-3,95 1H, dd), 4,05-4,08 (1H, d), 4,18 (1H, bs), 4,93 (1H, bs), 6,14-6,17 (1H, t), 6,68 (1H, s), 7,36 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,79-7,84 (4H, m), 8,64 (1H, s) (1 pico bajo agua o pico del disolvente).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 538; HPLC tR = 1,95min.

Morfolin-3-ilmetanol

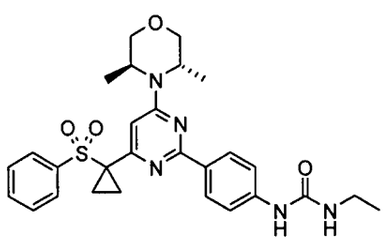


Se agitaron (4-bencilmorfolin-3-il)metanol (0,473 g, 2,28 mmol) y paladio (5% en carbono, 50% de humedad) (0,094 g, 0,02 mmol) en etanol (50 mL) bajo una atmósfera de hidrógeno a 5 bar y 25°C durante 18 horas. La mezcla se filtró y luego se agregó ácido clorhídrico (0,628 mL, 2,51 mmol). La reacción se agitó durante toda la noche a TA y luego el disolvente se retiró para proporcionar el material deseado (como una sal clorhidrato) como una goma marrón anaranjada (257 mg).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,43-1,46 (1H, t), 3,14-3,67 (3H, m), 3,81-4,18 (4H, m), 4,62 (1H, bs), 9,32 (bs), 9,60 (bs), 10,43 (bs).

La preparación de [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato se describió anteriormente.

Ejemplo 72: 1-[4-[4-[1-(Bencenosulfonil)ciclopropil]-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea



Se agregó DIPEA (0,141 mL, 0,81 mmol) a [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato (0,101 g, 0,20 mmol) y (3*S*,5*S*)-3,5-dimetilmorfolina (sal clorhidrato) (0,061 g, 0,40 mmol) en dioxano (5 mL) bajo nitrógeno. La solución resultante se agitó a 70°C durante toda la noche y luego a 90°C durante varias horas. Se agregó más (3*S*,5*S*)-3,5-dimetilmorfolina (sal clorhidrato) y la reacción se dejó agitar a 90°C durante toda la noche. Se agregó etil isocianato (0,320 mL, 4,05 mmol) y la reacción se dejó agitar a TA durante el fin de semana. Se agregó metanol y luego el disolvente se retiró. El producto bruto se purificó mediante HPLC preparativa, para proporcionar el material deseado como un sólido crema (0,029 g).

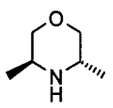
Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,05-1,08 (3H, t), 1,27-1,29 (6H, d), 1,61-1,71 (2H, m), 1,88-1,95 (2H, m), 3,09-3,16 (2H, m), 3,67-3,70 (2H, m), 4,10-4,16 (4H,

m), 6,14-6,16 (1H, t), 6,60 (1H, s), 7,39-7,41 (2H, d), 7,57-7,61 (2H, t), 7,69-7,73 (1H, tt), 7,78-7,81 (2H, dd), 7,86-7,89 (2H, d), 8,62 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 536; HPLC tR = 2,41min.

La preparación de [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato se describió anteriormente.

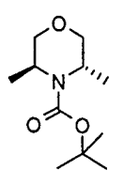
(3*S*,5*S*)-3,5-Dimetilmorfolina

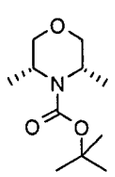


Se agregó cloruro de hidrógeno (solución 4M en dioxano, 30,1 mL, 120,25 mmol) a *terc*-butil (3*S*,5*S*)-3,5-dimetilmorfolina-4-carboxilato (5,23 g, 24,29 mmol) en dioxano (50 mL) y la solución resultante se agitó a TA durante toda la noche. El disolvente se retiró y el sólido se trituró con éter dietílico para proporcionar el material deseado (como la sal clorhidrato) como un sólido blanco (3,22 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,50-1,51(6H, d), 3,56-3,67 (4H, m), 3,97-4,00 (2H, dd), 9,96 (2H, bs).

terc-butil (3*S*,5*S*)-3,5-dimetilmorfolina-4-carboxilato y *terc*-butil (3*S*,5*R*)-3,5-dimetilmorfolina-4-carboxilato



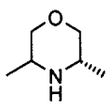


Se disolvió (3*S*)-3,5-dimetilmorfolina (13,73 g, 90,55 mmol) en una solución de hidróxido de sodio (3,91 mL, 208,26 mmol) en agua (100 mL) y se agregó en porciones di-*terc*-butil dicarbonato (22,88 mL, 99,60 mmol). La solución resultante se agitó a TA durante toda la noche y luego se extrajo con éter dietílico y los orgánicos se secaron sobre $MgSO_4$, se filtraron y se evaporaron para proporcionar un líquido claro. El material bruto se purificó y los diastereómeros se separaron utilizando cromatografía de sílice, eluyendo con 0-10% acetato de etilo en isohexano, para proporcionar *terc*-butil (3*S*,5*S*)-3,5-dimetilmorfolina-4-carboxilato

(primer producto en eluir) como un líquido incoloro (5,93 g) y *terc*-butil (3*S*,5*R*)-3,5-dimetilmorfolina-4-carboxilato (segundo producto en eluir) como un líquido incoloro (5,03 g).

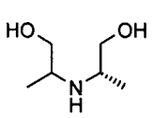
terc-butil (3*S*,5*S*)-3,5-dimetilmorfolina-4-carboxilato:
Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,28-1,29 (6H, d), 1,47 (9H, s), 3,43-3,48 (2H, m), 3,77-3,84 (4H, m).
terc-butil (3*S*,5*R*)-3,5-dimetilmorfolina-4-carboxilato
Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,30-1,31 (6H, d), 1,47 (9H, s), 3,52-3,56 (2H, dd), 3,68-3,71 (2H, d), 3,90-3,96 (2H, m).

(3*S*)-3,5-Dimetilmorfolina



Se enfrió 2-[[(2*S*)-1-hidroxipropan-2-il]amino]propan-1-ol (14,79 g, 111,01 mmol) hasta alcanzar 0°C con agitación y se agregó ácido sulfúrico concentrado (19,85 g, 202,39 mmol). La mezcla se calentó hasta alcanzar 180°C durante 5 horas. Se agregó lentamente hidróxido de potasio (23,95 g, 426,87 mmol) en agua (120 mL) luego la mezcla se filtró para proporcionar una solución negra oscura acuosa. Esta solución se destiló (el destilado se obtuvo a 98°C) y lo destilado se acidificó con ácido clorhídrico 2M. El agua se retiró para proporcionar el material deseado (como la sal clorhidrato) como un sólido blanco (13,73g). El material se utilizó en la siguiente etapa sin purificación adicional.
Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,44-1,46 (3H, d), 1,48-1,50 (3H, d), 3,31-3,34 (1H, m), 3,56-3,59 (1H, m), 3,62-3,72 (2H, m), 3,84-3,88 (1H, m), 3,96-3,99 (1H, dd), 9,69-10,12 (2H, bt).

2-[[(2*S*)-1-Hidroxipropan-2-il]amino]propan-1-ol

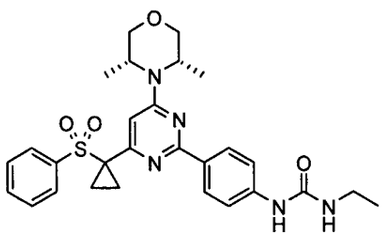


Se agitaron (*S*)-2-aminopropan-1-ol (9 g, 119,82 mmol), óxido de platino(IV) (0,052 g, 0,23 mmol) y 1-hidroxipropan-2-ona (11,54 g, 155,77 mmol) en metanol (100 mL) durante 1 hora

y luego se colocó bajo una atmósfera de hidrógeno a 1 bar y 25°C durante 3 horas. La solución se filtró y se evaporó para proporcionar un producto bruto que se purificó mediante destilación a (0,55 mBar, 92°C) para proporcionar el material deseado como un aceite amarillo (10,71 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,01-1,03 (3H, d), 1,07-1,09 (3H, d), 2,56 (1H, bs), 2,83-2,94 (2H, m), 3,27-3,32 (2H, m), 3,55-3,61 (2H, m).

Ejemplo 73: 1-[4-[4-[1-(Bencenosulfonil)ciclopropil]-6-[(3*R*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea

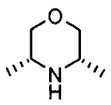


Se agregó DIPEA (0,140 mL, 0,81 mmol) a [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato (0,101 g, 0,20 mmol), (3*S*,5*R*)-3,5-dimetilmorfolina (como la sal clorhidrato) (0,052 g, 0,34 mmol) en dioxano (5 mL) bajo nitrógeno. La reacción se calentó hasta alcanzar 90°C durante toda la noche. La reacción se enfrió y el disolvente se retiró. El residuo se recogió en dioxano y se agregó etil isocianato (0,319 mL, 4,03 mmol). La reacción se dejó agitar durante el fin de semana. Se agregó metanol y el disolvente se retiró. El producto bruto se purificó mediante HPLC preparativa, para proporcionar el material deseado como un sólido blanco (9,00 mg).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,05-1,09 (3H, t), 1,17-1,20(6H, m), 1,62-1,68 (2H, m), 1,89-1,92 (2H, m), 3,09-3,14 (2H, m), 3,43-3,48 (2H, m), 3,86-3,90 (1H, dd), 3,94-4,16 (1H, dd), 4,12-4,16 (1H, m), 4,29-4,31 (1H, m), 6,12-6,15 (1H, t), 6,60 (1H, s), 7,37-7,40 (2H, d), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,79-7,86 (4H, m), 8,61 (1H, s).
Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 536; HPLC tR = 2,38min.

La preparación de [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato se describió anteriormente.

(3*S*,5*R*)-3,5-Dimetilmorfolina

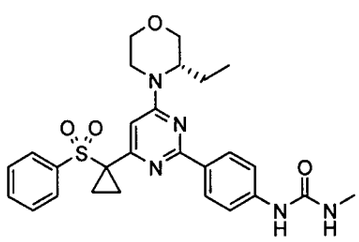


Se agregó cloruro de hidrógeno (solución 4M en dioxano, 9,98 mL, 39,92 mmol) a *terc*-butil (3*S*,5*R*)-3,5-dimetilmorfolina-4-carboxilato (1,910 g, 8,87 mmol) en dioxano (15 mL) y la solución resultante se agitó a TA durante toda la noche. El disolvente se retiró y el sólido se trituró con éter dietílico para proporcionar el material deseado (como la sal clorhidrato) como un sólido blanco (0,960 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,47-1,48 (6H, d), 3,31-3,40 (2H, m), 3,68-3,74 (2H, t), 3,86-3,90 (2H, dd), 9,77 (1H, bs), 10,22 (1H, bs).

La preparación de *terc*-butil (3*S*,5*R*)-3,5-dimetilmorfolina-4-carboxilato se describió anteriormente.

Ejemplo 74: 1-[4-[4-[1-(Bencenosulfonil)ciclopropil]-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea



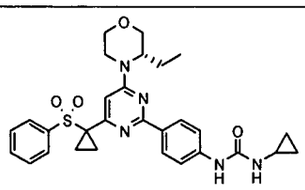
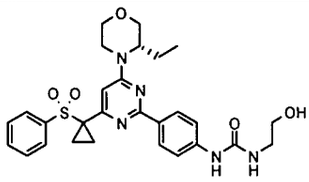
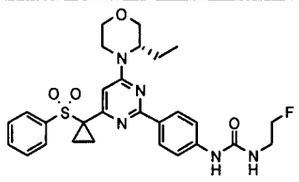
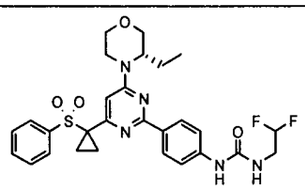
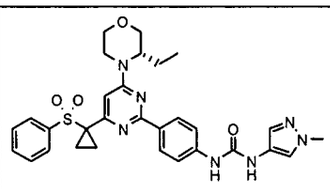
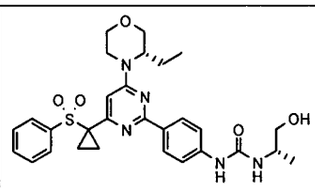
Se disolvieron fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,1 g, 0,17 mmol), trietilamina (0,072 mL, 0,51 mmol) y metilamina (0,51 mmol) en dioxano (10 mL) y se calentó a 50°C durante toda la noche. La reacción se evaporó hasta secarse y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco.

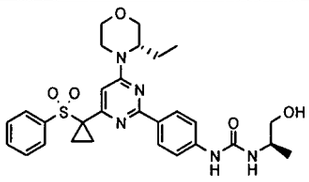
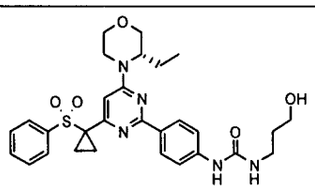
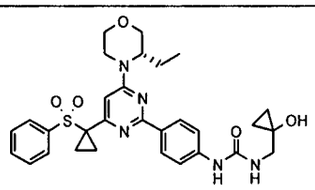
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,84 (3H, t), 1,65 - 1,56 (3H, m), 1,80 - 1,71 (1H, m), 1,91 - 1,87 (2H, m), 2,66 (3H, d), 3,12 (1H, ddd), 3,43 (1H, ddd), 3,51 (1H, dd), 3,85 (1H, d), 3,91 (1H, dd), 4,24 - 4,12 (2H, m), 6,04 (1H, q), 6,61 (1H, s), 7,39 (2H, d), 7,58 (2H, t), 7,71 (1H, t), 7,78 (2H, d), 7,84 (2H, d), 8,69 (1H, s).

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 522; HPLC tR = 2,31 min;

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-

(bencenosulfonil)ciclopropil]-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
74a		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea	548	2,46
74b		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	552	2,11
74c		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	554	1,95
74d		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea	572	2,45
74e		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	588	2,33
74f		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea	566	2,21

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
74g		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea	566	2,21
74h		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	578	2,28
74i		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-hidroxiciclopropil)metil]urea	578	2,29

Ejemplo 74a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,43 - 0,39 (2H, m), 0,67 - 0,62 (2H, m), 0,84 (3H, t), 1,64 - 1,58 (3H, m), 1,80 - 1,73 (1H, m), 1,92 - 1,85 (2H, m), 2,57 - 2,52 (1H, m), 3,12 (1H, ddd), 3,43 (1H, ddd), 3,51 (1H, dd), 3,85 (1H, d), 3,91 (1H, dd), 4,28 - 4,09 (2H, m), 6,40 (1H, s), 6,61 (1H, s), 7,39 (2H, d), 7,58 (2H, t), 7,71 (1H, t), 7,78 (2H, d), 7,85 (2H, d), 8,49 (1H, s);

Ejemplo 74b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,84 (3H, t), 1,64 - 1,58 (3H, m), 1,80 - 1,73 (1H, m), 1,91 - 1,86 (2H, m), 3,19 - 3,09 (3H, m), 3,48 - 3,40 (3H, m), 3,51 (1H, dd), 3,85 (1H, d), 3,91 (1H, dd), 4,26 - 4,08 (2H, m), 4,72 (1H, t), 6,23 (1H, t), 6,61 (1H, s), 7,38 (2H, d), 7,58 (2H, t), 7,71 (1H, t), 7,78 (2H, d), 7,85 (2H, d), 8,75 (1H, s);

Ejemplo 74c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,84 (3H, t), 1,64 - 1,58 (3H, m), 1,80 - 1,71 (1H, m), 1,91 - 1,87 (2H, m), 3,12 (1H, ddd), 3,47 - 3,36 (3H, m), 3,51 (1H, dd), 3,85 (1H, d), 3,91 (1H, dd), 4,28 - 4,09 (2H, m), 4,47 (2H, dt), 6,42 (1H, t), 6,62 (1H, s), 7,39 (2H, d), 7,58 (2H, t), 7,71 (1H, t), 7,78 (2H, d), 7,86 (2H, d), 8,77 (1H, s);

Ejemplo 74d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,84 (3H, t), 1,65 - 1,58 (3H, m), 1,80 -

1,73 (1H, m), 1,91 - 1,87 (2H, m), 3,12 (1H, ddd), 3,43 (1H, ddd), 3,59 - 3,50 (3H, m), 3,85 (1H, d), 3,92 (1H, dd), 4,27 - 4,12 (2H, m), 6,07 (1H, tt), 6,51 (1H, t), 6,62 (1H, s), 7,40 (2H, d), 7,58 (2H, t), 7,71 (1H, t), 7,78 (2H, d), 7,87 (2H, d), 8,87 (1H, s);

Ejemplo 74e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,85 (3H, t), 1,68 - 1,59 (3H, m), 1,80 - 1,73 (1H, m), 1,92 - 1,87 (2H, m), 3,12 (1H, ddd), 3,43 (1H, ddd), 3,52 (1H, dd), 3,79 (3H, s), 3,86 (1H, d), 3,92 (1H, dd), 4,30 - 4,18 (2H, m), 6,62 (1H, s), 7,38 (1H, s), 7,43 (2H, d), 7,59 (2H, t), 7,72 (1H, t), 7,76 (1H, s), 7,78 (2H, d), 7,88 (2H, d), 8,36 (1H, s), 8,78 (1H, s);

Ejemplo 74f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,84 (3H, t), 1,08 (3H, d), 1,65 - 1,58 (3H, m), 1,82 - 1,73 (1H, m), 1,90 - 1,88 (2H, m), 3,12 (1H, ddd), 3,39 - 3,33 (2H, m), 3,43 (1H, ddd), 3,51 (1H, dd), 3,73 - 3,67 (1H, m), 3,85 (1H, d), 3,91 (1H, dd), 4,25 - 4,13 (2H, m), 4,78 (1H, t), 6,07 (1H, d), 6,61 (1H, s), 7,36 (2H, d), 7,58 (2H, t), 7,71 (1H, t), 7,78 (2H, d), 7,85 (2H, d), 8,66 (1H, s);

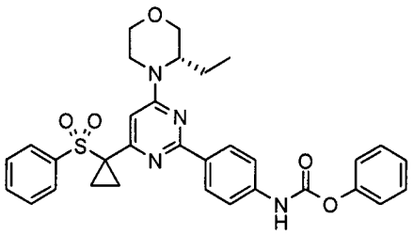
Ejemplo 74g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,84 (3H, t), 1,08 (3H, d), 1,67 - 1,58 (3H, m), 1,80 - 1,73 (1H, m), 1,90 - 1,88 (2H, m), 3,12 (1H, ddd), 3,40 - 3,32 (2H, m), 3,44 (1H, ddd), 3,51 (1H, dd), 3,73 - 3,67 (1H, m), 3,85 (1H, d), 3,91 (1H, dd), 4,27 - 4,08 (2H, m), 4,78 (1H, t), 6,07 (1H, d), 6,61 (1H, s), 7,36 (2H, d), 7,58 (2H, t), 7,71 (1H, t), 7,78 (2H, d), 7,85 (2H, d), 8,66 (1H, s);

Ejemplo 74h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,84 (3H, t), 1,64 - 1,56 (5H, m), 1,82 - 1,69 (1H, m), 1,91 - 1,87 (2H, m), 3,19 - 3,08 (3H, m), 3,53 - 3,40 (4H, m), 3,85 (1H, d), 3,91 (1H, dd), 4,26 - 4,08 (2H, m), 4,47 (1H, t), 6,18 (1H, t), 6,61 (1H, s), 7,38 (2H, d), 7,58 (2H, t), 7,71 (1H, t), 7,78 (2H, d), 7,85 (2H, d), 8,66 (1H, s);

Ejemplo 74i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,53 - 0,48 (2H, m), 0,59 - 0,56 (2H, m), 0,84 (3H, t), 1,64 - 1,58 (3H, m), 1,80 - 1,73 (1H, m), 1,92 - 1,88 (2H, m), 3,12 (1H, ddd), 3,21 (2H, d), 3,46 - 3,38 (1H, m), 3,51 (1H, dd), 3,85 (1H, d), 3,91 (1H, dd), 4,27 - 4,05 (2H, m), 6,30 (1H, t), 6,61 (1H, s), 7,38 (2H, d), 7,58 (2H, t), 7,71 (1H, t), 7,78 (2H, d), 7,85 (2H, d), 8,76 (1H, s), hidroxi faltante

La preparación de fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

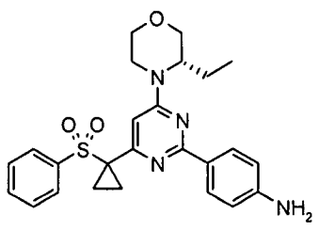


Se agregaron 4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]anilina (como la sal clorhidrato) (1,418 g, 2,83 mmol) y bicarbonato de sodio (2,377 g, 28,30 mmol) a DCM (60 mL) y se agitó durante 10 minutos. Se agregó lentamente fenil cloroformiato (0,462 mL, 3,68 mmol) y la reacción se agitó durante 1 hora. La mezcla de reacción se aplacó con una solución saturada acuosa de cloruro de amonio (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido naranja. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (1,22 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,84 (3H, t), 1,68 - 1,59 (3H, m), 1,80 - 1,73 (1H, m), 1,92 - 1,89 (2H, m), 3,13 (1H, ddd), 3,43 (1H, ddd), 3,52 (1H, dd), 3,85 (1H, d), 3,92 (1H, dd), 4,18 (2H, s), 6,66 (1H, s), 7,29 - 7,24 (3H, m), 7,45 (2H, t), 7,54 (2H, d), 7,58 (2H, t), 7,71 (1H, t), 7,79 (2H, d), 7,95 (2H, d), 10,39 (1H, s);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 585; HPLC tR = 3,12 min;

4-[4-[1-(Bencenosulfonil)ciclopropil]-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-2-il]anilina

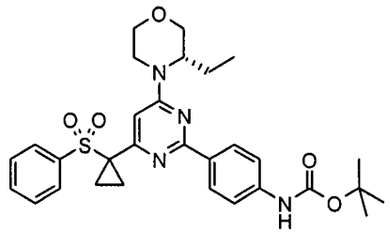


Se agregó *terc*-butil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (1,6 g, 2,83 mmol) a 6,0 N cloruro de hidrógeno en propan-2-ol (20 mL) y se agitó durante 2 horas a TA. La solución bruta se trituró con éter dietílico para proporcionar el material deseado (como la sal clorhidrato) como un sólido amarillo (1,40 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,81 - 0,71 (3H, m), 1,78 - 1,60 (5H, m), 1,96 - 1,87 (2H, m), 3,20 (1H, ddd), 3,41 (1H, ddd), 3,50 (1H, dd), 3,84 (1H, d), 3,93 (1H, dd), 6,56 (1H, s), 7,01 (2H, s), 7,61 (2H, t), 7,79 - 7,75 (4H, m), 7,95 (2H, d);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 465; HPLC tR = 2,54 min;

terc-butil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

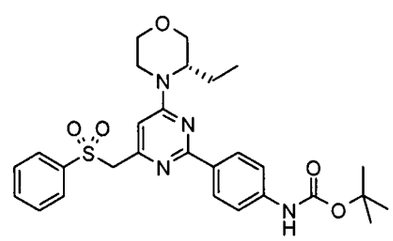


Se agregó rápidamente hidruro de sodio (0,724 g, 15,07 mmol) a *terc*-butil *N*-[4-[4-(bencenosulfonilmetil)-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (2,03 g, 3,77 mmol) en DMF (30 mL) y la mezcla se agitó a TA durante 10 minutos antes de la adición lenta de 1,2-dibromoetano (1,299 mL, 15,07 mmol) en DMF (30 mL). La suspensión resultante se agitó a TA durante 1 hora. Rápidamente se agregaron más hidruro de sodio (0,36 g, 7,53 mmol) y 1,2 dibromoetano (0,65 mL, 7,53 mmol) y la reacción se agitó durante otros 30 minutos. La mezcla de reacción se aplacó con agua (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma marrón. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano, para proporcionar una espuma amarilla. Esto se disolvió en 40% acetato de etilo en isohexano y se agitó lo que resultó en el material deseado que se precipitó como un sólido blanco (1,65 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,84 (3H, t), 1,49 (9H, s), 1,65 - 1,58 (3H, m), 1,80 - 1,73 (1H, m), 1,90 - 1,87 (2H, m), 3,12 (1H, ddd), 3,43 (1H, ddd), 3,51 (1H, dd), 3,85 (1H, d), 3,91 (1H, dd), 4,18 (2H, s), 6,63 (1H, s), 7,45 (2H, d), 7,58 (2H, t), 7,71 (1H, t), 7,78 (2H, d), 7,87 (2H, d), 9,49 (1H, s);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 565; HPLC tR = 3,23 min;

terc-butil *N*-[4-[4-(bencenosulfonilmetil)-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



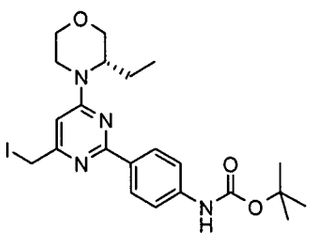
Se disolvieron bencenosulfinato de sodio (0,626 g, 3,81 mmol) y *terc*-butil *N*-[4-[4-[(3*S*)-3-

etilmorfolin-4-il]-6-(yodometil)pirimidin-2-il]fenil]carbamato (2,0 g, 3,81 mmol) en DMF (25 mL) y se agitaron durante 1 hora a TA. El disolvente se evaporó para proporcionar un sólido amarillo que se repartió entre solución acuosa de tiosulfato de sodio (50 mL) y DCM (75 mL). Los orgánicos se purificaron mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como una espuma blanca (1,99 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,86 (3H, t), 1,49 (9H, s), 1,66 - 1,57 (1H, m), 1,82 - 1,74 (1H, m), 3,14 (1H, ddd), 3,45 (1H, ddd), 3,53 (1H, dd), 3,87 (1H, d), 3,93 (1H, dd), 4,16 (2H, s), 4,69 (2H, s), 6,61 (1H, s), 7,45 (2H, d), 7,61 (2H, t), 7,74 (1H, t), 7,85 - 7,80 (4H, m), 9,49 (1H, s);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 539; HPLC tR = 3,00 min;

terc-butil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(yodometil)pirimidin-2-il]fenil]carbamato

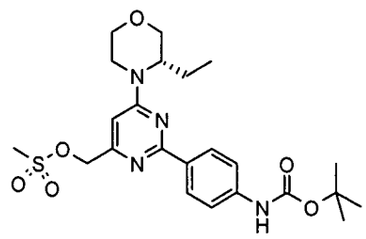


Se agregaron [6-[(3*S*)-3-etilmorfolin-4-il]-2-[4-[(2-metilpropan-2-il)oxicarbonilamino]fenil]pirimidin-4-il]metil metanosulfonato (10,34 g, 20,99 mmol) y yoduro de litio (1,208 mL, 31,49 mmol) a dioxano (250 mL) y se calentaron a 60°C durante 1 hora y luego a TA durante toda la noche. El disolvente se evaporó y la mezcla de reacción se aplacó con solución de cloruro de amonio saturado (100 mL) luego se extrajo con DCM (3 x 75 mL). Los extractos orgánicos se lavaron a través de un lecho de sílice de 2 pulgadas, eluyendo con acetato de etilo, para proporcionar una espuma marrón. Esto se disolvió en éter dietílico y se agregó cuidadosamente isohexano hasta que se observó una solución turbia. Al enfriarse hasta alcanzar 0°C, el material deseado se precipitó como un sólido blanco y se aisló mediante filtración (9,80 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,88 (3H, t), 1,50 (9H, s), 1,72 - 1,63 (1H, m), 1,83 - 1,76 (1H, m), 3,17 (1H, ddd), 3,47 (1H, ddd), 3,55 (1H, dd), 3,87 (1H, d), 3,93 (1H, dd), 4,29 (2H, s), 4,38 (2H, s), 6,81 (1H, s), 7,56 (2H, d), 8,22 (2H, d), 9,53 (1H, s);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 525; HPLC tR = 3,17 min;

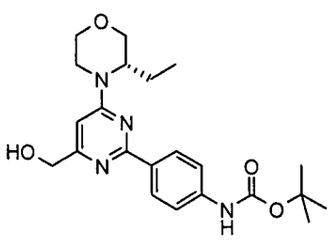
[6-[(3*S*)-3-Etilmorfolin-4-il]-2-[4-[(2-metilpropan-2-il)oxicarbonilamino]fenil]pirimidin-4-il]metil metanosulfonato



Se agregaron *terc*-butil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(hidroximetil)pirimidin-2-il]fenil]carbamato (8,7 g, 20,99 mmol) y DIPEA (4,40 mL, 25,19 mmol) a DCM (80 mL), a esto lentamente se agregó cloruro de metano sulfonilo (1,636 mL, 20,99 mmol) y la reacción se agitó durante 30 minutos. La mezcla de reacción se aplacó con solución de cloruro de amonio saturado (100 mL), se extrajo con DCM (2 x 100 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como una goma marrón (10,2 g). Esto se utilizó sin purificación adicional.

Espectro de LCMS: m/z (ES+) $(M+H)^+ = 493$; HPLC tR = 2,90 min;

terc-butil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(hidroximetil)pirimidin-2-il]fenil]carbamato



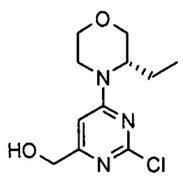
[2-Cloro-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-4-il]metanol (12 g, 46,56 mmol), *terc*-butil 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenilcarbamato (14,86 g, 46,56 mmol), carbonato de sodio (24,68 g, 232,81 mmol) y 1,1'-bis(difenilo fosfino)ferrocenodicloropaladio(II) (3,37 g, 4,66 mmol) se agregaron a DME (150 mL) y agua (37,5 mL) y se calentó hasta alcanzar 90°C durante toda la noche bajo nitrógeno. El disolvente se evaporó y el residuo se aplacó con agua (100 mL), se extrajo con acetato de etilo (3 x 100 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma marrón. El residuo se filtró a través de un lecho de sílice, eluyendo con acetato de etilo, para proporcionar una goma muy oscura. Esto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 40 a 100% acetato de etilo en isohexano, para proporcionar una goma naranja. La goma se disolvió en éter dietílico y se agregó cuidadosamente isohexano hasta que se observó una solución turbia; mediante agitación adicional se obtuvo el material deseado como un precipitado sólido blanco que se aisló mediante filtración (8,7 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,49 (9H, s), 1,73 -

1,64 (1H, m), 1,84 - 1,77 (1H, m), 3,19 (1H, ddd), 3,47 (1H, ddd), 3,55 (1H, dd), 3,88 (1H, d), 3,94 (1H, dd), 4,33 - 4,23 (2H, m), 4,45 (2H, d), 5,38 (1H, t), 6,67 (1H, s), 7,53 (2H, d), 8,21 (2H, d), 9,50 (1H, s);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 415; HPLC tR = 2,49 min;

[2-Cloro-6-[(3*S*)-3-etilmorfolin-4-il]pirimidin-4-il]metanol

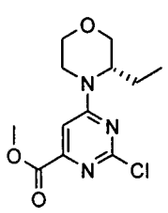


Se agregó gota a gota borohidruro de litio, 2M en THF (17,63 mL, 35,26 mmol) a metil 2-cloro-6-[(3*S*)-3-etilmorfolin-4-il]pirimidina-4-carboxilato (15,5 g, 54,25 mmol) en THF (100 mL) a 0°C durante un período de 30 minutos bajo nitrógeno. La solución resultante se agitó a 0°C durante 30 minutos luego se dejó entibiar hasta alcanzar TA. Se agregó agua (250 mL) y el THF se evaporó. Los residuos acuosos se extrajeron con acetato de etilo (2 x 500 mL) y los orgánicos combinados se lavaron con agua (2 x 300 mL). La capa orgánica se secó sobre $MgSO_4$ luego se evaporó hasta secarse para proporcionar un aceite viscoso, esto se trituró con éter dietílico caliente para proporcionar el material deseado como un sólido blanco (13,4 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,84 (3H, t), 1,80 - 1,66 (2H, m), 3,19 - 3,14 (1H, m), 3,42 (1H, ddd), 3,51 (1H, dd), 3,82 (1H, d), 3,89 (1H, dd), 4,15 - 4,06 (2H, m), 4,34 (2H, d), 5,50 (1H, t), 6,74 (1H, s);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 258; HPLC tR = 1,45 min;

Metil 2-cloro-6-[(3*S*)-3-etilmorfolin-4-il]pirimidina-4-carboxilato



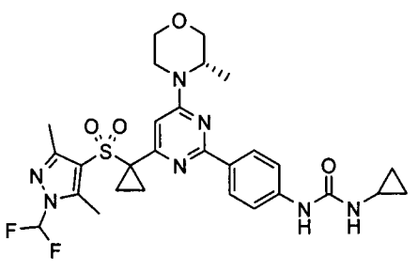
Una solución de (S)-3-etilmorfolina (10 g, 86,83 mmol) en DCM (75 mL) se agregó gota a gota a una solución agitada de metil 2,6-dicloropirimidina-4-carboxilato (19,77 g, 95,51 mmol) y trietilamina (24,20 ml, 173,65 mmol) en DCM (200 mL) a TA, durante un período de 2 horas al aire. La solución resultante se agitó a TA durante toda la noche. La mezcla de reacción se aplacó con agua (250 mL), se extrajo con DCM (300 mL) y el disolvente se retiró

hasta proporcionar 30% del volumen inicial. La solución oscura se hizo pasar a través de un lecho de sílice de 2 pulgadas, eluyendo con acetato de etilo, para proporcionar una goma naranja que se disolvió en acetato de etilo (40 mL). A esto se agregó éter dietílico (120 mL) y luego isohexano hasta que se observó una solución turbia. La reacción se sembró con 15 mg de metil 2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina-4-carboxilato y se agitó durante 15 minutos para proporcionar el material deseado como un sólido blanco (15,8 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,83 (3H, t), 1,75 (2H, septeto), 3,22 (1H, s), 3,44 (1H, ddd), 3,53 (1H, dd), 3,82 (1H, d), 3,91 - 3,87 (4H, m), 4,22 (2H, m), 7,32 (1H, s);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 286; HPLC tR = 1,81 min;

Ejemplo 75: 3-Ciclopropil-1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



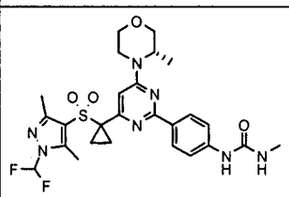
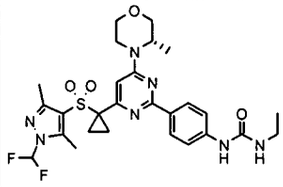
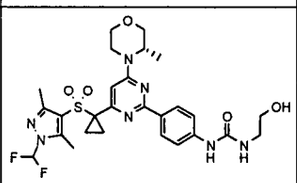
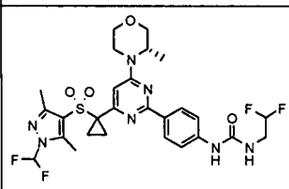
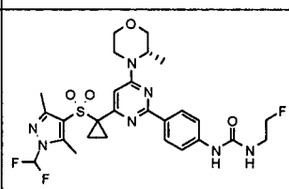
Se agregó ciclopropilamina (0,038 mL, 0,54 mmol) a una solución de fenil *N*-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,115g, 0,18mmol) en NMP (2 mL) seguido por trietilamina (0,076 mL, 0,54 mmol) y la reacción se calentó a 50°C durante toda la noche. El producto bruto se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blancuzco (88 mg).

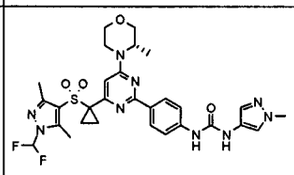
Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,63 - 0,68 (2H, m), 1,19 - 1,21 (3H, d), 1,46 - 1,54 (2H, m), 1,75 - 1,78 (2H, m), 2,07 (3H, s), 2,34 (3H, s), 2,53 - 2,58 (1H, m), 3,12 - 3,20 (1H, m), 3,44 - 3,50 (1H, m), 3,60 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,13 (1H, d), 4,51 (1H, s), 6,42 (1H, d), 6,69 (1H, s), 7,42 - 7,45 (2H, m), 7,64 - 7,93 (1H, t), 7,91 - 7,94 (2H, m), 8,53 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 602; HPLC tR = 2,20 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-[1-

(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
75a		1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	576	2,05
75b		3-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	590	2,19
75c		1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	606	1,89
75d		3-(2,2-difluoroetil)-1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	626	2,31
75e		1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	608	2,18

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
75f*		1-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	642	2,08

* Además de las condiciones de reacción descritas anteriormente esta reacción se sometió luego a la adición de DIPEA (3 equivalentes) y se calentó a 95°C durante 90 minutos.

Ejemplo 75a: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,46 - 1,54 (2H, m), 1,75 - 1,78 (2H, m), 2,07 (3H, s), 2,34 (3H, s), 2,68 (3H, d), 3,12 - 3,17 (1H, m), 3,44 - 3,50 (1H, m), 3,60 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,13 (1H, d), 4,51 (1H, s), 6,05 (1H, q), 6,69 (1H, s), 7,42 - 7,44 (2H, m), 7,64 - 7,92 (1H, t), 7,90 - 7,93 (2H, m), 8,73 (1H, s).

Ejemplo 75b: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,20 (3H, d), 1,49 - 1,51 (2H, m), 1,75 - 1,78 (2H, m), 2,07 (3H, s), 2,34 (3H, s), 3,10 - 3,20 (3H, m), 3,44 - 3,50 (1H, m), 3,60 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,11 - 4,15 (1H, m), 4,51 (1H, s), 6,14 (1H, t), 6,69 (1H, s), 7,41 - 7,44 (2H, m), 7,64 - 7,92 (1H, t), 7,91 - 7,93 (2H, d), 8,65 (1H, s).

Ejemplo 75c: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 (3H, s), 1,46 - 1,54 (2H, m), 1,75 - 1,78 (2H, m), 2,07 (3H, s), 2,34 (3H, s), 3,12 - 3,20 (3H, m), 3,45 - 3,50 (3H, m), 3,60 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,13 (1H, d), 4,51 (1H, s), 4,74 (1H, t), 6,24 (1H, t), 6,69 (1H, s), 7,42 (2H, d), 7,64 - 7,92 (1H, t), 7,92 (2H, d), 8,79 (1H, s).

Ejemplo 75d: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,46 - 1,54 (2H, m), 1,75 - 1,78 (2H, m), 2,07 (3H, s), 2,34 (3H, s), 3,16 - 3,19 (1H, m), 3,44 - 3,64 (4H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,12 - 4,15 (1H, m), 4,51 (1H, s), 5,93 - 6,23 (1H, m), 6,52 (1H, t), 6,70 (1H, s), 7,44 (2H, d), 7,64 - 7,92 (1H, t), 7,95 (2H, d), 8,92 (1H, s).

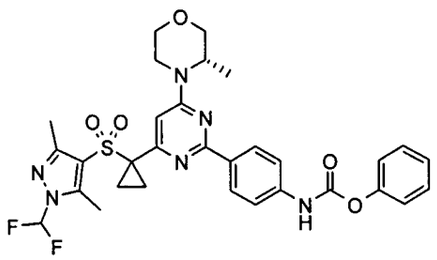
Ejemplo 75e: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,46 - 1,54 (2H, m), 1,73 - 1,78 (2H, m), 2,07 (3H, s), 2,34 (3H, s), 3,14 - 3,20 (1H, m), 3,36 - 3,50 (3H, m), 3,60 - 3,64 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,13 (1H, d), 4,42 (1H, t), 4,54 (2H, t), 6,42 (1H, t), 6,70 (1H, s), 7,43 (2H, d), 7,64 - 7,93 (1H, t), 7,93 (2H, d), 8,80 (1H, s).

Ejemplo 75f: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,20 - 1,21 (3H, m), 1,47 - 1,54 (2H, m),

1,74 - 1,79 (2H, m), 2,07 (3H, s), 2,35 (3H, s), 3,13 - 3,21 (1H, m), 3,44 - 3,51 (1H, m), 3,61 - 3,64 (1H, m), 3,75 - 3,78 (1H, m), 3,80 (3H, s), 3,95 - 3,99 (1H, m), 4,14 (1H, d), 4,52 (1H, s), 6,70 (1H, s), 7,39 - 7,39 (1H, m), 7,46 - 7,49 (2H, m), 7,78 (1H, s), 7,65 - 7,94 (1H, t), 7,96 (2H, d), 8,37 (1H, s), 8,84 (1H, s)

La preparación de fenil *N*-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

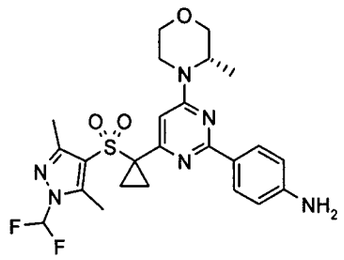


Se agregó gota a gota fenil cloroformiato (0,176 mL, 1,40 mmol) a una mezcla de 4-[4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (0,726 g, 1,4 mmol) e hidrogenocarbonato de sodio (0,176 g, 2,10 mmol) en dioxano (20 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. El precipitado se recogió mediante filtración, se lavó con una mezcla de isohexano (4 mL) y éter dietílico (2 mL), luego se suspendió en agua (20 mL) y se agitó durante 20 minutos. El precipitado se recogió mediante filtración, se lavó con agua (5 mL) luego con una mezcla de isohexano (10 mL) y éter dietílico (5 mL) y se secó al vacío para proporcionar el material deseado como un sólido blanco (0,826 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,48 - 1,55 (2H, m), 1,74 - 1,79 (2H, m), 2,07 (3H, s), 2,35 (3H, s), 3,14 - 3,17 (1H, m), 3,39 - 3,50 (1H, m), 3,61 - 3,64 (1H, m), 3,77 (1H, m), 3,95 - 3,99 (1H, m), 4,16 (1H, d), 4,53 (1H, s), 6,75 (1H, s), 7,24 - 7,31 (3H, m), 7,44 - 7,48 (2H, m), 7,57 (2H, d), 7,64 - 7,93 (1H, t), 8,00 - 8,03 (2H, m), 10,42 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 639; HPLC tR = 2,92 min.

4-[4-[1-[1-(Difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

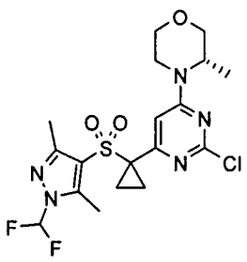


Se agregó diclorobis(trifenilfosfina)paladio(II) (0,412 g, 0,59 mmol) en una porción a una mezcla de carbonato de sodio (1,867 g, 17,61 mmol), 2-cloro-4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,712 g, 5,87 mmol) y pinacol éster de ácido (4-aminofenil)borónico (1,351 g, 6,16 mmol) en DME (50 mL) y agua (12,5 mL) bajo nitrógeno. La mezcla se agitó a 80°C durante 2 horas, se enfrió hasta alcanzar TA luego se diluyó con DCM (100 mL) y agua (50 mL). La capa orgánica se lavó con salmuera saturada (50 mL) luego se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 60% acetato de etilo en isohexano, para proporcionar al residuo que se purificó adicionalmente mediante trituración con isohexano (25 mL) y éter dietílico (25 mL), para proporcionar el material deseado como un sólido amarillo (2,84 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,18 (3H, m), 1,43 - 1,51 (2H, m), 1,73 - 1,76 (2H, m), 2,07 (3H, s), 2,34 (3H, s), 3,09 - 3,17 (1H, m), 3,42 - 3,49 (1H, m), 3,59 - 3,63 (1H, m), 3,75 (1H, d), 3,94 - 3,97 (1H, m), 4,48 (1H, s), 5,52 (2H, m), 6,52 - 6,55 (2H, m), 6,58 (1H, s), 7,75 - 7,78 (2H, m), 7,64 - 7,93 (1H, t).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 519; HPLC tR = 1,91 min.

2-Cloro-4-[1-[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

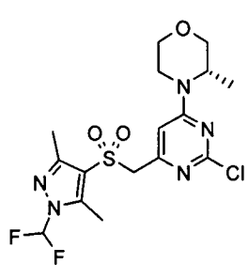


Se agregó hidróxido de sodio (33,0 mL, 412,50 mmol) a 2-cloro-4-[[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,27 g, 7,5 mmol), 1,2-dibromoetano (1,939 mL, 22,50 mmol) y bromuro de tetrabutilamonio (0,242 g, 0,75 mmol) en tolueno (132 mL). La solución resultante se agitó a 60°C durante 1 hora. La mezcla de reacción se diluyó con DCM (200 mL) y se lavó dos veces con agua (200 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (2,77 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,45 - 1,52 (2H, m), 1,69 - 1,76 (2H, m), 2,13 (3H, s), 2,37 (3H, s), 3,12 - 3,19 (1H, m), 3,37 - 3,44 (1H, m), 3,53 - 3,57 (1H, m), 3,71 (1H, d), 3,90 - 3,94 (2H, m), 4,35 (1H, s), 6,80 (1H, s), 7,71 - 8,00 (1H, t).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 462; HPLC tR = 2,26 min.

2-Cloro-4-[[1-(difluorometil)-3,5-dimetilpirazol-4-il]sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



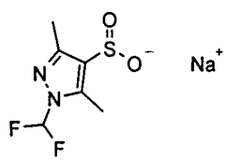
Se agregó 1-(difluorometil)-3,5-dimetilpirazol-4-sulfinato de sodio (3,44 g, 14,83 mmol) a una solución de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4,37 g, 12,36 mmol) en DMF (20 mL). La mezcla resultante se agitó a TA durante 1 hora. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en DCM (150 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se

purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blanco (5,22 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,19 (3H, d), 2,21 (3H, s), 2,42 (3H, s), 3,15 - 3,22 (1H, m), 3,40 - 3,47 (1H, m), 3,57 - 3,60 (1H, m), 3,73 (1H, d), 3,92 - 3,96 (2H, m), 4,25 (1H, s), 4,57 (2H, s), 6,82 (1H, s), 7,73 - 8,02 (1H, t).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 436; HPLC tR = 2,13 min.

1-(difluorometil)-3,5-dimetilpirazol-4-sulfinato de sodio

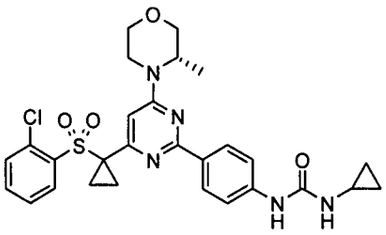


Se agregó hidrogenocarbonato de sodio (3,43 g, 40,88 mmol) a una solución de sulfito de sodio (2,58 g, 20,44 mmol) en agua (25 mL) y la solución resultante se agitó a 50°C durante 1 hora. Se agregó en porciones cloruro de 1-(difluorometil)-3,5-dimetil-1H-pirazol-4-sulfonilo (5 g, 20,44 mmol) y la solución se agitó a 50°C durante 18 horas. La mezcla de reacción se evaporó hasta secarse y se agregó metanol (75 mL). La suspensión se dejó agitar a TA durante 20 minutos, se filtró y el filtrado se evaporó. El residuo se disolvió en etanol (50 mL) a 50°C, se filtró y se evaporó para proporcionar el material deseado como un sólido blanco (4,59 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 2,24 (3H, s), 2,46 (3H, s), 7,44 - 7,74 (1H, t).

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 76: 1-[4-[4-[1-(2-Clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea

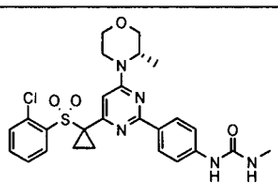


Se agregó ciclopropilamina (0,037 mL, 0,51 mmol) a una solución de fenil *N*-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,103g, 0,17mmol) en NMP (2 mL) seguido por trietilamina (0,072 mL, 0,51 mmol) y la reacción se calentó a 50°C durante toda la noche. El producto bruto se purificó mediante HPLC preparativa utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes, para proporcionar el material deseado como un sólido blancuzo (82mg, 80%).

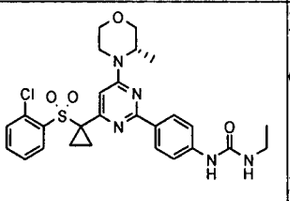
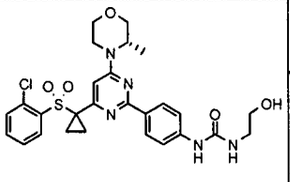
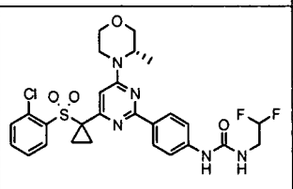
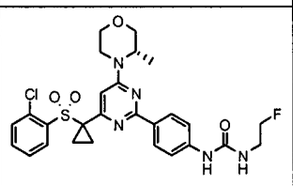
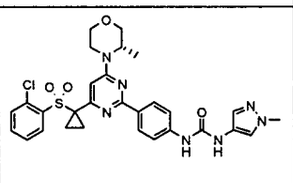
Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,63 - 0,68 (2H, m), 1,16 (3H, d), 1,71 - 1,75 (2H, m), 1,97 - 2,01 (2H, m), 2,53 - 2,57 (1H, m), 3,12 - 3,16 (1H, m), 3,41 - 3,48 (1H, m), 3,58 - 3,61 (1H, m), 3,74 (1H, d), 3,93 - 3,97 (1H, m), 4,10 (1H, d), 4,41 (1H, s), 6,42 (1H, d), 6,63 (1H, s), 7,37 - 7,40 (2H, m), 7,43 - 7,46 (1H, m), 7,60 - 7,64 (1H, m), 7,67 - 7,69 (1H, m), 7,78 - 7,82 (2H, m), 7,90 - 7,92 (1H, m), 8,50 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 568; HPLC tR = 2,30 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
76a		1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	542	2,16

1681

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
76b		3-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	556	2,30
76c		1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	572	1,99
76d		1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea	592	2,40
76e		1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	574	2,27
76f*		1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	608	2,12

* Además de las condiciones de reacción descritas anteriormente esta reacción se sometió luego a la adición de DIPEA (3 equivalentes) y se calentó a 95ºC durante 90 minutos.

Ejemplo 76a: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,15 - 1,16 (3H, m), 1,73 2H, m), 1,97 - 2,01 (2H, m), 2,66 (3H, d), 3,12 (1H, d), 3,40 – 3,48 (1H, m), 3,58 - 3,61 (1H, m), 3,74 (1H,

1802

d), 3,93 - 3,97 (1H, m), 4,08 (1H, m), 4,41 (1H, s), 6,06 (1H, d), 6,62 (1H, s), 7,38 (2H, d), 7,46 (1H, m), 7,60 - 7,62 (1H, m), 7,67 - 7,69 (1H, m), 7,79 (2H, d), 7,90 - 7,92 (1H, d), 8,70 (1H, s).

Ejemplo 76b: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,16 (3H, d), 1,72 - 1,75 (2H, m), 1,97 - 2,01 (2H, m), 3,10 - 3,16 (3H, m), 3,42 - 3,45 (1H, m), 3,58 - 3,61 (1H, m), 3,73 - 3,75 (1H, m), 3,93 – 3,98 (1H, m), 4,10 (1H, d), 4,41 (1H, s), 6,15 (1H, t), 6,63 (1H, s), 7,35 - 7,39 (2H, m), 7,43 - 7,47 (1H, m), 7,60 - 7,64 (1H, m), 7,67 - 7,70 (1H, m), 7,78 - 7,81 (2H, d), 7,90 - 7,92 (1H, m), 8,62 (1H, s).

Ejemplo 76c: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,15 - 1,16 (3H, m), 1,73 (2H, m), 1,97 - 2,01 (2H, m), 3,16 (1H, m), 3,17 - 3,19 (2H, m), 3,46 (3H, m), 3,58 - 3,61 (1H, m), 3,74 (1H, d), 3,93 - 3,97 (1H, m), 4,10 (1H, m), 4,42 (1H, s), 4,74 (1H, t), 6,24 (1H, t), 6,63 (1H, s), 7,36 (2H, d), 7,42 - 7,47 (1H, m), 7,60 - 7,62 (1H, m), 7,67 - 7,70 (1H, m), 7,80 (2H, d), 7,90 - 7,92 (1H, m), 8,76 (1H, s).

Ejemplo 76d: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,70 - 1,77 (2H, m), 1,96 - 2,03 (2H, m), 3,09 - 3,16 (1H, m), 3,41 - 3,48 (1H, m), 3,49 - 3,62 (3H, m), 3,74 (1H, d), 3,93 - 3,97 (1H, m), 4,08 - 4,12 (1H, d), 4,41 (1H, s), 5,92 - 6,22 (1H, m), 6,52 (1H, t), 6,64 (1H, s), 7,37 - 7,41 (2H, d), 7,44 - 7,47 (1H, m), 7,60 - 7,62 (1H, m), 7,67 - 7,70 (1H, m), 7,82 (2H, d), 7,90 - 7,92 (1H, m), 8,88 (1H, s).

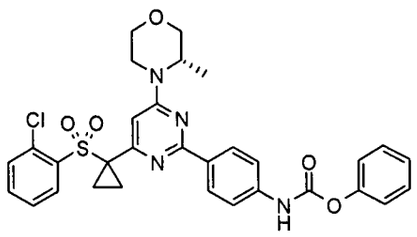
Ejemplo 76e: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,69 - 1,77 (2H, m), 1,95 - 2,03 (2H, m), 3,09 - 3,16 (1H, m), 3,36 - 3,48 (3H, m), 3,58 - 3,62 (1H, m), 3,74 (1H, d), 3,93 - 3,97 (1H, m), 4,10 (1H, d), 4,42 (2H, m), 4,54 (1H, t), 6,42 (1H, t), 6,63 (1H, s), 7,36 - 7,40 (2H, m), 7,43 - 7,47 (1H, m), 7,60 - 7,66 (1H, m), 7,67 - 7,70 (1H, m), 7,80 - 7,82 (2H, m), 7,90 - 7,92 (1H, m), 8,77 (1H, s).

Ejemplo 76f: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,10 - 1,17 (3H, d), 1,72 - 1,75 (2H, m), 1,98 - 2,01 (2H, m), 3,13 - 3,16 (1H, m), 3,42 - 3,48 (1H, m), 3,58 - 3,62 (1H, m), 3,75 (1H, d), 3,80 (3H, s), 3,94 - 3,97 (1H, m), 4,12 (1H, m), 4,42 (1H, s), 6,64 (1H, s), 7,40 - 7,47 (4H, m), 7,61 - 7,63 (1H, m), 7,68 - 7,71 (1H, m), 7,77 (1H, s), 7,83 (2H, d), 7,90 - 7,93 (1H, m), 8,38 (1H, s), 8,80 (1H, s).

La preparación de fenil *N*-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-

il]fenil]carbamato

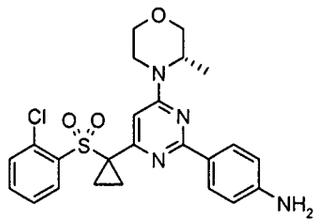


Se agregó gota a gota fenil cloroformiato (0,189 mL, 1,50 mmol) a una mezcla de 4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (0,727 g, 1,5 mmol) e hidrogenocarbonato de sodio (0,189 g, 2,25 mmol) en dioxano (20 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. El precipitado se recogió mediante filtración, se lavó con éter dietílico (10 mL), se suspendió en agua (20 mL), se agitó durante 20 minutos, se recogió mediante filtración, se lavó con agua (10 mL) luego éter (2 mL) y se secó al vacío para proporcionar el material deseado como un sólido blanco (0,735 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,72 - 1,77 (2H, m), 1,98 - 2,01 (2H, m), 3,10 - 3,18 (1H, m), 3,44 - 3,62 (2H, m), 3,74 (1H, d), 3,93 - 3,97 (1H, m), 4,12 (1H, d), 4,43 (1H, s), 6,67 (1H, s), 7,24 - 7,31 (3H, m), 7,43 - 7,48 (3H, m), 7,51 - 7,53 (2H, m), 7,60 - 7,63 (1H, m), 7,67 - 7,70 (1H, m), 7,88 - 7,92 (3H, m), 10,40 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 605; HPLC tR = 3,02 min.

4-[4-[1-(2-Clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



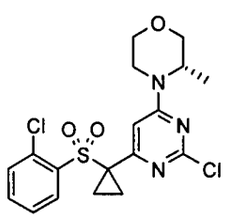
Se agregó diclorobis(trifenilfosfina)paladio(II) (0,519 g, 0,74 mmol) en una porción a una mezcla de carbonato de sodio (2,352 g, 22,20 mmol), 2-cloro-4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,169 g, 7,40 mmol) y pinacol éster de ácido (4-aminofenil)borónico (1,702 g, 7,77 mmol) en DME (56 mL)y agua (14 mL) bajo nitrógeno. La mezcla se agitó a 80°C durante 2 horas, se enfrió hasta alcanzar TA luego se diluyó con DCM (100 mL) y agua (50 mL). La capa orgánica se lavó con

salmuera saturada (50 mL) luego se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 60% acetato de etilo en isohexano, para proporcionar al residuo que se purificó adicionalmente mediante trituración con isohexano (25 mL) y éter dietílico (25 mL), para proporcionar el material deseado como un sólido amarillo (3,21 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,08 - 1,19 (3H, m), 1,67 - 1,75 (2H, m), 1,97 - 2,00 (2H, m), 3,05 - 3,13 (1H, m), 3,39 - 3,43 (1H, m), 3,56 - 3,60 (1H, m), 3,73 (1H, d), 3,91 - 3,96 (1H, m), 4,04 (1H, q), 4,37 (1H, s), 5,49 (2H, m), 6,47 - 6,49 (2H, m), 6,52 (1H, s), 7,43 - 7,47 (1H, m), 7,59 - 7,68 (4H, m), 7,90 - 7,93 (1H, m).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 485; HPLC tR = 1,94 min.

2-Cloro-4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

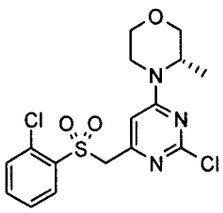


Se agregó hidróxido de sodio (solución 50% p/p) (35,2 mL, 440,00 mmol) a 2-cloro-4-[(2-clorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,22 g, 8 mmol), 1,2-dibromoetano (2,068 mL, 24,00 mmol) y bromuro de tetrabutilamonio (0,258 g, 0,80 mmol) en tolueno (141 mL). La solución resultante se agitó a 60°C durante 18 horas. La mezcla de reacción se diluyó con DCM (150 mL) y se lavó dos veces con agua (150 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% acetato de etilo en DCM, para proporcionar el material deseado como una película seca incolora (3,23 g).

Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,13 (3H, d), 1,64 - 1,67 (2H, m), 1,92 - 1,95 (2H, m), 3,07 - 3,15 (1H, m), 3,35 - 3,41 (1H, m), 3,51 - 3,55 (1H, m), 3,69 (1H, d), 3,88 - 3,92 (2H, m), 4,24 (1H, s), 6,72 (1H, s), 7,52 - 7,56 (1H, m), 7,66 - 7,73 (2H, m), 7,88 - 7,91 (1H, m).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 428; HPLC tR = 2,42 min.

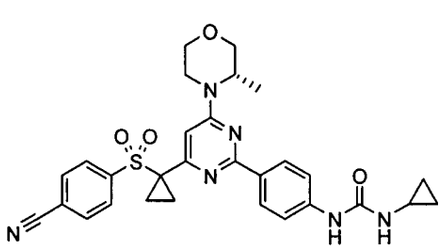
2-Cloro-4-[(2-clorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó 2-clorobencenosulfinato de sodio (3,19 g, 16,07 mmol) a una solución de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4,37 g, 12,36 mmol) en DMF (20 mL). La mezcla resultante se agitó a TA durante 1 hora. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (150 mL) y se lavó secuencialmente con agua (100 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blanco (4,34 g).
Espectro de NMR: ^{1}H NMR (399,9 MHz, DMSO-D_6) δ 1,16 - 1,18 (3H, d), 3,13 - 3,20 (1H, m), 3,39 - 3,46 (1H, m), 3,56 - 3,59 (1H, m), 3,72 (1H, d), 3,91 - 3,95 (2H, m), 4,22 (1H, s), 4,78 (2H, s), 6,79 (1H, s), 7,56 - 7,59 (1H, m), 7,74 - 7,79 (2H, m), 7,82 - 7,84 (1H, m).
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 402; HPLC tR = 2,26 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 77: 1-[4-[4-[1-(4-Cianofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea



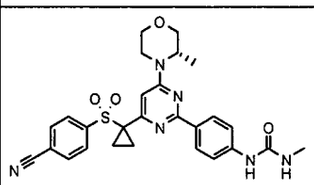
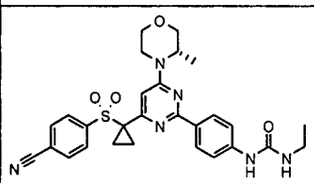
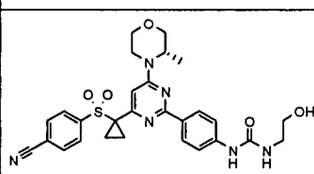
Se agregó ciclopropilamina (32 mg, 0,564 mmol) a fenil *N*-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (112 mg, 0,188 mmol) y trietilamina (0,080 mL, 0,564 mmol) en NMP (2 mL). La solución

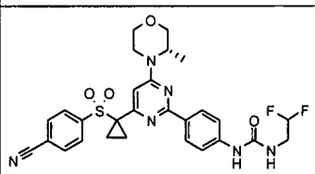
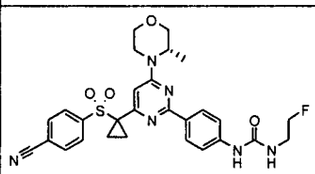
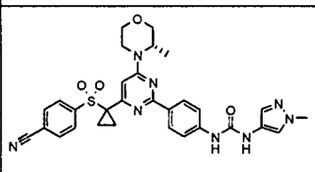
resultante se agitó a 50°C durante 16 horas y luego se enfrió hasta alcanzar TA y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido (81 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 0,42 (2H, m), 0,65 (2H, m), 1,19 (3H, d), 1,65 (2H, m), 1,96 (2H, m), 2,56 (1H, m), 3,17 (1H, m), 3,47 (1H, m), 3,61 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,16 (1H, m), 4,46 (1H, m), 6,41 (1H, d), 6,67 (1H, s), 7,39 (2H, d), 7,68 (2H, d), 7,98 (2H, d), 8,08 (2H, d), 8,53 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 559; HPLC tR = 2,36 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
77a		1-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	533	2,20
77b		3-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	547	2,34
77c		1-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	563	2,00

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
77d		1-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea	583	2,46
77e		1-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	565	2,34
77f		1-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	599	2,22

* Además de las condiciones de reacción descritas anteriormente esta muestra se sometió adicionalmente a la adición de más trietilamina (3 equivalentes) y se agitó durante 7 horas más a 80°C.

Ejemplo 77a: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,65 (2H, m), 1,95 (2H, m), 2,66 (3H, d), 3,16 (1H, m), 3,47 (1H, m), 3,61 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,16 (1H, m), 4,46 (1H, m), 6,06 (1H, q), 6,66 (1H, s), 7,39 (2H, d), 7,68 (2H, d), 7,98 (2H, d), 8,08 (2H, d), 8,73 (1H, s).

Ejemplo 77b: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,19 (3H, d), 1,65 (2H, m), 1,95 (2H, m), 3,09 - 3,20 (3H, m), 3,47 (1H, m), 3,62 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,16 (1H, m), 4,46 (1H, m), 6,15 (1H, t), 6,66 (1H, s), 7,38 (2H, d), 7,67 (2H, d), 7,98 (2H, d), 8,08 (2H, d), 8,65 (1H, s).

Ejemplo 77c: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,65 (2H, m), 1,96 (2H, m), 3,18 (3H, m), 3,47 (3H, m), 3,61 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,16 (1H, m), 4,46

(1H, m), 4,74 (1H, t), 6,25 (1H, t), 6,66 (1H, s), 7,37 (2H, d), 7,67 (2H, d), 7,98 (2H, d), 8,09 (2H, d), 8,79 (1H, s).

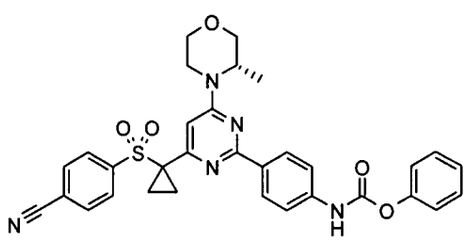
Ejemplo 77d: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,65 (2H, m), 1,96 (2H, m), 3,17 (1H, m), 3,43 - 3,63 (4H, m), 3,75 (1H, m), 3,96 (1H, m), 4,16 (1H, m), 4,46 (1H, m), 5,92 - 6,22 (1H, m), 6,52 (1H, t), 6,67 (1H, s), 7,39 (2H, d), 7,70 (2H, d), 7,98 (2H, d), 8,08 (2H, d), 8,91 (1H, s).

Ejemplo 77e: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,65 (2H, m), 1,96 (2H, m), 3,16 (1H, m), 3,39 (1H, m), 3,47 (2H, m), 3,61 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,16 (1H, m), 4,41 - 4,55 (3H, m), 6,43 (1H, t), 6,67 (1H, s), 7,39 (2H, d), 7,69 (2H, d), 7,98 (2H, d), 8,09 (2H, d), 8,80 (1H, s).

Ejemplo 77f: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 (4H, d), 1,65 (2H, m), 1,96 (3H, m), 3,17 (2H, m), 3,47 (1H, m), 3,62 (1H, m), 3,74 - 3,80 (4H, m), 3,97 (1H, m), 4,17 (1H, m), 4,47 (1H, m), 6,68 (1H, s), 7,38 (2H, s), 7,43 (3H, d), 7,71 (3H, d), 7,77 (2H, s), 7,98 (2H, d), 8,09 (2H, d), 8,38 (1H, s), 8,83 (1H, s).

La preparación de fenil *N*-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(4-cianofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

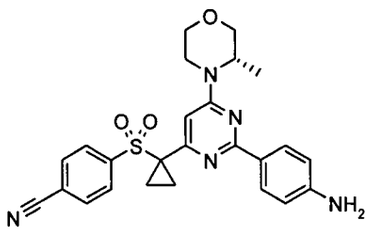


Se agregó gota a gota fenil cloroformiato (0,185 mL, 1,47 mmol) a 4-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzonitrilo (700 mg, 1,47 mmol) y bicarbonato de sodio (185 mg, 2,21 mmol) en dioxano (20 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. El precipitado se recogió mediante filtración, se lavó con éter dietílico (2 mL) y se suspendió en agua (20 mL) y se agitó durante 20 minutos. El precipitado se recogió mediante filtración, se lavó con agua (5 mL) luego éter dietílico (5 mL) y se secó al vacío para proporcionar el material deseado como un sólido blanco (786 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,67 (2H, m), 1,97 (2H, m), 3,18 (1H, m), 3,45 (1H, m), 3,62 (1H, m), 3,76 (1H, m), 3,97 (1H, m), 4,18 (1H, m), 4,47 (1H, m), 6,71 (1H, s), 7,27 (3H, m), 7,46 (2H, m), 7,53 (2H, d), 7,78 (2H, d), 7,98 (2H, d), 8,09 (2H, d), 10,44 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 596; HPLC tR = 3,01 min.

4-[1-[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzonitrilo



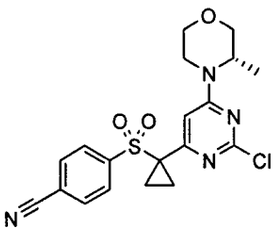
Se agregó carbonato de sodio (1,693 g, 15,97 mmol) a 4-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzonitrilo (2,23 g, 5,32 mmol) y pinacol éster de ácido (4-aminofenil)borónico (1,225 g, 5,59 mmol) en una mezcla de DME (40 mL) y agua (10,00 mL). La mezcla se burbujeó con nitrógeno durante 10 minutos luego diclorobis(trifenilfosfina)paladio(II) (0,374 g, 0,53 mmol) se agregó y la mezcla se agitó a 80°C durante 2 horas. La mezcla de reacción se enfrió hasta alcanzar TA luego se diluyó con DCM (100 mL) y agua (50 mL). La capa orgánica se lavó con salmuera saturada (50 mL) luego se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 40% acetato de etilo en isohexano seguido por 40% acetato de etilo en isohexano, para proporcionar el material deseado as un sólido naranja (2,31 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,62 (2H, m), 1,93 (2H, m), 3,14 (1H, m), 3,45 (1H, m), 3,60 (1H, m), 3,74 (1H, m), 3,95 (1H, m), 4,12 (1H, m), 4,42 (1H, m), 5,55 (2H, s), 6,48 (2H, d), 6,56 (1H, s), 7,50 (2H, d), 7,97 (2H, d), 8,08 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 476; HPLC tR = 2,37 min.

4-[1-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzonitrilo

1610

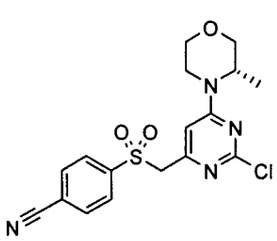


Se agregó hidruro de sodio, 60% dispersión en aceite mineral (0,316 g, 7,91 mmol) en una porción a 4-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]benzonitrilo (2,96 g, 7,53 mmol) en DMF (20 mL) a 0°C bajo nitrógeno. La suspensión resultante se agitó durante 10 minutos luego se agregó 1,2-dibromoetano (0,682 mL, 7,91 mmol). La mezcla se entibió hasta alcanzar 10°C durante 10 minutos luego se enfrió nuevamente hasta alcanzar 0°C y se agregó una porción adicional de hidruro de sodio, 60% dispersión en aceite mineral (0,316 g, 7,91 mmol). La mezcla se entibió hasta alcanzar 50°C y se agitó a 50°C durante 2 horas. Se agregó una porción adicional de hidruro de sodio, 60% dispersión en aceite mineral (0,158 g, 3,95 mmol) y 1,2-dibromoetano (0,341 ml, 3,95 mmol) y se agitó durante otras 2 horas. La mezcla de reacción se enfrió hasta alcanzar TA, se aplacó con cloruro de amonio acuoso saturado (2 mL) y los disolventes se evaporaron. Los residuos se agitaron en agua (50 mL) durante 15 minutos y luego el sólido resultante se recogió mediante filtración. El sólido se disolvió en DCM (50 mL), se lavó con agua (20 mL), luego salmuera saturada (20 mL), se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 40% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blanco (2,33 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,60 (2H, m), 1,90 (2H, m), 3,15 (1H, m), 3,40 (1H, m), 3,55 (1H, m), 3,70 (1H, m), 3,90 - 3,99 (2H, m), 4,27 (1H, m), 6,72 (1H, s), 7,96 (2H, d), 8,11 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 419; HPLC tR = 2,19 min.

4-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]benzonitrilo

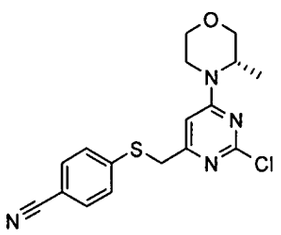


Se agregó ácido sulfúrico 2N (0,4 mL) a una solución agitada de 4-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]benzonitrilo (5,18 g, 14,35 mmol) en dioxano (125 mL) y la solución se calentó hasta alcanzar 55°C. Se agregó tungstato de sodio dihidrato (0,095 g, 0,29 mmol) en agua (3,5 mL) y la solución se dejó agitar durante 5 minutos. Se agregó gota a gota hidrógeno peróxido, solución 30% en peso en agua (8,80 mL, 86,13 mmol) y la solución se agitó a 55°C durante 3 horas. La reacción se enfrió hasta alcanzar TA y luego se agregó agua hasta que cesó la precipitación. El precipitado se recogió mediante filtración, se lavó con agua y se secó al vacío para proporcionar el material deseado como un sólido blanco (5,0 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,18 (3H, d), 3,18 (1H, m), 3,43 (1H, m), 3,58 (1H, m), 3,73 (1H, m), 3,91 (2H, m), 4,18 (1H, m), 4,77 (2H, s), 6,76 (1H, s), 7,99 (2H, d), 8,15 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 393; HPLC tR = 1,99 min.

4-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]benzonitrilo



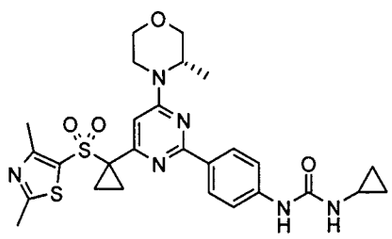
Se agregó 4-mercaptobenzonitrilo (3,48 g, 25,74 mmol) a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (7 g, 19,80 mmol) y DIPEA (5,32 mL, 29,70 mmol) en THF (50 mL). La suspensión resultante se agitó a TA durante 16 horas luego la temperatura se elevó hasta alcanzar 70°C durante otras 16 horas. La mezcla de reacción se enfrió hasta alcanzar TA luego se diluyó con DCM (200 mL) y se lavó secuencialmente con agua (200 mL) luego salmuera saturada (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 30% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (5,18 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (3H, d), 3,16 (1H, m), 3,42 (1H, m), 3,57 (1H, m), 3,71 (1H, m), 3,90 - 3,99 (2H, m), 4,26 (3H, m), 6,88 (1H, s), 7,55 (2H, d), 7,75 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 361; HPLC tR = 2,33 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 78: 3-Ciclopropil-1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea

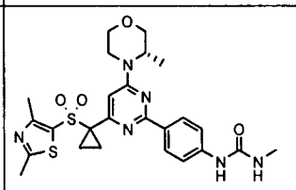
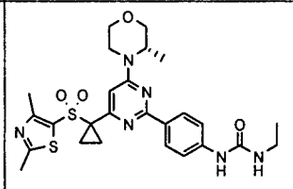
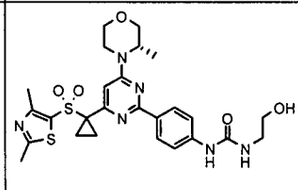
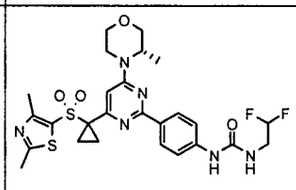
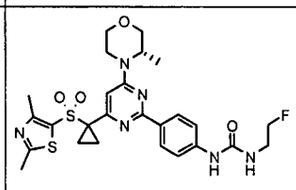
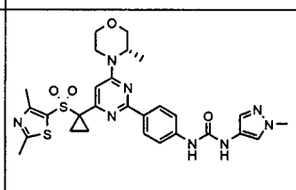


Se agregó ciclopropilamina (26 mg, 0,450 mmol) a fenil *N*-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (91 mg, 0,150 mmol) y trietilamina (0,063 mL, 0,450 mmol) en NMP (2 mL). La solución resultante se agitó a 50°C durante 16 horas y luego se enfrió hasta alcanzar TA y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (64 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 0,42 (2H, m), 0,66 (2H, m), 1,21 (3H, d), 1,62 (2H, m), 1,79 (2H, m), 2,22 (3H, s), 2,56 (1H, m), 2,62 (3H, s), 3,18 (1H, m), 3,48 (1H, m), 3,63 (1H, m), 3,76 (1H, m), 3,97 (1H, m), 4,16 (1H, m), 4,49 (1H, m), 6,43 (1H, d), 6,73 (1H, s), 7,45 (2H, d), 7,93 (2H, d), 8,53 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 569; HPLC tR = 2,27 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
78a		1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	543	2,08
78b		3-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	557	2,25
78c		1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	573	1,91
78d		3-(2,2-difluoroetil)-1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	593	2,38
78e		1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	575	2,24
78f*		1-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	609	2,13

* Se agitó durante 4 horas más a 80°C

Ejemplo 78a: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,61 (2H, m), 1,79 (2H, m), 2,22 (3H, s), 2,62 (3H, s), 2,67 (3H, d), 3,18 (1H, m), 3,48 (1H, m), 3,63 (1H, m), 3,76

(1H, m), 3,97 (1H, m), 4,16 (1H, m), 4,49 (1H, m), 6,06 (1H, q), 6,72 (1H, s), 7,44 (2H, d), 7,92 (2H, d), 8,74 (1H, s).

Ejemplo 78b: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,21 (3H, d), 1,62 (2H, m), 1,79 (2H, m), 2,22 (3H, s), 2,62 (3H, s), 3,10 - 3,22 (3H, m), 3,48 (1H, m), 3,63 (1H, m), 3,76 (1H, m), 3,98 (1H, m), 4,16 (1H, m), 4,49 (1H, m), 6,15 (1H, t), 6,72 (1H, s), 7,43 (2H, d), 7,92 (2H, d), 8,66 (1H, s).

Ejemplo 78c: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,62 (2H, m), 1,79 (2H, m), 2,22 (3H, s), 2,62 (3H, s), 3,14 - 3,22 (3H, m), 3,44 - 3,51 (3H, m), 3,63 (1H, m), 3,76 (1H, m), 3,97 (1H, m), 4,16 (1H, m), 4,49 (1H, m), 4,74 (1H, t), 6,24 (1H, t), 6,73 (1H, s), 7,43 (2H, d), 7,93 (2H, d), 8,80 (1H, s).

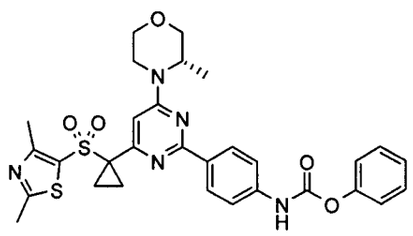
Ejemplo 78d: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,62 (2H, m), 1,79 (2H, m), 2,22 (3H, s), 2,62 (3H, s), 3,18 (1H, m), 3,45 - 3,65 (4H, m), 3,76 (1H, m), 3,97 (1H, m), 4,16 (1H, m), 4,49 (1H, m), 5,93 - 6,23 (1H, m), 6,53 (1H, t), 6,74 (1H, s), 7,45 (2H, d), 7,95 (2H, d), 8,92 (1H, s).

Ejemplo 78e: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,62 (2H, m), 1,79 (2H, m), 2,22 (3H, s), 2,62 (3H, s), 3,18 (1H, m), 3,37 - 3,51 (3H, m), 3,63 (1H, m), 3,77 (1H, m), 3,98 (1H, m), 4,16 (1H, m), 4,41 - 4,55 (3H, m), 6,43 (1H, t), 6,73 (1H, s), 7,44 (2H, d), 7,93 (2H, d), 8,81 (1H, s).

Ejemplo 78f: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,62 (2H, m), 1,80 (2H, m), 2,23 (3H, s), 2,63 (3H, s), 3,19 (1H, m), 3,48 (1H, m), 3,64 (1H, m), 3,77 (1H, m), 3,80 (3H, s), 3,98 (1H, m), 4,17 (1H, m), 4,49 (1H, m), 6,74 (1H, s), 7,39 (1H, s), 7,49 (2H, d), 7,78 (1H, s), 7,96 (2H, d), 8,38 (1H, s), 8,83 (1H, s).

La preparación de fenil *N*-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

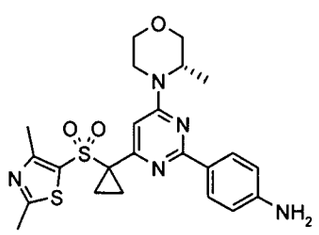


Se agregó gota a gota fenil cloroformiato (0,181 mL, 1,44 mmol) a 4-[4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (700 mg, 1,44 mmol) y bicarbonato de sodio (182 mg, 2,16 mmol) en dioxano (20 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. El precipitado se recogió mediante filtración, se lavó con éter dietílico (2 mL) y se suspendió en agua (20 mL) y se agitó durante 20 minutos. El precipitado se recogió mediante filtración, se lavó con agua (5 mL) luego éter dietílico (5 mL) y se secó al vacío para proporcionar el material deseado como un sólido beige (637 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,63 (2H, m), 1,81 (2H, m), 2,24 (3H, s), 2,61 (3H, s), 3,20 (1H, m), 3,49 (1H, m), 3,63 (1H, m), 3,77 (1H, m), 3,98 (1H, m), 4,17 (1H, m), 4,51 (1H, m), 6,78 (1H, s), 7,28 (3H, m), 7,46 (2H, m), 7,58 (2H, d), 8,02 (2H, d), 10,43 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 606; HPLC tR = 2,91 min.

4-[4-[1-[(2,4-Dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



Se agregó carbonato de sodio (2,105 g, 19,86 mmol) a 2-cloro-4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,84 g, 6,62 mmol) y pinacol éster de ácido (4-aminofenil)borónico (1,523 g, 6,95 mmol) en una mezcla de DME (40 mL) y agua (10 mL). La mezcla se burbujeó con nitrógeno durante 10 minutos luego diclorobis(trifenilfosfina)paladio(II) (0,465 g, 0,66 mmol) se agregó y la mezcla se agitó a 80°C durante 2 horas. Se agregó más diclorobis(trifenilfosfina)paladio(II) (0,232 g, 0,33 mmol) y la mezcla se agitó a 80°C durante otras 4 horas. La mezcla de reacción se enfrió hasta alcanzar TA luego se diluyó con DCM (250 mL) y agua (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 40 a 50% acetato de etilo en isohexano seguido por 50% acetato de etilo en isohexano, para proporcionar un material que se purificó adicionalmente mediante cromatografía de

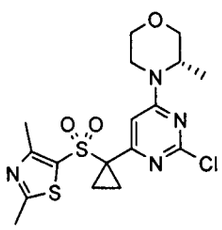
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intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 2M en metanol, para proporcionar el material deseado as un sólido naranja (2,59 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,59 (2H, m), 1,77 (2H, m), 2,22 (3H, s), 2,62 (3H, s), 3,15 (1H, m), 3,47 (1H, m), 3,61 (1H, m), 3,75 (1H, m), 3,96 (1H, m), 4,12 (1H, m), 4,45 (1H, m), 5,54 (2H, s), 6,54 (2H, d), 6,62 (1H, s), 7,76 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 486; HPLC tR = 2,17 min.

2-Cloro-4-[1-[(2,4-dimetil-1,3-tiazol-5-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

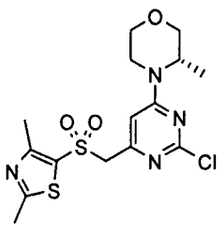


Se agregó hidróxido de sodio (15,94 g, 398,59 mmol) en agua (16 mL) a una solución agitada de 2-cloro-4-[(2,4-dimetil-1,3-tiazol-5-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,92 g, 7,25 mmol), 1,2-dibromoetano (1,874 mL, 21,74 mmol) y bromuro de tetrabutilamonio (0,234 g, 0,72 mmol) en tolueno (100 mL). La solución resultante se agitó a TA durante 90 minutos luego a 60°C durante 1 hora. La mezcla de reacción se diluyó con agua (300 mL), la capa orgánica se separó y se lavó con salmuera saturada (100 mL), luego se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blanco (2,84 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,59 (2H, m), 1,76 (2H, m), 2,29 (3H, s), 2,68 (3H, s), 3,17 (1H, m), 3,42 (1H, m), 3,56 (1H, m), 3,72 (1H, m), 3,91 - 4,00 (2H, m), 4,33 (1H, m), 6,82 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 429; HPLC tR = 2,09 min.

2-Cloro-4-[(2,4-dimetil-1,3-tiazol-5-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

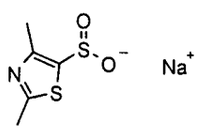


2,4-dimetiltiazol-5-sulfinato de sodio (5,2 g, 26,10 mmol) se agregó a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4,01 g, 11,35 mmol) en DMF (50 mL). La mezcla resultante se agitó a TA durante 1 hora. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (250 mL) y se lavó secuencialmente con agua (150 mL) y salmuera saturada (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano seguido por 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (4,77 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,19 (3H, d), 2,40 (3H, s), 2,67 (3H, s), 3,19 (1H, m), 3,44 (1H, m), 3,59 (1H, m), 3,73 (1H, m), 3,93 (2H, m), 4,23 (1H, m), 4,69 (2H, s), 6,83 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 403; HPLC tR = 1,82 min.

2,4-dimetiltiazol-5-sulfinato de sodio

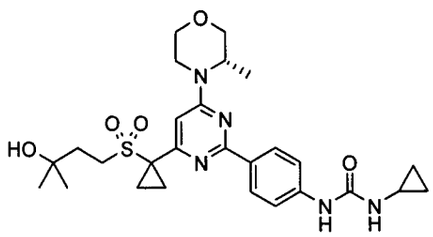


Una solución de sulfito de sodio (2,98 g, 23,62 mmol) en agua (25 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (3,97 g, 47,24 mmol) y la solución resultante se agitó a 50°C durante 1 hora. Se agregó en porciones cloruro de 2,4-Dimetiltiazol-5-sulfonilo (5 g, 23,62 mmol) a la solución y se continuó agitando a 50°C durante 18 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en metanol (75 mL). La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar el material deseado como un sólido amarillo (5,21 g), que se secó al vacío y se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 2,28 (3H, s).

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

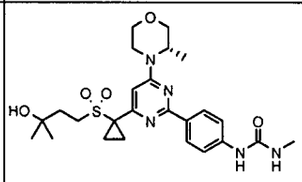
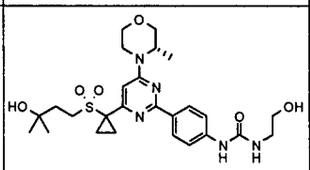
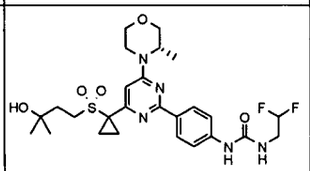
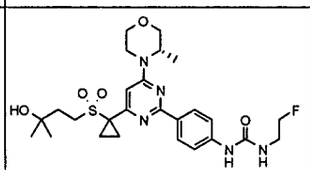
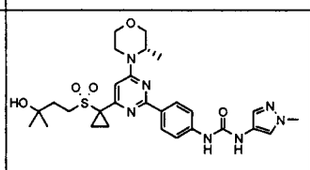
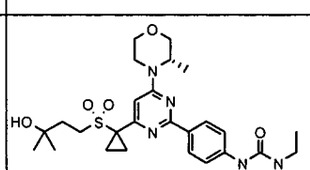
Ejemplo 79: 3-Ciclopropil-1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea



Se agregó ciclopropilamina (33 mg, 0,573 mmol) a fenil *N*-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (111 mg, 0,191 mmol) y trietilamina (0,080 mL, 0,573 mmol) en NMP (2 mL). La solución resultante se agitó a 50°C durante 16 horas y luego se enfrió hasta alcanzar TA y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (83 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 0,43 (2H, m), 0,65 (2H, m), 1,12 (6H, s), 1,24 (3H, d), 1,56 (2H, m), 1,65 (2H, m), 1,85 (2H, m), 2,56 (1H, m), 3,21 (1H, m), 3,49 (1H, m), 3,56 (2H, m), 3,63 (1H, m), 3,77 (1H, m), 3,98 (1H, m), 4,22 (1H, m), 4,49 (1H, s), 4,56 (1H, m), 6,44 (1H, d), 6,76 (1H, s), 7,50 (2H, d), 8,24 (2H, d), 8,57 (1H, s).
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 544; HPLC tR = 2,10 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
79a		1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	518	1,93
79b		3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	548	1,78
79c		3-(2,2-difluoroetil)-1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	568	2,18
79d		3-(2-fluoroetil)-1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	550	2,06
79e*		1-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	584	1,98
79f		1-etil-3-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	532	2,07

* Se utilizaron 6 equivalentes de trietilamina.

Ejemplo 79a: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,13 (6H, s), 1,23 (3H, d), 1,55 (2H, m), 1,65 (2H, m), 1,85 (2H, m), 2,67 (3H, d), 3,21 (1H, m), 3,45 - 3,58 (3H, m), 3,63 (1H, m), 3,77 (1H, m), 3,98 (1H, m), 4,22 (1H, m), 4,49 (1H, s), 4,57 (1H, m), 6,07 (1H, m), 6,75 (1H, s), 7,49 (2H, d), 8,23 (2H, d), 8,77 (1H, s).

Ejemplo 79b: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,13 (6H, s), 1,24 (3H, d), 1,55 (2H, m), 1,65 (2H, m), 1,85 (2H, m), 3,16 - 3,24 (3H, m), 3,45 - 3,49 (3H, m), 3,56 (2H, m), 3,63 (1H, m), 3,77 (1H, m), 3,98 (1H, m), 4,22 (1H, m), 4,49 (1H, s), 4,56 (1H, m), 4,74 (1H, t), 6,25 (1H, t), 6,76 (1H, s), 7,48 (2H, d), 8,23 (2H, d), 8,82 (1H, s).

Ejemplo 79c: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,13 (6H, s), 1,24 (3H, d), 1,56 (2H, m), 1,65 (2H, m), 1,85 (2H, m), 3,21 (1H, m), 3,45 - 3,65 (6H, m), 3,77 (1H, m), 3,98 (1H, m), 4,23 (1H, m), 4,49 (1H, s), 4,57 (1H, m), 5,93 - 6,23 (1H, m), 6,53 (1H, t), 6,77 (1H, s), 7,50 (2H, d), 8,26 (2H, d), 8,95 (1H, s).

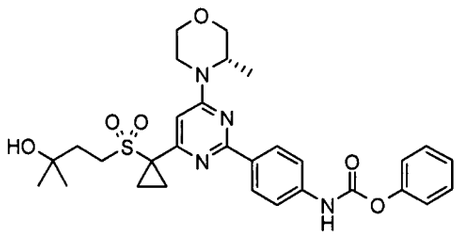
Ejemplo 79d: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,12 (6H, s), 1,24 (3H, d), 1,55 (2H, m), 1,65 (2H, m), 1,85 (2H, m), 3,21 (1H, m), 3,36 - 3,58 (5H, m), 3,64 (1H, m), 3,77 (1H, m), 3,98 (1H, m), 4,22 (1H, m), 4,41 - 4,58 (4H, m), 6,43 (1H, t), 6,76 (1H, s), 7,49 (2H, d), 8,25 (2H, d), 8,83 (1H, s).

Ejemplo 79e: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,13 (6H, s), 1,24 (3H, d), 1,56 (2H, m), 1,66 (2H, m), 1,86 (2H, m), 3,22 (1H, m), 3,49 (1H, m), 3,57 (2H, m), 3,64 (1H, m), 3,78 (4H, m), 3,98 (1H, m), 4,23 (1H, m), 4,50 (1H, s), 4,57 (1H, m), 6,77 (1H, s), 7,39 (1H, s), 7,54 (2H, d), 7,78 (1H, s), 8,27 (2H, d), 8,38 (1H, s), 8,86 (1H, s)

Ejemplo 79f: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,12 (6H, s), 1,23 (3H, d), 1,59 (4H, m), 1,84 (2H, m), 3,17 (3H, m), 3,54 (4H, m), 3,76 (1H, m), 3,98 (1H, m), 4,23 (1H, m), 4,56 (2H, m), 6,17 (1H, m), 6,75 (1H, s), 7,48 (2H, d), 8,23 (2H, d), 8,72 (1H, s)

La preparación de fenil *N*-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

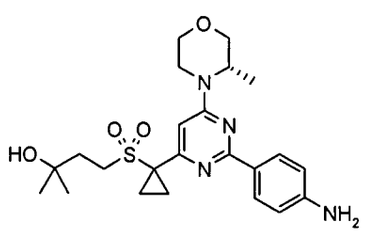


Se agregó gota a gota fenil cloroformiato (0,191 mL, 1,52 mmol) a 4-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-2-metilbutan-2-ol (700 mg, 1,52 mmol) y bicarbonato de sodio (192 mg, 2,28 mmol) en dioxano (20 mL) bajo nitrógeno. La suspensión resultante se agitó a TA durante 2 horas. El precipitado se recogió mediante filtración y luego se lavó con éter dietílico (2 mL). El precipitado se suspendió en agua (20 mL) luego se extrajo y se colocó en DCM (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como un sólido amarillo (774 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,12 (6H, s), 1,24 (3H, d), 1,57 (2H, m), 1,66 (2H, m), 1,85 (2H, m), 3,22 (1H, m), 3,46 - 3,57 (3H, m), 3,64 (1H, m), 3,77 (1H, m), 3,98 (1H, m), 4,24 (1H, m), 4,58 (1H, m), 6,80 (1H, s), 7,28 (3H, m), 7,46 (2H, m), 7,62 (2H, d), 8,33 (2H, d), 10,43 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 581; HPLC tR = 2,63 min.

4-[1-[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-2-metilbutan-2-ol



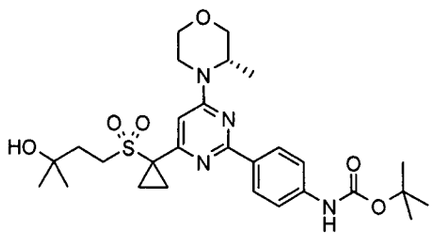
Se agregó tFA (5 mL) a *terc*-butil *N*-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (2,08 g, 3,71 mmol) en DCM (5 mL). La solución resultante se agitó a TA durante 1 hora y luego se agregó a una columna SCX. El producto bruto se eluyó de la columna utilizando amoníaco 2M en metanol luego se purificó adicionalmente mediante cromatografía de sílice instantánea, gradiente de elución de 40 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido blanco (1,15 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,13 (6H, s), 1,22 (3H, d), 1,52

(2H, m), 1,63 (2H, m), 1,85 (2H, m), 3,18 (1H, m), 3,48 (1H, m), 3,55 (2H, m), 3,62 (1H, m), 3,76 (1H, m), 3,97 (1H, m), 4,19 (1H, m), 4,48 (1H, s), 4,53 (1H, m), 5,57 (2H, s), 6,59 (2H, d), 6,65 (1H, s), 8,07 (2H, d).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 461; HPLC tR = 1,96 min.

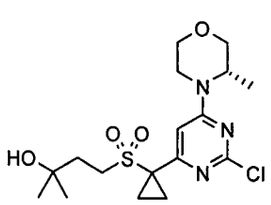
terc-butil *N*-[4-[4-[1-(3-hidroxi-3-metilbutil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



Se agregó carbonato de sodio (1,299 g, 12,25 mmol) a 4-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-2-metilbutan-2-ol (1,65 g, 4,08 mmol) y pinacol éster de ácido (4-boc-aminofenil)borónico(1,369 g, 4,29 mmol) en una mezcla de DME (40 mL) y agua (10 mL). La mezcla se burbujeó con nitrógeno durante 10 minutos y luego se agregó 1,1'-bis(difenilfosfino)ferrocenodicloropaladio(II) (0,296 g, 0,41 mmol) y la mezcla se agitó a 80°C durante 8 horas. La mezcla de reacción se enfrió hasta alcanzar TA luego se diluyó con DCM (150 mL) y se lavó con agua (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (2,08 g).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 561; HPLC tR = 2,69 min.

4-[1-[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-2-metilbutan-2-ol



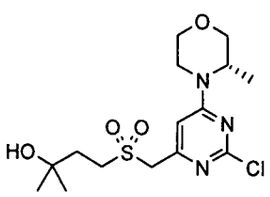
Se agregó hidróxido de sodio (11,93 g, 298,37 mmol) en agua (12 mL) a una solución agitada

de 4-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]-2-metilbutan-2-ol (2,05 g, 5,42 mmol), 1,2-dibromoetano (1,402 mL, 16,27 mmol) y bromuro de tetrabutilamonio (0,175 g, 0,54 mmol) en tolueno (75 mL). La solución resultante se agitó a TA durante 5 horas luego a 45°C durante 3 horas. La mezcla de reacción se diluyó con agua (100 mL), la capa orgánica se separó y se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como una película amarilla seca (1,75 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,13 (6H, s), 1,22 (3H, d), 1,52 (2H, m), 1,61 (2H, m), 1,80 (2H, m), 3,21 (1H, m), 3,36 - 3,47 (3H, m), 3,58 (1H, m), 3,72 (1H, m), 3,93 (1H, m), 4,05 (1H, m), 4,40 (1H, m), 4,46 (1H, s), 6,94 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 404; HPLC tR = 1,83 min.

4-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]-2-metilbutan-2-ol

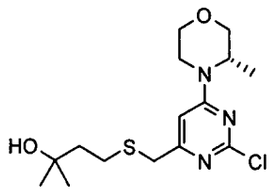


Se agregó ácido sulfúrico 2N (0,307 mL) a una solución agitada de 4-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]-2-metilbutan-2-ol (3,78 g, 10,93 mmol) en dioxano (100 mL) y la solución se calentó hasta alcanzar 55°C. Se agregó tungstato de sodio dihidrato (0,072 g, 0,22 mmol) en agua (3 mL) y la solución se dejó agitar durante 5 minutos. Se agregó gota a gota hidrógeno peróxido, solución 30% en peso en agua (6,7 mL, 65,57 mmol) y la solución se agitó a 55°C durante 2,5 horas. La mezcla de reacción se enfrió hasta alcanzar TA y se diluyó con agua (100 mL) y se extrajo con DCM (2 x 200 mL). La capa orgánica se lavó con salmuera (50 mL) luego se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como un sólido crema (4,39 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (6H, s), 1,23 (3H, d), 1,82 (2H, m), 3,19 - 3,30 (3H, m), 3,46 (1H, m), 3,61 (1H, m), 3,74 (1H, m), 3,93 - 4,02 (2H, m), 4,31 (1H, m), 4,46 (2H, s), 4,48 (1H, s), 6,95 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 378; HPLC tR = 1,64 min.

4-[[2-Cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]-2-metilbutan-2-ol

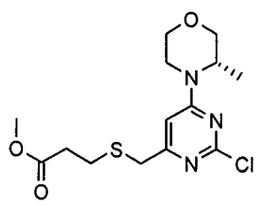


Se agregó gota a gota bromuro de metilmagnesio, 3M en éter dietílico (13,17 mL, 39,50 mmol) a metil 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]propanoato (4,14 g, 11,97 mmol) en THF (50 mL) a 0°C durante un período de 10 minutos bajo nitrógeno. La solución resultante se agitó a 0°C durante 30 minutos luego a TA durante 90 minutos. La mezcla de reacción se aplacó con solución de cloruro de amonio saturado acuoso (1 mL), se diluyó con agua (100 mL) luego se extrajo con DCM (3 x 100 mL), la capa orgánica se lavó con salmuera (100 mL), luego se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como una goma amarilla (3,96 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,08 (6H, s), 1,21 (3H, d), 1,61 (2H, m), 2,54 (2H, m), 3,18 (1H, m), 3,44 (1H, m), 3,57 (2H, s), 3,61 (1H, m), 3,72 (1H, m), 3,91 - 4,01 (2H, m), 4,23 (1H, s), 4,32 (1H, m), 6,78 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 346; HPLC tR = 1,79 min.

Metil 3-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfanil]propanoato



Se agregó metil 3-mercaptopropionato (2,55 g, 21,21 mmol) a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (5 g, 14,14 mmol) y DIPEA (3,80 mL, 21,21 mmol) en THF (50 mL). La suspensión resultante se agitó a TA durante 16 horas. La mezcla de reacción se diluyó con DCM (150 mL) y se lavó secuencialmente con agua (100 mL) luego salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 30% acetato de etilo en isohexano, para proporcionar el material deseado como un líquido incoloro (4,6 g).

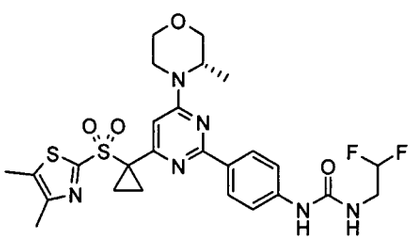
1825

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,21 (3H, d), 2,65 (2H, t), 2,76 (2H, t), 3,19 (1H, m), 3,45 (1H, m), 3,56 - 3,64 (6H, m), 3,72 (1H, m), 3,91 - 4,00 (2H, m), 4,33 (1H, m), 6,81 (1H, s).

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 346; HPLC tR = 2,05 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 80: 3-(2,2-Difluoroetil)-1-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea

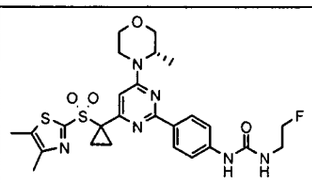
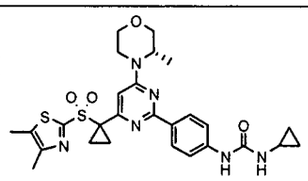
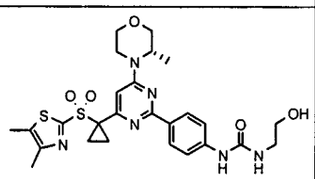
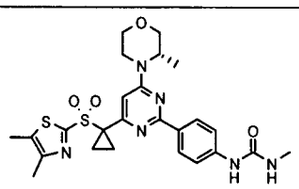
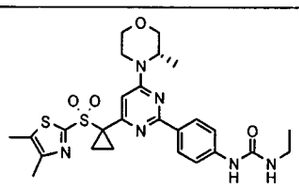


Se agregaron fenil *N*-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (150 mg, 0,25 mmol), trietilamina (0,104 mL, 0,74 mmol) y 2,2-difluoroetanamina (60,2 mg, 0,74 mmol) a dioxano (10 mL) y se calentó a 50°C durante 72 horas. La mezcla de reacción se evaporó bajo presión reducida hasta proporcionar una goma que se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (83 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,77 - 1,72 (2H, m), 1,95 - 1,88 (2H, m), 2,37 (3H, s), 2,40 (3H, s), 3,23 - 3,13 (1H, m), 3,66 - 3,41 (4H, m), 3,80 - 3,73 (1H, m), 3,97 (1H, d), 4,17 (1H, d), 4,51 - 4,41 (1H, m), 6,23 - 5,91 (1H, m), 6,51 (1H, t), 6,79 (1H, s), 7,44 (2H, d), 7,90 (2H, d), 8,91 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 493; HPLC tR = 2,42 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
80a		1-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	576	2,25
80b		3-ciclopropil-1-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	569	2,23
80c		1-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	573	1,90
80d*		1-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	543	2,06
80e*		3-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	557	2,21

* Se agitó a TA durante 16 horas

Ejemplo 80a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,78 - 1,71 (2H, m), 1,94 - 1,89 (2H, m), 2,37 (3H, s), 2,40 (3H, s), 3,24 - 3,13 (1H, m), 3,51 - 3,35 (4H, m), 3,65 - 3,59 (1H, m), 3,79 - 3,74 (1H, m), 4,01 - 3,94 (1H, m), 4,17 (1H, d), 4,56 - 4,38 (3H, m), 6,41 (1H, t), 7,43 (2H, d), 7,89 (2H, d), 8,80 (1H, s)

Ejemplo 80b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,45 - 0,38 (2H, m), 0,69 - 0,61 (2H, m), 1,21 (3H, d), 1,76 - 1,72 (2H, m), 1,94 - 1,89 (2H, m), 2,37 (3H, s), 2,41 (3H, s), 2,59 - 2,53 (1H, m), 3,24 - 3,13 (1H, m), 3,47 (1H, t), 3,64 - 3,59 (1H, m), 3,80 - 3,72 (1H, m), 3,98

(1H, d), 4,17 (1H, d), 4,50 - 4,41 (1H, m), 6,41 (1H, d), 6,78 (1H, s), 7,43 (2H, d), 7,88 (2H, d), 8,53 (1H, s)

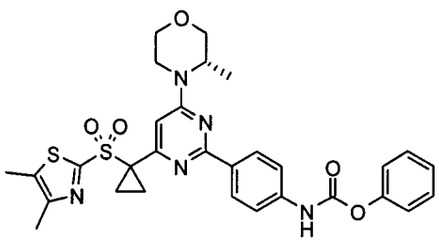
Ejemplo 80c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,77 - 1,72 (2H, m), 1,94 - 1,89 (2H, m), 2,37 (3H, s), 2,40 (4H, s), 3,51 - 3,42 (3H, m), 3,65 - 3,59 (1H, m), 3,79 - 3,74 (1H, m), 3,97 (1H, d), 4,06 (2H, q), 4,17 (1H, d), 4,50 - 4,41 (1H, m), 4,72 (1H, t), 6,23 (1H, t), 6,78 (1H, s), 7,41 (2H, d), 7,88 (2H, d), 8,79 (1H, s)

Ejemplo 80d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,78 - 1,72 (2H, m), 1,94 - 1,89 (2H, m), 2,37 (3H, s), 2,40 (3H, s), 2,66 (3H, d), 3,23 - 3,13 (1H, m), 3,52 - 3,42 (1H, m), 3,65 - 3,59 (1H, m), 3,79 - 3,74 (1H, m), 3,97 (1H, d), 4,20 - 4,13 (1H, m), 4,49 - 4,41 (1H, m), 6,07 - 6,03 (1H, m), 6,78 (1H, s), 7,43 (2H, d), 7,87 (2H, d), 8,73 (1H, s)

Ejemplo 80e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,21 (3H, d), 1,77 - 1,71 (2H, m), 1,95 - 1,88 (2H, m), 2,37 (3H, s), 2,41 (3H, s), 3,23 - 3,07 (3H, m), 3,47 (1H, t), 3,65 - 3,59 (1H, m), 3,79 - 3,73 (1H, m), 3,98 (1H, d), 4,16 (1H, d), 4,51 - 4,40 (1H, m), 6,14 (1H, t), 6,78 (1H, s), 7,42 (2H, d), 7,88 (2H, d), 8,65 (1H, s)

La preparación de fenil *N*-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



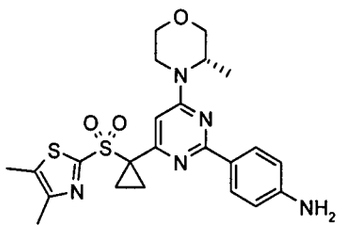
Se agregó gota a gota fenil cloroformiato (0,866 mL, 6,91 mmol) a 4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (2,58 g, 5,31 mmol) e hidrogenocarbonato de sodio (8,93 g, 106,26 mmol) en DCM (52,3 mL) a TA bajo nitrógeno. La suspensión resultante se agitó a TA durante 90 minutos, se agregó solución de cloruro de amonio saturado seguido por DCM (40 mL). Los orgánicos se separaron, se lavaron con agua (50 mL) y salmuera saturada (50 mL), se secaron sobre $MgSO_4$ y se evaporaron para proporcionar el material deseado (2,91 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,34 (3H, d), 1,87 - 1,77 (2H, m), 2,14

- 2,10 (2H, m), 2,34 (3H, s), 2,36 (3H, s), 3,32 (1H, t), 3,60 (1H, t), 3,77 - 3,72 (1H, m), 3,85 - 3,81 (1H, m), 4,04 (1H, d), 4,20 (1H, d), 4,53 - 4,44 (1H, m), 7,04 (1H, s), 7,10 (1H, s), 7,28 - 7,17 (3H, m), 7,40 (2H, t), 7,46 (2H, d), 8,16 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 606; HPLC tR = 2,90 min.

4-[4-[1-[(4,5-Dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

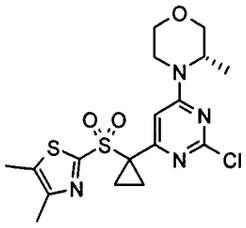


Se agregó diclorobis(trifenilfosfina)paladio(II) (0,219 g, 0,31 mmol) en una porción a 2-cloro-4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,68 g, 6,25 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,369 g, 6,25 mmol) y bicarbonato de sodio (15,62 mL, 31,24 mmol) en una mezcla de disolventes (18% DMF, 82% de una mezcla 7:3:2 de DME:agua:etanol) (75 mL) y la mezcla resultante se agitó a 80°C durante 16 horas bajo una atmósfera inerte. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó secuencialmente con agua (2 x 150 mL) y salmuera saturada (3 x 100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como una espuma amarilla(2,85 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,32 (3H, d), 1,88 - 1,75 (2H, m), 2,16 - 2,06 (2H, m), 2,34 (3H, s), 2,36 (3H, s), 3,33 - 3,24 (1H, m), 3,63 - 3,55 (1H, m), 3,88 - 3,71 (4H, m), 4,03 (1H, d), 4,18 (1H, d), 4,51 - 4,43 (1H, m), 6,64 (2H, d), 7,04 (1H, s), 8,01 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 486; HPLC tR = 1,65 min.

2-Cloro-4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

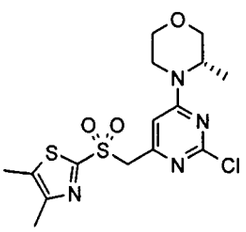


Se agregó hidróxido de sodio (50% p/p) (45,9 g, 573,32 mmol) en una porción a 2-cloro-4-[(4,5-dimetil-1,3-tiazol-2-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (4,2 g, 10,42 mmol), bromuro de tetrabutilamonio (0,336 g, 1,04 mmol) y 1,2-dibromoetano (2,69 mL, 31,27 mmol) en tolueno (52,1 mL) y la mezcla resultante se agitó a 60°C durante 5 horas. La mezcla de reacción se diluyó con tolueno (50 mL) y agua (100 mL) y se lavó secuencialmente con agua (2 x 100 mL) y salmuera saturada (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 50% acetato de etilo en DCM, para proporcionar el material deseado como una espuma blanca (3,42 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,34 (3H, d), 1,83 - 1,72 (2H, m), 2,11 - 2,02 (2H, m), 2,37 (3H, s), 2,44 (3H, s), 3,29 (1H, t), 3,54 (1H, t), 3,72 - 3,66 (1H, m), 3,82 - 3,76 (1H, m), 4,13 - 3,97 (2H, m), 4,35 (1H, s), 7,29 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 429; HPLC tR = 2,35 min.

2-Cloro-4-[(4,5-dimetil-1,3-tiazol-2-il)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



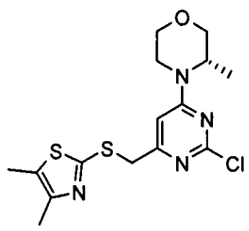
Se agregó ácido 3-cloroperoxibenzoico (11,18 g, 49,88 mmol) en porciones a (2-cloro-4-[(4,5-dimetil-1,3-tiazol-2-il)sulfanilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (7,4 g, 19,95 mmol) en DCM (100 mL) a 5°C durante un período de 15 minutos bajo nitrógeno. La suspensión resultante se agitó a 5°C durante 1 hora y luego se dejó entibiar hasta alcanzar TA y se agitó durante 3 horas. Se agregó una solución saturada de hidrogenocarbonato de sodio (100 mL) y los orgánicos se separaron y se lavaron con agua (100 mL) y salmuera (100 mL), se secaron sobre $MgSO_4$ y se evaporaron al vacío. El producto bruto se purificó mediante

cromatografía de sílice instantánea, gradiente de elución de 30 a 60% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (4,2 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,32 (3H, d), 2,42 (3H, s), 2,46 (3H, s), 3,28 (1H, t), 3,54 (1H, t), 3,71 - 3,66 (1H, m), 3,81 - 3,76 (1H, m), 4,09 - 3,96 (2H, m), 4,35 - 4,23 (1H, m), 4,51 (2H, s), 6,59 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 403; HPLC tR = 2,02 min.

2-Cloro-4-[(4,5-dimetil-1,3-tiazol-2-il)sulfanilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



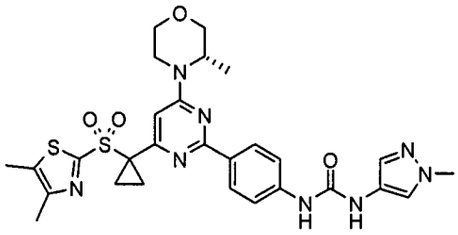
Se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (7 g, 19,80 mmol) a 4,5-dimetiltiazol-2-tiol (3,16 g, 21,78 mmol) y DIPEA (5,17 mL, 29,70 mmol) en THF (10 mL) y la suspensión se agitó a TA durante 7 horas. El disolvente se retiró bajo presión reducida y el residuo se diluyó con DCM y se lavó secuencialmente con agua y salmuera saturada. La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como una goma amarilla (7,95 g).

Espectro de NMR: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,16 - 1,19 (3H, m), 2,23 (3H, d), 2,29 (3H, d), 3,16 - 3,20 (1H, td), 3,39 - 3,46 (1H, td), 3,55 - 3,59 (1H, dd), 3,71 (1H, d), 3,91 - 3,94 (2H, dd), 4,21 - 4,29 (3H, m), 6,80 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 371; HPLC tR = 2,31 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Ejemplo 81: 1-[4-[4-[1-[(4,5-Dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea



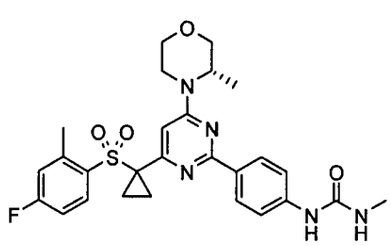
Se disolvieron fenil *N*-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (150 mg, 0,25 mmol), 1-metil-1H-pirazol-4-amina diclorhidrato (126 mg, 0,74 mmol) y DIPEA (0,428 mL, 2,48 mmol) en dioxano (10 mL) y se sellaron en un tubo de microondas. La reacción se calentó hasta alcanzar 100°C durante 150 minutos en el reactor de microondas y se enfrió hasta alcanzar TA. El disolvente se evaporó bajo presión reducida y el producto bruto se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (70 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,77 - 1,72 (2H, m), 1,95 - 1,89 (2H, m), 2,37 (3H, s), 2,41 (3H, s), 3,24 - 3,14 (1H, m), 3,52 - 3,43 (1H, m), 3,65 - 3,59 (1H, m), 3,81 - 3,75 (4H, m), 4,00 - 3,95 (1H, m), 4,22 - 4,11 (1H, m), 4,51 - 4,41 (1H, m), 6,79 (1H, s), 7,38 (1H, s), 7,47 (2H, d), 7,77 (1H, s), 7,92 (2H, d), 8,36 (1H, s), 8,83 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 609; HPLC tR = 2,09 min.

La preparación de fenil *N*-[4-[4-[1-[(4,5-dimetil-1,3-tiazol-2-il)sulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describió anteriormente.

Ejemplo 82: 1-[4-[4-[1-(4-Fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea



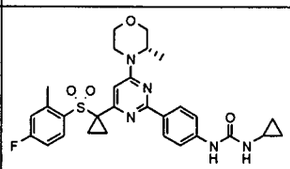
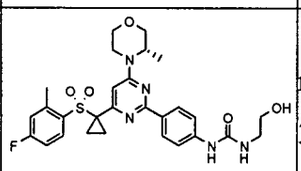
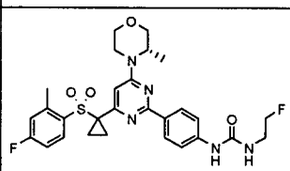
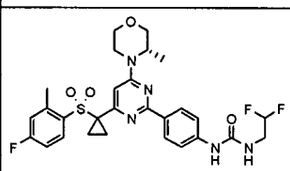
Se disolvieron fenil *N*-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,150 g, 0,25 mmol), trietilamina (0,104 mL, 0,75 mmol) y metilamina (0,75 mmol) en dioxano (10 mL) y se calentó a 50°C durante

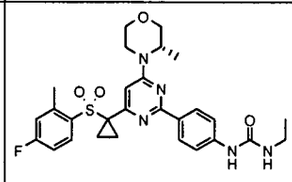
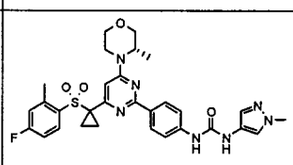
toda la noche. La reacción se evaporó hasta secarse y se purificó mediante HPLC preparativa, eluyendo con utilizando mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,63 - 1,60 (2H, m), 1,85 - 1,83 (2H, m), 2,44 (3H, s), 2,66 (3H, d), 3,13 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,42 (1H, s), 6,04 (1H, q), 6,62 (1H, s), 7,17 (1H, ddd), 7,24 (1H, dd), 7,40 (2H, d), 7,84 - 7,81 (3H, m), 8,71 (1H, s);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 540; HPLC tR = 2,34 min

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
82a		3-ciclopropil-1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	566	2,51
82b		1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	570	2,15
82c		3-(2-fluoroetil)-1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	572	2,50
82d		3-(2,2-difluoroetil)-1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-	590	2,62

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		il]fenil]urea		
82e		3-etil-1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	554	2,50
82f		1-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	606	2,36

Ejemplo 82a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,63 - 1,60 (2H, m), 1,85 - 1,83 (2H, m), 2,44 (3H, s), 2,66 (3H, d), 3,13 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,42 (1H, s), 6,04 (1H, q), 6,62 (1H, s), 7,17 (1H, ddd), 7,24 (1H, dd), 7,40 (2H, d), 7,84 - 7,81 (3H, m), 8,71 (1H, s);

Ejemplo 82b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,63 - 1,60 (2H, m), 1,85 - 1,83 (2H, m), 2,44 (3H, s), 3,20 - 3,09 (3H, m), 3,48 - 3,42 (3H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,42 (1H, s), 4,73 (1H, t), 6,23 (1H, t), 6,62 (1H, s), 7,17 (1H, ddd), 7,24 (1H, dd), 7,39 (2H, d), 7,85 - 7,80 (3H, m), 8,77 (1H, s);

Ejemplo 82c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,63 - 1,60 (2H, m), 1,85 - 1,83 (2H, m), 2,44 (3H, s), 3,13 (1H, ddd), 3,47 - 3,36 (3H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,55 - 4,40 (3H, m), 6,41 (1H, t), 6,63 (1H, s), 7,17 (1H, ddd), 7,24 (1H, dd), 7,40 (2H, d), 7,86 - 7,81 (3H, m), 8,78 (1H, s);

Ejemplo 82d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,63 - 1,60 (2H, m), 1,86 - 1,83 (2H, m), 2,44 (3H, s), 3,13 (1H, ddd), 3,62 - 3,42 (4H, m), 3,74 (1H, d), 3,95 (1H, dd), 4,10 (1H, d), 4,42 (1H, s), 6,07 (1H, ddt), 6,50 (1H, t), 6,63 (1H, s), 7,17 (1H, ddd), 7,24 (1H, dd), 7,41 (2H, d), 7,86 - 7,80 (3H, m), 8,90 (1H, s);

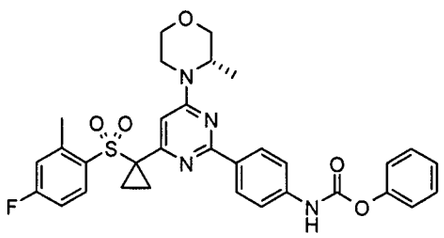
Ejemplo 82e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,16 (3H, d), 1,63 - 1,60 (2H, m), 1,85 - 1,83 (2H, m), 2,44 (3H, s), 3,18 - 3,09 (3H, m), 3,44 (1H, ddd), 3,60 (1H, dd),

3,74 (1H, d), 3,95 (1H, ddd), 4,42 (1H, s), 6,13 (1H, t), 6,62 (1H, s), 7,17 (1H, ddd), 7,24 (1H, dd), 7,39 (2H, d), 7,84 - 7,81 (3H, m), 8,63 (1H, s);

Ejemplo 82f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,64 - 1,61 (2H, m), 1,86 - 1,83 (2H, m), 2,45 (3H, s), 3,14 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,79 (3H, s), 3,96 (1H, dd), 4,11 (1H, d), 4,43 (1H, s), 6,64 (1H, s), 7,18 (1H, ddd), 7,25 (1H, dd), 7,38 (1H, s), 7,45 (2H, d), 7,77 (1H, s), 7,88 - 7,81 (3H, m), 8,36 (1H, s), 8,81 (1H, s);

La preparación de fenil *N*-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



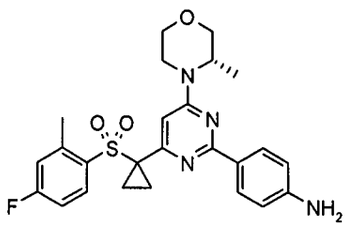
Se agregaron 4-[4-[1-(4-Fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (como la sal clorhidrato) (1,80 g, 3,47 mmol) y bicarbonato de sodio (2,91 g, 34,68 mmol) a DCM (60 mL) y se agitó durante 10 minutos. Se agregó lentamente fenil cloroformiato (0,566 mL, 4,51 mmol) y la reacción se agitó durante 1 hora. La mezcla de reacción se aplacó con una solución saturada acuosa de cloruro de amonio (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido naranja. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (1,73 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,65 - 1,62 (2H, m), 1,87 - 1,84 (2H, m), 2,45 (3H, s), 3,14 (1H, ddd), 3,49 - 3,42 (1H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,12 (1H, d), 4,45 (1H, s), 6,67 (1H, s), 7,17 (1H, ddd), 7,30 - 7,23 (4H, m), 7,45 (2H, t), 7,54 (2H, d), 7,83 (1H, dd), 7,93 (2H, d), 10,40 (1H, s);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 603; HPLC tR = 3,15 min

4-[4-[1-(4-Fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-

il]anilina

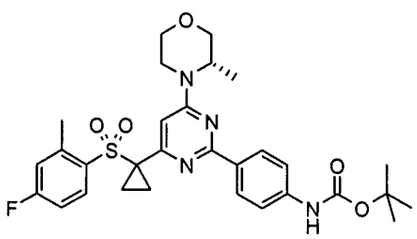


Se agregó *terc*-butil *N*-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (2,03 g, 3,48 mmol) a 6,0 N cloruro de hidrógeno en propan-2-ol (30 mL) y se agitó durante 2 horas a TA. La solución bruta se trituró con éter dietílico para proporcionar el material deseado (como la sal clorhidrato) como un sólido blanco (1,80 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,04 (3H, d), 1,70 - 1,65 (2H, m), 1,89 - 1,86 (2H, m), 2,45 (3H, s), 3,22 (1H, ddd), 3,44 (1H, ddd), 3,59 (1H, dd), 3,75 (1H, d), 3,97 (1H, dd), 4,21 (1H, s), 4,50 (1H, s), 6,14 (2H, s), 6,70 (1H, s), 7,14 - 7,03 (2H, m), 7,21 (1H, t), 7,31 (1H, d), 7,82 (1H, dd), 7,93 (2H, d);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 483; HPLC tR = 2,67 min

terc-butil *N*-[4-[4-[1-(4-fluoro-2-metilfenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



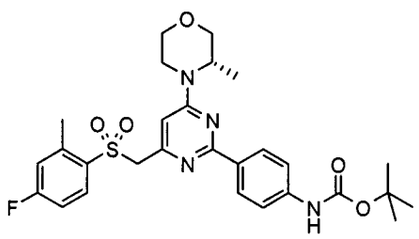
A *terc*-butil *N*-[4-[4-[(4-fluoro-2-metilfenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (3,36 g, 6,04 mmol) en DMF (30 mL) se agregó rápidamente hidruro de sodio (1,159 g, 24,14 mmol), esto se agitó a TA durante 10 minutos antes de la adición lenta de 1,2-dibromoetano (2,081 mL, 24,14 mmol) en DMF (30 mL). La suspensión resultante se agitó a TA durante 1 hora. Una porción adicional de hidruro de sodio (0,58 g, 12,07 mmol) y 1,2 dibromoetano (1,04 mL, 12,07 mmol) rápidamente se agregaron y la reacción se agitó durante otros 30 minutos. La mezcla de reacción se aplacó con agua (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se

filtró y se evaporó para proporcionar una goma marrón. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como una espuma blanca (2,05 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,49 (9H, s), 1,63 - 1,60 (2H, m), 1,86 - 1,83 (2H, m), 2,44 (3H, s), 3,13 (1H, ddd), 3,45 (1H, ddd), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,11 (1H, d), 4,43 (1H, s), 6,65 (1H, s), 7,17 (1H, ddd), 7,24 (1H, dd), 7,47 (2H, d), 7,82 (1H, dd), 7,86 (2H, d), 9,50 (1H, s);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 583; HPLC tR = 3,17 min

terc-butil *N*-[4-[4-[(4-fluoro-2-metilfenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

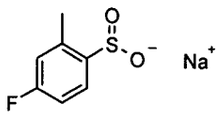


Se disolvió 4-fluoro-2-metilbencenosulfinato de sodio (1,663 g, 7,84 mmol) y *terc*-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (4,0 g, 7,84 mmol) en DMF (25 mL) y se agitó durante 1 hora a TA. El disolvente se evaporó para proporcionar un sólido amarillo. Esto se repartió entre solución acuosa de tiosulfato de sodio (50 mL) y DCM (75 mL). Los orgánicos se purificaron mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como una espuma blanca (4,20 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,49 (9H, s), 2,65 (3H, s), 3,16 (1H, ddd), 3,48 (1H, ddd), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,11 (1H, d), 4,39 (1H, s), 4,67 (2H, s), 6,67 (1H, s), 7,15 (1H, ddd), 7,39 (1H, dd), 7,45 (2H, d), 7,68 (1H, dd), 7,80 (2H, d), 9,50 (1H, s);

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 557; HPLC tR = 3,06 min

4-fluoro-2-metilbencenosulfinato de sodio

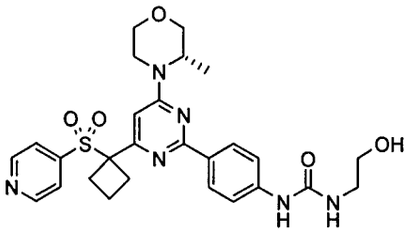


Una solución de sulfato de sodio (15,10 g, 119,82 mmol) en agua (100 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (20,13 g, 239,65 mmol) a la solución agitada. La solución resultante se agitó a 50°C durante 10 minutos. Se agregó en porciones cloruro de 4-fluoro-2-metilbenceno-1-sulfonilo (25 g, 119,82 mmol) a la solución y se agitó a 50°C durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en etanol (200 mL). La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar un sólido blanco, esto se agitó con acetonitrilo (50 mL) y luego se filtró para proporcionar el material deseado como un sólido blanco (17,5 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 2,46 (3H, s), 6,86 (1H, dd), 6,95 (1H, ddd), 7,66 (1H, dd);

La preparación de *terc*-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describió anteriormente.

Ejemplo 83: 3-(2-Hidroxietil)-1-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea

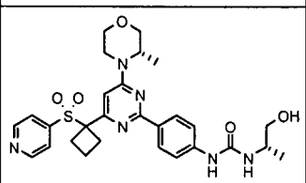
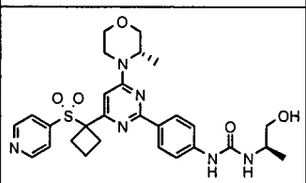
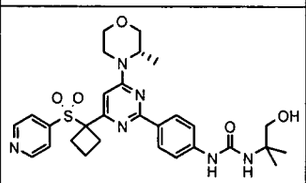
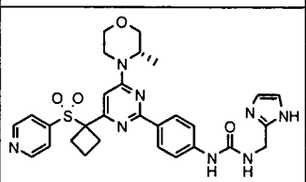


Una solución de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]carbamato (100 mg, 0,17 mmol) en NMP (2 mL) se trató con etanolamina (11 mg, 0,18 mmol) y trietilamina (51 mg, 0,5 mmol) y se agitó a TA durante toda la noche. La mezcla de reacción bruta se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado (66mg).

Espectro de NMR: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,20 - 1,22 (3H, m), 1,93 (1H, t), 2,11 - 2,16 (1H, m), 2,78 - 2,85 (2H, m), 3,09 - 3,19 (5H, m), 3,45 - 3,52 (3H, m), 3,63 - 3,66 (1H,

m), 3,75 - 3,78 (1H, m), 3,97 (1H, d), 4,15 - 4,19 (1H, m), 4,51 (1H, s), 4,78 (1H, s), 6,26 (1H, t), 6,63 (1H, s), 7,35 (2H, d), 7,46 (2H, d), 7,68 (2H, d), 8,72 (2H, d), 8,80 (1H, s)
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 553,48; HPLC tR = 1,93 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
83a		3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea	567,5	2,02
83b		3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea	567,5	2,02
83c		3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea	581,6	2,22
83d		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]urea	589,5	1,43

Ejemplo 83a: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,07 - 1,09 (3H, m), 1,20 (3H, d), 1,91 -

1,93 (1H, m), 2,13 (1H, t), 2,78 - 2,85 (2H, m), 3,08 - 3,19 (3H, m), 3,38 - 3,41 (2H, m), 3,45 - 3,54 (1H, td), 3,60 - 3,82 (3H, m), 3,96 (1H, dd), 4,16 (1H, d), 4,50 (1H, s), 4,83 (1H, t), 6,09 - 6,11 (1H, m), 6,63 (1H, s), 7,34 (2H, d), 7,46 - 7,47 (2H, m), 7,68 (2H, d), 8,70 - 8,72 (3H, m)

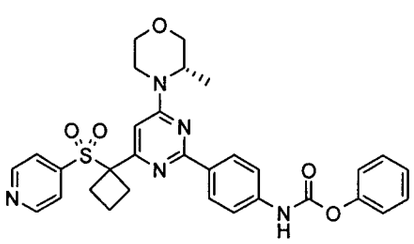
Ejemplo 83b: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,07 - 1,09 (3H, m), 1,20 (3H, d), 1,91 - 1,93 (1H, m), 2,13 (1H, t), 2,78 - 2,85 (2H, m), 3,08 - 3,19 (3H, m), 3,38 - 3,41 (2H, m), 3,45 - 3,54 (1H, td), 3,60 - 3,82 (3H, m), 3,96 (1H, dd), 4,16 (1H, d), 4,50 (1H, s), 4,83 (1H, t), 6,09 - 6,11 (1H, m), 6,63 (1H, s), 7,34 (2H, d), 7,46 - 7,47 (2H, m), 7,68 (2H, d), 8,70 - 8,72 (3H, m)

Ejemplo 83c: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,24 (6H, s), 1,91 - 1,93 (1H, m), 2,11 - 2,16 (1H, m), 2,77 - 2,84 (2H, m), 3,08 - 3,20 (3H, m), 3,39 (2H, d), 3,46 - 3,52 (1H, m), 3,62 - 3,66 (1H, m), 3,76 (1H, d), 3,95 - 3,99 (1H, m), 4,17 (1H, d), 4,51 (1H, s), 5,00 (1H, t), 6,00 (1H, s), 6,63 (1H, s), 7,29 - 7,32 (2H, m), 7,46 - 7,47 (2H, m), 7,65 - 7,67 (2H, m), 8,71 - 8,72 (3H, m)

Ejemplo 83d: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,92 (1H, q), 2,11 - 2,16 (1H, m), 2,81 (2H, s), 3,09 - 3,18 (3H, m), 3,49 (1H, t), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,17 (1H, d), 4,32 (2H, d), 4,51 (1H, s), 6,64 (2H, s), 6,84 (1H, s), 7,04 (1H, s), 7,38 (2H, d), 7,46 (2H, d), 7,69 (2H, d), 8,72 (2H, d), 8,92 (1H, s), 11,87 (1H, s)

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]fenil]carbamato



Se agregó gota a gota fenil cloroformiato (0,241 mL, 1,92 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]anilina (894 mg, 1,92 mmol) y bicarbonato de sodio (161 mg, 1,92 mmol) en dioxano (10 mL) a TA al aire. La solución resultante se agitó a TA durante 2 horas. La reacción se evaporó hasta secarse y el

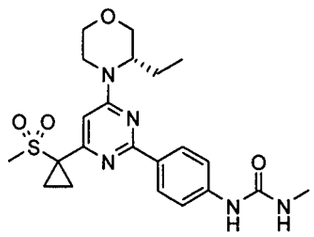
residuo se recogió en agua (100 mL) y se extrajo con acetato de etilo (200 mL). La capa orgánica se lavó con agua, salmuera y luego se secó ($MgSO_4$). La solución se evaporó hasta secarse y el material bruto se cromatografió sobre sílice, eluyendo con 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido color crema(690 mg).

Espectro de NMR: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,17 - 1,23 (3H, m), 1,90 - 1,92 (1H, m), 2,00 (1H, s), 2,12 (1H, t), 2,77 - 2,83 (2H, m), 3,06 - 3,17 (3H, m), 3,47 - 3,50 (1H, m), 3,61 - 3,65 (1H, m), 3,75 (1H, d), 3,94 - 3,98 (1H, m), 4,15 (1H, d), 4,50 (1H, s), 5,54 (1H, d), 6,46 (1H, d), 6,53 (1H, s), 6,75 - 6,79 (2H, m), 7,15 - 7,19 (1H, m), 7,43 - 7,49 (2H, m), 7,49 (1H, d), 7,53 (1H, s), 8,70 - 8,72 (2H, m), 9,34 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 586,18; HPLC tR = 2,87 min.

La preparación de 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclobutil)pirimidin-2-il]anilina se describió anteriormente.

Ejemplo 84: 1-[4-[4-[(3*S*)-3-Etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-metilurea



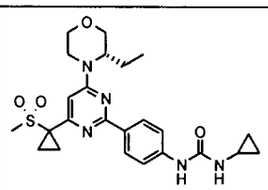
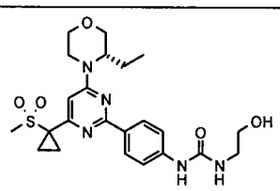
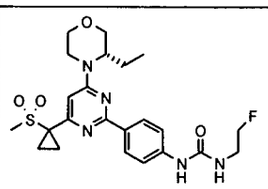
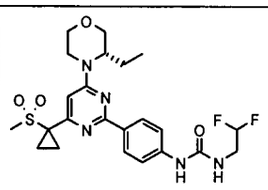
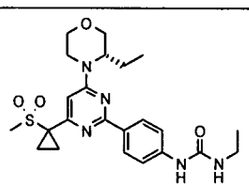
Se disolvieron fenil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato (54,0 mg, 0,10 mmol), trietilamina (0,043 mL, 0,31 mmol) y metil amina (-, 0,31 mmol) en dioxano (10 mL) y se calentó a 50 °C durante el fin de semana. La reacción se evaporó hasta secarse y se purificó mediante HPLC preparativa (columna Waters XTerra C18, sílice 5µ, 19 mm de diámetro, 100 mm de longitud), utilizando mezclas cada vez menos polares de agua (conteniendo 1% NH_3) y MeCN como eluyentes. Las fracciones que contenían el compuesto deseado se evaporaron hasta secarse para proporcionar (S)-1-(4-(4-(3-etilmorfolino)-6-(1-(metilsulfonil)ciclopropil)pirimidin-2-il)fenil)-3-metilurea como un sólido blanco.

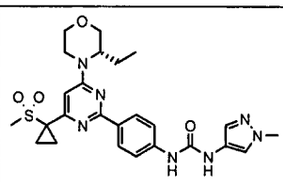
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,56 - 1,54 (2H, m), 1,69 - 1,64 (2H, m), 1,83 - 1,69 (2H, m), 2,66 (3H, d), 3,22 - 3,14 (1H, m), 3,27 (3H, s), 3,47 (1H, ddd), 3,55 (1H, dd), 3,87 (1H, d), 3,93 (1H, dd), 4,41 - 4,27 (2H, m), 6,07 (1H, q), 6,78

(1H, s), 7,50 (2H, d), 8,19 (2H, d), 8,74 (1H, s);

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 460; HPLC tR = 1,98 min.

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
84a		3-ciclopropil-1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	486	2,15
84b		1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	490	1,8
84c		1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	492	2,13
84d		3-(2,2-difluoroetil)-1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	510	2,27
84e		3-etil-1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea	474	2,13

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
84f		1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	526	2,03

Ejemplo 84a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,44 - 0,40 (2H, m), 0,65 - 0,64 (2H, m), 0,89 (3H, t), 1,57 - 1,53 (2H, m), 1,66 (2H, m), 1,68 - 1,64 (2H, m), 3,23 - 3,14 (1H, m), 3,50 - 3,44 (1H, m), 3,55 (1H, dd), 3,87 (1H, d), 3,94 - 3,92 (1H, m), 4,47 - 4,22 (2H, m), 6,44 (1H, s), 6,78 (1H, s), 7,51 (2H, d), 8,19 (2H, d), 8,54 (1H, s); 4 protones faltantes debido a muestra muy débil.

Ejemplo 84b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,57 - 1,53 (2H, m), 1,69 - 1,64 (2H, m), 1,83 - 1,71 (2H, m), 3,22 - 3,16 (3H, m), 3,27 (3H, s), 3,49 - 3,44 (3H, m), 3,55 (1H, dd), 3,87 (1H, d), 3,94 - 3,92 (1H, m), 4,39 - 4,24 (2H, m), 4,73 (1H, t), 6,25 (1H, t), 6,78 (1H, s), 7,49 (2H, d), 8,19 (2H, d), 8,80 (1H, s);

Ejemplo 84c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,58 - 1,54 (2H, m), 1,69 - 1,64 (2H, m), 1,83 - 1,69 (2H, m), 3,22 - 3,17 (1H, m), 3,29 (s, 3H), 3,49 - 3,37 (3H, m), 3,55 (1H, dd), 3,87 (1H, d), 3,94 - 3,92 (1H, m), 4,40 - 4,16 (2H, m), 4,48 (2H, dt), 6,44 (1H, t), 6,78 (1H, s), 7,50 (2H, d), 8,20 (2H, d), 8,81 (1H, s);

Ejemplo 84d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,57 - 1,54 (2H, m), 1,67 - 1,64 (2H, m), 1,83 - 1,69 (2H, m), 3,22 - 3,16 (1H, m), 3,29 (3H, s), 3,60 - 3,44 (4H, m), 3,87 (1H, d), 3,93 (1H, dd), 4,48 - 4,21 (2H, m), 6,07 (1H, tt), 6,53 (1H, t), 6,79 (1H, s), 7,51 (2H, d), 8,21 (2H, d), 8,92 (1H, s);

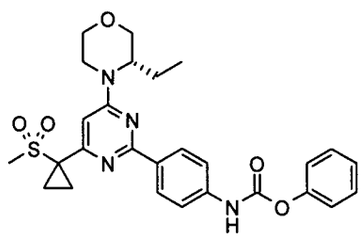
Ejemplo 84e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,07 (3H, t), 1,56 - 1,54 (2H, m), 1,68 - 1,65 (2H, m), 1,83 - 1,69 (2H, m), 3,22 - 3,09 (3H, m), 3,29 (3H, s), 3,47 (1H, ddd), 3,55 (1H, dd), 3,87 (1H, d), 3,93 (1H, dd), 4,40 - 4,24 (2H, m), 6,16 (1H, t), 6,78 (1H, s), 7,50 (2H, d), 8,19 (2H, d), 8,66 (1H, s);

Ejemplo 84f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,57 - 1,54 (2H, m), 1,69 - 1,65 (2H, m), 1,84 - 1,70 (2H, m), 3,23 - 3,17 (1H, m), 3,47 (1H, ddd), 3,56 (1H, dd), 3,79 (3H, s), 3,88 (1H, d), 3,94 (1H, dd), 4,41 - 4,23 (2H, m), 6,80 (1H, s), 7,38 (1H, s), 7,55 (2H, d), 7,76 (1H, s), 8,23 (2H, d), 8,39 (1H, s), 8,84 (1H, s); Metil sulfona oculta bajo pico de

agua (3H faltante).

La preparación de fenil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato

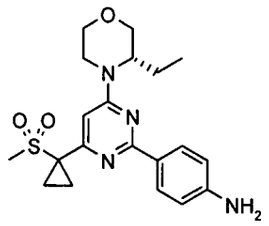


Se agregaron 4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina (como la sal clorhidrato) (0,43 g, 0,98 mmol) y bicarbonato de sodio (0,823 g, 9,80 mmol) a DCM (60 mL) y se agitó durante 10 minutos. Se agregó lentamente fenil cloroformiato (0,160 mL, 1,27 mmol) y la reacción se agitó durante 1 hora. La mezcla de reacción se aplacó con una solución saturada acuosa de cloruro de amonio (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido naranja. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (0,46 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,58 - 1,55 (2H, m), 1,69 - 1,65 (2H, m), 1,84 - 1,70 (2H, m), 3,20 (1H, ddd), 3,27 (3H, s), 3,47 (1H, ddd), 3,56 (1H, dd), 3,87 (1H, d), 3,93 (1H, dd), 4,41 - 4,24 (2H, m), 6,82 (1H, s), 7,30 - 7,24 (3H, m), 7,45 (2H, t), 7,64 (2H, d), 8,29 (2H, d), 10,44 (1H, s);

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 523; HPLC tR = 2,85 min.

4-[4-[(3*S*)-3-Etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina

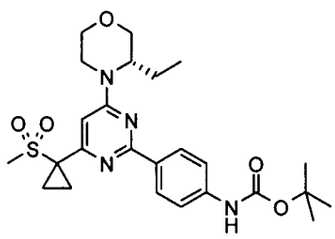


terc-butil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato (0,5 g, 0,99 mmol) se agregó a cloruro de hidrógeno 6,0 N en propan-2-ol (30 mL) y se agitó durante 2 horas a TA. La solución bruta se trituró con éter dietílico para proporcionar el material deseado (como la sal clorhidrato) como un sólido amarillo (0,43 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,65 - 1,60 (2H, m), 1,75 - 1,67 (2H, m), 1,83 - 1,80 (2H, m), 3,24 (3H, s), 3,38 - 3,28 (1H, m), 3,52 - 3,46 (1H, m), 3,58 (1H, dd), 3,89 (1H, d), 3,96 (1H, dd), 4,48 - 4,33 (2H, m), 7,09 - 6,98 (3H, m), 8,21 - 8,08 (2H, m); NH_2 faltante;

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 403; HPLC tR = 2,23 min.

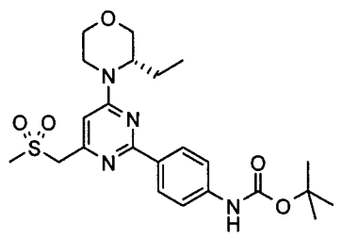
terc-butil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato



Se agregó rápidamente hidruro de sodio (0,705 g, 14,69 mmol) a *terc*-butil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]carbamato (1,75 g, 3,67 mmol) en DMF (30 mL) y la mezcla se agitó a TA durante 10 minutos antes de la adición lenta de 1,2-dibromoetano (1,266 mL, 14,69 mmol) en DMF (30 mL). La suspensión resultante se agitó a TA durante 1 hora. La reacción se calentó hasta alcanzar 40°C y se agregaron rápidamente una porción adicional de hidruro de sodio (2,0 eq) y 1,2 dibromoetano (2,0 eq) y la reacción se agitó durante otros 30 minutos. La mezcla de reacción se aplacó con agua (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma marrón. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como una espuma amarilla(0,30 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 (3H, t), 1,50 (9H, s), 1,57 - 1,54 (2H, m), 1,68 - 1,66 (2H, m), 1,83 - 1,70 (2H, m), 3,22 - 3,16 (1H, m), 3,50 - 3,44 (1H, m), 3,57 - 3,53 (1H, m), 3,87 (1H, d), 3,94 - 3,92 (1H, m), 4,38 - 4,24 (2H, m), 6,80 (1H, s), 7,57 (2H, d), 8,21 (2H, d), 9,55 (1H, s); pico de metilo bajo agua (3H faltante).

terc-butil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidin-2-il]fenil]carbamato



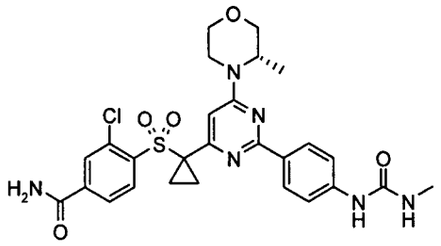
Se disolvió *terc*-butil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(yodometil)pirimidin-2-il]fenil]carbamato (2,0 g, 3,81 mmol) y metanosulfinato de sodio (0,389 g, 3,81 mmol) en DMF (25 mL) y se agitó durante 1 hora a TA. El disolvente se evaporó para proporcionar un sólido amarillo que se repartió entre solución acuosa de tiosulfato de sodio (50 mL) y DCM (75 mL). Las capas se separaron, la capa acuosa se extrajo adicionalmente con DCM (75 mL), los orgánicos combinados se purificaron mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como una espuma blanca (1,7 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,90 (3H, t), 1,50 (9H, s), 1,73 - 1,64 (1H, m), 1,85 - 1,78 (1H, m), 3,24 - 3,18 (4H, m), 3,48 (1H, ddd), 3,57 (1H, dd), 3,89 (1H, d), 3,95 (1H, dd), 4,30 (2H, s), 4,48 (2H, s), 6,80 (1H, s), 7,57 (2H, d), 8,23 (2H, d), 9,55 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 477; HPLC tR = 2,67 min.

La preparación de *terc*-butil *N*-[4-[4-[(3*S*)-3-etilmorfolin-4-il]-6-(yodometil)pirimidin-2-il]fenil]carbamato se describió anteriormente.

Ejemplo 85: 3-Cloro-4-[1-[2-[4-(metilcarbamoilamino)fenil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzamida

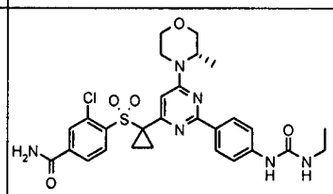
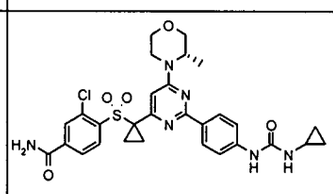


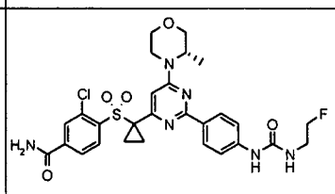
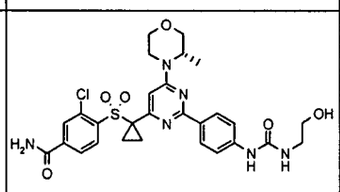
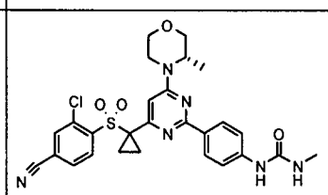
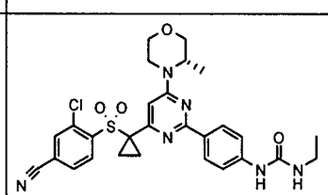
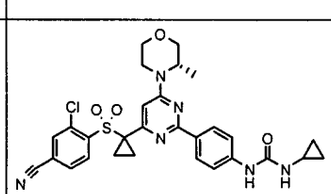
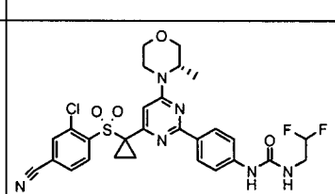
Se agregó metilamina (0,347 mL, 0,69 mmol) a fenil *N*-[4-[4-[1-(4-carbamoil-2-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (150 mg, 0,23 mmol) y trietilamina (0,096 mL, 0,69 mmol) en DMF (0,714 mL) y la solución resultante se agitó a 50°C durante 2 horas. La mezcla bruta se purificó mediante HPLC prep para proporcionar el material deseado .

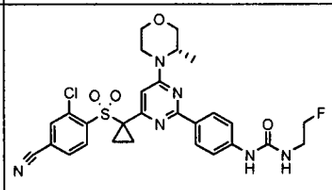
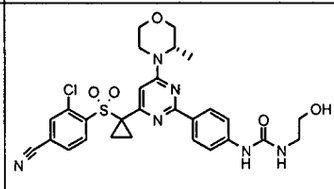
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15 (3H, d), 1,72 - 1,76 (2H, m), 1,99 - 2,02 (2H, m), 2,65 (3H, d), 3,09 - 3,17 (1H, m), 3,44 (1H, dt), 3,59 (1H, dd), 3,73 (1H, d), 3,94 (1H, d), 4,09 (1H, d), 4,41 (1H, s), 6,03 - 6,07 (1H, m), 6,61 (1H, s), 7,35 (2H, d), 7,67 (1H, s), 7,74 (2H, d), 7,88 (1H, dd), 7,99 (1H, d), 8,12 (1H, d), 8,20 (1H, s), 8,68 (1H, s)

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 586; HPLC tR = 1,86 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(4-carbamoil-2-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
85a		3-cloro-4-[1-[2-[4-(etilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzamida	598 $(M-H)^-$	1,98
85b		3-cloro-4-[1-[2-[4-(ciclopropilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzamida	610 $(M-H)^-$	2,00

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
85c		3-cloro-4-[1-[2-[4-(2-fluoroetilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzamida	616 $(M-H)^-$	1,98
85d		3-cloro-4-[1-[2-[4-(2-hidroxietilcarbamoilamino)fenil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzamida	615	1,76
85e		1-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	568	2,25
85f		3-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	582	2,39
85g		1-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea	592 (M-H)	2,40
85h		1-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea	618	2,51

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
85i		1-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	598 $(M-H)^-$	2,39
85j		1-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	598	2,06

Ejemplo 85a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06 (3H, t), 1,15 (3H, d), 1,72 - 1,76 (2H, m), 1,99 - 2,02 (2H, m), 3,09 - 3,18 (3H, m), 3,44 (1H, dt), 3,59 (1H, dd), 3,73 (1H, d), 3,94 (1H, d), 4,09 (1H, d), 4,41 (1H, s), 6,13 (1H, t), 6,61 (1H, s), 7,34 (2H, d), 7,67 (1H, s), 7,74 (2H, d), 7,88 (1H, dd), 7,99 (1H, d), 8,12 (1H, d), 8,21 (1H, s), 8,60 (1H, s)

Ejemplo 85b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,39 - 0,43 (2H, m), 0,62 - 0,67 (2H, m), 1,15 (3H, d), 1,72 - 1,76 (2H, m), 1,99 - 2,02 (2H, m), 2,54 - 2,55 (1H, m), 3,13 (1H, dt), 3,44 (1H, dt), 3,59 (1H, dd), 3,73 (1H, d), 3,94 (1H, dd), 4,09 (1H, d), 4,41 (1H, s), 6,40 (1H, d), 6,62 (1H, s), 7,35 (2H, d), 7,67 (1H, s), 7,74 (2H, d), 7,88 (1H, dd), 7,99 (1H, d), 8,12 (1H, d), 8,21 (1H, s), 8,48 (1H, s)

Ejemplo 85c: ^{1}H NMR (400,132 MHz, $CDCl_3$) δ 1,29 (3H, d), 1,54 - 1,56 (2H, m), 2,15 - 2,19 (2H, m), 3,27 (1H, dt), 3,51 - 3,62 (2H, m), 3,72 (1H, dd), 3,81 (1H, d), 4,02 (1H, dd), 4,08 (1H, d), 4,40 (1H, s), 4,46 (1H, t), 4,58 (1H, t), 5,63 (1H, t), 6,58 (1H, s), 7,17 (1H, s), 7,17 (1H, s), 7,24 (2H, d), 7,45 - 7,56 (2H, m), 7,64 - 7,69 (1H, m), 7,84 - 7,88 (2H, m), 7,90 (2H, d)

Ejemplo 85d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15 (3H, d), 1,72 - 1,76 (2H, m), 1,99 - 2,02 (2H, m), 3,09 - 3,12 (1H, m), 3,15 - 3,19 (2H, m), 3,43 - 3,48 (3H, m), 3,59 (1H, dd), 3,73 (1H, d), 3,93 (1H, dd), 4,09 (1H, d), 4,41 (1H, s), 4,72 (1H, t), 6,24 (1H, t), 6,61 (1H, s), 7,33 (2H, d), 7,66 (1H, s), 7,74 (2H, d), 7,88 (1H, dd), 7,99 (1H, d), 8,12 (1H, d), 8,21 (1H, s), 8,74 (1H, s)

Ejemplo 85e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,72 - 1,78 (2H, m), 2,00 - 2,03 (2H, m), 2,66 (3H, d), 3,10 - 3,15 (1H, m), 3,45 (1H, dt), 3,60 (1H, dd), 3,74 (1H, d), 4,06 (1H, q), 4,14 (1H, d), 4,47 (1H, s), 6,04 - 6,09 (1H, m), 6,66 (1H, s), 7,38 (2H, d), 7,66 (2H, d), 7,90 (1H, d), 8,02 (1H, d), 8,34 (1H, d), 8,71 (1H, s)

Ejemplo 85f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,18 (3H, d), 1,73 - 1,77 (2H, m), 1,99 - 2,03 (2H, m), 3,09 - 3,16 (2H, m), 3,16 - 3,19 (1H, m), 3,45 (1H, dt), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,14 (1H, d), 4,47 (1H, s), 6,16 (1H, t), 6,66 (1H, s), 7,37 (2H, d), 7,66 (2H, d), 7,90 (1H, dd), 8,02 (1H, d), 8,35 (1H, d), 8,62 (1H, s)

Ejemplo 85g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,62 - 0,67 (2H, m), 1,18 (3H, d), 1,73 - 1,77 (2H, m), 2,00 - 2,03 (2H, m), 2,53 - 2,59 (1H, m), 3,11 - 3,18 (1H, m), 3,45 (1H, dt), 3,58 - 3,62 (1H, m), 3,74 (1H, d), 3,95 (1H, dd), 4,14 (1H, d), 4,47 (1H, s), 6,42 (1H, d), 6,66 (1H, s), 7,38 (2H, d), 7,66 (2H, d), 7,90 (1H, dd), 8,02 (1H, d), 8,35 (1H, d), 8,50 (1H, s)

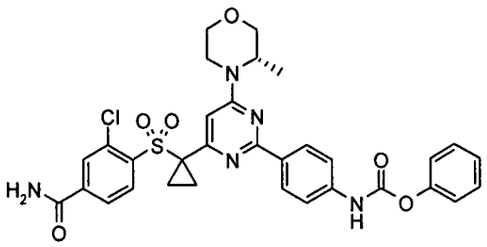
Ejemplo 85h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,73 - 1,77 (2H, m), 2,00 - 2,03 (2H, m), 3,15 (1H, dt), 3,42 - 3,51 (1H, m), 3,54 - 3,62 (3H, m), 3,74 (1H, d), 3,95 (1H, dd), 4,15 (1H, d), 4,47 (1H, s), 6,07 (1H, app t), 6,53 (1H, t), 6,67 (1H, s), 7,39 (2H, d), 7,68 (2H, d), 7,90 (1H, dd), 8,02 (1H, d), 8,35 (1H, d), 8,89 (1H, s)

Ejemplo 85i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,73 - 1,77 (2H, m), 2,00 - 2,03 (2H, m), 3,15 (1H, dt), 3,39 (1H, q), 3,42 - 3,48 (2H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,96 (1H, dd), 4,14 (1H, d), 4,42 (1H, t), 4,48 (1H, s), 4,53 (1H, t), 6,44 (1H, t), 6,66 (1H, s), 7,38 (2H, d), 7,67 (2H, d), 7,90 (1H, dd), 8,02 (1H, d), 8,35 (1H, d), 8,77 (1H, s)

Ejemplo 85j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,73 - 1,77 (2H, m), 2,00 - 2,03 (2H, m), 3,14 - 3,20 (3H, m), 3,43 - 3,48 (3H, m), 3,60 (1H, dd), 3,74 (1H, d), 3,95 (1H, dd), 4,14 (1H, d), 4,48 (1H, s), 4,73 (1H, t), 6,26 (1H, t), 6,66 (1H, s), 7,37 (2H, d), 7,66 (2H, d), 7,90 (1H, dd), 8,02 (1H, d), 8,35 (1H, d), 8,77 (1H, s)

La preparación de fenil *N*-[4-[4-[1-(4-carbamoil-2-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(4-carbamoil-2-clorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

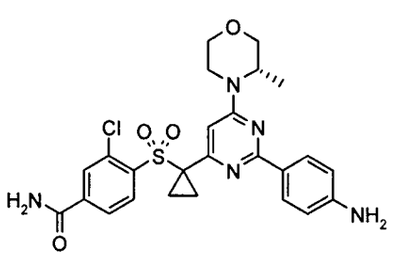


Se agregó bicarbonato de sodio (0,263 g, 3,12 mmol) a 4-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-3-clorobenzamida (1,1 g, 2,08 mmol), en 1,4-dioxano (10,15 mL) y a la suspensión resultante se agregó fenil cloroformiato (0,262 mL, 2,08 mmol) gota a gota durante 2 minutos. La reacción se agitó a TA durante 2 horas y luego se evaporó hasta secarse y el residuo se disolvió nuevamente en DCM (20 mL) y se lavó con agua (20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido que se trituró con éter dietílico para proporcionar el material deseado como un sólido beige (0,9 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,16 (3H, d), 1,73 - 1,77 (2H, m), 1,99 - 2,03 (2H, m), 3,12 - 3,17 (1H, m), 3,40 - 3,47 (1H, m), 3,57 - 3,61 (1H, m), 3,73 (1H, d), 3,91 - 3,96 (1H, m), 4,06 - 4,10 (1H, m), 4,44 (1H, s), 6,67 (1H, s), 7,24 - 7,30 (2H, m), 7,45 (2H, t), 7,50 (2H, d), 7,85 (2H, d), 7,88 - 7,90 (1H, m), 8,00 (1H, d), 8,13 (1H, d), 8,22 (1H, s), 10,40 (1H, s)

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 648; HPLC tR = 2,62 min.

4-[1-[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-3-clorobenzamida



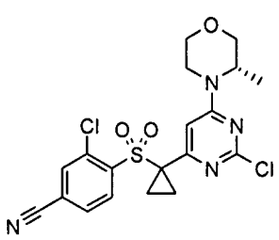
Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,271 g, 0,39 mmol) a 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (2,199 g, 10,04 mmol) y 3-cloro-4-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzonitrilo (3,5 g, 7,72 mmol) y solución acuosa de carbonato de sodio 2M (11,58 mL, 23,16 mmol) en una mezcla de disolventes de DME (20 mL), etanol (10 mL) y agua (10 mL) y la mezcla resultante se agitó a

95°C durante 16 horas. La mezcla de reacción se diluyó con acetato de etilo (20 mL) y se lavó con agua (2 x 20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% metanol en DCM, para proporcionar el material deseado como un sólido marrón (1,1 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 (3H, d), 1,71 - 1,73 (2H, m), 1,97 - 2,01 (2H, m), 3,06 - 3,13 (1H, m), 3,37 - 3,45 (1H, m), 3,58 (1H, dd), 3,72 (1H, d), 3,92 - 3,94 (1H, m), 4,04 - 4,08 (1H, m), 4,37 (1H, s), 5,48 (2H, s), 6,50 (1H, s), 7,58 (2H, d), 7,89 (1H, dd), 8,00 (2H, d), 8,11 (1H, d), 8,21 (1H, s)

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 528; HPLC tR = 1,99 min.

3-Cloro-4-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilbenzonitrilo

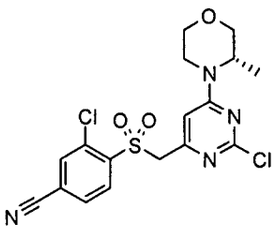


Se agregó 1,2-dibromoetano (1,654 ml, 19,19 mmol) a 3-cloro-4-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]benzonitrilo (4,1 g, 9,60 mmol), hidróxido de sodio (50% p/p) (9,60 mL, 95,95 mmol) y bromuro de tetrabutilamonio (0,619 g, 1,92 mmol) en DCM y la solución resultante se agitó a 40°C durante 5 horas. La mezcla de reacción se lavó secuencialmente con agua (200 mL) y salmuera saturada (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 5 a 50% acetato de etilo en DCM, para proporcionar el material deseado como un sólido crema (3,50 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15 (3H, d), 1,68 - 1,72 (2H, m), 1,95 - 1,98 (2H, m), 3,11 - 3,17 (1H, m), 3,29 - 3,30 (1H, m), 3,39 (1H, dt), 3,54 (1H, dd), 3,69 (1H, d), 3,91 (1H, dd), 4,30 (1H, s), 6,76 (1H, s), 8,03 (2H, s), 8,33 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 453; HPLC tR = 2,41 min.

3-Cloro-4-[[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]metilsulfonil]benzonitrilo

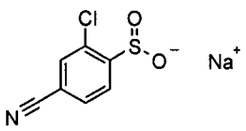


Se agregó 2-cloro-4-cianobencenosulfinato de sodio (4,43 g, 19,80 mmol) en una porción a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (7 g, 19,80 mmol) en acetonitrilo (99 mL) y la suspensión resultante se agitó a 80°C durante 6 horas. La mezcla de reacción se evaporó hasta secarse, se disolvió nuevamente en DCM (200 mL) y se lavó con agua (200 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en DCM, para proporcionar el material deseado como un sólido crema (6,20 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 3,15 - 3,21 (1H, m), 3,43 (1H, dt), 3,58 (1H, dd), 3,72 (1H, d), 3,93 (2H, m), 4,24 (1H, s), 4,86 (2H, s), 6,87 (1H, s), 7,96 (1H, d), 8,06 (1H, dd), 8,43 (1H, d)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 427; HPLC tR = 2,28 min.

2-cloro-4-cianobencenosulfinato de sodio



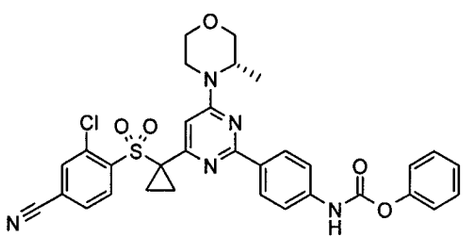
Una solución de sulfito de sodio (6,02 g, 47,74 mmol) en agua (100 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (8,02 g, 95,48 mmol) a la solución agitada. La solución resultante se agitó a 50°C durante 10 minutos. Se agregó gota a gota cloruro de 2-cloro-4-cianobenceno-1-sulfonilo (11,27 g, 47,74 mmol) a la solución y se agitó a 50°C durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en etanol (200 mL). La suspensión se dejó agitar a TA durante 20 minutos. La suspensión se filtró y el filtrado se evaporó para proporcionar un sólido blanco, esto se agitó con acetonitrilo (50 mL) y luego se filtró para proporcionar el material deseado como un sólido blanco (10,0 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 7,80 - 7,77 (2H, m), 7,84 (1H, d)

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

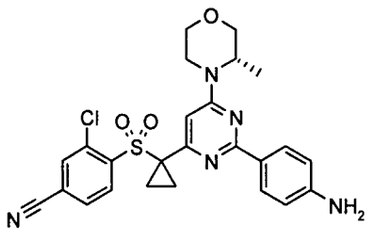
Fenil *N*-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



Se agregó bicarbonato de sodio (1,400 g, 16,67 mmol) a 4-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-3-clorobenzonitrilo (1,7 g, 3,33 mmol), en 1,4-dioxano (16,25 mL) y a la suspensión resultante se agregó fenil cloroformiato (0,42 mL, 3,33 mmol) gota a gota durante 2 minutos. La reacción se agitó a TA durante 2 horas y luego se evaporó hasta secarse, el residuo se disolvió nuevamente en DCM (20 mL) y se lavó con agua (20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido que se trituró con éter dietílico para proporcionar el material deseado como un sólido crema (1,4 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,76 - 1,80 (2H, m), 2,01 - 2,04 (2H, m), 3,14 - 3,19 (1H, m), 3,43 - 3,48 (1H, m), 3,59 - 3,62 (1H, m), 3,74 (1H, d), 3,94 - 3,97 (1H, m), 4,16 (1H, d), 4,49 (1H, s), 6,71 (1H, s), 7,24 - 7,30 (3H, m), 7,45 (2H, t), 7,53 (2H, d), 7,77 (2H, d), 7,90 - 7,92 (1H, m), 8,02 (1H, d), 8,35 (1H, d), 10,44 (1H, s)
Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 630; HPLC tR = 3,02 min.

4-[1-[2-(4-Aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonil-3-clorobenzonitrilo

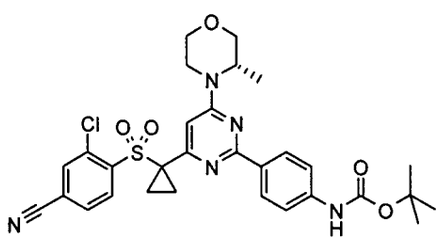


Se disolvió *terc*-butil *N*-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (3,4 g, 5,57 mmol) en metanol (17,86 mL) y a esto se agregó cloruro de hidrógeno 6 N en propan-2-ol (10 mL) y la reacción se agitó durante 2 horas a TA. La solución bruta se trituró con éter dietílico para proporcionar el material deseado como un sólido blanco (3,50 g). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,76 - 1,79 (2H, m), 2,01 - 2,04 (2H, m), 3,18 - 3,24 (1H, m), 3,42 - 3,48 (1H, m), 3,60 (1H, dd), 3,74 - 3,77 (1H, m), 3,94 - 3,98 (1H, m), 4,20 (1H, s), 4,51 (1H, s), 6,76 (1H, s), 7,11 - 7,14 (2H, m), 7,86 (2H, d), 7,95 - 7,97 (2H, m), 8,07 (1H, d), 8,37 (1H, d)

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 510; HPLC tR = 2,49 min.

terc-butil *N*-[4-[4-[1-(2-cloro-4-cianofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



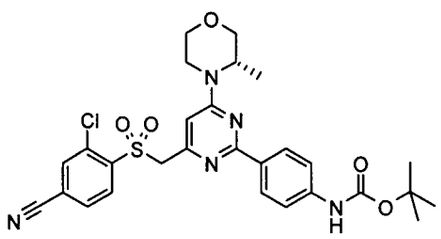
Se agregó hidruro de sodio (1,282 g, 26,71 mmol) rápidamente a *terc*-butil *N*-[4-[4-[(2-cloro-4-cianofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (3,9 g, 6,68 mmol) en DMF (70 mL) y la mezcla se agitó a TA durante 10 minutos antes de la adición lenta de 1,2-dibromoetano (2,302 mL, 26,71 mmol) en DMF (70 mL) a TA. La suspensión resultante se agitó a TA durante 90 minutos. Se agregaron rápidamente una porción adicional de hidruro de sodio (1,0 eq) y 1,2 dibromoetano (1,0 eq) y la reacción se agitó durante otros 30 minutos. La mezcla de reacción se aplacó con agua (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma marrón. El producto bruto se purificó mediante cromatografía de

sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (3,40 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,50 (9H, s), 1,73 - 1,78 (2H, m), 1,99 - 2,05 (2H, m), 3,12 - 3,18 (1H, m), 3,45 (1H, t), 3,60 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,15 (1H, d), 4,48 (1H, s), 6,68 (1H, s), 7,45 (2H, d), 7,69 (2H, d), 7,90 (1H, d), 8,01 (1H, d), 8,35 (1H, s), 9,52 (1H, s)

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 610; HPLC tR = 3,10 min.

terc-butil *N*-[4-[4-[(2-cloro-4-cianofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



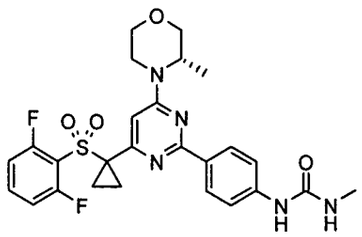
Se disolvió 2-cloro-4-cianobencenosulfinato de sodio (1,753 g, 7,84 mmol) y *terc*-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (4 g, 7,84 mmol) en DMF (50 mL) y se agitó durante 1 hora a TA. El disolvente se evaporó para proporcionar un sólido amarillo que se repartió entre agua (50 mL) y DCM (75 mL). Las capas se separaron, la capa acuosa se extrajo con DCM (75 mL) y los orgánicos combinados se concentraron al vacío para proporcionar un sólido amarillo. Esto rápidamente se agitó con éter (100 mL), para proporcionar el material deseado como un sólido blancuzco (3,90 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,49 (9H, s), 3,19 (1H, dt), 3,48 (1H, dt), 3,63 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,13 (1H, d), 4,41 (1H, s), 4,97 (2H, s), 6,79 (1H, s), 7,43 (2H, d), 7,61 (2H, d), 7,86 (1H, d), 7,91 (1H, dd), 8,53 (1H, d), 9,54 (1H, s)

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 583,94; HPLC tR = 3,07 min.

La preparación de *terc*-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describió anteriormente.

Ejemplo 86: 1-[4-[4-[1-(2,6-Difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea

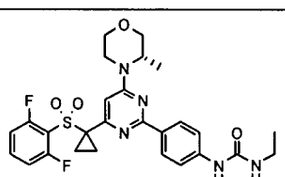


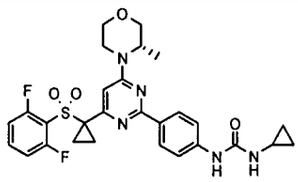
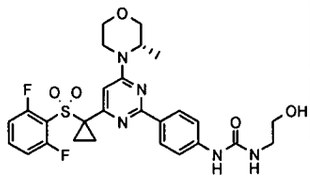
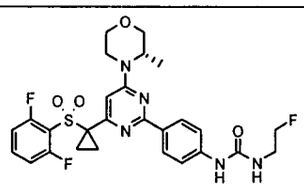
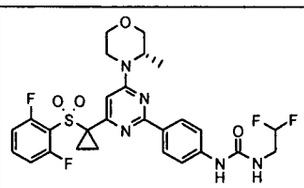
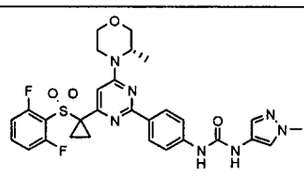
Se disolvió fenil *N*-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (0,15 g, 0,25 mmol), trietilamina (0,103 mL, 0,74 mmol) y metilamina (0,74 mmol) en dioxano (10 mL) y se agitó a TA durante toda la noche. La reacción se evaporó hasta secarse y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco.

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,69 - 1,67 (2H, m), 1,94 - 1,91 (2H, m), 2,66 (3H, d), 3,17 (1H, ddd), 3,47 (1H, ddd), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,16 (1H, d), 4,49 (1H, s), 6,04 (1H, q), 6,74 (1H, s), 7,25 (2H, t), 7,35 (2H, d), 7,80 - 7,73 (3H, m), 8,69 (1H, s);

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 544; HPLC tR = 1,82 min

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
86a		1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea	558	2,43

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
86b*		3-ciclopropil-1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	570	2,44
86c*		1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	574	2,07
86d*		1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	576	2,42
86e*		3-(2,2-difluoroetil)-1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	594	2,55
86f*		1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	610	2,28

* No se agregó trietilamina

Ejemplo 86a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06 (3H, t), 1,20 (3H, d), 1,71 - 1,65 (2H, m), 1,93 - 1,89 (2H, m), 3,20 - 3,09 (3H, m), 3,47 (1H, ddd), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (2H, ddd), 4,48 (1H, s), 6,14 (1H, t), 6,74 (1H, s), 7,25 (2H, t), 7,35 (2H, d), 7,80 - 7,73 (3H, m), 8,61 (1H, s);

Ejemplo 86b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,43 - 0,39 (2H, m), 0,67 - 0,62 (2H, m), 1,20 (3H, d), 1,71 - 1,65 (2H, m), 1,92 - 1,91 (2H, m), 2,57 - 2,54 (1H, m), 3,17 (1H, ddd), 3,47 (1H, ddd), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,16 (1H, d), 4,48 (1H, s),

6,40 (1H, s), 6,75 (1H, s), 7,25 (2H, t), 7,36 (2H, d), 7,80 - 7,73 (3H, m), 8,49 (1H, s);

Ejemplo 86c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,71 - 1,65 (2H, m), 1,94 - 1,88 (2H, m), 3,21 - 3,14 (3H, m), 3,50 - 3,44 (3H, m), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,16 (1H, d), 4,48 (1H, s), 4,72 (1H, t), 6,23 (1H, t), 6,74 (1H, s), 7,25 (2H, t), 7,34 (2H, d), 7,80 - 7,73 (3H, m), 8,75 (1H, s);

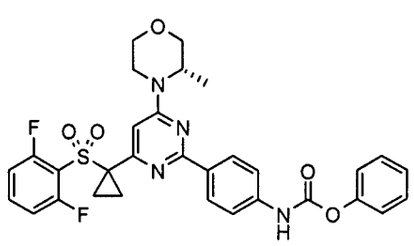
Ejemplo 86d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,69 - 1,67 (2H, m), 1,93 - 1,89 (2H, m), 3,17 (1H, ddd), 3,50 - 3,36 (3H, m), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,16 (1H, d), 4,47 (2H, tt), 4,49 (1H, s), 6,41 (1H, t), 6,75 (1H, s), 7,25 (2H, t), 7,36 (2H, d), 7,80 - 7,74 (3H, m), 8,76 (1H, s);

Ejemplo 86e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,69 - 1,67 (2H, m), 1,93 - 1,89 (2H, m), 3,17 (1H, ddd), 3,59 - 3,44 (3H, m), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,16 (1H, d), 4,48 (1H, s), 6,07 (1H, tt), 6,51 (1H, t), 6,75 (1H, s), 7,25 (2H, t), 7,37 (2H, d), 7,80 - 7,72 (3H, m), 8,87 (1H, s);

Ejemplo 86f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,70 - 1,68 (2H, m), 1,94 - 1,89 (2H, m), 3,18 (1H, ddd), 3,47 (1H, ddd), 3,63 (1H, dd), 3,76 (1H, d), 3,79 (3H, s), 3,97 (1H, dd), 4,16 (1H, d), 4,49 (1H, s), 6,76 (1H, s), 7,26 (2H, t), 7,41 - 7,38 (3H, m), 7,80 - 7,73 (4H, m), 8,36 (1H, s), 8,79 (1H, s).

La preparación de fenil *N*-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



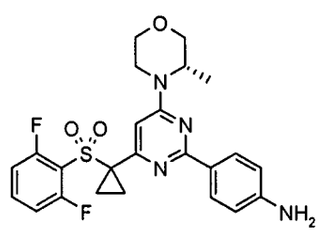
Se agregaron 4-[4-[1-(2,6-Difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (como la sal clorhidrato) (1,67 g, 3,19 mmol) y bicarbonato de sodio (2,68 g, 31,93 mmol) a DCM (60 mL) y se agitó durante 10 minutos. se agregó lentamente fenil cloroformiato (0,521 mL, 4,15 mmol) y la reacción se agitó durante 1 hora. La mezcla de reacción se aplacó con una solución saturada acuosa de cloruro de amonio (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó

para proporcionar un sólido naranja. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (1,4 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,72 - 1,66 (2H, m), 1,93 - 1,92 (2H, m), 3,18 (1H, ddd), 3,47 (1H, ddd), 3,62 (1H, dd), 3,76 (1H, d), 3,96 (1H, dd), 4,18 (1H, d), 4,50 (1H, s), 6,79 (1H, s), 7,30 - 7,23 (5H, m), 7,45 (2H, t), 7,49 (2H, d), 7,79 - 7,72 (1H, m), 7,84 (2H, d), 10,38 (1H, s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 607; HPLC tR = 3,02 min.

4-[4-[1-(2,6-Difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

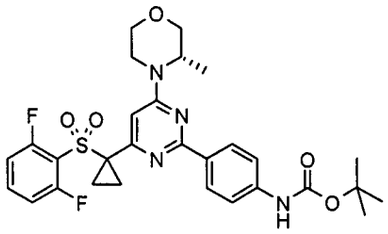


Se agregó *terc*-butil *N*-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (2,15 g, 3,66 mmol) a cloruro de hidrógeno 6,0 N en propan-2-ol (30 mL) y se agitó durante 2 horas a TA. La solución bruta se trituró con éter dietílico para proporcionar el material deseado (como la sal clorhidrato) como un sólido blanco (1,67 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,04 (3H, d), 1,76 - 1,72 (2H, m), 1,98 - 1,90 (2H, m), 3,24 (1H, ddd), 3,46 (1H, ddd), 3,60 (1H, dd), 3,76 (1H, d), 3,97 (1H, dd), 4,25 (1H, s), 4,53 (1H, s), 6,85 (1H, s), 7,15 - 7,02 (2H, m), 7,29 (2H, t), 7,84 - 7,77 (1H, m), 7,91 (2H, d); NH_2 not visible)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 487; HPLC tR = 2,45 min.

terc-butil *N*-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

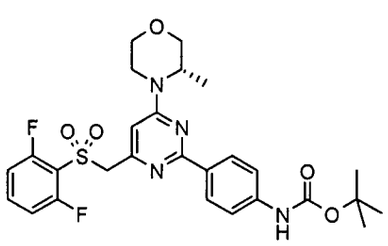


Se agregó rápidamente hidruro de sodio (1,027 g, 21,41 mmol) a *terc*-butil *N*-[4-[4-[(2,6-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (3,0 g, 5,35 mmol) en DMF (70 mL) y se agitó a TA durante 10 minutos antes de la adición lenta de 1,2-dibromoetano (1,845 mL, 21,41 mmol) en DMF (70 mL). La suspensión resultante se agitó a TA durante 1,5 horas. Se agregaron rápidamente una porción adicional de hidruro de sodio (2,0 eq) y 1,2 dibromoetano (2,0 eq) y la reacción se agitó durante otros 30 minutos. La mezcla de reacción se aplacó con agua (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar una goma marrón. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 50% acetato de etilo en isohexano, para proporcionar una espuma amarilla. Esto se disolvió en 40% acetato de etilo en isohexano y al agitar el material deseado se precipitó como un sólido blanco (2,15 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,49 (9H, s), 1,71 - 1,65 (2H, m), 1,93 - 1,90 (2H, m), 3,17 (1H, ddd), 3,47 (1H, ddd), 3,62 (1H, dd), 3,75 (1H, d), 3,96 (1H, dd), 4,16 (1H, d), 4,48 (1H, s), 6,76 (1H, s), 7,25 (2H, t), 7,42 (2H, d), 7,80 - 7,72 (3H, m), 9,49 (1H, s);

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 587; HPLC tR = 3,12 min.

terc-butil *N*-[4-[4-[(2,6-difluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



Se disolvieron 2,6-difluorobencenosulfonato de sodio (1,270 g, 5,88 mmol) y *terc*-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (3 g, 5,88 mmol) en DMF (50 mL) y se agitó durante 1 hora a TA. El disolvente se evaporó para proporcionar

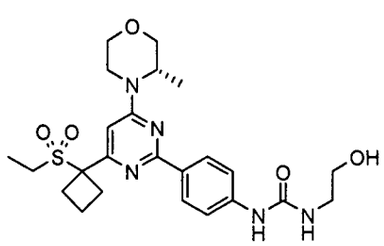
un sólido amarillo que se repartió entre agua (50 mL) y DCM (75 mL). Las capas se separaron, la capa acuosa se extrajo con DCM (75 mL) y los orgánicos combinados se concentraron al vacío para proporcionar un sólido amarillo. El sólido rápidamente se agitó con éter (100 mL), para proporcionar un sólido que se recogió mediante filtración y se secó al vacío para proporcionar el material deseado como un sólido blancuzco (3,0 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,49 (9H, s), 3,20 (1H, ddd), 3,49 (1H, ddd), 3,64 (1H, dd), 3,77 (1H, d), 3,98 (1H, dd), 4,14 (1H, d), 4,42 (1H, s), 4,78 (2H, s), 6,81 (1H, s), 7,32 (2H, t), 7,42 (2H, d), 7,73 (2H, d), 7,85 - 7,78 (1H, m), 9,50 (1H, s);

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 561; HPLC tR = 2,84 min.

La preparación de *terc*-butil *N*-[4-[4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describió anteriormente.

Ejemplo 87: 1-[4-[4-(1-Etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea

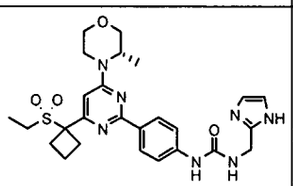
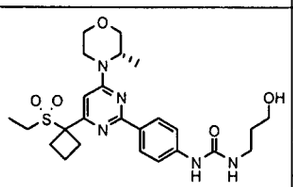
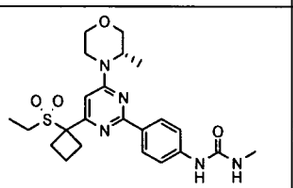
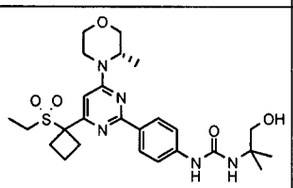
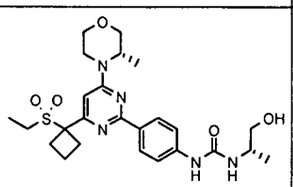
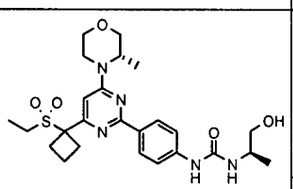


Se agregó en una porción etanolamina (0,023 mL, 0,37 mmol) a fenil *N*-[4-[4-(1-etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (101 mg, 0,19 mmol) y trietilamina (0,078 mL, 0,56 mmol) en NMP (2 mL) a TA y se agitó durante un período de 16 horas. El producto bruto se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido crema (71 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (t, 3H), 1,23 (d, 3H), 1,86 - 1,97 (m, 1H), 2,01 - 2,11 (m, 1H), 2,77 - 2,87 (m, 2H), 2,90 - 2,99 (m, 4H), 3,16 - 3,25 (m, 2H), 3,46 (q, 1H), 3,52 (dd, 3H), 3,65 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,20 - 4,28 (m, 1H), 4,52 - 4,61 (m, 1H), 4,77 (t, 1H), 6,28 (t, 1H), 6,72 (s, 1H), 7,50 (d, 2H), 8,22 (d, 2H), 8,84 (s, 1H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 504; HPLC tR = 1,79 min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-(1-etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
87a		1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)urea	540	1,87
87b		1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea	518	1,83
87c		1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	474	1,95
87d		1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-hidroxi-2-metilpropan-2-il)urea	532	2,08
87e		1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea	518	1,88
87f		1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea	518	1,89

Ejemplo 87a: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (t, 3H), 1,23 (d, 3H), 1,87 - 1,97 (m, 1H), 2,02 - 2,10 (m, 1H), 2,77 - 2,87 (m, 2H), 2,90 - 3,01 (m, 4H), 3,17 - 3,25 (m, 1H), 3,50 (td, 1H), 3,65 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,21 - 4,29 (m, 1H), 4,33 (d, 2H), 4,52 - 4,61 (m, 1H), 6,65 (t, 1H), 6,73 (s, 1H), 6,82 - 6,86 (m, 1H), 7,02 - 7,07 (m, 1H), 7,52 (d, 2H), 8,24 (d, 2H), 8,97 (s, 1H), 11,87 (s, 1H)

Ejemplo 87b: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (t, 3H), 1,23 (d, 3H), 1,60 (quinteto, 2H), 1,86 - 1,97 (m, 1H), 2,01 - 2,11 (m, 1H), 2,77 - 2,87 (m, 2H), 2,90 - 2,99 (m, 4H), 3,14 - 3,25 (m, 3H), 3,47 (q, 2H), 3,49 - 3,54 (m, 1H), 3,65 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,20 - 4,30 (m, 1H), 4,51 - 4,61 (m, 1H), 4,52 (t, 1H), 6,23 (t, 1H), 6,72 (s, 1H), 7,50 (d, 2H), 8,22 (d, 2H), 8,75 (s, 1H)

Ejemplo 87c: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (t, 3H), 1,23 (d, 3H), 1,85 - 1,97 (m, 1H), 2,00 - 2,10 (m, 1H), 2,66 (d, 3H), 2,77 - 2,87 (m, 2H), 2,90 - 3,00 (m, 4H), 3,21 (td, 1H), 3,50 (td, 1H), 3,65 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,20 - 4,29 (m, 1H), 4,52 - 4,60 (m, 1H), 6,09 (q, 1H), 6,72 (s, 1H), 7,51 (d, 2H), 8,22 (d, 2H), 8,79 (s, 1H)

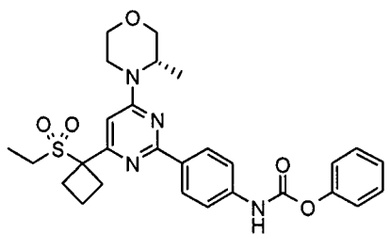
Ejemplo 87d: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (t, 3H), 1,23 (d, 3H), 1,24 (s, 6H), 1,86 - 1,97 (m, 1H), 2,01 - 2,11 (m, 1H), 2,76 - 2,87 (m, 2H), 2,90 - 3,01 (m, 4H), 3,22 (dd, 1H), 3,39 (d, 2H), 3,50 (td, 1H), 3,65 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,19 - 4,30 (m, 1H), 4,51 - 4,61 (m, 1H), 5,00 (t, 1H), 6,02 (s, 1H), 6,72 (s, 1H), 7,46 (d, 2H), 8,21 (d, 2H), 8,77 (s, 1H)

Ejemplo 87e: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,09 (d, 3H), 1,15 (t, 3H), 1,23 (d, 3H), 1,86 - 1,97 (m, 1H), 2,01 - 2,11 (m, 1H), 2,77 - 2,87 (m, 2H), 2,90 - 3,00 (m, 4H), 3,21 (td, 1H), 3,32 - 3,42 (m, 2H), 3,50 (td, 1H), 3,65 (dd, 1H), 3,68 - 3,74 (m, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,20 - 4,29 (m, 1H), 4,52 - 4,61 (m, 1H), 4,83 (t, 1H), 6,12 (d, 1H), 6,72 (s, 1H), 7,49 (d, 2H), 8,22 (d, 2H), 8,75 (s, 1H)

Ejemplo 87f: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,08 (d, 3H), 1,15 (t, 3H), 1,23 (d, 3H), 1,86 - 1,97 (m, 1H), 2,01 - 2,11 (m, 1H), 2,77 - 2,87 (m, 2H), 2,90 - 3,00 (m, 4H), 3,21 (td, 1H), 3,32 - 3,42 (m, 2H), 3,50 (td, 1H), 3,65 (dd, 1H), 3,68 - 3,74 (m, 1H), 3,76 - 3,79 (m, 1H), 3,98 (dd, 1H), 4,20 - 4,29 (m, 1H), 4,52 - 4,61 (m, 1H), 4,83 (t, 1H), 6,12 (d, 1H), 6,72 (s, 1H), 7,48 (d, 2H), 8,22 (d, 2H), 8,75 (s, 1H)

La preparación de fenil *N*-[4-[4-(1-etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación:

Fenil *N*-[4-[4-(1-etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

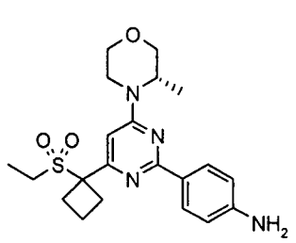


Se agregó gota a gota fenil cloroformiato (0,211 mL, 1,68 mmol) a 4-[4-(1-etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (700 mg, 1,68 mmol) e hidrogenocarbonato de sodio (141 mg, 1,68 mmol) en dioxano (20 mL) y la suspensión resultante se agitó a TA durante 3 horas. La mezcla de reacción se evaporó y se agregó DCM (50 mL) y se lavó secuencialmente con agua (20 mL) y salmuera saturada (20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como un aceite amarillo que solidificó en reposo. (930 mg)

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,16 (t, 3H), 1,25 (d, 3H), 1,87 - 1,98 (m, 1H), 2,02 - 2,12 (m, 1H), 2,78 - 2,88 (m, 2H), 2,92 - 3,00 (m, 4H), 3,23 (td, 1H), 3,48 - 3,55 (m, 1H), 3,66 (dd, 1H), 3,78 (d, 1H), 3,99 (dd, 1H), 4,21 - 4,32 (m, 1H), 4,53 - 4,64 (m, 1H), 6,76 (s, 1H), 7,24 - 7,32 (m, 3H), 7,46 (dt, 2H), 7,64 (d, 2H), 8,32 (d, 2H), 10,44 (s, 1H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 537,15; HPLC tR = 2,95 min.

4-[4-(1-Etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



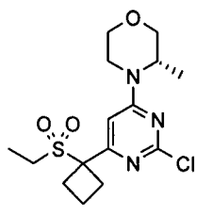
Cloruro de bis(trifenilfosfina)paladio(II) (0,137 g, 0,19 mmol) se agregó en una porción a 2-cloro-4-(1-etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (1,4 g, 3,89 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,852 g, 3,89 mmol) y carbonato de sodio (9,73 ml, 19,45 mmol) en una solución de DMF / DME / agua / etanol a TA bajo nitrógeno. La mezcla de reacción se desgasificó por completo y se agitó a 80°C durante 2

horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (50 mL) y se lavó secuencialmente con agua (50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 100% acetato de etilo en DCM, para proporcionar el material deseado como una película amarilla seca (1,536 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (t, 3H), 1,22 (d, 3H), 1,85 - 1,96 (m, 1H), 2,02 - 2,11 (m, 1H), 2,75 - 2,86 (m, 2H), 2,89 - 2,99 (m, 4H), 3,19 (td, 1H), 3,50 (td, 1H), 3,64 (dd, 1H), 3,76 (d, 1H), 3,97 (dd, 2H), 4,16 - 4,25 (m, 1H), 5,56 (s, 2H), 6,59 - 6,63 (m, 3H), 8,06 (d, 2H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 417,25; HPLC tR = 2,03 min.

2-Cloro-4-(1-etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina



Se agregó hidróxido de sodio (solución 50% p/p) (27,4 g, 683,96 mmol) a 2-cloro-4-(etilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (3,977 g, 12,44 mmol), 1,3-dibromopropano (3,79 mL, 37,31 mmol) y bromuro de tetrabutilamonio (0,401 g, 1,24 mmol) en tolueno (200 mL) y la suspensión resultante se agitó a 45°C durante 3 horas. Los orgánicos se lavaron con agua dos veces, se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 50% acetato de etilo en DCM, para proporcionar el material deseado como una película seca incolora (1,47 g).

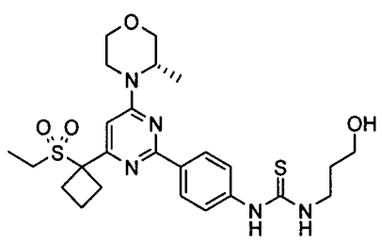
Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,13 - 1,19 (m, 3H), 1,22 (d, 3H), 1,84 - 1,95 (m, 1H), 1,98 - 2,10 (m, 1H), 2,65 - 2,77 (m, 2H), 2,82 - 2,92 (m, 2H), 2,96 (q, 2H), 3,18 - 3,25 (m, 1H), 3,45 (td, 1H), 3,60 (dd, 1H), 3,73 (d, 1H), 3,94 (dd, 1H), 3,99 - 4,12 (m, 1H), 4,36 - 4,50 (m, 1H), 6,83 (s, 1H)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 360,22; HPLC tR = 2,13 min.

La preparación de 2-cloro-4-(etilsulfonilmetil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se

describió anteriormente.

Ejemplo 88: 1-[4-[4-(1-Etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)tiourea

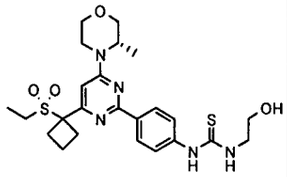
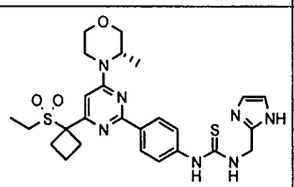
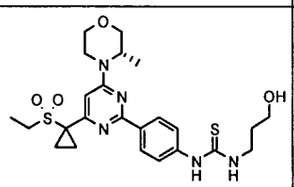
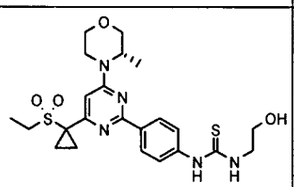
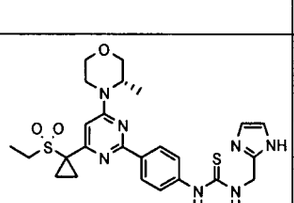


Una solución de 1,1'-tiocarbonildiimidazol (55,6 mg, 0,31 mmol) en DCM (2 mL) se agregó a una solución agitada de 4-[4-(1-etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (100 mg, 0,24 mmol) en THF (1 mL) y DCM (2 mL) a TA, durante un período de 2 minutos bajo nitrógeno. La solución resultante se agitó a TA durante 2 horas. Se agregaron trietilamina (0,033 mL, 0,24 mmol) y 3-amino-1-propanol (0,092 mL, 1,20 mmol) a la mezcla de reacción. La solución resultante se agitó a TA durante 60 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en acetonitrilo (2 mL), se filtró y se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, hasta secarse para proporcionar el material deseado como un sólido beige. (100 mg)

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (t, 3H), 1,24 (d, 3H), 1,72 (quinteto, 2H), 1,86 - 1,97 (m, 1H), 2,03 - 2,12 (m, 1H), 2,77 - 2,88 (m, 2H), 2,91 - 3,00 (m, 4H), 3,18 - 3,26 (m, 1H), 3,45 - 3,59 (m, 5H), 3,65 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,19 - 4,29 (m, 1H), 4,49 - 4,63 (m, 2H), 6,75 (s, 1H), 7,57 (d, 2H), 7,86 - 7,94 (m, 1H), 8,28 (d, 2H), 9,65 - 9,74 (m, 1H)

Espectro de LCMS: m/z (ES+) $(M+H)^+$ = 534,8; HPLC tR = 2,16 min.

Los compuestos a continuación se prepararon en forma análoga a partir de 4-[4-(1-etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina o 4-[4-(1-etilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
88a		1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea	521	2,13
88b		1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)tiourea	557	1,51
88c		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)tiourea	5,21	2,33
88d		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea	507	2,30
88e		1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)tiourea	543	2,36

Ejemplo 88a: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (t, 3H), 1,24 (d, 3H), 1,86 - 1,97 (m, 1H), 2,03 - 2,11 (m, 1H), 2,77 - 2,88 (m, 2H), 2,91 - 3,00 (m, 4H), 3,18 - 3,27 (m, 1H), 3,51 (td, 1H), 3,55 - 3,60 (m, 4H), 3,65 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,18 - 4,30 (m, 1H), 4,54 - 4,63 (m, 1H), 4,77 - 4,86 (m, 1H), 6,75 (s, 1H), 7,62 (d, 2H), 7,84 - 7,90 (m, 1H), 8,28 (d, 2H), 9,81 (s, 1H)

Ejemplo 88b: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,15 (t, 3H), 1,24 (d, 3H), 1,86 - 1,97 (m, 1H), 2,02 - 2,12 (m, 1H), 2,78 - 2,88 (m, 2H), 2,91 - 3,00 (m, 4H), 3,18 - 3,26 (m, 1H), 3,51 (td, 1H), 3,66 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,19 - 4,30 (m, 1H), 4,53 - 4,63 (m,

1H), 4,71 (d, 2H), 6,75 (s, 1H), 6,99 (s, 2H), 7,69 (d, 2H), 8,18 - 8,25 (m, 1H), 8,30 (d, 2H), 9,98 - 10,09 (m, 1H), 11,84 - 12,09 (m, 1H)

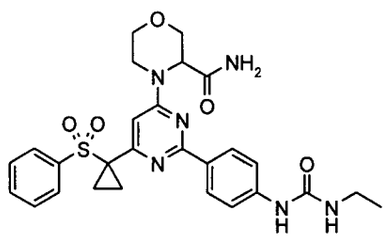
Ejemplo 88c: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,24 (d, 3H), 1,33 (t, 3H), 1,54 - 1,59 (m, 2H), 1,61 - 1,66 (m, 2H), 1,72 (quinteto, 2H), 3,22 (td, 1H), 3,40 - 3,59 (m, 7H), 3,64 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,16 - 4,28 (m, 1H), 4,52 - 4,64 (m, 2H), 6,83 (s, 1H), 7,58 (d, 2H), 7,90 - 7,97 (m, 1H), 8,25 (d, 2H), 9,74 (s, 1H)

Ejemplo 88d: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,24 (d, 3H), 1,33 (t, 3H), 1,55 - 1,59 (m, 2H), 1,61 - 1,66 (m, 2H), 3,22 (td, 1H), 3,44 (q, 2H), 3,45 - 3,52 (m, 1H), 3,55 - 3,60 (m, 4H), 3,64 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,15 - 4,28 (m, 1H), 4,52 - 4,63 (m, 1H), 4,82 - 4,90 (m, 1H), 6,82 (s, 1H), 7,63 (d, 2H), 7,88 - 7,93 (m, 1H), 8,25 (d, 2H), 9,85 (s, 1H)

Ejemplo 88e: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,24 (d, 3H), 1,33 (t, 3H), 1,54 - 1,59 (m, 2H), 1,61 - 1,66 (m, 2H), 3,22 (td, 1H), 3,45 (q, 2H), 3,45 - 3,52 (m, 1H), 3,64 (dd, 1H), 3,77 (d, 1H), 3,98 (dd, 1H), 4,15 - 4,28 (m, 1H), 4,53 - 4,63 (m, 1H), 4,69 - 4,74 (m, 2H), 6,83 (s, 1H), 6,86 - 7,15 (m, 2H), 7,70 (d, 2H), 8,22 - 8,29 (m, 1H), 8,27 (d, 2H), 10,05 (s, 1H), 11,95 (s, 1H)

La preparación de 4-[4-(1-etilsulfonilciclobutil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina y 4-[4-(1-etilsulfonilciclopropil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina se describió anteriormente.

<u>Ejemplo 89: 4-[6-[1-(Bencenosulfonil)ciclopropil]-2-[4-(etilcarbamoilamino)fenil]pirimidin-4-il]morfolina-3-carboxamida</u>



Se agregó DIPEA (0,411 mL, 2,36 mmol) a [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato (0,102 g, 0,20 mmol) y morfolina-3-carboxamida (como una mezcla de las sales de ácido trifluoroacético y la sal clorhidrato) (0,212 g, 1,63 mmol) en dioxano (5 mL) bajo nitrógeno. La reacción se agitó a 70°C durante varias horas. El disolvente se retiró y luego la goma se recogió nuevamente en dioxano. se agregó etil isocianato (0,032 mL, 0,41 mmol) y la reacción se agitó a TA durante el fin de semana. Se agregó más etil isocianato (un exceso) y la reacción se agitó durante

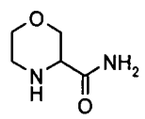
varios días. Se agregó metanol y el disolvente se retiró. El producto bruto se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido amarillo (0,027 g).

Espectro de NMR: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,05-1,08 (3H, t), 1,59-1,62 (1H, m), 1,65-1,68 (1H, m), 1,87-1,95 (2H, m), 3,09-3,17 (2H, m), 3,17-3,19 (1H, d), 3,41-3,54 (3H, m), 3,70-3,73 (1H, dd), 3,94-3,97 (1H, d), 4,30-4,33 (1H, d), 6,13-6,16 (1H, t), 6,72 (1H, s), 7,15 (1H, bs), 7,36-7,38 (2H, d), 7,52 (1H, bs), 7,57-7,61 (2H, t), 7,70-7,74 (1H, tt), 7,79-7,82 (4H, m), 8,62 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 551; HPLC tR = 1,84min.

La preparación de [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato se describió anteriormente

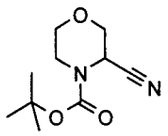
Morfolina-3-carboxamida



Se agregó cloruro de hidrógeno (2,420 mL, 9,68 mmol) (solución 4M en dioxano) a *terc*-butil 3-cianomorfolina-4-carboxilato (0,419 g, 1,98 mmol) en dioxano (15 mL) y la solución resultante se agitó a TA durante el fin de semana. El disolvente se retiró. El sólido se recogió en dioxano y se agregó ácido trifluoroacético (1,2 eq). La reacción se dejó agitar a TA durante toda la noche. El disolvente se retiró. El material bruto se recogió en DCM y se agregó ácido trifluoroacético (0,734 mL, 9,88 mmol). La reacción se agitó durante toda la noche y luego el disolvente se retiró para proporcionar el material deseado (aislado como una posible mezcla de las sales de ácido trifluoroacético y la sal clorhidrato). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400 MHz, DMSO-D_6) δ 3,07-3,16 (1H, m), 3,58-3,70 (1H, m), 3,79-3,82 (1H, m), 3,87-3,93 (1H, m), 4,00-4,07 (1H, m), 4,11-4,22 (1H, m), 4,71-4,89 (1H, m), 7,76-8,16 (t) (sal TFA), 9,15-9,78 (bt) (sal HCl).

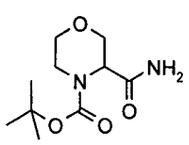
terc-butil 3-cianomorfolina-4-carboxilato



Se disolvió *terc*-butil 3-carbamoilmorfolina-4-carboxilato (0,929 g, 4,03 mmol) en DCM seco (10 mL) y se agregó trietilamina (1,181 mL, 8,47 mmol). La solución se colocó bajo nitrógeno y se enfrió hasta alcanzar 0°C. Luego se agregó anhídrido trifluoroacético (0,627 mL, 4,44 mmol) y la reacción se dejó entibiar lentamente hasta alcanzar TA, luego se agitó a TA durante al menos 3 horas. El disolvente se retiró y luego se agregó acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 30% acetato de etilo en DCM, para proporcionar el material deseado como un sólido cristalino amarillo claro (0,419 g).

Espectro de NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1,50 (9H, s), 3,24 (1H, bt), 3,45-3,52 (1H, td), 3,60-3,64 (1H, dd), 3,80-3,83 (1H, d), 3,94-3,97 (1H, d), 4,04-4,07 (1H, d), 4,89 (1H, bs).

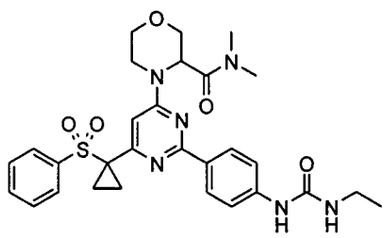
terc-butil 3-carbamoilmorfolina-4-carboxilato



Se agregó hATU (5,92 g, 15,57 mmol) a una solución de ácido 4-(*terc*-butoxicarbonil)morfolina-3-carboxílico (3 g, 12,97 mmol), DIPEA (3,40 mL, 19,46 mmol) y cloruro de amonio (3,47 g, 64,87 mmol) en DMF (70 mL) y la suspensión resultante se agitó a TA durante 12 horas bajo nitrógeno. La mezcla de reacción se concentró y se diluyó con acetato de etilo (150 mL) y se lavó secuencialmente con agua (2 x 50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como un aceite (4,0 g), que se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,39 (9H, s), 3,15 (2H, m), 3,54 (2H, m), 3,63 (2H, m), 3,75 (1H, m), 4,17 (2H, m).

Ejemplo 90: 4-[6-[1-(Bencenosulfonil)ciclopropil]-2-[4-(etilcarbamoilamino)fenil]pirimidin-4-il]-*N*,*N*-dimetilmorfolina-3-carboxamida



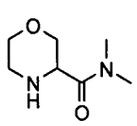
Se agregó DIPEA (0,141 mL, 0,81 mmol) a [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato (0,101 g, 0,20 mmol) y *N,N*-dimetilmorfolina-3-carboxamida (como la sal clorhidrato) (0,079 g, 0,41 mmol) en dioxano (5 mL) bajo nitrógeno. La reacción se agitó a 70°C durante varias horas y luego se dejó enfriar y se agregó etil isocianato (0,321 mL, 4,05 mmol). La reacción se agitó a TA durante toda la noche, se agregó más etil isocianato y la reacción se agitó a TA durante toda la noche. Se agregó metanol y el disolvente se retiró. El producto bruto se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido crema (0,047 g).

Espectro de NMR: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,05-1,08 (3H, t), 1,58-1,62 (1H, m), 1,68-1,73 (1H, m), 1,86-1,97 (2H, m), 2,82 (3H, bs), 3,09-3,16 (2H, m), 3,19 (3H, bs), 3,53-3,60 (1H, m), 3,67-3,71 (1H, m), 3,79-3,84 (1H, dd), 4,00-4,02 (1H, d), 4,14-4,17 (1H, d), 5,44 (1H, bs), 6,15-6,18 (1H, t), 6,77 (1H, s), 7,37-7,39 (2H, d), 7,56-7,60 (2H, t), 7,70-7,74 (1H, t), 7,76-7,80 (4H, m), 8,61 (1H, s). (1 pico bajo agua o pico del disolvente).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 579; HPLC tR = 2,01min.

La preparación de [2-(4-aminofenil)-6-[1-(bencenosulfonil)ciclopropil]pirimidin-4-il] trifluorometanosulfonato se describió anteriormente.

N,N-Dimetilmorfolina-3-carboxamida

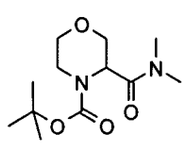


Se agregó cloruro de hidrógeno (3,57 mL, 14,28 mmol) (solución 4M en dioxano) a *terc*-butil 3-(dimetilcarbamoil)morfolina-4-carboxilato (0,820 g, 3,17 mmol) en dioxano (25 mL) y la

solución resultante se agitó a TA durante toda la noche. El disolvente se retiró y la goma se trituró con éter dietílico para proporcionar el material deseado (como la sal clorhidrato) como un sólido que en reposo se volvió una goma (0,70 g).

Espectro de NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,89 (3H, s), 3,07 (3H, s), 3,13-3,16 (1H, dd), 3,20-3,23 (1H, dt), 3,42-3,48 (1H, m), 3,69-3,75 (1H, td), 3,92-3,96 (1H, dt), 4,15-4,19 (1H, dd), 4,57-4,61 (1H, dd), 9,47 (1H, bs).

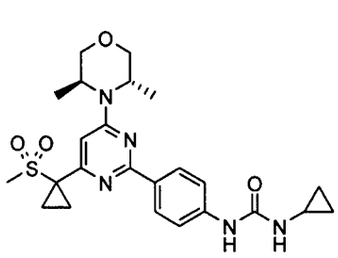
terc-butil 3-(dimetilcarbamoil)morfolina-4-carboxilato



Se agregó hATU (1,97 g, 5,19 mmol) a una solución de ácido 4-(*terc*-butoxicarbonil)morfolina-3-carboxílico (1 g, 4,32 mmol), DIPEA (1,133 ml, 6,49 mmol) y dimetilamina 2,0M en THF (10,81 mL, 21,62 mmol) en DMF y la solución resultante se agitó a TA durante 15 horas bajo nitrógeno. La mezcla de reacción se concentró y se diluyó con acetato de etilo (100 mL) y se lavó secuencialmente con agua (25 mL), solución de ácido cítrico acuoso al 5% (25 mL) y salmuera saturada (25 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto y se secó al vacío para proporcionar el material deseado como un aceite (0,91 g), que se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400 MHz, DMSO-D_6) δ 1,36 (9H, br s), 2,83 (3H, s), 2,98 (3H, s), 3,35 (1H, m), 3,48 (1H, m), 3,63 (1H, dd), 3,80 (1H, m), 3,90 - 4,04 (2H, m), 4,70 (1H, m).

Ejemplo 91: 3-Ciclopropil-1-[4-[4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea



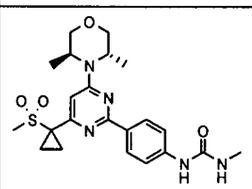
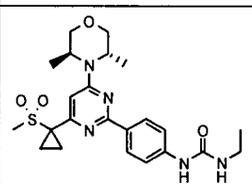
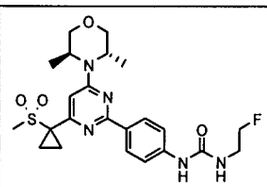
Se agregó ciclopropilamina (0,10 mmol) a fenil *N*-[4-[4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-

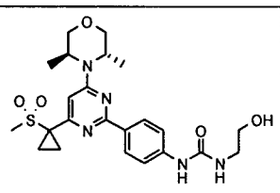
(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato (50 mg, 0,10 mmol) y trietilamina (0,027 mL, 0,19 mmol) en DMF (1 mL) a TA. La solución resultante se agitó a 50°C durante 2 horas y el material se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (40mg).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,63 - 0,67 (2H, m), 1,36 (6H, d), 1,53 - 1,61 (2H, m), 1,64 - 1,72 (2H, m), 2,54 - 2,59 (1H, m), 3,26 (3H, s), 3,72 (2H, dd), 4,16 (2H, dd), 4,25 - 4,31 (2H, m), 6,44 (1H, d), 6,72 (1H, s), 7,52 (2H, d), 8,21 (2H, d), 8,54 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 486; HPLC tR = 2,13min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
91a		1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-metilurea	460	1,70
91b		1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-etilurea	474	2,11
91c		1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	492	2,11

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
91d		1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	490	1,77

Ejemplo 91a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,36 (6H, d), 1,55 - 1,61 (2H, m), 1,64 - 1,70 (2H, m), 2,66 (3H, d), 3,26 (3H, s), 3,72 (2H, dd), 4,16 (2H, dd), 4,27 - 4,28 (2H, m), 6,07 - 6,08 (1H, m), 6,72 (1H, s), 7,51 (2H, d), 8,20 (2H, d), 8,74 (1H, s).

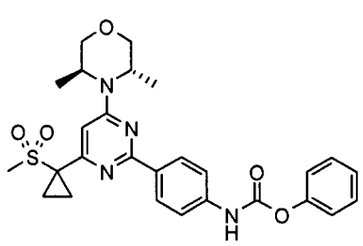
Ejemplo 91b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,36 (6H, d), 1,55 - 1,61 (2H, m), 1,64 - 1,73 (2H, m), 3,09 - 3,16 (2H, m), 3,26 (3H, s), 3,72 (2H, dd), 4,16 (2H, dd), 4,27 - 4,28 (2H, m), 6,17 (1H, t), 6,72 (1H, s), 7,50 (2H, d), 8,20 (2H, d), 8,66 (1H, s).

Ejemplo 91c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,36 (6H, d), 1,55 - 1,59 (2H, m), 1,64 - 1,70 (2H, m), 3,26 (3H, s), 3,42 (2H, dq), 3,72 (2H, dd), 4,16 (2H, dd), 4,26 - 4,29 (2H, m), 4,42 (1H, t), 4,54 (1H, t), 6,44 (1H, t), 6,72 (1H, s), 7,51 (2H, d), 8,21 (2H, d), 8,81 (1H, s).

Ejemplo 91d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,36 (6H, d), 1,55 - 1,60 (2H, m), 1,65 - 1,72 (2H, m), 3,16 - 3,20 (2H, m), 3,26 (3H, s), 3,44 - 3,48 (2H, m), 3,72 (2H, dd), 4,16 (2H, dd), 4,24 - 4,31 (2H, m), 4,73 (1H, t), 6,26 (1H, t), 6,72 (1H, s), 7,50 (2H, d), 8,20 (2H, d), 8,81 (1H, s).

La preparación de fenil *N*-[4-[4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]carbamato

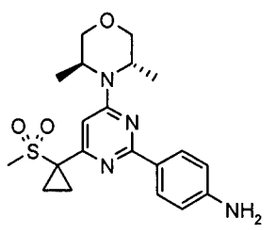


Se agregó bicarbonato de sodio (104 mg, 1,24 mmol) a 4-[4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina (250 mg, 0,62 mmol) en 1,4-dioxano (3 mL) y se agregó gota a gota fenil cloroformiato (0,078 mL, 0,62 mmol) a la suspensión resultante. La reacción se agitó a TA durante 2 horas y luego se evaporó hasta secarse, se disolvió nuevamente en DCM (20 mL) y se lavó con agua (20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido que se trituró con éter dietílico para proporcionar el material deseado como un sólido crema (250 mg).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,37 (6H, d), 1,56 - 1,62 (2H, m), 1,65 - 1,71 (2H, m), 3,27 (3H, s), 3,73 (2H, dd), 4,17 (2H, dd), 4,29 - 4,31 (2H, m), 6,77 (1H, s), 7,24 - 7,30 (3H, m), 7,45 (2H, t), 7,65 (2H, d), 8,30 (2H, d), 10,45 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 523; HPLC tR = 2,74min.

4-[4-[(3*S*,5*S*)-3,5-Dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]anilina

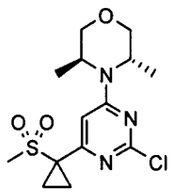


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (35,5 mg, 0,05 mmol) a 2-cloro-4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina (350 mg, 1,01 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (222 mg, 1,01 mmol) y solución de carbonato de sodio acuoso 2M (1,52 mL, 3,04 mmol), en etanol (0,89 mL), DME (1,77 mL) y agua (0,89 mL) y la reacción se agitó a 90°C durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (20 mL) y se lavó secuencialmente con agua (20 mL) y salmuera saturada (20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 2 a 10% metanol en DCM, para proporcionar el material deseado como un sólido beige (250 mg).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,34 (6H, d), 1,50 - 1,58 (2H, m), 1,62 - 1,70 (2H, m), 3,25 (3H, s), 3,70 (2H, dd), 4,14 (2H, dd), 4,22 - 4,25 (2H, m), 5,56 (1H, s), 6,61 (2H, d), 8,04 (2H, d).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 403; HPLC tR = 2,05min.

2-Cloro-4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidina

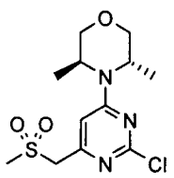


Una solución de hidróxido de sodio 50% p/v (6,12 mL, 154,44 mmol) se agregó en porciones a una solución agitada de 2-cloro-4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina (898 mg, 2,81 mmol), bromuro de tetrabutilamonio (91 mg, 0,28 mmol) y 1,2-dibromoetano (0,726 mL, 8,42 mmol) en tolueno (50 mL) y la suspensión resultante se agitó a 60°C durante 6 horas. La mezcla de reacción se diluyó con agua (50 mL) y se lavó secuencialmente con agua (2 x 50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como un sólido (350 mg).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,43 (3H, d), 1,44 (3H, d), 1,50 (2H, m), 1,82 (2H, m), 3,02 (3H, s), 3,78 (2H, dd), 4,16 (2H, m), 4,24 (2H, dd), 6,77 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 346; HPLC tR = 1,83min.

2-Cloro-4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(metilsulfonilmetil)pirimidina



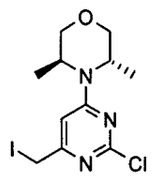
Se agregó en porciones metanosulfinato de sodio (0,542 g, 5,31 mmol) a 2-cloro-4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(yodometil)pirimidina (1,86 g, 5,06 mmol) en acetonitrilo (50 mL) y la suspensión resultante se agitó a 80°C durante 6 horas. Se agregó más metanosulfinato de sodio (0,5 equivalentes) y la reacción se calentó 8 horas más. El disolvente se retiró y el sólido se recogió en DMF. Se agregó más metanosulfinato de sodio (1 equivalente) y la mezcla se dejó agitar hasta que se completó la reacción. El disolvente se retiró y se agregó acetato de etilo. La mezcla se lavó con 10% tiosulfato de sodio, salmuera y agua y los orgánicos se secaron sobre $MgSO_4$, se filtraron y se evaporaron. El producto bruto

se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 25% acetato de etilo en DCM, para proporcionar el material deseado como una goma amarilla (0,898 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,44-1,45 (6H, d), 3,02 (3H, s), 3,77-3,80 (2H, dd), 4,14-4,16 (2H, m), 4,17-4,18 (2H, d), 4,23-4,27 (2H, dd), 6,46 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 320; HPLC tR = 1,59 min.

2-Cloro-4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(yodometil)pirimidina

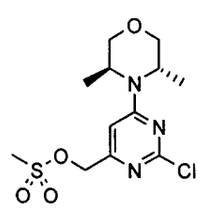


Se agregaron [2-cloro-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-4-il]metil metanosulfonato (5,21 g, 15,51 mmol) y yoduro de litio (1,190 mL, 31,03 mmol) a dioxano (250 mL) y se calentó a 60°C durante 1 hora y luego a TA durante toda la noche. La mezcla se evaporó hasta secarse y se repartió entre solución de cloruro de amonio saturado (100 mL) y DCM (75 mL). Las capas se separaron y la capa acuosa se extrajo adicionalmente con DCM (2 x 75 mL) luego los orgánicos combinados se lavaron secuencialmente con 10% tiosulfato de sodio solución (100 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto como un aceite marrón (5,59 g). El material se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,32 (6H, d), 3,69 (2H, dd), 4,08 (2H, m), 4,14 (2H, dd), 4,34 (2H, s), 6,84 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 368; HPLC tR = 2,26min.

[2-Cloro-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-4-il]metil metanosulfonato



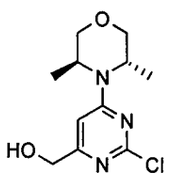
Se agregó gota a gota Cloruro de metanosulfonilo (1,802 mL, 23,28 mmol) a [2-cloro-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-4-il]metanol (4,00 g, 15,52 mmol) y DIPEA (4,03

mL, 23,28 mmol) en DCM (100 mL) a 0°C durante un período de 2 minutos y la solución resultante se dejó entibiar gradualmente hasta alcanzar TA durante un período de 2 horas. La mezcla de reacción se diluyó con DCM (50 mL) y se lavó con agua. La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el material deseado como una goma amarilla (5,56 g). Esto se utilizó sin purificación adicional.

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,42-1,44 (6H, d), 3,14 (3H, s), 3,76-3,80 (2H, dd), 4,13-4,18 (2H, m), 4,22-4,26 (2H, dd), 5,11 (2H, d), 6,48 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 336; HPLC tR = 1,88min.

[2-Cloro-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-4-il]metanol

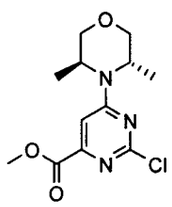


Se agregó gota a gota borohidruro de litio, 2M en THF (6,54 mL, 13,09 mmol) a metil 2-cloro-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidina-4-carboxilato (4,40 g, 15,40 mmol) en THF (75 mL) a 0°C durante un período de 30 minutos bajo nitrógeno. La solución resultante se agitó a 0°C durante 30 minutos luego se dejó entibiar hasta alcanzar TA. Se agregó agua (250 mL) y los orgánicos se eliminaron al vacío. Los residuos acuosos se extrajeron con acetato de etilo luego los orgánicos combinados se lavaron con salmuera. La capa orgánica se secó sobre $MgSO_4$ luego se evaporó hasta secarse para proporcionar el material deseado como un sólido blanco (4,0 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,41-1,42 (6H, d), 2,69-2,71 (1H, t), 3,75-3,78 (2H, dd), 4,12-4,18 (2H, m), 4,21-4,25 (2H, dd), 4,59-4,60 (2H, d), 6,39 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 258; HPLC tR = 1,38min.

Metil 2-cloro-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidina-4-carboxilato



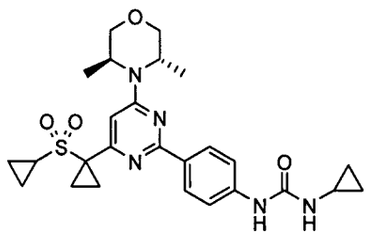
Se disolvió metil 2,4-dicloropirimidina-6-carboxilato (4,45 g, 21,50 mmol) en DCM seco (100mL) y se agregó DIPEA (9,67 mL, 55,89 mmol). Se agregó (3*S*,5*S*)-3,5-dimetilmorfolina (como la sal clorhidrato) (3,42 g, 22,57 mmol)en DCM (20 mL) a esta solución gota a gota durante varios minutos y la reacción se dejó agitar a TA durante 5 días luego a 50°C durante varios días. La mezcla de reacción bruta se lavó con agua, se secó sobre $MgSO_4$ y se filtró. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 25% acetato de etilo en DCM, para proporcionar el material deseado como un sólido crema (4,4 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,44-1,46 (6H, d), 3,78-3,81 (2H, dd), 3,98 (3H, s), 4,16-4,22 (2H, m), 4,24-4,28 (2H, dd), 7,10 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 286; HPLC tR = 1,72min.

La preparación de (3*S*,5*S*)-3,5-dimetilmorfolina se describió anteriormente.

Ejemplo 92: 3-Ciclopropil-1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]urea

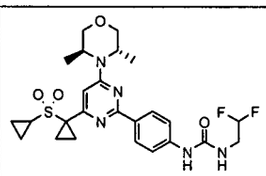
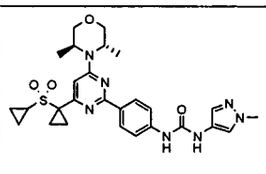
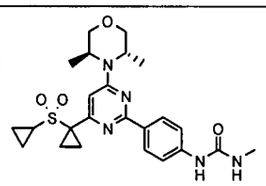
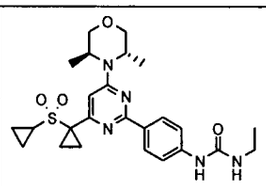
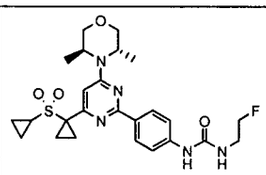


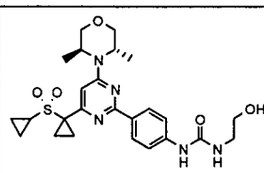
Se agregó ciclopropanamina (12,49 mg, 0,22 mmol) a fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (120 mg, 0,22 mmol) y trietilamina (0,091 mL, 0,66 mmol) en DMF (1 mL) a TA. La solución resultante se agitó a 50°C durante 2 horas. El producto bruto se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (82 mg).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,63 - 0,67 (2H, m), 0,87 - 1,04 (4H, m), 1,36 (6H, d), 1,57 - 1,70 (4H, m), 2,54 - 2,58 (1H, m), 2,91 - 2,97 (1H, m), 3,71 (2H, dd), 4,16 (2H, dd), 4,25 - 4,27 (2H, m), 6,43 (1H, s), 6,81 (1H, s), 7,51 (2H, d), 8,22 (2H, d), 8,52 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 512; HPLC tR = 2,25min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
92a		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea	537	2,39
92b		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	552	1,83
92c		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	486	2,06
92d		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea	500	1,91
92e		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	518	1,94

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
92f		1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	516	1,88

Ejemplo 92a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,87 - 1,06 (4H, m), 1,36 (6H, d), 1,55 - 1,70 (4H, m), 2,91 - 2,97 (1H, m), 3,50 - 3,60 (2H, m), 3,72 (2H, dd), 4,16 (2H, dd), 4,25 - 4,28 (2H, m), 6,07 (1H, t), 6,54 (1H, t), 6,82 (1H, s), 7,52 (2H, d), 8,24 (2H, d), 8,91 (1H, s).

Ejemplo 92b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,88 - 1,07 (4H, m), 1,36 (6H, d), 1,56 - 1,71 (4H, m), 2,91 - 2,98 (1H, m), 3,72 (2H, dd), 3,79 (3H, s), 4,16 (2H, dd), 4,26 - 4,29 (2H, m), 6,82 (1H, s), 7,39 (1H, s), 7,55 (2H, d), 7,76 (1H, s), 8,25 (2H, d), 8,39 (1H, s), 8,83 (1H, s).

Ejemplo 92c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,89 - 1,04 (4H, m), 1,36 (6H, d), 1,57 - 1,68 (4H, m), 2,66 (3H, d), 2,91 - 2,97 (1H, m), 3,71 (2H, ddd), 4,16 (2H, dd), 4,25 - 4,27 (2H, m), 6,06 - 6,07 (1H, m), 7,50 (2H, d), 7,55 - 7,58 (1H, m), 8,21 (2H, d), 8,73 (1H, s).

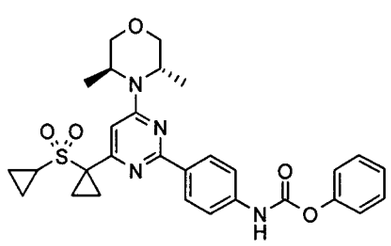
Ejemplo 92d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,87 - 1,04 (4H, m), 1,07 (3H, t), 1,36 (6H, d), 1,55 - 1,70 (4H, m), 2,91 - 2,97 (1H, m), 3,09 - 3,16 (2H, m), 3,71 (2H, dd), 4,16 (2H, dd), 4,24 - 4,27 (2H, m), 6,16 (1H, t), 6,81 (1H, s), 7,49 (2H, d), 8,21 (2H, d), 8,65 (1H, s).

Ejemplo 92e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,87 - 1,06 (4H, m), 1,36 (6H, d), 1,55 - 1,70 (4H, m), 2,91 - 2,97 (1H, m), 3,39 (1H, q), 3,46 (1H, q), 3,72 (2H, dd), 4,16 (2H, dd), 4,22 - 4,29 (2H, m), 4,42 (1H, t), 4,54 (1H, t), 6,44 (1H, t), 6,81 (1H, s), 7,51 (2H, d), 8,23 (2H, d), 8,80 (1H, s).

Ejemplo 92f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,87 - 1,04 (4H, m), 1,36 (6H, d), 1,55 - 1,69 (4H, m), 2,90 - 2,97 (1H, m), 3,16 - 3,20 (2H, m), 3,44 - 3,48 (2H, m), 3,71 (2H, dd), 4,16 (2H, dd), 4,24 - 4,29 (2H, m), 4,73 (1H, t), 6,26 (1H, t), 6,81 (1H, s), 7,49 (2H, d), 8,22 (2H, d), 8,79 (1H, s).

La preparación de fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

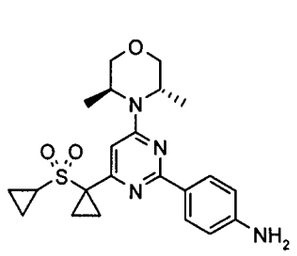


Se agregó bicarbonato de sodio (286 mg, 3,41 mmol) a 4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]anilina (730 mg, 1,70 mmol), en 1,4-dioxano (8,3 mL) y se agregó gota a gota fenil cloroformiato (0,214 mL, 1,70 mmol) a la suspensión resultante. La mezcla se agitó a TA durante 2 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en DCM (20 mL) y se lavó con agua (20 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido que se trituró con éter dietílico para proporcionar el material deseado como un sólido crema (800 mg).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 0,88 - 1,05 (4H, m), 1,37 (6H, d), 1,59 - 1,70 (4H, m), 2,92 - 2,99 (1H, m), 3,73 (2H, dd), 4,17 (2H, dd), 4,28 - 4,30 (2H, m), 6,86 (1H, s), 7,24 - 7,30 (3H, m), 7,45 (2H, t), 7,64 (2H, d), 8,30 (2H, d), 10,45 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 549; HPLC tR = 2,66min.

4-[4-(1-Ciclopropilsulfonilciclopropil)-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]anilina



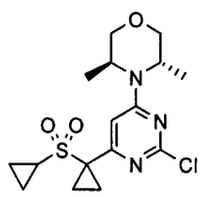
Se agregó cloruro de bis(trifenilfosfina)paladio(II) (60,4 mg, 0,09 mmol) a 2-cloro-4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidina (640 mg, 1,72

mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (490 mg, 2,24 mmol) y solución de carbonato de sodio 2M (2,6 mL, 5,16 mmol) en agua (1,5 mL), etanol (1,5 mL) y DME (3 mL) y la solución resultante se agitó a 95°C durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (20 mL) y se lavó secuencialmente con agua (10 mL) y salmuera saturada(10 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 10% metanol en DCM, para proporcionar el material deseado como un sólido beige (740 mg).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 0,89 - 1,03 (4H, m), 1,34 (6H, d), 1,54 - 1,67 (4H, m), 2,89 - 2,96 (1H, m), 3,70 (2H, dd), 4,14 (2H, dd), 4,20 - 4,24 (2H, m), 6,61 (2H, d), 6,73 (1H, s), 8,05 (2H, d)

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 429; HPLC tR = 2,18min.

2-Cloro-4-(1-ciclopropilsulfonilciclopropil)-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidina

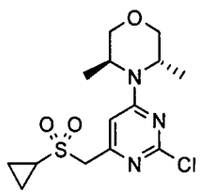


Una solución de hidróxido de sodio 50% p/v (7,06 mL, 176,52 mmol) se agregó en porciones a una solución agitada de 2-cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidina (1,11 g, 3,21 mmol), bromuro de tetrabutilamonio (0,103 g, 0,32 mmol) y 1,2-dibromoetano (0,830 mL, 9,63 mmol) en tolueno (50 mL) y la suspensión resultante se agitó a 60°C durante 6 horas. La mezcla de reacción se diluyó con agua (50 mL) y se lavó secuencialmente con agua (2 x 50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como un sólido (0,64 g).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 0,86 - 0,99 (2H, m), 1,01 (2H, m), 1,31 (3H, d), 1,33 (3H, d), 1,51 (2H, m), 1,63 (2H, m), 2,86 (1H, m), 3,70 (2H, dd), 4,13 (2H, m), 4,16 (2H, m), 6,90 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 372; HPLC tR = 1,97min.

2-Cloro-4-(ciclopropilsulfonilmetil)-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidina



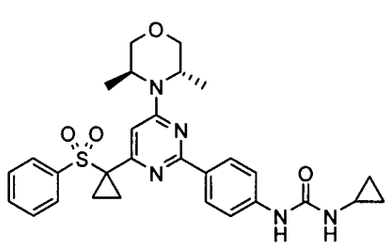
Se agregó en porciones ciclopropanosulfinato de sodio (0,648 g, 5,06 mmol) a 2-cloro-4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(yodometil)pirimidina (1,86 g, 5,06 mmol) en acetonitrilo (50 mL) y la suspensión resultante se agitó a 80°C durante 6 horas. Se agregó más ciclopropanosulfinato de sodio (259mg, 2,02mmol) en una porción y la suspensión se agitó a 80°C durante otras 2 horas. La mezcla de reacción se concentró y se diluyó con DCM (200 mL) y se lavó secuencialmente con agua (50 mL), solución de tiosulfato de sodio al 10% (50 mL) y salmuera saturada(50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como un sólido amarillo (1,11 g).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 0,97 (2H, m), 1,03 (2H, m), 1,32 (3H, d), 1,34 (3H, d), 2,79 (1H, m), 3,70 (2H, dd), 4,09 (2H, m), 4,15 (2H, dd), 4,49 (2H, d), 6,82 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 346; HPLC tR = 1,77 min.

La preparación de 2-cloro-4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(yodometil)pirimidina se describió anteriormente.

Ejemplo 93: 1-[4-[4-[1-(Bencenosulfonil)ciclopropil]-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea



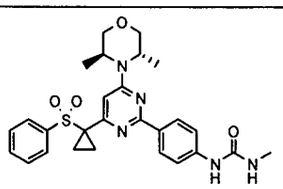
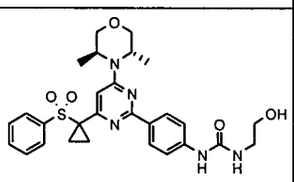
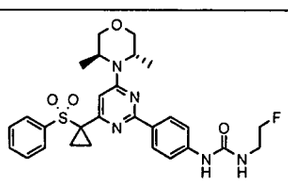
Se agregó ciclopropilamina (19,0 mg, 0,34 mmol) a fenil *N*-[4-[4-[1-

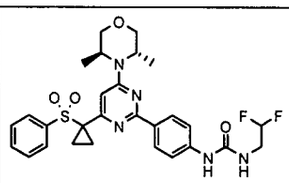
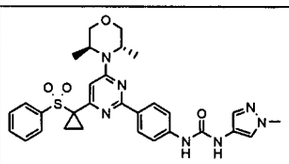
(bencenosulfonil)ciclopropil]-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (100 mg, 0,17 mmol) y trietilamina (52 mg, 0,51 mmol) en dioxano (10mL) a TA. La solución resultante se agitó a 50°C durante toda la noche. El producto bruto se purificó mediante HPLC preparativa, eluyendo con mezclas cada vez menos polares de agua (conteniendo 1% amoníaco) y acetonitrilo, para proporcionar el material deseado como un sólido blanco (64 mg).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 0,43 - 0,39 (2H, m), 0,67 - 0,62 (2H, m), 1,28 (6H, d), 1,69 - 1,62 (2H, m), 1,93 - 1,89 (2H, m), 2,59 - 2,50 (m, 1H), 3,70 - 3,67 (2H, m), 4,18 - 4,10 (4H, m), 6,41 (1H, s), 6,60 (1H, s), 7,41 (2H, d), 7,59 (2H, t), 7,70 (1H, t), 7,79 (2H, d), 7,88 (2H, d), 8,49 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 548; HPLC tR = 2,49min.

Los compuestos a continuación se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	**Estructura**	**NOMBRE**	**LCMS MH+**	**Tiempo de retención (min)**
93a		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	522	2,32
93b		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	552	2,13
93c		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-	554	2,47

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		fluoroetil)urea		
93d		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea	572	2,60
93e		1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	588	2,34

1-[4-[4-[1-(Bencenosulfonil)ciclopropil]-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea (**Ejemplo 72**) también puede prepararse de esta forma.

Ejemplo 93a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,28 (6H, d), 1,69 - 1,62 (2H, m), 1,93 - 1,89 (2H, m), 2,68 - 2,65 (3H, m), 3,70 - 3,67 (2H, m), 4,16 - 4,10 (4H, m), 6,05 (1H, q), 6,59 (1H, s), 7,40 (2H, d), 7,59 (2H, t), 7,70 (1H, t), 7,79 (2H, d), 7,87 (2H, d), 8,69 (1H, s).

Ejemplo 93b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,28 (6H, d), 1,69 - 1,63 (2H, m), 1,93 - 1,89 (2H, m), 3,18 - 3,15 (2H, m), 3,46 (2H, q), 3,70 - 3,67 (2H, m), 4,18 - 4,10 (4H, m), 4,72 (1H, t), 6,24 (1H, t), 6,60 (1H, s), 7,39 (2H, d), 7,59 (2H, t), 7,70 (1H, t), 7,79 (2H, d), 7,88 (2H, d), 8,76 (1H, s).

Ejemplo 93c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,28 (6H, d), 1,69 - 1,64 (2H, m), 1,93 - 1,89 (2H, m), 3,41 (2H, dq), 3,70 - 3,68 (2H, m), 4,18 - 4,10 (4H, m), 4,47 (2H, dt), 6,42 (1H, t), 6,60 (1H, s), 7,40 (2H, d), 7,59 (2H, t), 7,70 (1H, t), 7,79 (2H, d), 7,88 (2H, d), 8,76 (1H, s).

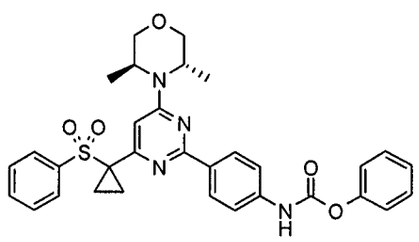
Ejemplo 93d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,28 (6H, d), 1,69 - 1,61 (2H, m), 1,93 - 1,90 (2H, m), 3,59 - 3,49 (2H, m), 3,70 - 3,68 (2H, m), 4,18 - 4,10 (4H, m), 6,07 (1H, tt), 6,52

(1H, t), 6,60 (1H, s), 7,41 (2H, d), 7,59 (2H, t), 7,70 (1H, t), 7,79 (2H, d), 7,89 (2H, d), 8,87 (1H, s).

Ejemplo 93e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,28 (6H, d), 1,72 - 1,62 (2H, m), 1,94 - 1,90 (2H, m), 3,70 - 3,68 (2H, m), 3,79 (3H, s), 4,18 - 4,10 (4H, m), 6,61 (1H, s), 7,38 (1H, s), 7,45 (2H, d), 7,59 (2H, t), 7,71 (1H, t), 7,76 (1H, s), 7,80 (2H, d), 7,91 (2H, d), 8,37 (1H, s), 8,79 (1H, s).

La preparación de fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

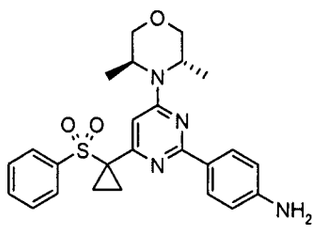


Se agregaron 4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]anilina (0,6 g, 1,29 mmol) y bicarbonato de sodio (1,085 g, 12,91 mmol) a DCM (60 mL) y se agitó durante 10 minutos. Se agregó lentamente fenil cloroformiato (0,211 mL, 1,68 mmol) y la reacción se agitó durante 1 hora. La mezcla de reacción se aplacó con solución de cloruro de amonio saturado (50 mL), se extrajo con acetato de etilo (3 x 50 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un sólido naranja. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (0,73 g).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,29 (6H, d), 1,71 - 1,64 (2H, m), 1,94 - 1,89 (2H, m), 3,71 - 3,68 (2H, m), 4,18 - 4,11 (4H, m), 6,63 (1H, s), 7,30 - 7,23 (3H, m), 7,45 (2H, t), 7,54 (2H, d), 7,59 (2H, t), 7,70 (1H, t), 7,81 - 7,79 (2H, m), 7,97 (2H, d), 10,39 (1H, s).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 585; HPLC tR = 3,02min.

4-[4-[1-(Bencenosulfonil)ciclopropil]-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]anilina

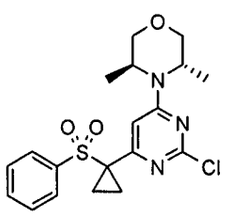


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,053 g, 0,07 mmol) a 4-[1-(bencenosulfonil)ciclopropil]-2-cloro-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidina (0,611 g, 1,50 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,427 g, 1,95 mmol) y solución de carbonato de sodio 2M (2,247 mL, 4,49 mmol) en agua (3 mL), etanol (3 mL) y DME (6 mL) y la solución resultante se agitó a 95°C durante toda la noche. La mezcla de reacción se diluyó con acetato de etilo (75 mL) y se lavó secuencialmente con agua (10 mL) y salmuera saturada (10 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar el producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 50% acetato de etilo en DCM, para proporcionar el material deseado como una espuma blanca (0,6 g).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,25 (6H, d), 1,69 - 1,60 (2H, m), 1,93 - 1,85 (2H, m), 3,68 - 3,64 (2H, m), 4,13 - 4,06 (4H, m), 5,50 (1H, s), 6,52 - 6,50 (4H, m), 7,58 (2H, t), 7,74 - 7,67 (3H, m), 7,80 - 7,78 (2H, m).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 465; HPLC tR = 2,50min.

4-[1-(Bencenosulfonil)ciclopropil]-2-cloro-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidina



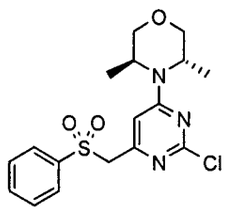
Una solución de hidróxido de sodio 50% p/v (4,99 mL, 124,73 mmol) se agregó en porciones a una solución agitada de 4-(bencenosulfonilmetil)-2-cloro-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidina (866 mg, 2,27 mmol), bromuro de tetrabutilamonio (73,1 mg, 0,23 mmol) y 1,2-dibromoetano (0,586 mL, 6,80 mmol) en tolueno (50 mL) y la suspensión resultante se agitó a 60°C durante 6 horas. La mezcla de reacción se diluyó con agua (50 mL) y se lavó secuencialmente con agua (2 x 50 mL) y salmuera saturada (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se

purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 20% acetato de etilo en DCM, para proporcionar el material deseado como un sólido (611 mg).

Espectro de NMR: ^{1}H NMR (400MHz, DMSO-D_6) δ 1,20 (6H, m), 1,59 (2H, m), 1,86 (2H, m), 3,66 (2H, dd), 4,02 (2H, m), 4,10 (2H, dd), 6,62 (1H, s), 7,61 (2H, m), 7,74 (1H, m), 7,75 (2H, m).

Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 408; HPLC tR = 2,26min.

4-(Bencenosulfonilmetil)-2-cloro-6-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]pirimidina



Se agregó bencenosulfinato de sodio (0,872 g, 5,31 mmol) en porciones a 2-cloro-4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(yodometil)pirimidina (1,86 g, 5,06 mmol) en acetonitrilo (50 mL) y la suspensión resultante se agitó a 80°C durante 6 horas. Se agregó más bencenosulfinato de sodio (0,5 equivalentes) y la reacción se calentó durante otras 8 horas. El disolvente se retiró y el sólido se recogió en DMF. Se agregó más bencenosulfinato de sodio (1 equivalente) y la reacción se dejó agitar hasta completarse (se agregó un poco de yoduro de sodio para acelerar la reacción). Se agregó solución de tiosulfato de sodio acuoso al 10% y el acetonitrilo se retiró, se agregó acetato de etilo y las capas se separaron. La capa orgánica se lavó con salmuera y agua, se secó sobre $MgSO_4$, se filtró y se evaporó. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 25% acetato de etilo en DCM, para proporcionar el material deseado como un sólido blanco (0,866 g).

Espectro de NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ 1,42-1,44(6H, d), 3,76-3,79(2H, dd), 4,10-4,16(2H, m), 4,22-4,26(2H, dd), 4,32(2H, s), 6,56(1H, s), 7,52-7,56(2H, t), 7,64-7,68(1H, t), 7,77-7,79(2H, d).

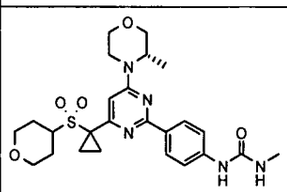
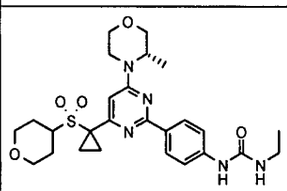
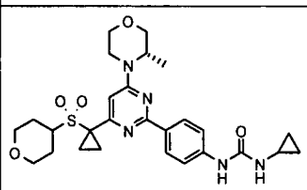
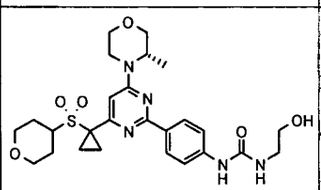
Espectro de LCMS: m/z (ES+)$(M+H)^+$ = 382; HPLC tR = 2,11min.

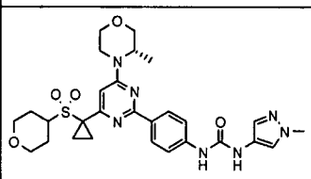
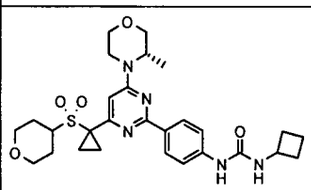
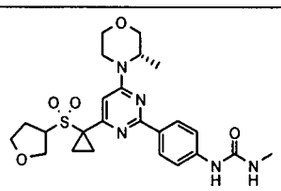
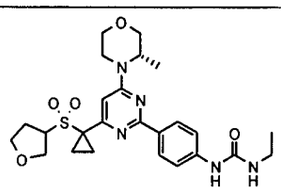
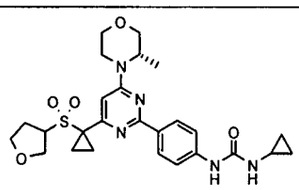
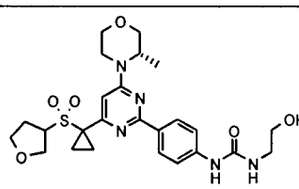
La preparación de 2-cloro-4-[(3*S*,5*S*)-3,5-dimetilmorfolin-4-il]-6-(yodometil)pirimidina se describió anteriormente.

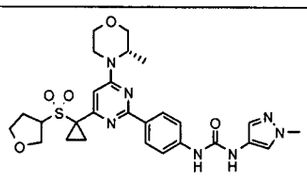
Ejemplo 94

Las siguientes muestras se prepararon calentando una mezcla del carbamato (1 equivalente), trietilamina (4 equivalentes) y la amina (4 equivalentes) en NMP (2 mL) a 70°C durante 2 horas. Los compuestos se purificaron mediante HPLC preparativa.

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
94a		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea	516	1,98
94b		1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea	530	2,14
94c		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea	542	2,16
94d		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea	546	1,80

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
94e		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	582	2,03
94f		3-ciclobutil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea	556	2,44
94g		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea	502	1,98
94h		1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea	516	2,13
94i		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea	528	2,15
94j		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-	532	1,81

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
		2-il]fenil]urea		
94k		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	568	2,03

Ejemplo 94a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,52 - 1,56 (2H, m), 1,58 - 1,61 (2H, m), 1,65 - 1,77 (2H, m), 2,10 - 2,19 (2H, m), 3,17 - 3,33 (3H, m), 3,48 (1H, td), 3,63 (1H, d), 3,75 - 3,87 (2H, m), 3,95 - 4,05 (3H, m), 4,17 - 4,27 (1H, m), 4,55 (1H, s), 6,00 - 6,15 (1H, m), 6,78 (1H, s), 7,52 (2H, d), 8,18 (2H, d), 8,75 (1H, s)

Ejemplo 94b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,24 (3H, d), 1,52 - 1,56 (2H, m), 1,57 - 1,62 (2H, m), 1,65 - 1,78 (2H, m), 2,09 - 2,19 (2H, m), 3,09 - 3,24 (3H, m), 3,26 - 3,35 (2H, m), 3,48 (1H, td), 3,63 (1H, d), 3,74 - 3,88 (2H, m), 3,94 - 4,04 (3H, m), 4,22 (1H, d), 4,55 (1H, s), 6,17 (1H, t), 6,78 (1H, s), 7,51 (2H, d), 8,18 (2H, d), 8,67 (1H, s)

Ejemplo 94c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,38 - 0,46 (2H, m), 0,62 - 0,69 (2H, m), 1,24 (3H, d), 1,50 - 1,56 (2H, m), 1,56 - 1,62 (2H, m), 1,66 - 1,78 (2H, m), 2,09 - 2,19 (2H, m), 2,54 - 2,60 (1H, m), 3,21 (1H, td), 3,28 - 3,34 (2H, m), 3,48 (1H, td), 3,63 (1H, d), 3,76 (1H, d), 3,79 - 3,88 (1H, m), 3,94 - 4,04 (3H, m), 4,22 (1H, d), 4,55 (1H, s), 6,45 (1H, s), 6,78 (1H, s), 7,52 (2H, d), 8,19 (2H, d), 8,55 (1H, s)

Ejemplo 94d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,50 - 1,56 (2H, m), 1,56 - 1,62 (2H, m), 1,64 - 1,77 (2H, m), 2,09 - 2,20 (2H, m), 3,15 - 3,23 (2H, m), 3,25 - 3,35 (2H, m), 3,43 - 3,50 (2H, m), 3,61 - 3,66 (1H, m), 3,74 - 3,87 (2H, m), 3,94 - 4,04 (3H, m), 4,22 (1H, d), 4,55 (1H, s), 4,73 (1H, t), 6,27 (1H, t), 6,78 (1H, s), 7,50 (2H, d), 8,18 (2H, d), 8,82 (1H, s)

Ejemplo 94e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,51 - 1,57 (2H, m), 1,58 - 1,62 (2H, m), 1,67 - 1,78 (2H, m), 2,10 - 2,21 (2H, m), 3,18 - 3,34 (3H, m), 3,49 (1H, td), 3,64 (1H, d), 3,73 - 3,88 (5H, m), 3,95 - 4,05 (3H, m), 4,23 (1H, d), 4,55 (1H, s), 6,79 (1H, s),

7,39 (1H, s), 7,56 (2H, d), 7,77 (1H, s), 8,22 (2H, d), 8,40 (1H, s), 8,85 (1H, s)

Ejemplo 94f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,49 - 1,77 (8H, m), 1,81 - 1,91 (2H, m), 2,09 - 2,25 (4H, m), 3,21 (1H, td), 3,26 - 3,35 (2H, m), 3,48 (1H, td), 3,63 (1H, d), 3,71 - 3,89 (2H, m), 3,94 - 4,04 (3H, m), 4,08 - 4,25 (2H, m), 4,55 (1H, s), 6,47 (1H, d), 6,78 (1H, s), 7,49 (2H, d), 8,18 (2H, d), 8,57 (1H, s)

Ejemplo 94g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,52 - 1,58 (2H, m), 1,62 - 1,70 (2H, m), 2,17 - 2,30 (2H, m), 2,66 (3H, d), 3,14 - 3,28 (1H, m), 3,49 (1H, td), 3,61 - 3,72 (2H, m), 3,73 - 3,82 (2H, m), 3,93 - 4,04 (2H, m), 4,21 (1H, d), 4,27 - 4,39 (1H, m), 4,55 (1H, s), 6,07 (1H, t), 6,79 (1H, s), 7,51 (2H, d), 8,20 (2H, d), 8,74 (1H, s)

Ejemplo 94h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,23 (3H, d), 1,52 - 1,59 (2H, m), 1,63 - 1,69 (2H, m), 2,18 - 2,30 (2H, m), 3,09 - 3,17 (2H, m), 3,17 - 3,24 (1H, m), 3,49 (1H, td), 3,61 - 3,71 (2H, m), 3,73 - 3,83 (2H, m), 3,94 - 4,02 (3H, m), 4,21 (1H, d), 4,30 - 4,38 (1H, m), 4,54 (1H, s), 6,17 (1H, t), 6,79 (1H, s), 7,50 (2H, d), 8,20 (2H, d), 8,66 (1H, s)

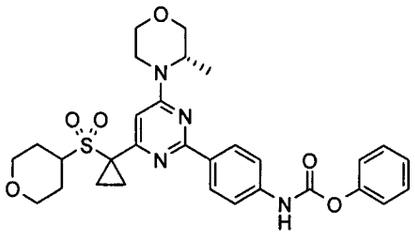
Ejemplo 94i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,40 - 0,44 (2H, m), 0,62 - 0,68 (3H, m), 1,23 (4H, d), 1,52 - 1,60 (4H, m), 1,63 - 1,70 (3H, m), 2,16 - 2,30 (3H, m), 2,52 - 2,61 (18H, m), 3,21 (3H, td), 3,49 (1H, td), 3,59 - 3,72 (3H, m), 3,72 - 3,84 (3H, m), 3,93 - 4,03 (3H, m), 4,21 (1H, d), 4,28 - 4,40 (1H, m), 4,54 (1H, s), 6,44 (1H, s), 6,80 (1H, s), 7,52 (2H, d), 8,20 (2H, d), 8,54 (1H, s)

Ejemplo 94j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,51 - 1,60 (2H, m), 1,62 - 1,69 (2H, m), 2,18 - 2,30 (2H, m), 3,14 - 3,24 (4H, m), 3,43 - 3,50 (2H, m), 3,61 - 3,71 (1H, m), 3,74 - 3,81 (2H, m), 3,94 - 4,02 (3H, m), 4,21 (1H, d), 4,30 - 4,38 (1H, m), 4,54 (1H, s), 4,69 - 4,77 (1H, m), 6,26 (1H, t), 6,79 (1H, s), 7,50 (2H, d), 8,20 (2H, d), 8,81 (1H, s)

Ejemplo 94k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,50 - 1,60 (2H, m), 1,63 - 1,68 (2H, m), 2,20 - 2,30 (2H, m), 3,16 - 3,28 (1H, m), 3,44 - 3,57 (1H, m), 3,61 - 3,70 (1H, m), 3,74 - 3,84 (4H, m), 3,94 - 4,05 (3H, m), 4,22 (1H, d), 4,31 - 4,38 (1H, m), 4,55 (1H, s), 6,81 (1H, s), 7,39 (1H, s), 7,56 (2H, d), 7,76 (1H, s), 8,24 (2H, d), 8,39 (1H, s), 8,84 (1H, s)

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]carbamato

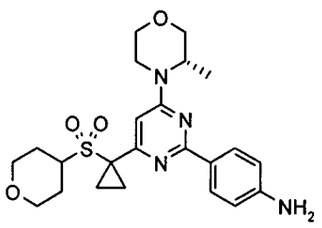


Se agregó fenil cloroformiato (0,436 mL, 3,47 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]anilina (1,06 g, 2,31 mmol), hidrogenocarbonato de sodio (0,291 g, 3,47 mmol) en dioxano (40 mL) a 5°C bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a TA durante 1,5 horas. La mezcla de reacción se diluyó con acetato de etilo (150 mL) y se lavó secuencialmente con agua (2 x 100 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto que se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido beige (1,14 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,52 - 1,58 (2H, m), 1,58 - 1,64 (2H, m), 1,65 - 1,77 (2H, m), 2,10 - 2,20 (2H, m), 3,17 - 3,54 (2H, m), 3,63 (2H, d), 3,74 - 3,87 (3H, m), 3,96 - 4,04 (3H, m), 4,24 (1H, d), 4,56 (1H, s), 6,83 (1H, s), 7,20 - 7,32 (3H, m), 7,42 - 7,50 (2H, m), 7,63 (2H, d), 8,28 (2H, d), 10,45 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 579; HPLC tR = 2,8 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidin-2-il]anilina



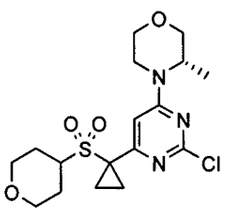
Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,187 g, 0,27 mmol) a 2-cloro-4-[(3S)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidina (1,6 g, 3,98 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,308 g, 5,97 mmol) y solución de carbonato de sodio acuoso 2M (1 mL, 2,00 mmol) en una mezcla de disolventes de DMF (5 mL), DME (12 mL), agua (1 mL) y etanol (1 mL) a TA . La mezcla resultante se agitó a 90°C durante 7 horas bajo una atmósfera inerte. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó secuencialmente con agua (2 x 100 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto

se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 50% acetato de etilo en isohexano y el producto bruto luego se purificó adicionalmente mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol, para proporcionar un sólido. El sólido se purificó adicionalmente mediante trituración con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido beige (1,0 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,48 - 1,53 (2H, m), 1,55 - 1,59 (2H, m), 1,66 - 1,76 (2H, m), 2,11 - 2,18 (2H, m), 3,18 (1H, dd), 3,30 - 3,34 (2H, m), 3,47 (1H, td), 3,62 (1H, d), 3,75 (1H, d), 3,81 - 3,90 (1H, m), 3,93 - 4,05 (3H, m), 4,18 (1H, d), 4,51 (1H, s), 5,58 (2H, s), 6,62 (2H, d), 6,67 (1H, s), 8,02 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 459; HPLC tR = 2,11 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(oxan-4-ilsulfonil)ciclopropil]pirimidina

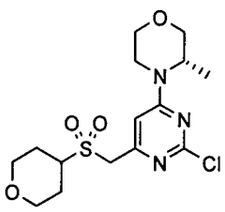


Se agregó solución acuosa de hidróxido de sodio (10 mL, 186,39 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(oxan-4-ilsulfonilmetil)pirimidina (1,5 g, 3,99 mmol), bromuro de tetraetilamonio (0,168 g, 0,80 mmol) y 1,2-dibromoetano (2,75 mL, 31,93 mmol) en tolueno (10 mL) a TA bajo una atmósfera de nitrógeno. Después de agitar a TA durante 2 horas la mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (100 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 5 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un aceite que solidificó en reposo (1,64 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 - 1,25 (3H, m), 1,50 - 1,54 (2H, m), 1,55 - 1,59 (2H, m), 1,61 - 1,72 (2H, m), 1,97 - 2,07 (2H, m), 3,18 - 3,27 (1H, m), 3,26 - 3,36 (2H, m), 3,44 (1H, td), 3,58 (1H, d), 3,65 - 3,78 (2H, m), 3,90 - 4,01 (3H, m), 4,01 - 4,10 (1H, m), 4,39 (1H, s), 6,96 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 402; HPLC tR = 1,99 min.

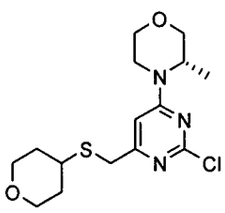
2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(oxan-4-ilsulfonilmetil)pirimidina



Se agregó ácido 3-cloroperoxibenzoico (381 mg, 2,21 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(oxan-4-ilsulfanilmetil)pirimidina (345 mg, 1,00 mmol)en DCM (10 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 2 horas y luego se diluyó con DCM (100 mL) y se lavó secuencialmente con solución de metabisulfito de sodio acuoso al 10% (200 mL), hidrogenocarbonato de sodio saturado acuoso (200 mL), se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido crema (200 mg).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,19 - 1,26 (3H, m), 1,60 - 1,76 (2H, m), 1,95 - 2,06 (2H, m), 3,19 - 3,29 (1H, m), 3,31 - 3,39 (2H, m), 3,40 - 3,65 (3H, m), 3,74 (1H, d), 3,90 - 4,04 (3H, m), 4,30 (1H, s), 4,48 (2H, s), 6,93 (1H, s)

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(oxan-4-ilsulfanilmetil)pirimidina



Se agregó DIPEA (1,762 mL, 10,18 mmol) a oxano-4-tiol (1,203 g, 10,18 mmol), en acetonitrilo (20 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 5 mins y luego se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,4 g, 6,79 mmol). La mezcla resultante se agitó a TA durante 1 hora y luego se diluyó con acetato de etilo (75 mL) y se lavó secuencialmente con agua (2 x 75 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 70% acetato de etilo en isohexano, para proporcionar el material deseado como una

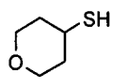
goma marrón (2,5 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,39 - 1,51 (2H, m), 1,82 - 1,92 (2H, m), 2,92 - 3,02 (1H, m), 3,13 - 3,23 (1H, m), 3,26 - 3,37 (2H, m), 3,44 (1H, td), 3,54 - 3,66 (1H, m), 3,72 (1H, d), 3,78 - 3,88 (2H, m), 3,90 - 4,02 (2H, m), 4,31 (1H, s), 6,81 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 344; HPLC tR = 1,99 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Oxano-4-tiol

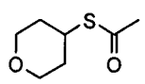


Se agregó amoníaco 7M en metanol (20 mL, 140,00 mmol) a *S*-(oxan-4-il) etanotioato (2,27 g, 14,17 mmol) a TA. La solución resultante se agitó a TA durante 1 hora y luego la mezcla se concentró al vacío y se utilizó sin purificación adicional.

Espectro de NMR: ninguno

Espectro de LCMS: sin ion másico; HPLC tR = 0,61 min.

S-(Oxan-4-il) etanotioato



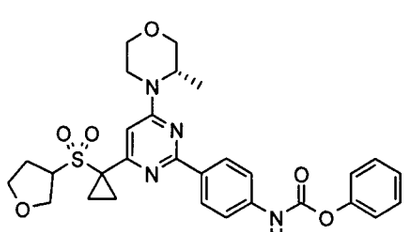
Se agregó tioacetato de potasio (4,68 g, 40,98 mmol) a oxan-4-il metanosulfonato (4,2 g, 23,30 mmol), en DMA (80 mL) a TA. La mezcla resultante se agitó a 65°C durante 18 horas. La mezcla de reacción se diluyó con acetato de etilo (400 mL) y se lavó secuencialmente con agua (2 x 150 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 5 a 30% acetato de etilo en isohexano, para proporcionar el material deseado as a orange aceite (2,27 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,47 - 1,65 (2H, m), 1,76 - 1,90 (2H, m), 2,35 (3H, s), 3,36 - 3,51 (2H, m), 3,53 - 3,69 (1H, m), 3,67 - 3,82 (2H, m).

Espectro de LCMS: sin ion másico; HPLC tR = 1,45 min.

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]carbamato se describe a continuación.

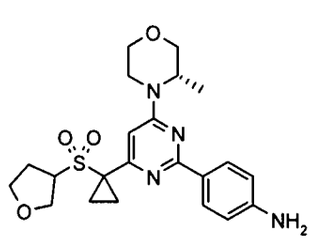
Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]carbamato



Se agregó fenil cloroformiato (0,297 mL, 2,36 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]anilina (700 mg, 1,57 mmol), hidrogenocarbonato de sodio (198 mg, 2,36 mmol) en dioxano (30 mL) a 5°C bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a TA durante 1,5 horas y luego se diluyó con acetato de etilo (150 mL) y se lavó secuencialmente con agua (2 x 100 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. La goma bruta se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido beige (600 mg).

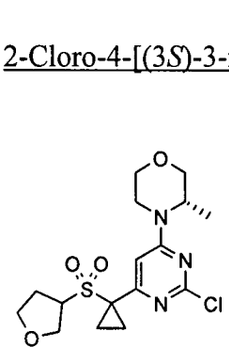
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,25 (3H, d), 1,52 - 1,59 (2H, m), 1,64 - 1,71 (2H, m), 2,15 - 2,30 (2H, m), 3,22 (1H, td), 3,44 - 3,54 (1H, m), 3,61 - 3,70 (2H, m), 3,73 - 3,83 (2H, m), 3,94 - 4,03 (3H, m), 4,23 (1H, d), 4,30 - 4,38 (1H, m), 4,56 (1H, s), 6,84 (1H, s), 7,21 - 7,32 (3H, m), 7,41 - 7,50 (2H, m), 7,64 (2H, d), 8,30 (2H, d), 10,44 (1H, s)

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidin-2-il]anilina



Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,233 g, 0,33 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidina (1,92 g, 4,95 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,627 g, 7,42 mmol) y carbonato de sodio (1 mL, 2,00 mmol) en una mezcla de disolventes de DMF (5 mL), DME (12 mL), agua (1 mL) y etanol (1 mL) a TA. La mezcla resultante se agitó a 90°C durante 7 horas bajo una atmósfera inerte. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó secuencialmente con agua (2 x 100 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 50% acetato de etilo en isohexano, para proporcionar un producto que se purificó adicionalmente mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol, para proporcionar un sólido. El sólido bruto se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido beige (0,821 g).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,22 (3H, d), 1,49 - 1,54 (2H, m), 1,61 - 1,66 (2H, m), 2,16 - 2,26 (2H, m), 3,18 (1H, dd), 3,39 - 3,53 (1H, m), 3,59 - 3,71 (3H, m), 3,70 - 3,83 (2H, m), 3,90 - 4,01 (3H, m), 4,17 (1H, d), 4,33 (1H, q), 4,51 (1H, s), 5,57 (2H, s), 6,61 (2H, d), 6,69 (1H, s), 8,03 (2H, d)
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 447; HPLC tR = 1,91 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(oxolan-3-ilsulfonil)ciclopropil]pirimidina



Se agregó solución acuosa de hidróxido de sodio (10 mL, 186,39 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(oxolan-3-ilsulfonilmetil)pirimidina (1,9 g, 5,25 mmol), bromuro de tetraetilamonio (0,221 g, 1,05 mmol), y 1,2-dibromoetano (3,62 mL, 42,01 mmol) en tolueno (30 mL) a TA bajo una atmósfera de nitrógeno. Después de agitarse a TA durante 1,5 horas la mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (125 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 60% acetato de etilo en isohexano, para proporcionar el material deseado

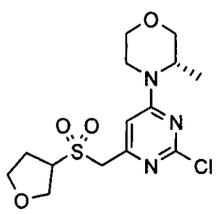
1900

como una goma incolora (1,92 g).

Espectro de NMR: ninguno

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 388; HPLC tR = 1,91 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(oxolan-3-ilsulfonilmetil)pirimidina

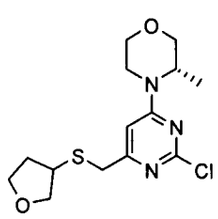


Se agregó ácido 3-cloroperoxibenzoico (4,26 g, 24,68 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(oxolan-3-ilsulfanilmetil)pirimidina (3,7 g, 11,22 mmol)en DCM (200 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó a TA durante 2 horas y luego se diluyó con DCM (100 mL) y se lavó secuencialmente con solución de metabisulfito de sodio acuoso al 10% (200 mL) y una solución saturada acuosa de hidrogenocarbonato de sodio (200 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El sólido bruto se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido crema (3,03 g).

Espectro de NMR: ^{1}H NMR (399,902 MHz, DMSO-D_6) δ 1,20 - 1,26 (3H, m), 2,18 - 2,31 (2H, m), 3,20 - 3,31 (1H, m), 3,37 - 3,52 (1H, m), 3,60 (1H, d), 3,65 - 3,77 (2H, m), 3,80 - 3,89 (1H, m), 3,90 - 3,99 (3H, m), 4,03 - 4,16 (2H, m), 4,31 (1H, s), 4,49 (2H, s), 6,94 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 362; HPLC tR = 1,59 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(oxolan-3-ilsulfanilmetil)pirimidina



Se agregó DIPEA (3,67 mL, 21,21 mmol) a oxolano-3-tiol (2,210 g, 21,21 mmol), en acetonitrilo (100 mL) a TA bajo una atmósfera de nitrógeno. La solución resultante se agitó durante 5 minutos y luego se agregó 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (5 g, 14,14 mmol). La mezcla resultante se agitó a TA durante 1 hora y luego se

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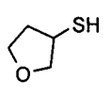
diluyó con acetato de etilo (75 mL) y se lavó secuencialmente con agua (2 x 75 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 70% acetato de etilo en isohexano, para proporcionar el material deseado como una goma marrón (3,75 g).

Espectro de NMR: ^{1}H NMR (399,902MHz, DMSO-D_6) δ 1,17 - 1,24 (3H, m), 1,63 - 1,75 (2H, m), 2,17 - 2,30 (2H, m), 3,19 (1H, td), 3,40 - 3,50 (2H, m), 3,59 (1H, d), 3,63 - 3,80 (3H, m), 3,91 - 4,04 (4H, m), 4,33 (1H, s), 6,82 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 330; HPLC tR = 1,89 min.

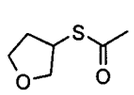
La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

Oxolano-3-tiol



Se agregó amoníaco 7M en metanol (20 mL, 140,00 mmol) a *S*-(oxolan-3-il) etanotioato (20,47 g, 140,00 mmol) a TA. La solución resultante se agitó a TA durante 1 hora y luego se concentró al vacío para proporcionar el material deseado que se utilizó sin purificación o caracterización adicional.

S-(Oxolan-3-il) etanotioato

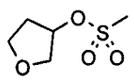


Se agregó tioacetato de potasio (16,60 g, 145,31 mmol) a oxolan-3-il metanosulfonato (13,8 g, 83,03 mmol), en DMA (150 mL) a TA. La mezcla resultante se agitó a 65°C durante 7 horas. La mezcla de reacción se diluyó con acetato de etilo (400 mL) y se lavó secuencialmente con agua (2 x 150 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 30% acetato de etilo en isohexano, para proporcionar el material deseado como un aceite marrón (9,50 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,70 - 1,80 (1H, m), 2,25 - 2,40

(4H, m), 3,44 - 3,52 (1H, m), 3,67 - 3,81 (2H, m), 3,84 - 3,94 (1H, m), 3,97 - 4,08 (1H, m)
Espectro de LCMS: sin ion másico; HPLC tR = 1,18 min.

Oxolan-3-ilo metanosulfonato

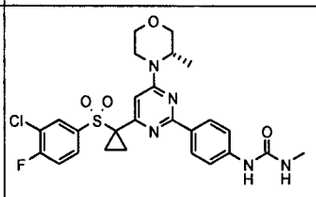
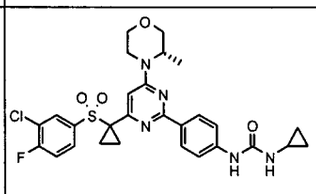
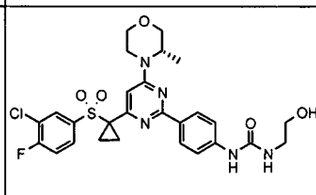
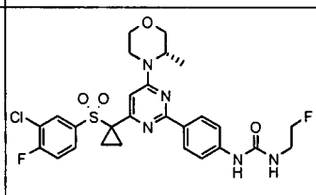
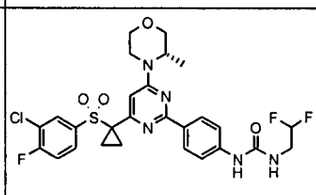


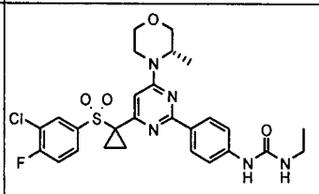
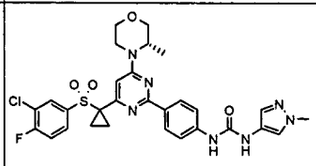
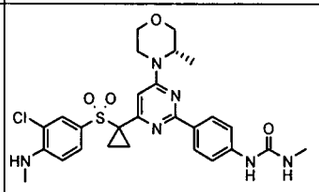
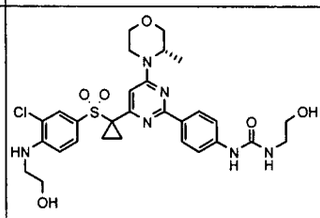
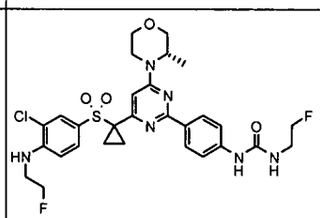
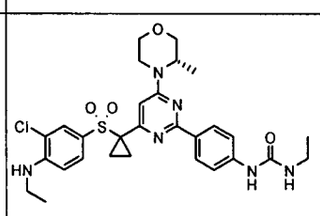
Se agregó gota a gota cloruro de metanosulfonilo (11,86 mL, 153,23 mmol) a tetrahidrofuran-3-ol (9 g, 102,15 mmol) y trietilamina (21,36 mL, 153,23 mmol) en DCM (300 mL) a TA durante un período de 30 minutos bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a TA durante 1 hora y luego se diluyó con acetato de etilo (400 mL) y se lavó con agua (250 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar el material deseado, que se utilizó sin purificación adicional.
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 2,03 - 2,14 (1H, m), 2,17 - 2,29 (1H, m), 3,21 (3H, s), 3,69 - 3,92 (4H, m), 5,28 - 5,33 (1H, m)

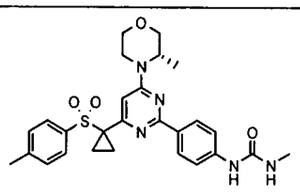
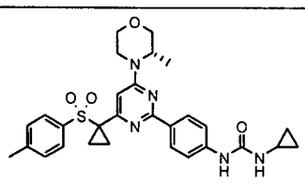
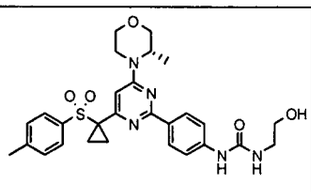
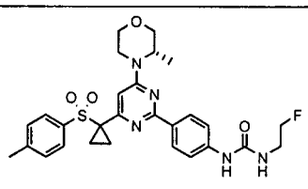
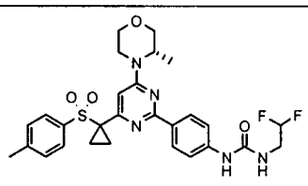
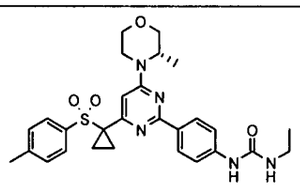
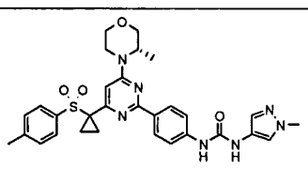
Ejemplo 95

Las siguientes muestras se prepararon calentando una mezcla del carbamato (1 equivalente), trietilamina (4 equivalentes) y la amina (1,2 equivalentes) en NMP (2 mL) a 50°C durante 2 horas. Los compuestos se purificaron mediante HPLC preparativa.

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
95a		1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	560	2,29
95b		1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea	586	2,44
95c		1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	590	2,10
95d		1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	592	2,41
95e		1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea	610	2,54

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
95f		3-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-etilurea	574	2,45
95g		1-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	626	2,29
95h*		1-[4-[4-[1-(3-cloro-4-metilaminofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea	571	2,11
95i*		1-[4-[4-[1-[3-cloro-4-(2-hidroxietilamino)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea	631	1,79
95j*		1-[4-[4-[1-[3-cloro-4-(2-fluoroetilamino)fenil]sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	635	2,30
95k*		1-[4-[4-[1-(3-cloro-4-etilaminofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea	599	2,41

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
95l		3-metil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea	522	2,14
95m		3-ciclopropil-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea	548	2,29
95n		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea	552	1,98
95o		3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea	554	2,28
95p		3-(2,2-difluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea	572	2,40
95q		1-etil-3-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea	536	2,28
95r		1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	588	2,16

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* 4 equivalentes de amina utilizada.

Ejemplo 95a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,59 - 1,64 (2H, m), 1,90 - 1,98 (2H, m), 2,68 (3H, s), 3,12 - 3,23 (1H, m), 3,46 (1H, dd), 3,61 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,15 (1H, d), 4,48 (1H, s), 6,04 (1H, s), 6,67 (1H, s), 7,39 (2H, d), 7,58 - 7,68 (1H, m), 7,73 - 7,83 (3H, m), 7,99 (1H, d), 8,74 (1H, s)

Ejemplo 95b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,37 - 0,44 (2H, m), 0,60 - 0,69 (2H, m), 1,20 (3H, d), 1,60 - 1,64 (2H, m), 1,89 - 1,98 (2H, m), 2,56 - 2,60 (1H, m), 3,11 - 3,23 (1H, m), 3,42 - 3,52 (1H, m), 3,61 (1H, d), 3,75 (1H, d), 3,95 (1H, d), 4,15 (1H, d), 4,49 (1H, s), 6,39 (1H, s), 6,67 (1H, s), 7,40 (2H, d), 7,57 - 7,68 (1H, m), 7,73 - 7,85 (3H, m), 7,92 - 8,03 (1H, m), 8,54 (1H, s)

Ejemplo 95c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,59 - 1,64 (2H, m), 1,91 - 1,96 (2H, m), 3,14 - 3,22 (2H, m), 3,40 - 3,50 (3H, m), 3,61 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,16 (1H, d), 4,48 (1H, s), 4,72 (1H, t), 6,23 (1H, s), 6,67 (1H, s), 7,38 (2H, d), 7,63 (1H, t), 7,75 - 7,84 (3H, m), 7,98 (1H, d), 8,80 (1H, s)

Ejemplo 95d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,59 - 1,65 (2H, m), 1,88 - 1,97 (2H, m), 3,36 - 3,51 (4H, m), 3,62 (1H, d), 3,75 (1H, d), 3,95 (1H, d), 4,12 - 4,23 (1H, m), 4,41 (1H, t), 4,45 - 4,51 (1H, m), 4,53 (1H, t), 6,40 (1H, s), 6,68 (1H, s), 7,39 (2H, d), 7,60 - 7,69 (1H, m), 7,72 - 7,86 (3H, m), 7,99 (1H, d), 8,81 (1H, s)

Ejemplo 95e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,59 - 1,65 (2H, m), 1,89 - 1,97 (2H, m), 3,12 - 3,22 (1H, m), 3,41 - 3,64 (3H, m), 3,75 (1H, d), 3,96 (1H, d), 4,15 (1H, d), 4,49 (1H, s), 5,87 - 6,22 (1H, m), 6,49 (1H, t), 6,68 (1H, s), 7,40 (2H, d), 7,63 (1H, t), 7,77 - 7,86 (3H, m), 7,97 - 8,00 (1H, m), 8,92 (1H, s)

Ejemplo 95f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,07 (3H, t), 1,20 (3H, d), 1,59 - 1,65 (2H, m), 1,90 - 1,98 (2H, m), 3,09 - 3,21 (3H, m), 3,42 - 3,52 (1H, m), 3,61 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,09 - 4,21 (1H, m), 4,44 - 4,53 (1H, m), 6,12 (1H, t), 6,67 (1H, s), 7,39 (2H, d), 7,63 (1H, t), 7,75 - 7,85 (3H, m), 7,99 (1H, d), 8,66 (1H, s)

Ejemplo 95g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,59 - 1,66 (2H, m), 1,91 - 1,99 (2H, m), 3,11 - 3,21 (1H, m), 3,47 (1H, td), 3,62 (1H, d), 3,70 - 3,83 (4H, m), 3,96 (1H, d), 4,17 (1H, d), 4,49 (1H, s), 6,69 (1H, s), 7,38 (1H, s), 7,44 (2H, d), 7,64 (1H, t), 7,75 - 7,85 (3H, m), 7,99 (1H, d), 8,34 (1H, s), 8,84 (1H, s)

Ejemplo 95h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,53 - 1,59 (2H, m), 1,77 - 1,83 (2H, m), 2,63 - 2,67 (3H, m), 2,82 (3H, d), 3,10 - 3,19 (1H, m), 3,46 (1H, dd), 3,61 (1H,

d), 3,75 (1H, d), 3,95 (1H, d), 4,09 (1H, d), 4,39 (1H, s), 6,00 - 6,08 (1H, m), 6,47 (1H, t), 6,59 (1H, s), 6,70 (1H, d), 7,41 (2H, d), 7,48 - 7,57 (2H, m), 7,94 (2H, d), 8,70 (1H, s)

Ejemplo 95i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,53 - 1,60 (2H, m), 1,77 - 1,83 (2H, m), 3,14 - 3,19 (2H, m), 3,25 - 3,32 (2H, m), 3,39 - 3,50 (3H, m), 3,55 - 3,65 (3H, m), 3,75 (1H, d), 3,96 (1H, d), 4,10 (1H, d), 4,38 (1H, s), 4,73 (1H, t), 4,82 (1H, t), 6,15 (1H, t), 6,24 (1H, t), 6,59 (1H, s), 6,84 (1H, d), 7,40 (2H, d), 7,48 (2H, d), 7,54 (1H, d), 7,95 (2H, d), 8,76 (1H, s)

Ejemplo 95j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,52 - 1,60 (2H, m), 1,78 - 1,83 (2H, m), 3,09 - 3,19 (1H, m), 3,35 - 3,49 (4H, m), 3,52 - 3,58 (1H, m), 3,57 - 3,65 (2H, m), 3,74 (1H, d), 3,95 (1H, d), 4,07 (1H, d), 4,37 - 4,44 (2H, m), 4,49 - 4,55 (1H, m), 4,63 (1H, t), 6,38 - 6,50 (2H, m), 6,58 (1H, s), 6,89 (1H, d), 7,40 (2H, d), 7,48 (2H, d), 7,53 (1H, s), 7,96 (2H, d), 8,76 (1H, s)

Ejemplo 95k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06 (3H, t), 1,13 - 1,21 (6H, m), 1,49 - 1,58 (2H, m), 1,78 - 1,82 (2H, m), 3,08 - 3,18 (2H, m), 3,22 - 3,33 (7H, m), 3,46 (1H, dd), 3,61 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,09 (1H, d), 4,39 (1H, s), 6,13 (1H, t), 6,28 (1H, t), 6,59 (1H, s), 6,77 (1H, d), 7,39 (2H, d), 7,46 (2H, d), 7,52 (1H, s), 7,96 (2H, d), 8,61 (1H, s)

Ejemplo 95l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,56 - 1,64 (2H, m), 1,82 - 1,89 (2H, m), 2,40 (3H, s), 2,68 (3H, s), 3,08 - 3,17 (1H, m), 3,45 (1H, td), 3,60 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,10 (1H, d), 4,38 (1H, s), 6,04 (1H, t), 6,61 (1H, s), 7,33 - 7,44 (4H, m), 7,66 (2H, d), 7,82 (2H, d), 8,70 (1H, s)

Ejemplo 95m: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,42 - 0,50 (2H, m), 0,66 - 0,75 (2H, m), 1,23 (3H, d), 1,60 - 1,69 (2H, m), 1,87 - 1,98 (2H, m), 2,46 (3H, s), 2,62 - 2,70 (1H, m), 3,19 (1H, td), 3,46 - 3,57 (1H, m), 3,66 (1H, d), 3,80 (1H, d), 4,01 (1H, d), 4,16 (1H, d), 4,43 (1H, s), 6,46 (1H, s), 6,67 (1H, s), 7,39 - 7,49 (4H, m), 7,71 (2H, d), 7,88 (2H, d), 8,56 (1H, s)

Ejemplo 95n: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,57 - 1,65 (2H, m), 1,83 - 1,90 (2H, m), 2,42 (3H, s), 3,13 - 3,20 (3H, m), 3,40 - 3,50 (3H, m), 3,60 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,09 (1H, d), 4,37 (1H, s), 4,72 (1H, t), 6,22 (1H, t), 6,61 (1H, s), 7,35 - 7,43 (4H, m), 7,66 (2H, d), 7,82 (2H, d), 8,77 (1H, s)

Ejemplo 95o: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,56 - 1,65 (2H, m), 1,81 - 1,90 (2H, m), 2,40 (3H, s), 3,07 - 3,22 (1H, m), 3,36 - 3,50 (3H, m), 3,60 (1H, d), 3,74 (1H, d), 3,96 (1H, d), 4,12 (1H, d), 4,33 - 4,45 (2H, m), 4,53 (1H, t), 6,41 (1H, t), 6,61 (1H, s), 7,34 - 7,43 (4H, m), 7,66 (2H, d), 7,83 (2H, d), 8,77 (1H, s)

Ejemplo 95p: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,56 - 1,65 (2H, m), 1,82 -

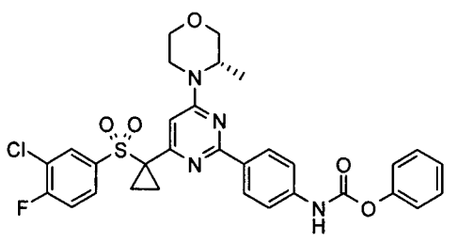
1,91 (2H, m), 2,40 (3H, s), 3,10 - 3,18 (1H, m), 3,41 - 3,65 (4H, m), 3,74 (1H, d), 3,96 (1H, d), 4,09 (1H, d), 4,37 (1H, s), 5,91 - 6,23 (1H, m), 6,50 (1H, t), 6,62 (1H, s), 7,35 - 7,44 (4H, m), 7,66 (2H, d), 7,84 (2H, d), 8,89 (1H, s)

Ejemplo 95q: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,06 (3H, t), 1,17 (3H, d), 1,52 - 1,66 (2H, m), 1,85 - 1,90 (2H, m), 2,40 (3H, s), 3,07 - 3,20 (3H, m), 3,45 (1H, td), 3,60 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,12 (1H, d), 4,37 (1H, s), 6,13 (1H, t), 6,61 (1H, s), 7,35 - 7,44 (4H, m), 7,66 (2H, d), 7,82 (2H, d), 8,62 (1H, s)

Ejemplo 95r: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,57 - 1,66 (2H, m), 1,84 - 1,90 (2H, m), 2,41 (3H, s), 3,08 - 3,18 (1H, m), 3,46 (1H, td), 3,61 (1H, d), 3,72 - 3,83 (4H, m), 3,96 (1H, d), 4,10 (1H, d), 4,37 (1H, s), 6,62 (1H, s), 7,35 - 7,49 (5H, m), 7,66 (2H, d), 7,76 (1H, s), 7,86 (2H, d), 8,35 (1H, s), 8,80 (1H, s)

La preparación de fenil *N*-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato



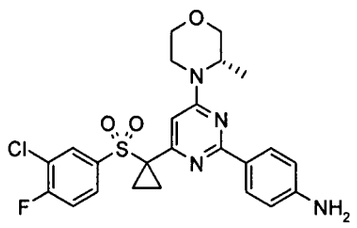
Se agregó hidrogenocarbonato de sodio (0,501 g, 5,96 mmol) a 4-[4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (2 g, 3,98 mmol) en dioxano (30 mL) a 5°C bajo nitrógeno. Luego se agregó fenil cloroformiato (0,749 mL, 5,96 mmol) y la mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con DCM (50 mL) y se lavó con agua (75 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido crema (1,45 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,59 - 1,66 (2H, m), 1,91 - 1,96 (2H, m), 3,12 - 3,24 (1H, m), 3,40 - 3,52 (1H, m), 3,62 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,18 (1H, d), 4,50 (1H, s), 6,74 (1H, s), 7,23 - 7,32 (3H, m), 7,41 - 7,49 (2H, m), 7,54 (2H, d), 7,58 - 7,68 (1H, m), 7,79 - 7,83 (1H, m), 7,88 (2H, d), 7,96 - 8,02 (1H, m), 10,40

(1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 622; HPLC tR = 3,21 min.

4-[4-[1-(3-Cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina

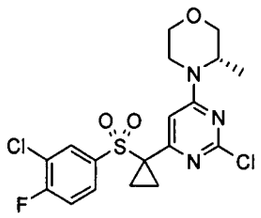


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,242 g, 0,35 mmol) a 2-cloro-4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidina (2,3 g, 5,15 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,411 g, 6,44 mmol) y solución de carbonato de sodio acuoso 2M (3 mL, 6,00 mmol) en una mezcla de disolventes de DMF (5 mL), DME (8 mL), agua (2 mL) y etanol (1,5 mL) a TA. La mezcla resultante se agitó a 90°C, bajo una atmósfera inerte durante 5 horas y luego se dejó a TA durante 16 horas. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó secuencialmente con agua (2 x 100 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 80% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (2,0 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,57 - 1,61 (2H, m), 1,87 - 1,96 (2H, m), 3,14 (1H, td), 3,41 - 3,50 (1H, m), 3,60 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,13 (1H, d), 4,44 (1H, s), 5,52 (1H, d), 6,49 (2H, d), 6,57 (1H, s), 7,57 - 7,68 (3H, m), 7,75 - 7,85 (1H, m), 7,99 (1H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 503; HPLC tR = 2,66 min.

2-Cloro-4-[1-(3-cloro-4-fluorofenil)sulfonilciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina

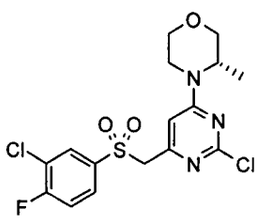


Se agregó solución acuosa de hidróxido de sodio (20 mL, 142,76 mmol) a 2-cloro-4-[(3-cloro-4-fluorofenil)sulfonilmetil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (2,5 g, 5,95 mmol), 1,2-dibromoetano (2,56 mL, 29,74 mmol) y bromuro de tetrabutilamonio (0,192 g, 0,59 mmol) en tolueno (100 mL) a TA bajo una atmósfera de nitrógeno y la mezcla se agitó durante 3 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó con agua (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 100% acetato de etilo en isohexano, para proporcionar el material deseado como una goma incolora (2,3 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 7,98 (1H, d), 1,18 (3H, d), 1,54 - 1,61 (2H, m), 1,84 - 1,91 (2H, m), 3,15 (1H, td), 3,36 - 3,45 (1H, m), 3,55 (1H, d), 3,70 (1H, d), 3,90 (1H, d), 4,08 (1H, s), 4,31 (1H, s), 6,74 (1H, s), 7,62 - 7,71 (1H, m), 7,76 - 7,83 (1H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 446; HPLC tR = 2,56 min.

2-Cloro-4-[(3-cloro-4-fluorofenil)sulfonilmetil]-6-[(3S)-3-metilmorfolin-4-il]pirimidina

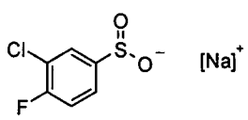


Se agregó 3-cloro-4-fluorobencenosulfinato de sodio (3,52 g, 16,26 mmol) a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (5 g, 14,14 mmol) en acetonitrilo (150 mL) a TA bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 80°C durante 3 horas. La mezcla de reacción se diluyó con acetato de etilo (150 mL) y se lavó con agua (100 mL), la capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 70% acetato de etilo en isohexano, para proporcionar un aceite

incoloro que solidificó en reposo. El sólido bruto se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido blanco (4,0 g).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 3,18 (1H, dd), 3,28 (1H, d), 3,43 (1H, td), 3,58 (1H, d), 3,72 (1H, d), 3,94 (1H, d), 4,21 (1H, s), 4,73 (2H, s), 6,78 (1H, s), 7,66 - 7,74 (1H, m), 7,78 - 7,87 (1H, m), 8,02 (1H, d)
Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 420; HPLC tR = 2,38 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

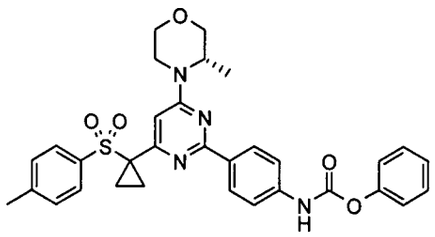
3-cloro-4-fluorobencenosulfinato de sodio



Una solución de sulfito de sodio (8,25 g, 65,49 mmol) en agua (75 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (11,0 g, 130,97 mmol) a la solución agitada y la solución resultante se agitó a 50°C durante 1 hora. Se agregó en porciones cloruro de 3-cloro-4-fluorobenceno-1-sulfonilo (15 g, 65,49 mmol) a la solución y se agitó a 50°C durante 18 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en metanol (300 mL). La suspensión se dejó agitar a TA durante 20 minutos luego se filtró y el filtrado se evaporó para proporcionar el material deseado como un sólido blanco, que se secó al aire durante toda la noche al vacío y se utilizó sin purificación adicional (16,5 g).
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 7,34 (1H, t), 7,40 - 7,46 (1H, m), 7,58 (1H, d)

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]carbamato

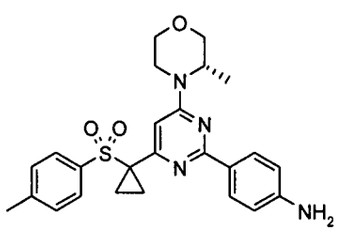


Se agregó hidrogenocarbonato de sodio (0,570 g, 6,78 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]anilina (2,1 g, 4,52 mmol) en dioxano (6 mL) a 5°C bajo una atmósfera de nitrógeno. Luego se agregó fenil cloroformiato (0,852 mL, 6,78 mmol) y la mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con DCM (50 mL) y se lavó con agua (75 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. La goma bruta se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido crema (1,52 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,17 (3H, d), 1,58 - 1,64 (2H, m), 1,85 - 1,91 (2H, m), 2,40 (3H, s), 3,09 - 3,23 (1H, m), 3,41 - 3,51 (1H, m), 3,60 (1H, d), 3,75 (1H, d), 3,96 (1H, d), 4,12 (1H, d), 4,39 (1H, s), 6,65 (1H, s), 7,21 - 7,31 (3H, m), 7,36 - 7,41 (2H, m), 7,42 - 7,48 (2H, m), 7,50 - 7,56 (2H, m), 7,63 - 7,71 (2H, m), 7,89 (2H, d), 10,38 (1H, s)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 535; HPLC tR = 3,1 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidin-2-il]anilina



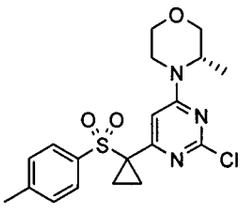
Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,225 g, 0,32 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidina (1,95 g, 4,78 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,362 g, 6,21 mmol) y solución de carbonato de sodio acuoso 2M (3 mL, 6,00 mmol) en una mezcla de disolventes de DMF (5 mL), DME (8 mL), agua (2 mL) y etanol (1,5 mL) a TA. La mezcla resultante se agitó a 90°C durante 5 horas bajo una atmósfera inerte, luego se dejó a TA durante 16 horas. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (2 x 100 mL). La capa

orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 80% acetato de etilo en isohexano, para proporcionar el material bruto que se purificó adicionalmente mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol, para proporcionar el material deseado como un sólido blanco (2,1 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15 (3H, d), 1,54 - 1,63 (2H, m), 1,81 - 1,89 (2H, m), 1,99 (3H, s), 3,11 (1H, td), 3,37 - 3,49 (1H, m), 3,59 (1H, d), 3,73 (1H, d), 3,94 (1H, d), 4,06 (1H, s), 4,32 (1H, s), 5,50 (1H, s), 6,50 (3H, d), 7,38 (2H, d), 7,62 - 7,72 (4H, m)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 465; HPLC tR = 2,48 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(4-metilfenil)sulfonilciclopropil]pirimidina

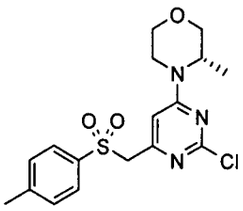


Se agregó solución acuosa de hidróxido de sodio (20 mL, 125,69 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metilfenil)sulfonilmetil]pirimidina (2 g, 5,24 mmol), 1,2-dibromoetano (2,257 mL, 26,19 mmol) y bromuro de tetrabutilamonio (0,169 g, 0,52 mmol) en DCM (100 mL) a TA bajo una atmósfera de nitrógeno luego se agitó durante 3 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó con agua (50 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como una goma incolora (1,9 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,13 (3H, d), 1,52 - 1,56 (2H, m), 1,79 - 1,84 (2H, m), 1,99 (3H, s), 3,12 (1H, td), 3,35 - 3,47 (1H, m), 3,54 (1H, d), 3,71 (1H, d), 3,84 - 3,95 (2H, m), 4,17 (1H, s), 6,63 (1H, s), 7,41 (2H, d), 7,63 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 408; HPLC tR = 2,35 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metilfenil)sulfonilmetil]pirimidina



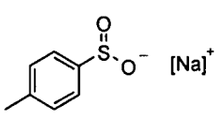
Se agregó 4-metilbencenosulfinato de sodio (2,9 g, 16,28 mmol) a 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina (5 g, 14,14 mmol), en acetonitrilo (150 mL) a TA bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a 80°C durante 3 horas. La mezcla de reacción se diluyó con acetato de etilo (150 mL) y se lavó con agua (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 0 a 40% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido beige (3,10 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,15 (3H, d), 2,41 (3H, s), 3,14 (1H, td), 3,38 - 3,46 (1H, m), 3,56 (1H, d), 3,71 (1H, d), 3,80 - 3,96 (2H, m), 4,13 (1H, s), 4,60 (2H, s), 6,60 (1H, s), 7,43 (2H, d), 7,66 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 382; HPLC tR = 2,16 min.

La preparación de 2-cloro-4-(yodometil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidina se describió anteriormente.

4-metilbencenosulfinato de sodio



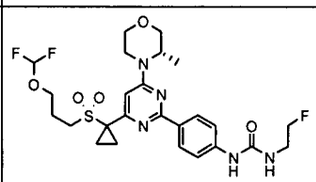
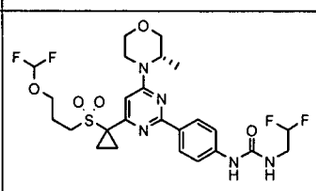
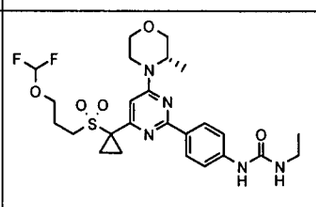
Una solución de sulfito de sodio (9,92 g, 78,68 mmol) en agua (75 mL) se agitó a TA durante 10 minutos. Se agregó bicarbonato de sodio (13,22 g, 157,36 mmol) a la solución agitada. La solución resultante se agitó a 50°C durante 1 hora. Se agregó en porciones cloruro de 4-metilbenceno-1-sulfonilo (15 g, 78,68 mmol) a la solución y se agitó a 50°C durante 18 horas. La mezcla de reacción se evaporó hasta secarse y se disolvió nuevamente en metanol (400 mL). La suspensión se dejó agitar a TA durante 20 minutos y luego se filtró y el filtrado se evaporó para proporcionar el material deseado como un sólido blanco, que se secó al aire durante toda la noche al vacío y se utilizó sin purificación adicional (17,3 g).

915

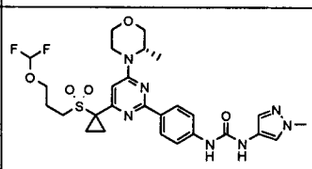
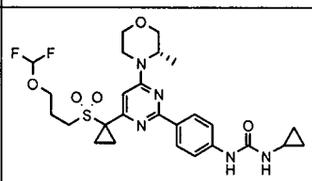
Ejemplo 96

Las siguientes muestras se prepararon calentando una mezcla del carbamato (1 equivalente), trietilamina (4 equivalentes) y la amina (4 equivalentes) en NMP (2 mL) a TA durante 2 – 16 horas. Los compuestos se purificaron mediante HPLC preparativa.

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato (contaminado con fenil *N*-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]propil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato) y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
96a		1-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea	572	2,28
96b.		3-(2,2-difluoroetil)-1-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	590	2,32
96c		1-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-etilurea	554	2,21

1916

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
96d		1-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1-metilpirazol-4-il)urea	606	2,09
96e		3-ciclopropil-1-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]urea	none	

Ejemplo 96a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,54 - 1,59 (2H, m), 1,62 - 1,69 (2H, m), 2,09 - 2,18 (2H, m), 3,17 - 3,25 (1H, m), 3,35 - 3,42 (1H, m), 3,43 - 3,52 (2H, m), 3,56 - 3,66 (3H, m), 3,78 (1H, d), 3,94 - 4,02 (3H, m), 4,21 (1H, d), 4,42 (1H, t), 4,52 - 4,60 (2H, m), 6,43 (1H, t), 6,47 - 6,89 (1H, m), 6,77 (1H, s), 7,49 (2H, d), 8,20 (2H, d), 8,81 (1H, s)

Ejemplo 96b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,23 (3H, d), 1,53 - 1,60 (2H, m), 1,62 - 1,69 (2H, m), 2,08 - 2,17 (2H, m), 3,16 - 3,25 (1H, m), 3,43 - 3,66 (6H, m), 3,76 (1H, d), 3,94 - 4,00 (3H, m), 4,22 (1H, d), 4,56 (1H, s), 5,91 - 6,23 (1H, m), 6,43 - 6,88 (1H, m), 6,52 (1H, t), 6,77 (1H, s), 7,50 (2H, d), 8,21 (2H, d), 8,93 (1H, s)

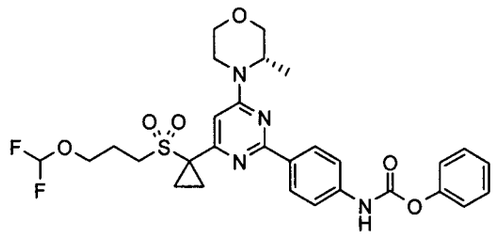
Ejemplo 96c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,08 (3H, t), 1,23 (3H, d), 1,54 - 1,60 (2H, m), 1,63 - 1,69 (2H, m), 2,09 - 2,18 (2H, m), 3,07 - 3,25 (3H, m), 3,48 (1H, td), 3,55 - 3,66 (3H, m), 3,76 (1H, d), 3,93 - 4,01 (3H, m), 4,21 (1H, d), 4,56 (1H, s), 6,15 (1H, t), 6,42 - 6,88 (1H, m), 6,76 (1H, s), 7,49 (2H, d), 8,18 (2H, d), 8,66 (1H, s)

Ejemplo 96d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,55 - 1,60 (2H, m), 1,63 - 1,69 (2H, m), 2,09 - 2,18 (2H, m), 3,18 - 3,26 (1H, m), 3,44 - 3,53 (1H, m), 3,55 - 3,67 (3H, m), 3,72 - 3,80 (4H, m), 3,93 - 4,03 (3H, m), 4,22 (1H, d), 4,57 (1H, s), 6,43 - 6,86 (1H, m), 6,78 (1H, s), 7,38 (1H, s), 7,54 (2H, d), 7,77 (1H, s), 8,22 (2H, d), 8,37 (1H, s), 8,85 (1H, s)

Ejemplo 96e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,38-0,40 (2H,m), 0,61-0,64 (2H,m), 1,20-1,22 (3H,d), 1,51-1,53 (2H,m), 1,61-1,64 (2H,m), 2,18-2,24 (2H,m), 2,52-2,58 (1H,m), 3,18-3,20 (1H,dd), 3,55-3,68 (3H,m), 3,72-3,78 (1H,m), 3,90-3,95 (3H,m), 4,20 (1H,s), 4,55 (1H,s), 6,40 (1H,s), 6,60 (1H,s), 7,45 (2H,d), 8,18 (2H,d), 8,54 (1H,s)

La preparación de fenil *N*-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato

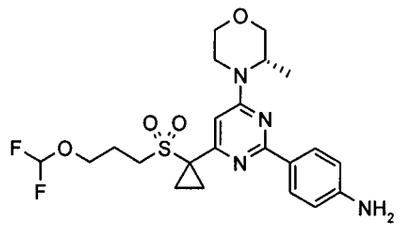


Se agregó hidrogenocarbonato de sodio (65,3 mg, 0,78 mmol) a 4-[4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (contaminado con 4-[4-[1-[3-(difluorometoxi)propilsulfonil]propil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina) (250 mg, 0,52 mmol) en dioxano (6 mL) a 5°C bajo una atmósfera de nitrógeno. Se agregó fenil cloroformiato (0,098 mL, 0,78 mmol) y la mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con DCM (50 mL), los orgánicos se secaron sobre Na_2SO_4, se filtraron y se evaporaron para proporcionar un producto bruto. El material bruto se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado (contaminado con fenil *N*-[4-[4-[1-[3-(difluorometoxi)propilsulfonil]propil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]carbamato) como un sólido crema (200 mg). El material se utilizó sin purificación adicional.

Espectro de NMR: ninguno

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 604; HPLC tR = 2,97 min.

4-[4-[1-[3-(Difluorometoxi)propilsulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina



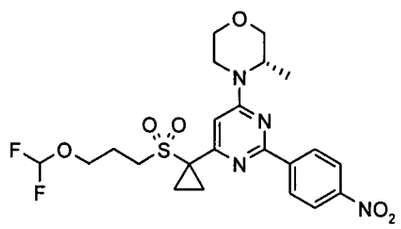
Se agregó 5% paladio sobre carbón (400 mg, 3,6 mmol) a 4-[1-[3-(difluorometoxi)propilsulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]-2-(4-nitrofenil)pirimidina (2 g, 3,90 mmol) en acetato de etilo (200 mL) y metanol (30 mL) a TA. El matraz se vació y la atmósfera se reemplazó primero con nitrógeno y luego hidrógeno y la mezcla se dejó agitando bajo hidrógeno a TA durante 36 horas. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 30 a 90% acetato de etilo en isohexano, para proporcionar un sólido blanco (1,7 g) que pareció ser el material deseado (~30%) contaminado con 4-[4-[1-[3-(difluorometoxi)propilsulfonil]propil]-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-2-il]anilina (~60%). El material se utilizó sin purificación adicional.

Espectro de NMR: ninguno

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 483; HPLC tR = 1,76 min.

Espectro de LCMS: (4-[4-[1-[3-(difluorometoxi)propilsulfonil]propil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]anilina) m/z (ESI+)$(M+H)^+$ = 485; HPLC tR = 2,0 min.

4-[1-[3-(Difluorometoxi)propilsulfonil]ciclopropil]-6-[(3*S*)-3-metilmorfolin-4-il]-2-(4-nitrofenil)pirimidina



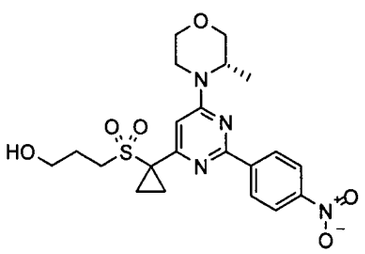
Una solución de ácido 2,2-difluoro-2-(fluorosulfonil)acético (4,56 mL, 44,11 mmol) en acetonitrilo (25 mL) se agregó gota a gota durante 1,5 horas hasta proporcionar una solución agitada de 3-[1-[6-[(3*S*)-3-metilmorfolin-4-il]-2-(4-nitrofenil)pirimidin-4-il]ciclopropil]sulfonilpropan-1-ol (3,4g, 7,35 mmol) y yoduro de cobre(I) (280 mg, 1,47 mmol) en acetonitrilo (100 mL) a 55°C bajo una atmósfera de nitrógeno. La mezcla se agitó a 55°C durante 1 hora más y luego se diluyó con acetato de etilo (300 mL) y se lavó con agua

(100 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (2,0 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,26 (3H, d), 1,59 - 1,64 (2H, m), 1,67 - 1,72 (2H, m), 2,11 - 2,17 (2H, m), 3,22 - 3,28 (1H, m), 3,46 - 3,59 (3H, m), 3,65 (1H, d), 3,78 (1H, d), 3,93 - 4,01 (3H, m), 4,25 (1H, s), 4,61 (1H, s), 6,96 (1H, s), 8,33 (2H, d), 8,55 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 513; HPLC tR = 2,87 min.

3-[1-[6-[(3*S*)-3-Metilmorfolin-4-il]-2-(4-nitrofenil)pirimidin-4-il]ciclopropil]sulfonilpropan-1-ol



Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,636 g, 0,91 mmol) a 3-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropoxi-tri(propan-2-il)silano (7,2 g, 13,53 mmol), solución de carbonato de sodio acuoso 2M (15 mL, 30,00 mmol) y 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)nitrobenceno (6,74 g, 27,06 mmol) en DME (100 mL) y agua (5 mL) a TA. La mezcla se agitó a 90°C durante 16 horas bajo una atmósfera de nitrógeno y luego se dejó enfriar. La mezcla de reacción se diluyó con acetato de etilo (400 mL) y se lavó secuencialmente con agua (100 mL) y luego agua adicional (200 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se disolvió en DCM y luego se agregó fluoruro de tetrabutilamonio (67,6 mL, 67,64 mmol) y se dejó agitando durante 1 hora. Se agregó una solución saturada acuosa de cloruro de amonio, los orgánicos se separaron y se secaron sobre Na_2SO_4, se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 100% acetato de etilo en isohexano, para proporcionar el material bruto que se purificó adicionalmente mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol, para proporcionar el material

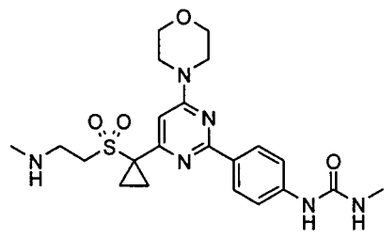
deseado como un sólido marrón (3,60 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,26 (3H, d), 1,56 - 1,63 (2H, m), 1,66 - 1,70 (2H, m), 1,91 - 1,98 (2H, m), 3,22 - 3,29 (3H, m), 3,47 - 3,57 (3H, m), 3,65 (1H, d), 3,78 (1H, d), 3,99 (1H, dd), 4,25 (1H, d), 4,60 (1H, s), 4,72 (1H, t), 6,96 (1H, s), 8,33 (2H, d), 8,58 (2H, d)

Espectro de LCMS: m/z (ESI+)$(M+H)^+$ = 463; HPLC tR = 2,37 min.

La preparación de 3-[1-[2-cloro-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropoxi-tri(propan-2-il)silano se describió anteriormente.

Ejemplo 97: 3-Metil-1-[4-[4-[1-(2-metilaminoetilsulfonil)ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]urea



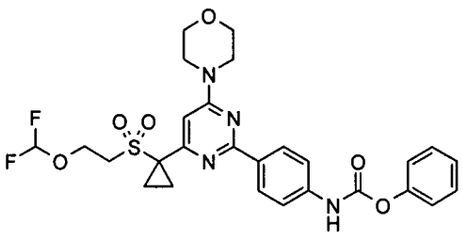
Se agregó metilamina (2 M en THF, 4 equivalentes) a fenil *N*-[4-[4-[1-[2-(difluorometoxi)etilsulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato en NMP y la solución resultante se agitó a TA durante 30 minutos y luego se purificó mediante HPLC preparativa para proporcionar el material deseado (0,012 g)

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,52 - 1,57 (2H, m), 1,62 - 1,66 (2H, m), 2,67 (3H, d), 2,92 - 3,01 (2H, m), 3,31 (3H, s), 3,55 - 3,64 (2H, m), 3,72 (8H, s), 6,06 (1H, t), 6,81 (1H, s), 7,50 (2H, d), 8,21 (2H, d), 8,75 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 475; HPLC tR = 1,65 min.

La preparación de fenil *N*-[4-[4-[1-[2-(difluorometoxi)etilsulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[1-[2-(difluorometoxi)etilsulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]fenil]carbamato

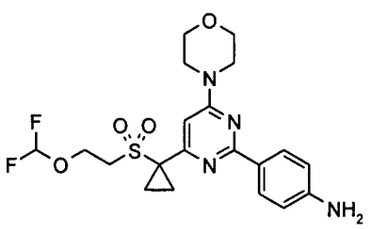


Se agregó hidrogenocarbonato de sodio (1,5 equivalentes) a 4-[4-[1-[2-(difluorometoxi)etilsulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]anilina (1 equivalente) en dioxano a 5°C bajo nitrógeno. Luego se agregó fenil cloroformiato (1,5 equivalentes). La mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con DCM, los orgánicos se secaron sobre Na_2SO_4, se filtraron y se evaporaron para proporcionar un producto bruto. La goma bruta se trituró con una mezcla de acetato de etilo e isohexano para proporcionar el material deseado como un sólido crema.

Espectro de NMR: ninguno

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 575; HPLC tR = 2,8 min.

4-[4-[1-[2-(Difluorometoxi)etilsulfonil]ciclopropil]-6-morfolin-4-ilpirimidin-2-il]anilina

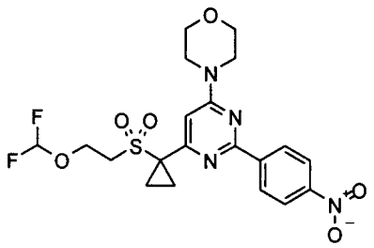


Se agregó paladio, 5% sobre carbón (6,59 mg, 0,06 mmol) a 4-[1-[2-(difluorometoxi)etilsulfonil]ciclopropil]-6-morfolin-4-il-2-(4-nitrofenil)pirimidina (150 mg, 0,31 mmol), en acetato de etilo (20 mL) y metanol (3 mL) a TA y se dejó agitando bajo una atmósfera de hidrógeno durante 24 horas. La mezcla se filtró a través de celite® y el filtrado se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 70% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (90 mg).

Espectro de NMR: ninguno

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 455; HPLC tR = 2,2 min.

4-[1-[2-(Difluorometoxi)etilsulfonil]ciclopropil]-6-morfolin-4-il-2-(4-nitrofenil)pirimidina

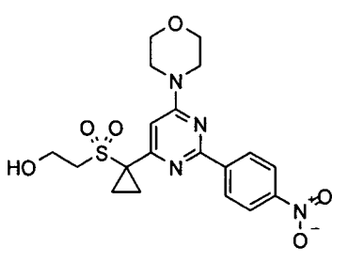


Una solución de ácido 2,2-difluoro-2-(fluorosulfonil) acético (0,856 mL, 8,29 mmol) en acetonitrilo (4 mL) se agregó gota a gota durante 1 hora hasta proporcionar una solución agitada de 2-[1-[6-morfolin-4-il-2-(4-nitrofenil)pirimidin-4-il]ciclopropil]sulfoniletanol (480 mg, 1,10 mmol) y yoduro de cobre(I) (742 mgl, 0,22 mmol) en acetonitrilo (15 mL) a 55°C bajo una atmósfera de nitrógeno. La mezcla se agitó a 55°C durante 90 minutos, se dejó enfriar y se diluyó con acetato de etilo (300 mL) y se lavó con agua (100 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (195 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,59 - 1,68 (2H, m), 1,70 - 1,78 (2H, m), 3,70 - 3,81 (8H, m), 3,88 - 3,96 (2H, m), 4,28 - 4,35 (2H, m), 7,01 (1H, s), 8,33 (2H, d), 8,56 (2H, d)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 485; HPLC tR = 2,73 min.

2-[1-[6-Mrpholin-4-il-2-(4-nitrofenil)pirimidin-4-il]ciclopropil]sulfoniletanol



Se agregó cloruro de bis(trifenilfosfina)paladio(II) (84 mg, 0,12 mmol) a 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfoniletoxi-tri(propan-2-il)silano (900 mg, 1,79 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)nitrobenceno (889 mg, 3,57 mmol) y solución acuosa de carbonato de sodio 2M (3 mL, 6,00 mmol) en una mezcla de disolventes de DME (25 mL) y agua (1 mL). La mezcla se agitó a 90°C durante 18 horas bajo una atmósfera inerte. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó con

agua (2 x 100 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se disolvió en DCM y luego se agregó solución 1M de fluoruro de tetrabutilamonio (8,93 mL, 8,93 mmol) y se dejó agitando 1 hora. Se agregó una solución saturada acuosa de cloruro de amonio, las capas se separaron y los orgánicos se secaron sobre Na_2SO_4, se filtraron y se evaporaron. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 70% acetato de etilo en isohexano, para proporcionar un material que se purificó adicionalmente mediante cromatografía de intercambio iónico utilizando una columna SCX, eluyendo con amoníaco 7M en metanol y finalmente se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido beige (670 mg).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,53 - 1,62 (2H, m), 1,65 - 1,73 (2H, m), 3,56 - 3,67 (2H, m), 3,66 - 3,82 (8H, m), 3,80 - 3,97 (2H, m), 5,01 (1H, t), 7,01 (1H, s), 8,34 (2H, d), 8,57 (2H, d)

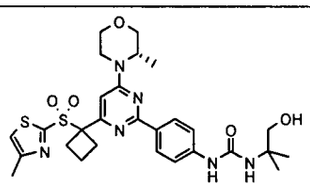
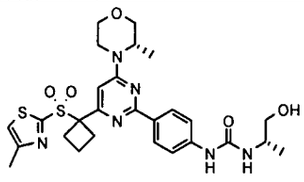
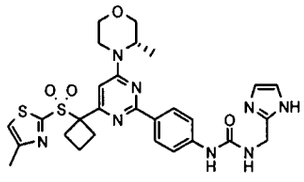
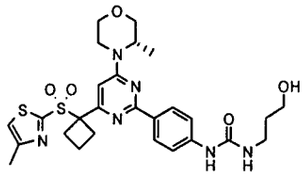
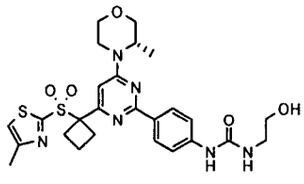
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 435; HPLC tR = 2,18 min.

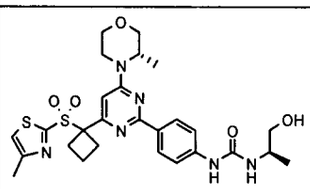
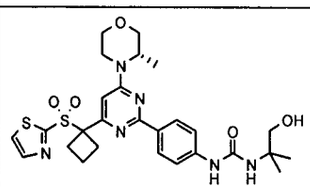
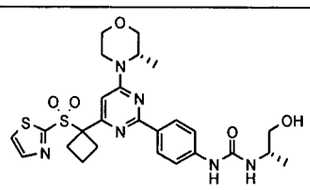
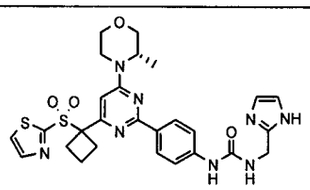
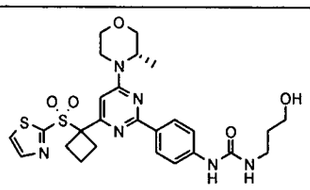
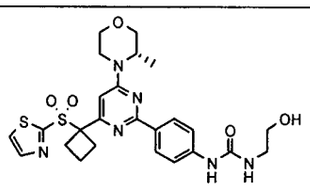
La preparación de 2-[1-(2-cloro-6-morfolin-4-ilpirimidin-4-il)ciclopropil]sulfoniletoxi-tri(propan-2-il)silano se describió anteriormente.

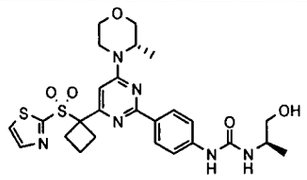
Ejemplo 98

Las siguientes muestras se prepararon calentando una mezcla del carbamato (1 equivalente), trietilamina (4 equivalentes) y la amina (4 equivalentes) en NMP (2 mL) a 50°C durante 2 horas. Los compuestos se purificaron mediante HPLC preparativa.

Los siguientes compuestos se prepararon en forma análoga a partir de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]carbamato o fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]carbamato y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
98a		3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea	601	2,49
98b		3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea	587	2,25
98c		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea	609	2,22
98d		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea	587	2,18
98e		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea	573	2,14

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
98f		3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea	587	2,24
98g		3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea	587	2,41
98h		3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea	573	2,20
98i		3-(1H-imidazol-2-ilmetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea	595	2,17
98j		3-(3-hidroxipropil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea	573	2,13
98k		3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea	559	2,09

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
98l		3-[(2R)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea	573	2,18

Ejemplo 98a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,24 (6H, s), 1,83 - 2,01 (1H, m), 2,12 - 2,20 (1H, m), 2,37 (3H, s), 2,83 - 2,92 (2H, m), 3,10 - 3,22 (4H, m), 3,36 - 3,41 (1H, m), 3,49 (1H, td), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,13 (1H, d), 4,48 (1H, s), 4,95 (1H, t), 5,99 (1H, s), 6,54 (1H, s), 7,36 (2H, d), 7,68 (1H, s), 7,86 (2H, d), 8,71 (1H, s)

Ejemplo 98b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,08 (3H, d), 1,21 (3H, d), 1,88 - 1,99 (1H, m), 2,12 - 2,21 (1H, m), 2,82 - 2,92 (2H, m), 3,10 - 3,23 (2H, m), 3,31 (3H, s), 3,32 - 3,42 (3H, m), 3,44 - 3,54 (1H, m), 3,61 - 3,78 (3H, m), 3,97 (1H, d), 4,09 - 4,17 (1H, m), 4,49 (1H, s), 4,78 (1H, t), 6,08 (1H, d), 6,54 (1H, s), 7,39 (2H, d), 7,68 (1H, s), 7,87 (2H, d), 8,68 (1H, s)

Ejemplo 98c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,89 - 1,99 (1H, m), 2,11 - 2,20 (1H, m), 2,37 (3H, s), 2,85 - 2,95 (2H, m), 3,10 - 3,22 (3H, m), 3,43 - 3,54 (1H, m), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,14 (1H, d), 4,33 (2H, s), 4,50 (1H, s), 6,53 - 6,63 (2H, m), 6,93 - 7,05 (1H, m), 7,43 (2H, d), 7,68 (1H, s), 7,85 - 7,93 (2H, m), 8,90 (1H, s)

Ejemplo 98d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,56 - 1,63 (2H, m), 1,86 - 1,97 (2H, m), 2,12 - 2,22 (2H, m), 2,77 - 2,92 (2H, m), 3,13 - 3,22 (3H, m), 3,25 - 3,34 (2H, m), 3,43 - 3,52 (3H, m), 3,64 (1H, d), 3,72 - 3,80 (1H, m), 3,97 (1H, d), 4,13 (1H, d), 4,44 - 4,53 (2H, m), 6,18 (1H, t), 6,54 (1H, s), 7,41 (2H, d), 7,68 (1H, s), 7,87 (2H, d), 8,68 (1H, s)

Ejemplo 98e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,87 - 1,97 (1H, m), 2,15 - 2,21 (1H, m), 2,37 (3H, s), 2,79 - 2,94 (2H, m), 3,12 - 3,21 (3H, m), 3,27 - 3,34 (2H, m), 3,42 - 3,52 (3H, m), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,13 (1H, d), 4,49 (1H, s), 4,72 (1H, t), 6,24 (1H, t), 6,54 (1H, s), 7,40 (2H, d), 7,68 (1H, s), 7,87 (2H, d), 8,78 (1H, s)

Ejemplo 98f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,08 (3H, d), 1,21 (3H, d), 1,87 - 1,99 (1H, m), 2,12 - 2,23 (1H, m), 2,37 (3H, s), 2,83 - 2,92 (2H, m), 3,12 - 3,23 (4H, m), 3,34 -

3,41 (1H, m), 3,45 - 3,52 (1H, m), 3,64 (1H, d), 3,75 (1H, d), 3,97 (1H, d), 4,13 (1H, d), 4,50 (1H, s), 4,78 (1H, t), 6,05 - 6,10 (1H, m), 6,54 (1H, s), 7,40 (2H, d), 7,68 (1H, s), 7,87 (2H, d), 8,68 (1H, s)

Ejemplo 98g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,25 (6H, s), 1,90 - 1,99 (1H, m), 2,14 - 2,21 (1H, m), 2,84 - 2,93 (2H, m), 3,17 - 3,25 (2H, m), 3,29 - 3,33 (1H, m), 3,45 - 3,52 (1H, m), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,13 (1H, d), 4,48 (1H, s), 4,95 (1H, t), 5,99 (1H, s), 6,53 (1H, s), 7,35 (2H, d), 7,83 (2H, d), 8,15 (1H, s), 8,70 (1H, s)

Ejemplo 98h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,08 (3H, d), 1,20 (3H, d), 1,91 - 2,00 (1H, m), 2,13 - 2,22 (1H, m), 2,85 - 2,95 (2H, m), 3,14 - 3,21 (2H, m), 3,30 - 3,42 (4H, m), 3,44 - 3,52 (1H, m), 3,64 - 3,78 (2H, m), 3,96 (1H, d), 4,13 (1H, d), 4,49 (1H, s), 4,78 (1H, t), 6,06 - 6,13 (1H, m), 6,53 (1H, s), 7,38 (2H, d), 7,85 (2H, d), 8,14 (1H, s), 8,67 (1H, s)

Ejemplo 98i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,93 - 2,00 (1H, m), 2,13 - 2,20 (1H, m), 2,83 - 2,93 (2H, m), 3,14 - 3,24 (3H, m), 3,43 - 3,53 (1H, m), 3,64 (1H, d), 3,76 (1H, d), 3,96 (1H, d), 4,15 (1H, d), 4,32 (2H, s), 4,48 (1H, s), 6,54 (1H, s), 6,63 (1H, t), 6,93 (1H, s), 7,42 (2H, d), 7,87 (2H, d), 8,14 (1H, s), 8,90 (1H, s)

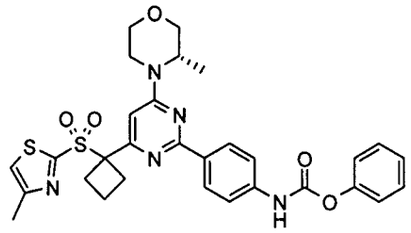
Ejemplo 98j: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,56 - 1,63 (2H, m), 1,88 - 2,01 (1H, m), 2,09 - 2,22 (1H, m), 2,84 - 2,94 (2H, m), 3,12 - 3,24 (5H, m), 3,43 - 3,54 (3H, m), 3,65 (1H, d), 3,76 (1H, d), 3,95 (1H, d), 4,06 - 4,20 (1H, m), 4,46 - 4,51 (1H, m), 6,19 (1H, t), 6,53 (1H, s), 7,39 (2H, d), 7,85 (2H, d), 8,15 (1H, s), 8,67 (1H, s)

Ejemplo 98k: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,20 (3H, d), 1,90 - 2,00 (1H, m), 2,12 - 2,22 (1H, m), 2,84 - 2,94 (2H, m), 3,14 - 3,22 (3H, m), 3,25 - 3,34 (2H, m), 3,39 - 3,52 (3H, m), 3,63 (1H, d), 3,76 (1H, d), 3,96 (1H, d), 4,13 (1H, d), 4,48 (1H, s), 4,72 (1H, t), 6,24 (1H, t), 6,53 (1H, s), 7,39 (2H, d), 7,85 (2H, d), 8,15 (1H, s), 8,76 (1H, s)

Ejemplo 98l: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,08 (3H, d), 1,20 (3H, d), 1,89 - 1,98 (1H, m), 2,12 - 2,23 (1H, m), 2,80 - 2,93 (2H, m), 3,14 - 3,24 (3H, m), 3,30 - 3,40 (2H, m), 3,45 - 3,53 (1H, m), 3,60 - 3,77 (3H, m), 3,96 (1H, d), 4,13 (1H, d), 4,49 (1H, s), 4,78 (1H, t), 6,08 (1H, d), 6,53 (1H, s), 7,38 (2H, d), 7,85 (2H, d), 8,15 (1H, s), 8,67 (1H, s)

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]carbamato se describe a continuación.

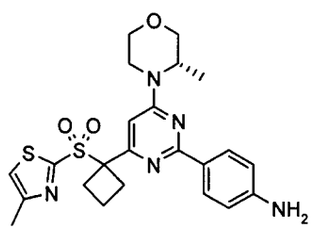
Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]carbamato



Se agregó hidrogenocarbonato de sodio (0,311 g, 3,71 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]anilina (1,2 g, 2,47 mmol) en dioxano (30 mL) a 5°C bajo nitrógeno. Luego se agregó fenil cloroformiato (0,466 mL, 3,71 mmol) y la mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL), se lavó con agua (75 mL) y la capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. La goma bruta se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido crema (1,2 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,88 - 2,00 (1H, m), 2,10 - 2,21 (1H, m), 2,36 (3H, s), 2,83 - 2,95 (2H, m), 3,10 - 3,24 (3H, m), 3,44 - 3,53 (1H, m), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,15 (1H, d), 4,52 (1H, s), 6,59 (1H, s), 7,21 - 7,32 (3H, m), 7,39 - 7,47 (2H, m), 7,55 (2H, d), 7,68 (1H, s), 7,97 (2H, d), 10,39 (1H, s)
Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 606; HPLC tR = 3,12 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]anilina



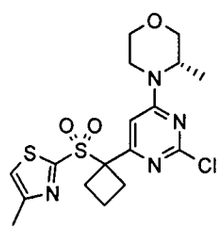
Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,115 g, 0,16 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidina (1,4 g, 3,26 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1,073 g, 4,90 mmol) y solución acuosa de carbonato sodio 2M (5 mL, 10,00 mmol) en una mezcla de disolventes de DMF (6 mL), DME (12 mL), etanol (3 mL) y agua (3,5 mL) y la mezcla resultante se agitó a 95°C durante 5 horas bajo una atmósfera inerte. La mezcla de reacción se diluyó con acetato de etilo (250 mL) y se lavó con agua (2 x 150 mL). La capa orgánica se secó sobre Na_2SO_4, se

filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido beige (1,17 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,19 (3H, d), 1,92 (1H, m), 1,99 (1H, s), 2,10 - 2,18 (1H, m), 2,39 (3H, s), 2,80 - 2,91 (2H, m), 3,09 - 3,24 (2H, m), 3,47 (1H, td), 3,62 (1H, d), 3,75 (1H, d), 3,95 (1H, d), 4,09 (1H, d), 4,45 (1H, s), 5,50 (2H, s), 6,43 (1H, s), 6,54 (2H, d), 7,61 - 7,80 (3H, m)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 486; HPLC tR = 2,51 min.

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidina



Se agregó bromuro de tetrabutilamonio (0,912 g, 2,83 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina (11 g, 28,29 mmol), 1,3-dibromopropano (17,23 mL, 169,71 mmol) y solución de hidróxido de sodio (50% p/p) (30 mL) en tolueno (200 mL) y la mezcla resultante se agitó a 35°C durante 2,5 horas bajo una atmósfera de nitrógeno. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 10 a 50% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (1,7 g).

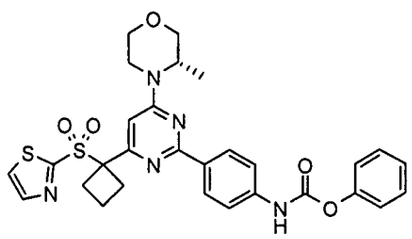
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 7,88 (1H, s), 1,18 (3H, d), 1,85 - 1,97 (1H, m), 2,04 - 2,18 (1H, m), 2,70 - 2,85 (2H, m), 3,00 - 3,21 (3H, m), 3,29 (3H, s), 3,37 - 3,49 (1H, m), 3,57 (1H, d), 3,71 (1H, d), 3,86 - 4,01 (2H, m), 4,34 (1H, s), 6,59 (1H, s) 7,91(1H,s).

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 429; HPLC tR = 2,36 min.

La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[(4-metil-1,3-tiazol-2-il)sulfonilmetil]pirimidina se describió anteriormente.

La preparación de fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]carbamato se describe a continuación.

Fenil *N*-[4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]carbamato

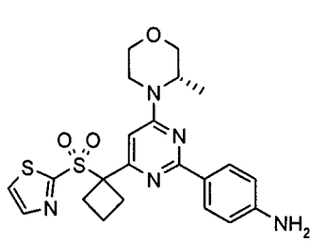


Se agregó hidrogenocarbonato de sodio (0,267 g, 3,18 mmol) a 4-[4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]anilina (1 g, 2,12 mmol) en dioxano (30 mL) a 5°C bajo nitrógeno. Luego se agregó fenil cloroformiato (0,4 mL, 3,18 mmol). La mezcla resultante se agitó a TA durante 2 horas. La mezcla de reacción se diluyó con acetato de etilo (100 mL) y se lavó con agua (75 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. La goma bruta se trituró con una mezcla de éter dietílico e isohexano para proporcionar el material deseado como un sólido crema (0,80 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,21 (3H, d), 1,89 - 2,01 (1H, m), 2,12 - 2,22 (1H, m), 2,84 - 2,97 (2H, m), 3,11 - 3,26 (3H, m), 3,44 - 3,54 (1H, m), 3,64 (1H, d), 3,76 (1H, d), 3,97 (1H, d), 4,15 (1H, d), 4,50 (1H, s), 6,57 (1H, s), 7,15 - 7,35 (3H, m), 7,38 - 7,48 (2H, m), 7,49 - 7,60 (2H, m), 8,15 (2H, s), 10,39 (1H, s)

Espectro de LCMS: m/z (ESI+) $(M+H)^+$ = 592; HPLC tR = 3,06 min.

4-[4-[(3*S*)-3-Metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]anilina

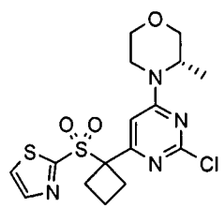


Se agregó cloruro de bis(trifenilfosfina)paladio(II) (0,093 g, 0,13 mmol) a 2-cloro-4-[(3*S*)-3-

metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidina (1,1 g, 2,65 mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (0,871 g, 3,98 mmol) y solución de carbonato de sodio acuoso 2M (5 mL, 10,00 mmol) en una mezcla de disolventes de DMF (6 mL), DME (12 mL), etanol (3 mL) y agua (3,5 mL) y la mezcla resultante se agitó a 95°C durante 5 horas bajo una atmósfera inerte. La mezcla de reacción se diluyó con acetato de etilo (250 mL) y se lavó con agua (2 x 150 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 70% acetato de etilo en isohexano, para proporcionar el material deseado como un sólido amarillo (0,99 g).

Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,18 (3H, d), 1,88 - 1,96 (1H, m), 2,11 - 2,21 (1H, m), 2,82 - 2,91 (2H, m), 3,05 - 3,23 (3H, m), 3,47 (1H, td), 3,62 (1H, d), 3,74 (1H, d), 3,95 (1H, d), 4,10 (1H, s), 4,44 (1H, s), 5,50 (2H, s), 6,42 (1H, s), 6,51 (2H, d), 7,70 (2H, d), 8,15 (2H, s)

2-Cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidina



Se agregó bromuro de tetrabutilamonio (0,559 g, 1,73 mmol) a 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1,3-tiazol-2-ilsulfonilmetil)pirimidina (6,5 g, 17,34 mmol), 1,3-dibromopropano (10,56 mL, 104,04 mmol) e hidróxido de sodio (50% p/p) (10 mL) en tolueno (20 mL) y la mezcla resultante se agitó a 70°C durante 30 minutos. La mezcla de reacción se diluyó con acetato de etilo (200 mL) y se lavó con agua (100 mL). La capa orgánica se secó sobre $MgSO_4$, se filtró y se evaporó para proporcionar un producto bruto. El producto bruto se purificó mediante cromatografía de sílice instantánea, gradiente de elución de 20 a 60% acetato de etilo en isohexano, para proporcionar el material deseado como una goma amarilla (1,0 g).

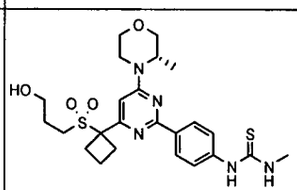
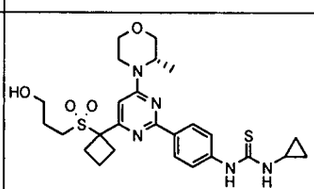
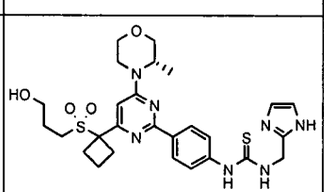
Espectro de NMR: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,86 - 1,97 (1H, m), 2,07 - 2,18 (1H, m), 2,72 - 2,84 (2H, m), 3,04 - 3,19 (3H, m), 3,42 (1H, td), 3,57 (1H, d), 3,70 (1H, d), 3,89 - 3,99 (2H, m), 4,33 (1H, s), 6,60 (1H, s), 8,19 (1H, d), 8,30 (1H, d)

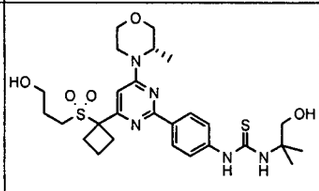
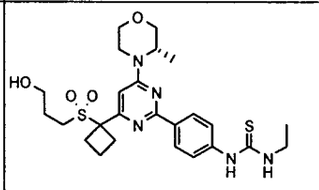
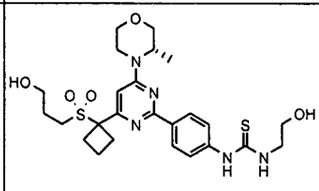
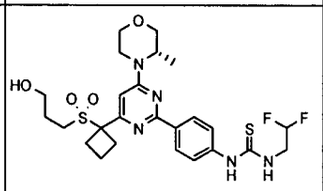
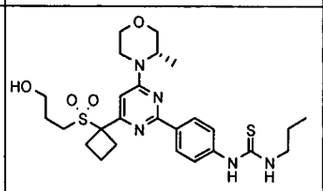
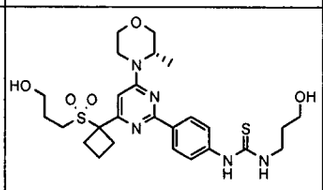
La preparación de 2-cloro-4-[(3*S*)-3-metilmorfolin-4-il]-6-(1,3-tiazol-2-ilsulfonilmetil)pirimidina se describió anteriormente.

Ejemplo 99

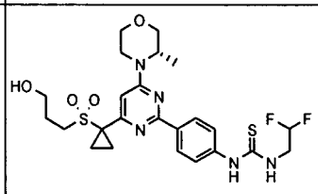
Las siguientes muestras se prepararon calentando una mezcla de la anilina (1 equivalente) y 1,1 tiocarbonildiimidazol (1,2 equivalentes) en una mezcla de DCM:THF (2:1) a TA durante 30 minutos y luego agregando la amina (5 equivalentes) y agitando a 50°C durante 2 horas. Los compuestos se purificaron mediante HPLC preparativa.

Los siguientes compuestos se prepararon en forma análoga a partir de 3-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclobutil]sulfonilpropan-1-ol o 3-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropan-1-ol y la amina apropiada.

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
99a		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea	520	1,92
99b		3-ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	546	2,07
99c		1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)tiourea	586	1,83

Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
99d		3-(1-hidroxi-2-metilpropan-2-il)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	578	2,02
99e		1-etil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	534	2,07
99f		3-(2-hidroxietil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	550	1,75
99g		3-(2,2-difluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	570	2,21
99h		3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-1-propiltiourea	548	2,38
99i		3-(3-hidroxipropil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	564	1,91

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Ejemplo	Estructura	NOMBRE	LCMS MH+	Tiempo de retención (min)
99j		3-(2,2-difluoroetil)-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea	556	2,06

Ejemplo 99a: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,73 - 1,81 (2H, m), 1,88 - 1,97 (1H, m), 2,03 - 2,10 (1H, m), 2,76 - 2,87 (2H, m), 2,89 - 3,05 (7H, m), 3,19 - 3,26 (1H, m), 3,36 - 3,41 (2H, m), 3,46 - 3,55 (1H, m), 3,66 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,23 (1H, d), 4,52 - 4,61 (2H, m), 6,76 (1H, s), 7,55 (2H, d), 7,85 (1H, s), 8,28 (2H, d), 9,73 (1H, s)

Ejemplo 99b: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 0,56 - 0,64 (2H, m), 0,73 - 0,80 (2H, m), 1,25 (3H, d), 1,72 - 1,81 (2H, m), 1,88 - 1,96 (1H, m), 2,03 - 2,10 (1H, m), 2,80 - 3,04 (6H, m), 3,17 - 3,26 (1H, m), 3,34 - 3,41 (2H, m), 3,45 - 3,57 (1H, m), 3,66 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,23 (1H, d), 4,49 - 4,64 (2H, m), 6,76 (1H, s), 7,59 - 7,66 (2H, m), 7,96 (1H, s), 8,28 (2H, d), 9,51 (1H, s)

Ejemplo 99c: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,25 (3H, d), 1,73 - 1,82 (2H, m), 1,89 - 1,97 (1H, m), 2,04 - 2,11 (1H, m), 2,78 - 2,88 (2H, m), 2,92 - 2,99 (2H, m), 2,98 - 3,05 (2H, m), 3,20 - 3,26 (1H, m), 3,34 - 3,42 (2H, m), 3,46 - 3,57 (1H, m), 3,66 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,04 - 4,10 (1H, m), 4,25 (1H, d), 4,54 - 4,63 (2H, m), 4,71 (2H, s), 6,76 (1H, s), 6,99 (2H, s), 7,69 (2H, d), 8,21 (1H, s), 8,29 (2H, d), 10,03 (1H, s)

Ejemplo 99d: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,25 (3H, d), 1,45 (6H, s), 1,73 - 1,80 (2H, m), 1,87 - 1,95 (1H, m), 2,03 - 2,10 (1H, m), 2,79 - 2,87 (2H, m), 2,92 - 2,98 (2H, m), 2,97 - 3,05 (2H, m), 3,20 - 3,24 (1H, m), 3,35 - 3,42 (2H, m), 3,48 - 3,57 (3H, m), 3,66 (1H, d), 3,77 (1H, d), 3,95 - 4,01 (1H, m), 4,03 - 4,09 (1H, m), 4,25 (1H, d), 4,52 - 4,62 (2H, m), 6,75 (1H, s), 7,61 (2H, d), 8,27 (2H, d), 9,92 (1H, s)

Ejemplo 99e: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,14 (3H, t), 1,24 (3H, d), 1,72 - 1,82 (2H, m), 1,88 - 1,98 (1H, m), 2,01 - 2,11 (1H, m), 2,76 - 2,87 (2H, m), 2,89 - 2,98 (2H, m), 2,98 - 3,06 (2H, m), 3,21 - 3,27 (1H, m), 3,35 - 3,42 (2H, m), 3,46 - 3,56 (3H, m), 3,66 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,24 (1H, d), 4,52 - 4,62 (2H, m), 6,75 (1H, s), 7,57 (2H, d), 7,89 (1H, s), 8,28 (2H, d), 9,63 (1H, s)

Ejemplo 99f: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,73 - 1,81 (2H, m), 1,86 - 1,97 (1H, m), 2,02 - 2,12 (1H, m), 2,79 - 2,87 (2H, m), 2,92 - 2,99 (2H, m), 2,97 - 3,05 (2H, m), 3,20 - 3,28 (1H, m), 3,35 - 3,43 (2H, m), 3,47 - 3,60 (3H, m), 3,66 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,25 (1H, d), 4,50 - 4,63 (2H, m), 4,81 (1H, s), 6,75 (1H, s), 7,63 (2H, d), 7,88 (1H, s), 8,28 (2H, d), 9,81 (1H, s)

Ejemplo 99g: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 10,01 (1H, s), 8,31 (2H, d), 8,12 (1H, s), 7,59 (2H, d), 6,77 (1H, s), 6,39 - 6,03 (1H, m), 4,64 - 4,54 (2H, m), 4,25 (1H, d), 4,05 - 3,94 (3H, m), 3,77 (1H, d), 3,66 (1H, d), 3,56 - 3,46 (1H, m), 3,42 - 3,36 (2H, m), 3,27 - 3,19 (1H, m), 3,05 - 2,98 (2H, m), 2,98 - 2,91 (2H, m), 2,89 - 2,79 (2H, m), 2,12 - 1,98 (1H, m), 1,97 - 1,87 (1H, m), 1,81 - 1,73 (2H, m), 1,25 (3H, d)

Ejemplo 99h: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 10,01 (1H, s), 8,31 (2H, d), 8,12 (1H, s), 7,59 (2H, d), 6,77 (1H, s), 6,39 - 6,03 (1H, m), 4,64 - 4,54 (2H, m), 4,25 (1H, d), 4,05 - 3,94 (3H, m), 3,77 (1H, d), 3,66 (1H, d), 3,56 - 3,46 (1H, m), 3,42 - 3,36 (2H, m), 3,27 - 3,19 (1H, m), 3,05 - 2,98 (2H, m), 2,98 - 2,91 (2H, m), 2,89 - 2,79 (2H, m), 2,12 - 1,98 (1H, m), 1,97 - 1,87 (1H, m), 1,81 - 1,73 (2H, m), 1,25 (3H, d)

Ejemplo 99i: ^{1}H NMR (400,132 MHz, DMSO-D_6) δ 1,24 (3H, d), 1,69 - 1,80 (4H, m), 1,88 - 1,98 (1H, m), 2,03 - 2,09 (1H, m), 2,78 - 2,89 (2H, m), 2,90 - 2,97 (2H, m), 2,98 - 3,05 (2H, m), 3,17 - 3,25 (1H, m), 3,35 - 3,42 (2H, m), 3,46 - 3,59 (5H, m), 3,66 (1H, d), 3,77 (1H, d), 3,98 (1H, d), 4,25 (1H, d), 4,52 - 4,61 (2H, m), 6,75 (1H, s), 7,58 (2H, d), 7,90 (1H, s), 8,28 (2H, d), 9,69 (1H, s)

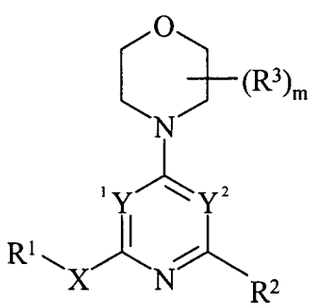
Ejemplo 99j: No se registró el espectro.

Las preparaciones de 3-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclobutil]sulfonilpropan-1-ol y 3-[1-[2-(4-aminofenil)-6-[(3*S*)-3-metilmorfolin-4-il]pirimidin-4-il]ciclopropil]sulfonilpropan-1-ol se describieron anteriormente.

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REIVINDICACIONES

1. Un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo; en donde

m es 0, 1, 2, 3 o 4;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de $-CR^4=CR^5CR^6R^7-$, $-CR^6R^7CR^5=CR^4-$, $-C\equiv CCR^6R^7-$, $-CR^6R^7C\equiv C-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-SCR^6R^7-$, $-S(O)CR^6R^7-$, $-S(O)_2CR^6R^7-$, $-C(O)NR^4CR^6R^7-$, $-NR^4C(O)CR^6R^7-$, $-NR^4C(O)NR^5CR^6R^7-$, $-NR^4S(O)_2CR^6R^7-$ y $-S(O)_2NR^4CR^6R^7-$;

R^1 es un grupo que se selecciona de hidrógeno, alquiloC_{1-6}, alqueniloC_{2-6}, alquiniloC_{2-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, $-OR^9$, $-SR^9$, $-SOR^9$, $-SO_2R^9$, $-COR^9$, $-CO_2R^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-NR^9COR^{10}$, $-NR^9CO_2R^{10}$, $-NR^9CONR^{10}R^{15}$, $-NR^9COCONR^{10}R^{15}$ y $-NR^9SO_2R^{10}$;

R^2 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, $-R^{11}$, $-OR^{11}$, $-SR^{11}$, $-SOR^{11}$, $-SO_2R^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CONR^{11}R^{12}$, $-NR^{11}R^{12}$, $-NR^{11}COR^{12}$, $-NR^{11}COCONR^{12}R^{16}$, $-NR^{11}SO_2R^{12}$, $-NR^{17}CONR^{18}R^{19}$ y $-NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona independientemente de halo, ciano, nitro, $-R^{13}$, $-OR^{13}$, $-SR^{13}$, $-SOR^{13}$, $-SO_2R^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-NR^{13}R^{14}$, $-NR^{13}COR^{14}$, $-NR^{13}CO_2R^{14}$ y $-NR^{13}SO_2R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o $\mathbf{R^1}$ y $\mathbf{R^4}$ junto con el átomo o átomos a los que están unidos forman un anillo carbocíclico o heterocíclico de 4 a 10 miembros en donde 1, 2 o 3 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

$\mathbf{R^8}$ se selecciona de hidrógeno, halo, ciano y alquiloC$_{1-6}$;

$\mathbf{R^9}$ y $\mathbf{R^{10}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{17}}$ y $\mathbf{R^{18}}$ son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$,

sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^{13}, **R^{14}**, **R^{15}** y **R^{16}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

R^{19} es hidrógeno, ciano o un grupo que se selecciona de alquiloC$_{1-6}$, carbociclilo, carbociclilalquiloC$_{1-6}$, heterociclilo y heterociclilalquiloC$_{1-6}$, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$, (alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, bis(alquilC$_{1-6}$)aminoalquiloC$_{1-6}$, cianoalquiloC$_{1-6}$, alquilC$_{1-6}$sulfonilo, alquilC$_{1-6}$sulfonilamino, alquilC$_{1-6}$sulfonil(alquilC$_{1-6}$)amino, sulfamoilo, alquilC$_{1-6}$sulfamoilo, bis(alquilC$_{1-6}$)sulfamoilo, alcanoilC$_{1-6}$amino, alcanoilC$_{1-6}$(alquilC$_{1-6}$)amino, carbamoilo, alquilC$_{1-6}$carbamoilo y bis(alquilC$_{1-6}$)carbamoilo;

o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 3 a 10 miembros en donde 1 o 2 átomos de carbono del anillo se reemplazan opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC$_{1-6}$, alcoxiC$_{1-6}$, haloalquiloC$_{1-6}$, haloalcoxiC$_{1-6}$, hidroxialquiloC$_{1-6}$, hidroxialcoxiC$_{1-6}$, alcoxiC$_{1-6}$alquiloC$_{1-6}$, alcoxiC$_{1-6}$alcoxiC$_{1-6}$, amino, alquilC$_{1-6}$amino, bis(alquilC$_{1-6}$)amino, aminoalquiloC$_{1-6}$,

(alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

2. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la reivindicación 1, en donde

m es 0, 1 o 2;

^{1}Y e **Y^2** son independientemente N o CR^8 siempre que uno de ^{1}Y e Y^2 sea N y el otro sea CR^8;

X es un grupo enlazante que se selecciona de -$NR^4CR^6R^7$-, -OCR^6R^7-, -SCR^6R^7-, -$S(O)CR^6R^7$-, -$S(O)_2CR^6R^7$-, -$C(O)NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$-, -$NR^4C(O)NR^5CR^6R^7$- y -$S(O)_2NR^4CR^6R^7$;

R^1 es un grupo que se selecciona de alquiloC_{1-6}, carbociclilo, carbociclilalquiloC_{1-6}, heterociclilo y heterociclilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, R^9, -OR^9, -COR^9, -$CONR^9R^{10}$, -NR^9R^{10} y -NR^9COR^{10};

o **X-R^1** es –CR^6R^7OH;

R^2 es un grupo que se selecciona de carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan independientemente de halo, ciano, nitro, -R^{11}, -OR^{11}, -SR^{11}, -SOR^{11}, -SO_2R^{11}, -COR^{11}, -CO_2R^{11}, -$CONR^{11}R^{12}$, -$NR^{11}R^{12}$, -$NR^{11}COR^{12}$, -$NR^{11}COCONR^{12}R^{16}$, -$NR^{11}SO_2R^{12}$, -$NR^{17}CONR^{18}R^{19}$ y -$NR^{17}CSNR^{18}R^{19}$;

cada R^3, cuando está presente, se selecciona de ciano, R^{13} y -$CONR^{13}R^{14}$;

R^4 y **R^5** son independientemente hidrógeno o alquiloC_{1-6};

o, cuando **X** es -$NR^4CR^6R^7$-, -$NR^4C(O)CR^6R^7$- o -$NR^4C(O)NR^5CR^6R^7$-, **R^1** y **R^4** junto con el átomo o átomos a los que están unidos forman un anillo heterocíclico de 5 o 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, oxo, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo,

alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo carbocíclico o anillo heterocíclico de 3 a 10 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N, O o S y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

R^8 se selecciona de hidrógeno, halo, ciano y alquiloC_{1-6};

R^9 y **R^{10}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino;

R^{11}, R^{12}, R^{17} y **R^{18}** son independientemente hidrógeno o un grupo que se selecciona de alquiloC_{1-6}, carbociclilo y heterociclilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino y bis(alquilC_{1-6})amino;

R^{13} y **R^{14}** son independientemente hidrógeno o un alquiloC_{1-3} que se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, hidroxi y alcoxiC_{1-3}; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de alquiloC_{1-6}, cicloaquiloC_{3-6}, arilo, heteroarilo, arilalquiloC_{1-6} y heteroarilalquiloC_{1-6}, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo;

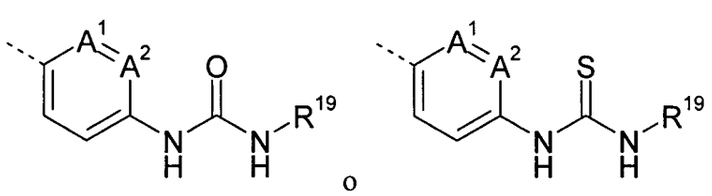
$_{6}$)amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo; o **R^{18}** y **R^{19}** junto con el átomo de nitrógeno al que están unidos forman un anillo heterocíclico de 6 miembros en donde 1 átomo de carbono del anillo se reemplaza opcionalmente por N u O y dicho anillo se sustituye opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

3. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la reivindicación 1 o 2 en donde ^{1}Y es CH e Y^{2} es N.

4. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 3 en donde **X** es un grupo enlazante -$S(O)_2CR^6R^7$-.

5. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 4 en donde R^1 es un grupo que se selecciona de metilo, etilo, propilo, butilo, isobutilo, *terc*-butilo, ciclopropilo, ciclopentilo ciclohexilo, fenilo, bencilo, fenetilo, imidazolilo, pirrolidinilo, tiadiazolilo, tiazolilo, piridinilo, pirazoliletilo, furanilmetilo, tienilmetilo, tiazolilmetilo, tiadiazolilmetilo y piraziniletilo, sustituyéndose este grupo opcionalmente por 1 o 2 grupos sustituyentes que se seleccionan de amino, halo, ciano, hidroxi, metilo, metoxi, trifluorometilo, trifluorometoxi, -$NHCOCH_3$, -$CONH_2$ y -$CONHCH_3$.

6. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 5 en donde R^2 es

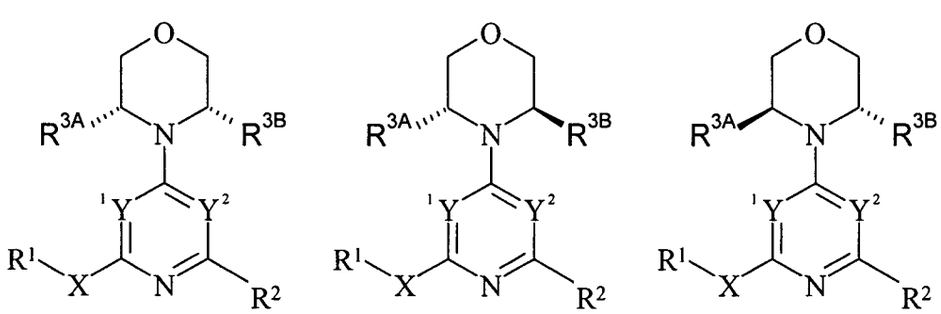


en donde A^1 y A^2 se seleccionan de CH o N siempre que al menos uno de A^1 o A^2 es CH.

7. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 6 en donde R^{19} es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, butilo, i-butilo, t-butilo, pentilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, tienilo, imidazoilmetilo, isoxazolilo, pirazolilo, pirazolilmetilo, piridinilo y pirimidinilo, sustituyéndose este grupo opcionalmente por uno o más grupos sustituyentes que se seleccionan de halo, ciano, nitro, hidroxi, alquiloC_{1-6}, alcoxiC_{1-6}, haloalquiloC_{1-6}, haloalcoxiC_{1-6}, hidroxialquiloC_{1-6}, hidroxialcoxiC_{1-6}, alcoxiC_{1-6}alquiloC_{1-6}, alcoxiC_{1-6}alcoxiC_{1-6}, amino, alquilC_{1-6}amino, bis(alquilC_{1-6})amino, aminoalquiloC_{1-6}, (alquilC_{1-6})aminoalquiloC_{1-6}, bis(alquilC_{1-6})aminoalquiloC_{1-6}, cianoalquiloC_{1-6}, alquilC_{1-6}sulfonilo, alquilC_{1-6}sulfonilamino, alquilC_{1-6}sulfonil(alquilC_{1-6})amino, sulfamoilo, alquilC_{1-6}sulfamoilo, bis(alquilC_{1-6})sulfamoilo, alcanoilC_{1-6}amino, alcanoilC_{1-6}(alquilC_{1-6})amino, carbamoilo, alquilC_{1-6}carbamoilo y bis(alquilC_{1-6})carbamoilo.

8. Un compuesto, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 7 en donde $\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo carbocíclico de 3 a 5 miembros.

9. Un compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde el compuesto de fórmula (I) es un compuesto de fórmula (IA), (IB) o (IC)



(IA) (IB) (IC)

en donde

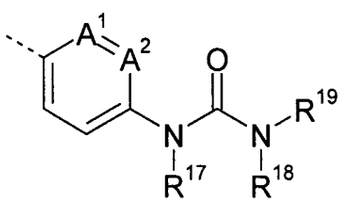
X es un grupo enlazante $-S(O)_2CR^6R^7-$;

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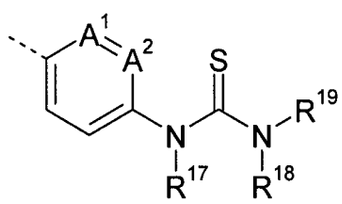
^{1}**Y** es CH e **Y**^{2} es N;

R^{1} es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, ciclopentilo, ciclohexilo, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2C(OH)(CH_3)_2$, $-CH_2CH_2CH_2OCHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH_2NHC(O)CH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2CH_2NHMe$, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-fluoro-4-metilaminofenilo, 4-fluoro-2-metilfenilo, 5-fluoro-2-metilfenilo, 3-fluoro-4-(2-hidroxietilamino)fenilo, 4-(difluorometoxi)fenilo, 4-carbamoil-2-clorofenilo, 4-clorofenilo, 2-clorofenilo, 3-cloro-4-fluorofenilo, 3-cloro-4-metilaminofenilo, 3-cloro-4-etilaminofenilo, 3-cloro-4-(2-fluoroetilamino)fenilo, 3-cloro-4-(2-hidroxietilamino)fenilo, 2-cloro-4-cianofenilo, 4-cianofenilo, 2,4-difluorofenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 3,4-difluorofenilo, 3,5-difluorofenilo, 2-(trifluorometil)fenilo, 2-metilfenilo, 4-metilfenilo, 4-(2-hidroxietilamino)fenilo, 1H-imidazol-2-ilo, 3,5-dimetilisoxazol-4-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, 1-(difluorometil)pirazol-4-ilo, 1-(difluorometil)-3,5-dimetilpirazol-4-ilo, 1,3-dimetilpirazol-4-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, 5-fluoropiridin-3-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo, 4,5-dimetiltiazol-2-ilo, 2,4-dimetiltiazol-5-ilo, 5-metil-1,3,4-tiadiazol-2-ilo, tetrahidrofuran-3-ilo y tetrahidropiran-4-ilo;

R^{2} es



o



en donde **A**^{1} y **A**^{2} son CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno; y

R^{19} es hidrógeno, ciano o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, i-butilo, t-butilo, ciclopropilo, ciclobutilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2SO_2Me$, $-CH_2CH(OH)CF_3$, $-CH_2CH_2CN$, $-CH_2CN$, $-CH_2CONMe_2$, $-CH_2CO_2H$, 1-(metil)ciclopropilo, $-CH_2$(1-hidroxiciclopropilo), 1-(hidroximetil)ciclopropilo, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-

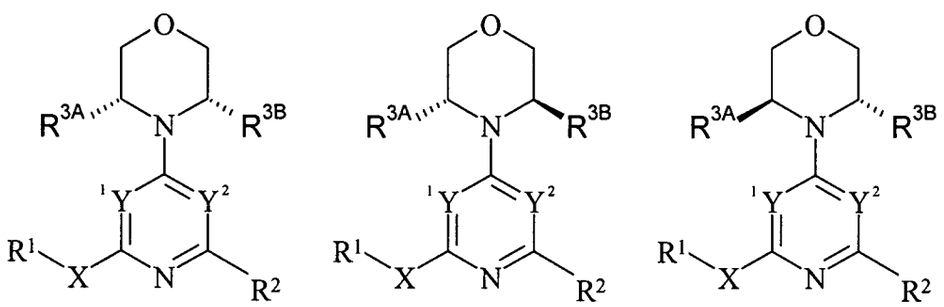
metiletilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 4-fluorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, -CH_2CH_2(pirrolidin-1-il), -CH_2(imidazol-2-ilo), 1-metilimidazol-4-ilo, oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 1,1-dioxotiolan-3-ilo, 5-metilisoxazol-3-ilo, -CH_2(1-metilpirazol-4-ilo), 1-metilpirazol-4-ilo, -CH_2(1-metilpirazol-4-ilo), 5-metilpirazin-2-ilo, -CH_2(2H-1,2,4-triazol-3-ilo), 6-metoxipiridin-3-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo;

$\mathbf{R^6}$ y $\mathbf{R^7}$ junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo; y

cuando $\mathbf{R^{3A}}$ es hidrógeno, $\mathbf{R^{3B}}$ es hidrógeno, metilo, etilo, hidroximetilo, dimetilcarbamoilo o carbamoilo; o

cuando $\mathbf{R^{3'}}$ es metilo, $\mathbf{R^3}$ es metilo.

10. Un compuesto de acuerdo con la reivindicación 9, o una sal farmacéuticamente aceptable del mismo, en donde el compuesto de fórmula (I) es un compuesto de fórmula (IA), (IB) o (IC)



(IA) (IB) (IC)

en donde

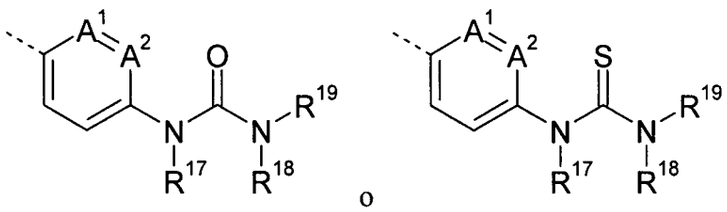
X es un grupo enlazante -$S(O)_2CR^6R^7$-;

^{1}**Y** es CH e $\mathbf{Y^2}$ es N;

$\mathbf{R^1}$ es un grupo que se selecciona de metilo, etilo, isopropilo, *terc*-butilo, ciclopropilo, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH_2CH_2C(OH)(CH_3)_2$, -$CH_2CH_2CH_2OCHF_2$, -$CH_2CH_2OCH_3$, -$CH_2CH_2NHC(O)CH_3$, -CH_2CH_2NHMe, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-fluoro-4-metilaminofenilo, 4-fluoro-2-metilfenilo, 5-fluoro-

2-metilfenilo, 3-fluoro-4-(2-hidroxietilamino)fenilo, 4-(difluorometoxi)fenilo, 4-carbamoil-2-clorofenilo, 4-clorofenilo, 2-clorofenilo, 3-cloro-4-fluorofenilo, 3-cloro-4-metilaminofenilo, 3-cloro-4-etilaminofenilo, 3-cloro-4-(2-fluoroetilamino)fenilo, 3-cloro-4-(2-hidroxietilamino)fenilo, 2-cloro-4-cianofenilo, 4-cianofenilo, 2,4-difluorofenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 3,4-difluorofenilo, 3,5-difluorofenilo, 2-metilfenilo, 4-metilfenilo, 1H-imidazol-2-ilo, 3,5-dimetilisoxazol-4-ilo, 2-(dimetilcarbamoil)piridin-3-ilo, 5-(dimetilcarbamoil)piridin-2-ilo, 1-(difluorometil)pirazol-4-ilo, 1,3-dimetilpirazol-4-ilo, piridin-4-ilo, piridin-2-ilo, 5-fluoropiridin-2-ilo, tiazol-2-ilo, 4-metiltiazol-2-ilo, 4,5-dimetiltiazol-2-ilo, 2,4-dimetiltiazol-5-ilo y 5-metil-1,3,4-tiadiazol-2-ilo;

R^2 es



o

en donde **A^1** y **A^2** son CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno; y

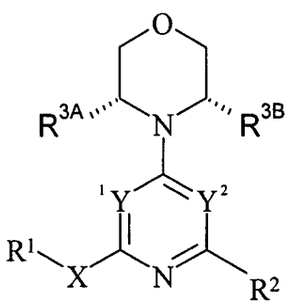
R^{19} es hidrógeno o un grupo que se selecciona de metilo, etilo, propilo, i-propilo, ciclopropilo, ciclobutilo, $-CH_2$(ciclopropilo), $-CH_2CH_2NMe_2$, $-CH(CH_3)CH_2OH$, $-C(CH_3)_2CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CH_2CN$, $-CH_2$(1-hidroxiciclopropilo), 1-(hidroximetil)ciclopropilo, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, fenilo, 4-metilfenilo, 4-clorofenilo, 4-metoxifenilo, 3,4-difluorofenilo, $-CH_2CH_2$(pirrolidin-1-il),$-CH_2$(imidazol-2-ilo), 1-metilimidazol-4-ilo, oxazolil-2-ilo, isoxazolil-3-ilo, oxetan-3-ilo, 5-metilisoxazol-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, 6-metoxipiridin-3-ilo, tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo y 1-metilpirazol-3-ilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo; y

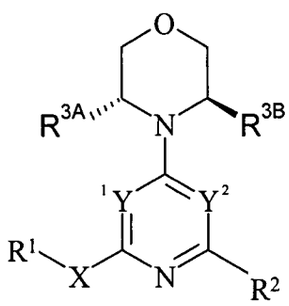
cuando **R^{3A}** es hidrógeno, **R^{3B}** es hidrógeno, metilo o etilo; o

cuando $\mathbf{R^{3A}}$ es metilo, $\mathbf{R^{3B}}$ es metilo.

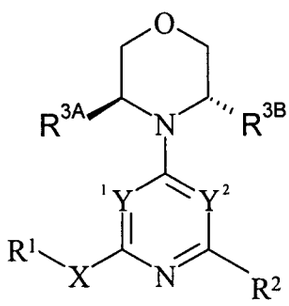
11. Un compuesto de acuerdo con la reivindicación 10, o una sal farmacéuticamente aceptable del mismo, en donde el compuesto de fórmula (I) es un compuesto de fórmula (IA), (IB) o (IC)



(IA)



(IB)



(IC)

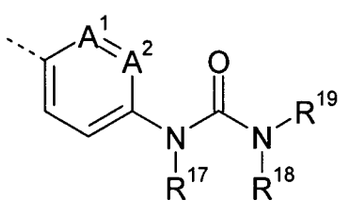
en donde

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

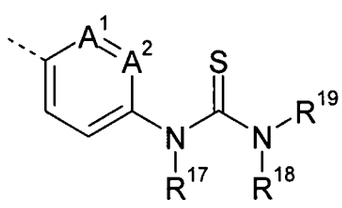
^{1}**Y** es CH e **Y**^{2} es N;

R^1 es un grupo que se selecciona de metilo, etilo, ciclopropilo, $-CH_2CH_2CH_2OH$, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-clorofenilo, 2-metilfenilo, 5-fluoropiridin-2-ilo, piridin-2-ilo, tiazol-2-ilo y 4-metiltiazol-2-ilo;

R^2 es



o



en donde **A**^{1} y **A**^{2} son CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno; y

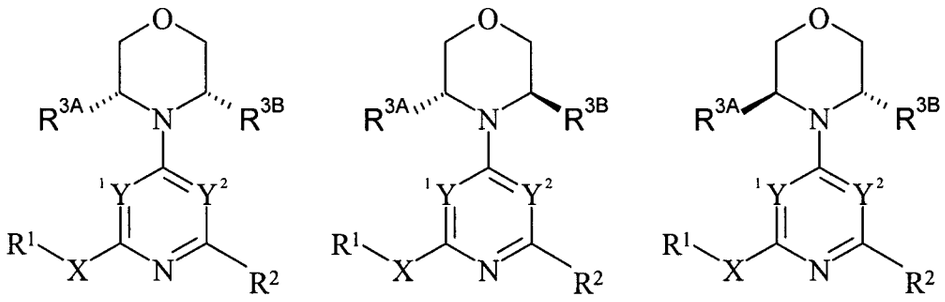
R^{19} es un grupo que se selecciona de metilo, etilo, ciclopropilo, ciclobutilo, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo, $-CH_2$(imidazol-2-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, tiazol-2-ilo y 1,2,4-tiadiazol-5-ilo;

R^6 y **R^7** junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo; y

cuando **R^{3A}** es hidrógeno, **R^{3B}** es hidrógeno, metilo o etilo; o

cuando **R^{3A}** es metilo, **R^{3B}** es metilo.

12. Un compuesto de acuerdo con la reivindicación 11, o una sal farmacéuticamente aceptable del mismo, en donde el compuesto de fórmula (I) es un compuesto de fórmula (Ia), (Ib) o (Ic)



(IA) (IB) (IC)

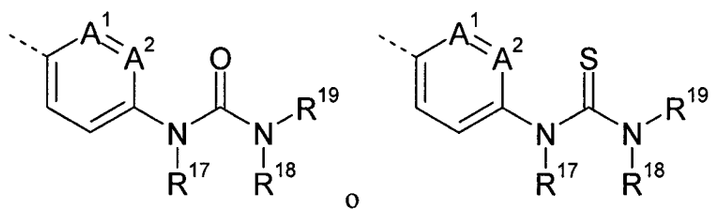
o una sal farmacéuticamente aceptable del mismo;

X es un grupo enlazante $-S(O)_2CR^6R^7-$;

^1Y es CH e **Y^2** es N;

R^1 es un grupo que se selecciona de metilo, etilo, ciclopropilo, $-CH_2CH_2CH_2OH$, fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-clorofenilo, 2-metilfenilo, 5-fluoropiridin-2-ilo, piridin-2-ilo, tiazol-2-ilo y 4-metiltiazol-2-ilo;

R^2 es



en donde **A^1** y **A^2** son CH;

R^{17} es hidrógeno;

R^{18} es hidrógeno; y

R^{19} es un grupo que se selecciona de metilo, etilo, ciclopropilo, ciclobutilo, $-CH(CH_3)CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2CN$, (1R)-2-hidroxi-1-metiletilo, (1S)-2-hidroxi-1-metiletilo,

-CH_2(imidazol-2-ilo), oxazolil-2-ilo, isoxazolil-3-ilo, 1-metilpirazol-4-ilo, 5-metilpirazin-2-ilo, tiazol-2-ilo y 1,2,4-tiadiazol-5-ilo;

R^6 y R^7 junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo, ciclobutilo, ciclopentilo, tetrahidropiranilo o piperidilo; y

cuando R^{3A} es hidrógeno, R^{3B} es metilo o etilo; o

cuando R^{3A} es metilo, R^{3B} es metilo.

13. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 12 en donde R^6 y R^7 junto con el átomo de carbono al que están unidos forman un anillo ciclopropilo o ciclobutilo.

14. Un compuesto de fórmula (I) de acuerdo con la reivindicación 1 que se selecciona de cualquiera de los Ejemplos, o una sal farmacéuticamente aceptable del mismo.

15. Un compuesto de fórmula (I) de acuerdo con la reivindicación 1 que se selecciona de cualquiera de

1-[4-[4-(1-etilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metil-urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

3-ciclopropil-1-[4-[4-(1-metilsulfonilciclopropil)-6-morfolin-4-ilpirimidin-2-il]fenil]urea,

1-[4-[4-[1-(4-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-2-ilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea,

3-ciclopropil-1-[4-[4-[1-(4-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

3-ciclopropil-1-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

1-etil-3-[4-[4-[1-(3-hidroxipropilsulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]tiourea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-metiltiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(1H-imidazol-2-ilmetil)tiourea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-(1-piridin-4-ilsulfonilciclopropil)pirimidin-2-il]fenil]tiourea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-(2,4-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(3-fluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(2-metilfenil)sulfonilciclopropil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclopropil]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(2-clorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-(1-ciclopropilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(bencenosulfonil)ciclobutil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea,

3-(2-fluoroetil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclopropil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-[(4-metil-1,3-tiazol-2-il)sulfonil]ciclobutil]pirimidin-2-il]fenil]urea,

3-(2-hidroxietil)-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2,2-difluoroetil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2R)-1-hidroxipropan-2-il]urea,

3-ciclopropil-1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S)-3-etilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(2,6-difluorofenil)sulfonilciclopropil]-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-(1-ciclopropilsulfonilciclopropil)-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

3-ciclopropil-1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]urea,

1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-metilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-ciclopropilurea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(2S)-1-hidroxipropan-2-il]urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-(3-hidroxipropil)urea,

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S)-3-etilmorfolin-4-il]pirimidin-2-il]fenil]-3-[(1-hidroxiciclopropil)metil]urea,

1-[4-[4-(1-etilsulfonilciclobutil)-6-[(3S)-3-metilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-hidroxietil)tiourea,

1-[4-[4-[(3S,5S)-3,5-dimetilmorfolin-4-il]-6-(1-metilsulfonilciclopropil)pirimidin-2-il]fenil]-3-etilurea,

3-[(2S)-1-hidroxipropan-2-il]-1-[4-[4-[(3S)-3-metilmorfolin-4-il]-6-[1-(1,3-tiazol-2-ilsulfonil)ciclobutil]pirimidin-2-il]fenil]urea y

1-[4-[4-[1-(bencenosulfonil)ciclopropil]-6-[(3S,5S)-3,5-dimetilmorfolin-4-il]pirimidin-2-il]fenil]-3-(2-fluoroetil)urea,

o una sal farmacéuticamente aceptable del mismo.

16. Un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo de acuerdo con cualquiera de las reivindicaciones 1 a 15 para su uso como un medicamento.

17. El uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en cualquiera de las reivindicaciones 1 a 15 en la fabricación de un medicamento para su uso en el tratamiento de una enfermedad proliferativa.

18. El uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en cualquiera de las reivindicaciones 1 a 15 para la producción de un efecto anti-proliferativo en un animal de sangre caliente tal como el hombre.

19. El uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en cualquiera de las reivindicaciones 1 a 15 en la fabricación de un medicamento para su uso en la producción de un efecto anti-proliferativo en un animal de sangre caliente tal como el hombre.

20. El uso de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en cualquiera de las reivindicaciones 1 a 15 en la fabricación de un medicamento para su uso en la obtención de un efecto inhibitorio de la mTOR quinasa en un animal de sangre caliente tal como el hombre.

21. Un método para producir un efecto anti-proliferativo en un animal de sangre caliente, tal como el hombre, que necesita dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en cualquiera de las reivindicaciones 1 a 15.

22. Un método para producir un efecto inhibitorio de la mTOR quinasa en un animal de sangre caliente, tal como el hombre, que necesita dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en cualquiera de las reivindicaciones 1 a 15.

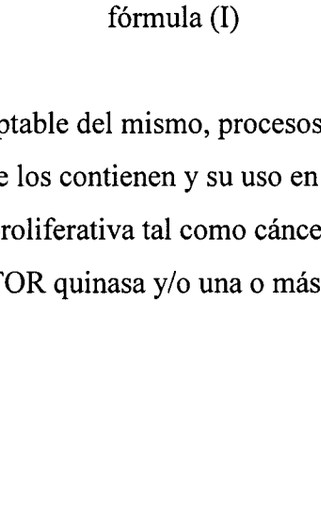
1953

23. Un método para el tratamiento de cáncer, enfermedades inflamatorias, enfermedades obstructivas de las vías respiratorias, enfermedades inmunes o enfermedades cardiovasculares en un animal de sangre caliente tal como el hombre que necesita dicho tratamiento que comprende administrar una cantidad efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, tal como se define en cualquiera de las reivindicaciones 1 a 15.

24. Una composición farmacéutica que comprende un compuesto de fórmula (I) tal como se define en cualquiera de las reivindicaciones 1 a 15, o una sal farmacéuticamente aceptable del mismo, en asociación con un diluyente o portador farmacéuticamente aceptable.

RESUMEN

Un compuesto de fórmula (I)



fórmula (I)

o una sal farmacéuticamente aceptable del mismo, procesos para su preparación, composiciones farmacéuticas que los contienen y su uso en terapia, por ejemplo en el tratamiento de una enfermedad proliferativa tal como cáncer y particularmente en una enfermedad mediada por una mTOR quinasa y/o una o más enzimas PI3K.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 102945-1P WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/GB2008/050546	International filing date *(day/month/year)* 08 July 2008 (08.07.2008)	Priority date *(day/month/year)* 09 July 2007 (09.07.2007)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ASTRAZENECA AB		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 12 January 2010 (12.01.2010)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Dorothée Mülhausen e-mail: pt01.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2008/050546	08.07.2008	09.07.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07D413/14 C07D417/14 A61K31/5377 A61P35/00 C07D413/04

Applicant
ASTRAZENECA AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Grassi, Damian Telephone No. +49 89 2399-8499

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2008/050546

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ on paper

   ☐ in electronic form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in electronic form.

   ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☒ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,4,6-15,17-23
	No:	Claims	1,3,5,16, 24
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1: WO 2007/42810
D2: DATABASE CA [Online]; accession no. 1967:421928, compound 4592-48-7
D3: US 2002/086858

Re Item IV

The International Searching Authority found multiple (groups of) inventions in this international application, the reasons being the following:

The closest state of the art for the present application is represented by D1 relating to inhibitors of PI3K which may be used to treat diseases such as cancer (cf. page 53 and claim 10).

Part of present claim 1 differs from the disclosure of D1 (e.g. examples O4, P4, V4, W4, X4) in that the present cyclic group CR^6R^7 is linked via a double or triple bond to the pyrimidine ring. Another part of present claim 1 (X is $NR^4CR^6R^7$, OCR^6R^7, $S(O)_{0-2}CR^6R^7$, $CONR^4CR^6R^7$, $NR^4COCR^6R^7$, $NR^4CONR^5CR^6R^7$, $NR^4SO_2CR^6R^7$ or $SO_2NR^4CR^6R^7$) overlaps with the disclosure of D1 (when Y is a bond and R^4 is an unsaturated carbocyclic or heterocyclic ring which is substituted with Z [cf. claim 1 and pages 4 and 8]).

The technical problem underlying the present application is seen in the provision of alternative inhibitors of PI3K (and/or mTOR) for the treatment of cancer.

In view of the above mentioned examples of D1 and the generic disclosure of the document, the common structure shared by all alternatives of present claim 1 cannot be the unifying criteria.

The requirement of a technical relationship as defined in Rule 13.2, 1st sentence, PCT, may be met when all claimed alternatives belong to a class of compounds which may be expected to behave in the same way in the context of the claimed inventions ("Markush claims"). The technical relationship involves those common special technical features that define a contribution over the state of the art (Rule 13.2, 2nd sentence, PCT). However, such contribution cannot be recognised on the basis of this expectation if members of the class have already been proposed in the prior art to behave in the

manner disclosed in the application. This is presently the case with the disclosure of D1.

Consequently, the different alternatives referred to in present claims 1 do not share a common or corresponding special technical feature as required by Rule 13.2 PCT. Therefore, the present application lacks unity of invention (Rule 13.1 PCT).

The following different inventions can be identified:

I Compounds according to claim 1 in which X is a linker group selected from $-CR^4=CR^5CR^6R^7-$, $-C{\equiv}CCR^6R^7-$, $-NR^4CR^6R^7-$, $-OCR^6R^7-$, $-S(O)_{0-2}CR^6R^7-$, $-CONR^4CR^6R^7-$, $-NR^4COCR^6R^7-$, $-NR^4CONR^5CR^6R^7-$, $-NR^4SO_2CR^6R^7-$ or $-SO_2NR^4CR^6R^7-$.

II Compounds according to claim 1 in which X is a linker group selected from $-CR^6R^7-CR^5=CR^4-$ or $-CR^6R^7CC-$.

Re Item V

The following considerations relate to invention I (claims 1 (part), 2, 3 (part), 4, 5-8 (part), 9-12, 13 (part), 14 (part), 15, 16-24 (part)).

1) Claims 21-23 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT.
The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.

2) The subject-matter according to the first invention is new (Article 33(2) PCT).

The subject-matter of present claim 1 (X is $NR^4CR^6R^7$, OCR^6R^7, $S(O)_{0-2}CR^6R^7$, $CONR^4CR^6R^7$, $NR^4COCR^6R^7$, $NR^4CONR^5CR^6R^7$, $NR^4SO_2CR^6R^7$ or $SO_2NR^4CR^6R^7$) overlaps with the disclosure of D1 (when Y is a bond and R^4 is an unsaturated carbocyclic or heterocyclic group which is substituted with Z [cf. claim 1 and pages 4 and 8]).

However, the document D1 does not comprise examples in which Y is a bond or in which the unsaturated carbocyclic or heterocyclic group R^4 is substituted on the atom which is also bound to Y or the pyrimidine ring.

Therefore, the subject-matter according to invention I is considered as novel selection from the more generic teaching of D1.

3) The subject-matter according to the first invention does not involve an inventive step (Article 33(3) PCT).

The closest state of the art for the present application is represented by D1 (cf. paragraphs IV and 2 above).

The technical problem underlying the present application is seen in the provision of alternative inhibitors of PI3K (and/or mTOR) for the treatment of cancer.

The present description provides the pharmacological data of a series of compounds. All of the tested compounds appear to comprise a cyclic moiety R^2, whereas the present claims also encompass compounds in which R^2 is alkyl.

Therefore, and also considering that the closely related compounds of D1 always comprise a cyclic moiety in the position of the present residue R^2, it is not credible, that the technical problem has been solved over the whole breath of invention I. Therefore, the subject-matter according to invention I of claim 1 does not involve an inventive step.

3.1) Moreover, the part of claim 1 which appears to solve the technical problem does not involve an inventive step over D1.
This part of the invention I represents a selection from the more generic teaching of D1 (cf. paragraph 2, above).
Such a selection can only be regarded as inventive, if the subgroup presents unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claim 1.

The claims relating to the use of the compounds of claim 1 as well as the claims

relating to a pharmaceutical composition containing the said would only involve an inventive step if the claim 1 fulfilled this requirement.

The following considerations relate to invention II (claims 1, 3, 5-8, 13, 14 and 16-24 (all part)).

4) Claims 21-23 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT.
The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.

5) The subject-matter according to invention II is not novel over the disclosure of D2 and D3 (Article 33(2) PCT).
The present claims 1, 3, 5, 16 and 24 encompass the compounds disclosed in the paragraphs [77] and [78] of D3. Additionally, the present claims essentially overlap with the group of compounds disclosed in claim 1 of D3. The above mentioned compounds of D3 show that the skilled person would seriously contemplate working within the overlapping area. Therefore, the subject-matter of the overlapping area is not regarded as novel.

6) The novel part according to invention II does not involve an inventive step (Article 33(3) PCT).

The closest state of the art for invention II is represented by D1 (cf. paragraphs IV and 2 above).

The technical problem underlying the present application is seen in the provision of alternative inhibitors of PI3K (and/or mTOR) for the treatment of cancer.

The present description provides the pharmacological data of a series of compounds. However, none of the tested compounds appears to contain a moiety X according to invention II. Moreover, all of the tested compounds appear to comprise a cyclic moiety R^2, whereas the present claims also encompass

compounds in which R^2 is alkyl.

Therefore, and also considering that the closely related compounds of D1 always comprise a cyclic moiety in the position of the present residue R^2, it is not credible, that the technical problem has been solved over the whole breath of invention II. Therefore, the subject-matter according to invention II of claim 1 does not involve an inventive step.

The claims relating to the use of the compounds of claim 1 as well as the claims relating to a pharmaceutical composition containing the said would only involve an inventive step if the claim 1 fulfilled this requirement.

REMARK

The claims 14 must not refer to the content of the description (cf. Guidelines Part II, 5.10).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 January 2009 (15.01.2009)

PCT

(10) International Publication Number
WO 2009/007748 A3

(51) International Patent Classification:
C07D 413/14 (2006.01) *A61P 35/00* (2006.01)
C07D 417/14 (2006.01) *C07D 413/04* (2006.01)
A61K 31/5377 (2006.01)

(21) International Application Number:
PCT/GB2008/050546

(22) International Filing Date: 8 July 2008 (08.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/948,566 9 July 2007 (09.07.2007) US
61/030,297 21 February 2008 (21.02.2008) US

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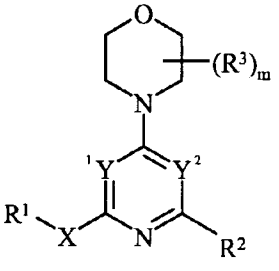
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
23 April 2009

(54) Title: TRISUBSTITUTED PYRIMIDINE DERIVATIVES FOR THE TREATMENT OF PROLIFERATIVE DISEASES



(I)

(57) Abstract: A compound of formula (I) or a pharamaceutically acceptable salt thereof, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, for example in the treatment of proliferative disease such as cancer and particularly in disease mediated by an mTOR kinase and/or one or more PI3K enzyme.

WO 2009/007748 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/050546

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 C07D417/14 A61K31/5377 A61P35/00 C07D413/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/042810 A (LUDWIG INST CANCER RES [CH]; CANCER REC TECH LTD [GB]; CANCER RES INST) 19 April 2007 (2007-04-19) page 53; claims 1,10; examples 04,P4,V4,W4,X4	1-24
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MINAMI, SHINSAKU ET AL: "2(or 6)-Nitrofurylvinyl-4-substituted aminopyrimidines" XP002505932 retrieved from STN Database accession no. 1967:421928 examples 4592-48-7	1,3,24

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2009	25/02/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Grassi, Damian

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/050546

1466

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& JP 42 004345 B4 (DAINIPPON PHARMACEUTICAL CO., LTD.) 22 February 1967 (1967-02-22)	
X	US 2002/086858 A1 (BREU VOLKER [DE] ET AL) 4 July 2002 (2002-07-04) paragraphs [0001], [0077], [0078]; claim 1	1,3,16, 24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2008/050546

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims:
1(part),2,3(part),4,5-8(part),9-12,
13(part),14(part),15,16-24(part)

Compounds according to claim 1 in which X is a linker group selected from -CR4=CR5CR6R7-, -C=CCR6R7-, -NR4CR6R7-, -OCR6R7-, -S(O)0-2CR6R7-, -CONR4CR6R7-, -NR4COCR6R7-, -NR4CONR5CR6R7-, -NR4SO2CR6R7- or -SO2NR4CR6R7-.

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2. claims: 1,3,5-8,13,14,16-24(all part)

Compounds according to claim 1 in which X is a linker group selected from -CR6R7-CR5=CR4- or -CR6R7CC-.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2008/050546

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007042810 A	19-04-2007	EP 1945627 A1	23-07-2008
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		DK 1335906 T3	05-02-2007
		WO 0238551 A1	16-05-2002
		EP 1335906 A1	20-08-2003
		ES 2271100 T3	16-04-2007
		JP 2004524279 T	12-08-2004
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		ZA 200302970 A	15-07-2004