

[001] Description of particular embodiments of the invention

[002] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

[003] The term "alkyl" refers to a hydrocarbon group selected from linear and branched saturated hydrocarbon groups of 1-18, or 1-12, or 1-6 carbon atoms. Examples of the alkyl group include methyl, ethyl, 1-propyl or n-propyl ("n-Pr"), 2-propyl or isopropyl ("i-Pr"), 1-butyl or n-butyl ("n-Bu"), 2-methyl-1-propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), and 1,1-dimethylethyl or t-butyl ("t-Bu"). Other examples of the alkyl group include 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl and 3,3-dimethyl-2-butyl groups.

[004] Lower alkyl means 1-8, preferably 1-6, more preferably 1-4 carbon atoms; lower alkenyl or alkynyl means 2-8, 2-6 or 2-4 carbon atoms.

[005] The term "alkenyl" refers to a hydrocarbon group selected from linear and branched hydrocarbon groups comprising at least one C=C double bond and of 2-18, or 2-12, or 2-6 carbon atoms. Examples of the alkenyl group may be selected from ethenyl or vinyl, prop-1-enyl, prop-2-enyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, and hexa-1,3-dienyl groups.

[006] The term "alkynyl" refers to a hydrocarbon group selected from linear and branched hydrocarbon group, comprising at least one C≡C triple bond and of 2-18, or 2-12, or 2-6 carbon atoms. Examples of the alkynyl group include ethynyl, 1-propynyl, 2-propynyl (propargyl), 1-butynyl, 2-butynyl, and 3-butynyl groups.

[007] The term "cycloalkyl" refers to a hydrocarbon group selected from saturated and partially unsaturated cyclic hydrocarbon groups, comprising monocyclic and polycyclic

(e.g., bicyclic and tricyclic) groups. For example, the cycloalkyl group may be of 3-12, or 3-8, or 3-6 carbon atoms. Even further for example, the cycloalkyl group may be a monocyclic group of 3-12, or 3-8, or 3-6 carbon atoms. Examples of the monocyclic cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl groups. Examples of the bicyclic cycloalkyl groups include those having 7-12 ring atoms arranged as a bicycle ring selected from [4,4], [4,5], [5,5], [5,6] and [6,6] ring systems, or as a bridged bicyclic ring selected from bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and bicyclo[3.2.2]nonane. The ring may be saturated or have at least one double bond (i.e. partially unsaturated), but is not fully conjugated, and is not aromatic, as aromatic is defined herein.

[008] The term “aryl” herein refers to a group selected from: 5- and 6-membered carbocyclic aromatic rings, for example, phenyl; bicyclic ring systems such as 7-12 membered bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, selected, for example, from naphthalene, indane, and 1,2,3,4-tetrahydroquinoline; and tricyclic ring systems such as 10-15 membered tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene.

[009] For example, the aryl group is selected from 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered cycloalkyl or heterocyclic ring optionally comprising at least one heteroatom selected from N, O, and S, provided that the point of attachment is at the carbocyclic aromatic ring when the carbocyclic aromatic ring is fused with a heterocyclic ring, and the point of attachment can be at the carbocyclic aromatic ring or at the cycloalkyl group when the carbocyclic aromatic ring is fused with a cycloalkyl group. Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in “-yl” by removal of one hydrogen atom from the carbon atom with the free valence are named by adding “-idene” to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene.

[010] The term “halogen” or “halo” refers to F, Cl, Br or I.

- [011]** The term "heteroalkyl" refers to alkyl comprising at least one heteroatom.
- [012]** The term "heteroaryl" refers to a group selected from:
- [013]** 5- to 7-membered aromatic, monocyclic rings comprising 1, 2, 3 or 4 heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon;
- [014]** 8- to 12-membered bicyclic rings comprising 1, 2, 3 or 4 heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in the aromatic ring; and
- [015]** 11- to 14-membered tricyclic rings comprising 1, 2, 3 or 4 heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in an aromatic ring.
- [016]** For example, the heteroaryl group includes a 5- to 7-membered heterocyclic aromatic ring fused to a 5- to 7-membered cycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings comprises at least one heteroatom, the point of attachment may be at the heteroaromatic ring or at the cycloalkyl ring.
- [017]** When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1.
- [018]** Examples of the heteroaryl group include, but are not limited to, (as numbered from the linkage position assigned priority 1) pyridyl (such as 2-pyridyl, 3-pyridyl, or 4-pyridyl), cinnoliny, pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 2,4-imidazolyl, imidazopyridinyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, thienyl, triazinyl, benzothienyl, furyl, benzofuryl, benzoimidazolyl, indolyl, isoindolyl, indolinyl, phthalazinyl, pyrazinyl, pyridazinyl, pyrrolyl, triazolyl, quinolinyl, isoquinolinyl, pyrazolyl, pyrrolopyridinyl (such as 1H-pyrrolo[2,3-b]pyridin-5-yl), pyrazolopyridinyl (such as 1H-pyrazolo[3,4-b]pyridin-5-yl), benzoxazolyl (such as benzo[d]oxazol-6-yl), pteridinyl, purinyl, 1-oxa-2,3-diazolyl, 1-oxa-2,4-diazolyl, 1-oxa-2,5-diazolyl, 1-oxa-3,4-diazolyl, 1-thia-2,3-diazolyl, 1-thia-2,4-diazolyl, 1-thia-2,5-diazolyl, 1-thia-3,4-diazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl, benzothiazolyl (such as benzo[d]thiazol-6-yl), indazolyl (such as 1H-indazol-5-yl) and 5,6,7,8-tetrahydroisoquinoline.

[019] The term "heterocyclic" or "heterocycle" or "heterocyclyl" refers to a ring selected from 4- to 12-membered monocyclic, bicyclic and tricyclic, saturated and partially unsaturated rings comprising at least one carbon atoms in addition to 1, 2, 3 or 4 heteroatoms, selected from oxygen, sulfur, and nitrogen. "Heterocycle" also refers to a 5- to 7-membered heterocyclic ring comprising at least one heteroatom selected from N, O, and S fused with 5-, 6-, and/or 7-membered cycloalkyl, carbocyclic aromatic or heteroaromatic ring, provided that the point of attachment is at the heterocyclic ring when the heterocyclic ring is fused with a carbocyclic aromatic or a heteroaromatic ring, and that the point of attachment can be at the cycloalkyl or heterocyclic ring when the heterocyclic ring is fused with cycloalkyl.

[020] "Heterocycle" also refers to an aliphatic spirocyclic ring comprising at least one heteroatom selected from N, O, and S, provided that the point of attachment is at the heterocyclic ring. The rings may be saturated or have at least one double bond (i.e. partially unsaturated). The heterocycle may be substituted with oxo. The point of the attachment may be carbon or heteroatom in the heterocyclic ring. A heterocycle is not a heteroaryl as defined herein.

[021] Examples of the heterocycle include, but not limited to, (as numbered from the linkage position assigned priority 1) 1-pyrrolidinyl, 2-pyrrolidinyl, 2,4-imidazolidinyl, 2,3-pyrazolidinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2,5-piperazinyl, pyranyl, 2-morpholinyl, 3-morpholinyl, oxiranyl, aziridinyl, thiranyl, azetidyl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, dihydropyridinyl, tetrahydropyridinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, 1,4-oxathianyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl and 1,4-diazepane 1,4-dithianyl, 1,4-azathianyl, oxazepinyl, diazepinyl, thiazepinyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, 1,4-dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinylimidazolinyl, pyrimidinonyl, 1,1-dioxo-thiomorpholinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl and azabicyclo[2.2.2]hexanyl. Substituted heterocycle also

includes ring systems substituted with one or more oxo moieties, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl and 1, 1-dioxo-1-thiomorpholinyl.

[022] The term "fused ring" herein refers to a polycyclic ring system, e.g., a bicyclic or tricyclic ring system, in which two rings share only two ring atoms and one bond in common. Examples of fused rings may comprise a fused bicyclic cycloalkyl ring such as those having from 7 to 12 ring atoms arranged as a bicyclic ring selected from [4,4], [4,5], [5,5], [5,6] and [6,6] ring systems as mentioned above; a fused bicyclic aryl ring such as 7 to 12 membered bicyclic aryl ring systems as mentioned above, a fused tricyclic aryl ring such as 10 to 15 membered tricyclic aryl ring systems mentioned above; a fused bicyclic heteroaryl ring such as 8- to 12-membered bicyclic heteroaryl rings as mentioned above, a fused tricyclic heteroaryl ring such as 11- to 14-membered tricyclic heteroaryl rings as mentioned above; and a fused bicyclic or tricyclic heterocyclyl ring as mentioned above.

[023] In embodiments substituents are selected from optionally substituted heteroatom and optionally substituted, optionally hetero-, optionally cyclic C1-C18 hydrocarbyl, particularly wherein the optionally substituted, optionally hetero-, optionally cyclic C1-C18 hydrocarbyl is optionally-substituted, optionally hetero-, optionally cyclic alkyl, alkenyl or alkynyl, or optionally-substituted, optionally hetero- aryl; and/or the optionally substituted heteroatom is halogen, optionally substituted hydroxyl (such as alkoxy, aryloxy), optionally substituted acyl (such as formyl, alkanoyl, carbamoyl, carboxyl, amido), optionally substituted amino (such as amino, alkylamino, dialkylamino, amido, sulfamidyl), optionally substituted thiol (such as mercapto, alkylthiol, aryl thiol), optionally substituted sulfinyl or sulfonyl (such as alkylsulfinyl, arylsulfinyl, alkyl sulfonyl, arylsulfonyl), nitro, or cyano.

[024] In embodiments, substituents are selected from: halogen, -R', -OR', =O, =NR', =N-OR', -NR'R'', -SR', -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR'-SO₂NR''', -NR''CO₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R', -CN and -NO₂, -N₃, -CH(Ph)₂, perfluoro(C1-C4)alkoxy and perfluoro(C1-C4)alkyl, in a number ranging from zero to three, with those groups having zero, one or two substituents being particularly preferred. R', R'' and R''' each independently refer to hydrogen, unsubstituted (C1-C8)alkyl and heteroalkyl, (C1-C8)alkyl and heteroalkyl substituted with one to three halogens, unsubstituted aryl, aryl substituted with one to three halogens, unsubstituted

alkyl, alkoxy or thioalkoxy groups, or aryl-(C1-C4)alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. Hence, -NR'R" includes 1-pyrrolidinyl and 4-morpholinyl, "alkyl" includes groups such as trihaloalkyl (e.g., -CF₃ and -CH₂CF₃), and when the aryl group is 1,2,3,4-tetrahydronaphthalene, it may be substituted with a substituted or unsubstituted (C3-C7)spirocycloalkyl group. The (C3-C7)spirocycloalkyl group may be substituted in the same manner as defined herein for "cycloalkyl".

[025] Preferred substituents are selected from: halogen, -R', -OR', =O, -NR'R", -SR', -SiR'R"R"', -OC(O)R', -C(O)R', -CO₂R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR"CO₂R', -NR'-SO₂NR"R"', -S(O)R', -SO₂R', -SO₂NR'R", -NR"SO₂R', -CN and -NO₂, perfluoro(C1-C4)alkoxy and perfluoro(C1-C4)alkyl, where R' and R" are as defined above.

[026] Preferred substituents are disclosed herein and exemplified in the tables, structures, examples, and claims, and may be applied across different compounds of the invention, i.e. substituents of any given compound may be combinatorially used with other compounds.

[027] In particular embodiments applicable substituents are independently substituted or unsubstituted heteroatom, substituted or unsubstituted, 0-3 heteroatom C1-C6 alkyl, substituted or unsubstituted, 0-3 heteroatom C2-C6 alkenyl, substituted or unsubstituted, 0-3 heteroatom C2-C6 alkynyl, or substituted or unsubstituted, 0-3 heteroatom C6-C14 aryl, wherein each heteroatom is independently oxygen, phosphorus, sulfur or nitrogen.

[028] In more particular embodiments, applicable substituents are independently aldehyde, aldimine, alkanoyloxy, alkoxy, alkoxycarbonyl, alkyloxy, alkyl, amine, azo, halogens, carbamoyl, carbonyl, carboxamido, carboxyl, cyanyl, ester, halo, haloformyl, hydroperoxyl, hydroxyl, imine, isocyanide, iscyante, N-tert-butoxycarbonyl, nitrate, nitrile, nitrite, nitro, nitroso, phosphate, phosphono, sulfide, sulfonyl, sulfo, sulfhydryl, thiol, thiocyanyl, trifluoromethyl or trifluoromethyl ether (OCF₃).

[029] The compounds may contain an asymmetric center and may thus exist as enantiomers. Where the compounds possess two or more asymmetric centers, they may additionally exist as diastereomers. Enantiomers and diastereomers fall within the broader class of stereoisomers. All such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers are intended to be included. All stereoisomers of the compounds and/or pharmaceutically acceptable salts

thereof are intended to be included. Unless specifically mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.

[030] The term “substantially pure” means that the target stereoisomer contains no more than 35%, such as no more than 30%, further such as no more than 25%, even further such as no more than 20%, by weight of any other stereoisomer(s). In some embodiments, the term “substantially pure” means that the target stereoisomer contains no more than 10%, for example, no more than 5%, such as no more than 1%, by weight of any other stereoisomer(s).

[031] When compounds contain olefin double bonds, unless specified otherwise, such double bonds are meant to include both E and Z geometric isomers.

[032] Some of the compounds may exist with different points of attachment of hydrogen, referred to as tautomers. For example, compounds including carbonyl $\text{-CH}_2\text{C(O)-}$ groups (keto forms) may undergo tautomerism to form hydroxyl -CH=C(OH)- groups (enol forms). Both keto and enol forms, individually as well as mixtures thereof, are also intended to be included where applicable.

[033] It may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography.

Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed ("SMB") and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. One skilled in the art will apply techniques most likely to achieve the desired separation.

[034] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction

with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

[035] A single stereoisomer, e.g., a substantially pure enantiomer, may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents. Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

[036] "Pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids, selected, for example, from hydrochlorates, phosphates, diphosphates, hydrobromates, sulfates, sulfinates, and nitrates; as well as salts with organic acids, selected, for example, from malates, maleates, fumarates, tartrates, succinates, citrates, lactates, methanesulfonates, p-toluenesulfonates, 2-hydroxyethylsulfonates, benzoates, salicylates, stearates, alkanoates such as acetate, and salts with $\text{HOOC}-(\text{CH}_2)_n\text{-COOH}$, wherein n is selected from 0 to 4. Similarly, examples of pharmaceutically acceptable cations include, but are not limited to, sodium, potassium, calcium, aluminum, lithium, and ammonium.

[037] In addition, if a compound is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, such as a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used without undue experimentation to prepare non-toxic pharmaceutically acceptable addition salts.

[038] “Treating,” “treat,” or “treatment” refers to administering at least one compound and/or at least one stereoisomer thereof, and/or at least one pharmaceutically acceptable salt thereof to a subject in recognized need thereof.

[039] An “effective amount” refers to an amount of at least one compound and/or at least one stereoisomer thereof, and/or at least one pharmaceutically acceptable salt thereof effective to “treat” a disease or disorder in a subject, and that will elicit, to some significant extent, the biological or medical response of a tissue, system, animal or human that is being sought, such as when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated. The therapeutically effective amount will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[040] The term “at least one substituent” includes, for example, from 1 to 4, such as from 1 to 3, further as 1 or 2, substituents. For example, “at least one substituent R¹⁶” herein includes from 1 to 4, such as from 1 to 3, further as 1 or 2, substituents selected from the list of R¹⁶ as described herein.

[041] The subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof may be employed alone or in combination with at least one other therapeutic agent for treatment. In some embodiments, the compounds, stereoisomers thereof, and pharmaceutically acceptable salts thereof can be used in combination with at least one additional therapeutic agent. The compound and/or one pharmaceutically acceptable salt disclosed herein may be administered with the at least one other therapeutic agent in a single dosage form or as a separate dosage form. When administered as a separate dosage form, the at least one other therapeutic agent may be administered prior to, at the same time as, or following administration of the compound and/or one pharmaceutically acceptable salt disclosed herein.

[042] Also provided is a composition comprising a subject compound and stereoisomers thereof, and pharmaceutically acceptable salts thereof, and at least one pharmaceutically acceptable carrier.

[043] The composition comprising a subject compound and stereoisomers thereof, and pharmaceutically acceptable salts thereof can be administered in various known manners, such as orally, topically, rectally, parenterally, by inhalation spray, or via an implanted

reservoir, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The term “parenteral” as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques. The compositions disclosed herein may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art.

[044] The subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosage forms that can also be used to administer the subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, i.e., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

[045] Gelatin capsules containing the compound and/or the at least one pharmaceutically acceptable salt thereof disclosed herein and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like, can also be used. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[046] Liquid dosage forms for oral administration can further comprise at least one agent selected from coloring and flavoring agents to increase patient acceptance.

[047] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols can be examples of suitable carriers for parenteral solutions. Solutions for parenteral administration may comprise a water soluble salt of the at least one compound describe herein, at least one suitable stabilizing agent, and if necessary, at least one buffer substance. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, can be examples of suitable stabilizing agents. Citric acid and its salts and sodium EDTA can also be used as examples of suitable stabilizing agents. In addition, parenteral solutions can further comprise at least one preservative, selected, for example, from benzalkonium chloride, methyl- and propylparaben, and chlorobutanol.

[048] A pharmaceutically acceptable carrier is, for example, selected from carriers that are compatible with active ingredients of the composition (and in some embodiments, capable of stabilizing the active ingredients) and not deleterious to the subject to be treated. For example, solubilizing agents, such as cyclodextrins (which can form specific, more soluble complexes with the at least one compound and/or at least one pharmaceutically acceptable salt disclosed herein), can be utilized as pharmaceutical excipients for delivery of the active ingredients. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and pigments such as D&C Yellow # 10. Suitable pharmaceutically acceptable carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in the art.

[049] For administration by inhalation, the subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof may also be delivered as powders, which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. One exemplary delivery system for inhalation can be metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a subject compound and stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein in at least one suitable propellant, selected, for example, from fluorocarbons and hydrocarbons.

[050] For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percentage of a solution or suspension of the subject compound and stereoisomers thereof, and pharmaceutically acceptable salts thereof in an appropriate ophthalmic vehicle, such that the subject compound and stereoisomers thereof, and at least one pharmaceutically acceptable salts thereof is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

[051] Useful pharmaceutical dosage-forms for administration of the subject compounds and stereoisomers thereof, and pharmaceutically acceptable salts thereof disclosed herein include, but are not limited to, hard and soft gelatin capsules, tablets, parenteral injectables, and oral suspensions.

[052] The dosage administered will be dependent on factors, such as the age, health and weight of the recipient, the extent of disease, type of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. In general, a daily dosage of the active ingredient can vary, for example, from 0.1 to 2000 milligrams per day. For example, 10-500 milligrams once or multiple times per day may be effective to obtain the desired results.

[053] In some embodiments, a large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with, for example, 100 milligrams of the subject compound and stereoisomers thereof, and pharmaceutically acceptable salt thereof disclosed herein in powder, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

[054] In some embodiments, a mixture of the compound, stereoisomers thereof, and pharmaceutically acceptable salts thereof a digestible oil such as soybean oil, cottonseed oil or olive oil can be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

[055] In some embodiments, a large number of tablets can be prepared by conventional procedures so that the dosage unit comprises, for example, 100 milligrams of the compound, stereoisomers thereof, and pharmaceutically acceptable salts thereof, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams

of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose.

Appropriate coatings may be applied to increase palatability or delay absorption.

[056] In some embodiments, a parenteral composition suitable for administration by injection can be prepared by stirring 1.5% by weight of the compound and/or at least an enantiomer, a diastereomer, or pharmaceutically acceptable salt thereof disclosed herein in 10% by volume propylene glycol. The solution is made to the expected volume with water for injection and sterilized.

[057] In some embodiment, an aqueous suspension can be prepared for oral administration. For example, each 5 milliliters of an aqueous suspension comprising 100 milligrams of finely divided compound, stereoisomers thereof, and pharmaceutically acceptable salts thereof, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin can be used.

[058] The same dosage forms can generally be used when the compound, stereoisomers thereof, and pharmaceutically acceptable salts thereof are administered stepwise or in conjunction with at least one other therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should be selected depending on the compatibility of the combined drugs. Thus the term coadministration is understood to include the administration of at least two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the at least two active components.

[059] The compounds, stereoisomers thereof, and pharmaceutically acceptable salt thereof disclosed herein can be administered as the sole active ingredient or in combination with at least one second active ingredient.

[060] The subject compounds are incorporated into pharmaceutical compositions or formulations. The compositions will contain pharmaceutically acceptable diluents and/or carriers, i. e. diluents or carriers that are physiologically compatible and substantially free from pathogenic impurities. Suitable excipients or carriers and methods for preparing administrable compositions are known or apparent to those skilled in the art and are described in more detail in such publications as Remington's Pharmaceutical Science, Mack Publishing Co, NJ (1991). The compositions may also be in the form of controlled release

or sustained release compositions as known in the art. For many applications the subject compounds are administered for morning/daytime dosing, with off period at night.

[061] The subject compounds may be used per se, or in the form of their pharmaceutically acceptable salts, such as hydrochlorides, hydrobromides, acetates, sulfates, citrates, carbonates, trifluoroacetates and the like. When compounds contain relatively acidic functionalities, salts can be obtained by addition of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salts, or the like. When compounds contain relatively basic functionalities, salts can be obtained by addition of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, for example, Berge et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19).

[062] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid, and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of this invention.

[063] In addition to salt forms, this invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed

in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be more bioavailable by oral administration than the parent drug. The prodrug may also have improved solubility in pharmacological compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity.

[064] Certain compounds of the invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the invention.

[065] Some of the subject compounds possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

[066] The compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds, such as deuterium, e.g. $-CD_3$, CD_2H or CDH_2 in place of methyl. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention.

[067] The compounds are generally administered in a "therapeutically effective amount", i.e. the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. The term "therapeutically effective amount" includes that amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being

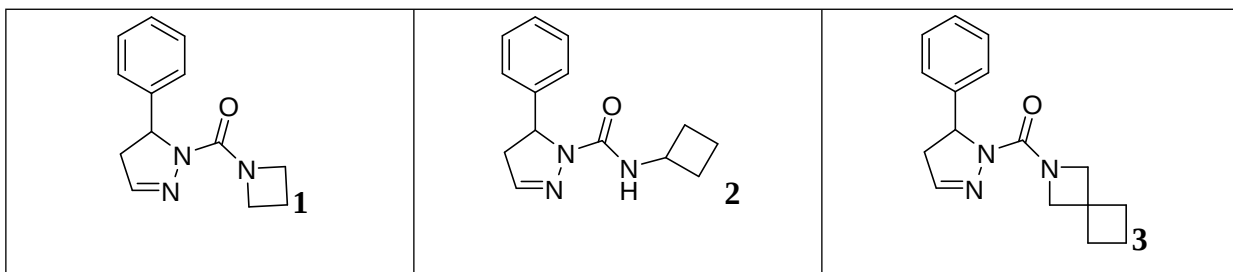
treated. The therapeutically effective amount will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

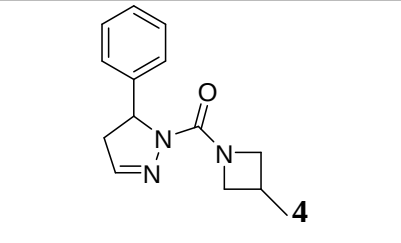
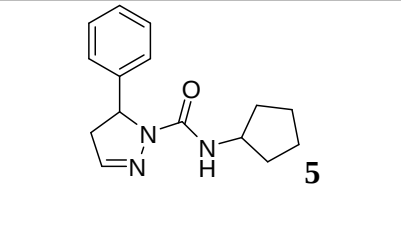
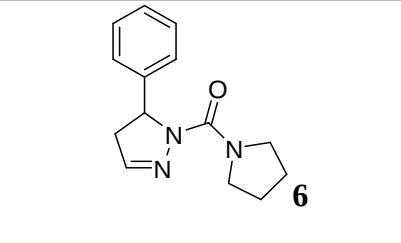
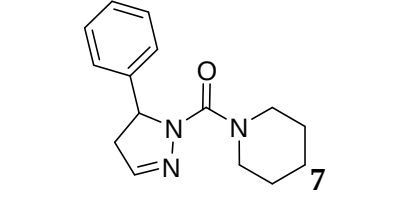
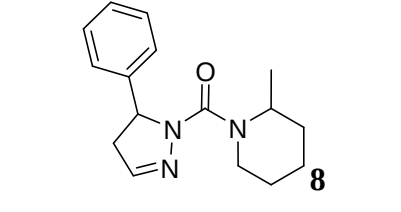
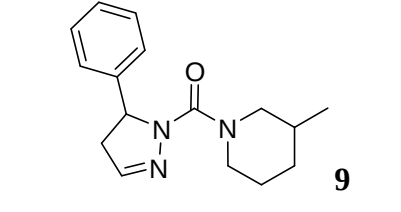
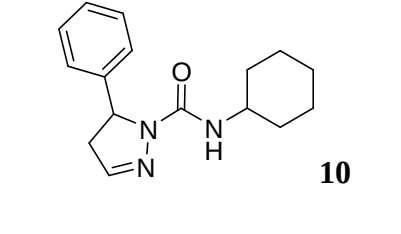
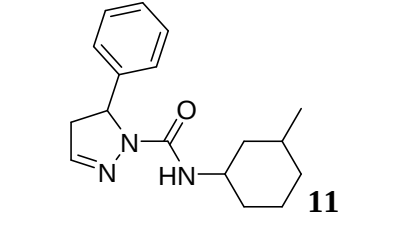
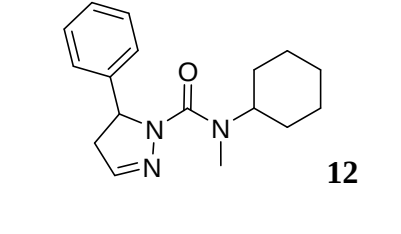
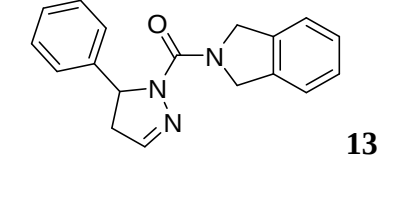
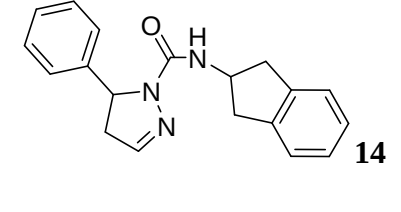
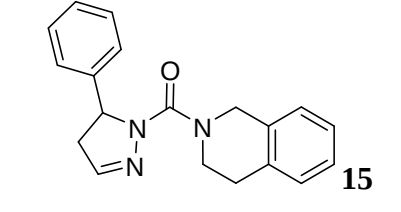
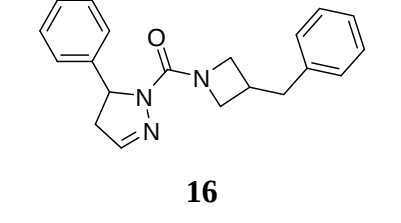
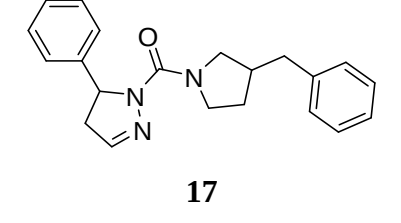
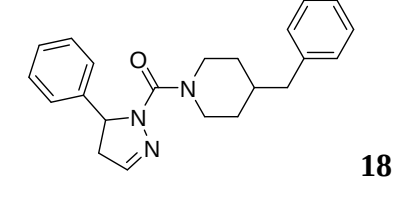
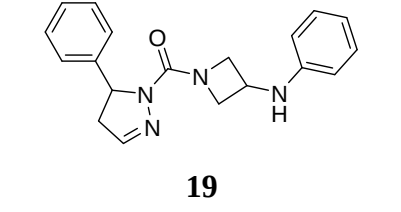
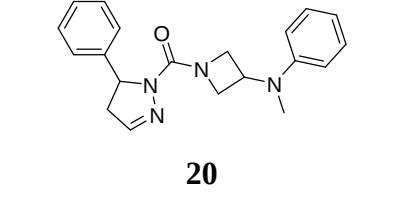
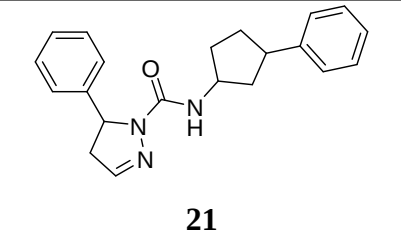
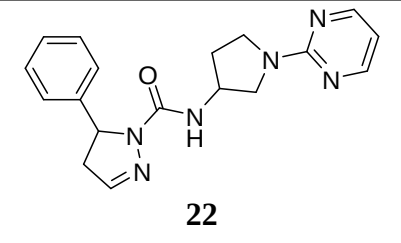
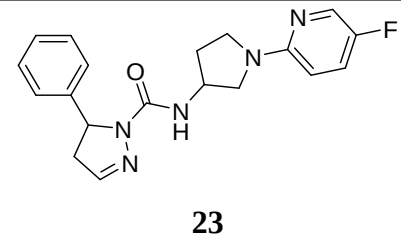
[068] The contacting is generally effected by administering to the subject an effective amount of one or more compounds having the general formula I (supra), including the various embodiments described above. Generally administration is adjusted to achieve a therapeutic dosage of about 0.1 to 50, preferably 0.5 to 10, more preferably 1 to 10 mg/kg, though optimal dosages are compound specific, and generally empirically determined for each compound.

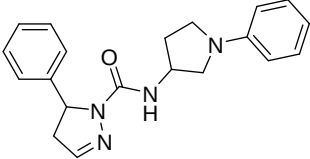
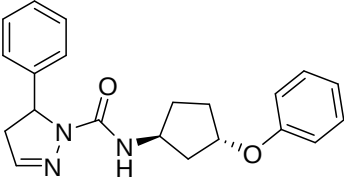
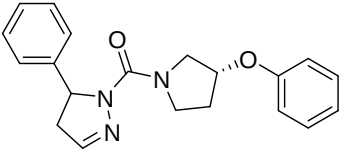
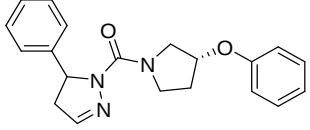
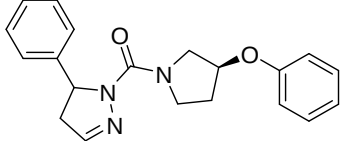
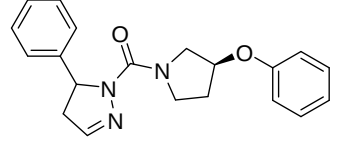
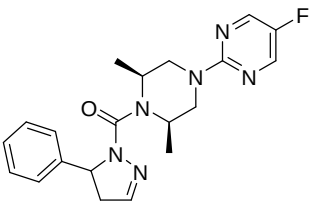
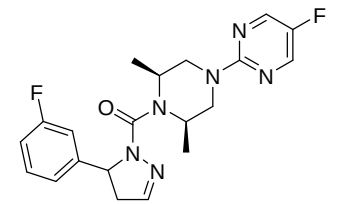
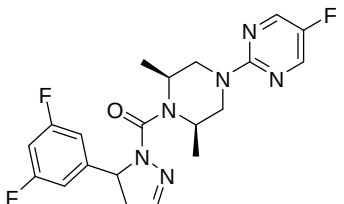
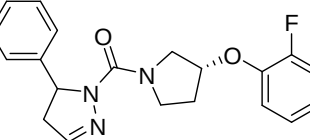
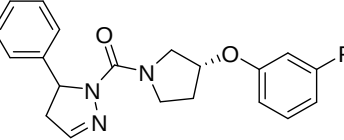
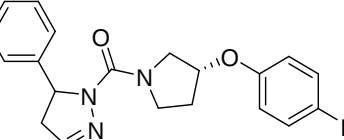
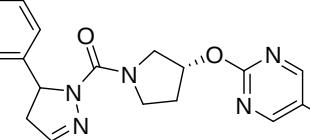
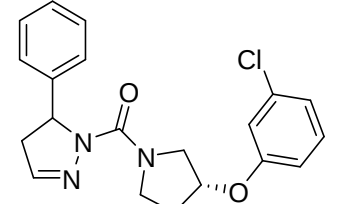
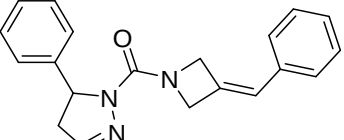
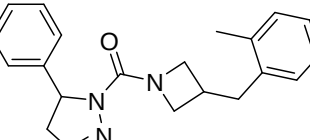
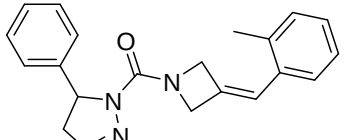
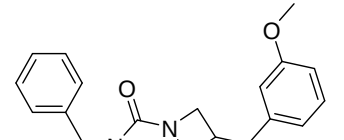
[069] The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules, lozenges or the like in the case of solid compositions. In such compositions, the mimetic is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form. Unit dosage formulations are preferably about of 5, 10, 25, 50, 100, 250, 500, or 1,000 mg per unit. In a particular embodiment, unit dosage forms are packaged in a multipack adapted for sequential use, such as blisterpack comprising sheets of at least 6, 9 or 12 unit dosage forms.

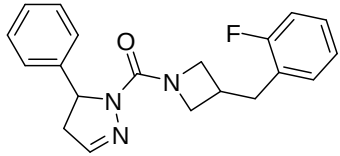
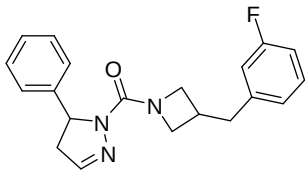
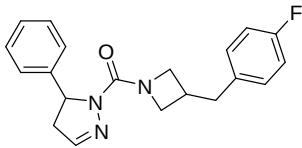
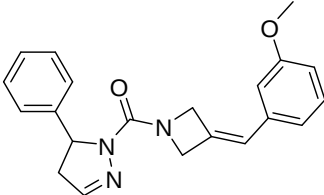
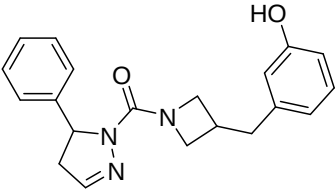
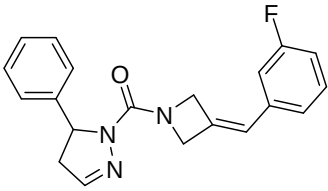
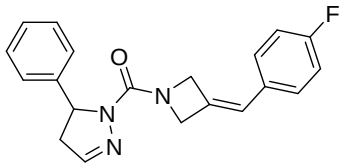
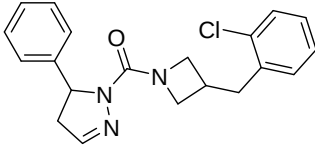
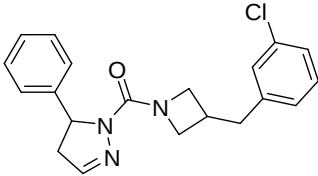
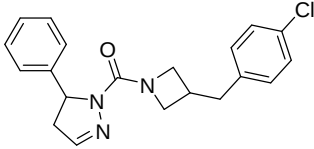
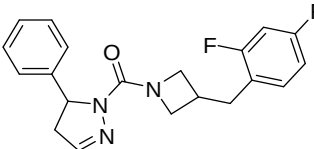
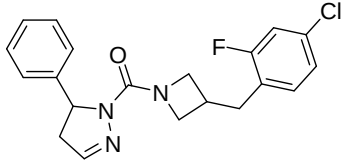
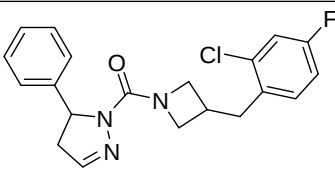
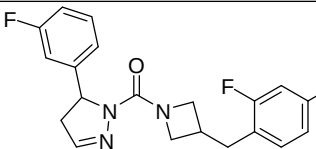
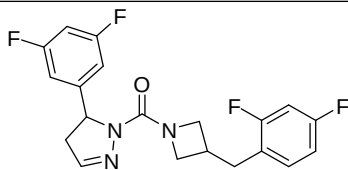
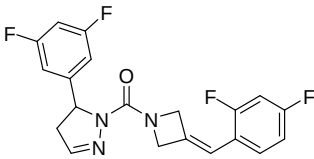
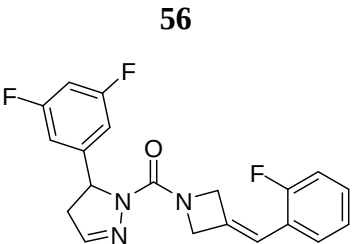
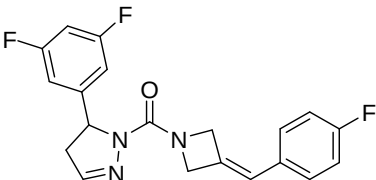
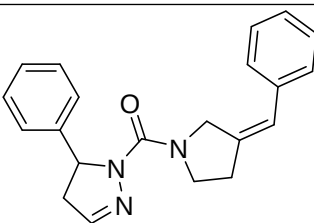
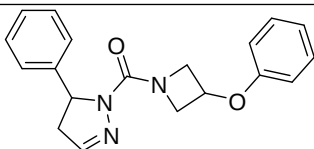
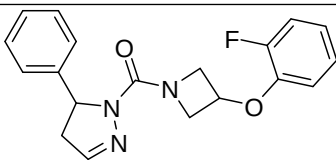
[070] The subject compositions may also be coformulated and/or coadministered with a different compound to treat programmed cell death.

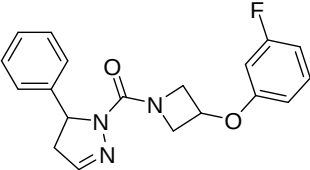
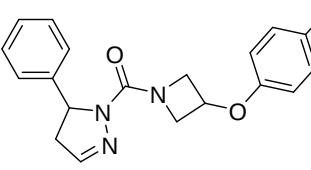
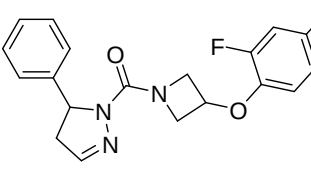
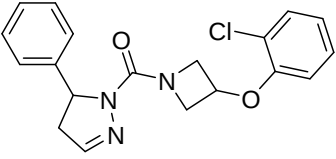
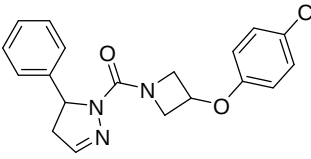
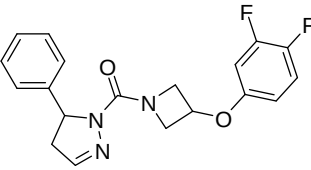
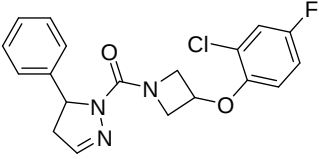
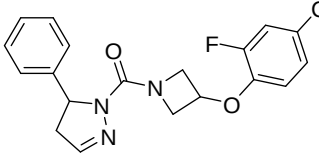
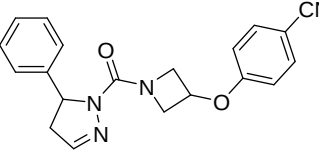
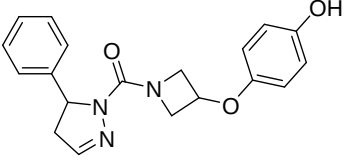
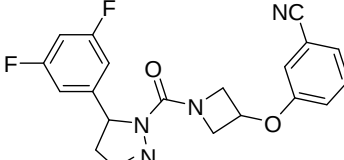
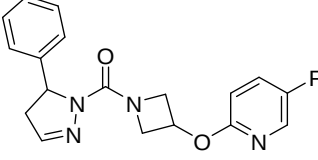
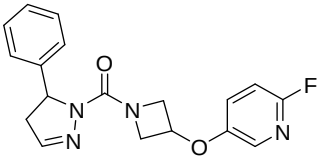
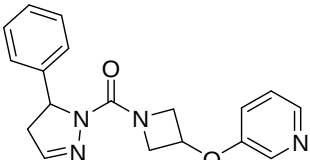
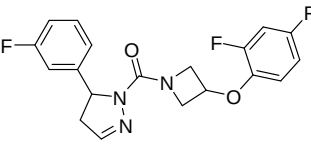
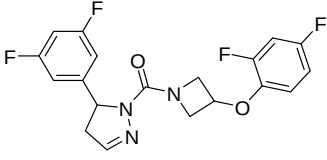
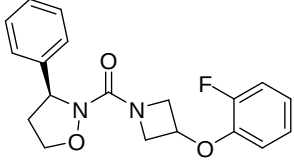
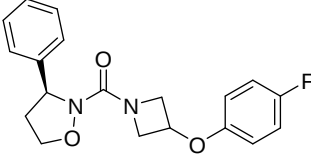
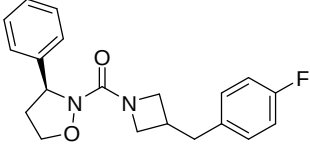
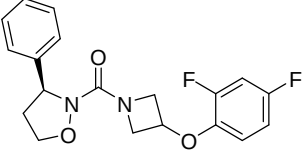
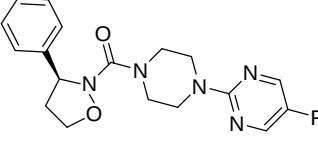
[071] Table 1 Active Compounds

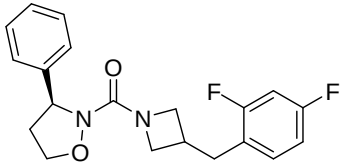
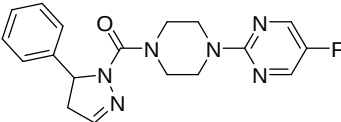
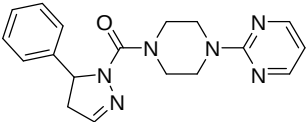
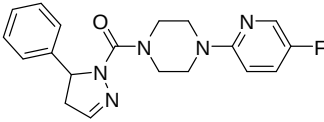
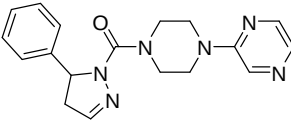
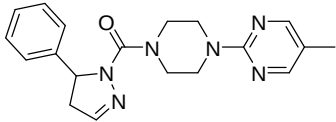
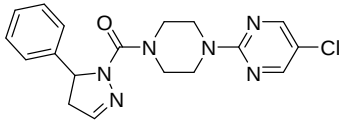
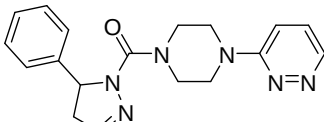
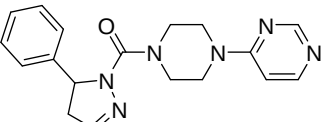
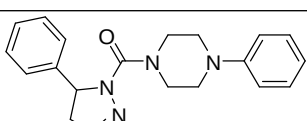
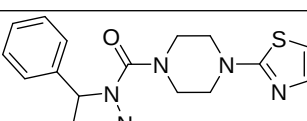
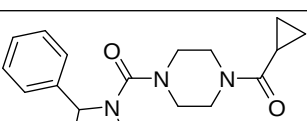
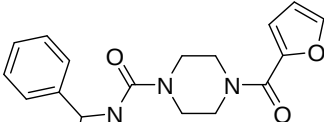
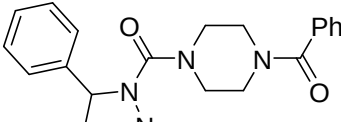
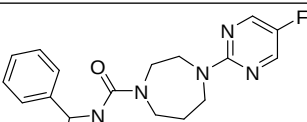
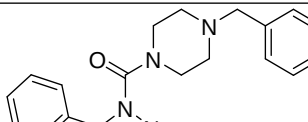
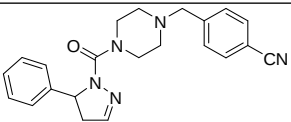
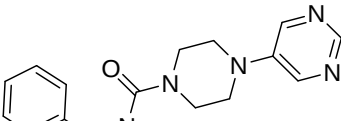
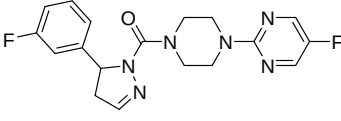
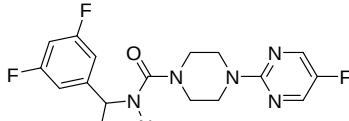


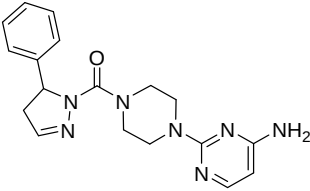
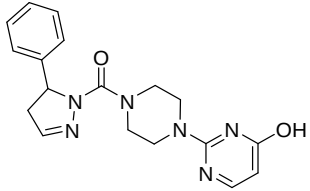
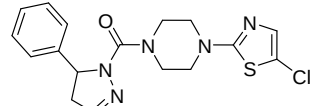
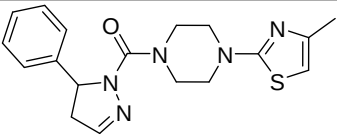
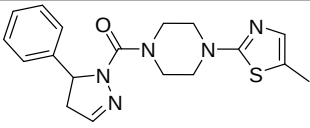
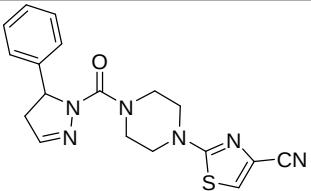
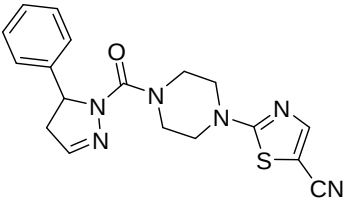
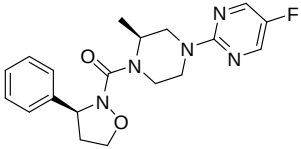
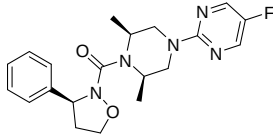
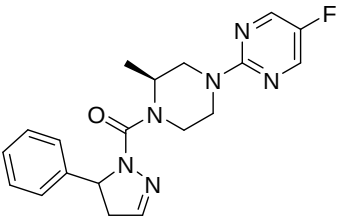
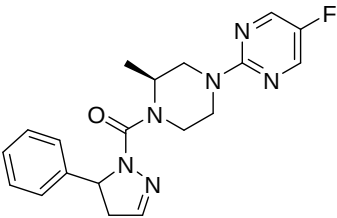
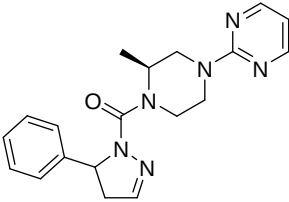
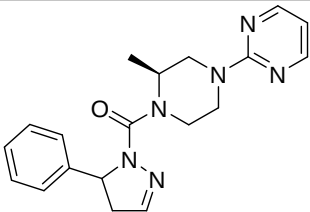
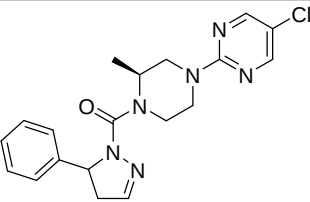
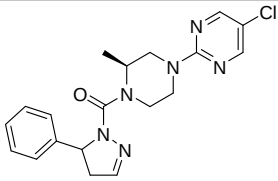
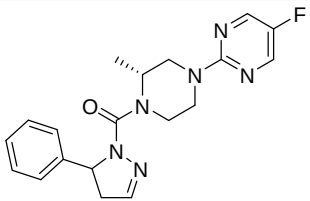
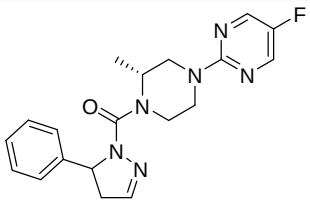
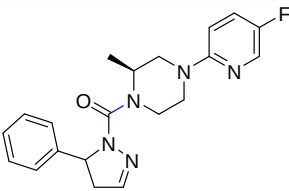
 4	 5	 6
 7	 8	 9
 10	 11	 12
 13	 14	 15
 16	 17	 18
 19	 20	
 21	 22	 23

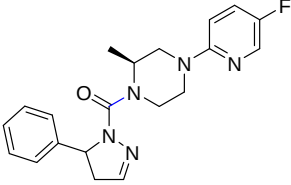
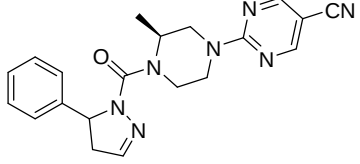
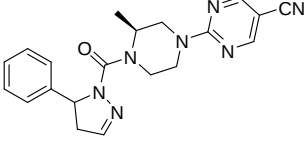
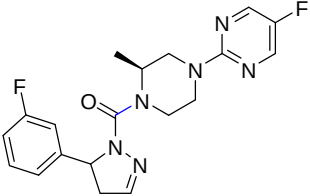
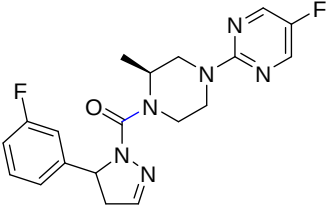
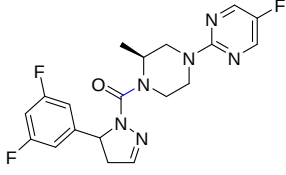
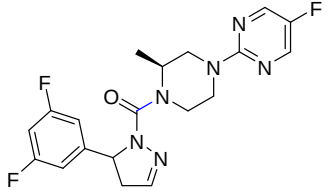
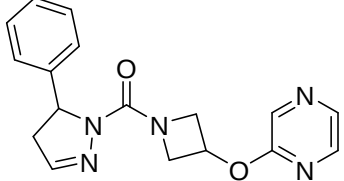
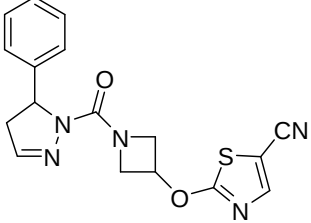
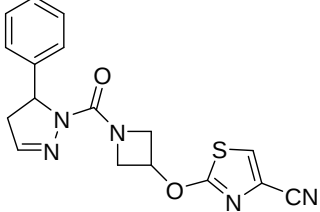
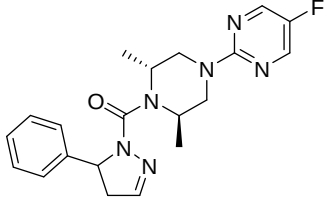
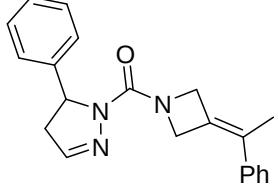
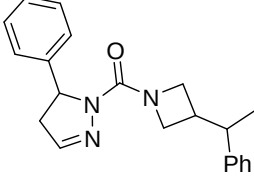
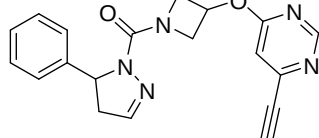
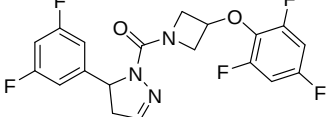
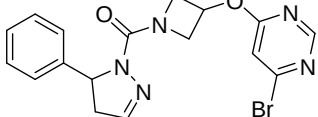
 24	 25	26A 
 26B	 27A	 27B
 28	 29	 30
 31	 32	 33
 34	 35	 36
 37	 38	 39

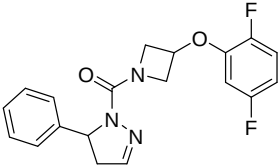
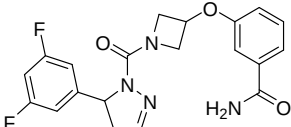
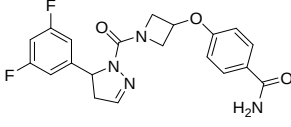
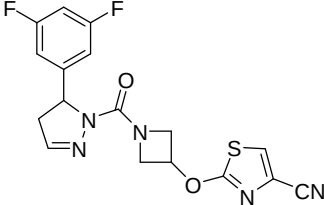
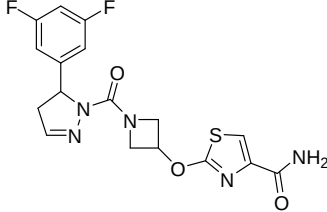
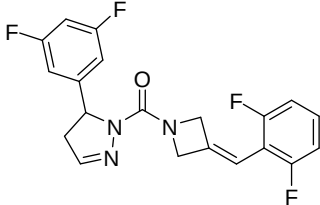
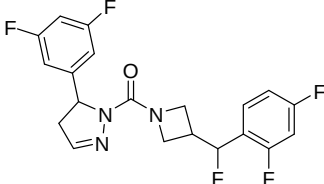
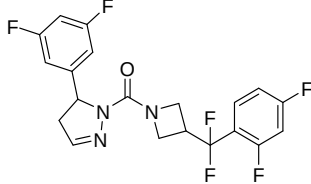
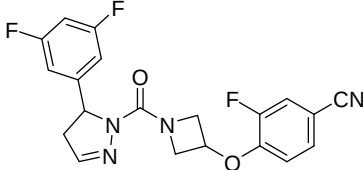
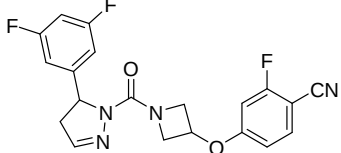
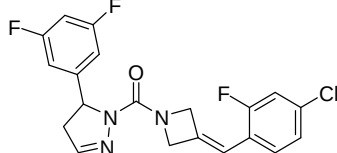
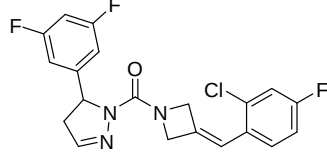
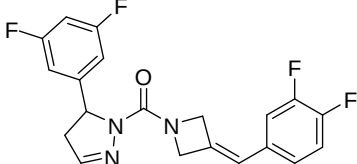
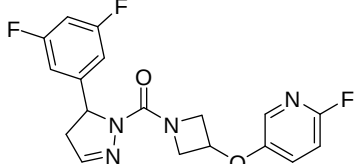
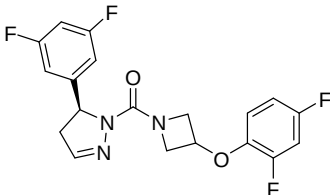
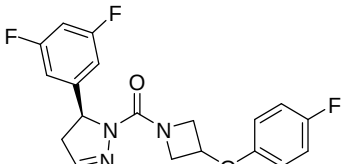
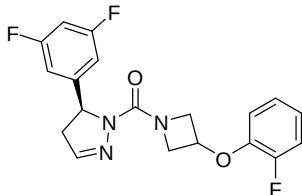
 40	 41	 42
 43	 44	 45
 46	 47	 48
 49	 50	 51
 52	 53	 54
 55	 56	 57
 58	 59	 60

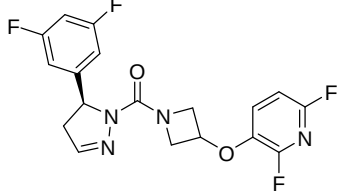
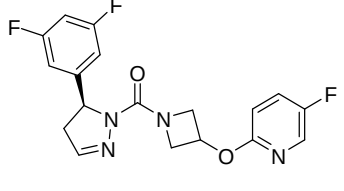
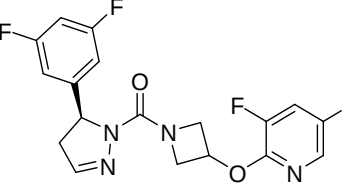
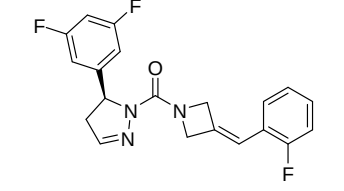
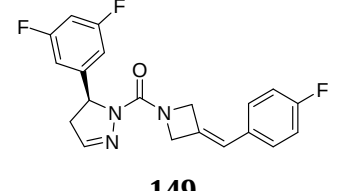
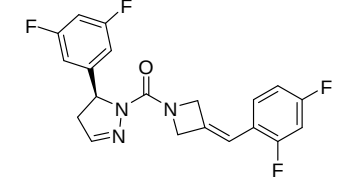
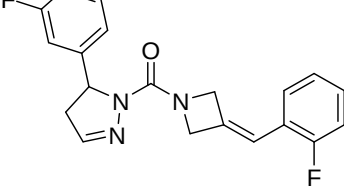
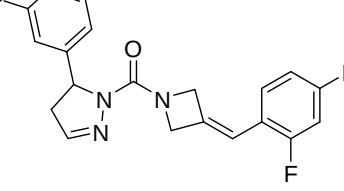
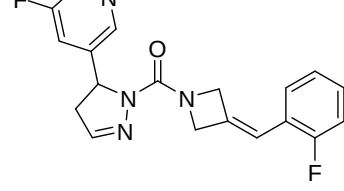
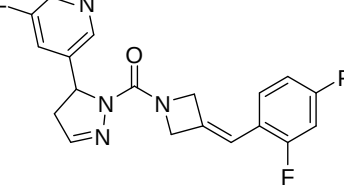
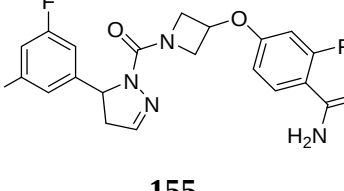
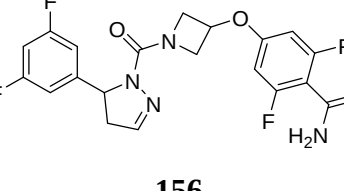
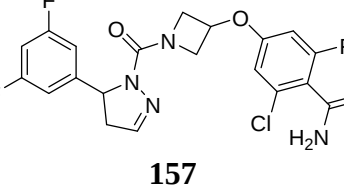
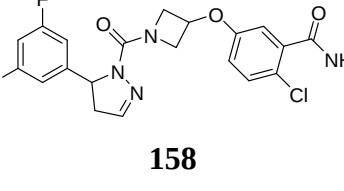
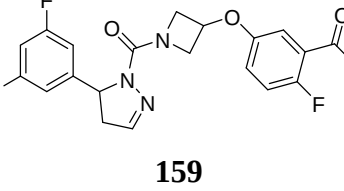
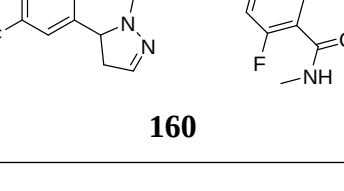
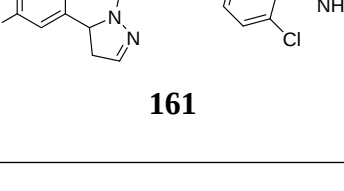
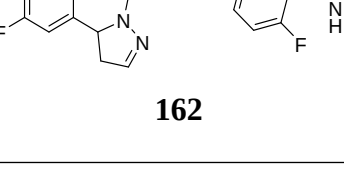
 61	 62	 63
 64	 65	 66
 67	 68	 69
 70	 71	 72
 73	 74	 75
 76	 77	 78
 79	 80	 81

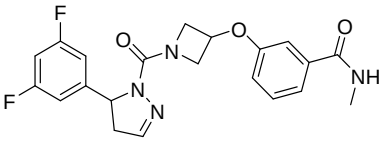
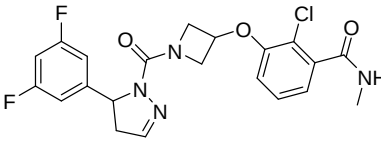
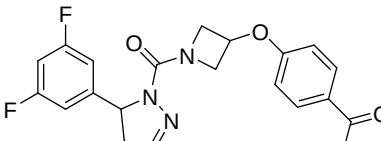
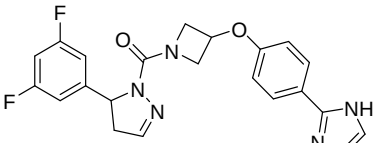
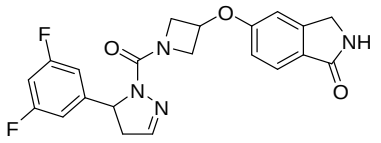
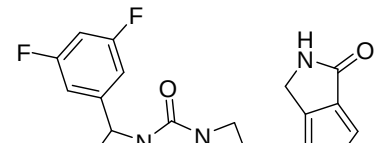
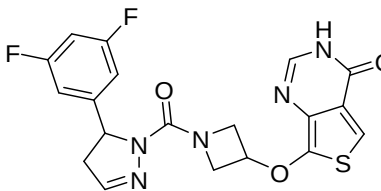
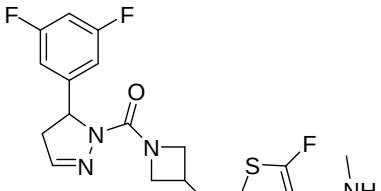
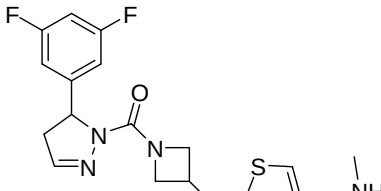
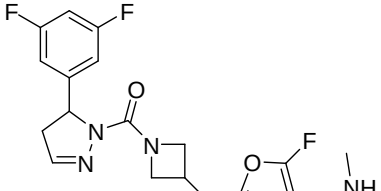
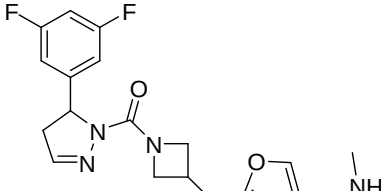
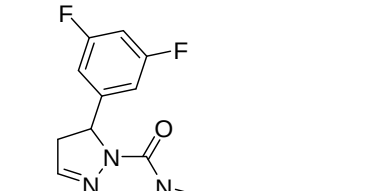
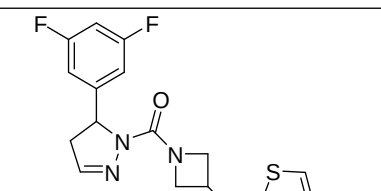
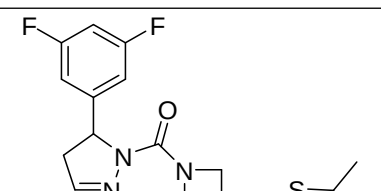
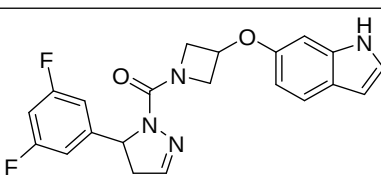
	80	
		
82	83	84
		
85	86	87
		
88	89	90
		
91	92	93
		
94	95	
		
96	97	98
		
99	100	101

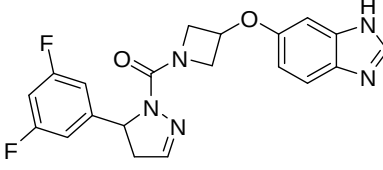
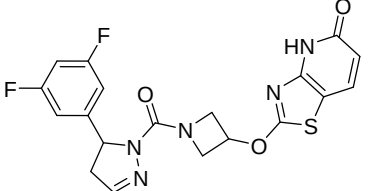
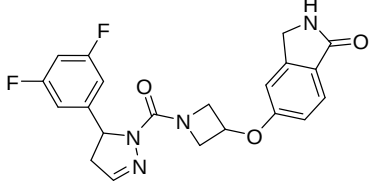
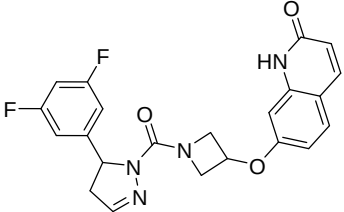
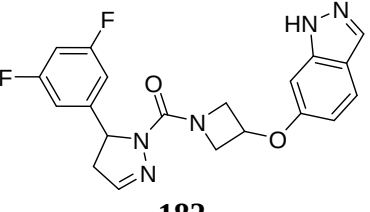
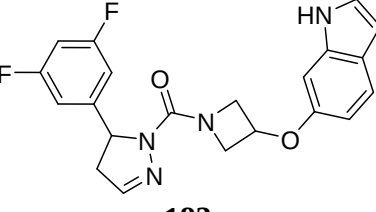
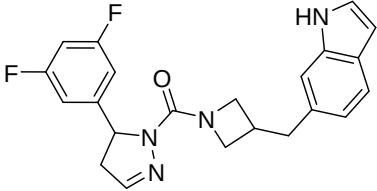
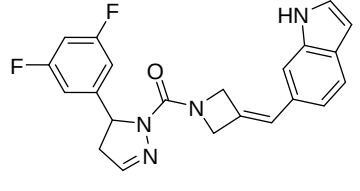
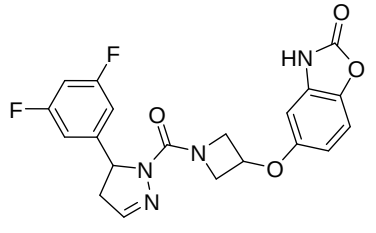
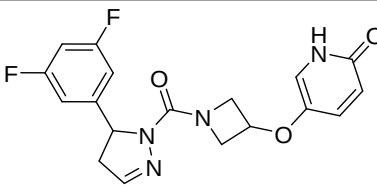
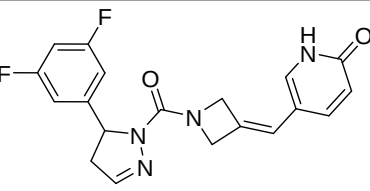
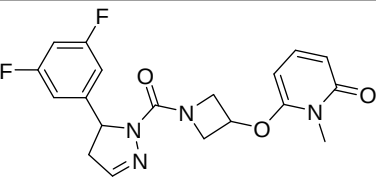
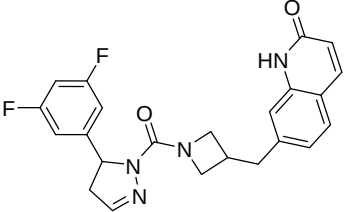
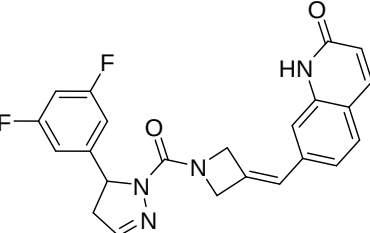
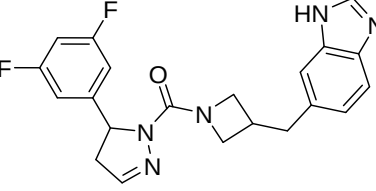
 102	 103	 104
 105	 106	 107
 108	 109	 110
 111A	 111B	 112A
 112B	 113A	 113B
 114A	 114B	 115A

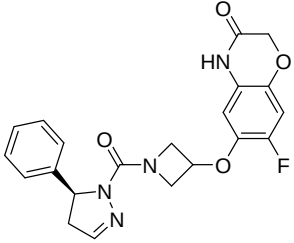
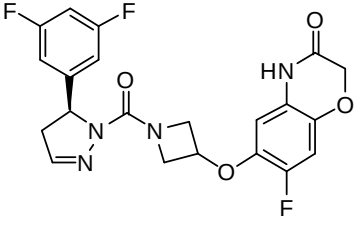
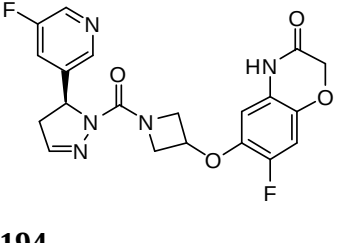
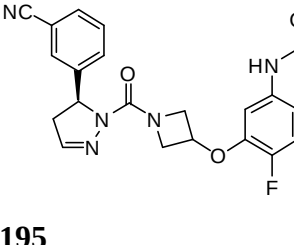
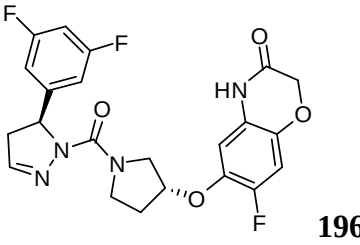
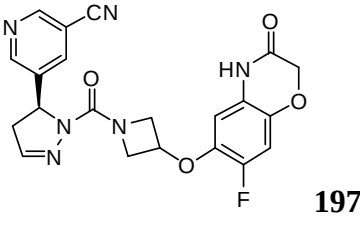
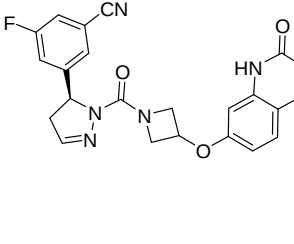
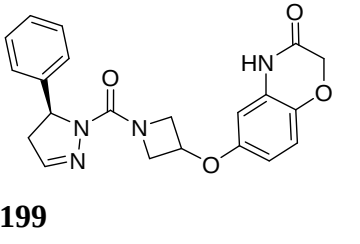
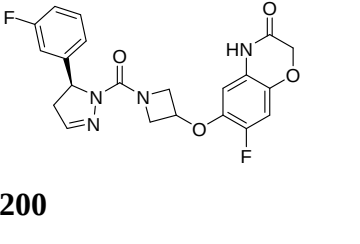
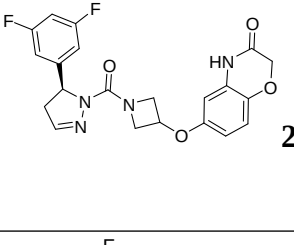
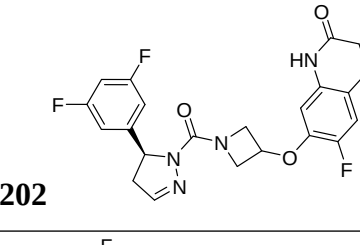
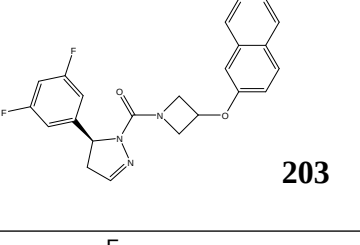
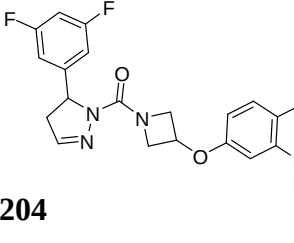
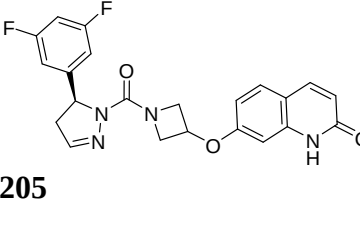
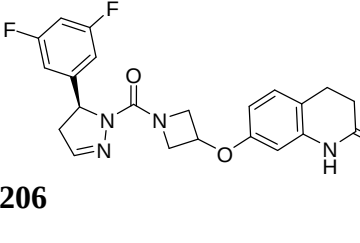
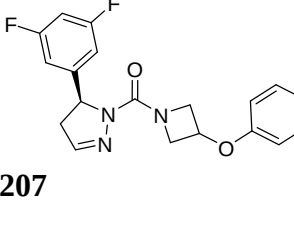
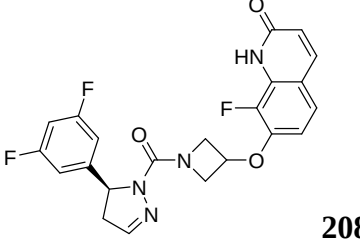
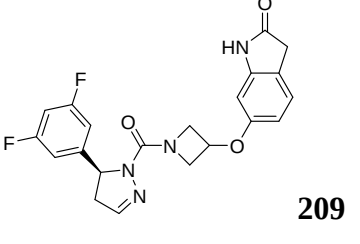
 115B	 116A	 116B
 117A	 117B	 118A
 118B		
 119	 120	 121
 122	 123	 124
 125	 126	 127

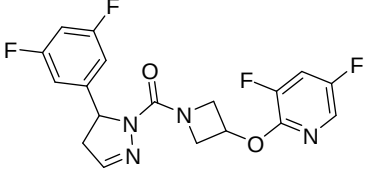
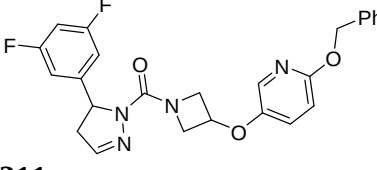
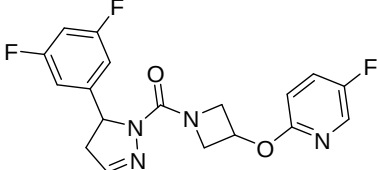
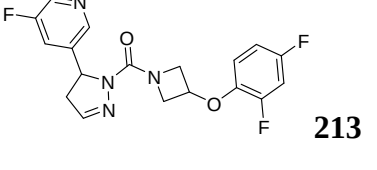
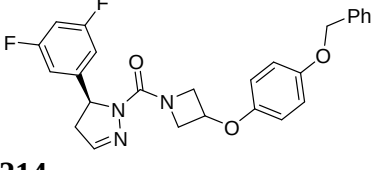
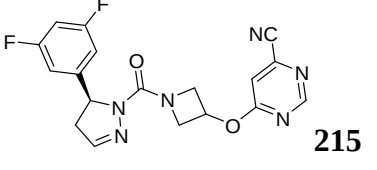
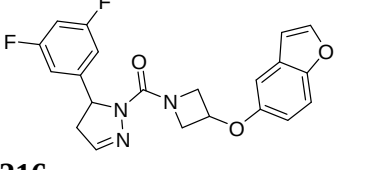
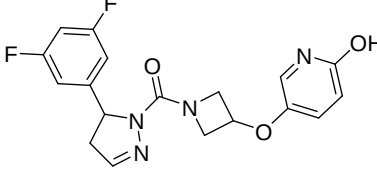
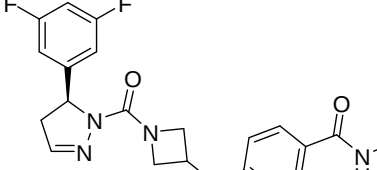
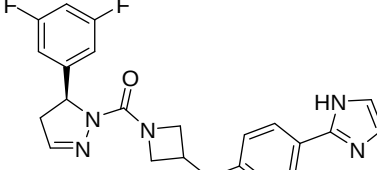
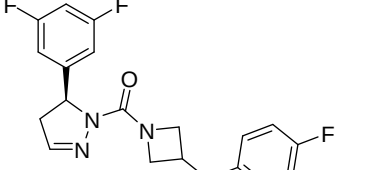
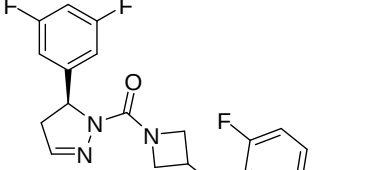
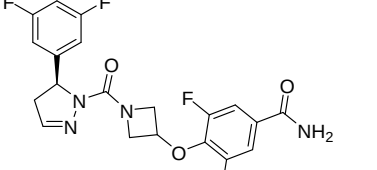
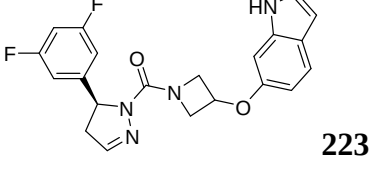
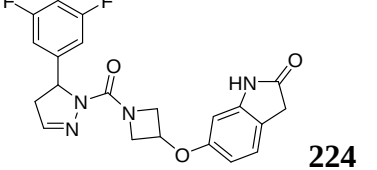
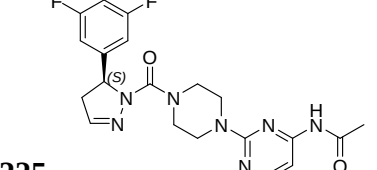
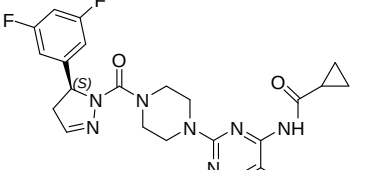
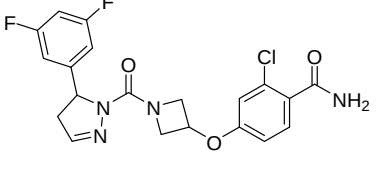
 128	 129	 130
 131	 132	 133
 134	 135	 136
 137	 138	 139
 140	 141	
 142	 143	 144

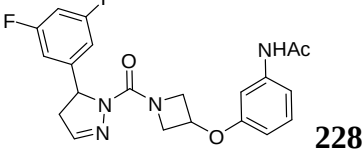
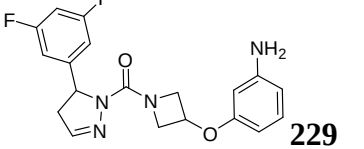
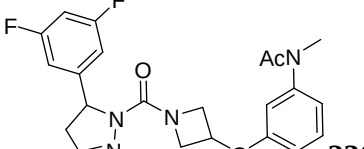
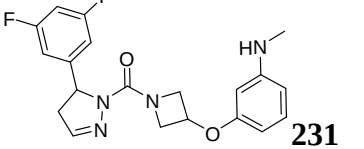
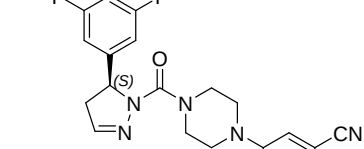
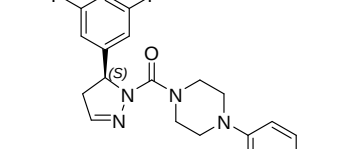
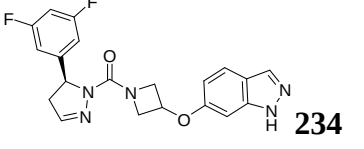
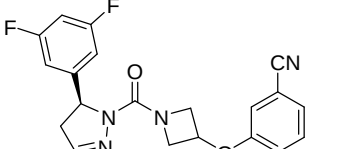
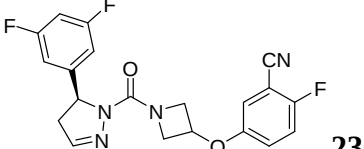
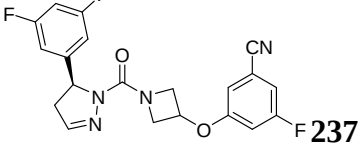
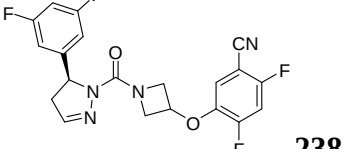
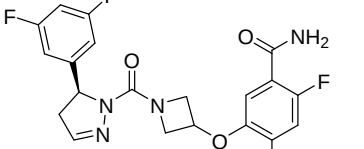
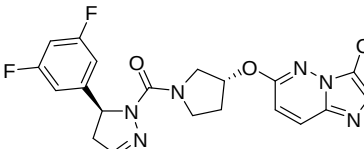
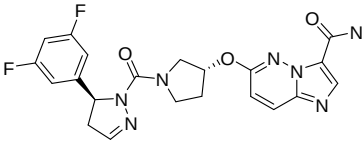
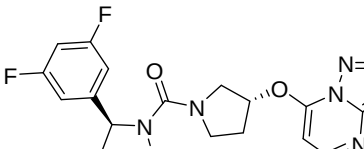
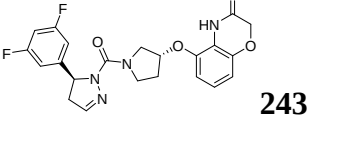
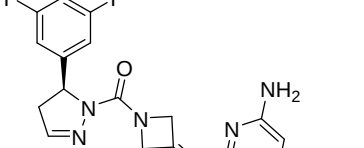
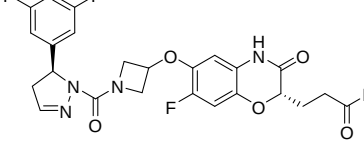
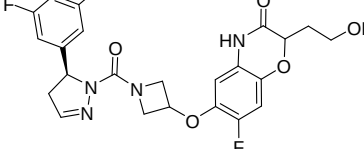
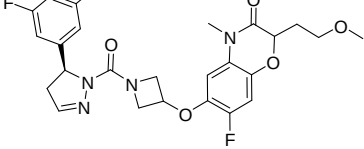
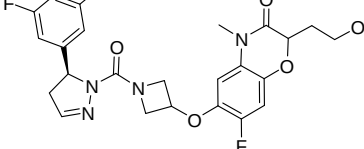
 145	 146	 147
 148	 149	 150
 151	 152	 153
 154	 155	 156
 157	 158	 159
 160	 161	 162

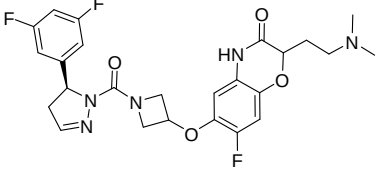
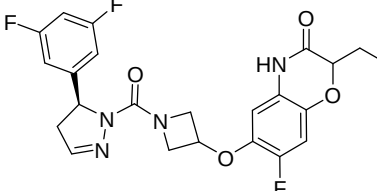
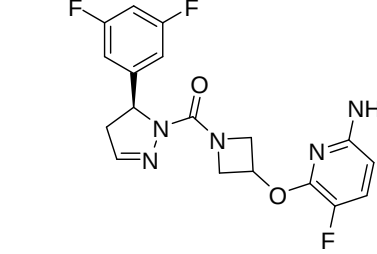
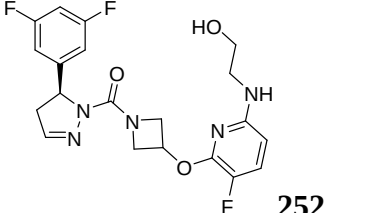
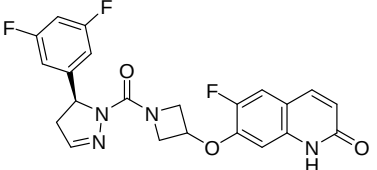
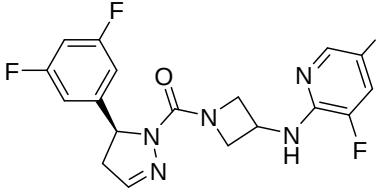
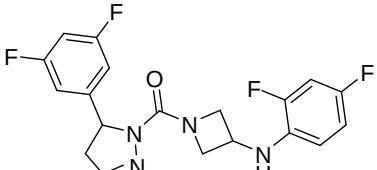
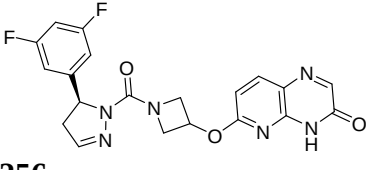
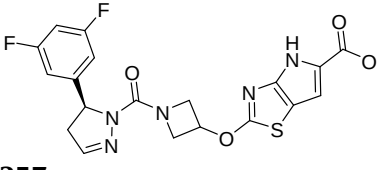
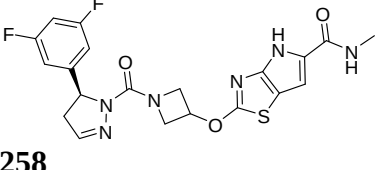
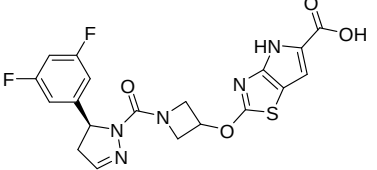
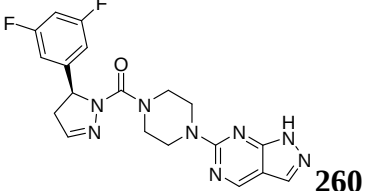
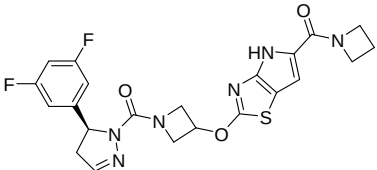
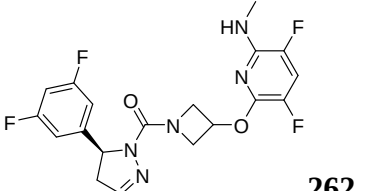
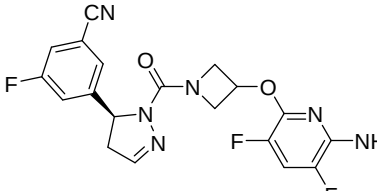
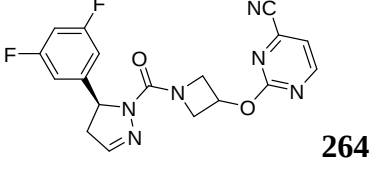
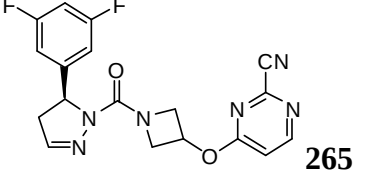
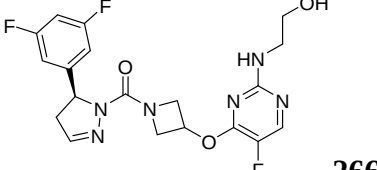
 163	 164	 165
 166	 167	 168
 169	 170	 171
 172	 173	 174
 175	 176	 177

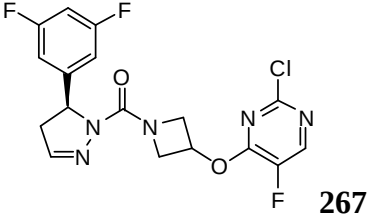
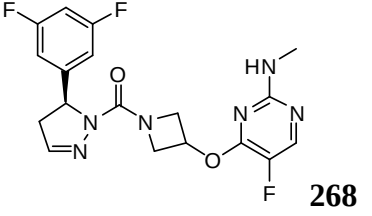
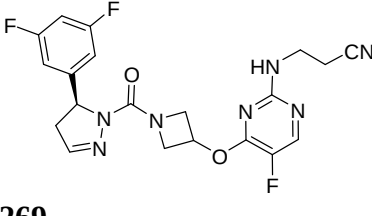
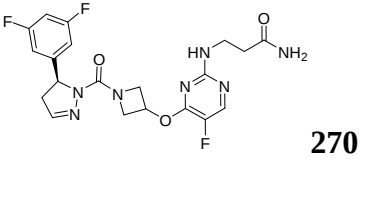
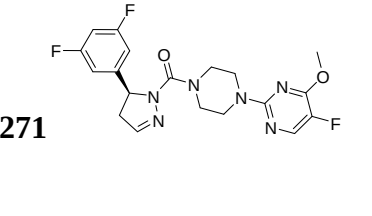
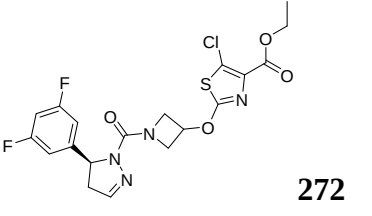
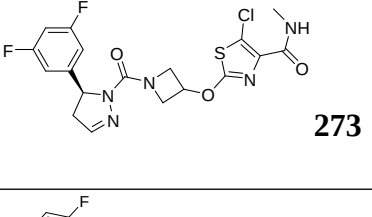
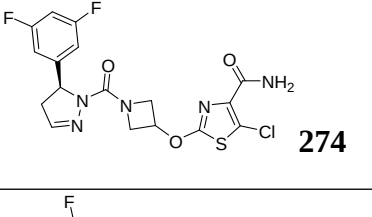
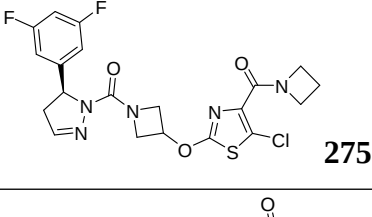
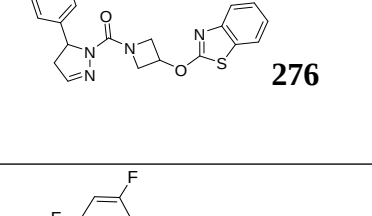
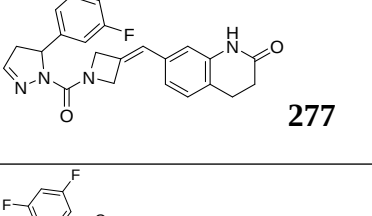
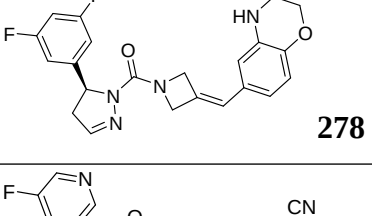
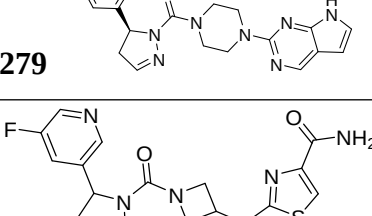
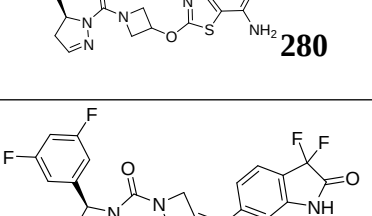
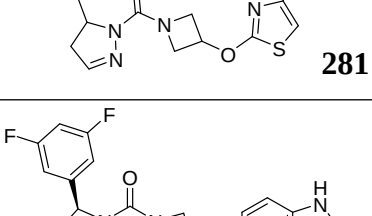
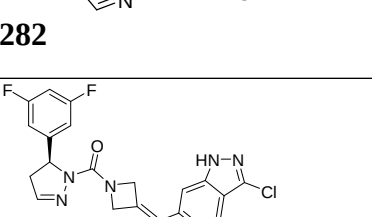
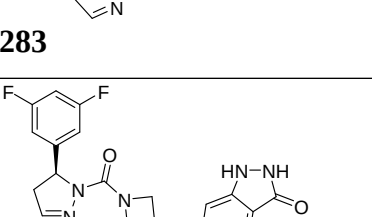
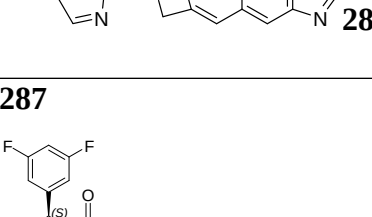
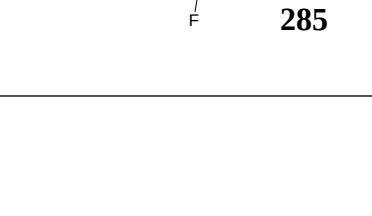
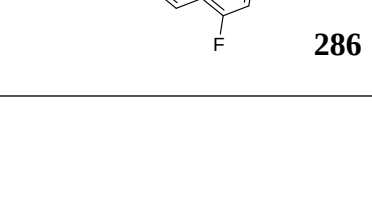
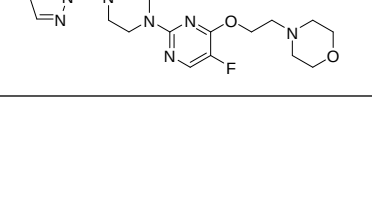
 178	 179	 180
 181	 182	 183
 183	 184	 185
 186	 187	 188
 189	 190	 191

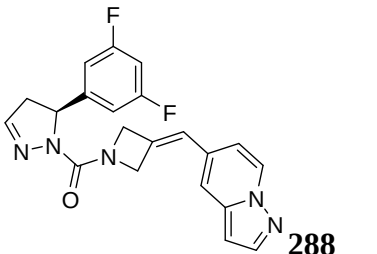
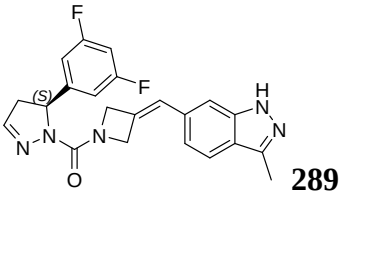
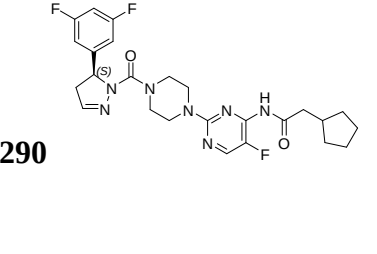
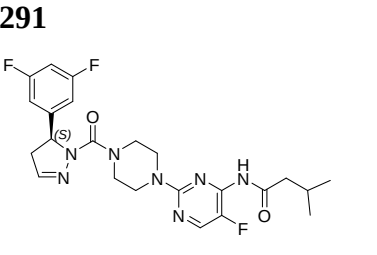
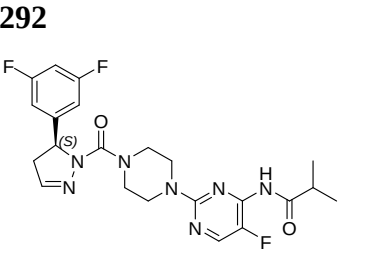
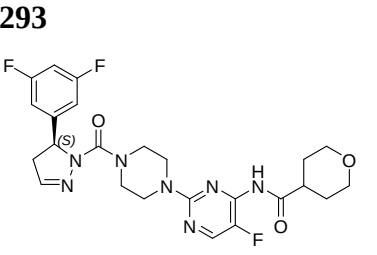
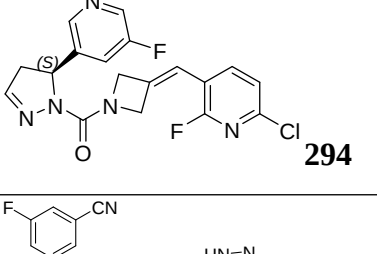
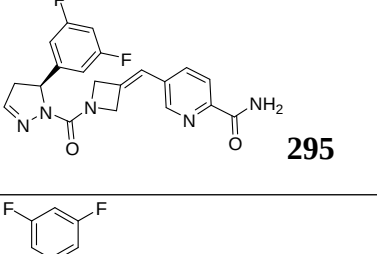
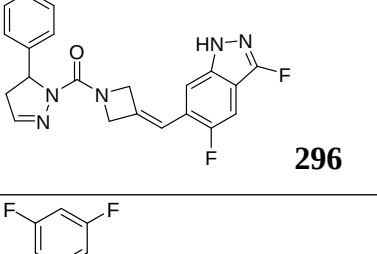
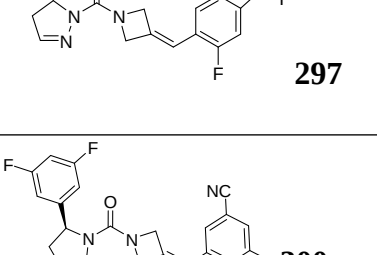
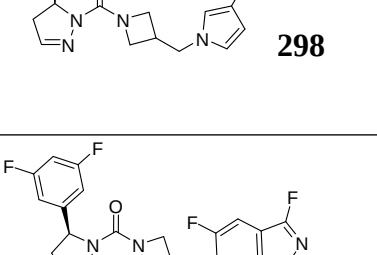
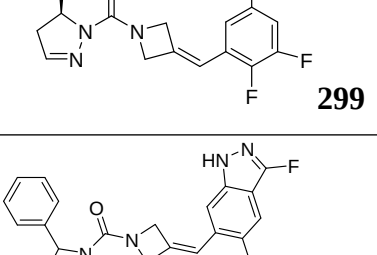
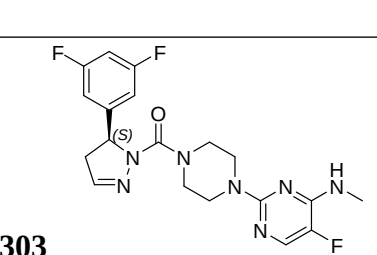
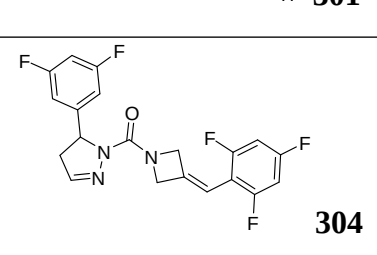
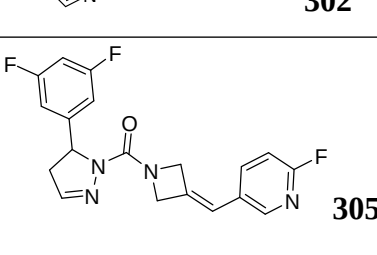
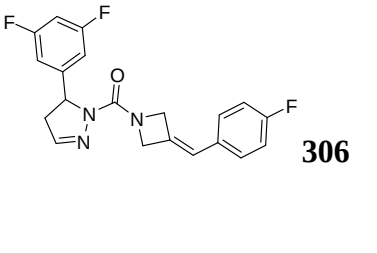
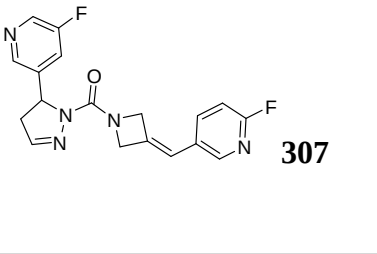
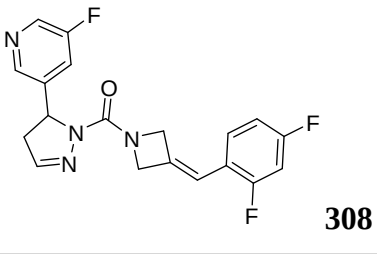
 192	 193	 194
 195	 196	 197
 198	 199	 200
 201	 202	 203
 204	 205	 206
 207	 208	 209

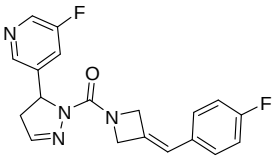
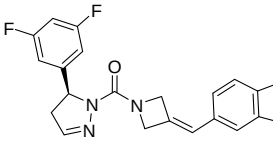
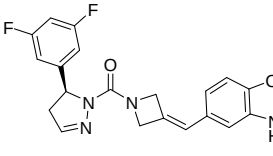
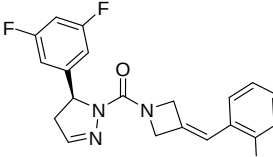
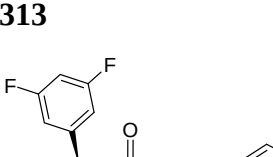
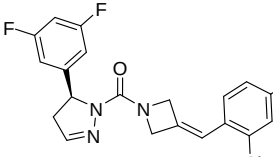
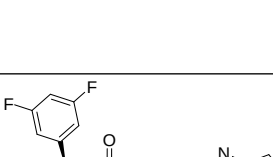
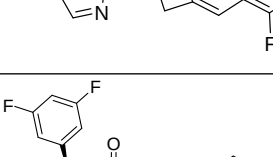
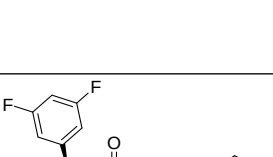
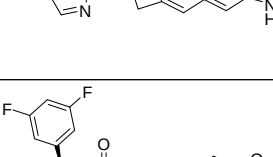
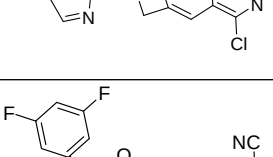
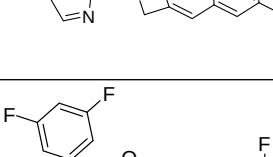
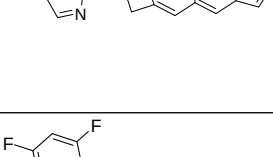
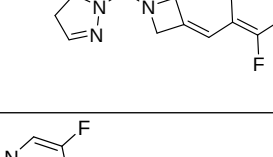
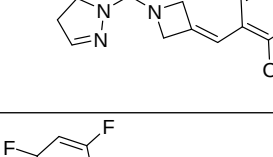
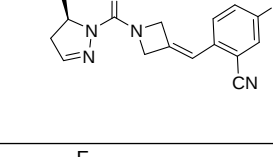
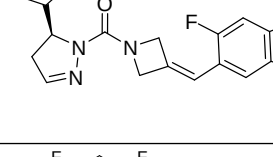
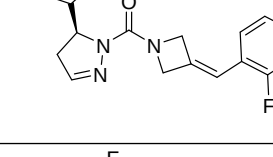
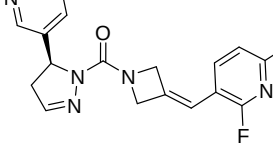
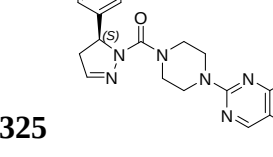
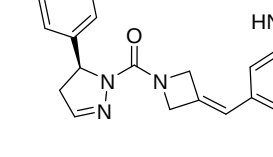
 210	 211	 212
 213	 214	 215
 216	 217	 218
 219	 220	 221
 222	 223	 224
 225	 226	 227

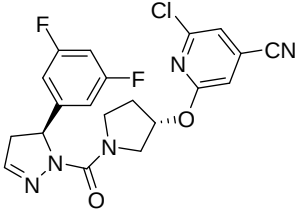
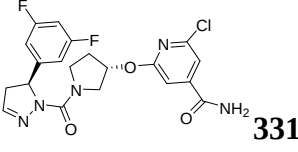
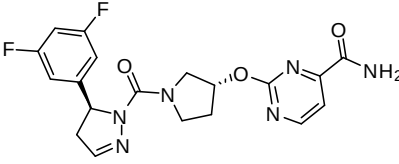
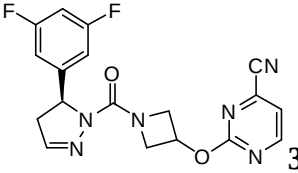
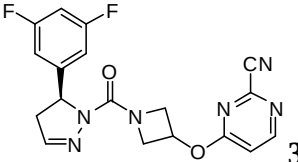
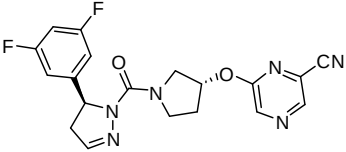
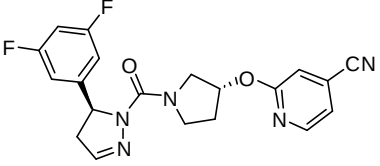
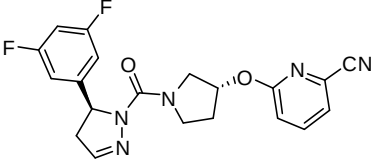
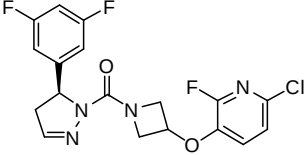
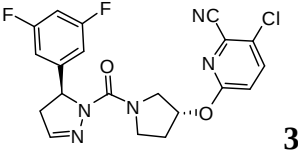
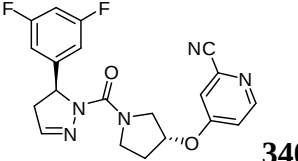
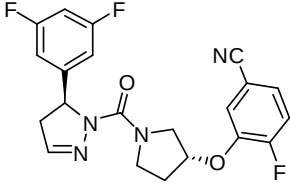
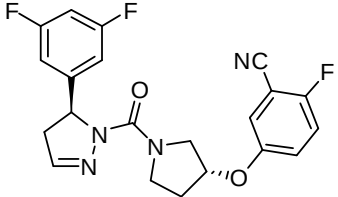
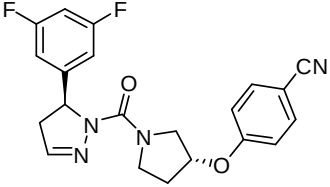
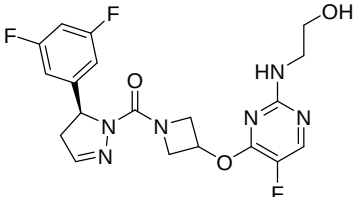
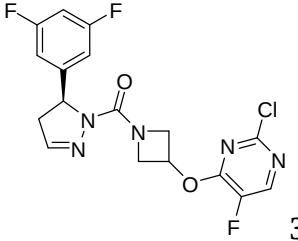
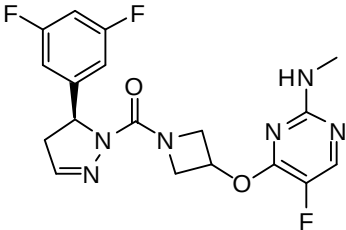
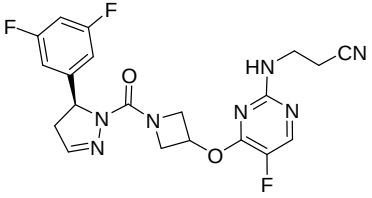
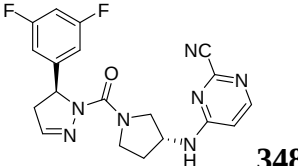
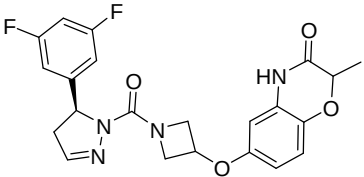
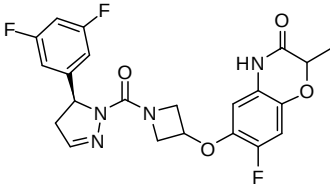
 228	 229	 230
 231	 232	 233
 234	 235	 236
 237	 238	 239
 240	 241	 242
 243	 244	 245
 246	 247	 248

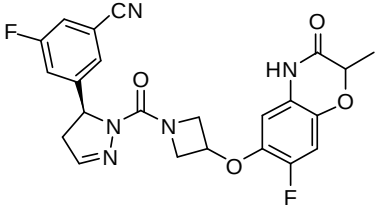
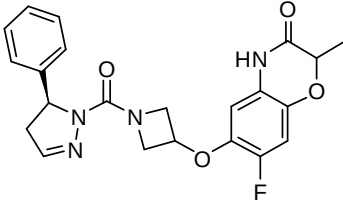
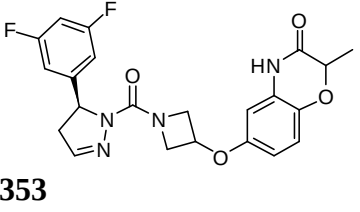
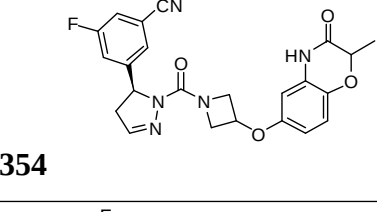
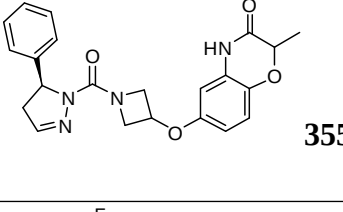
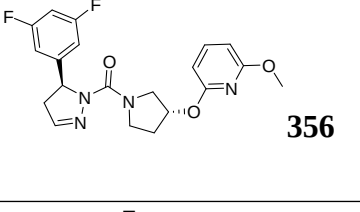
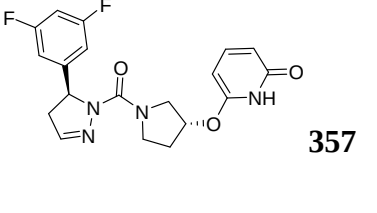
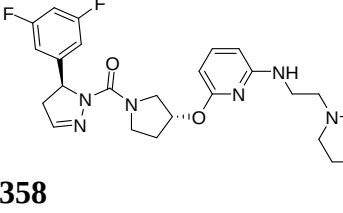
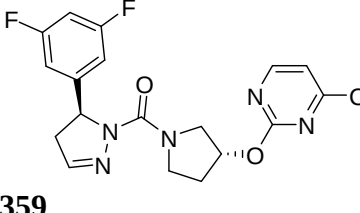
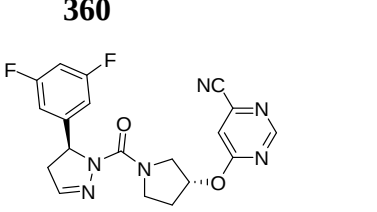
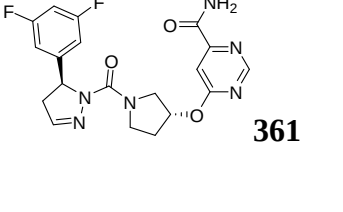
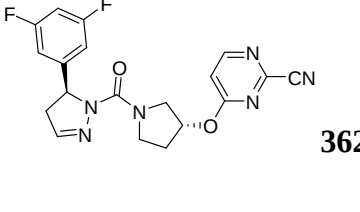
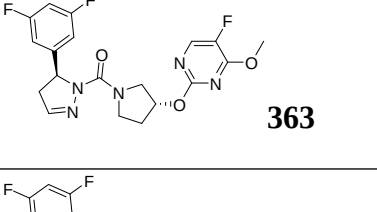
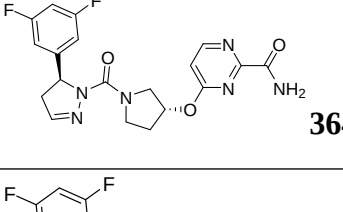
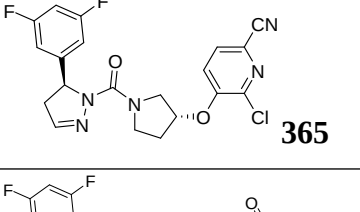
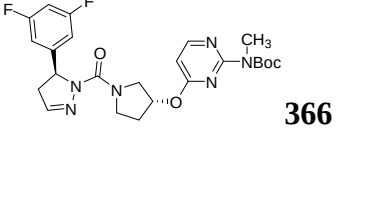
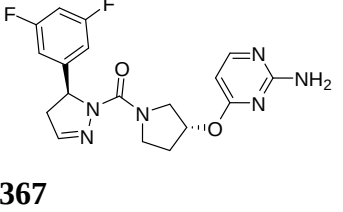
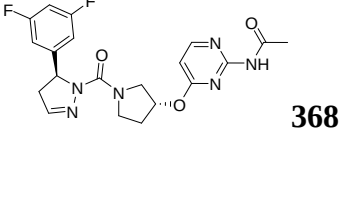
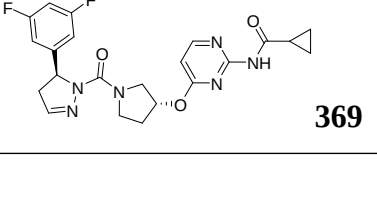
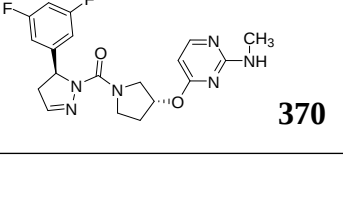
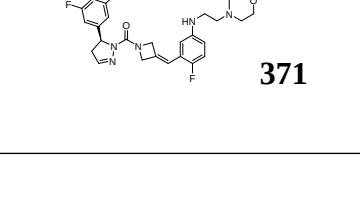
 249	 250	 251
 252	 253	 254
 255	 256	 257
 258	 259	 260
 261	 262	 263
 264	 265	 266

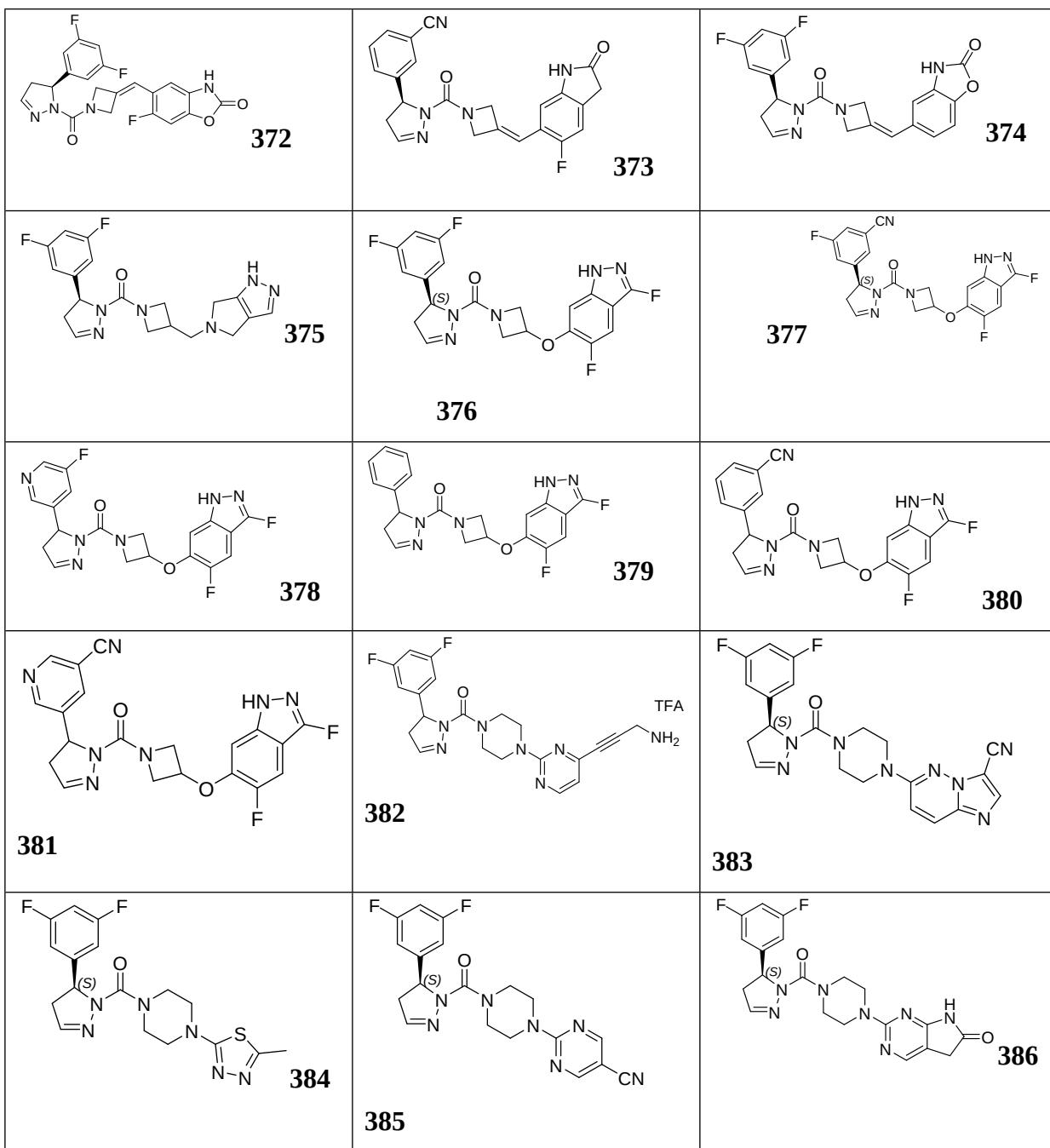
 267	 268	 269
 270	 271	 272
 273	 274	 275
 276	 277	 278
 279	 280	 281
 282	 283	 284
 285	 286	 287

 288	 289	 290
 291	 292	 293
 294	 295	 296
 297	 298	 299
 300	 301	 302
 303	 304	 305
 306	 307	 308

 309	 310	 311
 312	 313	 314
 315	 316	 317
 318	 319	 320
 321	 322	 323
 324	 325	 326
 327	 328	 329

 330	 331	 332
 333	 334	 335
 336	 337	 338
 339	 340	 341
 342	 343	 344
 345	 346	 347
 348	 349	 350

 351	 352	 353
 354	 355	 356
 357	 358	 359
 360	 361	 362
 363	 364	 365
 366	 367	 368
 369	 370	 371



[072]

[073] Active compounds: Necrosis Inhibitory Activity; EC data for 142-191 extrapolated

#	EC ₅₀	#	EC ₅₀	#	EC ₅₀	#	EC ₅₀
1	1-10uM	53	1-1000 nM	107	1-1000 nM	163	1-1000 nM
2	1-1000 nM	54	1-1000 nM	108	1-1000 nM	164	1-1000 nM

3	1-1000 nM	55	1-1000 nM	109	1-1000 nM	165	1-1000 nM
4	1-1000 nM	56	1-1000 nM	110	1-1000 nM	166	1-1000 nM
5	1-1000 nM	57	1-1000 nM	111A	1-1000 nM	167	1-1000 nM
6	1-1000 nM	58	1-1000 nM	111B	1-10uM	168	1-1000 nM
7	1-1000 nM	59	1-1000 nM	112A	1-1000 nM	169	1-1000 nM
8	1-10uM	60	1-1000 nM	112B	1-10uM	170	1-1000 nM
9	1-1000 nM	61	1-1000 nM	113A	1-1000 nM	171	1-1000 nM
10	1-10uM	62	1-1000 nM	113B	1-10uM	172	1-1000 nM
11	1-1000 nM	63	1-1000 nM	114A	1-1000 nM	173	1-1000 nM
12	1-10uM	64	1-1000 nM	114B	1-10uM	174	1-1000 nM
13	1-1000 nM	65	1-1000 nM	115A	1-1000 nM	175	1-1000 nM
14	1-1000 nM	66	1-1000 nM	116B	1-10uM	176	1-1000 nM
15	1-10uM	67	1-1000 nM	117A	1-1000 nM	177	1-1000 nM
16	1-1000 nM	68	1-1000 nM	117B	1-1000 nM	178	1-1000 nM
17	1-1000 nM	69	1-1000 nM	118A	1-1000 nM	179	1-1000 nM
18	1-1000 nM	70	1-10uM	118B	1-1000 nM	180	1-1000 nM
19	1-10uM	71	1-1000 nM	119	1-1000 nM	181	1-1000 nM
20	1-10uM	72	1-1000 nM	120	1-10uM	182	1-1000 nM

21	1-1000 nM	73	1-1000 nM	121	1-1000 nM	183	1-1000 nM
22	1-10uM	74	1-1000 nM	122	1-10uM	184	1-1000 nM
23	1-1000 nM	75	1-1000 nM	123	1-1000 nM	185	1-1000 nM
24	1-1000 nM	76	1-1000 nM	124	1-10uM	186	1-1000 nM
25	1-10uM	77	1-1000 nM	125	1-10uM	187	1-1000 nM
26A	1-1000 nM	78	1-1000 nM	126	1-1000 nM	188	1-1000 nM
26B	1-10uM	79	1-1000 nM	127	1-1000 nM	189	1-1000 nM
27A	1-10uM	80	1-1000 nM	128	1-1000 nM	190	1-1000 nM
27B	1-1000 nM	81	1-1000 nM	129	1-1000 nM	191	1-1000 nM
28	1-1000 nM	82	1-1000 nM	130	1-1000 nM	169	1-1000 nM
29	1-1000 nM	83	1-1000 nM	131	1-1000 nM	170	1-1000 nM
30	1-1000 nM	84	1-1000 nM	131	1-1000 nM	171	1-1000 nM
31	1-1000 nM	85	1-1000 nM	132	1-1000 nM	172	1-1000 nM
32	1-1000 nM	86	1-1000 nM	133	1-1000 nM	173	1-1000 nM
33	1-1000 nM	87	1-1000 nM	134	1-1000 nM	174	1-1000 nM
34	1-10uM	88	1-1000 nM	135	1-1000 nM	175	1-1000 nM

35	1-10uM	89	1-10uM	136	1-1000 nM	176	1-1000 nM
36	1-1000 nM	90	1-10uM	137	1-1000 nM	177	1-1000 nM
37	1-1000 nM	91	1-10uM	138	1-1000 nM	178	1-1000 nM
38	1-1000 nM	92	1-1000 nM	139	1-1000 nM	179	1-1000 nM
39	1-1000 nM	93	1-10uM	140	1-1000 nM	180	1-1000 nM
40	1-1000 nM	94	1-10uM	141	1-1000 nM	181	1-1000 nM
41	1-1000 nM	95	1-10uM	142	1-1000 nM	182	1-1000 nM
42	1-1000 nM	96	1-10uM	143	1-1000 nM	183	1-1000 nM
43	1-1000 nM	97	1-10uM	144	1-1000 nM	184	1-1000 nM
44	1-10uM	98	1-10uM	145	1-1000 nM	185	1-1000 nM
45	1-1000 nM	99	1-10uM	155	1-1000 nM	186	1-1000 nM
46	1-1000 nM	100	1-1000 nM	156	1-1000 nM	187	1-1000 nM
47	1-1000 nM	101	1-1000 nM	157	1-1000 nM	188	1-1000 nM
48	1-1000 nM	102	1-10uM	158	1-1000 nM	189	1-1000 nM
49	1-1000 nM	103	1-10uM	159	1-1000 nM	190	1-1000 nM

50	1-1000 nM	104	1-1000 nM	160	1-1000 nM	191	1-1000 nM
51	1-1000 nM	105	1-10uM	161	1-1000 nM		
52	1-1000 nM	106	1-10uM	162	1-1000 nM		

[074]

#	EC ₅₀	#	EC ₅₀	#	EC ₅₀	#	EC ₅₀
192	1-1000nM	241	1-1000nM	290	1-1000nM	339	1-1000nM
193	1-1000nM	242	1-1000nM	291	1-1000nM	340	1-1000nM
194	1-1000nM	243	1-1000nM	292	1-1000nM	341	1-1000nM
195	1-1000nM	244	1-1000nM	293	1-1000nM	342	1-1000nM
196	1-1000nM	245	1-1000nM	294	1-1000nM	343	1-1000nM
197	1-1000nM	246	1-1000nM	295	1-1000nM	344	1-1000nM
198	1-1000nM	247	1-1000nM	296	1-1000nM	345	1-1000nM
199	1-1000nM	248	1-1000nM	297	1-1000nM	346	1-1000nM
200	1-1000nM	249	1-1000nM	298	1-1000nM	347	1-1000nM
201	1-1000nM	250	1-1000nM	299	1-1000nM	348	1-1000nM
202	1-1000nM	251	1-1000nM	300	1-1000nM	349	1-1000nM
203	1-1000nM	252	1-1000nM	301	1-1000nM	350	1-1000nM
204	1-1000nM	253	1-1000nM	302	1-1000nM	351	1-1000nM
205	1-1000nM	254	1-1000nM	303	1-1000nM	352	1-1000nM
206	1-1000nM	255	1-1000nM	304	1-1000nM	353	1-1000nM
207	1-1000nM	256	1-1000nM	305	1-1000nM	354	1-1000nM
208	1-1000nM	257	1-1000nM	306	1-1000nM	355	1-1000nM
209	1-1000nM	258	1-1000nM	307	1-1000nM	356	1-1000nM
210	1-1000nM	259	1-1000nM	308	1-1000nM	357	1-1000nM
211	1-1000nM	260	1-1000nM	309	1-1000nM	358	1-1000nM
212	1-1000nM	261	1-1000nM	310	1-1000nM	359	1-1000nM
213	1-1000nM	262	1-1000nM	311	1-1000nM	360	1-1000nM

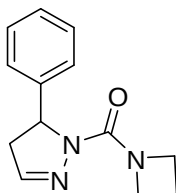
214	1-1000nM	263	1-1000nM	312	1-1000nM	361	1-1000nM
215	1-1000nM	264	1-1000nM	313	1-1000nM	362	1-1000nM
216	1-1000nM	265	1-1000nM	314	1-1000nM	363	1-1000nM
217	1-1000nM	266	1-1000nM	315	1-1000nM	364	1-1000nM
218	1-1000nM	267	1-1000nM	316	1-1000nM	365	1-1000nM
219	1-1000nM	268	1-1000nM	317	1-1000nM	366	1-1000nM
220	1-1000nM	269	1-1000nM	318	1-1000nM	367	1-1000nM
221	1-1000nM	270	1-1000nM	319	1-1000nM	368	1-1000nM
222	1-1000nM	271	1-1000nM	320	1-1000nM	369	1-1000nM
223	1-1000nM	272	1-1000nM	321	1-1000nM	370	1-1000nM
224	1-1000nM	273	1-1000nM	322	1-1000nM	371	1-1000nM
225	1-1000nM	274	1-1000nM	323	1-1000nM	372	1-1000nM
226	1-1000nM	275	1-1000nM	324	1-1000nM	373	1-1000nM
227	1-1000nM	276	1-1000nM	325	1-1000nM	374	1-1000nM
228	1-1000nM	277	1-1000nM	326	1-1000nM	375	1-1000nM
229	1-1000nM	278	1-1000nM	327	1-1000nM	376	1-1000nM
230	1-1000nM	279	1-1000nM	328	1-1000nM	377	1-1000nM
231	1-1000nM	280	1-1000nM	329	1-1000nM	378	1-1000nM
232	1-1000nM	281	1-1000nM	330	1-1000nM	379	1-1000nM
233	1-1000nM	282	1-1000nM	331	1-1000nM	380	1-1000nM
234	1-1000nM	283	1-1000nM	332	1-1000nM	381	1-1000nM
235	1-1000nM	284	1-1000nM	333	1-1000nM	382	1-1000nM
236	1-1000nM	285	1-1000nM	334	1-1000nM	383	1-1000nM
237	1-1000nM	286	1-1000nM	335	1-1000nM	384	1-1000nM
238	1-1000nM	287	1-1000nM	336	1-1000nM	385	1-1000nM
239	1-1000nM	288	1-1000nM	337	1-1000nM	386	1-1000nM
240	1-1000nM	289	1-1000nM	338	1-1000nM		

[075] IC₅₀ of hRIP1 kinase assay correlated with our IC₅₀ of cell necrosis assay;
representative, exemplary data:

Compound No	Human RIP1 kinase assay IC50(nM)	Cell viability assay, EC50 (nM)
14	100-1000nM	1-1000 nM
1	~1000nM	1-10000 nM
80	<100nM	1-100 nM
76	<100nM	1-100 nM
132	<100nM	1-100 nM
26A	<100nM	1-1000 nM
26B	>1000nM	>1000nM
41	<100nM	1-100 nM

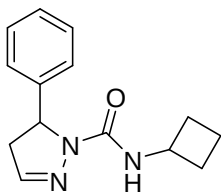
[076] Synthesis

[077] Compound1: azetidin-1-yl(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



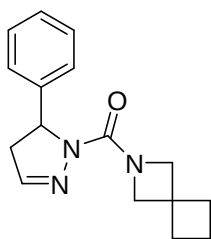
To a cooled solution of 5-phenyl-4,5-dihydro-1H-pyrazole (200mg, 1.37mmol) in dry DCM was added pyridine(216.7 mg, 2.74mmol), followed by added triphosgene (162.6 mg, 0.548mmol) in batches. The mixture was stirred at 0°C for 3h. Azetidine (150mg, 2.7mmol) and TEA(270mg, 2.7mmol) were dissolved in dry DCM(5ml), and the aboved reaction mixture was added to the solution and stirred for overnight. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give compound **1**. ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.15 (m, 3H), 6.73 (t, *J* = 1.7 Hz, 1H), 5.29 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.22 – 4.04 (m, 4H), 3.30 (ddd, *J* = 18.5, 12.2, 1.7 Hz, 1H), 2.69 (ddd, *J* = 18.5, 6.5, 1.7 Hz, 1H), 2.26 – 2.11 (m, 2H). LC-MS (*m/z*) 230.30 (M+H⁺).

[078] Compound 2 : N-cyclobutyl-5-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide



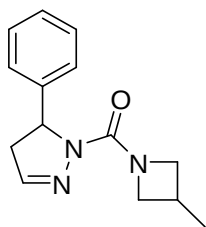
The titled compound **2** was prepared in 35% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (300 mg), cyclobutanamine (180 mg) and triphosgene (280 mg) according to the procedure outlined for compound **1**. LC-MS (m/z) 244.3 (M+H⁺)

[079] Compound 3: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(2-azaspiro[3.3]heptan-2-yl)methanone



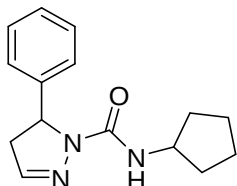
The titled compound **3** was prepared in 40% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (300 mg), 2-azaspiro[3.3]heptane (530 mg) and triphosgene (280 mg) according to the procedure outlined for compound **1**. LC-MS (m/z) 270.4 (M+H⁺)

[080] Compound 4: (3-methylazetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



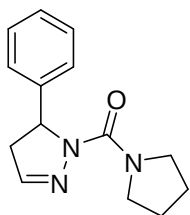
The titled compound **4** was prepared in 16% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (200 mg), 3-methylazetidine hydrochloride (290 mg) and triphosgene (162.5 mg) according to the procedure outlined for compound **1**. ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.26 (m, 2H), 7.23-7.19 (m, 3H), 6.73 (t, *J* = 1.7 Hz, 1H), 5.29 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.23 (dt, *J* = 21.5, 8.6 Hz, 2H), 3.69 (ddd, *J* = 34.7, 8.8, 5.7 Hz, 2H), 3.30 (ddd, *J* = 18.4, 12.2, 1.7 Hz, 1H), 2.69 (ddd, *J* = 18.4, 6.5, 1.7 Hz, 1H), 2.66 – 2.58 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 3H). LC-MS (m/z) 244.3 (M+H⁺)

[081] Compound 5: N-cyclopentyl-5-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide



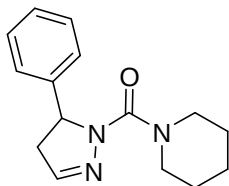
The titled compound **5** was prepared in 36% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (200 mg), cyclopentanamine (230 mg) and triphosgene (162.5 mg) according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, CDCl_3) δ 7.32 – 7.27 (m, 2H), 7.26 – 7.17 (m, 3H), 6.74 (t, J = 1.7 Hz, 1H), 5.27 (dd, J = 12.2, 6.1 Hz, 2H), 4.12-4.02 (m, 1H), 3.40 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.78 (ddd, J = 18.6, 6.2, 1.8 Hz, 1H), 1.99-1.88 (m, 2H), 1.71 – 1.50 (m, 4H), 1.45 – 1.34 (m, 2H). LC-MS (m/z) 258.34 ($\text{M}+\text{H}^+$)

[082] Compound 6: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(pyrrolidin-1-yl)methanone



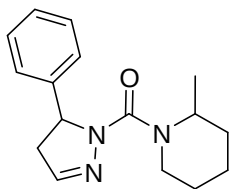
The titled compound **6** was prepared in 35% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (200 mg), pyrrolidine (190 mg) and triphosgene (162.5 mg) according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.26 (m, 3H), 7.26 – 7.19 (m, 2H), 6.74 (t, J = 1.7 Hz, 1H), 5.34 (dd, J = 12.0, 9.1 Hz, 1H), 3.64 – 3.55 (m, 2H), 3.51 – 3.44 (m, 2H), 3.28 (ddd, J = 18.2, 12.0, 1.8 Hz, 1H), 2.70 (ddd, J = 18.3, 9.1, 1.7 Hz, 1H), 1.93 – 1.72 (m, 4H). LC-MS (m/z) 244.31 ($\text{M}+\text{H}^+$)

[083] Compound 7: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(piperidin-1-yl)methanone



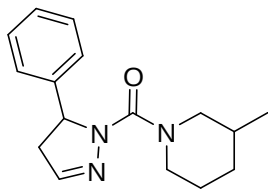
The titled compound **7** was prepared in 8.5% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (200 mg), piperidine (235 mg) and triphosgene (250 mg) according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.25 (m, 4H), 7.24-7.19 (m, 1H), 6.78 (brs, 1H), 5.33 (dd, J = 11.6, 10.4 Hz, 1H), 3.61 – 3.38 (m, 4H), 3.25 (ddd, J = 18.1, 11.7, 1.6 Hz, 1H), 2.68 (ddd, J = 18.2, 10.3, 1.5 Hz, 1H), 1.70 – 1.40 (m, 6H). LC-MS (m/z) 258.3 ($\text{M}+\text{H}^+$)

[084] Compound 8: (2-methylpiperidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **8** was prepared in 17% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (13 mg), 2-methylpiperidine (8.91 mg) and triphosgene (7.1 mg) according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, CDCl_3) δ 7.32 – 7.27 (m, 3H), 7.26 – 7.18 (m, 2H), 6.79 (brs, 1H), 5.32 (t, J = 11.1 Hz, 1H), 4.72-4.66 (m, 1H), 3.89 (dd, J = 13.6, 3.2 Hz, 1H), 3.24 (ddd, J = 18.0, 11.6, 1.2 Hz, 1H), 3.02 (td, J = 13.4, 2.8 Hz, 1H), 2.73 – 2.61 (m, 1H), 1.81 – 1.69 (m, 1H), 1.62-1.35 (m, 5H), 1.11 (d, J = 7.0 Hz, 3H). LC-MS (m/z) 272.4 ($\text{M}+\text{H}^+$)

[085] Compound 9: (3-methylpiperidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone

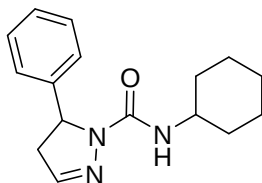


To a cooled solution of triphosgene (320 mg, 1.08 mmol) in dry DCM (5ml) was added dropwise a mixture solution of 5-phenyl-4,5-dihydro-1H-pyrazole (400 mg, 2.74mmol) and TEA (550mg, 5.44mmol). The mixture was stirred at 0°C for 3h.

3-methylpiperidine (260mg, 2.7mmol) and TEA(270mg, 2.7mmol) were dissolved in dry DCM(5ml), and the a volume of half aboved reaction mixture was added to the solution and stirred for overnight. The mixture was extracted with DCM, washed with brine, dried with (Na_2SO_4), and concentrated in vacuo. Purification by silica gel

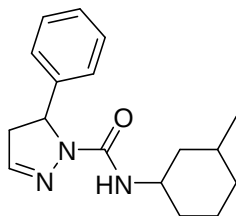
chromatography(EA/PE=1/3) to give compound **9** (180mg, 48.2%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.25 (m, 3H), 7.24-7.22 (m, 2H), 6.78 (d, J = 1.2 Hz, 1H), 5.39 – 5.24 (t, J = 10.81 Hz, 1H), 4.22 (ddd, J = 11.1, 3.3, 1.7 Hz, 1H), 4.13 – 3.99 (m, 1H), 3.25 (ddd, J = 18.1, 11.7, 1.7 Hz, 1H), 2.97 – 2.83 (m, 1H), 2.68 (ddd, J = 12.1, 10.3, 1.4 Hz, 1H), 2.53 – 2.36 (m, 1H), 1.74 (dddd, J = 25.1, 10.4, 7.7, 3.8 Hz, 1H), 1.70 – 1.50 (m, 2H), 1.16 – 1.00 (m, 2H), 0.89 – 0.78 (m, 3H). LC-MS (m/z) 272.40 ($\text{M}+\text{H}^+$).

[086] Compound 10: N-cyclohexyl-5-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide



The titled compound **10** was prepared in 8.5% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (300 mg), cyclohexanamine (240 mg) and triphosgene (280 mg) according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.27 (m, 2H), 7.24 – 7.13 (m, 3H), 6.74 (t, J = 1.6 Hz, 1H), 5.79 (d, J = 7.8 Hz, 1H), 5.30 – 5.22 (m, 1H), 3.60 (ddd, J = 14.8, 10.6, 4.2 Hz, 1H), 3.39 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.79 (ddd, J = 18.6, 6.2, 1.7 Hz, 1H), 1.90 (dd, J = 18.0, 14.6 Hz, 2H), 1.73 – 1.61 (m, 2H), 1.39 – 1.05 (m, 6H). LC-MS (m/z) 272.4 ($\text{M}+\text{H}^+$).

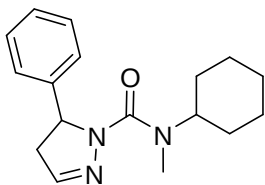
[087] Compound 11: N-(3-methylcyclohexyl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide



The titled compound **11** was prepared in 25.5% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (200 mg), 3-methylcyclohexan-1-amine (233 mg) and triphosgene (162.3 mg) according to the procedure outlined for compound **9**. ^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.29 (m, 2H), 7.26 – 7.19 (m, 2H), 6.79 – 6.75 (m, 1H), 6.09 (s, 1H), 5.76 (d, J = 8.2 Hz, 1H), 5.29 (ddd, J = 12.3, 6.1, 3.3 Hz, 1H), 3.68 – 3.54 (m, 1H), 3.42 (dddd, J = 18.5, 12.2, 3.1, 1.7 Hz, 1H), 3.25 (dt, J = 14.3, 4.5 Hz, 2H), 2.86 – 2.77 (m, 1H), 2.05 – 1.91 (m, 3H),

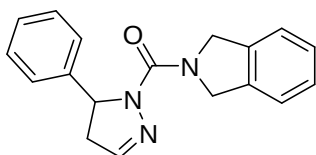
1.73 – 1.61 (m, 2H), 0.92-0.87(m, 3H). LC-MS (m/z) 286.4 (M+H⁺)

[088] Compound 12: N-cyclohexyl-N-methyl-5-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide



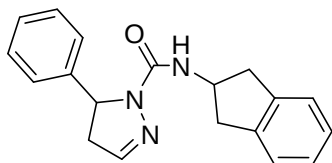
The titled compound **12** was prepared in 15% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (200 mg), 3-methylcyclohexan-1-amine (305 mg) and triphosgene (162 mg) according to the procedure outlined for compound **1**. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.30 (m, 3H), 7.26 – 7.23 (m, 2H), 6.80 (s, 1H), 5.34 (t, J = 11.1 Hz, 1H), 4.02 (t, J = 11.6 Hz, 1H), 3.27 (dd, J = 17.2, 12.4 Hz, 1H), 2.90 (s, 3H), 2.70 (dd, J = 18.6, 11.3 Hz, 1H), 1.81-1.58 (m, 4H), , 1.51 – 1.24 (m, 5H), 1.13 – 1.01 (m, 1H).LC-MS (m/z) 286.20 (M+H⁺)

[089] Compound 13 : isoindolin-2-yl(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **13** was prepared in 23% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (300 mg), isoindoline (320 mg) and triphosgene (162.5 mg) according to the procedure outlined for compound **1**. ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.30 (m, 2H), 7.25-7.22(m, 2H)7.23 – 7.11 (m, 5H), 6.72 (t, J = 1.7 Hz, 1H), 5.28 (dd, J = 12.2, 6.1 Hz, 1H), 4.72 – 4.55 (m, 1H), 3.40 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 3.34 – 3.23 (m, 2H), 2.87 – 2.74 (m, 3H).LC-MS (m/z) 292.4 (M+H⁺)

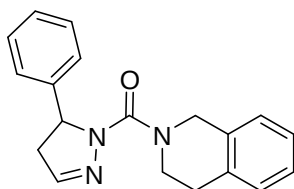
[090] Compound 14: N-(2,3-dihydro-1H-inden-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide



The titled compound **14** was prepared in 20% yield from 5-phenyl-4,5-dihydro-1H-

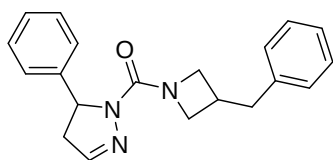
pyrazole (300 mg), 2,3-dihydro-1H-inden-2-amine (450 mg) and triphosgene (162.5 mg) according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.30(m, 2H), 7.25-7.22 (m, 2H), 7.21 – 7.11 (m, 5H), 6.72 (t, J = 1.7 Hz, 1H), 6.10 (d, J = 7.9 Hz, 1H), 5.28 (dd, J = 12.2, 6.1 Hz, 1H), 4.72 – 4.55 (m, 1H), 3.40 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 3.34 – 3.23 (m, 2H), 2.87 – 2.74 (m, 3H). LC-MS (m/z) 306.4 ($\text{M}+\text{H}^+$). LC-MS (m/z) 306.4 ($\text{M}+\text{H}^+$)

[091] Compound 15: (3,4-dihydroisoquinolin-2(1H)-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



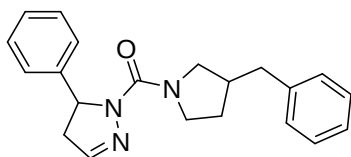
The titled compound **15** was prepared in 30.6% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (25 mg), 1,2,3,4-tetrahydroisoquinoline (50 mg) and triphosgene (12.7 mg) according to the procedure outlined for compound **1**. LC-MS (m/z) 306.4 ($\text{M}+\text{H}^+$)

[092] Compound 16: (3-benzylazetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



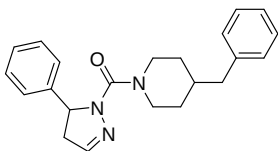
The titled compound **16** was prepared in 64.6% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (25 mg), 3-benzylazetidine and triphosgene according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.26 (m, 4H), 7.26-7.12 (m, 6H), 6.75 (t, 1H, J = 1.6 Hz), 5.31 (dd, 1H, J = 12.4, 6.4 Hz), 4.25 (t, 1H, J = 8.4 Hz), 4.18 (t, 1H, J = 8.4 Hz), 3.92 (dd, 1H, J = 8.8, 5.6 Hz), 3.83 (dd, 1H, J = 8.8, 5.6 Hz), 3.32 (ddd, 1H, J = 18.5, 12.0, 1.6 Hz), 2.95-2.90 (m, 2H), 2.89-2.84 (m, 1H), 2.72 (ddd, 1H, J = 18.4, 6.4, 1.6 Hz). LC-MS (m/z):320.35 [$\text{M}+\text{H}$] $^+$.

[093] Compound 17 : (3-benzylpyrrolidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



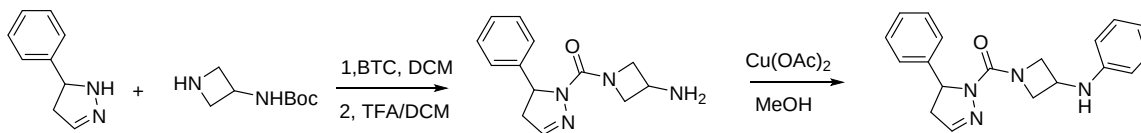
The titled compound **17** was prepared in 64.6% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (25 mg), 3-benzylazetidine and triphosgene according to the procedure outlined for compound **1**. ^1H NMR (400 MHz, CDCl_3) δ 7.27-7.35 (m, 7H), 7.13-7.25 (m, 3H), 6.74-6.76 (m, 1H), 5.31-5.37 (m, 1H), 3.78-3.88 (m, 1H), 3.55-3.63 (m, 1H), 3.28-3.35 (m, 1H), 3.21-3.26 (m, 1H), 2.59-2.77 (m, 3H), 2.29-2.46 (m, 2H), 1.87-1.96 (m, 1H), 1.51-1.68 (m, 1H). LC-MS (m/z): 334.41 $[\text{M}+\text{H}]^+$.

[094] Compound 18: (4-benzylpiperidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **18** was prepared in 14% yield from 5-phenyl-4,5-dihydro-1H-pyrazole, 4-benzylpiperidine and triphosgene according to the procedure outlined for compound **9**. ^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.28 (m, 5H), 7.27 – 7.23 (m, 2H), 7.21-7.17 (m, 1H), 7.15-7.13 (m, 2H), 6.80 (t, $J = 1.7$ Hz, 1H), 5.35 (dd, $J = 11.7, 10.3$ Hz, 1H), 4.33 – 4.25 (m, 1H), 4.19 (ddt, $J = 13.4, 4.4, 2.3$ Hz, 1H), 3.28 (ddd, $J = 18.2, 11.8, 1.8$ Hz, 1H), 2.86 – 2.77 (m, 1H), 2.77 – 2.65 (m, 2H), 2.54 (d, $J = 7.1$ Hz, 2H), 1.80 – 1.58 (m, 1H), 1.40 – 1.29 (m, 2H), 1.24 – 1.08 (m, 2H). LC-MS (m/z) 348.5 ($\text{M}+\text{H}^+$)

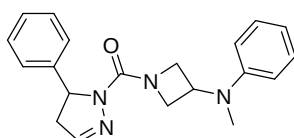
[095] Compound 19: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(3-(phenylamino)azetidin-1-yl)methanone



tert-butyl (1-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)carbamate (50mg) was prepared by the method described for compound **1**, which was dissolved in DCM (6mL), 1mL of TFA was added. The mixture was stirred at room temperature for 2h, and concentrated to give the crude (3-aminoazetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone (30mg). LC-MS (m/z) 244.4 ($\text{M}+\text{H}^+$).

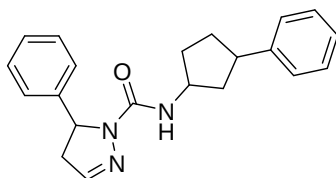
A mixture of (3-aminoazetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone (30mg), phenylboronic acid(20 mg), Cu(OAc)₂ (3mg), TEA(30 mg,) in DCM(10mL) was stirred at 65°C for 16h. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **19**(14 mg, 32%). ¹H NMR (400 MHz, CDCl₃) δ 7.50 – 7.22 (m, 9H), 6.74 (s, 1H), 6.51 (s, 1H), 4.84 - 4.10 (m, 5H), 3.33 (dd, J = 18.6, 12.4 Hz, 1H), 2.97 (s, 3H), 2.72 (dd, J = 18.8, 5.8 Hz, 1H) LC-MS (m/z) 321.40 (M+H⁺)

[096] Compound 20 : (3-(methyl(phenyl)amino)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



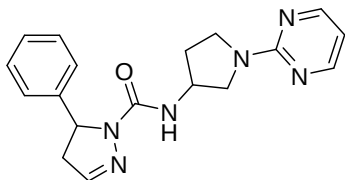
The titled compound **20** was prepared in 15% yield from 5-phenyl-4,5-dihydro-1H-pyrazole, N-methyl-N-phenylazetidin-3-amine and triphosgene according to the procedure outlined for compound **9**. ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.26 (m, 3H), 7.24 – 6.98 (m, 7H), 6.77 (s, 1H), 5.30 (dd, J = 11.9, 5.8 Hz, 1H), 4.34-4.28 (m, 5H), 3.33 (dd, J = 18.6, 12.4 Hz, 1H), 2.97 (s, 3H), 2.72 (dd, J = 18.8, 5.8 Hz, 1H). LC-MS (m/z) 335.5 (M+H⁺)

[097] Compound 21 : 5-phenyl-N-(3-phenylcyclopentyl)-4,5-dihydro-1H-pyrazole-1-carboxamide



The titled compound **21** was prepared in 14% yield from 5-phenyl-4,5-dihydro-1H-pyrazole (100 mg), 3-phenylcyclopentan-1-amine (100 mg) and triphosgene (81mg) according to the procedure outlined for compound **1**. ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.14 (m, 10H), 6.79 (d, J = 5.1 Hz, 1H), 5.99 (d, J = 7.2 Hz, 1H), 5.31 (dd, J = 12.2, 6.0 Hz, 1H), 4.39-4.23 (m, 1H), 3.44 (dd, J = 18.4, 12.4 Hz, 1H), 3.29 – 2.99 (m, 2H), 2.83 (d, J = 18.7 Hz, 1H), 2.64 – 2.50 (m, 1H), 2.38 – 1.96 (m, 3H), 1.85 – 1.45 (m, 3H). LC-MS (m/z) 334.4 (M+H⁺)

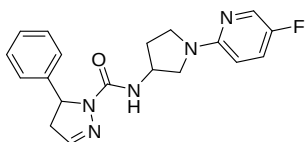
[098] Compound 22 : 5-phenyl-N-(1-(pyrimidin-2-yl)pyrrolidin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide



To a solution of 2-bromopyrimidine (150 mg) in DMF (5 mL) was added tert-butyl pyrrolidin-3-ylcarbamate (200 mg) and K_2CO_3 (400 mg). The mixture was stirred at 95°C for overnight under N_2 . The mixture was diluted with H_2O (10 mL), extracted with EA(15mL*3) . The combined organic layer were washed with brine, dried over(Na_2SO_4) and concentrated in vacuo. Purification by silica gel chromatography (EA/PE= 1/1) to give tert-butyl (1-(pyrimidin-2-yl)pyrrolidin-3-yl)carbamate (170 mg, 68.5%) as a light yellow solid. LC-MS (m/z) 265.4 ($M+H^+$)

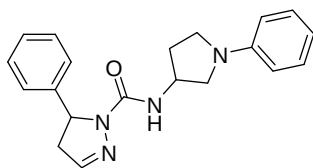
To a solution of tert-butyl (1-(pyrimidin-2-yl)pyrrolidin-3-yl)carbamate (170 mg) in DCM(5mL) at 0°C was added 1ml of TFA. The mixture was stirred at room temperature for 3 hours. The mixture was concentrated to dryness and dissolved in DCM(5mL) , and TEA(270 mg) was added. A solution of 5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl chloride(1.35 mmol, prepared by procedure outlined for compound 1) in 2.5ml of DCM was added to the aboved mixture at 0°C and stirred at room temperature for overnight. The mixture was extracted with DCM, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography(EA/PE= 1/1) to give compound **22** (74mg, 16.2%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 4.8 Hz, 1H), 7.37 – 7.26 (m, 2H), 7.26 – 7.13 (m, 3H), 6.78 (t, J = 1.6 Hz, 1H), 6.54 (t, J = 4.8 Hz, 1H), 6.06 (d, J = 6.8 Hz, 1H), 5.29 (ddd, J = 12.1, 6.0, 3.3 Hz, 1H), 4.53 (dd, J = 11.9, 5.8 Hz, 1H), 3.87 (ddd, J = 11.6, 6.2, 2.2 Hz, 1H), 3.72 (ddd, J = 13.8, 7.6, 4.9 Hz, 2H), 3.59 – 3.37 (m, 2H), 2.82 (ddt, J = 18.7, 6.0, 1.6 Hz, 1H), 2.28 (dd, J = 13.6, 6.7 Hz, 1H), 2.04 (dd, J = 14.8, 6.7 Hz, 1H). LC-MS (m/z) 337.40 ($M+H^+$)

[099] Compound 23: N-(1-(5-fluoropyridin-2-yl)pyrrolidin-3-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide



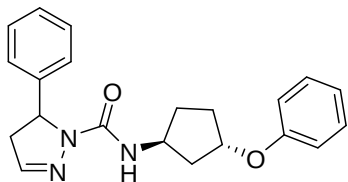
The titled compound **23** was prepared in 34% yield from 5-phenyl-4,5-dihydro-1H-pyrazole, 1-(5-fluoropyridin-2-yl)pyrrolidin-3-amine and triphosgene according to the procedure outlined for compound **9**. ^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, 1H, $J = 2.8$ Hz), 7.34-7.31 (m, 2H), 7.25-7.19 (m, 3H), 6.78 (t, 1H, $J = 1.6$ Hz), 6.29 (dd, 1H, $J = 9.2$, 3.2 Hz), 6.06 (d, 1H, $J = 7.2$ Hz), 5.29 (dd, 1H, $J = 12.4$, 6.0 Hz), 4.55-4.48 (m, 1H), 3.70 (dd, 1H, $J = 10.4$, 6.4 Hz), 3.63-3.56 (m, 1H), 3.54-3.48 (m, 1H), 3.43 (ddd, 1H, $J = 18.8$, 12.4, 1.6 Hz), 3.34 (dd, 1H, $J = 10.4$, 4.4 Hz), 2.82 (ddd, 1H, $J = 18.4$, 6.0, 1.6 Hz), 2.32-2.24 (m, 1H), 2.08-1.92 (m, 1H). LC-MS (m/z): 354.39 $[\text{M}+\text{H}]^+$.

[0100] Compound 24: 5-phenyl-N-(1-phenylpyrrolidin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide



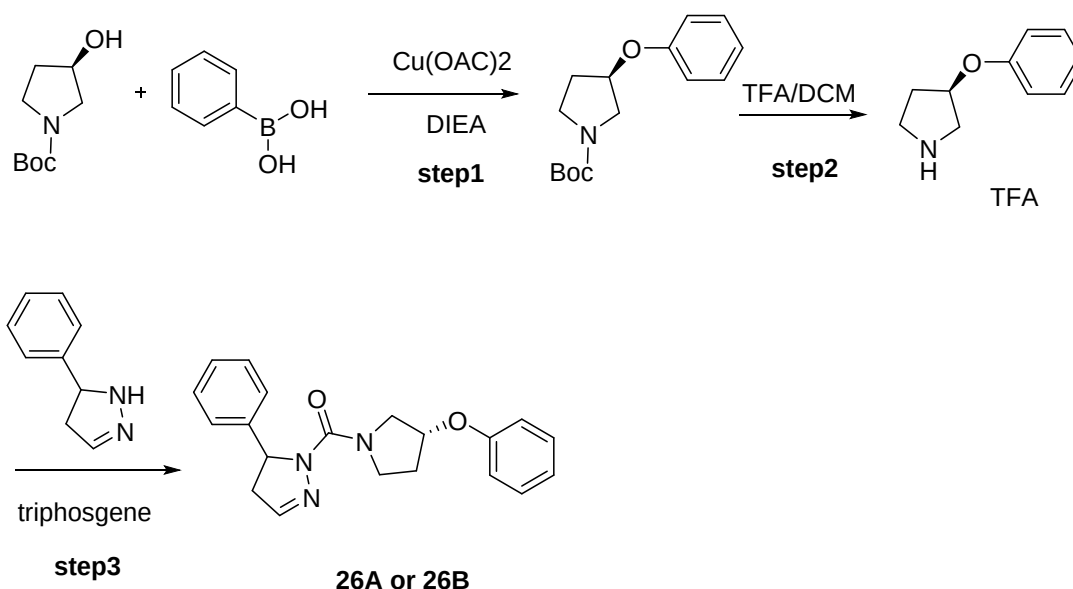
The titled compound **24** was prepared in 8.1% yield from 5-phenyl-4,5-dihydro-1H-pyrazole, 1-phenylpyrrolidin-3-amine and triphosgene according to the procedure outlined for compound **9**. ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.30 (m, 3H), 7.29-7.26 (m, 1H), 7.25-7.20 (m, 4H), 6.78 (t, 1H, $J = 1.6$ Hz), 6.71-6.67 (m, 1H), 6.58-6.55 (m, 1H), 6.09 (d, 1H, $J = 7.6$ Hz), 5.28 (dd, 1H, $J = 12.4$, 6.0 Hz), 4.56-4.48 (m, 1H), 3.59 (dd, 1H, $J = 10.0$, 6.4 Hz), 3.50-3.45 (m, 1H), 3.45-3.38 (m, 1H), 3.37-3.29 (m, 1H), 3.23 (dd, 1H, $J = 8.4$, 4.0 Hz), 2.82 (ddd, 1H, $J = 18.8$, 6.0, 1.6 Hz), 2.33-2.24 (m, 1H), 2.02-1.94 (m, 1H). LC-MS (m/z): 335.40 $[\text{M}+\text{H}]^+$

[0101] Compound 25: N-((1S,3S)-3-phenoxy-cyclopentyl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide



The titled compound **25** was prepared in 23% yield from 5-phenyl-4,5-dihydro-1H-pyrazole, (1S,3S)-3-phenoxy-cyclopentan-1-amine and triphosgene according to the procedure outlined for compound **9**. LC-MS (m/z) 350.4 (M+H⁺)

[0102] Compound 26: ((R)-3-phenoxy-pyrrolidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



Step1: Prepare of tert-butyl (R)-3-phenoxy-pyrrolidine-1-carboxylate

A mixture of tert-butyl (R)-3-hydroxypyrrolidine-1-carboxylate(500mg, 2.67mmol), phenylboronic acid(490mg, 4mmol), Cu(OAc)₂(1.07g, 5.34mmol), pyridine(422mg, 5.34mmol)and DIEA(0.9ml) in DCM(10mL) was stirred at room temperature for 16h. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give 200mg of the desired product. LC-MS (m/z) 264.4 (M+H⁺)

Step2: Prepare of (R)-3-phenoxy-pyrrolidine trifluoroacetic acid

tert-butyl (R)-3-phenoxy-pyrrolidine-1-carboxylate (200mg) was dissolved in DCM(3ml) was added TFA(865mg). The mixture was stirred at room temperature for 2h. The mixture was concentrated in vacuo, and extracted with DCM, washed with saturated aqueous NaHCO₃, dried with (Na₂SO₄), and concentrated to give the crude product(200mg) ,which used for next step without further purification. LC-MS (m/z) 164.2 (M+H⁺)

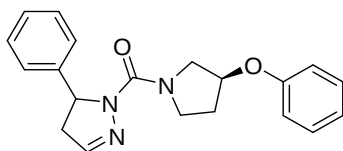
Step3: Prepare of ((R)-3-phenoxy-pyrrolidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone (**26**)

To a cooled solution of 5-phenyl-4,5-dihydro-1H-pyrazole(121mg, 0.83mmol) in dry DCM (2ml)was added TEA (168 mg, 1.66mmol), followed by added triphosgene(99 mg, 0.33mmol) in three batches. The mixture was stirred at 0°C for 30min and at room temperature for 2h. (R)-3-phenoxyppyrolidine trifluoroacetic acid (200 mg) and TEA(231mg, 2.28 mmol) were dissolved in dry DCM(5mL), and the aboved reaction mixture was added to the solution and stirred for overnight. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give a mixture of racemate. Purification by silica gel chromatography to give compound **26A** and **26B**.

Compound **26A**: ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.25 (m, 5H), 7.24 – 7.20 (m, 2H), 6.94 (ddd, *J* = 8.4, 2.1, 1.1 Hz, 1H), 6.87 – 6.85 (m, 1H), 6.84 (dd, *J* = 2.0, 1.0 Hz, 1H), 6.75 (t, *J* = 1.7 Hz, 1H), 5.35 (dd, *J* = 12.0, 9.2 Hz, 1H), 4.88 (t, *J* = 4.3 Hz, 1H), 3.94 (dd, *J* = 12.8, 4.4 Hz, 1H), 3.84 (td, *J* = 11.1, 6.6 Hz, 1H), 3.72 (d, *J* = 12.8 Hz, 1H), 3.68 – 3.61 (m, 1H), 3.29 (ddd, *J* = 18.4, 12.1, 1.8 Hz, 1H), 2.70 (ddd, *J* = 18.4, 9.2, 1.6 Hz, 1H), 2.19 (ddd, *J* = 13.4, 6.6, 1.7 Hz, 1H), 2.07 – 1.95 (m, 1H). LC-MS (*m/z*) 336.4 (M+H⁺).

Compound **26B**: ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.20 (m, 7H), 6.94 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.89 – 6.83 (m, 2H), 6.75 (t, *J* = 1.7 Hz, 1H), 5.35 (dd, *J* = 13.6, 5.9 Hz, 1H), 4.89-4.85 (m, 1H), 3.96 – 3.80 (m, 3H), 3.67-3.60 (m, 1H), 3.28 (ddd, *J* = 18.3, 11.9, 1.7 Hz, 1H), 2.69 (ddd, *J* = 18.3, 7.7, 1.7 Hz, 1H), 2.12 (ddd, *J* = 7.3, 6.3, 3.5 Hz, 2H). LC-MS (*m/z*) 336.4 (M+H⁺).

Compound 27: ((S)-3-phenoxyppyrolidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone

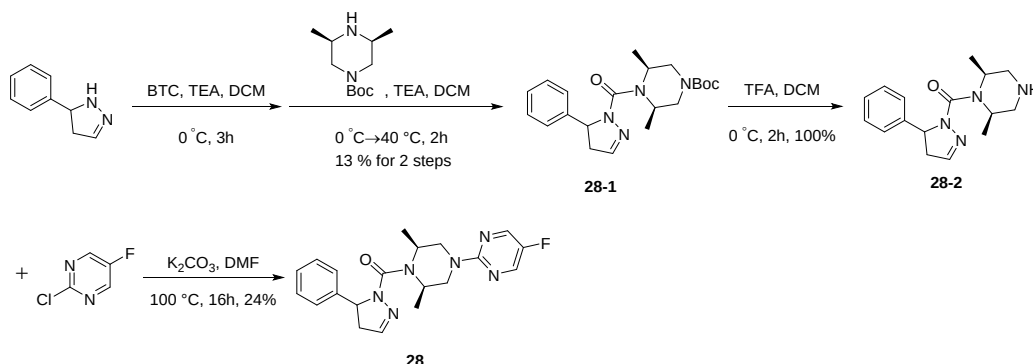


Compound **27A** and **27B** were prepared from (S)-3-hydroxyppyrolidine-1-carboxylate (200 mg), TFA, triphosgene and 5-phenyl-4,5-dihydro-1H-pyrazole according to the procedure outlined for compound **26** and purified by silica gel chromatography.

Compound **27A**: ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.20 (m, 7H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 2H), 6.76(brs, 1H), 5.37-5.32 (m, 1H), 4.88 (brs, 1H), 3.98 – 3.78 (m, 3H), 3.74-3.63 (m, 1H), 3.38 – 3.24 (m, 1H), 2.70 (dd, *J* = 19.8, 9.2 Hz, 1H), 2.25-2.18 (m, 1H), 2.07 – 1.99 (m, 1H). LC-MS (*m/z*) 336.4 (M+H⁺).

Compound **27B**: ^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.18 (m, 7H), 6.93 (t, J = 7.3 Hz, 1H), 6.85 (d, J = 7.9 Hz, 2H), 6.76 (brs, 1H), 5.37 – 5.31 (m, 1H), 4.95 – 4.84 (m, 1H), 4.02 – 3.75 (m, 2H), 3.63 (dd, J = 24.1, 13.1 Hz, 1H), 3.40 – 3.19 (m, 1H), 2.77 – 2.59 (m, 1H), 2.26 – 2.20 (m, 1H), 2.18 – 2.06 (m, 1H), 2.01–1.95 (m, 1H). LC-MS (m/z) 336.4 ($\text{M}+\text{H}^+$).

[0103] Compound 28: ((2R,6S)-4-(5-fluoropyrimidin-2-yl)-2,6-dimethylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



Step 1.

To a solution of 5-phenyl-4,5-dihydro-1H-pyrazole (73.5 mg, 0.5 mmol) in DCM was added BTC (148 mg, 0.25 mmol), and TEA (0.28 ml, 1.0 mmol) at 0 °C. After 3 hours, a mixture of (3R,5S)-tert-butyl 3,5-dimethylpiperazine-1-carboxylate (107 mg, 0.5 mmol) and TEA (0.28 ml, 1.0 mmol) in DCM was added to the reaction in 0 °C. Then the mixture was stirred at 40 °C for 2 hours. UPLC-MS monitored the completion of the reaction. The reaction mixture was poured into water and extracted with EA. The organic layer was separated, and the aqueous layer was repeatedly extracted with EA (2×5 mL). The combined extracts were dried with Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (PE: EA = 2: 1) to give 24 mg of **28-1** as a yellow solid, yield: 13% (2 steps). LC-MS (ESI) m/z : 331.41 [$\text{M}+\text{H}$] $^+$.

Step 2.

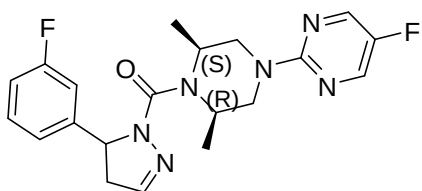
28-1 (24 mg, 0.06 mmol) is dissolved in DCM and cooled to 0°C. TFA (0.09ml, 1.2 mmol) was added dropwise and the mixture was stirred for 2 hours. UPLC-MS monitored the completion of the reaction. The reaction was quench with saturated NaHCO_3 and extracted with EA. The organic layer was separated, and the aqueous layer was repeatedly extracted with EA (2×5 mL). The combined extracts were dried with Na_2SO_4 and concentrated to give compound **28-2**, which was used in the next reaction step without any further

purification. For **28-2**, LC-MS (ESI) m/z : 287.35, $[M+H]^+$.

Step 3.

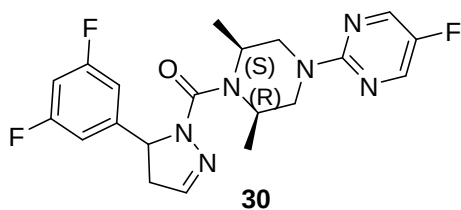
To a solution of **28-2** (26 mg, 0.09 mmol) in DMF (5 mL) was added 2-chloro-5-fluoropyrimidine (24 mg, 0.18 mmol) and K_2CO_3 (25 mg, 0.18 mmol) at r.t., then the mixture was stirred at 100 °C for 16 hours. UPLC-MS monitored the completion of the reaction. The reaction mixture was poured into water and extracted with EA. The organic layer was separated, and the aqueous layer was repeatedly extracted with EA (2×5 mL). The combined extracts were dried with Na_2SO_4 and concentrated. The resulting residue was purified by silica gel chromatography (PE: EA = 2: 1) to give 6 mg of **28** as a yellow solid, yield: 24%. ^1H -NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 2H), 7.39-7.20 (m, 5H), 6.83 (s, 1H), 5.37 (dd, J = 11.6, 9.6 Hz, 1H), 4.80 (m, 1H), 4.48-4.25 (m, 3H), 3.53-3.03 (m, 3H), 2.80-2.61 (m, 1H), 1.35 (d, J = 6.8 Hz, 3H), 1.25 (d, J = 6.8 Hz, 3H). LC-MS (ESI) m/z : 383.35, $[M+H]^+$.

[0104] Compound 29: (5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((2R,6S)-4-(5-fluoropyrimidin-2-yl)-2,6-dimethylpiperazin-1-yl)methanone



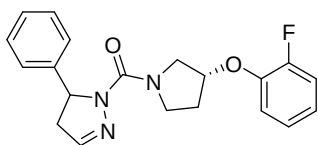
Compound **29** was synthesized according to the method of compound **28** while using ((2R,6S)-2,6-dimethylpiperazin-1-yl)(5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone and 2-chloro-5-fluoropyrimidine. (5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((2R,6S)-4-(5-fluoropyrimidin-2-yl)-2,6-dimethylpiperazin-1-yl)methanone was obtained as white powder (yield 31%). ^1H NMR (400 MHz, Chloroform- d) δ 8.19 (t, J = 0.6 Hz, 2H), 7.29 (m, 1H), 7.09 (dt, J = 7.8, 1.2 Hz, 1H), 7.00 (ddd, J = 9.8, 2.6, 1.6 Hz, 1H), 6.93 (tdd, J = 8.4, 2.8, 1.0 Hz, 1H), 6.83 (t, J = 1.8 Hz, 1H), 5.41-5.32 (m, 1H), 4.85-4.74 (m, 1H), 4.47-4.29 (m, 3H), 3.42 – 3.22 (m, 2H), 3.17 (dd, J = 13.0, 4.2 Hz, 1H), 2.67 (ddd, J = 18.2, 10.2, 1.6 Hz, 1H), 1.35 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 6.9 Hz, 3H). LC-MS (m/z) 401.45 $[M+H]^+$.

[0105] Compound 30: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((2R,6S)-4-(5-fluoropyrimidin-2-yl)-2,6-dimethylpiperazin-1-yl)methanone



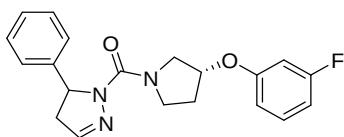
Compound **30** was synthesized according to the method of compound **28** while using (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((2R,6S)-2,6-dimethylpiperazin-1-yl)methanone and 2-chloro-5-fluoropyrimidine. (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((2R,6S)-4-(5-fluoropyrimidin-2-yl)-2,6-dimethylpiperazin-1-yl)methanone was obtained as white powder (yield 23%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.26 (s, 2H), 6.89-6.77 (m, 3H), 6.74-6.65 (m, 1H), 5.34 (t, *J* = 10.9 Hz, 1H), 4.83 (s, 1H), 4.50 (d, *J* = 13.1 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 2H), 3.43 (dd, *J* = 13.2, 4.5 Hz, 1H), 3.35-3.19 (m, 2H), 2.66 (dd, *J* = 18.2, 10.2 Hz, 1H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.29 (d, *J* = 6.8 Hz, 3H). LC-MS (*m/z*) 418.49 [M+H]⁺.

[0106] Compound 31: ((R)-3-(2-fluorophenoxy)pyrrolidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



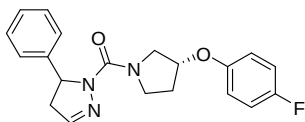
(R)-3-(2-fluorophenoxy)pyrrolidine (304 mg) and (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone(403 mg) and TEA(506 mg) were dissolved in THF(10 ml) and stirred at room temperature for 16h. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give **31** (186 mg, 31.4%). ¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.27 (m, 3H), 7.26 – 7.19 (m, 2H), 7.11 – 7.00 (m, 2H), 6.98 – 6.89 (m, 2H), 6.77 (t, *J* = 1.6 Hz, 1H), 5.40 – 5.32 (m, 1H), 4.94-4.87 (m, 1H), 4.05 – 3.66 (m, 4H), 3.38-3.26 (m, 1H), 2.78 – 2.66 (m, 1H), 2.26 – 2.05 (m, 2H). LC-MS (*m/z*) 354.4 (M+H⁺)

[0107] Compound 32: ((R)-3-(3-fluorophenoxy)pyrrolidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



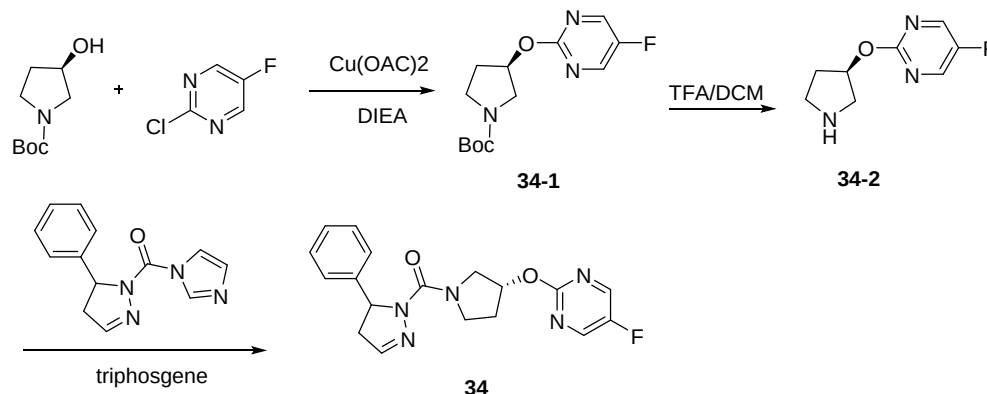
(R)-3-(3-fluorophenoxy)pyrrolidine was prepared by procedure outlined for compound **26** (130 mg) and (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone(172 mg) and TEA(513mg) were dissolved in THF(5ml) and stirred at room temperature for 16h. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give **32** (95.8mg, 38%).
¹H NMR (400 MHz, CDCl₃) δ 7.51 – 7.25 (m, 4H), 7.24 – 7.11 (m, 3H), 6.77-6.75 (m, 1H), 6.70-6.50 m, 2H), 5.38 – 5.29 (m, 1H), 4.84 (m, 1H), 3.99 – 3.78 (m, 2H), 3.75 – 3.50 (m, 2H), 3.36 – 3.21 (m, 1H), 2.70 (dd, *J* = 18.4, 7.8 Hz, 1H), 2.21 – 2.08 (m, 1H), 2.08 – 1.96 (m, 1H). LC-MS (m/z) 354.4 (M+H⁺)

[0108] Compound 33: ((R)-3-(4-fluorophenoxy)pyrrolidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **33** was prepared in 12% yield from (R)-3-(4-fluorophenoxy)pyrrolidine and (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **32**. ¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.25 (m, 3H), 7.24 – 7.19 (m, 2H), 6.98-6.91(m, 2H), 6.82-6.77 (m, 2H), 6.75 (t, *J* = 1.6 Hz, 1H), 5.33 (ddd, *J* = 12.0, 8.4, 4.0 Hz, 1H), 4.84 – 4.75 (m, 1H), 3.98 – 3.75 (m, 3H), 3.74 – 3.56 (m, 2H), 3.35-3.23 (m, 1H), 2.75-2.65 (m, 1H), 2.21 – 2.12 (m, 1H). LC-MS (m/z) 354.4 (M+H⁺)

[0109] Compound 34: ((R)-3-((5-fluoropyrimidin-2-yl)oxy)pyrrolidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



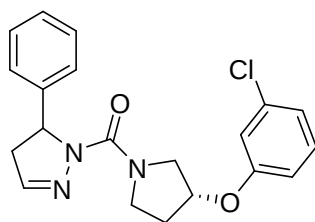
Step1 :To a cold solution of NaH(128mg) in 5mL of DMF(5mL) was added a solution of

tert-butyl (R)-3-hydroxypyrrolidine-1-carboxylate(300mg) in DMF(2mL). The mixture was stirred at room temperature for 1h, and then cooled to 0°C, 2-chloro-5-fluoropyrimidine(212 mg) was added. The mixture was stirred at room temperature for 16h. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give **34-1** (100 mg). LC-MS (m/z) 284.4 (M+H⁺)

Step2: Compound 34-1(100 mg) was dissolved in DCM(2 ml) was added TFA(401mg). The mixture was stirred at room temperature for 2h. The mixture was concentrated in vacuo, and extracted with DCM, washed with saturated aqueous NaHCO₃, dried with (Na₂SO₄), and concentrated to give the residue (**34-2** (65mg) ,which used for next step without purification.

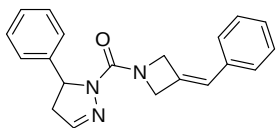
Step3: (R)-5-fluoro-2-(pyrrolidin-3-yloxy)pyrimidine (64 mg) and (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone(84 mg) and TEA(106 mg) were dissolved in THF(10 ml) and stirred at room temperature for 16h. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give **34** (118 mg, 94.4%). ¹H NMR (400 MHz, CDCl₃) δ 8.35 (d, *J* = 2.9 Hz, 2H), 7.31 – 7.26 (m, 3H), 7.23 – 7.19 (m, 2H), 6.75-6.73 (m, 1H), 5.37 – 5.29 (m, 1H), 3.93-3.88 (m, 3H), 3.74-3.66 (m, 2H), 3.33-3.28 (m, 1H), 2.74 – 2.65 (m, 1H). 2.21 – 2.12 (m, 1H). LC-MS (m/z) 356.4 (M+H⁺)

[0110] Compound 35: ((R)-3-(3-chlorophenoxy)pyrrolidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



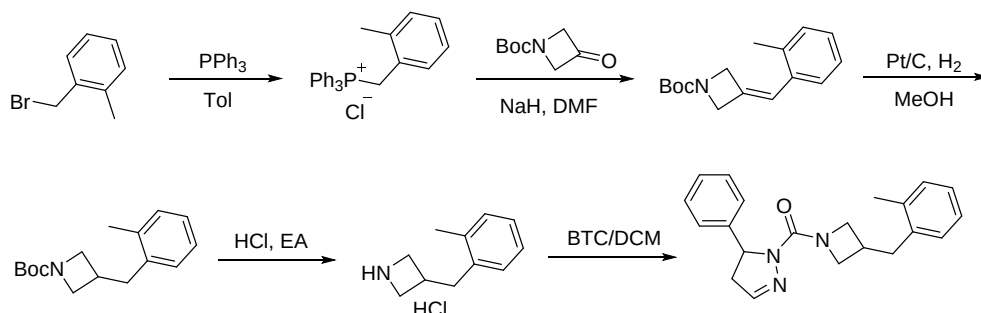
The titled compound **35** was prepared in 19% yield from (R)-3-(3-chlorophenoxy)pyrrolidine and (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **32**. ¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.24 (m, 7H), 7.23 – 7.14 (m, 1H), 6.95 – 6.82 (m, 1H), 6.77-6.71 (m, 1H), 5.38-5.30 (m, 1H), 4.88- 4.82 (m, 1H), 3.96-3.78 (m, 2H), 3.75 – 3.54 (m, 2H), 3.35-3.23(m, 1H), 2.70 (dd, *J* = 18.8, 8.4 Hz, 1H), 2.18-2.09 (m, 1H), 2.07-1.94 (m, 1H). LC-MS (m/z) 370.8 (M+H⁺).

[0111] Compound 36: (3-benzylideneazetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **36** was prepared in 23% yield from 5-phenyl-4,5-dihydro-1H-pyrazole, 3-benzylideneazetidine and triphosgene according to the procedure outlined for compound **9**. ^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.28 (m, 4H), 7.26 – 7.17 (m, 7H), 7.11 (d, J = 7.2 Hz, 2H), 6.81 (t, J = 1.7 Hz, 1H), 6.25 – 6.21 (m, 1H), 5.34 (dd, J = 12.1, 6.3 Hz, 1H), 5.04 (dd, J = 34.9, 14.4 Hz, 2H), 4.82 (dd, J = 31.0, 14.9 Hz, 2H), 3.35 (ddd, J = 18.5, 12.2, 1.7 Hz, 1H), 2.75 (ddd, J = 18.5, 6.3, 1.7 Hz, 1H). LC-MS (m/z) 318.4 ($\text{M}+\text{H}^+$)

[0112] Compound 37: (3-(2-methylbenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl) methanone



Step 1. Preparation of (2-methylbenzyl)triphenylphosphonium bromide

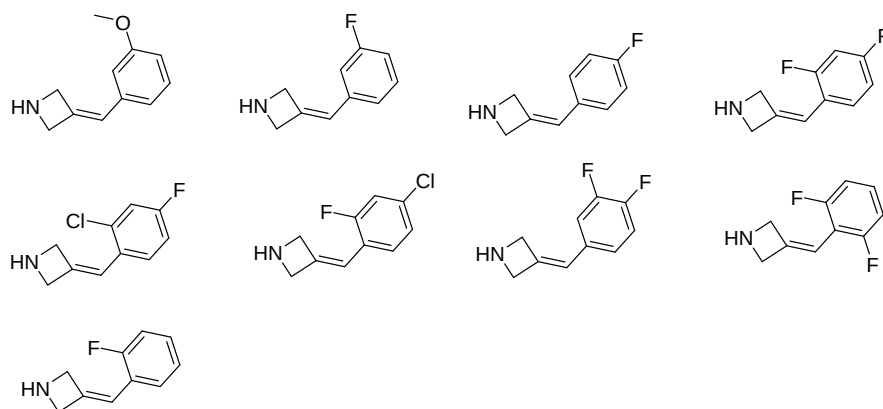
A mixture of 1-(bromomethyl)-2-methylbenzene (1.5g, 8.15 mmol), PPh_3 (2.14 g, 8.15 mmol) and Tol (20 mL) was stirred at 110°C for 18 h. The mixture was filtrated and the solid was washed with Et_2O for three times and dried to give the desired product as a white solid (1.8g, 49.6%). LC-MS (m/z) 368.5 ($\text{M}+\text{H}^+$)

Step 2. Preparation of tert-butyl 3-(2-methylbenzylidene)azetidine-1-carboxylate

To a suspension of (2-methylbenzyl)triphenylphosphonium bromide (236 mg, 0.528 mmol) in DMF (4 mL) was added NaH (13mg) at 0°C , then the mixture was stirred at r.t. for 15 min before tert-butyl 3-oxoazetidine-1-carboxylate (86 mg, 0.503 mmol) was added, then the mixture was stirred at room temperature for 2 days. Water was added and a large amount of white solid precipitated, the solid was collected by filtration, and dried to give the crude product (470mg), which was used for the next step without further purification.

LC-MS (m/z) 260.4 (M+H⁺).

The following intermediates used for the preparation of titled example compounds were synthesized using the above methods analogous to give different substituted tert-butyl 3-benzylideneazetidine-1-carboxylate, and followed by removed Boc using TFA in DCM to give the desired intermediates.



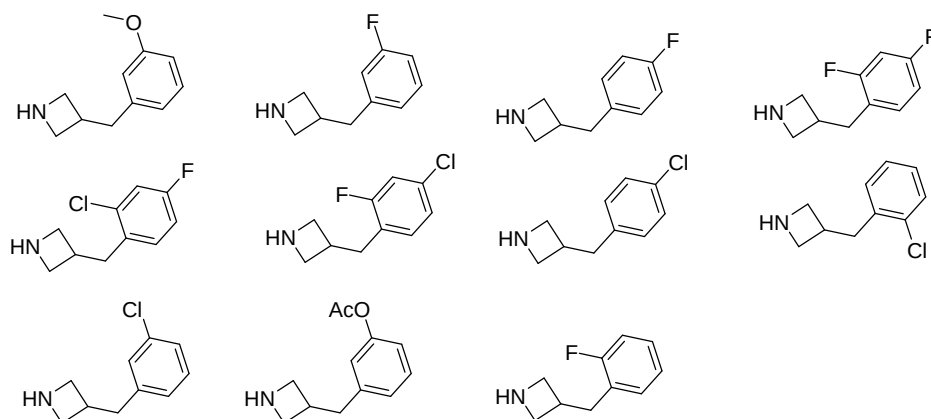
Step 3. Preparation of tert-butyl 3-(2-methylbenzyl)azetidine-1-carboxylate

To a solution of tert-butyl 3-(2-methylbenzylidene)azetidine-1-carboxylate (270 mg) in MeOH (5 mL) was added Pt/C(30mg), the mixture was stirred at r.t. for 18 h under H₂ atmosphere. The mixture was filtrated and the filtrate was concentrated to give the desired product as a white solid (270 mg, 99.6%). LC-MS (m/z) 262.4 (M+H⁺)

Step 4. Preparation of 3-(2-methylbenzyl)azetidine hydrochloride

A mixture of tert-butyl 3-(2-methylbenzyl)azetidine-1-carboxylate(270 mg) and HCl/EA (4 mL) was stirred at r.t. for 4 h. The mixture was concentrated to give the desired product, which was used for next step without further purification.

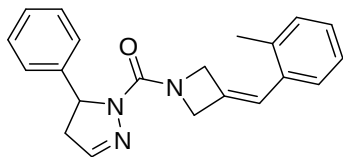
The following intermediates used for the preparation of titled example compounds were synthesized using the methods analogous to 3-(2-methylbenzyl)azetidine hydrochloride described above. TFA/DCM may be instead of HCl/EA or basified by saturated NaHCO₃ to give free base.



Step 5. Preparation of (3-(2-methylbenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone

To a cooled solution of triphosgene (60 mg) in dry DCM (5ml) was added dropwise a mixture solution of 5-phenyl-4,5-dihydro-1H-pyrazole (148 mg) and TEA (0.14ml). The mixture was stirred at 0°C for 3h. 3-(2-methylbenzyl)azetidine hydrochloride (100mg) and TEA(0.14ml) were dissolved in dry DCM(2 ml), and the aboved reaction mixture was added to the solution and stirred for overnight. The mixture was extracted with DCM, washed with brine, dried with (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography(EA/PE=1/3) to give compound **37** (80mg, 47.3%) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.29 (m, 2H), 7.25-7.21 (m, 3H), 7.17-7.10 (m, 3H), 7.07-7.02 (m, 1H), 6.74 (t, 1H, *J* = 1.6 Hz), 5.31 (dd, 1H, *J* = 12.0, 1.6 Hz), 4.34 -4.17 (m, 2H), 3.93 (dd, 1H, *J* = 9.6, 4.4 Hz), 3.83 (dd, 1H, *J* = 9.2, 4.4 Hz), 3.32 (ddd, 1H, *J* = 18.4, 12.4, 2.0 Hz), 2.92-2.89 (m, 3H), 2.72 (ddd, 1H, *J* = 18.4, 6.4, 1.6 Hz), 2.30 (s, 3H). LC-MS (*m/z*): 334.55 [M+H]⁺.

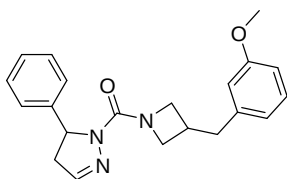
[0113] Compound 38: (3-(2-methylbenzylidene)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **38** was prepared in 51.6% yield from 3-benzylideneazetidine hydrochloride, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.30 (m, 2H), 7.25-7.21 (m, 3H), 7.19-7.12 (m, 3H), 7.08-7.06 (m, 1H), 6.81 (t, 1H, *J* = 1.6 Hz), 6.45-6.42 (m, 1H), 5.36 (dd, 1H, *J* = 12.0, 6.4 Hz), 5.07-4.93 (m, 2H), 4.90-4.77 (m, 2H), 3.37 (ddd, 1H, *J* = 18.4, 12.0, 1.6 Hz), 2.76 (ddd, 1H, *J* = 18.4, 6.4, 2.0 Hz), 2.32 (s, 3H). LC-

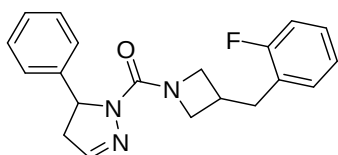
MS (m/z): 332.36 [M+H]⁺.

[0114] Compound 39: (3-(3-methoxybenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl) methanone



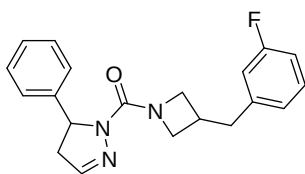
The titled compound **39** was prepared in 36.6% yield from 3-(4-methoxybenzyl)azetidine hydrochloride, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ¹H-NMR (400 MHz, CDCl₃) δ 7.35 – 7.29 (m, 2H), 7.26 – 7.17 (m, 4H), 6.79 – 6.72 (m, 3H), 6.69 (t, *J* = 2.4 Hz, 1H), 5.31 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.22 (dt, *J* = 28.4, 8.4 Hz, 2H), 3.87 (ddd, *J* = 32.8, 8.0, 4.8 Hz, 2H), 3.79 (s, 3H), 3.32 (ddd, *J* = 18.4, 12.4, 1.6 Hz, 1H), 2.93 – 2.80 (m, 3H), 2.72 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H). LC-MS(m/z): 350.34[M+H]⁺.

[0115] Compound 40: (3-(2-fluorobenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



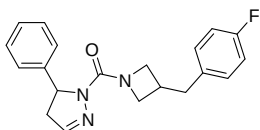
The titled compound **40** was prepared in 22.4% yield from 3-(2-fluorobenzyl)azetidine hydrochloride, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ¹H-NMR (400 MHz, CDCl₃) δ 7.37 – 7.29 (m, 2H), 7.25 – 7.12 (m, 5H), 7.09 – 6.98 (m, 2H), 6.77 (t, *J* = 1.5 Hz, 1H), 5.32 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.26 (t, *J* = 8.0 Hz, 1H), 4.20 (t, *J* = 8.8 Hz, 1H), 3.93 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.86 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.33 (ddd, *J* = 18.4, 12.0, 1.6 Hz, 1H), 2.96-2.84 (m, 3H), 2.73 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H). LC-MS(m/z) :338.36[M+H]⁺.

[0116] Compound 41: (3-(3-fluorobenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



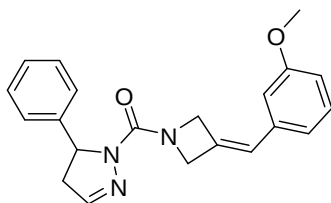
The titled compound **41** was prepared in 32.6% yield from 3-(3-fluorobenzyl) azetidine hydrochloride, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ¹H-NMR (400 MHz, CDCl₃) δ 7.35 – 7.29 (m, 2H), 7.26 – 7.19 (m, 4H), 6.95 – 6.80 (m, 3H), 6.75 (t, *J* = 1.6 Hz, 1H), 5.31 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.22 (dt, *J* = 28.2, 8.4 Hz, 2H), 3.86 (ddd, *J* = 32.4, 8.8, 5.2 Hz, 2H), 3.32 (ddd, *J* = 18.4, 12.4, 1.6 Hz, 1H), 2.92 (d, *J* = 7.6 Hz, 2H), 2.90-2.80(m, 1H), 2.72 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H). LC-MS(*m/z*) :338.34[M+H]⁺.

[0117] Compound 42: (3-(4-fluorobenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **42** was prepared in 22.4% yield from 3-(4-fluorobenzyl) azetidine hydrochloride, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ¹H-NMR (400 MHz, CDCl₃) δ 7.32 (t, *J* = 7.6 Hz, 2H), 7.26-7.18 (m, 3H), 7.10 (dd, *J* = 8.4, 5.6 Hz, 2H), 6.97 (t, *J* = 8.4 Hz, 2H), 6.76-6.73 (m, 1H), 5.31 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.21 (dt, *J* = 28.2, 8.4 Hz, 2H), 3.85 (ddd, *J* = 32.4, 9.0, 5.2 Hz, 2H), 3.32 (dd, *J* = 18.4, 12.0 Hz, 1H), 2.89 (d, *J* = 7.6 Hz, 2H), 2.85-2.77 (m, 1H), 2.72 (dd, *J* = 18.4, 6.4 Hz, 1H). LC-MS(*m/z*) :338.17[M+H]⁺.

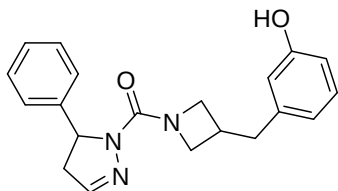
[0118] Compound 43: (3-(3-methoxybenzylidene)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **42** was prepared 3-(3-methoxybenzylidene)azetidine hydrochloride, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene to give **43** in 36.6% yield, according to the procedure outlined for compound **37**. ¹H-NMR (400 MHz, CDCl₃) δ 7.36 – 7.30 (m, 2H), 7.27 – 7.22 (m, 4H), 6.82 (t, *J* = 1.6 Hz, 1H), 6.77 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.67 – 6.64 (m, 1H), 6.22 (t, *J* = 2.4 Hz, 1H), 5.36 (dd, *J* = 12.4, 6.4 Hz, 1H), 5.05 (dd, *J* = 37.6, 14.4 Hz, 2H), 4.83 (dd, *J* = 32.4, 15.0 Hz, 2H), 3.80 (s, 3H), 3.37 (ddd, *J*

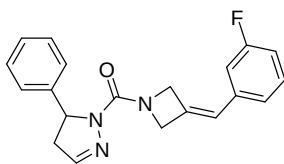
= 18.4, 12.0, 1.6 Hz, 1H), 2.77 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H). LC-MS(m/z): 348.32[M+H]⁺.

[0119] Compound 44: (3-(3-hydroxybenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



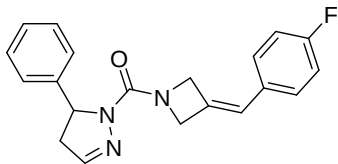
3-((1-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)methyl)phenyl acetate prepared by the procedure outlined for compound **37** (10mg) was dissolved in MeOH(1mL), and 1N LiOH (0.041mmol) was added. The mixture was stirred at room temperature for 2h. The mixture was adjusted to PH 2-3 with con. HCl, and extracted with EA, washed with brine, dried with (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography(EA/PE=1/1) to give compound **37**(7mg, 77.8%). ¹H-NMR (400 MHz, CDCl₃) δ 7.35 – 7.27 (m, 2H), 7.26 – 7.19 (m, 3H), 7.10 (t, J = 7.8 Hz, 1H), 6.77-6.74 (m, 1H), 6.72 – 6.55 (m, 3H), 5.31 (dd, J = 12.4, 6.4 Hz, 1H), 4.28-4.15 (m, 2H), 3.95-3.78 (m, 2H), 3.32 (ddd, J = 18.8, 12.4, 1.6 Hz, 1H), 2.82 (s, 3H), 2.71 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H). LC-MS(m/z) :336.39[M+H]⁺.

[0120] Compound 45: (3-(3-fluorobenzylidene)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



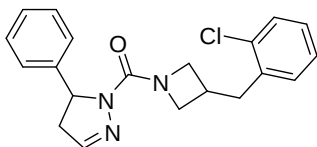
The titled compound **45** was prepared in 36.3% yield from 3-(3-fluorobenzylidene)azetidine hydrochloride, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ¹H-NMR (400 MHz, CDCl₃) δ 7.36 – 7.31 (m, 2H), 7.28 (m, 2H), 7.26 – 7.23 (m, 2H), 6.95 – 6.87 (m, 2H), 6.86 – 6.76 (m, 2H), 6.22 (t, J = 7.8 Hz, 1H), 5.36 (dd, J = 12.0, 6.4 Hz, 1H), 5.14-4.96 (m, 2H), 4.90 – 4.74(m, 2H), 3.38 (ddd, J = 18.4, 12.0, 1.6 Hz, 1H), 2.77 (ddd, J = 18.4, 6.4, 16 Hz, 1H). LC-MS(m/z) :336.38[M+H]⁺.

[0121] Compound 46: (3-(4-fluorobenzylidene)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



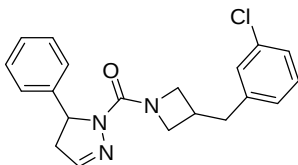
The titled compound **46** was prepared in 36.6% yield from 3-(4-fluorobenzylidene)azetidine hydrochloride, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.36 – 7.30 (m, 2H), 7.27-7.22 (m, 3H), 7.11-7.06 (m, 2H), 7.05-6.99 (m, 2H), 6.82 (t, J = 1.6 Hz, 1H), 6.21 (t, J = 2.4 Hz, 1H), 5.36 (dd, J = 12.0, 6.4 Hz, 1H), 5.02 (dd, J = 35.4, 14.6 Hz, 2H), 4.82 (dd, J = 32.2, 14.4 Hz, 2H), 3.37 (ddd, J = 18.4, 12.0, 1.6 Hz, 1H), 2.77 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H). LC-MS(m/z) :336.29[$\text{M}+\text{H}$] $^+$.

[0122] Compound 47: (3-(2-chlorobenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **47** was prepared in 22.4% yield from 3-(2-chlorobenzyl)azetidine, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.36-7.27 (m, 3H), 7.26 – 7.18 (m, 3H), 7.18 – 6.94 (m, 3H), 6.74-6.71 (m, 1H), 5.29 (dd, J = 12.2, 6.5 Hz, 1H), 4.20 (dt, J = 25.9, 8.5 Hz, 2H), 3.87 (ddd, J = 32.7, 8.9, 5.3 Hz, 2H), 3.31 (dd, J = 18.5, 12.2 Hz, 1H), 3.14 – 2.82 (m, 3H), 2.70 (dd, J = 18.5, 6.4 Hz, 1H). LC-MS (m/z) 354.9 ($\text{M}+\text{H}^+$).

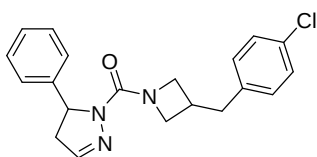
[0123] Compound 48: (3-(3-chlorobenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **48** was prepared in 28.2% yield from 3-(3-chlorobenzyl)

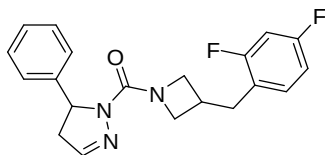
azetidine and (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **34** . LC-MS (m/z) 354.9(M+H⁺). ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.28 (m, 1H), 7.24 – 7.11 (m, 7H), 7.04 – 6.96 (m, 1H), 6.74 (s, 1H), 5.29 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.20 (dt, *J* = 29.6, 8.0 Hz, 2H), 3.80 (ddd, *J* = 31.8, 26.4, 5.2 Hz, 2H), 3.37 – 3.26 (m, 1H), 3.00-2.76 (m, 3H), 2.75 – 2.66 (m, 1H). LC-MS (m/z) 354.9 (M+H⁺).

[0124] Compound 49: (3-(4-chlorobenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



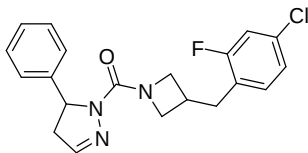
The titled compound **49** was prepared in 11% yield from 3-(4-chlorobenzyl)azetidine, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **34**. LC-MS (m/z) 354.9(M+H⁺). ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.28 (m, 1H), 7.24 – 7.11 (m, 7H), 7.04 – 6.96 (m, 1H), 6.74 (s, 1H), 5.29 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.20 (dt, *J* = 29.6, 8.0 Hz, 2H), 3.80 (ddd, *J* = 31.8, 26.4, 5.2 Hz, 2H), 3.37 – 3.26 (m, 1H), 3.00-2.76 (m, 3H), 2.75 – 2.66 (m, 1H). LC-MS (m/z) 338.4 (M+H⁺).

[0125] Compound 50: (3-(2,4-difluorobenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



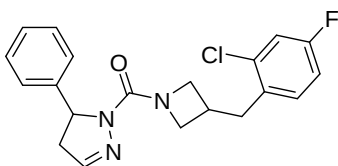
The titled compound **50** was prepared in 24.7% yield from 1-(bromomethyl)-2,4-difluorobenzene, PPh₃, NaH, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ¹H-NMR (400 MHz, CDCl₃) δ 7.35 – 7.29 (m, 2H), 7.25-7.19 (m, 3H), 7.14 – 7.06 (m, 1H), 6.84 – 6.77 (m, 2H), 6.76 (t, *J* = 1.7 Hz, 1H), 5.31 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.24 (t, *J* = 8.4 Hz, 1H), 4.18 (t, *J* = 8.4 Hz, 1H), 3.89 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.81 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.33 (ddd, *J* = 18.4, 12.0, 1.6 Hz, 1H), 2.93-2.79 (m, 3H), 2.72 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H). LC-MS(m/z) :356.56[M+H]⁺.

[0126] Compound 51: (3-(4-chloro-2-fluorobenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



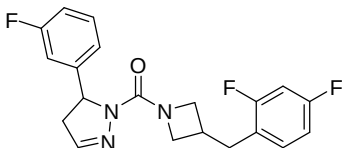
The titled compound **51** was prepared in 24.2% yield from 3-(4-chloro-2-fluorobenzyl)azetidine hydrochloride, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.30 (m, 2H), 7.24 – 7.21 (m, 3H), 7.11 – 7.02 (m, 3H), 6.75 (t, J = 2.0 Hz, 1H), 5.30 (dd, J = 12.0, 6.4 Hz, 1H), 4.24 (t, J = 8.4 Hz, 1H), 4.17 (t, J = 8.4 Hz, 1H), 3.89 (dd, J = 9.2, 5.2 Hz, 1H), 3.80 (dd, J = 9.2, 5.2 Hz, 1H), 3.32 (ddd, J = 18.4, 12.0, 1.6 Hz, 1H), 2.92 – 2.89 (m, 2H), 2.88 – 2.80 (m, 1H), 2.72 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H). LC-MS (m/z):372.29 $[\text{M}+\text{H}]^+$.

[0127] Compound 52: (3-(2-chloro-4-fluorobenzyl)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



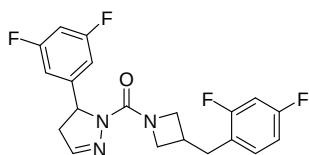
The titled compound **52** was prepared in 24.2% yield from 3-(2-chloro-4-fluorobenzyl)azetidine hydrochloride, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ^1H NMR (400 MHz, CDCl_3) δ 7.34–7.31 (m, 2H), 7.26 – 7.22 (m, 3H), 7.15 – 7.10 (m, 2H), 6.91 (td, J = 8.0, 2.8 Hz, 1H), 6.77–6.74 (m, 1H), 5.31 (dd, J = 12.8, 6.4 Hz, 1H), 4.25 (t, J = 8.8 Hz, 1H), 4.18 (t, J = 8.8 Hz, 1H), 3.91 (dd, J = 9.2, 5.2 Hz, 1H), 3.81 (dd, J = 9.2, 5.2 Hz, 1H), 3.33 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H), 3.00 – 2.99 (m, 2H), 2.96–2.87 (m, 1H), 2.73 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H). LC-MS (m/z):372.49 $[\text{M}+\text{H}]^+$.

[0128] Compound 53: (3-(2,4-difluorobenzyl)azetidin-1-yl)(5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



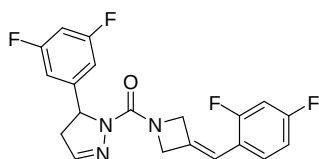
The titled compound **53** was prepared in 23.5% yield from 3-(2,4-difluorobenzyl) azetidine hydrochloride, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.25 (m, 1H), 7.14-7.07 (m, 1H), 7.01 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.83 – 6.73 (m, 3H), 5.29 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.21 (dt, *J* = 23.6, 8.2 Hz, 2H), 3.86 (ddd, *J* = 29.6, 8.7, 4.9 Hz, 2H), 3.32 (ddd, *J* = 18.4, 12.0, 1.6 Hz, 1H), 2.92-2.88 (m, 2H), 2.88-2.80 (m, 1H), 2.68 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H). LC-MS (*m/z*): 374.36 [M+H]⁺.

[0129] Compound 54: (3-(2,4-difluorobenzyl)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



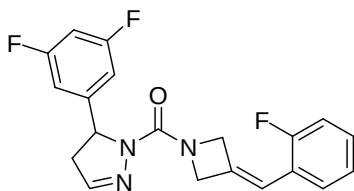
The titled compound **54** was prepared in 22.3% yield from 3-(2,4-difluorobenzyl) azetidine hydrochloride, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ¹H NMR (400 MHz, CDCl₃) δ 7.14-7.08 (m, 1H), 6.83 – 6.66 (m, 6H), 5.28 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.28-4.20 (m, 2H), 3.95 – 3.83 (m, 2H), 3.33 (ddd, *J* = 18.4, 12.2, 1.6 Hz, 1H), 2.96-2.84 (m, 3H), 2.68 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H). LC-MS (*m/z*): 392.20 [M+H]⁺.

[0130] Compound 55: (3-(2,4-difluorobenzylidene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



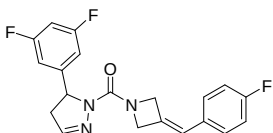
The titled compound **55** was prepared in 27.9% yield from 3-(2,4-difluorobenzylidene) azetidine hydrochloride, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ¹H NMR (400 MHz, CDCl₃) δ 7.11-7.03 (m, 1H), 6.89 – 6.73 (m, 5H), 6.69 (tt, *J* = 8.0, 2.4 Hz, 1H), 6.39 (t, *J* = 2.0 Hz, 1H), 5.31 (dd, *J* = 12.0, 6.4 Hz, 1H), 4.99 (q, *J* = 14.4 Hz, 2H), 4.85 (q, *J* = 14.4 Hz, 2H), 3.42-3.32 (m, 1H), 2.71 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H). LC-MS (*m/z*): 390.26 [M+H]⁺.

[0131] Compound 56: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(2-fluorobenzylidene)azetidin-1-yl)methanone



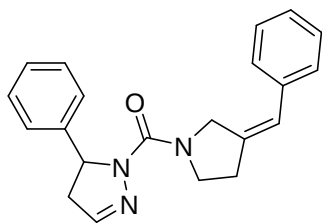
The titled compound **56** was prepared in 18.7% yield 3-(2-fluorobenzylidene) azetidine hydrochloride, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ^1H NMR (400 MHz, CDCl_3) δ 7.23 – 7.17 (m, 1H), 7.13 – 7.00 (m, 3H), 6.83 – 6.74 (m, 3H), 6.69 (tt, J = 8.8, 2.4 Hz, 1H), 6.47 (t J = 2.4 Hz, 1H), 5.32 (dd, J = 12.0, 6.4 Hz, 1H), 5.10-4.96(m, 2H), 4.94 – 4.76 (m, 2H), 3.37 (ddd, J = 18.4, 12.0, 1.6 Hz, 1H), 2.71 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H). LC-MS (m/z):372.30 $[\text{M}+\text{H}]^+$.

[0132] Compound 57: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(4-fluorobenzylidene)azetidin-1-yl)methanone



The titled compound **57** was prepared in 25.5% yield 3-(4-fluorobenzylidene) azetidine hydrochloride, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ^1H NMR (400 MHz, CDCl_3) δ 7.09 – 7.04 (m, 2H), 7.04 – 6.94 (m, 2H), 6.81 – 6.71 (m, 3H), 6.67 (tt, J = 8.8, 2.4 Hz, 1H), 6.24 – 6.17 (m, 1H), 5.30 (dd, J = 12.0, 6.4 Hz, 1H), 5.02 (q, J = 13.6 Hz, 2H), 4.82 (q, J = 13.6 Hz, 2H), 3.35 (ddd, J = 18.4, 12.0, 1.6 Hz, 1H), 2.69 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H). LC-MS (m/z):372.29 $[\text{M}+\text{H}]^+$.

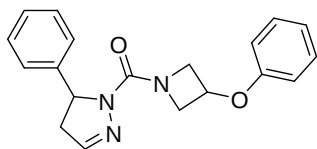
[0133] Compound 58: (Z)-(3-benzylidenepyrrolidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **58** was prepared in 25% yield (Z)-3-benzylidenepyrrolidine, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure

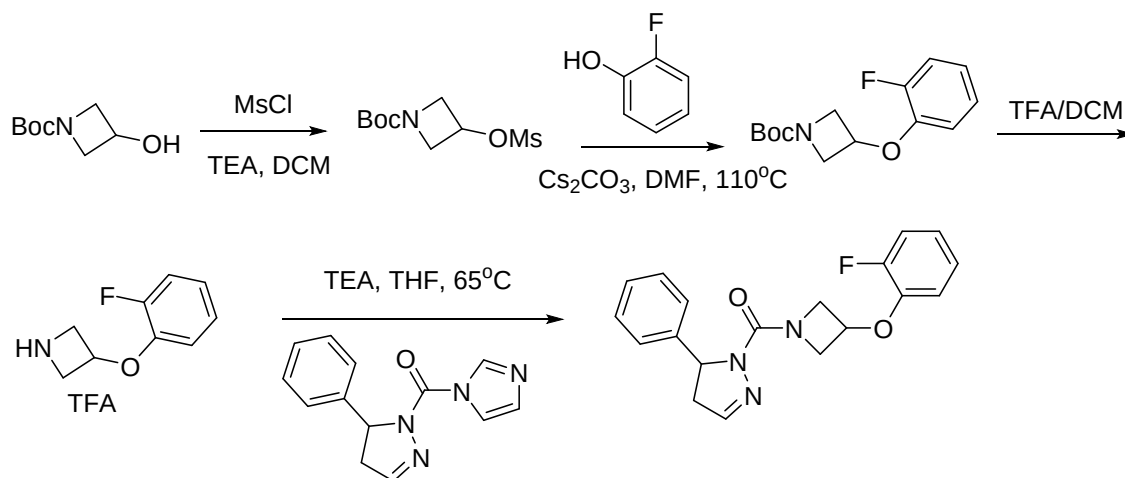
outlined for compound **37**. ^1H NMR (400 MHz, Chloroform- d) δ 7.48-7.12 (m, 10H), 6.80 (s, 1H), 6.42 (d, J = 8.4 Hz, 1H), 5.37 (q, J = 9.2 Hz, 1H), 4.65 (dd, J = 26.4, 16.4 Hz, 1H), 4.29 (t, J = 18.4 Hz, 1H), 3.84 (dq, J = 35.2, 8.8 Hz, 1H), 3.67 (dq, J = 25.6, 10.2, 8.4 Hz, 1H), 3.32 (ddd, J = 18.2, 12.0, 4.6 Hz, 1H), 2.77 (td, J = 22.2, 18.0, 7.8 Hz, 3H). LC-MS (m/z) 332.6 $[\text{M}+\text{H}]^+$.

[0134] Compound 59: (3-phenoxyazetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **59** was prepared in 18.7% yield from 3-(phenoxy)-azetidine hydrochloride, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **26**. ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.26 (m, 4H), 7.25-7.20 (m, 3H), 6.98 (t, 1H, J = 7.6 Hz), 6.80-6.70 (m, 3H), 5.32 (dd, 1H, J = 12.0, 6.4 Hz), 4.94-4.88 (m, 1H), 4.55 (dd, 1H, J = 10.0, 6.4 Hz), 4.48 (dd, 1H, J = 10.0, 6.4 Hz), 4.24 (dd, 1H, J = 10.0, 4.0 Hz), 4.17 (dd, 1H, J = 10.0, 4.0 Hz), 3.34 (ddd, 1H, J = 18.4, 12.4, 1.6 Hz), 2.74 (ddd, 1H, J = 18.4, 6.4, 1.6 Hz). LC-MS (m/z): 322.21 $[\text{M}+\text{H}]^+$.

[0135] Compound 60: (3-(2-fluorophenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



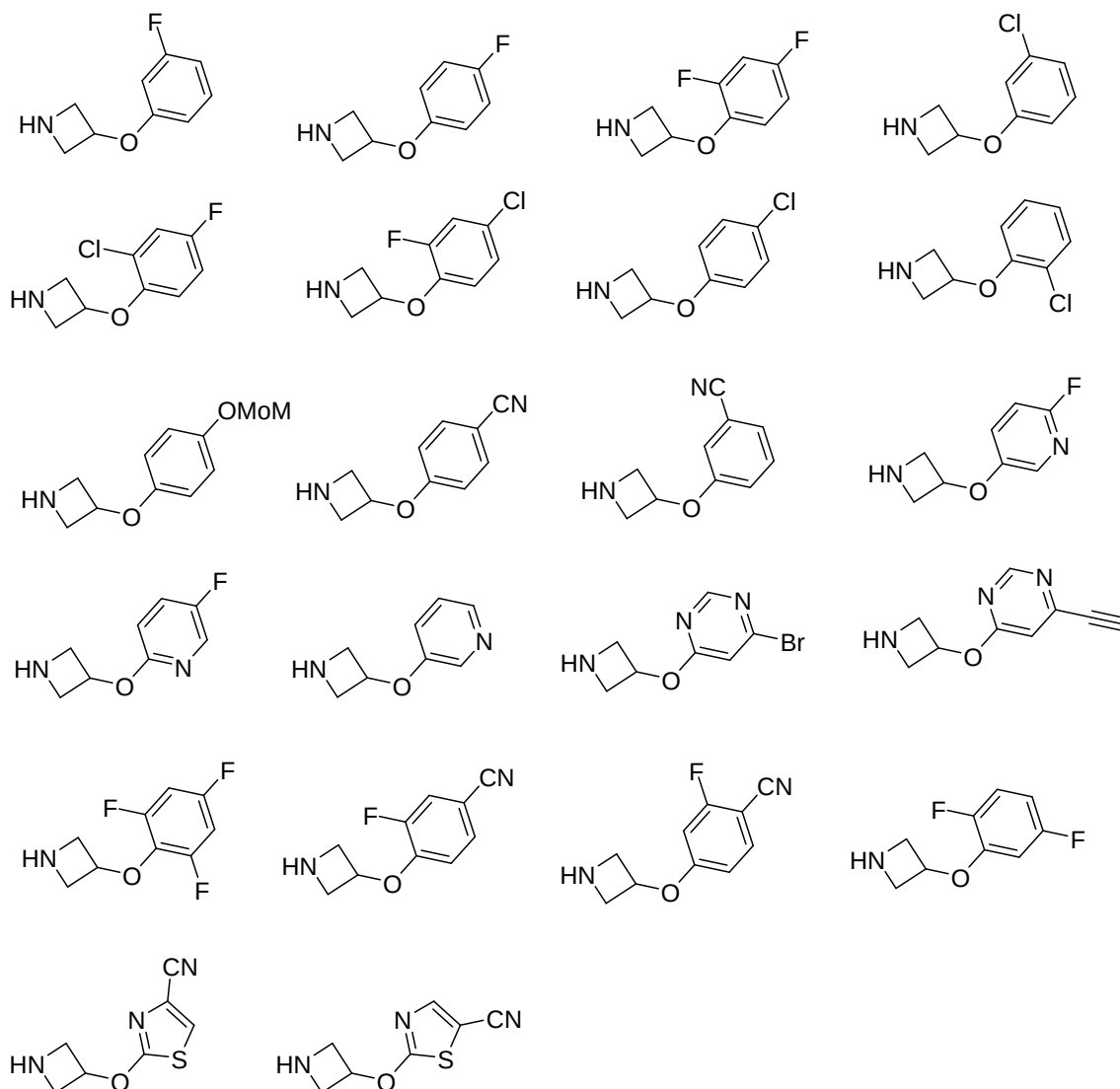
Step 1: Prepared of tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate
tert-butyl 3-hydroxyazetidine-1-carboxylate (1g, 5.35mmol) was dissolved in 10 ml of dry DCM, TEA (1.08g, 10.7mmol) was added. MsCl (0.738g, 6.42 mmol) was added slowly to the above solution at 0°C. The mixture was stirred for overnight. The mixture was extracted

with DCM, washed with brine, dried (Na_2SO_4), and concentrated to dryness to give the desired product. LC-MS (m/z) 252.3 ($\text{M}+\text{H}^+$).

Step 2: Prepared of tert-butyl 3-(2-fluorophenoxy)azetidine-1-carboxylate
tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate(200mg, 0.796mmol),
 Cs_2CO_3 (518mg, 1.6mmol) and KI(3mg) were placed in DMF(2mL). The mixture was stirred 110°C for overnight, water was added and extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated to dryness to give the desired product. LC-MS (m/z) 268.3 ($\text{M}+\text{H}^+$).

Step 3: Prepared of 3-(2-fluorophenoxy)azetidine trifluoroacetic acid
tert-butyl 3-(2-fluorophenoxy)azetidine-1-carboxylate was dissolved in stirred at r.t. for 4 h. The mixture was concentrated to give the desired product, which was used for next step without further purification. LC-MS (m/z) 168.3 ($\text{M}+\text{H}^+$).

[0136] The following intermediates used for the preparation of titled example compounds were synthesized using the methods analogous to 3-(2-fluorophenoxy)azetidine trifluoroacetic acid described above, may be as TFA salt or free base was used in next step without further purification.

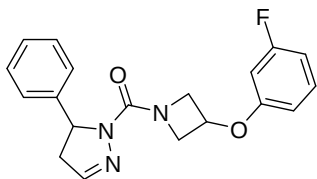


Step 4: Prepared of (3-(2-fluorophenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone

3-(2-fluorophenoxy)azetidine (100 mg) and (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone(50 mg) and TEA(0.8mL) were dissolved in THF(10 ml) and stirred at 65°C for 16h. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **60**(53 mg, 74.4%). ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.35 (m, 2H), 7.21-7.27 (m, 3H), 7.01-7.12 (m, 2H), 6.90-6.96 (m, 1H), 6.78 (t, 1H, $J = 1.6$ Hz), 6.70 (td, 1H, $J = 8.4, 1.6$ Hz), 5.33 (dd, 1H, $J = 12.0, 6.4$ Hz), 4.91-4.94 (m, 1H), 4.55 (dd, 1H, $J = 10.0, 6.8$ Hz), 4.49 (dd, 1H, $J = 10.0, 6.8$ Hz), 4.30 (dd, 1H, $J = 10.0, 4.0$ Hz), 4.23 (dd, 1H, $J = 10.0, 4.0$ Hz), 3.34 (ddd, 1H, $J = 18.8, 12.0, 1.6$ Hz), 2.74 (ddd, 1H, $J = 18.4, 6.4, 1.6$ Hz).

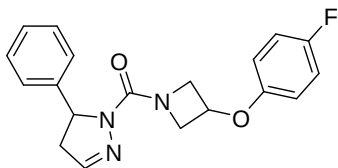
Hz). LC-MS (m/z): 340.40 [M+H]⁺.

[0137] Compound 61: (3-(3-fluorophenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



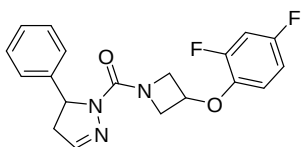
The titled compound **61** was prepared in 75.5% yield from 3-(3-fluorophenoxy)azetidine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.35 (m, 2H), 7.15-7.26 (m, 4H), 6.75-6.79 (m, 1H), 6.62-6.72 (m, 1H), 6.40-6.55 (m, 2H), 5.32 (dd, 1H, *J* = 12.0, 6.4 Hz), 4.85-4.91 (m, 1H), 4.46-4.57 (m, 2H), 4.09-4.25 (m, 2H), 3.30-3.39 (m, 1H), 2.71-2.78 (m, 1H). LC-MS (m/z): 340.32 [M+H]⁺.

[0138] Compound 62: (3-(4-fluorophenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



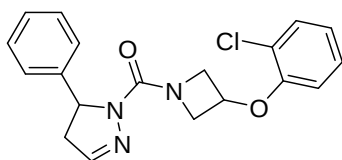
The titled compound **62** was prepared in 70.2% yield from 3-(4-fluorophenoxy)azetidine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.35 (m, 2H), 7.21-7.27 (m, 3H), 6.92-7.00 (m, 2H), 6.77 (t, 1H, *J* = 1.6 Hz), 6.66-6.72 (m, 2H), 5.32 (dd, 1H, *J* = 12.0, 6.4 Hz), 4.82-4.89 (m, 1H), 4.53 (dd, 1H, *J* = 9.6, 6.4 Hz), 4.46 (dd, 1H, *J* = 9.6, 6.4 Hz), 4.22 (dd, 1H, *J* = 10.0, 4.0 Hz), 4.14 (dd, 1H, *J* = 10.0, 4.0 Hz), 3.33 (ddd, 1H, *J* = 18.4, 12.0, 1.6 Hz), 2.73 (ddd, 1H, *J* = 18.4, 6.4, 1.6 Hz). LC-MS (m/z): 340.40 [M+H]⁺.

[0139] Compound 63: (3-(2,4-difluorophenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



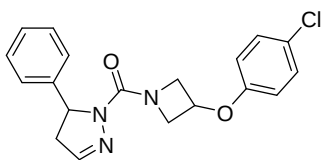
The titled compound **63** was prepared in 70.7% yield from 3-(2,4-difluorophenoxy)azetidine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.34 (m, 2H), 7.20-7.25 (m, 3H), 6.84-6.90 (m, 1H), 6.78-6.79 (m, 1H), 6.74-6.77 (m, 1H), 6.67 (td, 1H, *J* = 8.8, 6.4 Hz), 5.31 (dd, 1H, *J* = 12.4, 6.4 Hz), 4.85-4.90 (m, 1H), 4.51 (dd, 1H, *J* = 10.0, 6.4 Hz), 4.46 (dd, 1H, *J* = 10.0, 6.4 Hz), 4.27 (dd, 1H, *J* = 10.0, 4.0 Hz), 4.20 (dd, 1H, *J* = 10.0, 4.0 Hz), 3.34 (ddd, 1H, *J* = 18.8, 12.4, 2.0 Hz), 2.74 (ddd, 1H, *J* = 18.4, 6.4, 1.6 Hz). LC-MS (*m/z*): 358.45 [M+H]⁺.

[0140] Compound 64: (3-(2-chlorophenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **64** was prepared in 52% yield from 3-(2-chlorophenoxy)azetidine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.27 (m, 3H), 7.26 – 7.14 (m, 4H), 6.93 (td, *J* = 7.7, 1.4 Hz, 1H), 6.78 (t, *J* = 1.7 Hz, 1H), 6.60 (dd, *J* = 8.2, 1.3 Hz, 1H), 5.32 (dd, *J* = 12.3, 6.5 Hz, 1H), 4.94 (ddd, *J* = 10.7, 5.4, 3.2 Hz, 1H), 4.61 – 4.44 (m, 2H), 4.28 (ddd, *J* = 31.8, 10.2, 4.0 Hz, 2H), 3.35 (ddd, *J* = 18.5, 12.2, 1.7 Hz, 1H), 2.75 (ddd, *J* = 18.5, 6.3, 1.7 Hz, 1H). LC-MS (*m/z*) 356.8 (M+H⁺)

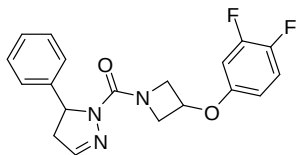
[0141] Compound 65: (3-(4-chlorophenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **65** was prepared in 40% yield from 3-(4-chlorophenoxy)azetidine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.26 (m, 3H), 7.25 – 7.18 (m, 4H), 6.78 (t, *J* = 1.7 Hz, 1H), 6.71 – 6.65 (m, 2H), 5.35 – 5.28 (m, 1H), 4.86 (ddd, *J* = 10.6, 5.3, 3.2 Hz, 1H), 4.59 – 4.43 (m, 2H), 4.18

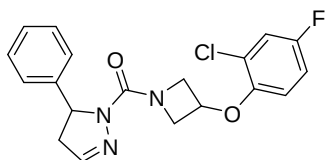
(ddd, $J = 31.7, 10.1, 3.6$ Hz, 2H), 3.35 (ddd, $J = 18.5, 12.2, 1.7$ Hz, 1H), 2.75 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H). LC-MS (m/z) 356.8 ($M+H^+$)

[0142] Compound 66: (3-(3,4-difluorophenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



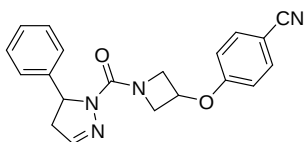
The titled compound **66** was prepared in 74.7% yield from 3-(3,4-difluorophenoxy)azetidine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.35 (m, 2H), 7.21-7.27 (m, 3H), 7.06 (dd, 1H, $J = 18.8, 8.8$ Hz), 6.78 (t, 1H, $J = 1.6$ Hz), 6.58 (ddd, 1H, $J = 9.6, 6.8, 3.2$ Hz), 6.41-6.45 (m, 1H), 5.31 (dd, 1H, $J = 12.0, 6.0$ Hz), 4.80-4.85 (m, 1H), 4.53 (dd, 1H, $J = 10.0, 6.4$ Hz), 4.46 (dd, 1H, $J = 10.0, 6.4$ Hz), 4.21 (dd, 1H, $J = 10.0, 4.0$ Hz), 4.13 (dd, 1H, $J = 10.0, 4.0$ Hz), 3.34 (ddd, 1H, $J = 18.8, 12.0, 1.6$ Hz), 2.74 (ddd, 1H, $J = 18.4, 6.4, 1.6$ Hz). LC-MS (m/z): 358.42 [$M+H$] $^+$.

[0143] Compound 67: (3-(2-chloro-4-fluorophenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



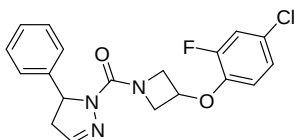
The titled compound **67** was prepared in 35% yield from 3-(2-chloro-4-fluorophenoxy)azetidine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.30 (m, 2H), 7.26 – 7.20 (m, 3H), 7.15 (dd, $J = 8.0, 3.2$ Hz, 1H), 6.90 (ddd, $J = 9.2, 7.6, 3.2$ Hz, 1H), 6.79 (t, $J = 1.6$ Hz, 1H), 6.56 (dd, $J = 9.0, 4.7$ Hz, 1H), 5.32 (dd, $J = 12.0, 6.0$ Hz, 1H), 4.92-4.86 (m, 1H), 4.58-4.52 (dd, $J = 9.6, 6.4$ Hz, 1H), 4.51-4.45 (dd, $J = 9.6, 6.4$ Hz, 1H), 4.30 (dd, $J = 10.4, 3.8$ Hz, 1H), 4.22 (dd, $J = 10.0, 4.0$ Hz, 1H), 3.35 (ddd, $J = 18.4, 12.0, 1.6$ Hz, 1H), 2.75 (ddd, $J = 18.4, 6.4, 1.6$ Hz, 1H). LC-MS (m/z) 374.8 ($M+H^+$)

[0144] Compound 68: 4-((1-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)benzonitrile



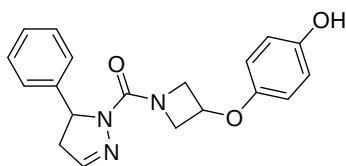
The titled compound **67** was prepared in 70.7% yield from 4-(azetidin-3-yloxy) benzonitrile trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.57-7.61 (m, 2H), 7.30-7.35 (m, 2H), 7.25-7.27 (m, 1H), 7.21-7.23 (m, 2H), 6.81-6.82 (m, 1H), 6.79-6.80 (m, 2H), 5.31 ((dd, 1H, *J* = 12.0, 6.0 Hz), 4.92-4.97 (m, 1H), 4.57 (dd, 1H, *J* = 9.6, 6.0 Hz), 4.51 (dd, 1H, *J* = 10.0, 6.4 Hz), 4.24 (dd, 1H, *J* = 10.0, 4.0 Hz), 4.16 (dd, 1H, *J* = 10.0, 4.0 Hz), 3.35 (ddd, 1H, *J* = 18.8, 12.0, 2.0 Hz), 2.76 (ddd, 1H, *J* = 18.4, 6.4, 2.0 Hz). LC-MS (*m/z*): 347.40 [*M*+H]⁺.

[0145] Compound 69: (3-(4-chloro-2-fluorophenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **69** was prepared in 10.6% yield from 3-(2-chloro-4-fluorophenoxy)azetidine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.28(m, 2H), 7.23 – 7.17 (m, 3H), 7.10 (dd, *J* = 10.8, 2.5 Hz, 1H), 7.03 – 6.97 (m, 1H), 6.76 (t, *J* = 1.6 Hz, 1H), 6.61 (t, *J* = 8.7 Hz, 1H), 5.30 (dd, *J* = 12.4, 6.4 Hz, 1H), 4.94 – 4.83 (m, 1H), 4.48 (ddd, *J* = 24.5, 9.6, 6.4 Hz, 2H), 4.23 (ddd, *J* = 29.0, 10.0, 4.0 Hz, 2H), 3.33 (ddd, *J* = 18.4, 12.4, 1.6 Hz, 1H), 2.73 (ddd, *J* = 18.4, 6.4, 1.6 Hz, 1H). LC-MS (*m/z*) 374.8 (*M*+H⁺)

[0146] Compound 70: (3-(4-hydroxyphenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone

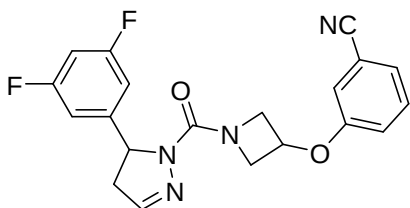


(3-(4-(methoxymethoxy)phenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone was prepared in 16% yield from 3-(4-(methoxymethoxy)

phenoxy)azetidine, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**, which was reacted with con.HCl(1mL) in MeOH(3mL) for 1h. The mixture was concentrated and purified by Pre-TLC to give the titled compound **70**(18mg, 41%). LC-MS (m/z) 338.4 (M+H⁺)

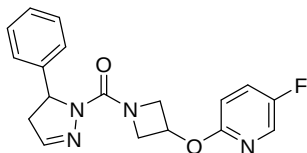
¹H NMR (400 MHz, CDCl₃) δ 7.38-7.28 (m, 2H), 7.23-7.13 (m, 3H), 6.77 (brs, 1H), 6.66 (d, J = 8.6 Hz, 2H), 6.55 (d, J = 8.7 Hz, 2H), 5.30 (dd, J = 12.0, 6.2 Hz, 1H), 4.78 (brs, 1H), 4.55 – 4.35 (m, 2H), 4.16 (dd, J = 29.5, 6.6 Hz, 2H), 3.32 (dd, J = 18.5, 12.2 Hz, 1H), 2.72 (dd, J = 18.5, 6.2 Hz, 1H).

[0147] Compound 71: 3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)benzonitrile



The titled compound **71** was prepared in 22.3% yield from 3-(azetidin-3-yloxy)benzonitrile trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.39 (t, J = 8.0 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.05 – 6.94 (m, 2H), 6.82 – 6.62 (m, 4H), 5.28 (dd, J = 12.2, 6.4 Hz, 1H), 4.93 (ddd, J = 10.4, 5.2, 3.2 Hz, 1H), 4.67-4.48 (m, 2H), 4.29 – 4.03 (m, 2H), 3.35 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.70 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H).LC-MS (m/z) 383.4 (M+H⁺)

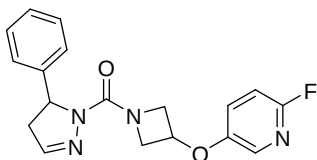
[0148] Compound 72: (3-((5-fluoropyridin-2-yl)oxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol- 1-yl)methanone



The titled compound **72** was prepared in 32% yield from 2-(azetidin-3-yloxy)-5-fluoropyridine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, J = 3.0 Hz, 1H), 7.37 – 7.27 (m, 4H), 7.24-7.21 (m, 1H), 7.20-7.18 (m,

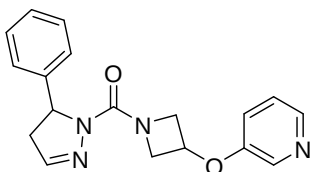
1H), 6.76 – 6.69 (m, 2H), 5.33 – 5.24 (m, 2H), 4.57 – 4.44 (m, 2H), 4.13 (ddd, J = 24.4, 10.5, 4.3 Hz, 2H), 3.32 (ddd, J = 18.5, 12.2, 1.7 Hz, 1H), 2.71 (ddd, J = 18.5, 6.4, 1.7 Hz, 1H). LC-MS (m/z) 341.4 (M+H⁺)

[0149] Compound 73: (3-((6-fluoropyridin-3-yl)oxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



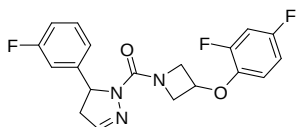
The titled compound **73** was prepared in 9.3% yield from 5-(azetidin-3-yloxy)-2-fluoropyridine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.62 (m, 1H), 7.33-7.28 (m, 2H), 7.24 – 7.16 (m, 4H), 6.85 (dd, J = 8.9, 3.5 Hz, 1H), 6.77 (t, J = 1.6 Hz, 1H), 5.34 – 5.26 (m, 1H), 4.89 (ddd, J = 10.4, 6.3, 4.0 Hz, 1H), 4.58 – 4.41 (m, 2H), 4.22 (dd, J = 10.2, 3.9 Hz, 1H), 4.14 (dd, J = 10.2, 3.9 Hz, 1H), 3.34 (ddd, J = 18.6, 12.1, 1.6 Hz, 1H), 2.74 (ddd, J = 18.6, 6.3, 1.7 Hz, 1H). LC-MS (m/z) 341.4 (M+H⁺)

[0150] Compound 74: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(3-(pyridin-3-yloxy)azetidin-1-yl)methanone



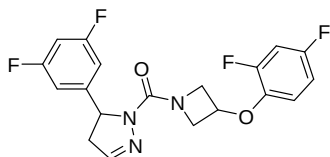
The titled compound **74** was prepared in 3.1% yield from 3-(azetidin-3-yloxy)pyridine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.31 (m, 2H), 7.27 – 7.20 (m, 7H), 6.79 (s, 1H), 5.31 (dd, J = 12.0, 8.0 Hz, 1H), 4.99 (s, 1H), 4.61 – 4.51 (m, 2H), 4.22 (dd, J = 32.0, 8.0 Hz, 2H), 3.39-3.32 (m, 1H), 2.79-2.73 (m, 1H). LC-MS (m/z) 323.43 [M+H]⁺.

[0151] Compound 75: (3-(2,4-difluorophenoxy)azetidin-1-yl)(5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



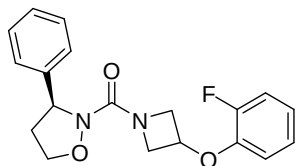
The titled compound **75** was prepared in 16.8% yield from 3-(2,4-difluorophenoxy)azetidine trifluoroacetic acid, 5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.28 (m, 1H), 7.24–7.19 (m, 2H), 7.04 – 6.81 (m, 3H), 6.78 – 6.71 (m, 1H), 6.66 (td, J = 9.0, 5.2 Hz, 1H), 5.29 (dd, J = 12.2, 6.3 Hz, 1H), 4.92–4.85 (m, 1H), 4.54–4.42 (m, 2H), 4.34–4.16 (m, 2H), 3.33 (dd, J = 18.5, 12.1 Hz, 1H), 2.77 – 2.58 (m, 1H). LC-MS (m/z) 376.4 ($\text{M}+\text{H}^+$)

[0152] Compound 76: (3-(2,4-difluorophenoxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **76** was prepared in 22.6% yield from 3-(2,4-difluorophenoxy)azetidine trifluoroacetic acid, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ^1H NMR (400 MHz, CDCl_3) δ 6.89 (ddd, J = 11.3, 8.3, 2.9 Hz, 1H), 6.80 – 6.74 (m, 3H), 6.73 – 6.65 (m, 2H), 5.28 (dd, J = 12.2, 6.5 Hz, 1H), 4.91 (ddd, J = 10.5, 6.3, 4.0 Hz, 1H), 4.57 – 4.43 (m, 2H), 4.27 (ddd, J = 14.4, 10.1, 3.3 Hz, 2H), 3.35 (ddd, J = 18.5, 12.2, 1.5 Hz, 1H), 2.69 (ddd, J = 18.6, 6.5, 1.5 Hz, 1H). LC-MS (m/z) 394.4 ($\text{M}+\text{H}^+$)

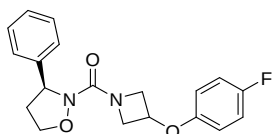
[0153] Compound 77: (S)-(3-(2-fluorophenoxy)azetidin-1-yl)(3-phenylisoxazolidin-2-yl)methanone



The titled compound **77** was prepared in 13% yield from 3-(2-fluorophenoxy)azetidine trifluoroacetic acid, (S)-3-phenylisoxazolidine and triphosgene according to the procedure outlined for compound **26**. ^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.30 (m, 3H), 7.26–7.21 (m, 2H), 7.14 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 6.69 (t, J = 8.2 Hz, 1H), 5.55

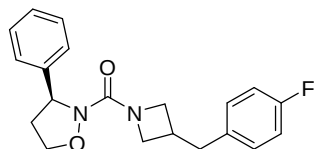
(dd, $J = 8.6, 5.3$ Hz, 1H), 4.97 (ddd, $J = 10.6, 6.5, 4.2$ Hz, 1H), 4.54 (dt, $J = 14.6, 7.4$ Hz, 2H), 4.35 (dd, $J = 10.6, 3.9$ Hz, 1H), 4.22 (dd, $J = 10.1, 3.4$ Hz, 1H), 4.12 (td, $J = 8.0, 3.4$ Hz, 1H), 3.82 (dd, $J = 16.3, 8.1$ Hz, 1H), 2.82 – 2.71 (m, 1H), 2.37 – 2.25 (m, 1H). LC-MS (m/z) 343.4 ($M+H^+$)

[0154] Compound 78: (S)-(3-(4-fluorophenoxy)azetidin-1-yl)(3-phenylisoxazolidin-2-yl)methanone



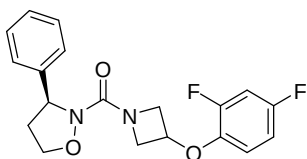
The titled compound **78** was prepared in 16% yield from 3-(4-fluorophenoxy)azetidine trifluoroacetic acid, (S)-3-phenylisoxazolidine and triphosgene according to the procedure outlined for compound **26**. ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.30 (m, 3H), 7.26–7.22(m, 1H), 7.02 – 6.94 (m, 2H), 6.72 – 6.66 (m, 2H), 5.54 (dd, $J = 8.8, 5.4$ Hz, 1H), 4.94 – 4.84 (m, 1H), 4.58 – 4.48 (m, 2H), 4.25 (dd, $J = 10.4, 4.0$ Hz, 1H), 4.12 (ddd, $J = 11.4, 7.6, 3.7$ Hz, 2H), 3.82 (dd, $J = 16.1, 8.1$ Hz, 1H), 2.82 – 2.68 (m, 1H), 2.42 – 2.28 (m, 1H). LC-MS (m/z) 343.4 ($M+H^+$)

[0155] Compound 79: (S)-(3-(4-fluorobenzyl)azetidin-1-yl)(3-phenylisoxazolidin-2-yl)methanone



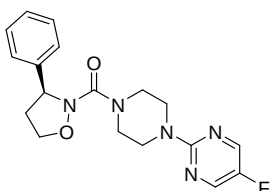
The titled compound **78** was prepared in 16% yield from 3-(4-fluorobenzyl)azetidine trifluoroacetic acid, (S)-3-phenylisoxazolidine and triphosgene according to the procedure outlined for compound **26**. ^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.29 (m, 4H), 7.26 – 7.22 (m, 1H), 7.10 (dd, $J = 8.1, 5.6$ Hz, 2H), 6.98 (t, $J = 8.3$ Hz, 2H), 5.54 (dd, $J = 8.7, 5.2$ Hz, 1H), 4.26 (t, $J = 8.2$ Hz, 1H), 4.17 (brs, 1H), 4.09 (td, $J = 8.0, 3.4$ Hz, 1H), 3.89–3.80 (m, 3H), 3.78 (dd, $J = 16.2, 8.3$ Hz, 1H), 2.93 – 2.80 (m, 3H), 2.78 – 2.69 (m, 1H), 2.29 (ddd, $J = 15.2, 7.8, 3.9$ Hz, 1H).LC-MS (m/z) 341.4 ($M+H^+$)

[0156] Compound 80: (S)-(3-(2,4-difluorophenoxy)azetidin-1-yl)(3-phenylisoxazolidin-2-yl)methanone



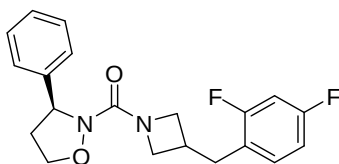
The titled compound **80** was prepared in 12% yield from 3-(2,4-difluorophenoxy) azetidine trifluoroacetic acid, (S)-3-phenylisoxazolidine and triphosgene according to the procedure outlined for compound **26**. ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.30 (m, 3H), 7.26–7.22 (m, 2H), 6.93 – 6.86 (m, 1H), 6.81 – 6.74 (m, 1H), 6.67 (td, J = 9.0, 5.5 Hz, 1H), 5.54 (dd, J = 8.7, 5.3 Hz, 1H), 4.96 – 4.88 (m, 1H), 4.57 – 4.46 (m, 2H), 4.32 (dd, J = 10.5, 3.8 Hz, 1H), 4.20 (d, J = 9.0 Hz, 1H), 4.12 (td, J = 8.0, 3.3 Hz, 1H), 3.82 (dd, J = 16.1, 8.2 Hz, 1H), 2.81 – 2.70 (m, 1H), 2.36 – 2.26 (m, 1H). LC-MS (m/z) 361.4 ($\text{M}+\text{H}^+$)

[0157] Compound 81: (S)-(4-(5-fluoropyrimidin-2-yl)piperazin-1-yl)(3-phenylisoxazolidin-2-yl)methanone



The titled compound **81** was prepared in 61.8% yield from 5-fluoro-2-(piperazin-1-yl)pyrimidine, (S)-3-phenylisoxazolidine and triphosgene according to the procedure outlined for compound **26**. ^1H NMR (400 MHz, CDCl_3) δ 8.21 (s, 2H), 7.42 – 7.30 (m, 4H), 7.26 – 7.23 (m, 1H), 5.46 (dd, J = 8.5, 4.9 Hz, 1H), 4.13 (td, J = 8.0, 4.1 Hz, 1H), 3.93 (q, J = 7.9 Hz, 1H), 3.86 – 3.57 (m, 8H), 2.85 – 2.76 (m, 1H), 2.36 – 2.26 (m, 1H). LC-MS (m/z) 358.4 ($\text{M}+\text{H}^+$)

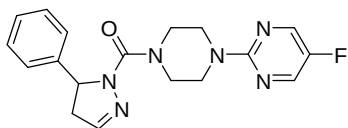
[0158] Compound 82: (S)-(3-(2,4-difluorobenzyl)azetidin-1-yl)(3-phenylisoxazolidin-2-yl)methanone



The titled compound **82** was prepared in 11.6% yield from 3-(2,4-difluorobenzyl) azetidine, (S)-3-phenylisoxazolidine and triphosgene according to the procedure outlined for compound **26**. ^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.35 (m, 2H), 7.35 – 7.29 (m, 2H), 7.26 – 7.20 (m, 1H), 7.13–7.06 (m, 1H), 6.84 – 6.75 (m, 2H), 5.53 (dd, J = 8.8, 5.2 Hz, 1H),

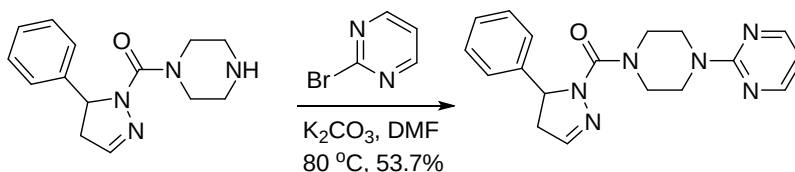
4.30 – 4.14 (m, 2H), 4.14 – 4.05 (m, 1H), 3.92-3.82 (m, 2H), 3.81 – 3.74 (m, 1H), 2.95 – 2.83 (m, 3H), 2.78 – 2.67 (m, 1H), 2.33-2.23 (m, 1H). LC-MS (m/z):359.51 [M+H]⁺.

[0159] Compound 83: (4-(5-fluoropyrimidin-2-yl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **81** was prepared in 61.8% yield from 5-fluoro-2-(piperazin-1-yl)pyrimidine, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **26**. ¹H NMR (400Hz, CDCl₃): δ 8.21 (s, 2H), 7.36-7.23 (m, 5H), 6.85 (s, 1H), 5.37 (dd, *J* = 11.6, 9.6 Hz, 1H), 3.95-3.56 (m, 8H), 3.36-3.28 (m, 1H), 2.79-2.71 (m, 1H). LC-MS (m/z) 355.4 (M+H⁺)

[0160] Compound 84: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone

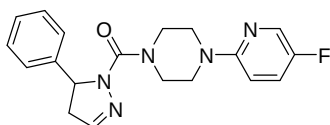


84

Step 1.

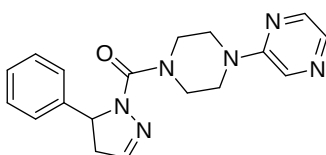
To a solution of (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone (50 mg, 0.19 mmol) and K₂CO₃ (67 mg, 0.48 mmol) in DMF (5mL), (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(4-(pyrimidin-2-yl)piperazin-1-yl)methanone (31 mg, 0.19 mmol) were added. The mixture was heated to 80 °C for 2.5hrs. And then 30 mL H₂O was added, extracted with EA (20 ml x 3). The solvent was evaporated under reduced pressure to provide crude product **84** and further purified by silica gel column chromatography (PE/EA=1/1) to give 35mg of **84** as a light yellow solid. For **84**, ¹H NMR (400 MHz, CDCl₃) δ 8.31 (d, *J* = 4.0 Hz, 2H), 7.35-7.22 (m, 5H), 6.84 (t, *J* = 4.0 Hz, 1H), 6.50 (t, *J* = 4.0 Hz, 1H), 5.37-5.31 (m, 1H), 3.93-3.86 (m, 2H), 3.81-3.72 (m, 4H), 3.64-3.57 (m, 2H), 3.35-3.27 (m, 1H), 2.78-2.70 (m, 1H). LC-MS (m/z) 337.31 [M+H]⁺.

[0161] Compound 85: (4-(5-fluoropyridin-2-yl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **84** was prepared in 62.3% yield from 1-(5-fluoropyridin-2-yl)piperazine, 5-phenyl-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **26**. ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, 1H, *J* = 3.0 Hz), 7.35-7.28 (m, 5H), 7.25-7.21 (m, 1H), 6.84 (t, 1H, *J* = 1.6 Hz), 6.64 (dd, 1H, *J* = 9.6, 3.6 Hz), 5.36 (dd, 1H, *J* = 9.6, 11.6 Hz), 3.86-3.76 (m, 2 H), 3.73-3.63 (m, 2H), 3.62-3.54 (m, 2H), 3.50-3.42 (m, 2H), 3.32 (ddd, 1H, *J* = 18.4, 12.0, 1.6 Hz), 2.75 (ddd, 1H, *J* = 18.4, 9.6, 1.6 Hz). LC-MS (*m/z*): 354.40 [M+H]⁺.

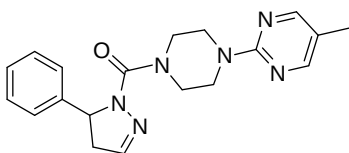
[0162] Compound 86: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(4-(pyrazin-2-yl)piperazin-1-yl)methanone



86

The titled compound **86** was prepared in a yield of 22% (15 mg) as a yellow solid according to the procedure for compound **28**. ¹H NMR (400Hz, CDCl₃): δ 8.20-8.03 (m, 2H), 7.87 (s, 1H), 7.38-7.22 (m, 5H), 6.86 (s, 1H), 5.37 (dd, *J* = 11.6, 9.6 Hz, 1H), 3.90-3.50 (m, 8H), 3.40-3.21 (m, 1H), 2.79-2.72 (m, 1H). LC-MS (ESI) *m/z*: 337.41, [M+H]⁺.

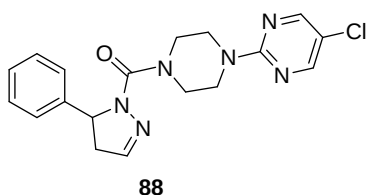
[0163] Compound 87:(4-(5-methylpyrimidin-2-yl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



87

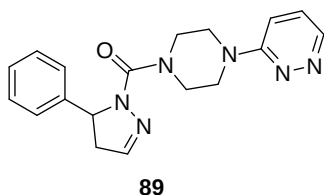
The titled compound **87** was prepared in a yield of 36% (25 mg) as a yellow solid according to the procedure for compound **28**. ¹H NMR (400Hz, CDCl₃): δ 8.16 (s, 2H), 7.40-7.20 (m, 5H), 6.84 (s, 1H), 5.37 (dd, *J* = 11.6, 9.6 Hz, 1H), 4.06-3.46 (m, 8H), 3.31 (m, 1H), 2.77-2.63 (m, 1H), 2.12 (s, 3H). LC-MS (ESI) *m/z*: 351.40, [M+H]⁺.

[0164] Compound 88:(4-(5-chloropyrimidin-2-yl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



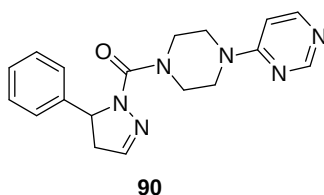
The titled compound **88** was prepared in a yield of 24% (18 mg) as a yellow solid according to the procedure for compound **28**. ^1H NMR (400Hz, CDCl_3): δ 8.23 (s, 2H), 7.36-7.23 (m, 5H), 6.85 (s, 1H), 5.37 (dd, $J = 11.6, 9.6$ Hz, 1H), 3.95-3.56 (m, 8H), 3.36-3.28 (m, 1H), 2.79-2.71 (m, 1H). LC-MS (ESI) m/z : 371.37, $[\text{M}+\text{H}]^+$.

[0165] Compound 89: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(4-(pyridazin-3-yl)piperazin-1-yl)methanone



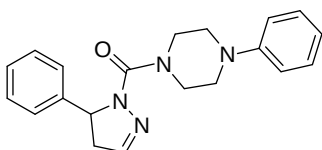
The titled compound **89** was prepared in a yield of 13% (9 mg) as a yellow solid according to the procedure for compound **28**. ^1H NMR (400Hz, CDCl_3): δ 8.86 (s, 1H), 7.44-7.25 (m, 7H), 6.90 (s, 1H), 5.36 (dd, $J = 11.6, 9.6$ Hz, 1H), 3.88-3.69 (m, 8H), 3.35 (m, 1H), 2.79 (m, 1H). LC-MS (ESI) m/z : 337.37, $[\text{M}+\text{H}]^+$.

[0166] Compound 90: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(4-(pyrimidin-4-yl)piperazin-1-yl)methanone



The titled compound **90** was prepared in a yield of 44% (29 mg) as a white solid according to the procedure for compound **28**. ^1H NMR (400Hz, CDCl_3): δ 8.62 (s, 1H), 8.28 (d, $J = 6.8$ Hz, 1H), 7.36-7.24 (m, 5H), 6.87 (s, 1H), 6.56 (d, $J = 6.8$ Hz, 1H), 5.35 (dd, $J = 11.6, 9.6$ Hz, 1H), 3.86-3.59 (m, 8H), 3.34 (m, 1H), 2.77 (m, 1H). LC-MS (ESI) m/z : 337.41, $[\text{M}+\text{H}]^+$.

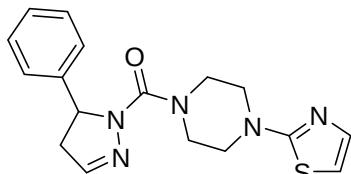
[0167] Compound 91: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(4-phenylpiperazin-1-yl)methanone



91

The titled compound **91** was prepared in a yield of 23% (15 mg) as a white solid according to the procedure for compound **28**. ^1H NMR (400Hz, CDCl_3): δ 7.38-7.25 (m, 7H), 7.18 (d, J = 8.4 Hz, 2H), 7.11 (t, J = 7.2 Hz, 1H), 6.87 (s, 1H), 5.37 (dd, J = 11.6, 9.6 Hz, 1H), 3.97-3.81 (m, 4H), 3.41-3.24 (m, 5H), 2.76 (m, 1H). LC-MS (ESI) m/z : 335.39, $[\text{M}+\text{H}]^+$.

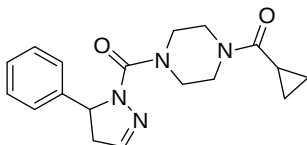
[0168] Compound 92: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(4-(thiazol-2-yl)piperazin-1-yl)methanone



92

The titled compound **92** was prepared in a yield of 19.7% (13.0 mg) as a light yellow solid according to the procedure for **84**. ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.25 (m, 6H), 6.89 (s, 1H), 6.63 (d, J = 4.0 Hz, 1H), 5.34 (dd, J = 12.0, 12.0 Hz, 1H), 3.88- 3.82 (m, 2H), 3.78- 3.70 (m, 4H), 3.66-3.61 (m, 2H), 3.38-3.30 (m, 1H), 2.81-2.74 (m, 1H). LC-MS (m/z) 342.41 $[\text{M}+\text{H}]^+$.

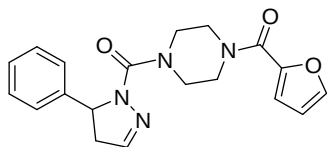
[0169] Compound 93: (4-(cyclopropanecarbonyl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



93

The titled compound **93** was prepared in a yield of 76% (49 mg) as a white solid according to the procedure for compound **28**. ^1H NMR (400Hz, CDCl_3): δ 7.36-7.26 (m, 5H), 6.85 (s, 1H), 5.35 (dd, J = 11.6, 9.6 Hz, 1H), 3.77-3.52 (m, 8H), 3.31(m, 1H), 2.75 (m, 1H), 1.14 (m, 1H), 1.02-0.98 (m, 2H), 0.80-0.75 (m, 2H) LC-MS (ESI) m/z : 327.35, $[\text{M}+\text{H}]^+$.

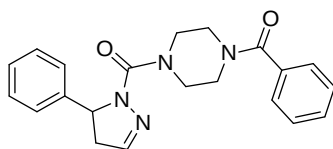
[0170] Compound 94: (4-(furan-2-carbonyl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



94

The titled compound **94** was prepared in a yield of 77% (54 mg) as a white solid according to the procedure for compound **28**. ^1H NMR (400Hz, CDCl_3): δ 7.48 (m, 1H), 7.36-7.25 (m, 5H), 7.02 (m, 1H), 6.85 (s, 1H), 6.49 (m, 1H), 5.36 (dd, $J = 11.6, 9.6$ Hz, 1H), 3.91-3.55 (m, 8H), 3.31 (m, 1H), 2.75 (m, 1H). LC-MS (ESI) m/z : 353.35, $[\text{M}+\text{H}]^+$.

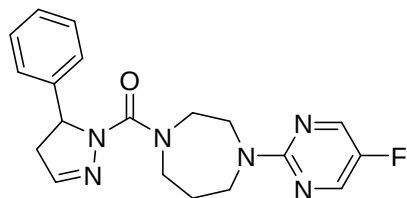
[0171] Compound 95: (4-benzoylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



95

The titled compound **95** was prepared in a yield of 71% (51 mg) as a yellow solid according to the procedure for compound **28**. ^1H NMR (400Hz, CDCl_3): δ 7.43- 7.25(m, 10H), 6.83 (s, 1H), 5.34 (dd, $J = 11.6, 9.6$ Hz, 1H), 3.91-3.17 (m, 9H), 2.72 (m, 1H). LC-MS (ESI) m/z : 363.42, $[\text{M}+\text{H}]^+$.

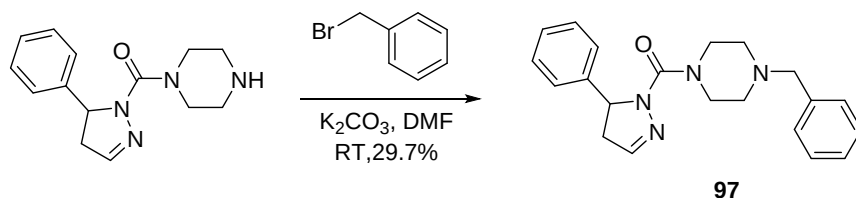
[0172] Compound 96: (4-(5-fluoropyrimidin-2-yl)-1,4-diazepan-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



96

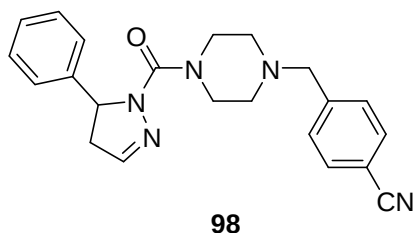
The titled compound **96** was prepared in a yield of 13.1% (13.0 mg) as a light yellow solid according to the procedure for **84**. ^1H NMR (400 MHz, CDCl_3) δ 8.14 (s, 2H), 7.28-7.18 (m, 5H), 6.77 (t, $J = 4.0$ Hz, 1H), 5.36-5.30 (m, 1H), 4.02-3.89 (m, 2H), 3.81-3.73 (m, 2H), 3.70-3.62 (m, 2H), 3.47-3.33 (m, 2H), 3.28-3.20 (m, 1H), 2.71-2.64 (m, 1H), 2.11-2.01 (m, 1H), 1.90-1.81 (m, 1H). LC-MS (m/z) 369.42 $[\text{M}+\text{H}]^+$.

[0173] Compound 97: (4-benzylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



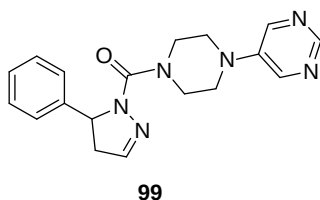
To a solution of (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone (50 mg, 0.19 mmol) and K_2CO_3 (66.7 mg, 0.48 mmol) in DMF (5mL), (bromomethyl)benzene (33 mg, 0.19 mmol) were added. The mixture was stirred at RT for 2hrs. And then 30 ml H_2O was added, extracted with EA (20 ml x 3). The solvent was evaporated under reduced pressure to provide crude product **97** and further purified by silica gel column chromatography (PE/EA=1/1) to give 20 mg of **97** as a light yellow solid. For **97**, ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.23 (m, 10H), 6.80 (t, $J = 4.0$ Hz, 1H), 5.37-5.31 (m, 1H), 3.73-3.67 (m, 2H), 3.56-3.50 (m, 4H), 3.32-3.24 (m, 1H), 2.74-2.66 (m, 1H), 2.52-2.47 (m, 2H), 2.44-2.39 (m, 2H). LC-MS (m/z) 349.43 [$M+H$] $^+$.

[0174] Compound 98: 4-((4-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)methyl)benzonitrile



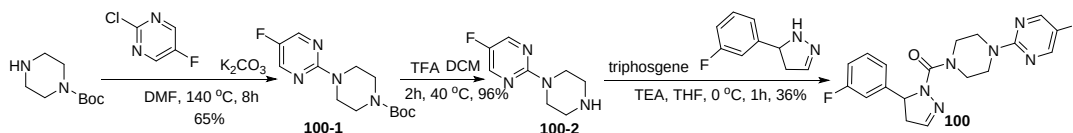
The titled compound **98** was prepared in a yield of 47% (34.0 mg) as a light yellow solid according to the procedure for **97**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, $J = 8.0$ Hz, 2H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.34-7.23 (m, 5H), 6.81 (t, $J = 4.0$ Hz, 1H), 5.34-5.29 (m, 1H), 3.73-3.67 (m, 2H), 3.56-3.50 (m, 4H), 3.33-3.25 (m, 1H), 2.74-2.67 (m, 1H), 2.51-2.45 (m, 2H), 2.42-2.37 (m, 2H). LC-MS (m/z) 374.51 [$M+H$] $^+$.

[0175] Compound 99: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(4-(pyrimidin-5-yl)piperazin-1-yl)methanone



The titled compound **99** was prepared in a yield of 15% (19 mg) as a yellow solid according to the procedure for compound **28**. ^1H NMR (400Hz, CDCl_3): δ 8.71 (s, 1H), 8.38 (s, 2H), 7.36-7.24 (m, 5H), 6.86 (s, 1H), 5.37 (dd, $J = 11.6, 9.6$ Hz, 1H), 3.89-3.69 (m, 4H), 3.37-3.19 (m, 5H), 2.76 (m, 1H). LC-MS (ESI) m/z : 337.32, $[\text{M}+\text{H}]^+$.

[0176] Compound 100: (5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-(5-fluoropyrimidin-2-yl)piperazin-1-yl)methanone



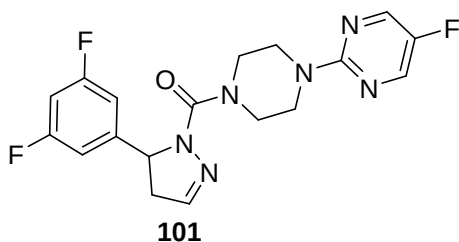
Step1: Compound **100-1** was synthesized according to the method of compound **28** while using tert-butyl piperazine-1-carboxylate (1.0 g, 5.37 mmol) and 2-chloro-5-fluoropyrimidine (782 mg, 5.91 mmol). tert-butyl 4-(5-fluoropyrimidin-2-yl)piperazine-1-carboxylate was obtained as pale yellow powder (980 mg, yield 65%). LC-MS (m/z) 283.34 $[\text{M}+\text{H}]^+$.

Step2: To a solution of tert-butyl 4-(5-fluoropyrimidin-2-yl)piperazine-1-carboxylate (980 mg, 3.47 mmol) in dichloromethane (10 mL), trifluoroacetic was added dropwise at 0°C. then the mixture was refluxed for 2 hours. The volatiles was removed *in vacuo* and the residue was suspension in dichloromethane, sat The organic layer was washed with water, sat. $\text{NaHCO}_3(\text{aq})$ and brine respectively. Then dried over MgSO_4 , filtered, and concentrated under reduced pressure. 5-fluoro-2-(piperazin-1-yl)pyrimidine was obtained as light pink solid (610 mg, yield 96%). The crude product was used in next step directly without further purification. LC-MS (m/z) 183.44 $[\text{M}+\text{H}]^+$.

Step3: To a solution of 5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazole (50 mg, 0.3 mmol) and triethylamine (93 mg, 0.94 mmol) in super dry dichloromethane (8 mL), triphosgene (36 mg, 0.12 mmol) was added at 0°C under argon protection. the mixture was stirred for 30 mins before a solution of 5-fluoro-2-(piperazin-1-yl)pyrimidine (73 mg, 0.4 mmol) and triethylamine (61 mg, 0.61 mmol) in super dry dichloromethane (2 mL) was added

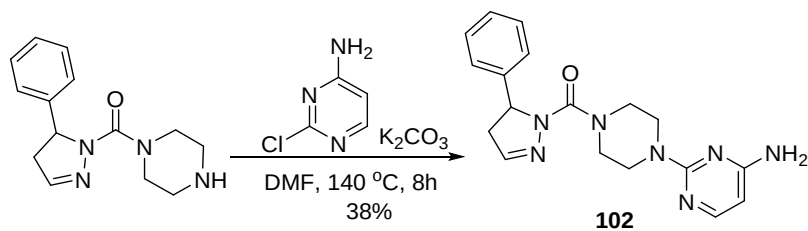
dropwise. The mixture was stirred for other 30 mins. The reaction was quenched by sat.NaHCO₃(aq), the volatiles was removed *in vacuo* and the residue was suspension in dichloromethane, sat The organic layer was washed with water, and brine respectively. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt,1/1) to give (5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-(5-fluoropyrimidin-2-yl)piperazin-1-yl)methanone **100** (40.5 mg, yield 36%) as a white powder after lyophilization. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.22-8.19 (s, 2H), 7.33-7.27 (m, 1H), 7.08 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.03-6.91 (m, 2H), 6.84 (q, *J* = 1.8 Hz, 1H), 5.36 (dd, *J* = 11.8, 9.8 Hz, 1H), 3.90-3.79 (m, 2H), 3.79-3.70 (m, 4H), 3.67-3.54 (m, 2H), 3.32 (ddt, *J* = 18.2, 11.8, 1.8 Hz, 1H), 2.71 (ddt, *J* = 18.4, 9.8, 1.6 Hz, 1H). LC-MS (*m/z*) 373.42 [M+H]⁺.

[0177] Compound 101: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-(5-fluoropyrimidin-2-yl)piperazin-1-yl)methanone



Compound **101** was synthesized according to the method of compound **100** while using 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole. (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-(5-fluoropyrimidin-2-yl)piperazin-1-yl)methanone was obtained as white powder (yield 39%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 0.6 Hz, 2H), 6.87-6.78 (m, 3H), 6.69 (tt, *J* = 8.8, 2.4 Hz, 1H), 5.33 (dd, *J* = 11.6, 9.8 Hz, 1H), 3.92-3.81 (m, 2H), 3.81-3.70 (m, 4H), 3.69-3.57 (m, 2H), 3.32 (ddd, *J* = 18.2, 11.8, 1.8 Hz, 1H), 2.68 (ddd, *J* = 18.2, 9.8, 1.6 Hz, 1H). LC-MS (*m/z*) 391.76 [M+H]⁺.

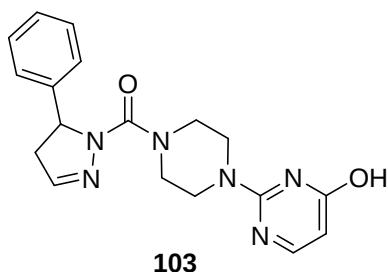
[0178] Compound 102: (4-(4-aminopyrimidin-2-yl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



To a solution of (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone (50.0

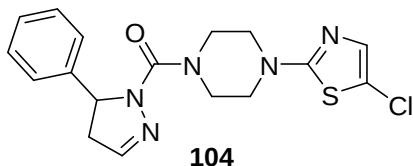
mg, 0.19 mmol) and 2-chloropyrimidin-4-amine (30.1 mg, 0.23 mmol) in super dry DMF (3.0 mL), K₂CO₃ (80.3 mg, 0.58 mmol) was added under argon protection. The mixture was stirred at 140°C for 8h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica gel, ethyl acetate/methanol = 1:0 to 10:1) to afford (4-(4-aminopyrimidin-2-yl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone (compound **102**) as pale yellow powder (26 mg, yield 38%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 5.8 Hz, 1H), 7.40-7.19 (m, 5H), 6.83 (t, *J* = 2.8 Hz, 1H), 5.82 (d, *J* = 5.8 Hz, 1H), 5.35 (t, *J* = 11.7 Hz, 1H), 4.97 (br, 2H), 3.91-3.78 (m, 2H), 3.77-3.65 (m, 4H), 3.57 (m, 2H), 3.36-3.24 (m, 1H), 2.73 (m, 1H). LC-MS (*m/z*) 352.63 [M+H]⁺.

[0179] Compound 103: (4-(4-hydroxypyrimidin-2-yl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



Compound **103** was synthesized according to the method of compound **102** while using 2-chloropyrimidin-4-ol. (4-(4-hydroxypyrimidin-2-yl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone was obtained as a white powder (yield 46%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.07 (s, 1H), 7.42-7.15 (m, 5H), 6.85 (d, *J* = 2.8 Hz, 1H), 5.33 (d, *J* = 9.8 Hz, 1H), 3.74-3.45 (m, 6H), 3.46-3.24 (m, 4H), 2.75 (d, *J* = 8.6 Hz, 2H). LC-MS (*m/z*) 353.36 [M+H]⁺.

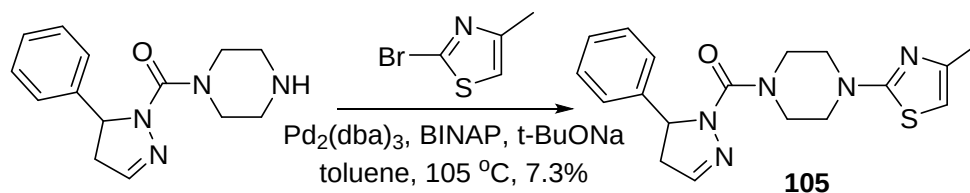
[0180] Compound 104: (4-(5-chlorothiazol-2-yl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **104** was prepared in a yield of 2.8% (2.0 mg) as a light yellow solid according to the procedure for **84**. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.24 (m, 5H), 6.99 (s, 1H), 6.85 (s, 1H), 5.38-5.33 (m, 1H), 3.81-3.75 (m, 2H), 3.69-3.63 (m, 2H), 3.53-3.48

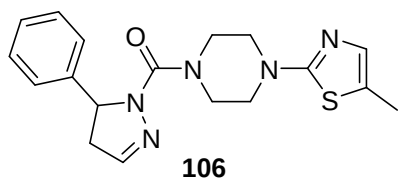
(m, 2H), 3.41-3.35 (m, 2H), 3.34-3.29 (m, 1H), 2.79-2.72 (m, 1H). LC-MS (m/z) 376.94 [M+H]⁺.

[0181] Compound 105: (4-(4-methylthiazol-2-yl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



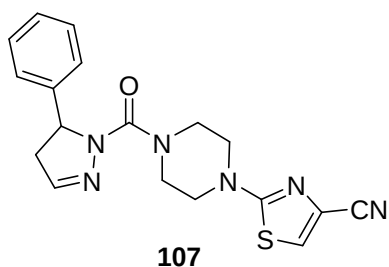
To a solution of (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone (50 mg, 0.19 mmol), 2-bromo-4-methylthiazole (35 mg, 0.19 mmol), $\text{Pd}_2(\text{dba})_3$ (30 mg, 0.033 mmol), BINAP (36 mg, 0.058 mmol) and $t\text{-BuONa}$ (22.3 mg, 0.23 mmol) in toluene (5mL). The mixture was heated to $105\text{ }^\circ\text{C}$ overnight. The solvent was evaporated under reduced pressure to provide crude product **105** and further purified by silica gel column chromatography (PE/EA=1/1) to give 5 mg of **105** as a light yellow solid. For **105**, ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.32 (m, 2H), 7.28-7.26 (m, 3H), 6.90 (s, 1H), 6.20 (s, 1H), 5.35-5.30 (m, 1H), 3.88-3.82 (m, 2H), 3.77-3.74 (m, 4H), 3.69-3.65 (m, 2H), 3.38-3.31 (m, 1H), 2.82-2.75 (m, 1H), 2.32 (s, 3H). LC-MS (m/z) 356.51 [M+H]⁺.

[0182] Compound 106: (4-(5-methylthiazol-2-yl)piperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



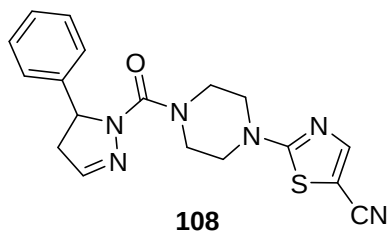
The titled compound **106** was prepared in a yield of 10.2% (7.0 mg) as a light yellow solid according to the procedure for **105**. ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.32 (m, 2H), 7.28-7.25 (m, 3H), 7.06 (s, 1H), 6.90 (s, 1H), 5.35-5.30 (m, 1H), 3.88-3.82 (m, 2H), 3.78-3.70 (m, 4H), 3.67-3.61 (m, 2H), 3.39-3.31 (m, 1H), 2.82-2.75 (m, 1H), 2.32 (s, 3H). LC-MS (m/z) 356.51 [M+H]⁺.

[0183] Compound 107: 2-(4-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)thiazole-4-carbonitrile



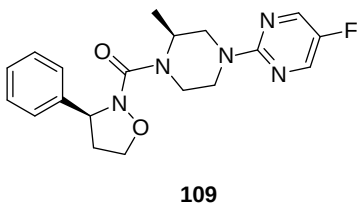
Compound **107** was synthesized according to the method of compound **102** while using 2-bromothiazole-4-carbonitrile. 2-(4-(5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbonyl)piperazin-1-yl)thiazole-4-carbonitrile was obtained as white powder (yield 42%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.38-7.22 (m, 6H), 6.86 (t, *J* = 1.8 Hz, 1H), 5.35 (dd, *J* = 11.8, 9.6 Hz, 1H), 3.79 (m, 2H), 3.67 (m, 2H), 3.59 (m, 2H), 3.47 (m, 2H), 3.33 (m, 1H), 2.76 (m, 1H). LC-MS (*m/z*) 367.45 [M+H]⁺.

[0184] Compound 108: 2-(4-(5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbonyl)piperazin-1-yl)thiazole-5-carbonitrile



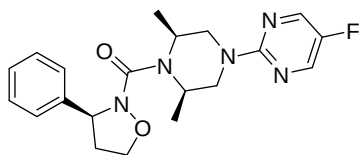
Compound **108** was synthesized according to the method of compound **102** while using 2-chlorothiazole-5-carbonitrile. 2-(4-(5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbonyl)piperazin-1-yl)thiazole-5-carbonitrile was obtained as white powder (yield 45%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.69 (s, 1H), 7.37-7.23 (m, 5H), 6.86 (t, *J* = 1.8 Hz, 1H), 5.35 (dd, *J* = 11.8, 9.4 Hz, 1H), 3.86-3.75 (m, 2H), 3.73-3.62 (m, 4H), 3.60-3.48 (m, 2H), 3.34 (m, 1H), 2.77 (m, 1H). LC-MS (*m/z*) 367.63 [M+H]⁺.

[0185] Compound 109: ((S)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)((S)-3-phenylisoxazolidin-2-yl)methanone



The titled compound 109 was prepared in a yield of 65% (24 mg) as a white solid according to the procedure for compound 28. ¹H NMR (400Hz, CDCl₃): δ 8.19 (s, 2H), 7.42-7.24 (m, 5H), 5.48 (dd, J = 8.4, 4.4 Hz, 1H), 4.54-4.40 (m, 3H), 4.20- 4.10 (m, 2H), 3.91 (m, 1H), 3.25-3.02 (m, 3H), 2.80 (m, 1H), 2.31 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H). LC-MS (ESI) m/z: 372.39, [M+H]⁺.

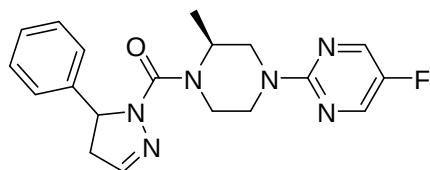
[0186] Compound 110: ((2R,6S)-4-(5-fluoropyrimidin-2-yl)-2,6-dimethylpiperazin-1-yl)((S)-3-phenylisoxazolidin-2-yl)methanone



110

The titled compound 110 was prepared in a yield of 37% (14 mg) as a white solid according to the procedure for compound 28. ¹H NMR (400Hz, CDCl₃): δ 8.19 (s, 2H), 7.42-7.25 (m, 5H), 5.46 (dd, J = 8.4, 4.8 Hz, 1H), 4.67 (m, 1H), 4.43-4.34 (m, 3H), 4.13 (m, 1H), 3.92 (m, 1H), 3.32-3.09 (m, 2H), 2.82 (m, 1H), 2.32 (m, 1H), 1.36 (d, J = 6.8 Hz, 3H), 1.28 (d, J = 6.8 Hz, 3H). LC-MS (ESI) m/z: 386.39, [M+H]⁺.

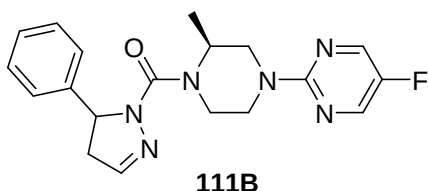
[0187] Compound 111A: (S)-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



111A

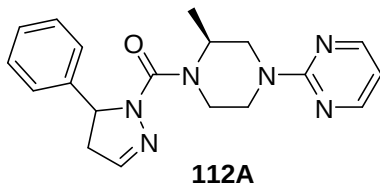
The titled compound **111A** was prepared in a yield of 16% (23.0 mg) as a light yellow solid according to the procedure for **84**. ¹H NMR (400 MHz, CDCl₃) δ 8.18 (s, 2H), 7.35-7.22 (m, 5H), 6.82 (t, J = 4.0 Hz, 1H), 5.41-5.35 (m, 1H), 4.50- 4.47 (m, 2H), 4.44- 4.40 (m, 1H), 4.28-4.24 (m, 1H), 3.34-3.07 (m, 4H), 2.75-2.68 (m, 1H), 1.26 (d, J = 8.0 Hz, 3H). LC-MS (m/z) 369.42 [M+H]⁺.

[0188] 111B: (S)-(4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **111B** was prepared in a yield of 22.3% (32.0 mg) as a light yellow solid according to the procedure for **84**. ^1H NMR (400 MHz, CDCl_3) δ 8.18 (s, 2H), 7.36-7.22 (m, 5H), 6.85 (t, $J = 4.0$ Hz, 1H), 5.38-5.33 (m, 1H), 4.79-4.73 (m, 1H), 4.55-4.51 (m, 1H), 4.40-4.36 (m, 1H), 3.96-3.93 (m, 1H), 3.39-3.27 (m, 3H), 3.01-2.94 (m, 1H), 2.77-2.70 (m, 1H), 1.15 (d, $J = 8.0$ Hz, 3H). LC-MS (m/z) 369.41 $[\text{M}+\text{H}]^+$.

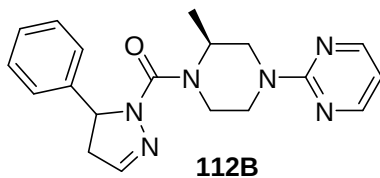
[0189] Compound 112A: (S)-2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **112A** was prepared in a yield of 49.7% (32.0 mg) as a light yellow solid according to the procedure for **84**. ^1H NMR (400 MHz, CDCl_3) δ 8.30 (d, $J = 4.0$ Hz, 2H), 7.35-7.22 (m, 5H), 6.83-6.82 (m, 1H), 6.49-4.47 (m, 1H), 5.41-5.35 (m, 1H), 4.60-4.47 (m, 3H), 4.29-4.25 (m, 1H), 3.33-3.11 (m, 4H), 2.75-2.67 (m, 1H), 1.26 (d, $J = 4.0$ Hz, 3H). LC-MS (m/z) 351.41 $[\text{M}+\text{H}]^+$.

[0190] Compound 112B:

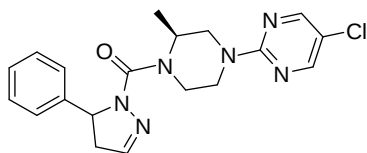
(S)-2-methyl-4-(pyrimidin-2-yl)piperazin-1-yl(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **112B** was prepared in a yield of 45.1% (29.0 mg) as a light yellow solid according to the procedure for **84**. ^1H NMR (400 MHz, CDCl_3) δ 8.29 (d, $J = 4.0$ Hz, 2H), 7.35-7.22 (m, 5H), 6.86-6.85 (m, 1H), 6.49-6.47 (m, 1H), 5.39-5.33 (m, 1H), 4.80-4.73 (m, 1H), 4.65-4.61 (m, 1H), 4.49-4.45 (m, 1H), 3.98-3.93 (m, 1H), 3.40-3.26 (m, 3H),

3.00-2.95 (m, 1H), 2.77-2.70 (m, 1H), 1.15 (d, $J = 8.0$ Hz, 3H). LC-MS (m/z) 351.42 $[M+H]^+$.

[0191] Compound 113A: ((S)-4-(5-chloropyrimidin-2-yl)-2-methylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone

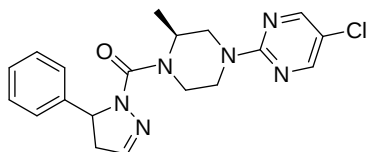


113A

The titled compound 113A was prepared in a yield of 41% (32 mg) as a yellow solid according to the procedure for compound 28. ^1H NMR (400Hz, $CDCl_3$): δ 8.21 (s, 2H), 7.35-7.22 (m, 5H), 6.82 (s, 1H), 5.38 (dd, $J = 11.6, 10.0$ Hz, 1H), 4.56-4.41 (m, 3H), 4.25 (m, 1H), 3.34-3.07 (m, 4H), 2.71 (m, 1H), 1.24 (d, $J = 6.8$ Hz, 3H). LC-MS (ESI) m/z : 385.34, $[M+H]^+$.

[0192] Compound 113B:

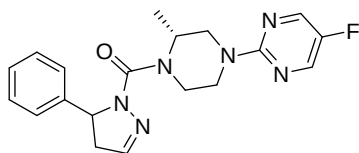
((S)-4-(5-chloropyrimidin-2-yl)-2-methylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



113B

The titled compound 113B was prepared in a yield of 91% (70 mg) as a yellow solid according to the procedure for compound 28. ^1H NMR (400Hz, $CDCl_3$): δ 8.21 (s, 2H), 7.36-7.21 (m, 5H), 6.85 (s, 1H), 5.35 (dd, $J = 11.6, 10.0$ Hz, 1H), 4.79-4.39 (m, 3H), 3.95 (m, 1H), 3.38-3.25 (m, 3H), 3.03-2.94 (m, 1H), 2.72 (m, 1H), 1.13 (d, $J = 7.2$ Hz, 3H). LC-MS (ESI) m/z : 385.34, $[M+H]^+$.

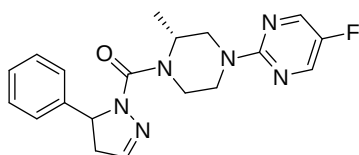
[0193] Compound 114A: ((R)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



114A

The titled compound **114A** was prepared in a yield of 15% (11.2 mg) as a yellow solid according to the procedure for compound **28**. ¹H NMR (400Hz, CDCl₃): δ 8.18 (s, 2H), 7.35-7.23 (m, 5H), 6.83 (s, 1H), 5.38 (dd, *J* = 12.0, 10.0 Hz, 1H), 4.52-4.23 (m, 4H), 3.35-3.07 (m, 4H), 2.72 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 3H). LC-MS (ESI) *m/z*: 369.36, [M+H]⁺.

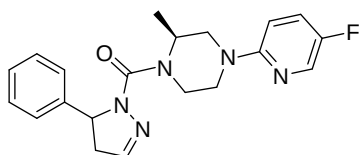
[0194] Compound 114B: ((R)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



114B

The titled compound **114B** was prepared in a yield of 38% (28 mg) as a yellow solid according to the procedure for compound **28**. ¹H NMR (400Hz, CDCl₃): δ 8.18 (s, 2H), 7.35-7.23 (m, 5H), 6.86 (s, 1H), 5.36 (dd, *J* = 12.0, 10.0 Hz, 1H), 4.78-4.36 (m, 3H), 3.95 (m, 1H), 3.40-3.24 (m, 3H), 2.97 (m, 1H), 2.72 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H). LC-MS (ESI) *m/z*: 369.37, [M+H]⁺.

[0195] Compound 115A: ((S)-4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone

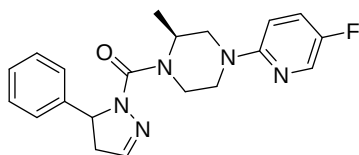


115A

The titled compound **115A** was prepared in a yield of 14% (10 mg) as a yellow solid according to the procedure for compound **28**. ¹H NMR (400Hz, CDCl₃): δ 8.07 (d, *J* = 2.8 Hz, 1H), 7.35-7.21 (m, 6H), 6.83 (s, 1H), 6.65 (d, *J* = 9.2, 2.8 Hz, 1H), 5.37 (dd, *J* = 11.6, 9.6 Hz, 1H), 4.53 (m, 1H), 4.30 (m, 1H), 4.04-3.92 (m, 2H), 3.37-3.09 (m, 4H), 2.72 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H). LC-MS (ESI) *m/z*: 368.34, [M+H]⁺.

[0196] Compound 115B:

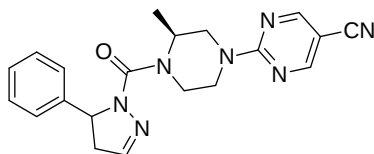
((S)-4-(5-fluoropyridin-2-yl)-2-methylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



115B

The titled compound **115B** was prepared in a yield of 12% (9 mg) as a yellow solid according to the procedure for compound **28**. ^1H NMR (400Hz, CDCl_3): δ 8.05 (d, J = 3.2 Hz, 1H), 7.34-7.23 (m, 6H), 6.85 (s, 1H), 6.63(d, J = 9.2, 3.2 Hz, 1H), 5.35 (dd, J = 11.6, 9.6 Hz, 1H), 4.80 (m, 1H), 4.09-3.89 (m, 3H), 3.48-3.07 (m, 4H), 2.72 (m, 1H), 1.23 (d, J = 6.8 Hz, 3H). LC-MS (ESI) m/z : 368.35, $[\text{M}+\text{H}]^+$.

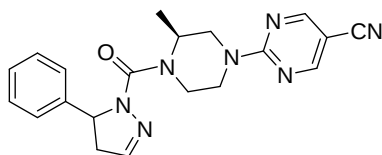
[0197] Compound 116A: 2-((3S)-3-methyl-4-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)pyrimidine-5-carbonitrile



116A

The titled compound **116A** was prepared in a yield of 32% (12 mg) as a white solid according to the procedure for compound **28**. ^1H NMR (400Hz, CDCl_3): δ 8.48 (s, 2H), 7.36-7.24 (m, 5H), 6.84 (s, 1H), 5.37 (dd, J = 11.6, 9.6 Hz, 1H), 4.69-4.51 (m, 3H), 4.29 (m, 1H), 3.36-3.18(m, 4H), 2.74 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H). LC-MS (ESI) m/z : 376.44, $[\text{M}+\text{H}]^+$.

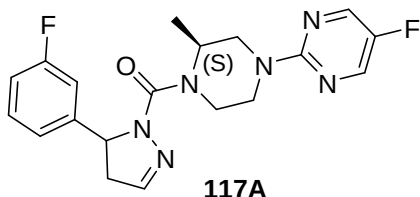
[0198] Compound 116B: 2-((3S)-3-methyl-4-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)pyrimidine-5-carbonitrile



116B

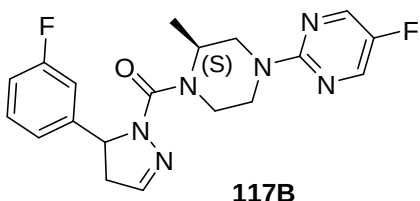
The titled compound **116B** was prepared in a yield of 48% (18 mg) as a white solid according to the procedure for compound **28**. ^1H NMR (400Hz, CDCl_3): δ 8.48 (s, 2H), 7.35-7.25 (m, 5H), 6.87 (s, 1H), 5.35 (dd, J = 11.6, 9.6 Hz, 1H), 4.82-4.54 (m, 3H), 3.99 (m, 1H), 3.41-3.28(m, 3H), 3.06 (m, 1H), 2.75 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H). LC-MS (ESI) m/z : 376.41, $[\text{M}+\text{H}]^+$.

[0199] Compound 117A: ((S)-5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((S)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)methanone



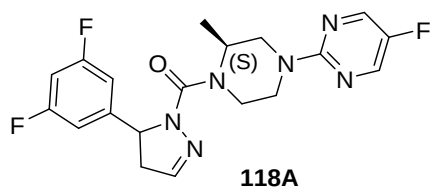
Compound **117A** was synthesized according to the method of compound **102** while using (5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((S)-2-methylpiperazin-1-yl)methanone and 2-chloro-5-fluoropyrimidine. ((S)-5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((S)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)methanone was obtained as white powder (yield 26%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.19 (s, 2H), 7.08 (s, 1H), 7.02-6.91 (m, 3H), 6.83 (s, 1H), 5.37 (s, 1H), 4.37-4.56 (m, 3H), 4.26 (m, 1H), 3.04-3.40 (m, 4H), 2.70 (m, 1H), 1.26 (s, 3H). LC-MS (m/z) 387.56 [M+H]⁺.

[0200] Compound 117B: ((R)-5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((S)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)methanone



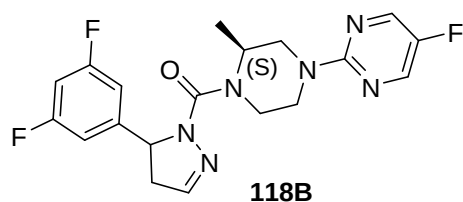
Compound **117B** was synthesized according to the method of compound **102** while using (5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((S)-2-methylpiperazin-1-yl)methanone and 2-chloro-5-fluoropyrimidine. ((S)-5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((S)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)methanone was obtained as white powder (yield 22%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.20 (s, 2H), 7.08 (s, 1H), 7.02-6.91 (m, 3H), 6.83 (s, 1H), 5.32 (s, 1H), 4.36-4.52 (m, 3H), 4.26 (m, 1H), 3.05-3.36 (m, 4H), 2.71 (m, 1H), 1.24 (s, 3H). LC-MS (m/z) 387.69 [M+H]⁺.

[0201] Compound 118A: ((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((S)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)methanone



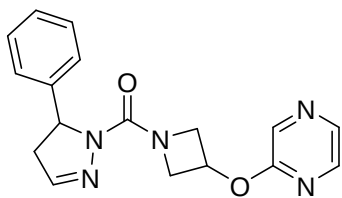
Compound **118A** was synthesized according to the method of compound **102** while using (5-(3,5-difluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)((*S*)-2-methylpiperazin-1-yl)methanone and 2-chloro-5-fluoropyrimidine. ((*S*)-5-(3,5-difluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)((*S*)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)methanone was obtained as white powder (yield 14%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.22 (s, 2H), 6.86-6.76 (m, 3H), 6.74-6.64 (m, 1H), 5.34 (t, *J* = 10.8 Hz, 1H), 4.60-4.40 (m, 3H), 4.28 (d, *J* = 13.0 Hz, 1H), 3.24 (ddd, *J* = 43.0, 16.2, 11.2 Hz, 4H), 2.66 (dd, *J* = 18.2, 10.0 Hz, 1H), 1.28 (d, *J* = 6.7 Hz, 3H). LC-MS (*m/z*) 405.82 [*M*+*H*]⁺.

[0202] Compound 118B: ((*R*)-5-(3,5-difluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)((*S*)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)methanone



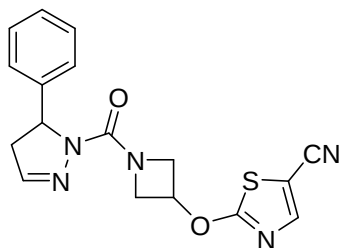
Compound **118B** was synthesized according to the method of compound **102** while using (5-(3,5-difluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)((*S*)-2-methylpiperazin-1-yl)methanone and 2-chloro-5-fluoropyrimidine. ((*R*)-5-(3,5-difluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)((*S*)-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazin-1-yl)methanone was obtained as white powder (yield 16%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.22 (s, 2H), 6.84- 6.73 (m, 3H), 6.74-6.65 (m, 1H), 5.30 (t, *J* = 10.9 Hz, 1H), 4.60-4.41 (m, 3H), 4.28 (d, *J* = 13.0 Hz, 1H), 3.24 (ddd, *J* = 43.0, 16.2, 11.1 Hz, 4H), 2.66 (dd, *J* = 18.2, 10.0 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 3H). LC-MS (*m/z*) 405.76 [*M*+*H*]⁺.

[0203] Compound 119 : (5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(3-(pyrazin-2-yloxy)azetidin-1-yl)methanone



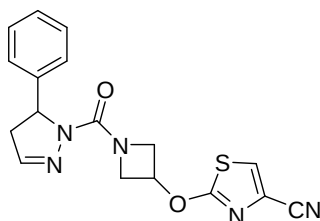
The titled compound **119** was prepared in 40% yield from 2-(azetidin-3-yloxy) pyrazine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ^1H NMR (400 MHz, CDCl_3) δ 8.26 (s, 1H), 8.14 (d, J = 2.7 Hz, 1H), 8.06 – 8.00 (m, 1H), 7.34 – 7.27 (m, 2H), 7.24-7.18 (m, 3H), 6.81 – 6.72 (m, 1H), 5.36-5.26 (m, 2H), 4.62 – 4.44 (m, 2H), 4.17 (dd, J = 26.0, 6.5 Hz, 2H), 3.33 (dd, J = 18.5, 12.1 Hz, 1H), 2.73 (dd, J = 18.6, 6.3 Hz, 1H). LC-MS (m/z) 324.4 ($\text{M}+\text{H}^+$)

[0204] Compound 120 : 2-((1-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-5-carbonitrile



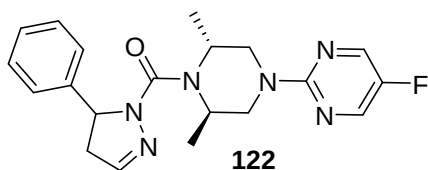
The titled compound **120** was prepared in 30% yield from 2-(azetidin-3-yloxy) thiazole-5-carbonitrile trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ^1H NMR (400 MHz, CDCl_3) δ 7.63 (s, 1H), 7.35 – 7.25 (m, 2H), 7.23-7.13 (m, 3H), 6.77 (t, J = 1.7 Hz, 1H), 5.47 – 5.39 (m, 1H), 5.29 (dd, J = 12.1, 6.3 Hz, 1H), 4.61 – 4.43 (m, 2H), 4.22 (dd, J = 31.0, 9.3 Hz, 2H), 3.40 – 3.27 (m, 1H), 2.74 (ddd, J = 18.6, 6.3, 1.7 Hz, 1H). LC-MS (m/z) 354.4 ($\text{M}+\text{H}^+$)

[0205] Compound 121: 2-((1-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-4-carbonitrile



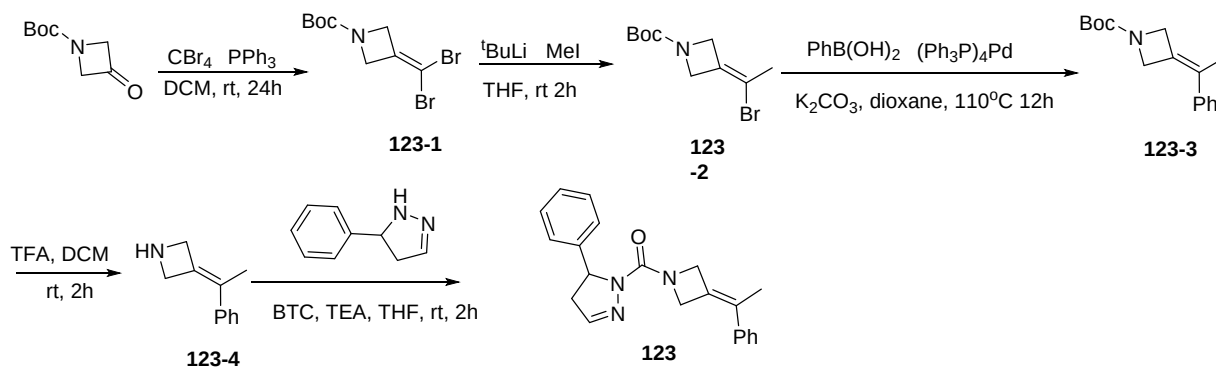
The titled compound **121** was prepared in 28% yield from 2-(azetidin-3-yloxy)thiazole-4-carbonitrile trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. LC-MS (m/z) 354.4 (M+H⁺)

[0206] Compound 122 : ((2R,6R)-4-(5-fluoropyrimidin-2-yl)-2,6-dimethylpiperazin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone ()



The titled compound **122** was prepared in a yield of 40.5% (6.0 mg) as a light yellow solid according to the procedure for **84**. ¹H NMR (400 MHz, CDCl₃) δ 8.23 (s, 2H), 7.35-7.29 (m, 4H), 7.27-7.23 (m, 1H), 6.89 (s, 1H), 5.37 (dd, J = 12.0, 8.0 Hz, 1H), 4.53-4.46 (m, 2H), 3.85-3.84 (m, 4H), 3.38-3.30 (m, 1H), 2.82-2.75 (m, 1H), 1.17 (d, J = 4.0 Hz, 6H). LC-MS (m/z) 383.43 [M+H]⁺.

[0207] Compound 123 : (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(3-(1-phenylethylidene)azetidin-1-yl)methanone



Step1: To a solution of triphenylphosphine (6.13g, 23.37mmol) in anhydrous dichloromethane (15mL), Carbon tetrabromide (3.87g, 11.68mmol) was added at 0°C under argon protection. The solution was stirred for 5 mins at the same temperature before a solution of tert-butyl 3-oxoazetidine-1-carboxylate (1g, 5.84mmol) in anhydrous dichloromethane (5mL) was added dropwise. After stirring for 20 mins. The reaction was allowed to stirred for 24h at room temperature. Hexane was added and the resulting precipitate removed by filtration. The filtrate was concentrated to give off-white solid. This

solid was stirred in hexane with sonication, and then residual solids removed by suction filtration. The filtrate was concentrated to give tert-butyl 3-(dibromomethylene)azetidine-1-carboxylate (1.57g, 82%). LC-MS (m/z) 325.87 [M+H]⁺.

Step2: To a solution of tert-butyl 3-(dibromomethylene)azetidine-1-carboxylate (1.57g, 4.80mmol) in anhydrous tetrahydrofuran (20 mL) at -78°C n-butyllithium(4.43 mL, 1.3M) was added dropwise under argon protection. After 10 mins iodomethane was added dropwise, the reaction was stirred for 2h at same temperature. The reaction was quenched with sat.NH₄Cl(aq) and extracted with ether for two times, the organic layer were combine and washed by water, brine respectively, dry over MgSO₄, filtered, and concentrated under reduced pressure. Subject to purified by silica gel column chromatography (petroleum ether/AcOEt, 30/1) give tert-butyl 3-(1-bromoethylidene)azetidine-1-carboxylate (720mg, 57%) as colorless oil. LC-MS (m/z) 263.45 [M+H]⁺.

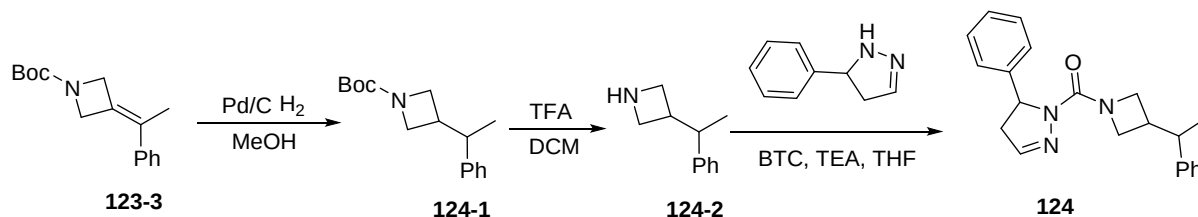
Step3: To a solution of tert-butyl 3-(1-bromoethylidene)azetidine-1-carboxylate (100mg, 0.38mmol) and phenylboronic acid (56mg, 0.46mmol) in anhydrous 1,4-dioxane (10 mL), Tetrakis(triphenylphosphine)palladium (88mg, 0.76mmol) and potassium carbonate (158mg, 1.14mmol) were added under argon protection. The reaction mixture was stirred at 110°C for 12h. the volatiles was removed *in vacuo* and the residue was suspension in dichloromethane, sat The organic layer was washed with water, and brine respectively. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt, 1/1) give tert-butyl 3-(1-phenylethylidene)azetidine-1-carboxylate (76mg, 77%) as pale yellow oil. LC-MS (m/z) 260.68 [M+H]⁺.

Step4: Intermediate **123-4** was synthesized according to the method of intermediate **100-2** while using tert-butyl 3-(1-phenylethylidene)azetidine-1-carboxylate. 3-(1-phenylethylidene)azetidine was obtained as pale yellow oil (yield 95%). LC-MS (m/z) 160.46 [M+H]⁺.

Step5: Compound **123** was synthesized according to the method of compound **100** while using 5-phenyl-4,5-dihydro-1*H*-pyrazole and 3-(1-phenylethylidene)azetidine. (5-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)(3-(1-phenylethylidene)azetidin-1-yl) methanone was obtained (22mg, yield 17%) as pale white powder. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.07 (m, 10H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.50 – 5.27 (m, 1H), 5.03 – 4.66 (m, 4H), 3.36 (dd, *J* = 17.6, 10.8 Hz, 1H), 2.76 (d, *J* = 18.8 Hz, 1H), 1.94 (s, 3H). LC-

MS (m/z) 332.57 [M+H]⁺.

[0208] Compound 124: (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(3-(1-phenylethyl)azetidin-1-yl)methanone

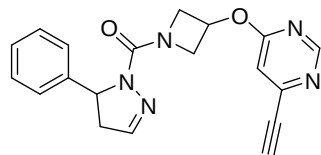


Step1 : To a solution of tert-butyl 3-(1-phenylethylidene)azetidine-1-carboxylate (217mg, 836.71mmol) in methanol (10 mL), Palladium 10% on Carbon was added under argon protection. Hydrogen was bubbled with balloon. The reaction mixture was stirred at r,t for 12h. the mixture was filtered with celite and the filtrate was concentrated. The crude product (123mg, 56%) was used directly in next step without further purification. LC-MS (m/z) 262.83 [M+H]⁺.

Step2: Intermediate 124-2 was synthesized according to the method of intermediate 100-2 while using tert-butyl 3-(1-phenylethyl)azetidine-1-carboxylate. 3-(1-phenylethyl)azetidine was obtained (72mg, 94%) as pale yellow oil. The crude product was used directly in next step without further purification. LC-MS (m/z) 162.67 [M+H]⁺.

Step3: Compound 124 was synthesized according to the method of compound 100 while using 5-phenyl-4,5-dihydro-1H-pyrazole and 3-(1-phenylethyl)azetidine. (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(3-(1-phenylethyl)azetidin-1-yl)methanone was obtained (41mg, yield 27%) as pale white powder. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.09 (m, 10H), 6.74 (s, 1H), 5.31 (s, 1H), 4.29 (d, *J* = 28.8 Hz, 1H), 3.92 (d, *J* = 31.2 Hz, 2H), 3.71 (d, *J* = 29.8 Hz, 1H), 3.30 (d, *J* = 16.8 Hz, 1H), 2.89 (s, 1H), 2.74 (s, 2H), 1.20 (d, *J* = 5.6 Hz, 3H). LC-MS (m/z) 334.84 [M+H]⁺.

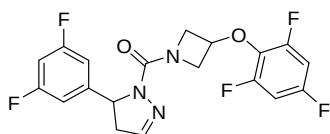
[0209] Compound 125: (3-((6-ethynylpyrimidin-4-yl)oxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound 125 was prepared in 18% yield from (5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)(3-((6-((trimethylsilyl)ethynyl)pyrimidin-4-yl)oxy)azetidin-1-yl)

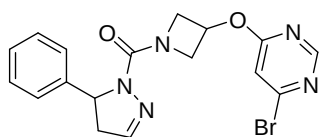
methanone removed TMS group, which was prepared from 4-(azetidin-3-yloxy)-6-((trimethylsilyl)ethynyl)pyrimidine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. LC-MS (m/z) 348.4(M+H⁺)

[0210] Compound 126: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(2,4,6-trifluorophenoxy)azetidin-1-yl)methanone



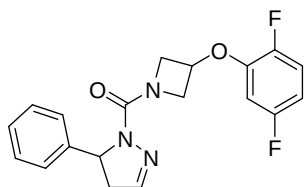
The titled compound **126** was prepared in 21% yield from 3-(2,4,6-trifluorophenoxy)azetidine, (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 6.80 – 6.63 (m, 6H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 4.93- 4.80 (m, 1H), 4.49-4.40 (m, 2H), 4.38-4.24 (m, 2H), 3.22 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.69 (ddd, 6.5 Hz, 1H). LC-MS (m/z) 412.33 (M+H⁺)

[0211] Compound 127: (3-((6-bromopyrimidin-4-yl)oxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **127** was prepared in 18% yield from 4-(azetidin-3-yloxy)-6-bromopyrimidine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. LC-MS (m/z) 402.35 (M+H⁺)

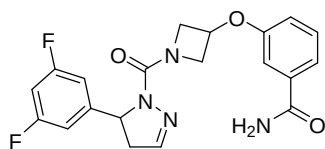
[0212] Compound 128: (3-(2,5-difluorophenoxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **128** was prepared in 37.7% yield from 3-(2,5-difluorophenoxy)

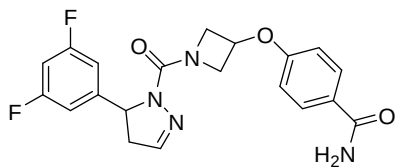
azetidine trifluoroacetic acid, (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 7.06 – 6.97 (m, 1H), 6.77 (brs, 1H), 6.60 (ddt, *J* = 9.0, 7.8, 3.1 Hz, 1H), 6.40 (ddd, *J* = 9.5, 6.6, 3.0 Hz, 1H), 5.30 (dd, *J* = 12.2, 6.2 Hz, 1H), 4.92-4.86 (m, *J* = 10.6, 6.4, 4.2 Hz, 1H), 4.58-4.45(m, *J* = 25.1, 10.1, 6.5 Hz, 2H), 4.28 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.21 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.33 (dd, *J* = 18.7, 12.4 Hz, 1H), 2.73 (ddd, *J* = 18.6, 6.3, 1.6 Hz, 1H). LC-MS (*m/z*) 358.4 (M+H⁺)

[0213] Compound 129: 3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)benzamide



To a solution of tert-butyl 3-(3-cyanophenoxy)azetidine-1-carboxylate prepared by the method described for tert-butyl 3-(2-fluorophenoxy)azetidine-1-carboxylate (200mg) in MeOH (3mL) was added DMSO (0.1mL), 30% H₂O₂ (0.4 mL) and 1N NaOH (0.9mL) at 0°C. The mixture was stirred at 50°C for 3h. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give the crude desired product (250mg). LC-MS (*m/z*) 293.43 (M+H⁺). tert-butyl 3-(3-carbamoylphenoxy)azetidine-1-carboxylate was removed Boc group and coupling with 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole using triphosgene to give the titled product **129** (46mg, 32%). ¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.31 (m, 2H), 7.29 – 7.25 (m, 1H), 7.24 – 7.20 (m, 1H), 6.95 (ddd, *J* = 7.9, 6.5, 2.8 Hz, 1H), 6.82 – 6.63 (m, 3H), 6.16 (brs, 2H), 5.26 (dd, *J* = 12.1, 6.4 Hz, 1H), 4.96 (ddd, *J* = 10.4, 6.3, 4.0 Hz, 1H), 4.67-4.46 (m, 2H), 4.21 (dd, *J* = 24.1, 7.2 Hz, 2H), 3.33 (ddd, *J* = 18.6, 12.2, 1.5 Hz, 1H), 2.67 (ddd, *J* = 18.6, 6.4, 1.6 Hz, 1H). LC-MS (*m/z*) 401.4 (M+H⁺).

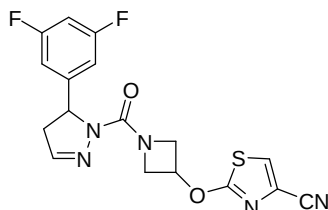
[0214] Compound 130: 4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)benzamide



The titled compound **130** was prepared in 37% yield from 4-(azetidin-3-yloxy)

benzamide trifluoroacetic acid, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole using triphosgene, according to the procedure outlined for compound **129**. LC-MS (m/z) 401.40 (M+H⁺)

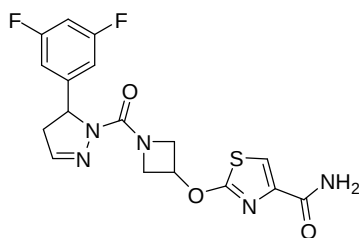
[0215] Compound 131: 2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-4-carbonitrile



The titled compound **128** was prepared in 37.7% yield from 2-(azetidin-3-yloxy)thiazole-4-carbonitrile trifluoroacetic acid, (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.42 (s, 1H), 6.81 – 6.60 (m, 4H), 5.45-5.35 (m, 1H), 5.25 (dd, J = 11.9, 6.1 Hz, 1H), 4.64 – 4.48 (m, 2H), 4.23 (dd, J = 17.2, 11.1 Hz, 2H), 3.34 (dd, J = 18.3, 11.9 Hz, 1H), 2.68 (dd, J = 18.2, 5.2 Hz, 1H).

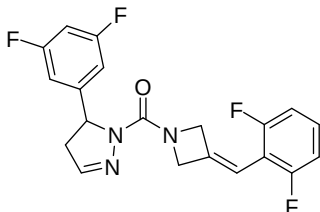
LC-MS (m/z) 390.4 (M+H⁺)

[0216] Compound 132: 2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-4-carboxamide



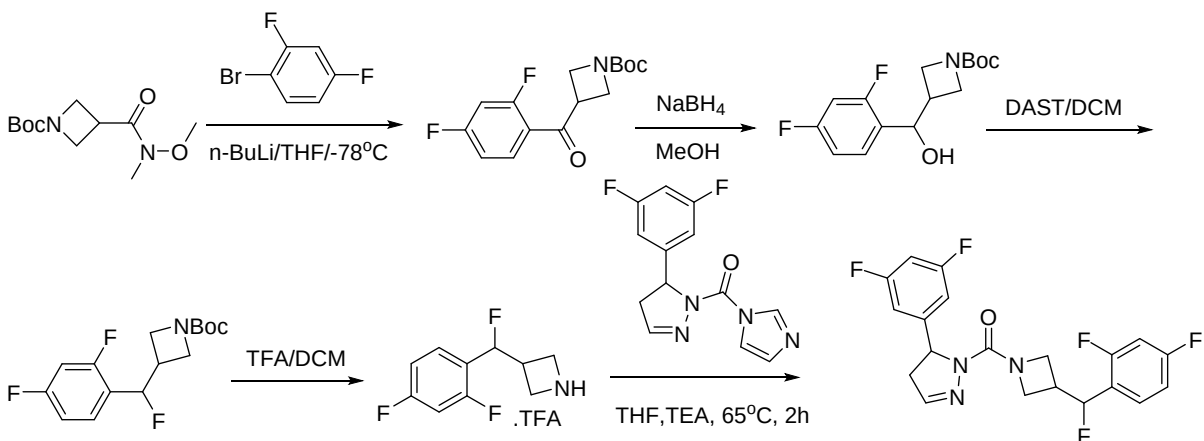
The titled compound **132** was prepared in 27.7% yield from 2-(azetidin-3-yloxy)thiazole-4-carboxamide trifluoroacetic acid, (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according to the procedure outlined for compound **129**. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (s, 1H), 6.86 – 6.59 (m, 5H), 5.61 (s, 1H), 5.44-5.36 (m, 1H), 5.26 (dd, J = 12.2, 6.5 Hz, 1H), 4.65-4.45 (m, 2H), 4.27 (ddd, J = 30.4, 10.6, 3.3 Hz, 2H), 3.34 (ddd, J = 18.6, 12.2, 1.6 Hz, 1H), 2.68 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H). LC-MS (m/z) 408.4 (M+H⁺)

[0217] Compound 133: (3-(2,6-difluorobenzylidene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **133** was prepared in 37% yield from 3-(2,6-difluorobenzylidene)azetidine hydrochloride, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ^1H NMR (400 MHz, CDCl_3) δ 7.23 – 7.13 (m, 1H), 6.87 (t, J = 8.4 Hz, 2H), 6.81 – 6.73 (m, 3H), 6.72 – 6.65 (m, 1H), 6.34 – 6.27 (m, 1H), 5.31 (dd, J = 12.0, 6.4 Hz, 1H), 4.95-4.75 (m, 4H), 3.36 (ddd, J = 18.4, 12.0, 1.6 Hz, 1H), 2.70 (ddd, J = 18.4, 6.0, 1.6 Hz, 1H). LC-MS (m/z):390.31 $[\text{M}+\text{H}]^+$.

[0218] Compound 134: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2,4-difluorophenyl)fluoromethyl)azetidin-1-yl)methanone



Step1 :1-bromo-2,4-difluorobenzene (474 mg, 2.46 mmol) was dissolved in 5 mL dry THF. Let it cool to -78°C . n-BuLi (1.28 mL, 2.4 M, 3.07 mmol) was added dropwise at -78°C . Let it stir at -78°C for 1h. Then tert-butyl 3-(methoxy(methyl)carbamoyl)azetidine-1-carboxylate (0.5g, 2.05 mmol) in 2 ml THF was added slowly to the solution at -78°C . Let it stir at -78°C for 1h. The starting material was consumed completely by TLC. Sat. NH_4Cl solution was added to quench the reaction and extracted with EtOAc (20 ml X 3). The organic layer was evaporated to dryness and purified by column chromatography (PE/EA=

3/1) to give 360 mg tert-butyl 3-(2,4-difluorobenzoyl)azetidine-1-carboxylate as light-yellow-oil. Yield: 74.4%. LC-MS (m/z): 298.40 [M+H]⁺.

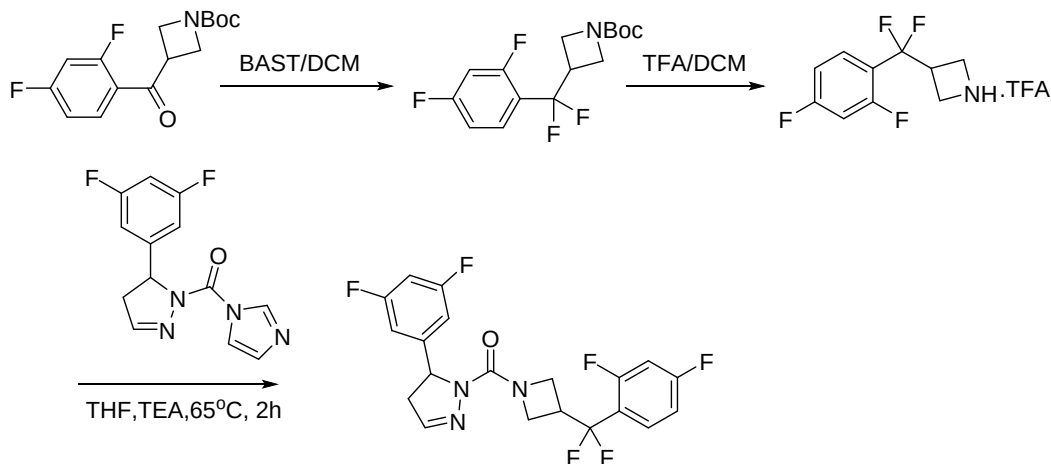
Step2: Tert-butyl 3-(2,4-difluorobenzoyl)azetidine-1-carboxylate (160 mg, 0.537 mmol) was dissolved in 5 ml MeOH. NaBH₄ (128.3 mg, 3.29 mmol) was added in portions at 0°C. Let it stir at r.t. for 16 hrs. Water was added to quench the reaction. The solvent was evaporated to dryness and extracted with DCM (15 ml X 3). Dried with Na₂SO₄ and filtered. Evaporated to dryness and purified by Prep-TLC (PE/EA = 2/1) to give 160 mg tert-butyl 3-((2,4-difluorophenyl)(hydroxy)methyl)azetidine-1-carboxylate as brown oil. Yield: 99.3%. LC-MS (m/z): 300.45 [M+H]⁺.

Step3: Tert-butyl 3-((2,4-difluorophenyl)(hydroxy)methyl)azetidine-1-carboxylate (160 mg, 0.533 mmol) was dissolved in 7.5 ml dry DCM. Diethylaminosulfur trifluoride (174 mg, 1.07 mmol) in 1 mL DCM was added slowly to the solution at 0°C. Let it stir at 0°C for 0.5 h. Then stir at r.t. for 0.5 h. It was washed with H₂O and the organic layer was evaporated to dryness and purified by column chromatography (PE/EA = 4/1) to give 115 mg tert-butyl 3-((2,4-difluorophenyl)fluoromethyl)azetidine-1-carboxylate as light-yellow oil. Yield: 71.7%. LC-MS (m/z): 302.40 [M+H]⁺.

Step4: Tert-butyl 3-((2,4-difluorophenyl)fluoromethyl)azetidine-1-carboxylate (40 mg, 0.133 mmol) was dissolved in 2 mL dry DCM. 5 ml TFA/DCM (3/1) solution was added to the solution at 0°C. Let it stir at r.t. for 1.5 hrs. The solvent was evaporated to dryness to give 3-((2,4-difluorophenyl)fluoromethyl)azetidine as brown oil and it was used for next step without further purification. Yield: quantitative. LC-MS (m/z): 203.30 [M+H]⁺.

Step5: The obtained above product 3-((2,4-difluorophenyl)fluoromethyl)azetidine was dissolved in 2 ml THF. (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (36.8 mg, 0.133 mmol) was added. 0.2 ml TEA was added to the solution. Let it stir at 65°C for 16 hrs. The solvent was evaporated to dryness and purified by Prep-TLC (PE/EA = 2/1) to give 40 mg (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2,4-difluorophenyl)fluoromethyl)azetidin-1-yl) methanone as light-yellow oil. Yield: 73.7%. ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.58 (m 1H), 6.83-6.94 (m, 2H), 6.73-6.77 (m, 3H), 6.65-6.70 (m, 1H), 5.91-6.05 (m, 1H), 5.26 (dd, 1H, J = 12.0, 6.4 Hz), 4.09-4.41 (m, 3H), 3.71-3.82 (m, 1H), 3.38-3.47 (m, 1H), 3.28-3.37 (m 1H), 2.66 (ddd, 1H, J = 18.4, 6.4, 1.6 Hz). LC-MS (m/z): 410.40 [M+H]⁺.

[0219] Compound 135: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2,4-difluorophenyl)difluoromethyl)azetidin-1-yl)methanone



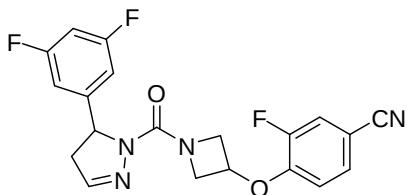
Step1: Tert-butyl 3-(2,4-difluorobenzoyl)azetidine-1-carboxylate (205 mg, 0.688 mmol) was dissolved in 4 ml dry DCM. Bis(2-methoxyethyl)aminosulfur trifluoride (1.272 ml, 6.89 mmol) was added slowly to the solution at r.t.. Let it stir at r.t for 5 d. The solvent was poured into ice and extracted with DCM (15 ml X 3). The organic layers were combined and washed with sat. NaHCO₃. The solvent was evaporated to dryness and purified by Prep-TLC (PE/EA = 2/1) to give 122 mg tert-butyl 3-((2,4-difluorophenyl)difluoromethyl)azetidine-1-carboxylate as yellow-light oil. Yield: 61.6%. LC-MS (m/z): 320.3 [M+H]⁺.

Step2: 3-((2,4-difluorophenyl)difluoromethyl)azetidine-1-carboxylate (60 mg, 0.188 mmol) was dissolved in in 2 mL dry DCM. 5 ml TFA/DCM (3/1) solution was added to the solution at 0°C. Let it stir at r.t. for 1.5 hrs. The solvent was evaporated to dryness to give 3-((2,4-difluorophenyl)difluoromethyl)azetidine as brown oil and it was used for next step without further purification. Yield: quantitative. LC-MS (m/z): 221.30 [M+H]⁺.

Step3: The obtained above product 3-((2,4-difluorophenyl)difluoromethyl)azetidine was dissolved in 3 ml THF. (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (51.9 mg, 0.187 mmol) was added. 0.4 ml TEA was added to the solution. Let it stir at 65°C for 16 hrs. The solvent was evaporated to dryness and purified by Prep-TLC (PE/EA = 2/1) to give 40 mg (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((2,4-difluorophenyl)difluoromethyl)azetidin-1-yl)methanone as light-yellow oil. Yield: 50.1%. ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.67 (m, 1H), 6.88-6.99 (m, 2H), 6.62-6.77 (m,

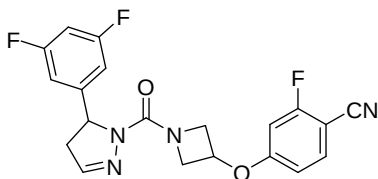
3H), 6.65-6.71 (m, 1H), 5.27 (dd, 1H, $J = 12.0, 6.4$ Hz), 4.35-4.39 (m, 1H), 4.19-4.32 (m, 3H), 3.47-3.60 (m, 1H), 3.34 (ddd, 1H, $J = 18.4, 12.4, 1.6$ Hz), 2.68 (ddd, 1H, $J = 18.4, 6.4, 1.6$ Hz). LC-MS (m/z): 428.35 $[M+H]^+$.

[0220] Compound 136: 4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-3-fluorobenzonitrile



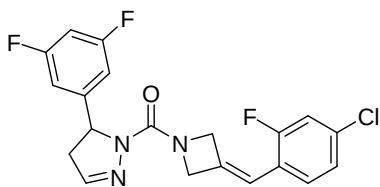
The titled compound **136** was prepared in 74.7% yield from 4-(azetidin-3-yloxy)-3-fluorobenzonitrile trifluoroacetic acid, (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according to the procedure outlined for compound **60**. ^1H NMR (400 MHz, CDCl_3) δ 7.41-7.39 (m, 1H), 7.38-7.36 (m, 1H), 6.81 – 6.62 (m, 5H), 5.25 (dd, $J = 12.2, 6.4$ Hz, 1H), 5.05 – 4.96 (m, 1H), 4.55 (dd, $J = 17.1, 10.8$ Hz, 2H), 4.40-4.20 (m, 2H), 3.34 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.77-2.63 (m, 1H). LC-MS (m/z) 301.4 ($M+H^+$)

[0221] Compound 137: 4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2-fluorobenzonitrile



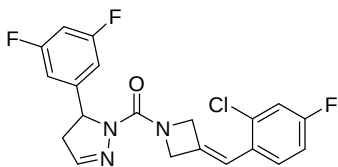
The titled compound **137** was prepared in 74.7% yield from 4-(azetidin-3-yloxy)-2-fluorobenzonitrile trifluoroacetic acid, (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according to the procedure outlined for compound **60**. ^1H NMR (400 MHz, CDCl_3) δ 7.55-7.50 (m, 1H), 6.78 (t, $J = 1.7$ Hz, 1H), 6.74 – 6.52 (m, 5H), 5.25 (dd, $J = 12.2, 6.4$ Hz, 1H), 4.93 (tt, $J = 6.4, 4.0$ Hz, 1H), 4.63 – 4.45 (m, 2H), 4.28 – 4.12 (m, 2H), 3.34 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.69 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H). LC-MS (m/z) 301.4 ($M+H^+$)

[0222] Compound 138: (3-(4-chloro-2-fluorobenzylidene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



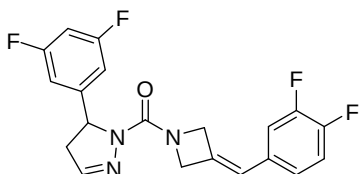
The titled compound **138** was prepared in 36.3% yield from 3-(4-chloro-2-fluorobenzylidene)azetidine hydrochloride, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ^1H NMR (400 MHz, CDCl_3) δ 7.13 – 7.06 (m, 2H), 7.05-6.99 (m, 1H), 6.83 – 6.74 (m, 3H), 6.72-6.66 (m, 1H), 6.40 (t, J = 2.0 Hz, 1H), 5.31 (dd, J = 12.0, 6.4 Hz, 1H), 4.99 (dd, J = 30.6, 15.4 Hz, 2H), 4.85 (dd, J = 28.0, 14.4 Hz, 2H), 3.37 (ddd, J = 18.4, 12.0, 1.6 Hz, 1H), 2.72 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H). LC-MS (m/z):406.29 $[\text{M}+\text{H}]^+$.

[0223] Compound 139: (3-(2-chloro-4-fluorobenzylidene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **139** was prepared in 36.3% yield from 3-(2-chloro-4-fluorobenzylidene)azetidine hydrochloride, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ^1H NMR (400 MHz, CDCl_3) δ 7.18-7.04 (m, 2H), 6.97 (td, J = 8.4, 2.8 Hz, 1H), 6.84 – 6.73 (m, 3H), 6.73-6.66 (m, 1H), 6.60 (t, J = 2.4 Hz, 1H), 5.31 (dd, J = 12.0, 6.4 Hz, 1H), 5.08 – 4.77 (m, 4H), 3.37 (ddd, J = 18.4, 12.0, 1.6 Hz, 1H), 2.72 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H). LC-MS (m/z):406.33 $[\text{M}+\text{H}]^+$.

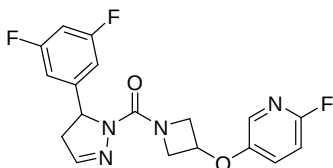
[0224] Compound 140 : (3-(3,4-difluorobenzylidene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **140** was prepared in 36.3% yield from 3-(3,4-difluorobenzylidene)azetidine hydrochloride, 5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole and triphosgene according to the procedure outlined for compound **37**. ^1H NMR

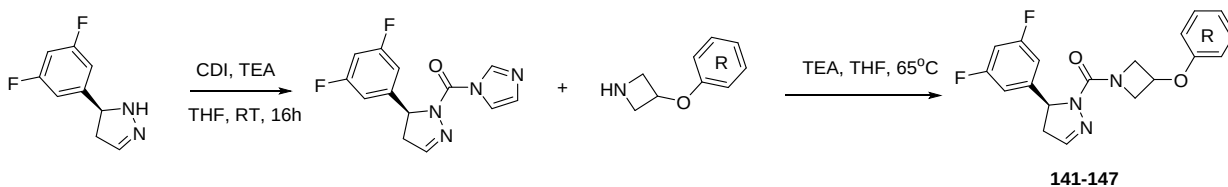
(400 MHz, CDCl₃) δ 7.17-7.07 (m, 1H), 6.94-6.88 (m, 1H), 6.87-6.81 (m, 2H), 6.81 – 6.66 (m, 3H), 6.19 (t, J = 2.0 Hz, 1H), 5.31 (dd, J = 12.0, 6.4 Hz, 1H), 5.03 (dd, J = 30.0, 14.8 Hz, 2H), 4.83 (dd, J = 28.0, 14.4 Hz, 2H), 3.38 (ddd, J = 18.4, 12.0, 1.6 Hz, 1H), 2.72 (ddd, J = 18.5, 6.5, 1.7 Hz, 1H). LC-MS (m/z):390.29 [M+H]⁺.

[0225] Compound 141: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((6-fluoropyridin-3-yl)oxy)azetidin-1-yl)methanone

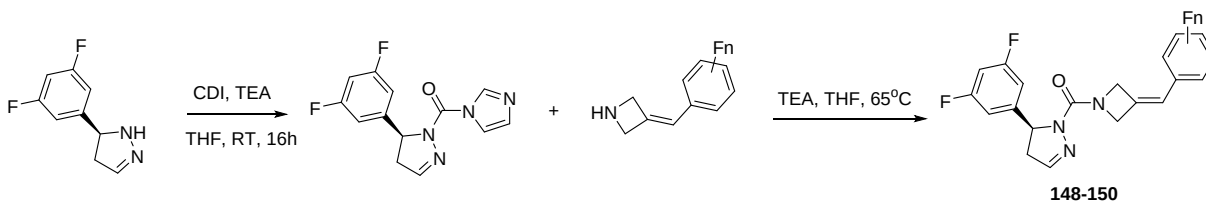


The titled compound **141** was prepared in 34.7% yield from 5-(azetidin-3-yloxy)-2-fluoropyridine trifluoroacetic acid, (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according to the procedure outlined for compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.65 (s, 1H), 7.23 – 7.11 (m, 2H), 6.86 (brs, 1H), 6.78-6.62 (m, 3H), 5.30-5.25 (m, 1H), 4.98-4.86 (m, 1H), 4.64-4.45 (m, 2H), 4.30-4.12 (m, 2H), 3.41-3.26 (m, 1H), 2.75-2.60 (m, 1H). LC-MS (m/z) 377.4 (M+H⁺)

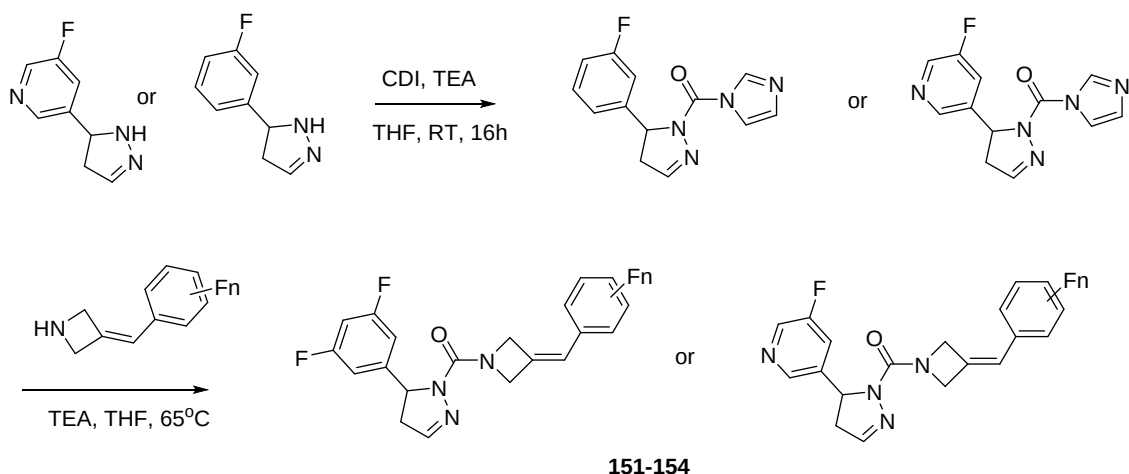
[0226] Compound 142-147: preparation of 142-47 according to the following route:



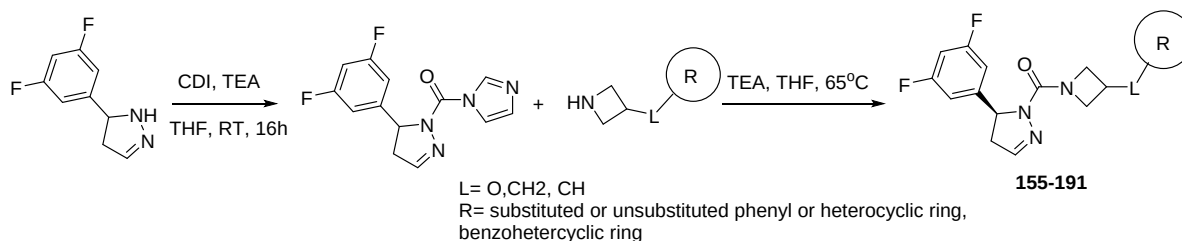
[0227] Compound 148-150: preparation of 148-150 according to the following route:



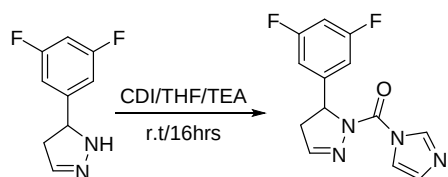
[0228] Compound 151-154: preparation of 151-154 according to the following route:



[0229] Compound 155-191: preparation of **155-191** according to the following route:

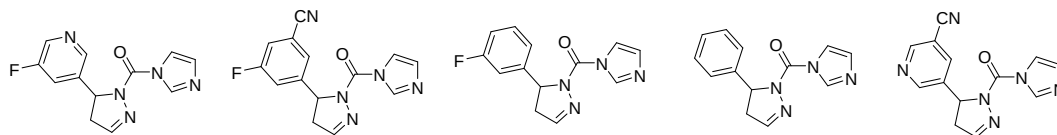


[0230] Preparation of intermediate 1: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone

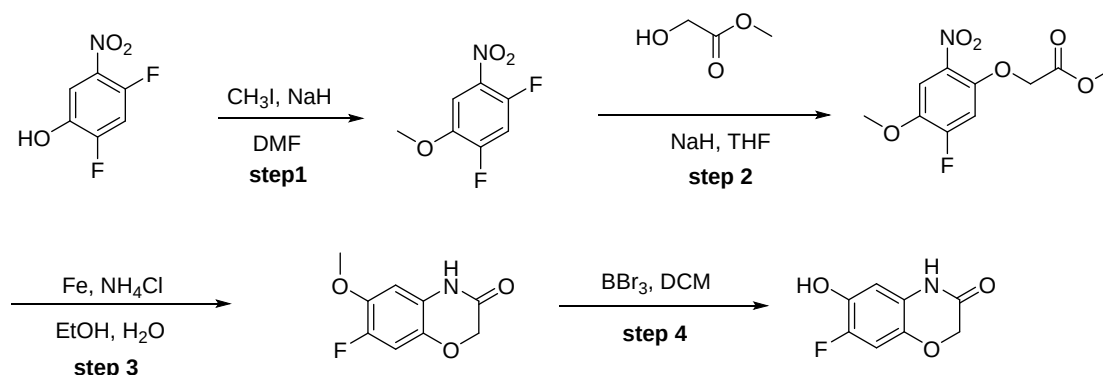


CDI (44.5 g, 274.7 mmol) was dissolved in 450 mL THF and added TEA (38.00g, 375.00 mmol). Compound A2 (45.50g, 249.75 mmol) was dissolved in 460 mL THF and added to the mixture. Let it stir at r.t over night. The mixture was evaporated to dryness and purified by column chromatography (PE/EA=3/1~1/1) to give the titled compound as a light-yellow solid (40.7g, 59%). LCMS (m/z): 277, [M+H]⁺. H-NMR

[0231] The following intermediates used for the preparation of the titled example compounds were synthesized using the methods analogous to the ones described above.



[0232] The above intermediates were isolated as racemates. Chiral HPLC separation to yield two single- enantiomer, The absolute configuration of the active enantiomer was assigned as (S) in each case, based on the assignment of XXX as described in example, and the S configuration enantiomer was carried on selected examples, as indicated by the structure.



[0233] Step1: 2,4-difluoro-5-nitrophenol (10 g,) in DMF 150ml was added NaH (4.57 g, 60% in oil) at 0°C under nitrogen protection, 30 min later, CH_3I (12.17 g) was added. The mixture was stirred at room temperature for 12 h. The solution was added H_2O and extracted by EA. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification by column chromatography to afford 10 g of 1,5-difluoro-2-methoxy-4-nitrobenzene as a yellow solid. LC-MS (m/z) 199.2 ($\text{M}+\text{H}^+$)

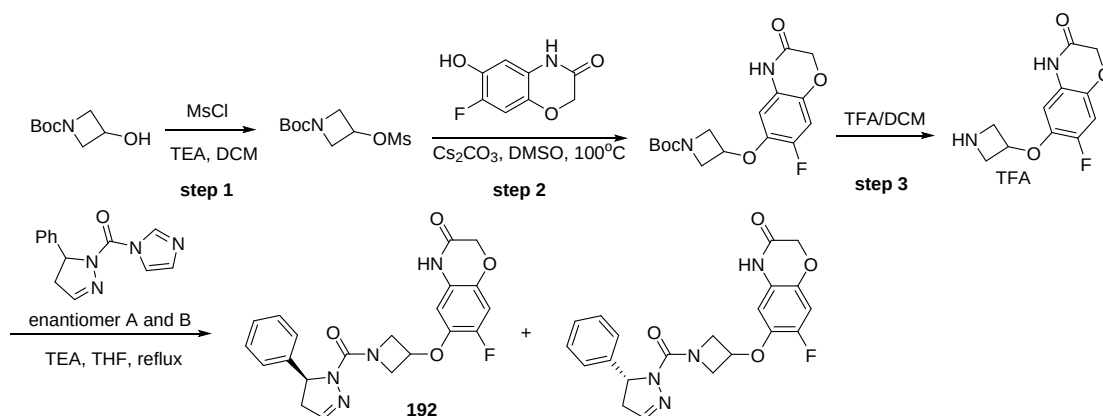
[0234] Step2: 3.44 g of methyl 2-hydroxyacetate was dissolved in **150 ml of THF**, NaH (1.8 g, 60% in oil) was added at 0°C under nitrogen protection, 30 min later, 6.56 g of 1,5-difluoro-2-methoxy-4-nitrobenzene was added. The mixture was stirred for 3 h at room temperature. The reaction mixture was added EA and H_2O . After separation, the combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. 8 g of crude methyl 2-(5-fluoro-4-methoxy-2-nitrophenoxy)acetate was obtained and used for the next step without further purification. LC-MS (m/z) 260.2 ($\text{M}+\text{H}^+$)

[0235] Step3: Fe (11.63 g), NH_4Cl (9.3 g) were added to a suspension of methyl 2-(5-fluoro-4-methoxy-2-nitrophenoxy)acetate(8g) in $\text{C}_2\text{H}_5\text{OH}$ and H_2O (v/v =10:1, 110 ml) at rt. The mixture was stirred at 70°C for 2 h. The resultant precipitate was filtered. The filtrate was concentrated in vacuo and added DCM. The mixture was filtered once more

and concentrated in vacuo. Purification by column chromatography to afford 2.8 g of 7-fluoro-6-methoxy-2H-benzo[b][1,4]oxazin-3(4H)-one as brown solid (purity 80%, UPLC). LC-MS (m/z) 198.2 (M+H⁺)

[0236] Step4: 2.8 g of 7-fluoro-6-methoxy-2H-benzo[b][1,4]oxazin-3(4H)-one was dissolved in 60 ml of DCM, BBr₃ (20ml) was added slowly at -78°C under nitrogen protection. The mixture was *allowed* to warm to *rt* and *stirred* for 12 h. The resulting solution was quenched by H₂O and extracted by EA. The organic layers were dried by Na₂SO₄ and concentrated in vacuo. Purification by column chromatography to afford 0.29 g of 7-fluoro-6-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one as yellow solid. LC-MS (m/z) 184.2 (M+H⁺).

[0237] Compound 192: (S)-7-fluoro-6-((1-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-3(4H)-one



[0238] Step 1: tert-butyl 3-hydroxyazetidine-1-carboxylate (15 g, 86.6 mmol) was dissolved in 150 ml of dry DCM, TEA (26.2 g, 259.8 mmol) was added. MsCl (1.2 g, 103.92 mmol) was added slowly to the above solution at 0°C. The mixture was stirred for overnight. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated. The crude product was crystalized with EtOH/petroleum to yield tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate (13g, 59.8%). LCMS (m/z) 252.3 (M+H⁺).

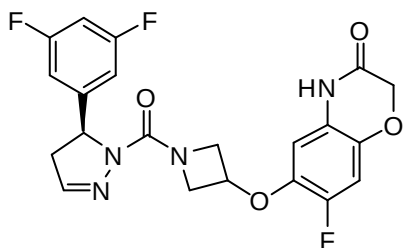
[0239] Step 2: To a solution of tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate (26.5g, 144.7mmol), 7-fluoro-6-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one (40g, 159.17mmol) in DMSO (270 ml) was added Cs₂CO₃ (94.3 g, 289.4 mmol) at r.t., then the temperature was allowed to rise to 100°C and stir for another 3h. Upon completion, the reaction was diluted with ethyl acetate (500 ml), washed with H₂O (700 ml), brine (250 ml),

dried over Na₂SO₄, and concentrated to give the crude product. The crude product was then purified by added EA/PE=1:3 (300 ml) to afford tert-butyl 3-((7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)azetidine-1-carboxylate (35.1g,71.8%). MS (m/z) 338.4 (M+H⁺).

[0240] Step 3: tert-butyl 3-((7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)azetidine-1-carboxylate (100 mg, 0.3mmol) was dissolved in DCM(5 mL) , and TFA(350 mg, 10 mmol) was added. The mixture was stirred at r.t. for 4 h. The mixture was concentrated to give 6-(azetidin-3-yloxy)-7-fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one as TFA salt, which was used for next step without further purification. LC-MS (m/z) 238.4 (M+H⁺).

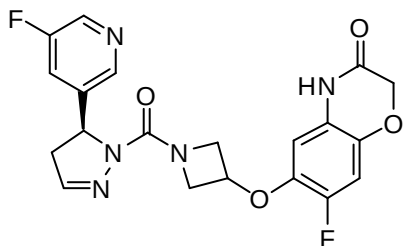
[0241] Step 4: half part of the above crude 6-(azetidin-3-yloxy)-7-fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one trifluoroacetic acid salt and (S)-(1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone (65 mg, enantiomer B) and TEA(0.2 ml) were dissolved in THF(5 ml) and stirred at room temperature for 16h. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by Pre-HPLC to give the titled compound **192** (36 mg) as a white solid with potent activity based on the cell activity assay. LC-MS (m/z) 411.2(M+H⁺). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.30 (s, 1H), 7.30 – 7.24 (m, 2H), 7.23 – 7.17 (m, 3H), 6.81 (t, *J* = 1.7 Hz, 1H), 6.73 (d, *J* = 11.2 Hz, 1H), 6.20 (d, *J* = 8.0 Hz, 1H), 5.48 (dd, *J* = 12.1, 5.9 Hz, 1H), 4.77 – 4.69 (m, 1H), 4.54 – 4.46 (m, 3H), 4.46 – 4.39 (m, 1H), 4.38 – 4.31 (m, 1H), 4.14 – 4.06 (m, 1H), 3.38 (ddd, *J* = 18.5, 12.1, 1.7 Hz, 1H), 2.72 (ddd, *J* = 18.5, 5.9, 1.8 Hz, 1H). while another part of 6-(azetidin-3-yloxy)-7-fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one trifluoroacetic acid salt was reacted with (R)-(1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone to give (R)-7-fluoro-6-((1-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-3(4H)-one with weak activity based on the cell activity assay

[0242] Compound 193; (S)-6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-7-fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one



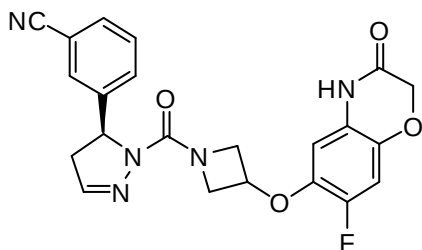
The titled compound **193** was synthesized in an analogous manner to the preparation of compound **192**. LC-MS (m/z): 447.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.93 (s, 1H), 6.83 – 6.80 (m, 1H), 6.78 (s, 1H), 6.77 – 6.73 (m, 2H), 6.66 (tt, J = 9.0, 2.4 Hz, 1H), 6.22 (d, J = 7.8 Hz, 1H), 5.46 (dd, J = 12.1, 6.1 Hz, 1H), 4.88 – 4.79 (m, 1H), 4.60 – 4.45 (m, 4H), 4.43 – 4.34 (m, 1H), 4.19 – 4.08 (m, 1H), 3.44 – 3.33 (m, 1H), 2.75 – 2.64 (m, 1H).

[0243] Compound 194 : (S)-7-fluoro-6-((1-(5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-3(4H)-one



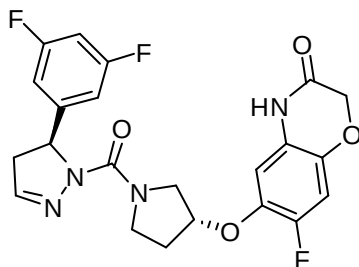
The titled compound **194** were synthesized in an analogous manner to the preparation of compound **1**. LC-MS (m/z): 430.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.43 – 8.36 (m, 2H), 7.38 (d, J = 8.8 Hz, 1H), 6.87 – 6.84 (m, 1H), 6.78 (dd, J = 11.2, 2.3 Hz, 1H), 6.27 – 6.21 (m, 1H), 5.58 – 5.45 (m, 1H), 4.91 – 4.81 (m, 1H), 4.57 – 4.54 (m, 2H), 4.53 – 4.44 (m, 2H), 4.39 – 4.28 (m, 1H), 4.23 – 4.10 (m, 1H), 3.50 – 3.40 (m, 1H), 2.75 (dd, J = 18.5, 6.4 Hz, 1H).

[0244] Compound 195 : (S)-3-(1-(3-((7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)azetidine-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)benzonitrile



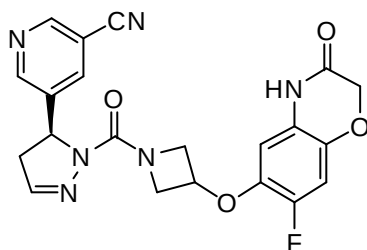
The titled compound **195** were synthesized in an analogous manner to the preparation of compound **192**. LC-MS (m/z): 436.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.11 (s, 1H), 7.54 – 7.39 (m, 4H), 6.83 (t, J = 1.7 Hz, 1H), 6.76 (d, J = 11.2 Hz, 1H), 6.25 (d, J = 7.8 Hz, 1H), 5.47 (dd, J = 12.2, 6.3 Hz, 1H), 4.87 – 4.80 (m, 1H), 4.54 (s, 2H), 4.53 – 4.45 (m, 2H), 4.39 – 4.30 (m, 1H), 4.21 – 4.11 (m, 1H), 3.41 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.69 (ddd, J = 18.6, 6.3, 1.8 Hz, 1H).

[0245] Compound 196 : 7-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)-6-fluoro-3,4-dihydroquinolin-2(1H)-one



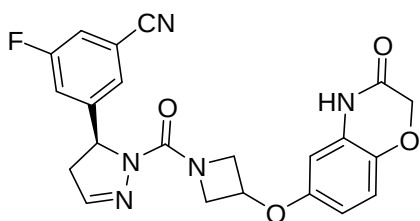
The titled compound **196** were synthesized in an analogous manner to the preparation of compound **192**. LC-MS (m/z): 461.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.83 – 6.73 (m, 4H), 6.72 – 6.65 (m, 1H), 6.42 (d, J = 7.7 Hz, 1H), 5.33 (dd, J = 12.0, 7.7 Hz, 1H), 4.84 – 4.78 (m, 1H), 4.56 (s, 2H), 4.07 – 4.00 (m, 1H), 3.99 – 3.90 (m, 1H), 3.77 – 3.67 (m, 2H), 3.36 – 3.26 (m, 1H), 2.71 – 2.62 (m, 1H), 2.25 – 2.15 (m, 1H), 2.14 – 2.04 (m, 1H).

[0246] Compound 197: (S)-5-(1-(3-((7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)azetidine-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)nicotinonitrile



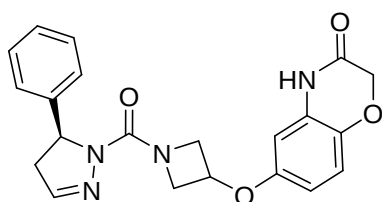
The titled compound **197** were synthesized in an analogous manner to the preparation of compound **192**. LC-MS (m/z): 437.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.96 – 8.82 (br, 1H), 8.80 – 8.71 (m, 2H), 7.84 (t, *J* = 2.1 Hz, 1H), 6.91 – 6.84 (m, 1H), 6.77 (d, *J* = 11.1 Hz, 1H), 6.22 (d, *J* = 7.8 Hz, 1H), 5.65 – 5.54 (m, 1H), 4.88 – 4.81 (m, 1H), 4.54 (s, 2H), 4.52 – 4.43 (m, 2H), 4.42 – 4.33 (m, 1H), 4.19 – 4.07 (m, 1H), 3.48 (ddd, *J* = 18.7, 12.2, 1.7 Hz, 1H), 2.73 (ddd, *J* = 18.6, 6.7, 1.7 Hz, 1H).

[0247] Compound 198 : (S)-3-fluoro-5-(1-(3-((3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)azetidine-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)benzonitrile



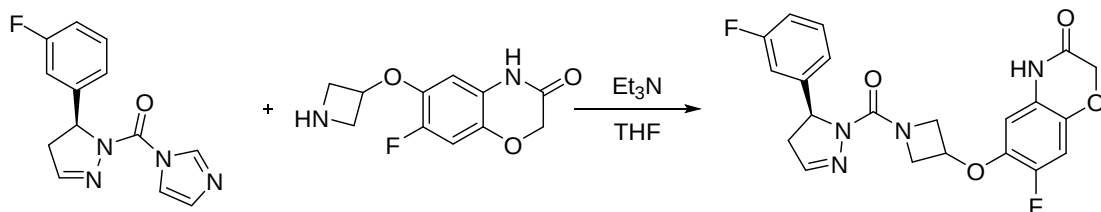
The titled compound **198** were synthesized in an analogous manner to the preparation of compound **192**. Yield 92.9% ¹H NMR (400 MHz, Chloroform-*d*) δ 8.86 (s, 1H), 7.33 (t, *J* = 1.6 Hz, 1H), 7.24 – 7.17 (m, 2H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.81 (t, *J* = 1.6 Hz, 1H), 6.34 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.25 (d, *J* = 2.8 Hz, 1H), 5.47 – 5.37 (m, 1H), 4.88-4.80 (m, 1H), 4.64-4.40 (m, 4H), 4.32 – 4.04 (m, 2H), 3.46-3.35 (m, 1H), 2.73-2.63 (m, 1H). LC-MS (m/z) 436.2 (M+H⁺)

[0248] Compound 199: (S)-6-((1-(5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-3(4H)-one



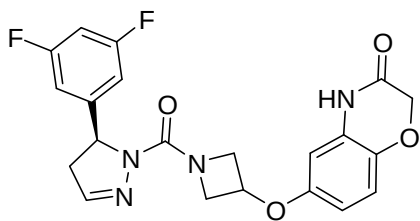
The titled compound **199** were synthesized in an analogous manner to the preparation of compound **192**. Yield 90.9% ¹H NMR (400 MHz, Chloroform-*d*) δ 8.82 (s, 1H), 7.36 – 7.27 (m, 2H), 7.26-7.17 (m, 3H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.78 (t, *J* = 1.6 Hz, 1H), 6.32 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.23 (d, *J* = 2.8 Hz, 1H), 5.39 (dd, *J* = 12.0, 6.2 Hz, 1H), 4.82-4.74 (m, 1H), 4.53 (s, 2H), 4.51 – 4.41 (m, 2H), 4.26-4.04 (m, 2H), 3.42-3.30 (m, 1H), 2.78-2.68 (m, 1H). LC-MS (m/z) 393.2 (M+H⁺)

[0249] Compound 200: (S)-7-fluoro-6-((1-(5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-3(4H)-one



(S)-5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-ylmethanone (64 mg, 0.25 mmol) was added to a solution of Et_3N (303 mg, 3.0 mmol) in MeOH and 6-(azetidin-3-yloxy)-7-fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one (71 mg, 0.25 mmol) was added in portions, and the whole reaction mixture was stirred and refluxed at 25°C overnight. After the organic solvent was concentrated and further purified by silica gel column chromatography (PE/EA = 2/1), to give 30 mg of (S)-7-fluoro-6-((1-(5-(3-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-3(4H)-one in a yield of 28% (30 mg) as a white solid. ^1H NMR (400 MHz, CHCl_3) δ 9.04 (s, 1H), 7.26 – 7.21 (m, 1H), 7.03 – 6.98 (m, 1H), 6.94 – 6.87 (m, 2H), 6.81 (t, J = 1.6 Hz, 1H), 6.74 (d, J = 11.2 Hz, 1H), 6.20 (d, J = 7.9 Hz, 1H), 5.49 (dd, J = 12.1, 6.0 Hz, 1H), 4.82 – 4.75 (m, 1H), 4.59 – 4.50 (m, 3H), 4.48 – 4.33 (m, 2H), 4.10 (d, J = 10.1 Hz, 1H), 3.39 (ddd, J = 18.5, 12.2, 1.7 Hz, 1H), 2.70 (ddd, J = 18.5, 6.1, 1.8 Hz, 1H). LC-MS (ESI, m/z): $M+H$ $^+$ = 429.2.

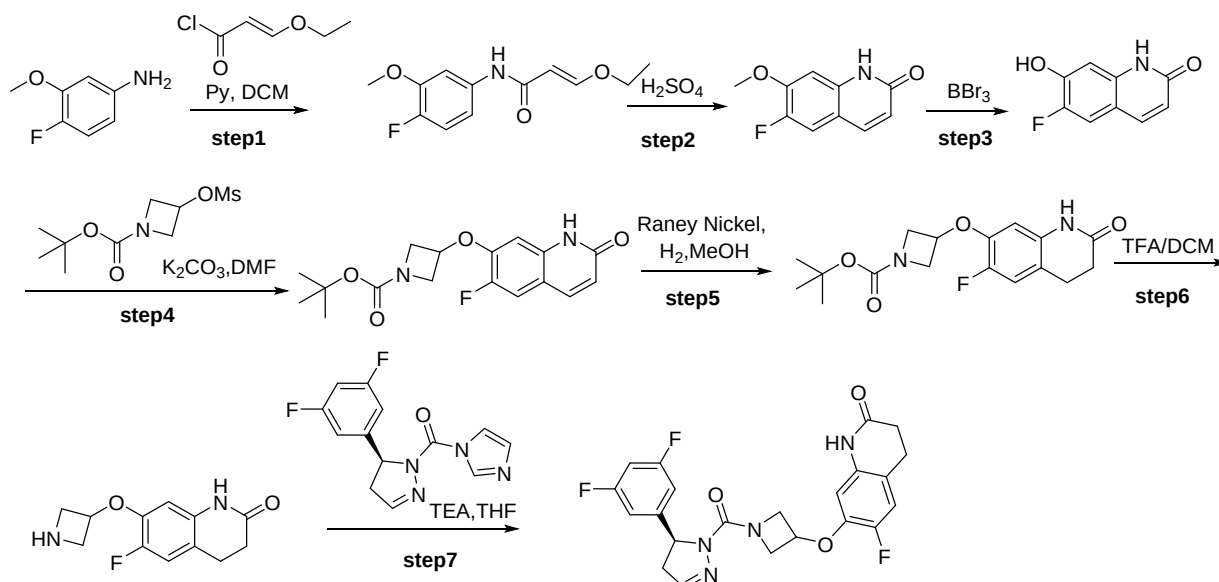
[0250] Compound 201 : (S)-6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-3(4H)-one.



The titled compound **201** were synthesized in an analogous manner to the preparation of compound **192**. yield 41.0 %. ^1H NMR (400 MHz, CHCl_3) δ 8.50 (brs, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.81 – 6.71 (m, 3H), 6.70 – 6.60 (m, 1H), 6.34 (dd, J = 8.8, 2.8 Hz, 1H), 6.24 (d, J = 2.8 Hz, 1H), 5.36 (dd, J = 12.0, 6.4 Hz, 1H), 4.87-4.80 (m, 1H), 4.55 (s, 2H), 4.53-4.45 (m, 2H), 4.31-4.21 (m, 1H), 4.16 – 4.06 (m, 1H), 3.42-3.30 (m, 1H), 2.74-2.64 (m, 1H).

LC-MS (m/z) 429.2 (M+H⁺).

[0251] Compound 202: (S)-7-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-6-fluoro-3,4-dihydroquinolin-2(1H)-one



[0252] Step 1: 4-fluoro-3-methoxyaniline (3g, 21.26mmol) was dissolved in dry DCM(80mL), pyridine(2.02g, 25.51mmol)was added, (E)-3-ethoxy-N-(4-fluoro-3-methoxyphenyl)acrylamide(3.43g, 25.506mmol)in 5mL dry DCM was added to the mixture at 0°C. The mixture was stirred at room temperature for 16 hour, and then evaporated to dryness and the residue was purified by flash chromatography(PE/EA= 3/2) to give (E)-N-(4-fluoro-3-methoxyphenyl)-3-methoxyacrylamide as an orange solid(5.1g, 99%) . LC-MS(ESI) m/z=240.2 [M+H⁺]

[0253] Step 2: (E)-N-(4-fluoro-3-methoxyphenyl)-3-methoxyacrylamide (5.1g, 21.32 mmol)was added to 57mL of con. H₂SO₄ at 0°C, and the mixture was stirred at room temperature for 1.5h. The reaction mixture was slowly added to the ice with strong stirring and the resulting solid was filtered and washed with water, evaporated to dryness to give 6-fluoro-7-methoxyquinolin-2(1H)-one as pale pink solid(3.21g, 77.6%) . ¹H NMR (DMSO ,400 MHz) δ 11.68 (s, 1H), 7.78 (d, 1H, J = 9.6 Hz), 7.54 (d, 1H, J = 11.6 Hz), 6.96 (d, 1H, J = 7.6 Hz), 6.38 (d, 1H, J = 9.6 Hz), 3.88 (s, 3H). LC-MS(ESI) m/z=194.2[M+H⁺]

[0254] Step 3: 6-fluoro-7-methoxyquinolin-2(1H)-one (3.41g, 17.57 mmol)was suspension in DCM(100mL), and BBr₃(1M in DCM, 30mL) was added to the mixture at 0°C. The mixture was stirred at room temperature for 16 hour, and was quenched by added

MeOH and water, the resulting solid was filtered and washed with water, evaporated to dryness to give 6-fluoro-7-hydroxyquinolin-2(1H)-one as pale pink solid (3.06g, 97%) as a light yellow solid. ¹H NMR (DMSO, 400 MHz) δ 11.59 (s, 1H), 10.67 (brs, 1H), 7.72 (d, 1H, *J* = 9.6 Hz), 7.45 (d, 1H, *J* = 11.6 Hz), 6.88 (d, 1H, *J* = 7.6 Hz), 6.30 (d, 1H, *J* = 9.6 Hz). LC-MS(ESI) *m/z*=180.2 [M+H⁺].

[0255] Step 4: A mixture of 6-fluoro-7-hydroxyquinolin-2(1H)-one (300mg, 1.676mmol), tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate (420 mg, 1.676mmol) and K₂CO₃ (275mg, 2.01mmol) in dry DMF (5mL) were stirred at 120°C for 60h. The mixture was evaporated to dryness and purified by flash chromatography (MeOH/DCM = 1/20) to give tert-butyl 3-((6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl)oxy)azetidine-1-carboxylate as a yellow solid (258mg, 46%). LC-MS(ESI) *m/z*=335.4 [M+H⁺].

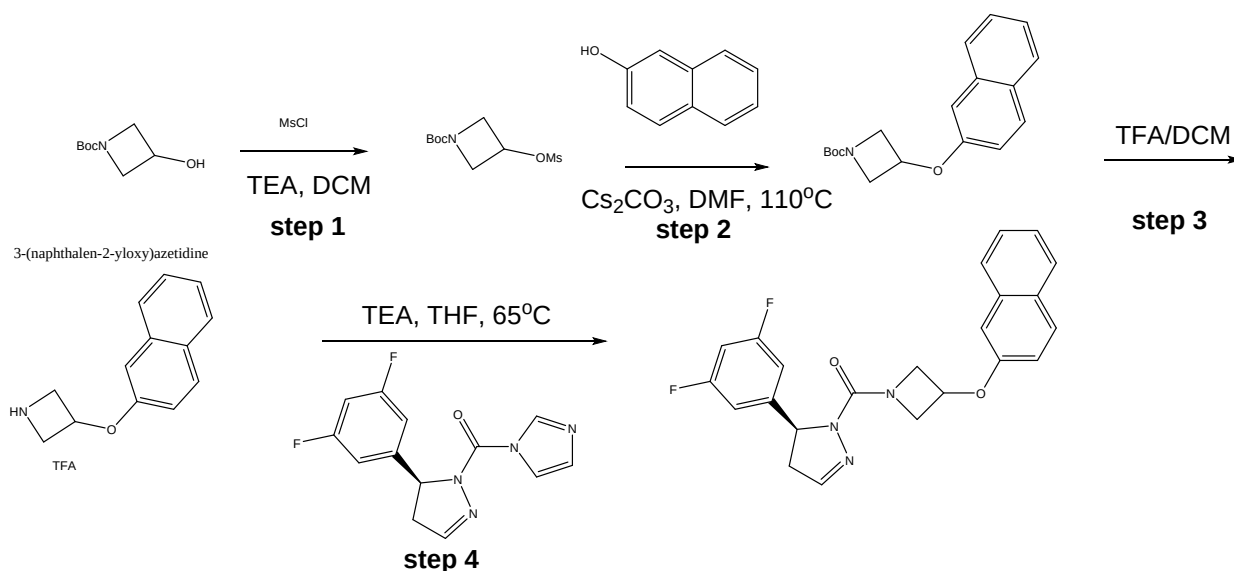
[0256] Step 5 : tert-butyl 3-((6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl)oxy)azetidine-1-carboxylate (200mg) was dissolved in MeOH (20mL), Raney Nickel (50% in water, 20mg) and AcOH (2-3 drops) was added. The mixture was stirred under H₂ at 1atm for 16h. The mixture was filtered and evaporated to dryness to give tert-butyl 3-((6-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)azetidine-1-carboxylate (200mg, crude) which was used for next step without purification. LC-MS(ESI) *m/z*=337.4 [M+H⁺]

[0257] Step 6: tert-butyl 3-((6-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)oxy)azetidine-1-carboxylate (200mg, crude) was dissolved in DCM (5mL), TFA (1mL) was added. The mixture was stirred at room temperature for 2h, and then evaporated to dryness to give 7-(azetidin-3-yloxy)-6-fluoro-3,4-dihydroquinolin-2(1H)-one (180 mg, crude), which was used for next step without purification. LC-MS(ESI) *m/z*=237.3 [M+H⁺]

[0258] Step 7: A mixture of (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (149 mg) and 7-(azetidin-3-yloxy)-6-fluoro-3,4-dihydroquinolin-2(1H)-one (180 mg) in dry THF (5mL) was added TEA (0.1mL). The mixture was stirred at room temperature for 2h, and evaporated to dryness and the residue was purified by pre-HPLC to give the titled compound **202** (40mg, 15% in three steps) as a white solid. LC-MS(ESI) *m/z*=445.2 [M+H⁺] ¹H NMR (400 MHz, CDCl₃) δ 8.44 (s, 1H), 6.88 (d, *J* = 11.0 Hz, 1H), 6.77-6.76 (m, 1H), 6.73 (dd, *J* = 8.0, 2.2 Hz, 2H), 6.64 (tt, *J* = 8.9, 2.3 Hz, 1H), 6.13 (d, *J* = 7.2 Hz, 1H), 5.37 (dd, *J* = 12.2, 6.3 Hz, 1H), 4.92 – 4.84 (m, 1H), 4.51 (d, *J* = 6.7 Hz, 2H), 4.23 (dd, *J* = 75.9, 9.8 Hz, 3H), 3.35 (ddd, *J* = 18.5, 12.2, 1.5

Hz, 1H), 2.85 (t, J = 7.5 Hz, 2H), 2.67 (ddd, J = 18.6, 6.3, 1.7 Hz, 1H), 2.56 (t, J = 7.5 Hz, 2H).

[0259] Compound 203: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(naphthalen-2-yloxy)azetidin-1-yl)methanone



[0260] Step 1: tert-butyl 3-hydroxyazetidine-1-carboxylate (15 g, 86.6 mmol) was dissolved in 150 ml of dry DCM, TEA (26.2 g, 259.8 mmol) was added. MsCl (1.2 g, 103.92 mmol) was added slowly to the above solution at 0°C. The mixture was stirred for overnight. The mixture was extracted with DCM, washed with brine, dried (Na₂SO₄), and concentrated. The crude product was crystallized with EtOH/petroleum to yield tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate (13g, 59.8%). LCMS (m/z) 252.3 (M+H⁺).

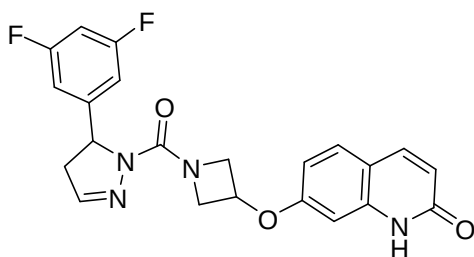
[0261] Step 2: A mixture of tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate (1.0 g, 6.94 mmol), naphthalen-2-ol (1g, 6.94 mmol) Cs₂CO₃ (4.52 g, 13.88 mmol) were placed in DMF (20 mL). The mixture was stirred 110°C for overnight, water was added and extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated. The crude product was purified by column chromatography on silica gel eluted with (EA/PE = 1:5) to give tert-butyl 3-(naphthalen-2-yloxy)azetidine-1-carboxylate (880mg, 48%) as a yellow oil. LC-MS (m/z) 300.4 (M+H⁺).

[0262] Step 3: tert-butyl 3-(naphthalen-2-yloxy)azetidine-1-carboxylate (300 mg, 1mmol) was dissolved in DCM (5 mL), and TFA (1.14g, 10mmol) was added. The mixture was stirred at r.t. for 4 h. The mixture was concentrated to give the desired product: 3-

(naphthalen-2-yloxy)azetidine trifluoroacetic acid as TFA salt, which was used for next step without further purification. LC-MS (m/z) 200.3 (M+H⁺).

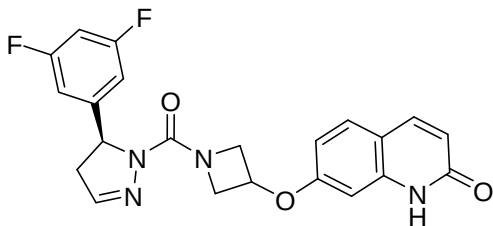
[0263] Step 4: 3-(naphthalen-2-yloxy)azetidine trifluoroacetic acid (43 mg, 0.22 mmol) and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (50 mg, 0.18 mmol) and TEA(55 mg, 0.54 mmol) were dissolved in THF(5 ml) and stirred at room temperature for 16h. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by Pre -TLC(EA/PE= 1:1) to give the titled compound **204** (71mg, 97%) as a yellow solid. LC-MS (m/z) 408.4(M+H⁺). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 9.0 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.47-7.43(m, 1H), 7.38 – 7.33 (m, 1H), 7.13 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.86 (d, *J* = 2.5 Hz, 1H), 6.78-6.75 (m, 3H), 6.69 (tt, *J* = 8.8, 2.3 Hz, 1H), 5.35 – 5.22 (m, 1H), 5.10-5.05 (m, 1H), 4.70 – 4.55 (m, 2H), 4.39 – 4.21 (m, 2H), 3.35 (dd, *J* = 18.6, 12.0 Hz, 1H), 2.69 (dd, *J* = 18.5, 6.2 Hz, 1H).

[0264] Compound 204 : 7-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)quinolin-2(1H)-one



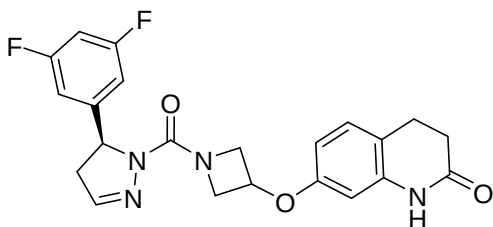
The titled compound **204** was synthesized in an analogous manner to the preparation of compound **203** yield: 40.9%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.55 (s, 1H), 7.82 (d, *J* = 9.6Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.16-7.08 (m, 1H), 7.04 – 6.98 (m, 1H), 6.96 – 6.87 (m, 2H), 6.74 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 6.32 (dd, *J* = 9.6, 2.0 Hz, 1H), 5.24 (dd, *J* = 12.0, 6.4 Hz, 1H), 5.08 – 4.99 (m, 1H), 4.49 (s, 2H), 4.00 (s, 2H), 3.44 – 3.34 (m, 1H), 2.69-2.60 (m, 1H). LC-MS (m/z) 425.3(M+H⁺).

[0265] Compound 205 : (S)-7-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)quinolin-2(1H)-one



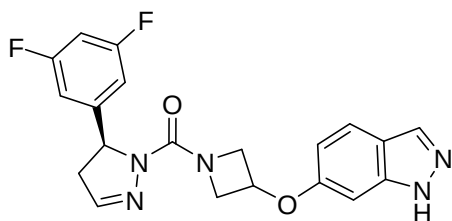
The titled compound **205** was synthesized in an analogous manner to the preparation of compound **203** yield:56.9%. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.71 (s, 1H), 7.77 (d, J = 9.4 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 6.81 – 6.71 (m, 4H), 6.70 – 6.58 (m, 3H), 5.36 (dd, J = 12.2, 6.4 Hz, 1H), 5.08-4.98 (m, 1H), 4.69 -4.52(m, 2H), 4.31 (d, J = 5.3 Hz, 1H), 4.19 (d, J = 10.2 Hz, 1H), 3.36 (m, 1H), 2.72 – 2.61 (m, 1H). LC-MS (m/z) 425.3(M+H⁺).

[0266] Compound 206: (S)-7-(((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-3,4-dihydroquinolin-2(1H)-one



The titled compound **206** was synthesized in an analogous manner to the preparation of compound **203**. yield:65.2%. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.06 – 7.02 (m, 1H), 6.81 – 6.71 (m, 3H), 6.71 – 6.63 (m, 1H), 6.34 (dd, J = 8.4, 2.4 Hz, 1H), 6.21 (d, J = 2.4 Hz, 1H), 5.36 – 5.22 (m, 1H), 4.94 – 4.81 (m, 1H), 4.60-4.42 (m, 2H), 4.24 (d, J = 10.1 Hz, 1H), 4.14 (d, J = 8.8 Hz, 1H), 3.35 (m, 1H), 2.89 (dd, J = 8.4, 6.4 Hz, 2H), 2.68 (m, 1H), 2.61 (dd, J = 8.4, 6.4 Hz, 2H). LC-MS (m/z) 427.3(M+H⁺).

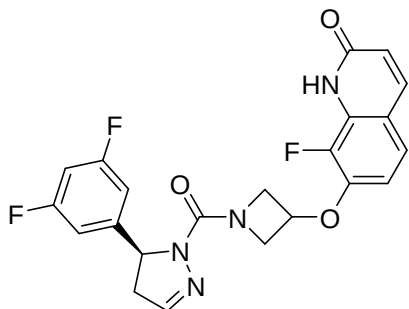
[0267] Compound 207 : (S)-(3-(((1H-indazol-6-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **207** was synthesized in an analogous manner to the preparation of compound **203**. yield:11.4% ^1H NMR (400 MHz, Chloroform-*d*) δ 7.99 (s, 1H), 7.64 (d, J =

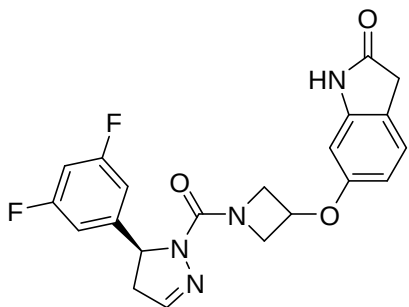
8.8 Hz, 1H), 6.86 – 6.54 (m, 5H), 5.29 (dd, $J = 12.0, 6.4$ Hz, 1H), 5.06 – 4.91 (m, 1H), 4.70 – 4.52 (m, 2H), 4.35 – 4.14 (m, 2H), 3.78 – 3.68 (m, 1H), 3.40-3.30(m,1H), 2.73-2.64(m, 1H). LC-MS (m/z) 398.2($M+H^+$).

[0268] Compound 208: (S)-7-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-8-fluoroquinolin-2(1H)-one



The titled compound **208** was prepared in 36% yield from (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-pyrrol-1-yl)methanone and 7-(azetidin-3-yloxy)-8-fluoroquinolin-2(1H)-one according to the procedure outlined for compound **203**. LC-MS (m/z) 443.4 ($M+H^+$). ^1H NMR (400 MHz, $DMSO-d_6$) δ 11.68 (s, 1H), 7.86 (dd, $J = 9.6, 1.5$ Hz, 1H), 7.43 (dd, $J = 8.8, 1.7$ Hz, 1H), 7.14 – 7.06 (m, 1H), 7.04 – 7.00 (m, 1H), 6.95 – 6.87 (m, 2H), 6.82 (dd, $J = 8.8, 7.5$ Hz, 1H), 6.39 (d, $J = 9.6$ Hz, 1H), 5.24 (dd, $J = 12.1, 6.6$ Hz, 1H), 5.18-5.13(m, 1H), 4.51 (s, 2H), 4.10 – 3.91 (m, 2H), 3.39 (ddd, $J = 18.7, 12.1, 1.7$ Hz, 1H), 2.65 (ddd, $J = 18.7, 6.6, 1.7$ Hz, 1H).

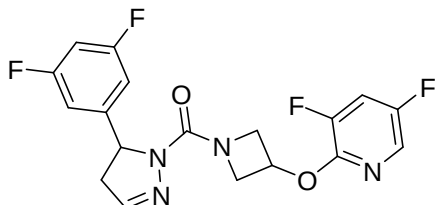
[0269] Compound 209: (S)-6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)indolin-2-one



The titled compound **209** was prepared in 90% yield from (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-pyrrol-1-yl)methanone and 6-(azetidin-3-yloxy)indolin-2-one according to the procedure outlined for compound **203**. LC-MS (m/z) 413.4($M+H^+$). ^1H NMR (400 MHz, $Chloroform-d$) δ 7.47 (brs, 1H), 7.10 – 7.06 (m, 1H), 6.77 – 6.71 (m, 2H),

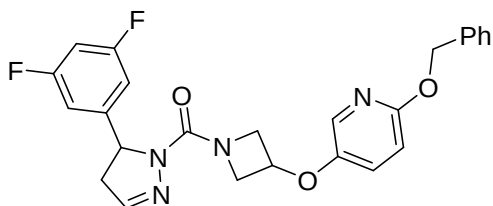
6.71 – 6.63 (m, 1H), 6.35 – 6.30 (m, 2fH), 5.26 (dd, $J = 12.3, 6.4$ Hz, 1H), 4.92 – 4.85 (m, 1H), 4.55-4.45 (m, 2H), 4.26 – 4.12 (m, 2H), 3.45 (s, 2H), 3.33 (dd, $J = 18.6, 12.3$ Hz, 1H), 2.67 (ddd, $J = 18.5, 6.5, 1.6$ Hz, 1H).

[0270] Compound 210: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3,5-difluoropyridin-2-yl)oxy)azetidin-1-yl)methanone



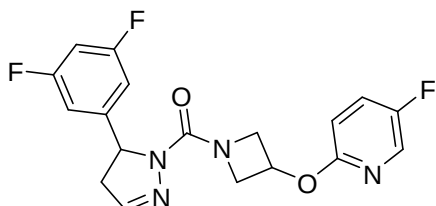
The titled compound **210** was synthesized in an analogous manner to the preparation of compound **203**. ^1H NMR (400 MHz, Chloroform- d) δ 7.79 (d, $J = 2.6$ Hz, 1H), 7.25 – 7.20 (m, 1H), 6.78-6.74 (m, 3H), 6.68 (tt, $J = 8.9, 2.3$ Hz, 1H), 5.40-5.34 (m, 1H), 5.28 (dd, $J = 12.2, 6.5$ Hz, 1H), 4.61-4.53 (m, 2H), 4.32 – 4.14 (m, 2H), 3.34 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.69 (ddd, $J = 18.5, 6.5, 1.7$ Hz, 1H).

[0271] Compound 211: (3-((6-(benzyloxy)pyridin-3-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



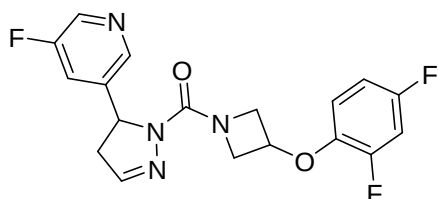
The titled compound **211** was synthesized in an analogous manner to the preparation of compound **203**. ^1H NMR (400 MHz, Chloroform- d) δ 7.63 – 7.59 (m, 1H), 7.47 – 7.25 (m, 5H), 7.15 (dd, $J = 8.9, 3.0$ Hz, 1H), 6.78 – 6.71 (m, 4H), 6.67 (tt, $J = 8.9, 2.3$ Hz, 1H), 5.30 (s, 2H), 5.25 (dd, $J = 12.2, 6.5$ Hz, 1H), 4.90-4.85 (m, 1H), 4.57 – 4.38 (m, 2H), 4.28 – 4.11 (m, 2H), 3.33 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.68 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H).

[0272] Compound 212: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoropyridin-2-yl)oxy)azetidin-1-yl)methanone SN-038-91



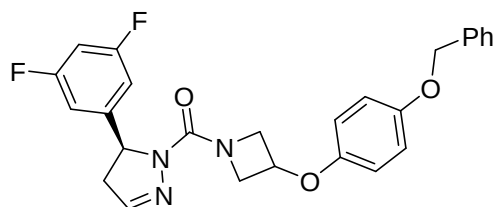
The titled compound **212** was synthesized in an analogous manner to the preparation of compound **203**. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 3.1 Hz, 1H), 7.36 (ddd, *J* = 9.0, 7.5, 3.1 Hz, 1H), 6.79 – 6.72 (m, 3H), 6.68 (tt, *J* = 8.9, 2.3 Hz, 1H), 5.33 – 5.24 (m, 2H), 4.55 (dd, *J* = 21.6, 11.6 Hz, 2H), 4.17 (ddd, *J* = 20.8, 10.6, 4.3 Hz, 2H), 3.34 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.68 (ddd, *J* = 18.5, 6.6, 1.7 Hz, 1H).

[0273] Compound 213: (3-(2,4-difluorophenoxy)130zetidine-1-yl)(5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



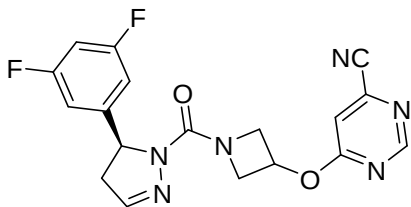
The titled compound **213** was prepared from 3-(2,4-difluorophenoxy)azetidine trifluoroacetic acid salt and (5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according to the procedure outlined for compound **203**. LC-MS (*m/z*) 377.5 (*M*+*H*⁺). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.47 (brs, 2H), 7.48 (d, *J* = 8.2 Hz, 1H), 6.93 – 6.83 (m, 2H), 6.78 (dddd, *J* = 9.3, 7.8, 3.0, 1.6 Hz, 1H), 6.69 (td, *J* = 9.0, 5.2 Hz, 1H), 5.40 (dd, *J* = 12.1, 6.2 Hz, 1H), 4.99 – 4.87 (m, 2H), 4.37 – 4.17 (m, 2H), 3.45 (dd, *J* = 18.5, 12.0 Hz, 1H), 2.77 (dd, *J* = 18.6, 6.4 Hz, 1H).

[0274] Compound 214: (S)-(3-(4-(benzyloxy)phenoxy)azetidine-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



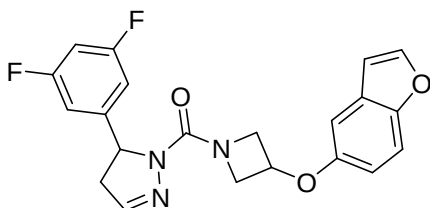
The titled compound **214** was synthesized in an analogous manner to the preparation of compound **203**. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.27 (m, 5H), 6.92 – 6.86 (m, 2H), 6.78 – 6.63 (m, 6H), 5.26 (dd, *J* = 12.6, 6.9 Hz, 1H), 4.99 (s, 2H), 4.87–4.82 (m, 1H), 4.56 – 4.40 (m, 2H), 4.26 – 4.10 (m, 2H), 3.32 (dd, *J* = 18.6, 12.1 Hz, 1H), 2.72 – 2.62 (m, 1H).

[0275] Compound 215 : (S)-6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)130zetidine-3-yl)oxy)pyrimidine-4-carbonitrile



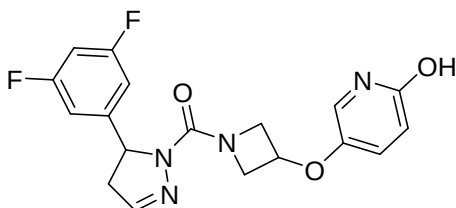
The titled compound **215** was synthesized in an analogous manner to the preparation of compound **203**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.83 (d, *J* = 1.2 Hz, 1H), 7.17 (d, *J* = 1.1 Hz, 1H), 6.79 (s, 1H), 6.77 – 6.73 (m, 2H), 6.70 (tt, *J* = 8.8, 2.3 Hz, 1H), 5.49-5.44 (m, 1H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.63-4.55 (m, 2H), 4.29 – 4.13 (m, 2H), 3.36 (dd, *J* = 18.7, 11.9 Hz, 1H), 2.70 (dd, *J* = 18.6, 6.1 Hz, 1H).

[0276] Compound 216: (3-(benzofuran-5-yloxy)1,3-zetidine-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **216** was synthesized in an analogous manner to the preparation of compound **203**. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 2.2 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 6.85 – 6.73 (m, 5H), 6.71 – 6.65 (m, 2H), 5.28 (dd, *J* = 12.1, 6.4 Hz, 1H), 4.98 – 4.95 (m, 1H), 4.64 – 4.48 (m, 2H), 4.26 (dd, *J* = 31.3, 9.6 Hz, 2H), 3.34 (dd, *J* = 18.6, 12.0 Hz, 1H), 2.69 (dd, *J* = 18.5, 6.2 Hz, 1H).

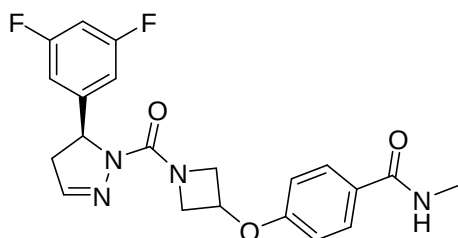
[0277] Compound 217: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((6-hydroxypyridin-3-yl)oxy)1,3-zetidine-1-yl)methanone



The titled compound **217** was prepared from 5-(1,3-zetidine-3-yloxy)1,3-zetidin-2-ol trifluoroacetic acid salt and (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according to the procedure outlined for compound **203**. LC-MS (*m/z*) 375.5 (*M*+*H*⁺) ¹H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.28 (m, 1H), 6.78 (t, *J* = 1.7 Hz, 1H), 6.76-6.74 (m, 3H), 6.73 – 6.66 (m, 1H), 6.60 (d, *J* = 9.8 Hz, 1H), 5.26 (dd, *J* =

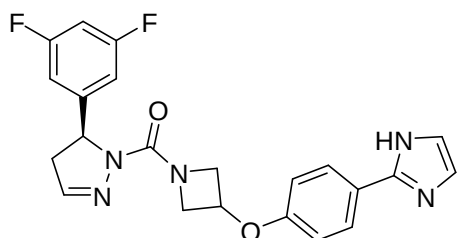
12.2, 6.5 Hz, 1H), 4.72 – 4.65 (m, 1H), 4.51-4.42 (m, 2H), 4.22 – 4.18 (m, 2H), 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.69 (ddd, $J = 18.6, 6.5, 1.8$ Hz, 1H).

[0278] Compound 218: (S)-4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-N-methylbenzamide



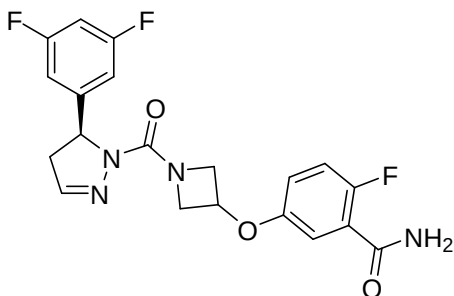
The titled compound **218** was synthesized in an analogous manner to the preparation of compound **203**. ^1H NMR (400 MHz, Chloroform- d) δ 7.72 – 7.69 (m, 2H), 6.77 – 6.64 (m, 5H), 6.05 (s, 1H), 5.25 (dd, $J = 12.0, 8.0$ Hz, 1H), 4.97-4.92 (m, 1H), 4.57 – 4.53 (m, 2H), 4.25 – 4.15 (m, 2H), 3.37-3.29 (m, 1H), 2.98 (d, $J = 4.0$ Hz, 3H), 2.71-2.64 (m, 1H).

[0279] Compound 219: (S)-3-(4-(1H-imidazol-2-yl)phenoxy)azetidin-1-yl(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



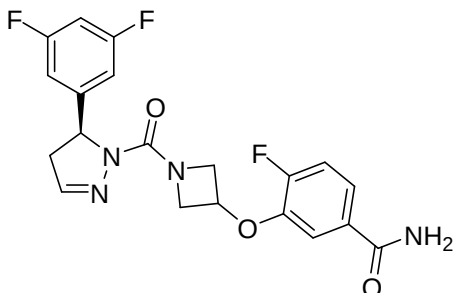
The titled compound **219** was synthesized in an analogous manner to the preparation of compound **203**. ^1H NMR (400 MHz, Chloroform- d) δ 7.89 (d, $J = 8.0$ Hz, 2H), 7.08 (s, 2H), 6.80 (s, 1H), 6.71 – 6.61 (m, 5H), 5.23 (s, 1H), 4.86 (s, 1H), 4.49 (s, 2H), 4.11 (s, 2H), 3.34 (dd, $J = 20.0, 12.0$ Hz, 1H), 2.67 (dd, $J = 16.0, 4.0$ Hz, 1H).

[0280] Compound 220 : (S)-4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2-fluorobenzamide



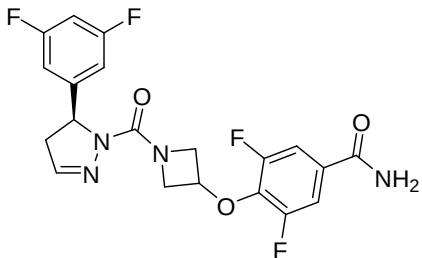
The titled compound **220** was synthesized in an analogous manner to the preparation of compound **203**. ^1H NMR (400 MHz, Chloroform- d) δ 7.39 – 7.36 (m, 1H), 7.10 – 7.05 (m, 1H), 6.99 – 6.94 (m, 1H), 6.76 – 6.65 (m, 4H), 5.93 (s, 1H), 5.26 (dd, J = 12.0, 8.0, 1H), 4.96-4.91(m, 1H), 4.56 (dd, J = 16.0, 8.0 Hz, 2H), 4.18 (dd, J = 24.0, 8.0 Hz, 2H), 3.33 (dd, J = 20.0,12.0Hz, 1H), 2.70– 2.64(m, 1H), 2.08 (s, 2H). LC-MS (m/z) 419.4($M+H^+$)

[0281] Compound 221: (S)-4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-3-fluorobenzamide



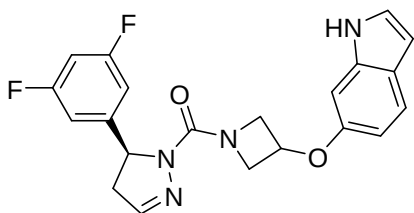
The titled compound **221** was synthesized in an analogous manner to the preparation of compound **203** ^1H NMR (400 MHz, DMSO- d_6) δ 8.00 (s, 1H), 7.53-7.49 (m, 1H), 7.43 (s, 1H), 7.34 – 7.29 (m, 2H), 7.11 – 7.05 (m, 1H), 6.99 (s, 1H), 6.91 – 6.86 (m, 2H), 5.21 (dd, J = 12.0, 4.0 Hz, 1H), 5.09 (s, 1H), 4.48 (s, 2H), 3.98 (s, 2H), 3.40 – 3.34 (m, 1H), 2.64-2.57 (m, 1H). LC-MS (m/z) 419.4($M+H^+$)

[0282] Compound 222: (S)-4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-3,5-difluorobenzamide



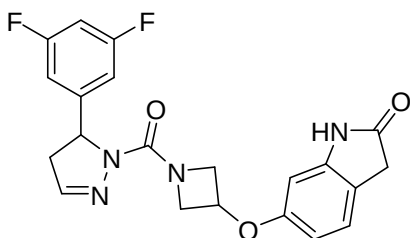
The titled compound **222** was synthesized in an analogous manner to the preparation of compound **203** ¹H NMR (400 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 8.0 Hz, 2H), 6.77 – 6.65 (m, 4H), 5.26 (dd, *J* = 12.0, 8.0 Hz, 1H), 5.07 (s, 1H), 4.48-4.44 (m, 2H), 4.37-4.26 (m, 2H), 3.34 (dd, *J* = 16.0, 12.0 Hz, 1H), 2.68 (dd, *J* = 20.0, 8.0 Hz, 1H), 1.79 (s, 2H).

[0283] Compound 223 : (S)-(3-((1H-indol-6-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



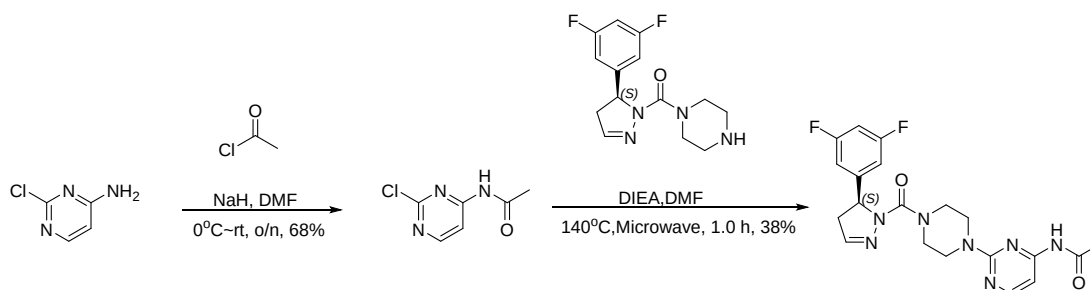
The titled compound **223** was synthesized in an analogous manner to the preparation of compound **203** ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.40 (d, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 4.0 Hz, 1H), 6.91 (s, 1H), 6.83 – 6.78 (m, 3H), 6.72 (d, *J* = 2.4 Hz, 1H), 6.61 (dd, *J* = 12.0, 4.0 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.2 Hz, 1H), 5.26 (dd, *J* = 12.0, 8.0 Hz, 1H), 5.01-4.96 (m, 1H), 4.56 (s, 2H), 4.14 (dd, *J* = 28.0, 12.0 Hz, 2H), 3.44-3.36 (m, 1H), 2.71-2.64 (m, 1H).

[0284] Compound 224: 6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)indolin-2-one



The titled compound **224** was synthesized in an analogous manner to the preparation of compound **203**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.28 (s, 1H), 7.11 – 7.05 (m, 2H), 6.98 (s, 1H), 6.90 – 6.85 (m, 2H), 6.33 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.26 (d, *J* = 4.0 Hz, 1H), 5.20 (dd, *J* = 12.0, 8.0 Hz, 1H), 4.93 (s, 1H), 4.40 (s, 2H), 3.90 (s, 2H), 3.36-3.29 (m, 3H), 2.64-2.57 (m, 1H).

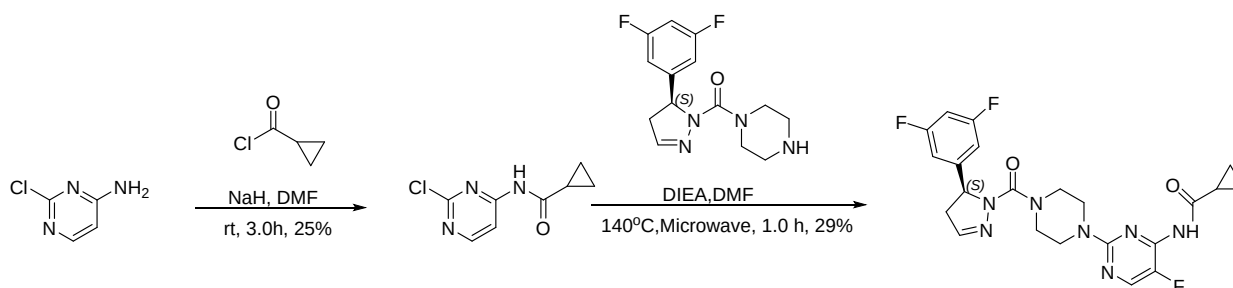
[0285] Compound 225 : (S)-N-(2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)pyrimidin-4-yl)acetamide



[0286] Step 1 : 2-chloropyrimidin-4-amine (3.0 g, 23.16 mmol) was dissolved in 30 ml of dry DMF. NaH(1.38g, 34.80 mmol) was added to the above solution under nitrogen at 0 degrees C. The mixture was stirred for 0.5 hour at 0 degrees C. To this was added acetyl chloride (2.16g, 27.69 mmol), the mixture was stirred for another 1 overnight at room temperature. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give N-(2-chloropyrimidin-4-yl)acetamide (2.7 g, 68%) as a white solid. (ES, m/s): 172.1[M+H]⁺

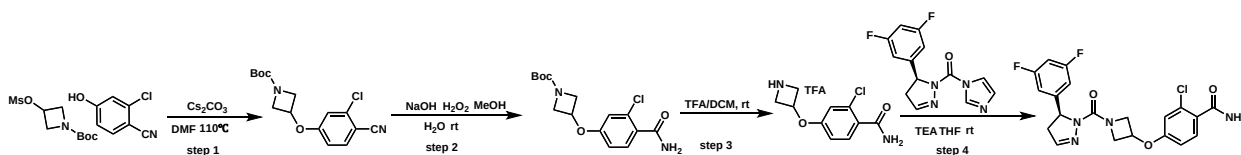
[0287] Step 2: (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(piperazin-1-yl)methanone(1.0 g, 3.39 mmol) was dissolved in 15 ml of dry DMF. N-(2-chloropyrimidin-4-yl)acetamide (1.2 g, 6.97 mmol) and DIEA(870 mg, 6.74 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 1.0 hour at 140 degrees C under microwave. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound 225 (950 mg, 38%) as a white solid. (ES, m/s): 430.4[M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.35 (s, 1H), 8.22 (d, *J* = 5.6 Hz, 1H), 7.25 (d, *J* = 5.6 Hz, 1H), 7.14 – 7.05 (m, 2H), 7.01 – 6.94 (m, 2H), 5.28 – 5.20 (m, 1H), 3.79 – 3.45 (m, 8H), 3.39 – 3.33 (m, 1H), 2.67 – 2.58 (m, 1H), 2.08 (s, 3H).

[0288] Compound 226 : (S)-N-(2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)-5-fluoropyrimidin-4-yl)cyclopropanecarboxamide



The titled compound **226** as a white solid (62 mg, 29 %) was prepared from (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone and N-(2-chloropyrimidin-4-yl)cyclopropanecarboxamide according to the procedure outlined for compound **225** (ES, m/s): 474.4 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.59 (brs, 1H), 8.32 (d, *J* = 2.8 Hz, 1H), 7.13 – 7.05 (m, 2H), 6.99 – 6.96 (m, 2H), 5.24 (dd, *J* = 11.6, 10.0 Hz, 1H), 3.73 – 3.66 (m, 2H), 3.65–3.57 (m, 4H), 3.54 – 3.46 (m, 2H), 3.38 – 3.32 (m, 1H), 2.65–2.59 (m, 1H), 2.03 – 1.94 (m, 1H), 0.87 – 0.77 (m, 4H).

[0289] Compound 227 : 2-chloro-4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)benzamide



[0290] Step1: Synthesis of tert-butyl 3-(4-chloro-3-cyanophenoxy)azetidine-1-carboxylate

To a solution of tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate (200 mg, 0.80 mmol, 1.0 equivs) and 2-chloro-4-hydroxybenzonitrile (134 mg, 0.88 mmol, 1.1 equivs) in anhydrous N,N-dimethylformamide (10 mL), Caesium carbonate (777.9 mg, 3.0 equivs) was added at room temperature. The reaction mixture was heated to 110°C and stirred for 4 hours. The volatiles were removed *in vacuo* and the residue was suspended in dichloromethane, saturated. The organic layer was washed with water and brine respectively. Then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt, 4/1) to give tert-butyl 3-(3-chloro-4-cyanophenoxy)azetidine-1-carboxylate (190 mg, yield 77.3%) as a pale yellow solid. LC-MS (m/z) 254.4, 252.5 [M-tBu]⁺.

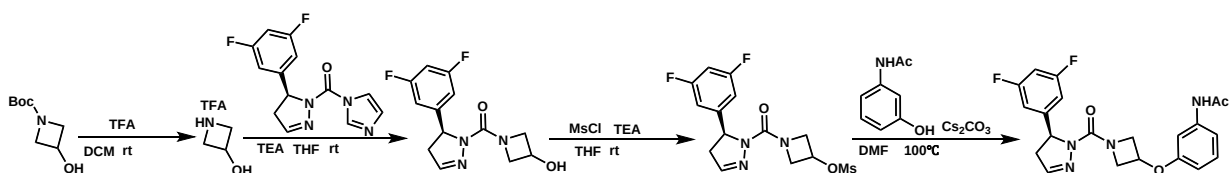
[0291] Step2: Synthesis of tert-butyl 3-(3-carbamoyl-4-chlorophenoxy)azetidine-1-carboxylate

A solution of tert-butyl 3-(3-chloro-4-cyanophenoxy)azetidine-1-carboxylate (190 mg, 0.615 mmol, 1.0 equivs) in methanol (6 mL) was treated with 30 percent hydrogen peroxide aqueous (75 mL) and 1M aqueous sodium hydroxide solution (3 mL), the reaction mixture was stirred for overnight at 40°C. quenched with sat. NaHCO₃(aq) and the volatiles were removed *in vacuo* and the residue was suspended in dichloromethane, filtered and the filtrate was concentrated and used in next step directly without further purification. LC-MS (m/z) 327.5 [M+H]⁺

[0292] Step3: Synthesis of 5-(azetidin-3-yloxy)-2-chlorobenzamide--2,2,2-trifluoroacetaldehyde. To a solution of tert-butyl 3-(3-carbamoyl-4-chlorophenoxy)azetidine-1-carboxylate in dichloromethane, trifluoroacetic was added dropwise at 0°C. then the mixture was refluxed for 2 hours. The volatiles was removed *in vacuo* and the residue was used in next step directly without further purification. LC-MS (m/z) 227.6 [M+H]⁺.

[0293] Step4: Synthesis of (S)-2-chloro-5-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)benzamide (intermediate 4). To a solution of 4-(azetidin-3-yloxy)-2-chlorobenzamide--2,2,2-trifluoroacetaldehyde (1/1) in tetrahydrofuran (10 mL), triethylamine was added dropwise slowly at 0°C. afterwards, (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (50 mg, 0.18mmol, 1.0 equivs) was added at room temperature. The reaction mixture was stirred for overnight at the same temperature. The reaction was quenched with sat.NH₄Cl(aq), extracted with dichloromethane 3 times. The organic layer was combined and washed with water, sat.NaHCO₃(aq), and brine respectively. Then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/methanol, 20/1) to give 28.6 mg of 2-chloro-4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)benzamide **227** as white powder. yield:36.3%. ¹H NMR (400 MHz, Chloroform-d) δ 7.48 – 7.06 (m, 2H), 7.04 – 6.43 (m, 5H), 5.31 (s, 1H), 4.97 (s, 1H), 4.62 (s, 2H), 4.18 (s, 2H), 3.31-3.42 (m, 1H), 2.81 – 2.62 (m, 1H). LC-MS (m/z) 435.5, 437.4 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-d) δ 7.48 – 7.06 (m, 2H), 7.04 – 6.43 (m, 5H), 5.31 (s, 1H), 4.97 (s, 1H), 4.62 (s, 2H), 4.18 (s, 2H), 3.31-3.42 (m, 1H), 2.81 – 2.62 (m, 1H). LC-MS (m/z) 435.3 [M+H]⁺.

[0294] Compound 228: N-(3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)phenyl)acetamide



[0295] Step1: Synthesis of 2,2,2-trifluoroacetaldehyde--azetidin-3-ol (1/1) (intermediate 1)

To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (4.0g, 23.09mmol) in dichloromethane, trifluoroacetic was added dropwise at 0°C. then the mixture was refluxed for 2 hours. The volatiles was removed *in vacuo* and the residue was used in next step directly without further purification. LC-MS (m/z) 74.2 [M+H]⁺.

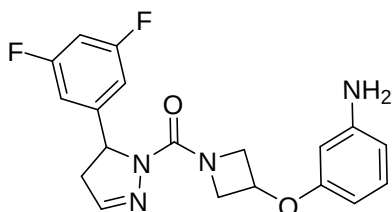
[0296] Step2: Synthesis of (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-hydroxyazetidin-1-yl)methanone. To a solution of 2,2,2-trifluoroacetaldehyde--azetidin-3-ol (1/1) in tetrahydrofuran (100 mL), triethylamine was added dropwise slowly at 0°C. afterwards, (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (1.05g, 0.18mmol, 1.3 equivs) was added at room temperature. The reaction mixture was stirred for overnight at the same temperature. The reaction was quenched with sat.NH₄Cl(aq), extracted with dichloromethane 3 times. The organic layer was combined and washed with water, sat.NaHCO₃(aq), and brine respectively. Then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt, 1/1) to give 2.05g of (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-hydroxyazetidin-1-yl)methanone as pale yellow solid in a yield of 71.9%. LC-MS (m/z) 283.6 [M+H]⁺.

[0297] Step3: Synthesis of (S)-1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl methanesulfonate (intermediate 3). To a solution of (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-hydroxyazetidin-1-yl)methanone (1.55g, 5.51mmol, 1.0 equivs) in tetrahydrofuran (60 mL), triethylamine was added dropwise slowly at room temperature. afterwards, methanesulfonyl chloride (469mmL, 6.06mmol, 1.1 equivs) was added dropwise at 0°C. The reaction mixture was stirred for overnight at the same temperature. The reaction was quenched with sat.NaHCO₃(aq), extracted with dichloromethane 2 times. The organic layer was combined and washed with water, sat.NH₄Cl(aq), and brine respectively. Then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt, 1/1) to give 1.9g of (S)-1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl methanesulfonate as pale yellow solid in a yield of 95.9%. LC-MS (m/z) 360.6 [M+H]⁺.

[0298] Step 4: Synthesis of (S)-N-(3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)phenyl)acetamide (37) .To a solution of (S)-1-(5-

(3,5-difluorophenyl)-4,5-dihydro-1*H*-pyrazole-1-carbonyl)azetidin-3-yl methanesulfonate (200 mg, 0.56mmol, 1.0 equivs) and N-(3-hydroxyphenyl)acetamide (92.6 mg, 0.61 mmol, 1.1 equivs) in anhydrous N,N-dimethylformamide (5 mL), Caesium carbonate (544 mg, 1.67mmol, 3.0 equivs) was added at room temperature. The reaction mixture was heated to 100°C and stirred for 4 hours. The volatiles was removed *in vacuo* and the residue was suspension in dichloromethane, sat The organic layer was washed with water and brine respectively. Then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt, 1/1) to give 48 mg of N-(3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1*H*-pyrazole-1-carbonyl)azetidin-3-yl)oxy)phenyl)acetamide **228** as pale yellow powder, in a yield of 20.8%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.23 – 7.17 (m, 2H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 9.3 Hz, 3H), 6.68 (t, *J* = 8.8 Hz, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 5.26 (d, *J* = 9.6 Hz, 1H), 4.93 (s, 1H), 4.54 (s, 2H), 4.21 (dd, *J* = 27.9, 9.4 Hz, 2H), 3.34 (d, *J* = 6.6 Hz, 1H), 2.69 (d, *J* = 18.7 Hz, 1H), 2.18 (s, 3H). LC-MS (*m/z*) 415.5 [M+H]⁺.

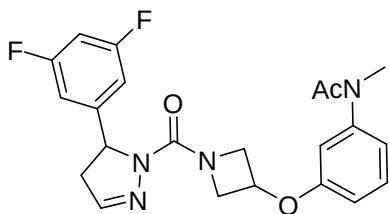
[0299] Compound 229 : (3-(3-aminophenoxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)methanone



To a solution of N-(3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1*H*-pyrazole-1-carbonyl)azetidin-3-yl)oxy)phenyl)acetamide (16 mg, 0.038mmol, 1.0 equivs) in methanol (2 mL), a solution of hydrochloric acid in ethyl acetate was added at room temperature. The reaction mixture was heated to 69°C and stirred for 2 hours. The reaction was quenched with sat. NaHCO₃(aq), The volatiles was removed *in vacuo* and the residue was suspension in dichloromethane, The organic layer was washed with water and brine respectively. Then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt, 1/5) to give 2.7 mg of (3-(3-aminophenoxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)methanone **229** as pale white solid. In a yield of 18.8%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.06 (s, 1H), 6.93 – 6.61 (m, 4H), 6.38 (s, 1H), 6.28 – 6.09 (m, 2H), 5.27

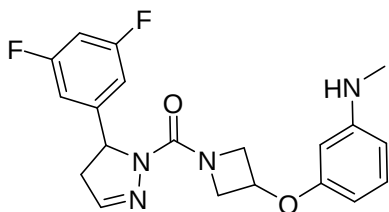
(s, 1H), 4.88 (s, 1H), 4.51 (s, 2H), 4.20 (d, $J = 28.6$ Hz, 2H), 3.51 (d, $J = 22.0$ Hz, 1H), 2.68 (d, $J = 18.9$ Hz, 1H). LC-MS (m/z) 373.1 $[M+H]^+$.

[0300] Compound 230 : N-(3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)phenyl)-N-methylacetamide



To a solution of N-(3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)phenyl)acetamide (20 mg, 0.048mmol, 1.0 equivs) in super dry tetrahydrofuran (5 mL), sodium hydride (60% in mineral oil) was added as several portions at 0°C with ice-water bath. Then iodomethane was added dropwise at room temperature. The mixture was stirred for overnight at the same temperature. The reaction was quenched with sat.NH₄Cl(aq), extracted with dichloromethane 3 times. The organic layer was combined and washed with water, sat.NaHCO₃(aq), and brine respectively. Then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt, 1/3) to give 16 mg of N-(3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)phenyl)-N-methylacetamide as yellow oil in a yield of 77.4%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.32 (t, $J = 8.0$ Hz, 2H), 6.74 (m, 6H), 5.28 (dd, $J = 12.2, 6.5$ Hz, 1H), 4.92 (dd, $J = 7.6, 3.2$ Hz, 1H), 4.56 (s, 2H), 4.35 – 4.11 (m, 2H), 3.35 (ddd, $J = 18.5, 12.2, 1.8$ Hz, 1H), 3.26 (s, 3H), 2.79 – 2.65 (m, 1H), 1.90 (s, 3H). LC-MS (m/z) 429.3 $[M+H]^+$.

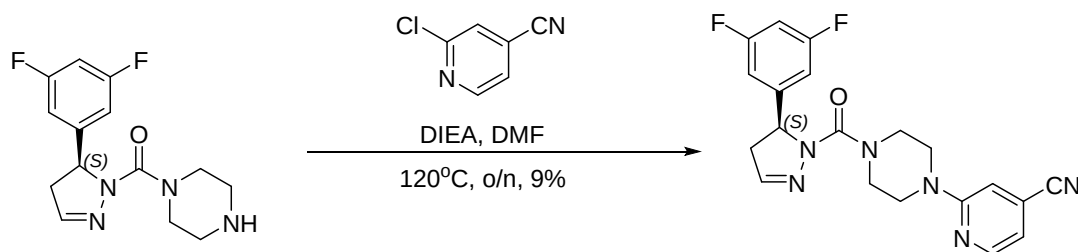
[0301] Compound 231: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(3-(methylamino)phenoxy)azetidin-1-yl)methanone



To a solution of N-(3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)phenyl)-N-methylacetamide (10 mg, 0.023 mmol) in methanol (5 mL), a solution of 1M aqueous sodium hydroxide (15 mL) was added at room

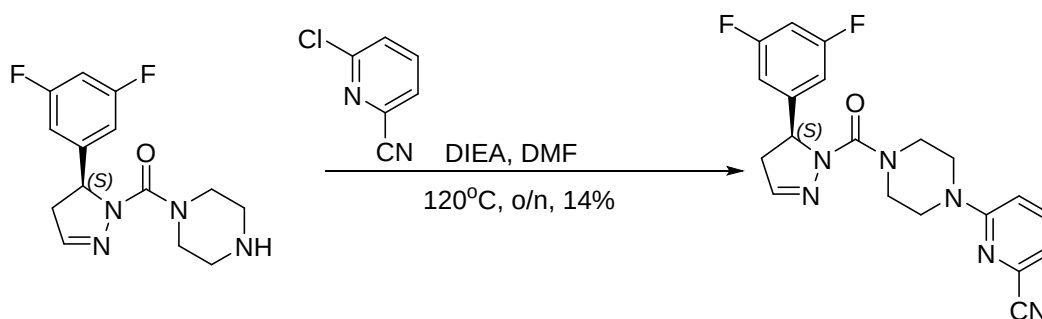
temperature. The reaction mixture was heated to 100°C and stirred for 4 hours. The mixture was cooled to room temperature and extracted with dichloromethane 3 times. The organic layer was combined and washed with water, sat. NaHCO₃(aq), and brine respectively. Then dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by preparation thin liquid chromatography (development by ethyl acetate) to give 3.5 mg of (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(3-(methylamino)phenoxy)azetidin-1-yl)methanone as pale yellow powder in a yield of 38.88%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.09 (t, *J* = 8.0 Hz, 1H), 6.75 (dd, *J* = 8.3, 2.1 Hz, 3H), 6.72 – 6.64 (m, 1H), 6.33 (d, *J* = 8.0 Hz, 1H), 6.13 (m, 2H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 5.00 – 4.86 (m, 1H), 4.52 (s, 2H), 4.22 (d, *J* = 30.9 Hz, 2H), 3.41 – 3.26 (m, 1H), 2.84 (s, 3H), 2.68 (ddd, *J* = 18.4, 6.5, 1.7 Hz, 1H). LC-MS (*m/z*) 387.4 [M+H]⁺.

[0302] Compound 232 : (S)-2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)isonicotinonitrile



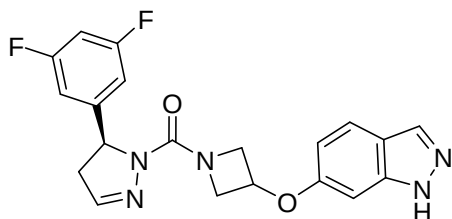
(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(piperazin-1-yl)methanone (213 mg, 0.72 mmol) was dissolved in 5 ml of dry DMF. 2-chloroisonicotinonitrile (100mg, 0.72 mmol) and DIEA(188 mg, 1.45 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 1 overnight at 120 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **232** (26 mg, 9%) as a yellow solid. (ES, *m/s*): 397.4[M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.46–8.40 (m, 1H), 7.47–7.41 (m, 2H), 7.28–7.19 (m, 2H), 7.17–7.08 (m, 2H), 5.43–5.33 (m, 1H), 3.84–3.63 (m, 8H), 3.52 – 3.47(m, 1H), 2.83 – 2.71(m, 1H).

[0303] Compound 233 : (S)-6-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)picolinonitrile



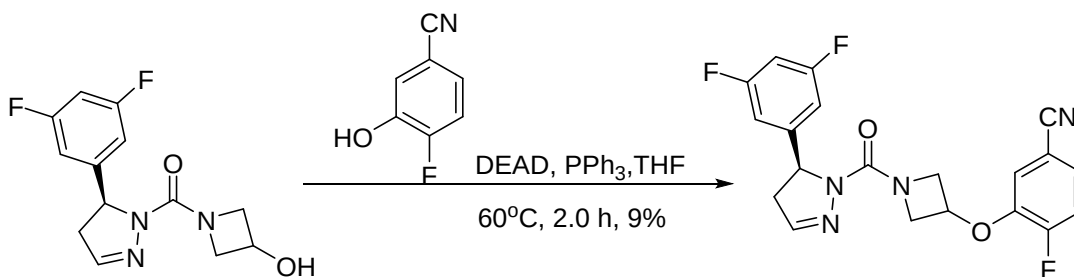
(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(piperazin-1-yl)methanone (213 mg, 0.72 mmol) was dissolved in 5 ml of dry DMF. 6-chloropicolinonitrile (100mg, 0.72 mmol) and DIEA(188 mg, 1.45 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 1 overnight at 120 degrees C. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **233**(40 mg, 14%) as a yellow solid. (ES, m/s): 397.4 $[\text{M}+\text{H}]^+$ ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.73–7.68 (m, 1H), 7.23 – 7.15 (m, 2H), 7.13 – 7.06 (m, 2H), 7.02–6.95 (m, 2H), 5.32 – 5.16 (m, 1H), 3.70 – 3.45 (m, 8H), 3.39 – 3.33 (m, 1H), 2.68 – 2.59 (m, 1H).

[0304] Compound 234 : (S)-3-((1H-indazol-6-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



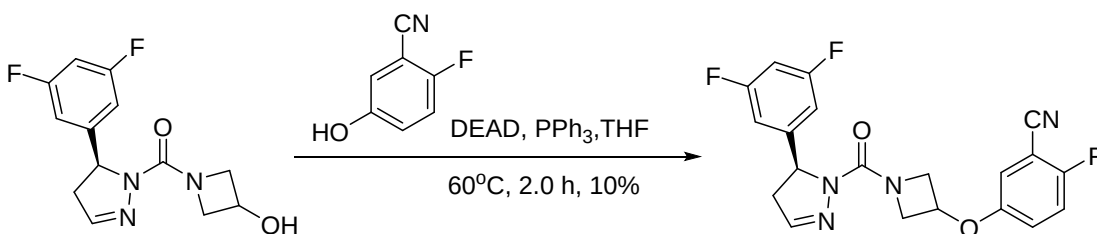
The titled compound **234** was synthesized in an analogous manner to the preparation of compound **203**. yield:11.4% ^1H NMR (400 MHz, Chloroform- d) δ 7.99 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 6.86 – 6.54 (m, 5H), 5.29 (dd, J = 12.0, 6.4 Hz, 1H), 5.06 – 4.91 (m, 1H), 4.70 – 4.52 (m, 2H), 4.35 – 4.14 (m, 2H), 3.78 – 3.68 (m, 1H), 3.40-3.30(m,1H), 2.73-2.64(m , 1H). LC-MS (m/z) 398.2($\text{M}+\text{H}^+$).

[0305] Compound 235: (S)-3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-4-fluorobenzonitrile



(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-hydroxyazetidin-1-yl)methanone (187 mg, 0.66 mmol) was dissolved in 10 ml of dry THF. DEAD (160 mg, 0.92 mmol), 4-fluoro-3-hydroxybenzonitrile (100 mg, 0.72 mmol), PPh₃ (240 mg, 0.92 mmol) was added to the above solution at room temperature. The mixture was stirred for 2.0 hour at 60 degrees C under nitrogen. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **235** (25 mg, 9 %) as a white solid. (ES, m/s): 401.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.56 – 7.51 (m, 2H), 7.50 – 7.46 (m, 1H), 7.10 (tt, *J* = 9.4, 2.4 Hz, 1H), 7.01 (t, *J* = 1.6 Hz, 1H), 6.93 – 6.87 (m, 2H), 5.23 (dd, *J* = 12.2, 6.6 Hz, 1H), 5.13 (tt, *J* = 6.6, 3.6 Hz, 1H), 4.52 (brs, 2H), 4.00 (brs, 2H), 3.42 – 3.36 (m, 1H), 2.68-2.55 (m, 1H).

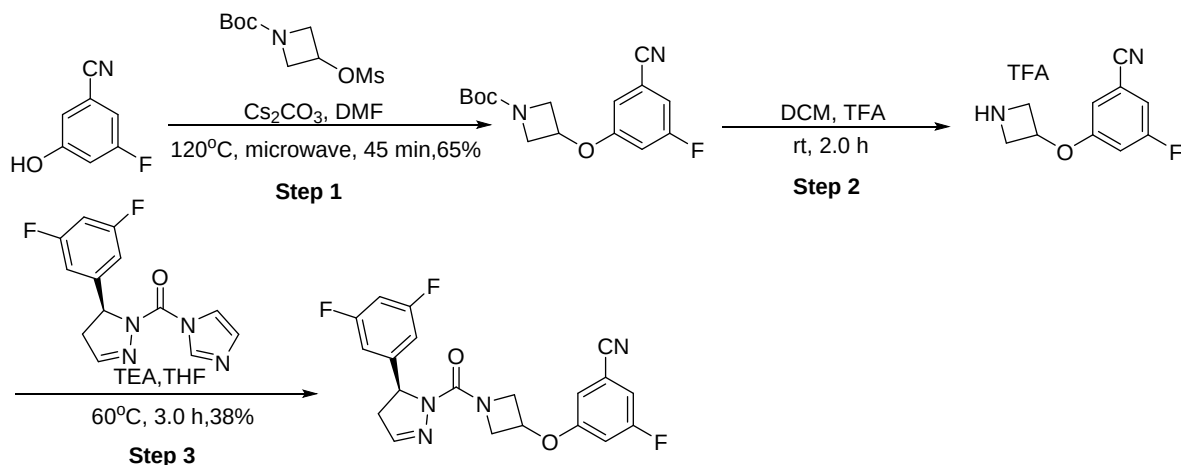
[0306] Compound 236 : (S)-5-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2-fluorobenzonitrile



(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-hydroxyazetidin-1-yl)methanone (187 mg, 0.66 mmol) was dissolved in 10 ml of dry THF. DEAD (160 mg, 0.92 mmol), 2-fluoro-5-hydroxybenzonitrile (100 mg, 0.72 mmol), PPh₃ (240 mg, 0.92 mmol) was added to the above solution at room temperature. The mixture was stirred for 2 hours at 60°C under nitrogen. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **236** (30 mg, 10 %) as a white solid. (ES, m/s): 401.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.73 – 7.61 (m, 2H), 7.56-7.48 (m, 1H), 7.37-7.28 (m, 1H), 7.23

(d, $J = 3.2$ Hz, 1H), 7.16-7.08 (m, 2H), 5.49 – 5.39 (m, 1H), 5.26 (brs, 1H), 4.72 (brs, 2H), 4.17 (brs, 2H), 3.66 – 3.57 (m, 1H), 2.91-2.81 (m, 1H).

[0307] Compound 237 : (S)-3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluorobenzonitrile



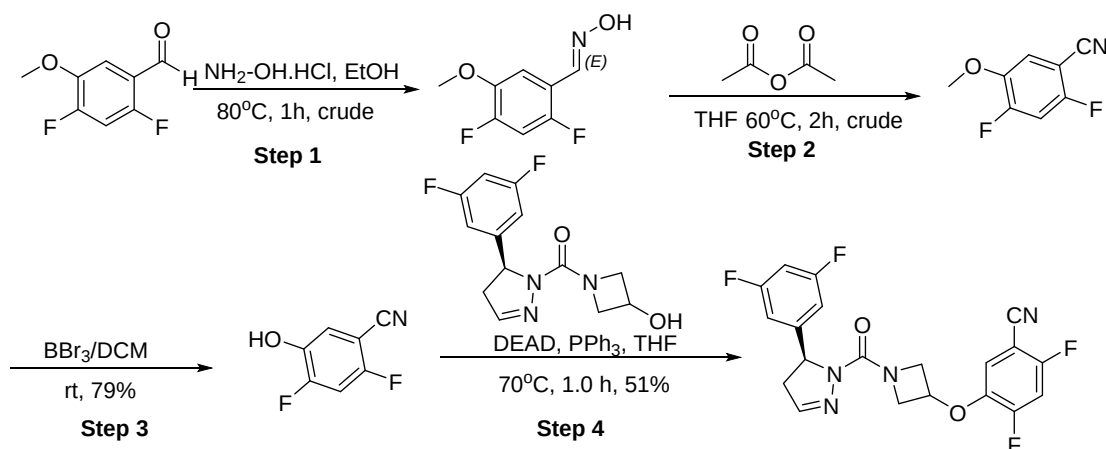
[0308] Step 1 : 3-fluoro-5-hydroxybenzonitrile(200 mg, 1.46 mmol) was dissolved in 10 ml of dry DMF. Cs_2CO_3 (958 mg, 2.92 mmol) and tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate (439 mg, 1.75 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 45 minutes at 120 degrees C under Microwave. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give tert-butyl 3-(3-cyano-5-fluorophenoxy)azetidine-1-carboxylate (280 mg, 655%) as a white solid. (ES, m/s): 293.3 $[\text{M}+\text{H}]^+$

[0309] Step 2 : tert-butyl 3-(3-cyano-5-fluorophenoxy)azetidine-1-carboxylate(280 mg, 0.96 mmol)was dissolved in 6 ml of dry DCM. TFA(2 mL) was added to the above solution at room temperature. The mixture was stirred for 2.0 hours at room temperature. The mixture was concentrated in vacuo to give 3-(azetidin-3-yloxy)-5-fluorobenzonitrile trifluoroacetate (300 mg, crude) as brown oil which was used for next step without further purification. (ES, m/s): 191.3 $[\text{M}-\text{H}]^-$

[0310] Step 3: (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone(200 mg, 0.72 mmol)was dissolved in 10 ml of dry THF and TEA(3 mL). 3-(azetidin-3-yloxy)-5-fluorobenzonitrile trifluoroacetate (300 mg ,crude) in 5 mL of THF was added to the above solution at room temperature. The mixture was stirred for 3.0 hours

at 60°C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **237** (146 mg, 38%) as a white solid. (ES, m/s): 401.0 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.46 (ddd, *J* = 8.4, 2.2, 1.2 Hz, 1H), 7.25 (t, *J* = 2.0 Hz, 1H), 7.19 (dt, *J* = 10.8, 2.4 Hz, 1H), 7.10 (tt, *J* = 9.4, 2.4 Hz, 1H), 7.01 – 6.98 (m, 1H), 6.92 – 6.85 (m, 2H), 5.22 (dd, *J* = 12.2, 6.6 Hz, 1H), 5.11-5.05 (m, 1H), 4.51 (brs, 2H), 3.94 (brs, 2H), 3.42 – 3.33 (m, 1H), 2.63 (ddd, *J* = 18.6, 6.6, 1.8 Hz, 1H).

[0311] Compound 238 : (S)-5-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2,4-difluorobenzonitrile



[0312] Step 1 : 2,4-difluoro-5-methoxybenzaldehyde(3 g, 17.44 mmol) was dissolved in 100 ml of dry EtOH. Hydroxylamine hydrochloride(2.4 g, 34.78 mmol) was added to the above solution under at room temperature. The mixture was stirred for 1.0 hour at 80 °C. The mixture was concentrated in vacuo to (E)-2,4-difluoro-5-methoxybenzaldehyde oxime (4.5 g, crude) as yellow solids, which was used for next step without further purification. (ES, m/s): 188.1 [M+H]⁺

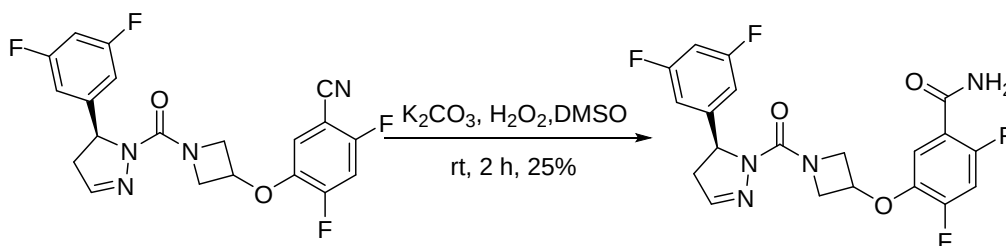
[0313] Step 2: (E)-2,4-difluoro-5-methoxybenzaldehyde oxime(4.5 g, crude) was dissolved in 60 ml of dry THF. acetic anhydride(15 mL) was added to the above solution under at room temperature. The mixture was stirred for 2.0 hours at 60°C. The mixture was concentrated in vacuo to give 2,4-difluoro-5-methoxybenzonitrile (5.0 g, crude) as yellow solids, which was used for next step without further purification. (ES, m/s): 170.1 [M+H]⁺

[0314] Step 3: 2,4-difluoro-5-methoxybenzonitrile(1.3 g, crude) was dissolved in 20 ml of dry DCM. BBr₃(35 mL, 1 N in DCM) was added to the above solution under at room temperature. The mixture was stirred for room temperature. The mixture was extracted with

EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give 2,4-difluoro-5-hydroxybenzonitrile (950 mg, 79%) as a white solid. (ES, m/s): 156.1 [M+H]⁺

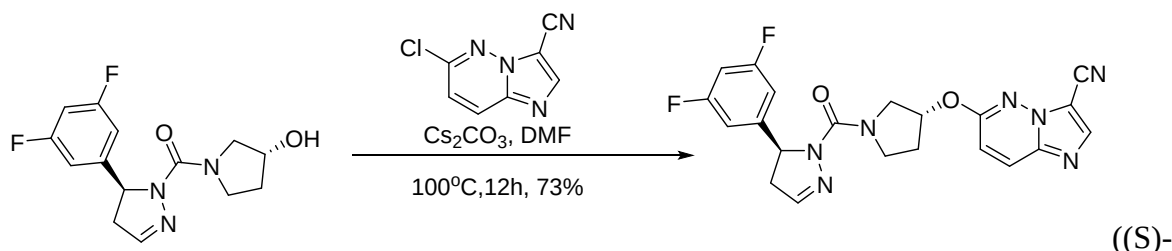
[0315] Step 4: (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-hydroxyazetidin-1-yl)methanone (1.73 g, 6.13 mmol) was dissolved in 10 ml of dry THF. DEAD (1.56 g, 9.17 mmol), 2,4-difluoro-5-hydroxybenzonitrile (950mg, 6.13 mmol), PPh₃ (2.4 g, 9.16 mmol) was added to the above solution at room temperature. The mixture was stirred for 1.0 hour at 70 °C under nitrogen. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **238** (1.3 g, 51 %) as a white solid. (ES, m/s): 419.4 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.76 (t, *J* = 10.2 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.10 (t, *J* = 9.4 Hz, 1H), 7.01 (s, 1H), 6.89 (d, *J* = 7.6 Hz, 2H), 5.22 (dd, *J* = 12.2, 6.6 Hz, 1H), 5.08 (brs, 1H), 4.50 (brs, 2H), 3.98 (brs, 2H), 3.37 (dd, *J* = 18.6, 12.2 Hz, 1H), 2.63 (dd, *J* = 18.6, 6.6 Hz, 1H).

[0316] Compound 239: (S)-5-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2,4-difluorobenzamide



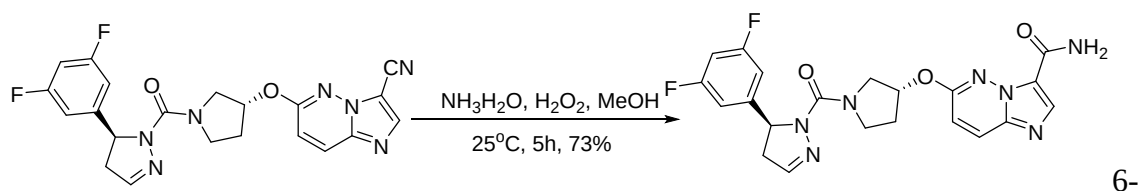
(S)-5-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2,4-difluorobenzonitrile(150 mg, 0.36 mmol) was dissolved in 6 ml of dry DMSO and H₂O₂(1.5 mL). K₂CO₃ (10 mg, 0.07 mmol) was added to the above solution at room temperature. The mixture was stirred for 2.0 hours at room temperature. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **48**(38 mg, 25%) as a white solid. (ES, m/s): 437.4 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 (brs, 2H), 7.42 (t, *J* = 10.6 Hz, 1H), 7.14 – 7.02 (m, 2H), 7.00-6.96 (m, 1H), 6.88 (d, *J* = 7.8 Hz, 2H), 5.20 (dd, *J* = 12.2, 6.6 Hz, 1H), 5.07 (brs, 1H), 4.43 (brs, 2H), 3.97 (brs, 2H), 3.40 – 3.33 (m, 1H), 2.60 (dd, *J* = 18.6, 6.6 Hz, 1H).

[0317] Compound 240 : 6-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)imidazo[1,2-b]pyridazine-3-carbonitrile



5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl) ((R)-3-hydroxypyrrolidin-1-yl)methanone (180 mg, 1.2 mmol) was dissolved in 6 ml of dry DMF. CS_2CO_3 (652 mg, 2.0 mmol) and 6-chloroimidazo[1,2-b]pyridazine-3-carbonitrile (300 mg, 1 mmol) were added to the above solution at room temperature. The mixture was stirred for 12 hour at 100 degrees C. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **240** (320 mg, 73%) as a white solid. (ES, m/s): 438.4 $[\text{M}+\text{H}]^+$ ^1H NMR (400 MHz, Chloroform- d) δ 8.10 (s, 1H), 7.94 (d, J = 9.7 Hz, 1H), 6.91 (d, J = 9.6 Hz, 1H), 6.84 – 6.76 (m, 3H), 6.68 (m, 1H), 5.67 (t, J = 4.2 Hz, 1H), 5.32 (dd, J = 12.0, 9.1 Hz, 1H), 4.08 (dd, J = 13.6, 4.3 Hz, 1H), 3.91 – 3.80 (m, 2H), 3.73 (t, J = 9.9 Hz, 1H), 3.33 (m, 1H), 2.68 (m, 1H), 2.39 – 2.17 (m, 2H).

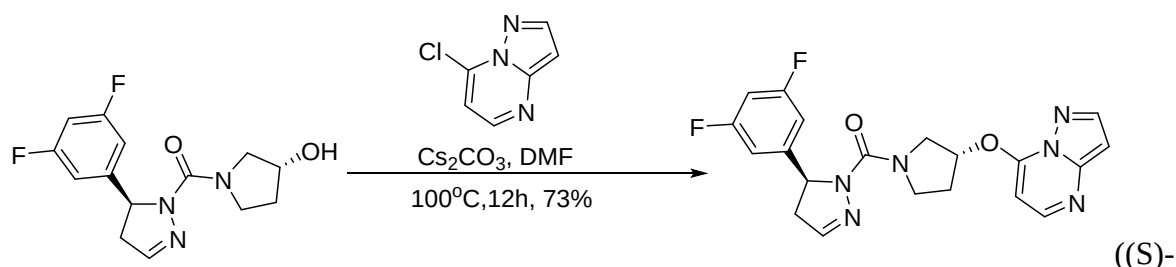
[0318] Compound 241: 6-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)imidazo[1,2-b]pyridazine-3-carboxamide



(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)imidazo[1,2-b]pyridazine-3-carbonitrile (40 mg, 0.092 mmol) was dissolved in 6 ml of dry MeOH. aqueous ammonia (25 ul) and hydrogen peroxide (25 ul) were added to the above solution at room temperature. The mixture was stirred for 5 hour at 25 degrees C. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **241** (10

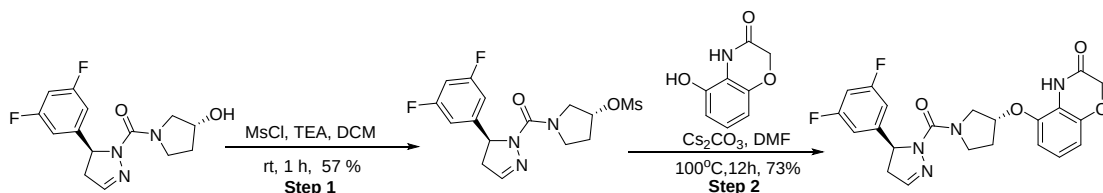
mg, 24%) as a white solid. (ES, m/s): 438.4[M+H]⁺ ¹H NMR (400 MHz, Chloroform-*d*) δ 8.37 (s, 1H), 8.01 (d, *J* = 9.7 Hz, 1H), 6.86 (d, *J* = 9.7 Hz, 1H), 6.82 – 6.78 (m, 3H), 6.69 (tt, *J* = 8.8, 2.3 Hz, 1H), 5.97 (s, 1H), 5.46 (t, *J* = 4.4 Hz, 1H), 5.31 (dd, *J* = 12.0, 9.2 Hz, 1H), 4.08 (dd, *J* = 13.4, 4.3 Hz, 1H), 3.96 – 3.85 (m, 2H), 3.78 (t, *J* = 10.0 Hz, 1H), 3.34 (ddd, *J* = 18.5, 12.0, 1.8 Hz, 1H), 2.69 (ddd, *J* = 18.4, 9.2, 1.6 Hz, 1H), 2.45 – 2.35 (m, 1H), 2.30 – 2.16 (m, 1H).

[0319] Compound 242: ((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((R)-3-(pyrazolo[1,5-a]pyrimidin-7-yloxy)pyrrolidin-1-yl)methanone



5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((R)-3-hydroxypyrrolidin-1-yl)methanone (100 mg, 0.339 mmol) was dissolved in 6 ml of dry DMF. Cs₂CO₃ (260 mg, 0.68 mmol) and 7-chloropyrazolo[1,5-a]pyrimidine (62.24 mg, 0.4068 mmol) were added to the above solution at room temperature. The mixture was stirred for 12 hour at 100 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **242** (8.6 mg, 6.1%) as a white solid. (ES, m/s): 413.4[M+H]⁺ ¹H NMR (400 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 8.17 (d, *J* = 2.3 Hz, 1H), 6.83 – 6.65 (m, 5H), 6.22 (d, *J* = 4.7 Hz, 1H), 5.39 – 5.22 (m, 2H), 4.22 – 3.83 (m, 4H), 3.33 (dd, *J* = 18.5, 11.9 Hz, 1H), 2.68 (dd, *J* = 18.4, 8.6 Hz, 1H), 2.58 – 2.44 (m, 2H), 2.33 (m, 1H).

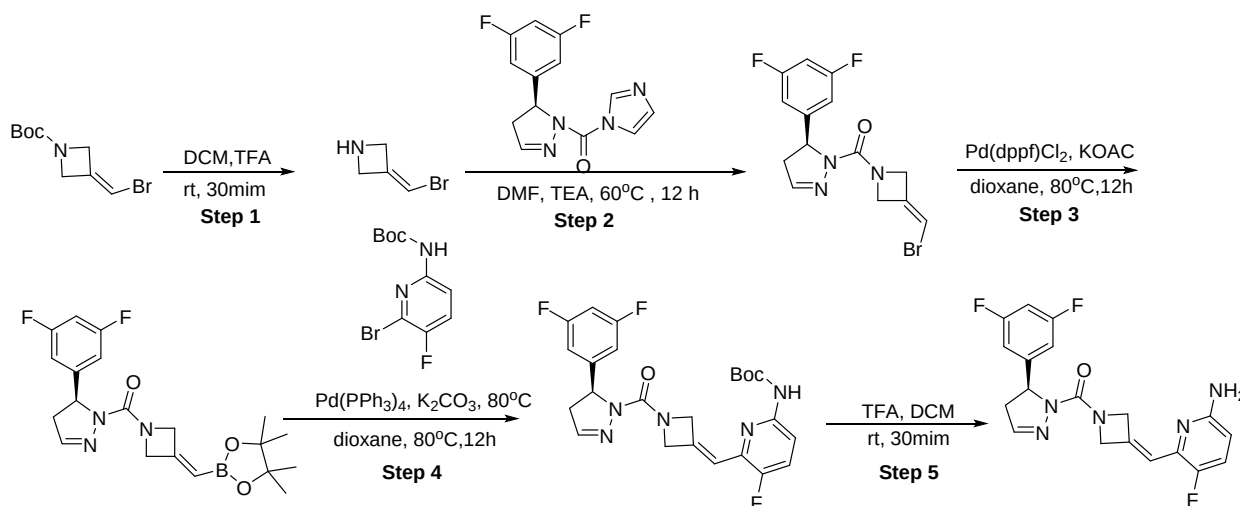
[0320] Compound 243 : 5-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl) pyrrolidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-3(4H)-one



[0321] Step 1: ((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((R)-3-hydroxypyrrolidin-1-yl)methanone (200 mg, 0.68 mmol) was dissolved in 4 ml of dry DCM. TEA (150 mg, 1.10 mmol) and MsCl (386 mg, 1.36 mmol) were added to the above solution at room temperature. The mixture was stirred for 1.0 hour at room temperature. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give (R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl methanesulfonate (260 mg, crude) as a yellow solid. (ES, m/s): 374.4 $[\text{M}+\text{H}]^+$

[0322] Step 2 : (R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl methanesulfonate (100 mg, 0.27 mmol) was dissolved in 4 ml of dry DMF. CS_2CO_3 (260 mg, 0.68 mmol) and 5-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one (36.9 mg, 0.23 mmol) were added to the above solution at room temperature. The mixture was stirred for 12 hours at 100 degrees C. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **243** (8.6 mg, 6.1%) as a white solid. (ES, m/s): 443.1 $[\text{M}+\text{H}]^+$
 ^1H NMR (400 MHz, Chloroform- d) δ 8.03 (s, 1H), 6.98 – 6.44 (m, 7H), 5.30 (ddd, J = 11.3, 7.6, 3.0 Hz, 1H), 4.94 (s, 1H), 4.58 (d, J = 3.1 Hz, 2H), 4.09 – 3.80 (m, 3H), 3.67 (q, J = 8.3 Hz, 1H), 3.31 (m, 1H), 2.66 (dd, J = 18.3, 7.8 Hz, 1H), 2.19 (s, 2H).

[0323] Compound 244: tert-butyl (S)-6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)-5-fluoropyridin-2-yl)carbamate



[0324] Step 1 : tert-butyl 3-(bromomethylene)azetidine-1-carboxylate (3 g, 12.1 mmol) was dissolved in 40 ml of dry DCM, TFA (12 ml) were added to the above solution at

room temperature . The mixture was stirred for 30 min at room temperature. The mixture was concentrated in vacuo to give 3-(bromomethylene)azetidine (2.8 g, crude) as a yeollow oil. (ES, m/s): 148.0 [M+H]⁺

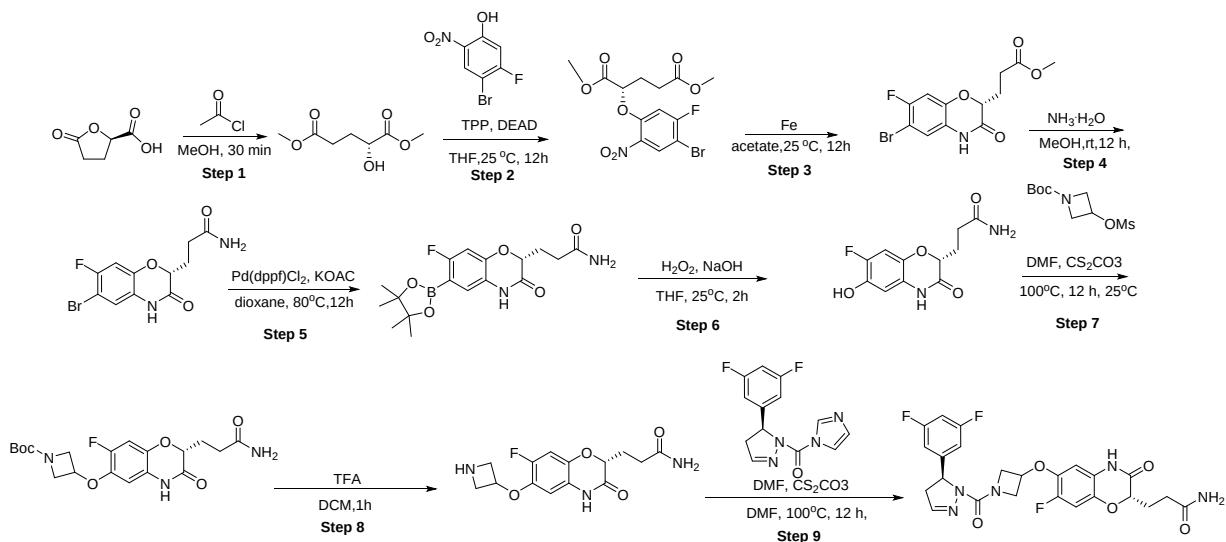
[0325] Step 2 : 3-(bromomethylene)azetidine (2.8 g, crude, 12.1 mmol) was dissolved in 30 ml of dry THF.TEA(5 ml) and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (3.7 g, 13.3 mmol) were added to the above solution at room temperature. The mixture was stirred for 12 hour at 60 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give (S)-(3-(bromomethylene) azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (2.1 mg, 49%) as a white solid. (ES, m/s): 356.4 [M+H]⁺

[0326] Step 3: (S)-(3-(bromomethylene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (200 mg, 0.56 mmol) was dissolved in 3 ml of dry dioxane. (Pd(dppf)Cl₂ (40 mg, 0.17 mmol), KOAc (166 mg, 1.68 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (215 mg, 1.12 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 12.0 hour at 80 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)azetidin-1-yl)methanone (2.1 mg, 49%) as a white solid. (ES, m/s): 404.2 [M+H]⁺

[0327] Step 4: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)azetidin-1-yl)methanone (200 mg, 0.50 mmol) was dissolved in 3 ml of dry dioxane. (Pd(PPh₃)₄ (72 mg, 0.07 mmol), K₂CO₃ (170 mg, 1.5 mmol) and(S)-(3-(bromomethylene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (120 mg, 0.41 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 12.0 hour at 80 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give (S)-(3-((6-amino-3-fluoropyridin-2-yl)methylene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (80 mg, 40%) as a white solid. (ES, m/s): 488.2 [M+H]⁺

[0328] Step 5: (S)-3-((6-amino-3-fluoropyridin-2-yl)methylene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (80 mg, 0.16 mmol) was dissolved in 2 ml of dry DCM. TFA (0.6 ml) was added to the above solution at room temperature. The mixture was stirred for 30 min at room temperature. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **244** (17 mg, 20.7%) as a white solid. (ES, m/s): 391.1 [M+H]⁺ ¹H NMR (400 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 7.61 (t, *J* = 8.7 Hz, 1H), 6.96 (d, *J* = 9.5 Hz, 1H), 6.86 (d, *J* = 1.7 Hz, 1H), 6.79 (s, 1H), 6.77 – 6.62 (m, 2H), 5.25 (dd, *J* = 12.1, 6.0 Hz, 1H), 5.08 (s, 2H), 4.49 (dd, *J* = 17.6, 5.5 Hz, 1H), 4.32 (d, *J* = 17.3 Hz, 1H), 3.48 (dd, *J* = 18.7, 12.1 Hz, 1H), 2.83 – 2.73 (m, 1H).

[0329] Compound 245 : 3-((S)-6-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanamide:



[0330] Step 1: (R)-5-oxotetrahydrofuran-2-carboxylic acid (5 g, 3.84 mmol) was dissolved in 40 ml of dry MeOH. acetyl chloride (1 ml) was added to the above solution at room temperature. The mixture was stirred for 12.0 hour at 60 degrees C. The mixture was concentrated in vacuo to give dimethyl (R)-2-hydroxypentanedioate (2.8 g, crude) as a colorless oil. (ES, m/s): 177.2 [M+H]⁺

[0331] Step 2 : dimethyl (R)-2-hydroxypentanedioate (1.38g, 7.83 mmol) was dissolved in 10 ml of dry THF. DEAD(1.82 ml, 9.4 mmol), 4-bromo-5-fluoro-2-nitrophenol (2.22 g, 9.4 mmol), PPh₃ (3.15 g, 12.03 mmol) was added to the above solution at room temperature.

The mixture was stirred for 12.0 hour at 25 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to (R)-3-(7-fluoro-6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanamide (2.1 g, 57 %) as a white solid. (ES, m/s): 395.2 [M+H]⁺

[0332] Step 3 : (R)-3-(7-fluoro-6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanamide (500 mg, 1.27 mmol) was dissolved in 10 ml of dry acetate. Fe (71 mg, 12.6mmol) was added to the above solution at room temperature. The mixture was stirred for 12.0 hour at 25 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give methyl (R)-3-(6-bromo-7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanoate (360 mg, 86%) as a white solid. (ES, m/s): 333.2 [M+H]⁺

[0333] Step 4 : methyl (R)-3-(6-bromo-7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanoate (300 mg, 0.9 mmol) was dissolved in 2 ml of MeOH and Ammonia (2 mL, 15%) were added to the above solution at room temperature. The mixture was stirred for 12.0 hour at 60 degrees C. The mixture was concentrated in vacuo to give (R)-3-(6-bromo-7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanamide (100 mg, 35%) as a white solid. (ES, m/s): 318.1 [M+H]⁺

[0334] Step 5 : (R)-3-(6-bromo-7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanamide (50 mg, 0.157 mmol) was dissolved in 1 ml of dry dioxane. (Pd(dppf)Cl₂ (11 mg, 0.015 mmol), KOAc (46 mg, 0.48 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (80 mg, 0.31mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 12.0 hour at 100 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give (R)-3-(7-fluoro-3-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanamide (52 mg, crude) as a white solid. (ES, m/s): 365.2 [M+H]⁺

[0335] Step 6 : (R)-3-(7-fluoro-3-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanamide (52 mg, crude) was dissolved in 1 ml of

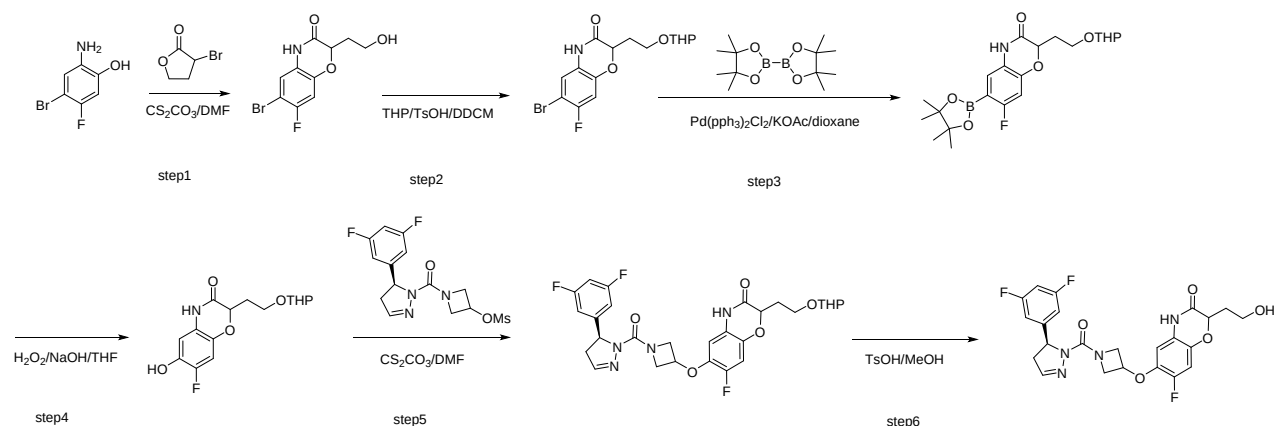
THF and NaOH(aq)(0.2 mL, 1 N). H₂O₂(0.1 mL, 30% in H₂O) was added to the above solution at room temperature. The mixture was stirred for 1.0 hours at 0 degrees C slowly warmed to room temperature. The pH of resulting mixture was adjusted to 3-4 with HCl(aq, 1N). The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give (R)-3-(7-fluoro-6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl) propanamide (30 mg, crude) as a white solid. (ES, m/s): 255.2[M+H]⁺

[0336] Step 7 : (R)-3-(7-fluoro-6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanamide (30 mg, crude) was dissolved in 1 ml of dry DMF. CS₂CO₃(60 mg, 0.24 mmol) and tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate (65 mg, 0.2 mmol) were added to the above solution at room temperature. The mixture was stirred for 12 hour at 100 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give tert-butyl (R)-3-((2-(3-amino-3-oxopropyl)-7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)azetidine-1-carboxylate (39 mg, crude) as a oil.

[0337] Step 8 : tert-butyl (R)-3-((2-(3-amino-3-oxopropyl)-7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)azetidine-1-carboxylate (39 mg, crude) was dissolved in 1 ml of dry DCM. TFA(0.3 ml) were added to the above solution at room temperature. The mixture was stirred for 1.0 hour at room temperature. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give (R)-3-(6-(azetidin-3-yloxy)-7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanamide (45 mg, crude) as a brown solid. (ES, m/s): 410.2 [M+H]⁺

[0338] Step 9 : (R)-3-(6-(azetidin-3-yloxy)-7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)propanamide (39 mg, crude) was dissolved in 1 ml of dry THF and 0.1 mL of TEA. (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (32.2 mg, 0.12) in 5 mL of THF was added to the above solution at room temperature. The mixture was stirred for 1 overnight at 60 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **245** (2.4 mg) as a white solid. (ES, m/s): 518.2 [M+H]⁺

[0339] Compound 246 : 6-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-7-fluoro-2-(2-hydroxyethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one



[0340] Step 1: 2-amino-4-bromo-5-fluorophenol (4.4 g, 21.4 mmol), 3-bromodihydrofuran-2(3H)-one (3.9 g, 23.5 mmol) and CS_2CO_3 (10.5 g, 32.1 mmol) were dissolved in DMF (70 mL). The mixture was stirred at 80°C for 15 hrs. The solvent was evaporated to dryness and purified by flash chromatography (PE/EA=2/1) to give the product as a yellow solid (4.5 g). Yield 72.6 % LC-MS (m/z) 291.2 ($\text{M}+\text{H}^+$)

[0341] Step 2: THP (2.67 g, 31 mmol) was added to the solution of 6-bromo-7-fluoro-2-(2-(2-hydroxyethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (4.5 g, 15.5 mmol) and TsOH (1.33 g, 7.75 mmol) in DCM (80 mL). The mixture was stirred at r.t. overnight. The solvent was evaporated to dryness and purified by flash chromatography (PE/EA=8/1) to give the product as a yellow oil (8.0 g). Yield 100 % LC-MS (m/z) 374.2 ($\text{M}+\text{H}^+$)

[0342] Step 3: 6-bromo-7-fluoro-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (8.0 g, 21.4 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (10.9 g, 42.9 mmol), $\text{Pd}(\text{pPh}_3)_2\text{Cl}_2$ (1.5 g, 2.14 mmol) and KOAc (6.3 g, 64.3 mmol) were added to dioxane (100 mL) under N_2 atmosphere. The mixture was stirred at 100°C for 3 hrs. The solvent was evaporated to dryness and used for next step directly. LC-MS (m/z) 422.2 ($\text{M}+\text{H}^+$).

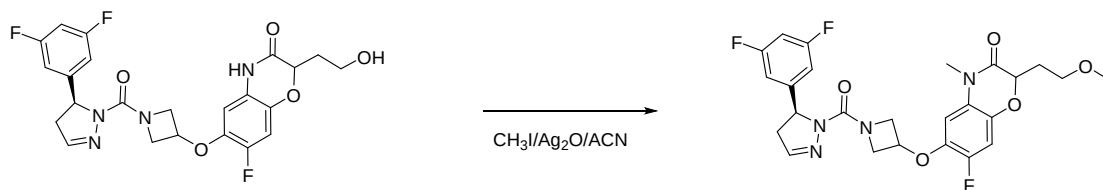
[0343] Step 4: H_2O_2 (4 mL) was added to the solution of 7-fluoro-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one (4.5 g, 10.7 mmol) and 1N NaOH (4 mL) in THF (60 mL) at 0°C . The mixture was stirred at r.t. for 2 hrs. Then 1N HCl was added to adjust pH=6 and

EA added to extracted. The solvent was evaporated to dryness and purified by flash chromatography (PE/EA=5/1) to give the product as a yellow solid (1.7 g). Yield 51.5 % LC-MS (m/z) 334.2 (M+Na⁺).

[0344] Step 5: 7-fluoro-6-hydroxy-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (710 mg, 2.28 mmol), (S)-1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl methanesulfonate (820 mg, 2.28 mmol) and CS₂CO₃ (829 mg, 2.74 mmol) were dissolved in DMF (10 mL). The mixture was stirred at 100°C for 15 hrs. The solvent was evaporated to dryness and purified by HPLC to give the product as yellow solid (190 mg). Yield 17.3 % LC-MS (m/z) 575.3 (M+H⁺).

[0345] Step 6: TsOH (2 mg, 0.009 mmol) was added to the solution of 6-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-7-fluoro-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (50 mg, 0.087 mmol) in MeOH (2 mL). The mixture was stirred at r.t. for 1 hrs. The solvent was evaporated to dryness and purified by flash chromatography (PE/EA=1/1) to give the titled compound **246** as a white solid (40 mg). Yield 93.7 % ¹H NMR (400 MHz, Chloroform-*d*) δ 8.91 (d, *J* = 10.8 Hz, 1H), 6.81 (t, *J* = 7.6 Hz, 1H), 6.79-6.72 (m, 2H), 6.69-6.62 (m, 1H), 6.23 (d, *J* = 7.8 Hz, 1H), 5.49-5.39 (m, 1H), 4.86-4.79 (m, 1H), 4.71-4.61 (m, 1H), 4.61 – 4.43 (m, 2H), 4.41-4.33 (m, 1H), 4.20-4.08 (m, 1H), 3.91 – 3.80 (m, 2H), 3.38 (dd, *J* = 18.4, 12.0 Hz, 1H), 2.74-2.64 (m, 1H), 2.30 – 2.05 (m, 2H). LC-MS (m/z) 491.4 (M+H⁺)

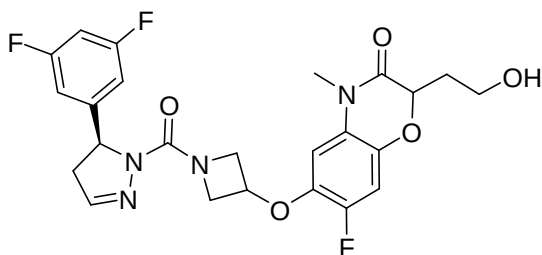
[0346] Compound 247 : 6-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-7-fluoro-2-(2-methoxyethyl)-4-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one



CH₃I (28 mg, 0.2 mmol) and Ag₂O (24 mg, 0.1 mmol) were added to the solution of 6-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-7-fluoro-2-(2-hydroxyethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (10 mg, 0.02 mmol) in CAN (2 mL). The mixture was stirred at r.t. for 24 hrs. The solvent was evaporated to dryness and purified by TLC (DCM/MeOH=25/1) to give the titled compound **247** as a

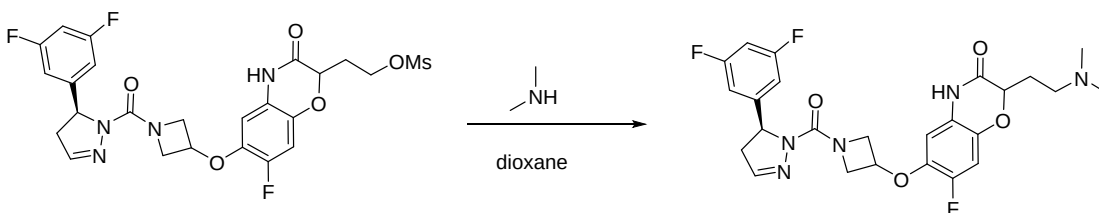
white solid 2.5 mg. Yield 25.0 %. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.91 – 6.61 (m, 5H), 6.44 (dd, J = 7.6, 1.2 Hz, 1H), 5.31 – 5.23 (m, 1H), 4.94 (t, J = 5.2 Hz, 1H), 4.66 (dd, J = 9.0, 4.2 Hz, 1H), 4.49 (d, J = 6.8 Hz, 2H), 4.33 – 4.28 (m, 1H), 4.24 (d, J = 10.4 Hz, 1H), 3.68 – 3.47 (m, 2H), 3.41-3.33 (m, 4H), 3.30 (s, 3H), 2.75-2.65 (m, 1H), 2.06-1.94 (m, 2H). LC-MS (m/z) 519.5($M+H^+$)

[0347] Compound 248 : 6-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-7-fluoro-2-(2-hydroxyethyl)-4-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one



The titled compound **248** was synthesized in an analogous manner to the preparation of compound **246**. Yield 25.0 % ^1H NMR (400 MHz, Chloroform-*d*) δ 6.86 – 6.77 (m, 2H), 6.78 – 6.58 (m, 3H), 6.46 (d, J = 7.6 Hz, 1H), 5.30 – 5.24 (m, 1H), 4.98 – 4.91 (m, 1H), 4.68 (dd, J = 7.6, 5.6 Hz, 1H), 4.49 (dd, J = 18.0, 10.4 Hz, 2H), 4.30 (t, J = 6.8 Hz, 1H), 4.23 (d, J = 9.2 Hz, 1H), 3.86 (dd, J = 6.8, 4.8 Hz, 2H), 3.42 – 3.24 (m, 4H), 2.74-2.66 (m, 1H), 2.26 – 2.13 (m, 2H). LC-MS (m/z) 505.5($M+H^+$)

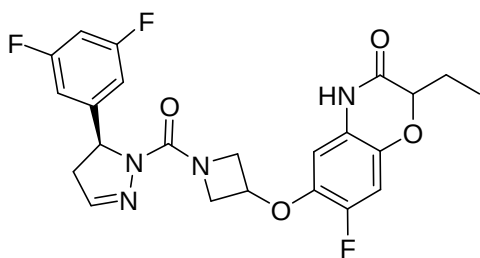
[0348] Compound 249 : 6-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2-(2-(dimethylamino)ethyl)-7-fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one



2-(6-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-7-fluoro-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-2-yl)ethyl methanesulfonate (10 mg, 0.018 mmol) and dimethylamine (4 mg, 0.09 mmol) were dissolved in dioxane (2 mL). The mixture was stirred at 90°C for 2 hrs. The solvent was evaporated to dryness and purified by HPLC to give the titled compound **249** as a white

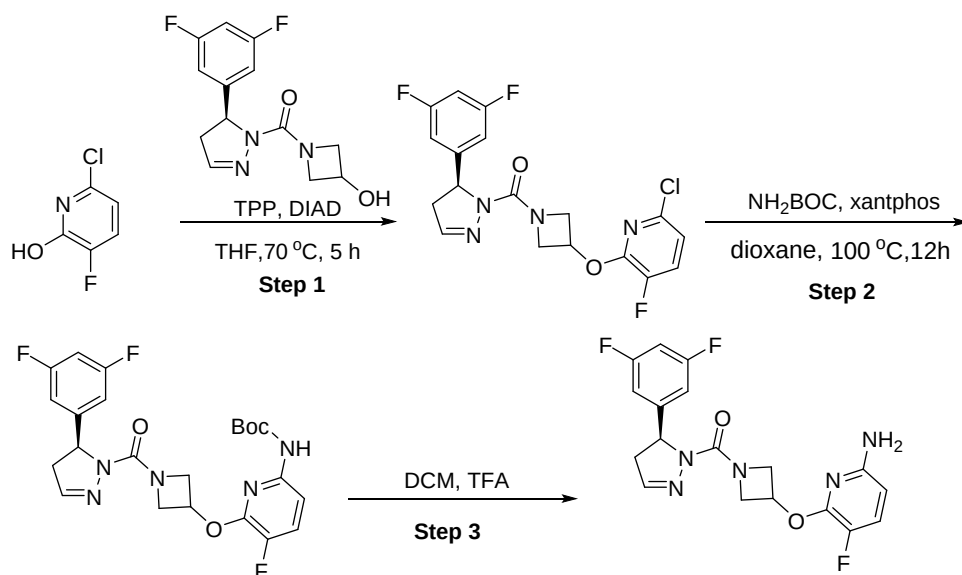
solid (2.5 mg). Yield 27.8 % ^1H NMR (400 MHz, Chloroform-*d*) δ 12.17 (s, 1H), 9.24 (s, 1H), 6.95 – 6.57 (m, 3H), 6.40-6.28 (m, 1H), 5.68 – 5.50 (m, 1H), 5.40-5.21 (m, 1H), 4.92-4.80 (m, 1H), 4.63-4.42 (m, 2H), 4.35-4.12 (m, 2H), 3.89 – 3.66 (m, 1H), 3.43-3.27 (m, 2H), 3.04-2.63 (m, 7H), 2.25 (t, J = 7.6 Hz, 1H), 2.05-1.98 (m, 1H), 1.69-1.60 (m, 1H). LC-MS (m/z) 518.5(M+H⁺)

[0349] Compound 250 : 6-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2-ethyl-7-fluoro-2H-benzo[b][1,4]oxazin-3(4H)-one



The titled compound **250** was synthesized in an analogous manner to the preparation of compound **246**. Yield 16.3 % . ^1H NMR (400 MHz, Chloroform-*d*) δ 9.12 (d, J = 20.0 Hz, 1H), 6.81 (t, J = 1.7 Hz, 1H), 6.79 – 6.69 (m, 3H), 6.69 – 6.59 (m, 1H), 6.21 (d, J = 8.0 Hz, 1H), 5.52-5.43 (m, 1H), 4.87-4.77 (m, 1H), 4.63 – 4.25 (m, 4H), 4.20 – 4.05 (m, 1H), 3.45-3.32 (m, 1H), 2.68 (m, 1H), 1.98 – 1.72 (m, 2H), 1.08 (t, J = 7.2 Hz, 3H). LC-MS (m/z) 475.4(M+H⁺)

[0350] Compound 251: (S)-3-((6-amino-3-fluoropyridin-2-yl)oxy)azetidin-1-yl(5-(3,5-difluorophenyl) -4,5-dihydro-1H-pyrazol-1-yl)methanone

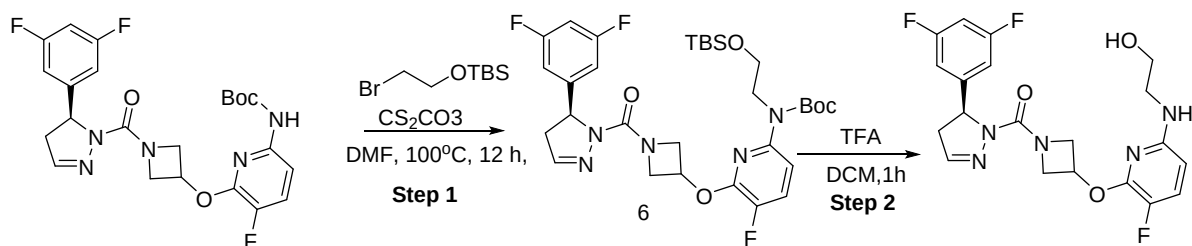


[0351] Step 1 : 6-chloro-3-fluoropyridin-2-ol (200 mg, 1.36 mmol) was dissolved in 3 ml of dry THF. DEAD(328 mg ml, 1.63mmol), (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-hydroxyazetidin-1-yl)methanone (400 mg, 1.423 mmol),PPh₃ (540 mg, 2.04 mmol) was added to the above solution at room temperature. The mixture was stirred for 12.0 hour at 25 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give (S)-(3-((6-chloro-3-fluoropyridin-2-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (300 mg, 51 %) as a white solid. (ES, m/s): 411.2 [M+H]⁺.

[0352] Step 2 : (S)-(3-((6-amino-3-fluoropyridin-2-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (300 mg, 0.72 mmol) was dissolved in 2 ml of dry dioxane. Pd₂(dba)₃(33.6 mg ml, 0.036mmol), 2-(Dicyclohexylphosphino)-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (51.4 mg, 0.108mmol), Cs₂CO₃(240 mg, 0.74 mmol)was added to the above solution at room temperature. The mixture was stirred for 3 hour at 100 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give tert-butyl (S)-(6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)carbamate (300 mg, 84 %) as a white solid. (ES, m/s): 411.2 [M+H]⁺

[0353] Step 3: tert-butyl (S)-(6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)carbamate (100 mg , 0.2mml) was dissolved in 1 ml of dry DCM. TFA(0.3 ml) were added to the above solution at room temperature. The mixture was stirred for 1.0 hour at room temperature. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give the titled compound **251** (30 mg) as a white solid. (ES, m/s): 388.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.69 (d, *J* = 8.6 Hz, 2H), 7.51 (t, *J* = 9.2 Hz, 1H), 6.82 (m, 1H), 6.66 (m, 4H), 5.37 (m, 1H), 5.22 (m, 1H), 4.86 – 4.65 (m, 2H), 3.81 (m, 4.9 Hz, 1H), 3.66 (m, 1H), 3.45 (dd, *J* = 18.7, 12.2 Hz, 1H), 2.74 (m, 1H).

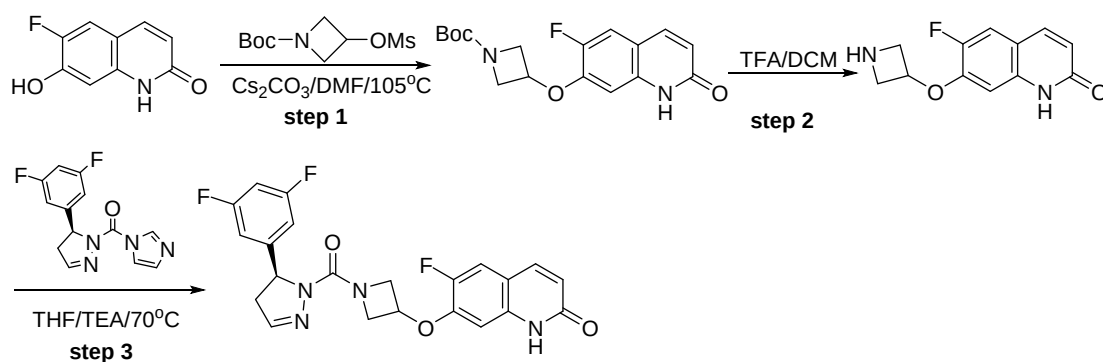
[0354] Compound 252 : (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-fluoro-6-((2-hydroxyethyl)amino)pyridin-2-yl)oxy)azetidin-1-yl)methanone



[0355] Step 1 : tert-butyl (S)-6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl) azetidin-3-yl)oxy)-5-fluoropyridin-2-yl)carbamate (200 mg , 0.4mmol) and (2-bromoethoxy)(tert-butyl)dimethylsilane(140 mg, 0.6 mmol) $\text{Pd}_2(\text{dba})_3$ (33.6 mg ml, 0.036mmol) was dissolved in 2 ml of dry DMF. Cs_2CO_3 (240 mg, 0.74 mmol) was added to the above solution at room temperature. The mixture was stirred for 12 hour at 100 degrees C. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give (S)-3-(((6-amino-3-fluoropyridin-2-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (300 mg, 84 %) as a white solid. LC-MS (ES, m/s): 650.8 [M+H].

[0356] Step 2 : (S)-3-(((6-amino-3-fluoropyridin-2-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (300 mg) was dissolved in 1 ml of dry DCM. TFA(0.3 ml) were added to the above solution at room temperature. The mixture was stirred for 1.0 hour at room temperature. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the titled compound **252** (30 mg) as a white solid. (ES, m/s): 436.4 [M+H]⁺ ¹H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.09 (td, J = 9.7, 7.7 Hz, 1H), 7.15 – 7.00 (m, 2H), 6.81 (tdd, J = 6.4, 4.4, 2.1 Hz, 2H), 6.60 (dt, J = 9.7, 2.9 Hz, 1H), 5.46 (m, 1H), 5.19 (ddd, J = 12.2, 8.9, 6.1 Hz, 1H), 4.52 (dd, J = 11.5, 9.1 Hz, 1H), 4.28 (ddd, J = 20.5, 11.5, 7.3 Hz, 1H), 3.66 – 3.50 (m, 4H), 3.40 – 3.30 (m, 2H), 2.69 (ddd, J = 18.8, 6.1, 1.8 Hz, 1H).

[0357] Compound 253 : (S)-7-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidine-3-yl)oxy)-6-fluoroquinolin-2(1H)-one

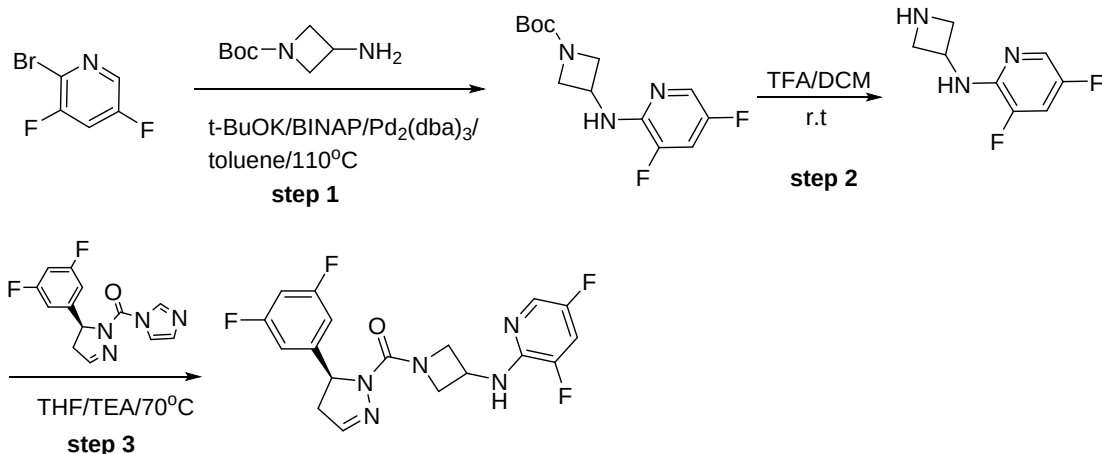


[0358] Step 1. 6-fluoro-7-hydroxyquinolin-2(1H)-one (1.2 g, 6.7 mmol) and tert-butyl 3-((methylsulfonyl)oxy)azetidine-1-carboxylate (1.85 g, 17.37 mmol) were dissolved in 15 mL DMF. Cs_2CO_3 (3.28 g, 10.067 mmol) was added. Let it stir at 105°C for 3 days. The solvent was evaporated to dryness and purified by column chromatography (100% EA) to give 1.7 g of tert-butyl 3-((6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl)oxy)azetidine-1-carboxylate as yellow solid mg of white solid. Yield: 76%. LC-MS (m/z) 335.3 $[\text{M}+\text{H}]^+$.

[0359] Step 2. 3-((6-fluoro-2-oxo-1,2-dihydroquinolin-7-yl)oxy)azetidine-1-carboxylate (24 mg, 0.072 mmol) was dissolved in 2 mL DCM. 2 mL DCM/TFA (1/1) was added slowly to the solution at 0°C. Let it stir r.t for 1h. The solvent was evaporated to dryness 7-(azetidin-3-yloxy)-6-fluoroquinolin-2(1H)-one as TFA salt, which was used for next step without further purification. LC-MS (m/z) 235.4 $[\text{M}+\text{H}]^+$.

[0360] Step 3. The above residue was dissolved in 2 mL THF. 0.2 mL of TEA and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (20 mg, 0.072 mmol) were added. The mixture was stirred at 70°C for 36 hrs. The solvent was evaporated to dryness and purified by Prep-TLC (DCM/MeOH = 15/1) to give the titled compound **253** as light-brown solid. (9 mg, 28.3% yield in two steps) ^1H NMR (400 MHz, CDCl_3) δ (ppm): δ 12.25 (brs, 1H), 7.67 (d, J = 9.6 Hz, 1H), 7.23-7.25 (m, 1H), 6.71-6.79 (m, 4H), 6.59-6.67 (m, 2H), 5.40-5.44 (m, 1H), 5.01-5.12 (m, 1H), 4.58-4.74 (m, 2H), 4.32-4.45 (m, 1H), 4.15-4.26 (m, 1H), 3.37 (dd, J = 12.0, 18.8 Hz, 1H), 2.68 (dd, J = 6.0, 18.4 Hz, 1H). LC-MS (ESI): m/z calcd for $\text{C}_{22}\text{H}_{17}\text{F}_3\text{N}_4\text{O}_3$ 442.4, found 443.5 $[\text{M}+\text{H}]^+$.

[0361] Compound 254 : (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((3-(3,5-difluoro-2-oxo-1,2-dihydroquinolin-7-yloxy)azetidin-1-yl)methanone

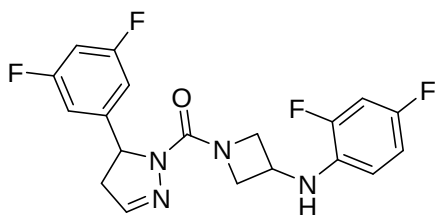


[0362] Step 1. 2-bromo-3,5-difluoropyridine(150 mg, 0.77 mmol), tert-butyl 3-aminoazetidine-1-carboxylate(146.5 mg, 0.85 mmol) and t-BuOK (111 mg, 1 mmol) were mixed in 2 mL of toluene. BINAP (70.8 mg, 0.114 mmol) and $\text{Pd}_2(\text{dba})_3$ (96.3 mg, 0.105 mmol) were added. Let it stir at 110°C under nitrogen for 16 hrs. The solvent was evaporated to dryness and purified by column chromatography (PE/EA = 2/1) to give 90 mg tert-butyl 3-((3,5-difluoropyridin-2-yl)amino)azetidine-1-carboxylate as brown oil. Yield: 41%. LC-MS (m/z) 286.3 $[\text{M}+\text{H}]^+$.

[0363] Step 2. Tert-butyl 3-((3,5-difluoropyridin-2-yl)amino)azetidine-1-carboxylate (35 mg, 0.123 mmol) was dissolved in 2 mL DCM. 2 mL DCM/TFA(1/1) was added slowly to the solution at 0°C. Let it stir r.t for 1h. The solvent was evaporated to dryness and used for next step without further purification. LC-MS (m/z) 186.2 $[\text{M}+\text{H}]^+$.

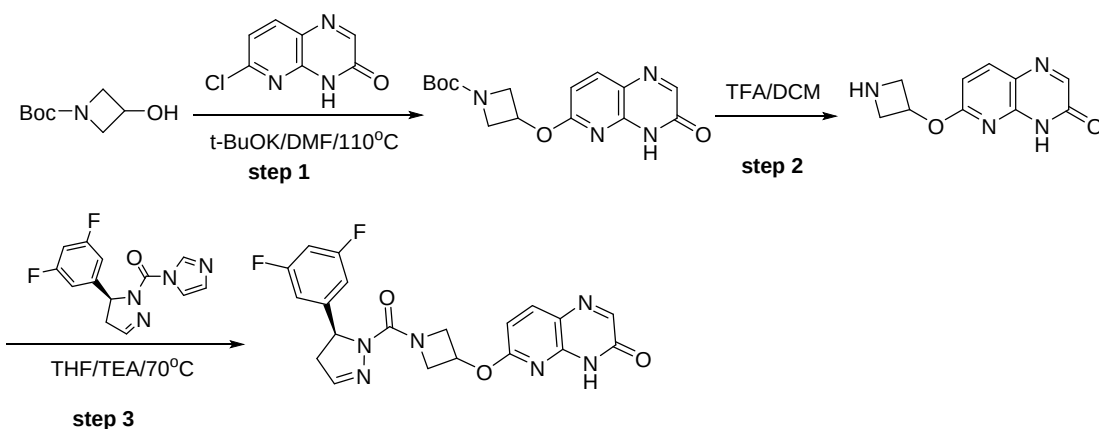
[0364] Step 3. The above residue was dissolved in 2mL THF. 0.2 mL of TEA was added. (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(1H-imidazol-1-yl)methanone (25 mg, 0.09 mmol) was added. Let it stir at 70°C for 16 hrs. The solvent was evaporated to dryness and purified by Prep-TLC (PE/EA = 1/1) to give 12 mg of the titled compound **254** as brown oil. Yield:33.8%. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.81 (dd, J = 0.8, 2.4 Hz, 1H), 7.06-7.11 (m, 1H), 6.73-6.78 (m, 3H), 6.66-6.71 (m, 1H), 5.27 (dd, J = 6.4, 12.0 Hz, 1H), 4.79-4.88 (m, 1H), 4.66-4.75 (m, 1H), 4.58 (t, J = 7.6 Hz, 1H), 4.51 (t, J = 8.0 Hz, 1H), 3.95-3.98 (m, 1H), 3.34 (dd, J = 12.4, 18.8 Hz, 1H), 2.68 (dd, J = 6.8, 18.8 Hz, 1H). LC-MS (ESI): m/z calcd for $\text{C}_{18}\text{H}_{15}\text{F}_4\text{N}_5\text{O}$ 393.4, found 394.3 $[\text{M}+\text{H}]^+$.

[0365] Compound 255 : (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((2,4-difluorophenyl) amino)azetidin-1-yl)methanone



The titled compound **255** was synthesized in an analogous manner to the preparation of compound **254**. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.55 (m, 1H), 6.85 – 6.81 (m, 2H), 6.80 – 6.73 (m, 2H), 6.70 (tt, J = 8.9, 2.3 Hz, 1H), 6.37 – 6.33 (m, 1H), 5.31 (dd, J = 12.2, 6.5 Hz, 1H), 5.05–4.81 (m, 4H), 3.38 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.72 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H). LC-MS (m/z) 393.4 $[\text{M}+\text{H}]^+$.

[0366] Compound 256: (S)-6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)pyrido[2,3-b]pyrazin-3(4H)-one

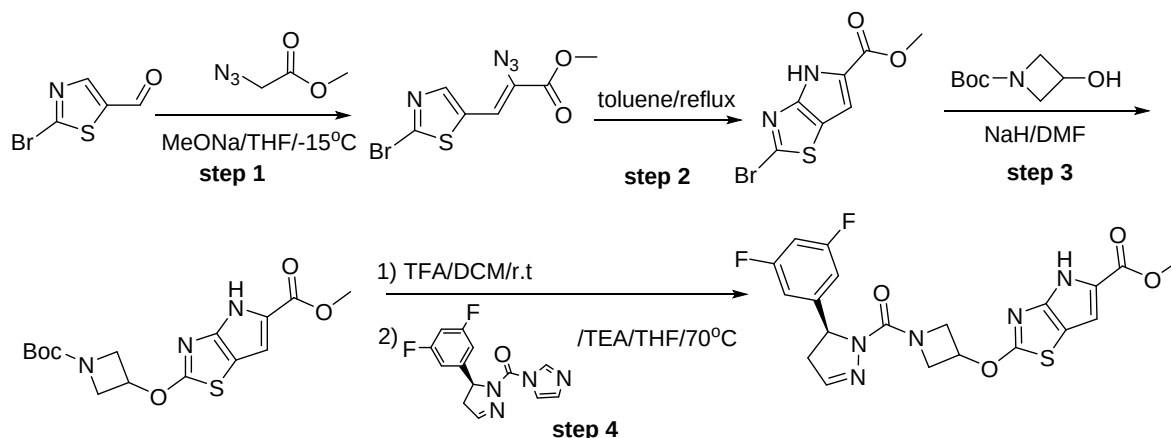


[0367] Step 1. 6-chloropyrido[2,3-b]pyrazin-3(4H)-one (80 mg, 0.44 mmol) and tert-butyl 3-hydroxyazetidine-1-carboxylate (76.3 mg, 0.44 mmol) were dissolved in 2 mL DMF. $t\text{-BuOK}$ (74 mg, 0.66 mmol) was added. Let it stir at 110°C for 16 hrs. The solvent was evaporated to dryness and purified by Prep-TLC (EA) to give 100 mg light-yellow solid. Yield: 71.5%. LC-MS (m/z): 319.2 $[\text{M}+\text{H}]^+$.

[0368] Step 2 and 3. The titled compound **256** was prepared in 12.9% yield from 6-((azetidin-3-yl)oxy)pyrido[2,3-b]pyrazin-3(4H)-one and (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl-(1H-imidazol-1-yl)methanone according to the procedure outlined for compound **62**. ^1H NMR (400 MHz, CDCl_3) δ (ppm): δ 9.63 (brs, 1H), 8.17 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 6.75–6.80 (m, 4H), 6.66 (t, J = 8.8 Hz, 1H), 5.38–5.44 (m, 1H), 5.32 (dd, J = 6.4, 12.8 Hz, 1H), 4.59–4.68 (m, 2H), 4.26–4.29 (m, 1H), 4.17–4.20 (m, 1H), 3.36

(dd, J = 12.0, 18.4 Hz, 1H), 2.69 (dd, J = 6.4, 18.8 Hz, 1H). LC-MS (ESI): m/z calcd for C₂₀H₁₆F₂N₆O₃ 426.4, found 427.5 [M+H]⁺.

[0369] Compound 257: methyl (S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-4H-pyrrolo[2,3-d]thiazole-5-carboxylate



[0370] Step 1. 11.57 mL of MeONa in MeOH solution (5.4 M, 62.5 mmol) was added slowly to the mixture of 2-bromothiazole-5-carbaldehyde (3 g, 15.625 mmol) and methyl 2-azidoacetate (7.2 g, 62.61 mmol) in 80 mL THF at -15°C. Let it stir at -15°C for 2 hrs. Sat. NH₄Cl solution was added to quench the reaction and extracted with EtOAc (100 mL X3). Dried with Na₂SO₄ and filtered. The solvent was evaporated to dryness and purified by column chromatography (PE/EA = 3/1) to give 680 mg of methyl (Z)-2-azido-3-(2-bromothiazol-5-yl)acrylate as light-yellow solid. Yield: 15%. LC-MS (m/z) 289.2 [M+H]⁺.

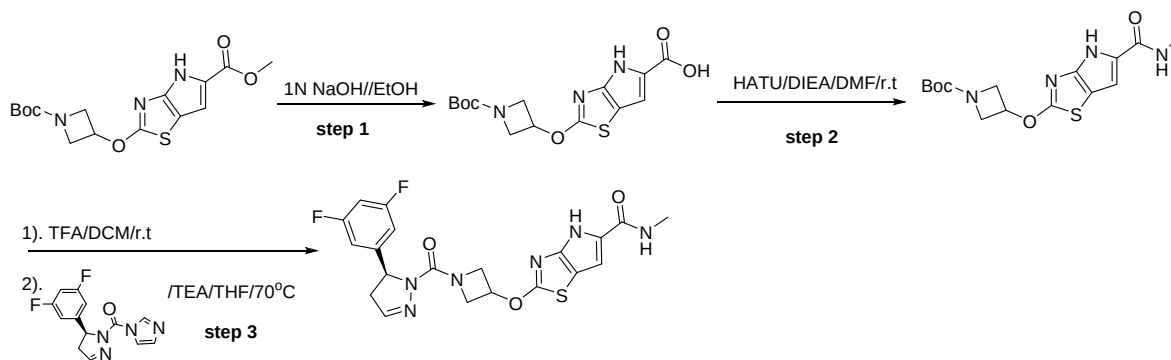
[0371] Step 2. methyl (Z)-2-azido-3-(2-bromothiazol-5-yl)acrylate (680 mg, 2.28 mmol) in 3 mL toluene was added slowly to the refluxed toluene solution. Let it stir at reflux for another 2 hrs. The solvent was evaporated to dryness and purified by column chromatography (PE/EA = 4/1) to give 585 mg methyl 2-bromo-4H-pyrrolo[2,3-d]thiazole-5-carboxylate as light-yellow solid. Yield: 98.2%. LC-MS (m/z) 261.1 [M+H]⁺.

[0372] Step 3. Tert-butyl 3-hydroxyazetidine-1-carboxylate (199.6 mg, 1.156 mmol) was dissolved in 5 mL DMF. NaH (97.1 mg, 2.43 mmol) was added in portions at r.t. Let it stir at r.t for 1 h. Then methyl 2-bromo-4H-pyrrolo[2,3-d]thiazole-5-carboxylate (150 mg, 0.577 mmol) in 3 mL DMF was added to the solution. Let it stir at 80°C for 3 h. Water was added to quench the reaction and extracted with EtOAc (20 mL X 3). The solvent was evaporated to dryness and purified by column chromatography (PE/EA = 3/1) to give 140

mg methyl 2-((1-(tert-butoxycarbonyl)azetidin-3-yl)oxy)-4H-pyrrolo[2,3-d]thiazole-5-carboxylate as light-yellow solid. Yield: 68.7%. LC-MS (m/z) 298.2 [M+H-56]⁺.

[0373] Step 4. Methyl 2-((1-(tert-butoxycarbonyl)azetidin-3-yl)oxy)-4H-pyrrolo[2,3-d]thiazole-5-carboxylate (80 mg, 0.227 mmol) was dissolved in 2 mL DCM. 2 mL DCM/TFA(1/1) was added slowly to the solution at 0°C. Let it stir r.t for 1h. The solvent was evaporated to dryness and used for next step without further purification. LC-MS (m/z) 254.1 [M+H]⁺. The above residue was dissolved in 3 mL THF. (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (65 mg, 0.235 mmol) and 0.2 mL TEA were added. Let it stir at 70°C for 32 hrs. The solvent was evaporated to dryness and purified by Prep-HPLC to give 47 mg of the titled compound **257** as a white solid. Yield: 44.9%. ¹H NMR (400 MHz, CDCl₃) δ (ppm): δ 9.19 (s, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.66-6.79 (m, 4H), 5.43-5.48 (m, 1H), 5.27 (dd, *J* = 6.4, 12.4 Hz, 1H), 4.55-4.62 (m, 2H), 4.33 (dd, *J* = 2.0, 10.4 Hz, 1H), 4.26 (dd, *J* = 2.4, 10.8 Hz, 1H), 3.88 (s, 3H), 3.35 (ddd, *J* = 1.6, 12.0, 13.6 Hz, 1H), 2.69 (ddd, *J* = 1.6, 6.4, 8.4 Hz, 1H). LC-MS (ESI): m/z calcd for C₂₀H₁₇F₂N₅O₄S 461.4, found 462.5 [M+H]⁺.

[0374] Compound 258 : (S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-N-methyl-4H-pyrrolo[2,3-d]thiazole-5-carboxamide

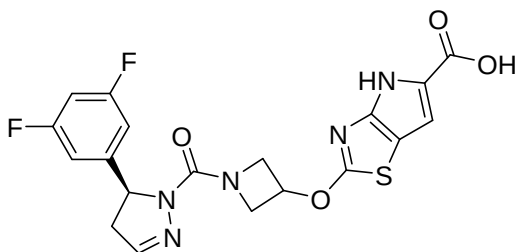


[0375] Step 1. Methyl 2-((1-(tert-butoxycarbonyl)azetidin-3-yl)oxy)-4H-pyrrolo[2,3-d]thiazole-5-carboxylate (300 mg, 0.85 mmol) was suspended in 8 mL EtOH. 6 mL 1N NaOH was added. Let it stir at 60°C under nitrogen for 7 hrs. The solvent was evaporated to dryness and adjusted to PH = 5 with 1N HCl. The amaranth solid was filtered and used for next step without further purification. Amount: 100 mg. Yield : 34.7%. LC-MS (m/z) 339.9 [M+H]⁺.

[0376] Step 2 : the product was prepared in 60% field from 2-((1-(tert-butoxycarbonyl)azetidin-3-yl)oxy)-4H-pyrrolo[2,3-d]thiazole-5-carboxylic acid and methylamine hydrochloride by coupling reaction using HATU.

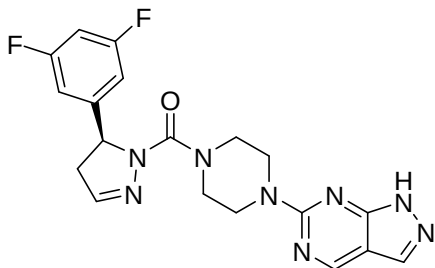
[0377] Step 3 The titled compound **67** was prepared in 25.6% yield from 2-(azetidin-3-yloxy)-N-methyl-4H-pyrrolo[2,3-d]thiazole-5-carboxamide and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according to the procedure outlined for compound **258**. ¹H NMR (400 MHz, CDCl₃) δ (ppm): δ 9.49 (brs, 1H), 6.67-6.78 (m, 4H), 6.58 (s, 1H), 5.41-5.52 (m, 1H), 5.27 (dd, J = 5.6, 12.0 Hz, 1H), 4.51-4.64 (m, 2H), 4.22-4.36 (m, 2H), 3.34 (dd, J = 12.0, 17.6 Hz, 1H), 2.99 (s, 3H), 2.69 (dd, J = 6.8, 18.4 Hz, 1H). LC-MS (ESI): m/z calcd for C₂₀H₁₈F₂N₆O₃S 460.5, found 461.4 [M+H]⁺.

[0378] Compound 259: (S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-4H-pyrrolo[2,3-d]thiazole-5-carboxylic acid



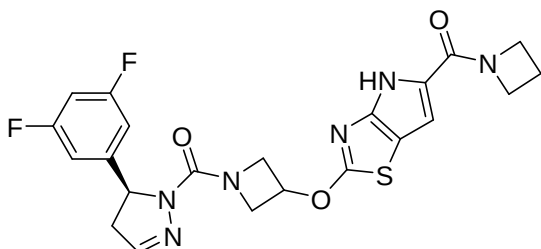
Methyl(S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-4H-pyrrolo[2,3-d]thiazole-5-carboxylate (28 mg, 0.06 mmol) was dissolved in 2 mL MeOH. 1N NaOH (1 mL) was added. Let it stir at 60°C for 10 hrs. The solvent was evaporated to dryness and dissolved with H₂O. It was adjusted to PH= 5 with 1N HCl. The brown solid was filtered and without further purification to give the titled compound **259**. Amount: 10 mg, yield: 37%. ¹H NMR (400 MHz, CDCl₃) δ (ppm): δ 6.97 (s, 1H), 6.74-6.77 (m, 1H), 6.63-6.72 (m, 3H), 5.39-5.44 (m, 1H), 5.19-5.25 (m, 1H), 4.45-4.65 (m, 2H), 4.20-4.33 (m, 2H), 3.25-3.35 (m, 1H), 2.62-2.70 (m, 1H). LC-MS (ESI): m/z calcd for C₁₉H₁₅F₂N₅O₄S 447.2, found 448.3 [M+H]⁺.

[0379] Compound 260: (S)-(4-(1H-pyrazolo[3,4-d]pyrimidin-6-yl)piperazin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



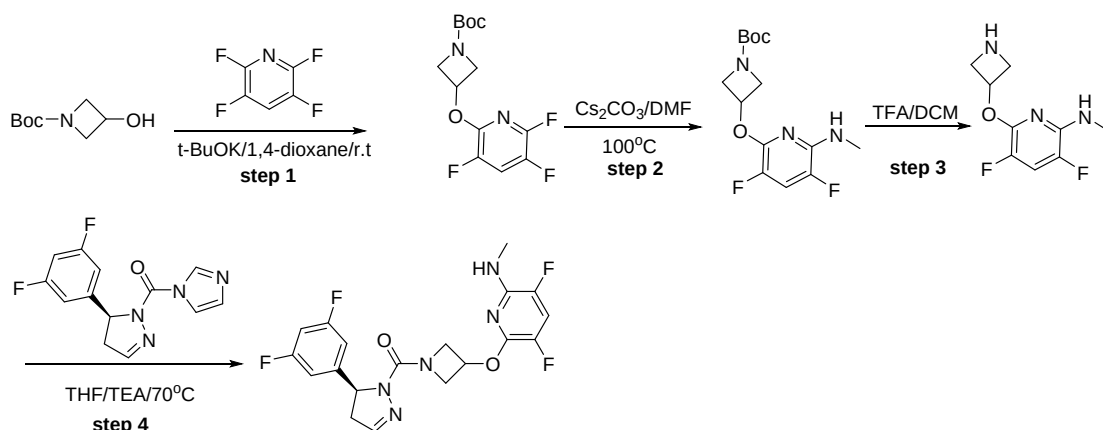
(S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone (100 mg, 0.34 mmol) and 6-chloro-1H-pyrazolo[3,4-d]pyrimidine (57.8 mg, 0.37 mmol) were dissolved in 2 mL DMF. 0.5 mL DIEA was added. Let it stir at 150°C under microwave for 40 mins. The solvent was evaporated to dryness and purified by prep-TLC (PE/EA = 1/2) to give 56 mg of the titled compound **260** as a white solid . Yield: 39.9%. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 11.41(brs, 1H), 8.82 (s, 1H), 7.92 (s, 1H), 6.75-6.96 (m, 3H), 6.60-6.72 (m, 1H), 5.36 (t, J = 9.6 Hz , 1H), 3.99-4.10 (m, 2H), 3.87-3.97 (m, 2H), 3.76-3.86 (m, 2H), 3.60-3.75 (m, 2H), 3.32 (dd, J = 8.4, 17.2 Hz, 1H), 2.68 (dd, J = 8.8, 17.2 Hz, 1H). Mass (ESI): m/z calcd for C₁₉H₁₈F₂N₈O 412.4, found 413.3 [M+H]⁺.

[0380] Compound 261: (S)-azetidin-1-yl(2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-4H-pyrrolo[2,3-d]thiazol-5-yl)methanone



The titled compound **261** was prepared in 46% yield from azetidine and (S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-4H-pyrrolo[2,3-d]thiazole-5-carbonyl chloride according to the procedure outlined for compound **67**. ¹H NMR (400 MHz, CDCl₃) δ (ppm): δ 9.47 (brs, 1H), 6.74-6.78 (m, 3H), 6.67-6.72 (m, 1H), 6.48 (d, J = 2.0 Hz, 1H), 5.43-5.48 (m, 1H), 5.27 (dd, J = 6.4, 12.0 Hz ,1H), 4.52-4.65 (m, 2H), 4.35-4.46 (m, 2H), 4.17-4.34 (m, 4H), 3.34 (ddd, J = 1.6, 12.4, 14.0 Hz ,1H), 2.69 (ddd, J = 1.6, 6.4,8.4 Hz, 1H), 2.38-2.47 (m, 2H). LC-MS (ESI): m/z calcd for C₂₂H₂₀F₂N₆O₃S 486.5, found 487.3 [M+H]⁺.

[0381] Compound 262 : (S)-3-((3,5-difluoro-6-(methylamino)pyridin-2-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



[0382] Step 1. 2,3,5,6-tetrafluoropyridine (350 mg, 2.32 mmol) and tert-butyl 3-hydroxyazetidine-1-carboxylate (441 mg, 2.55 mmol) and t-BuOK (415.6 mg, 3.70 mmol) were mixed in 10 mL 1,4-dioxane. Let it stir at r.t for 16 hrs. Water was added and extracted with EtOAc (30 mL X 3). The solvent was evaporated to dryness and purified by column chromatography (PE/EA = 85/15) to give 460 mg tert-butyl 3-((3,5,6-trifluoropyridin-2-yl)oxy)azetidine-1-carboxylate as light-yellow solid. Yield: 63.9%. LC-MS (m/z) 305.2 [M+H]⁺.

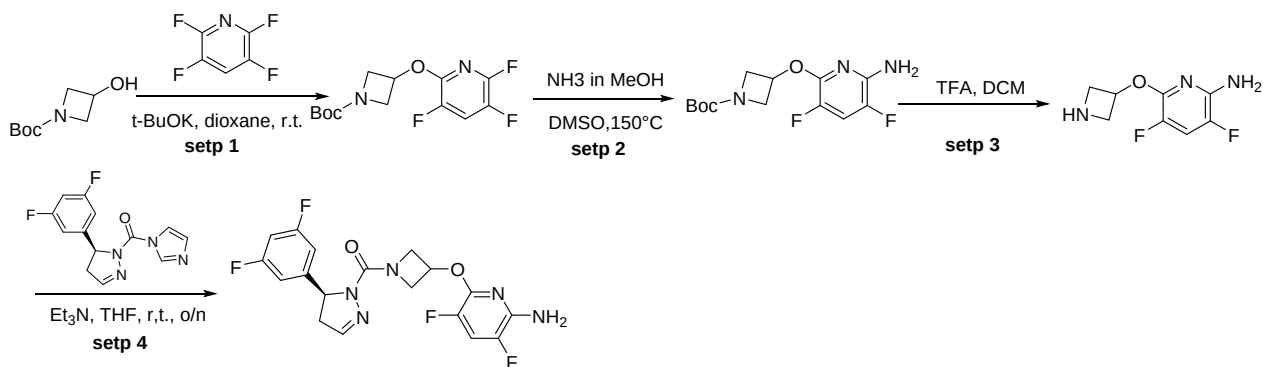
[0383] Step 2. Tert-butyl 3-((3,5,6-trifluoropyridin-2-yl)oxy)azetidine-1-carboxylate (200 mg, 0.66 mmol), methylamine hydrochloride (48.8 mg, 0.73 mmol) and Cs₂CO₃ (427.6 mg, 1.316 mmol) were mixed in 5 mL DMF. Let it stir at 100°C for 16 hrs. Water was added and extracted with EtOAc (30 mL X 3). The solvent was evaporated to dryness and purified by Prep-TLC (PE/EA = 4/1) to give 170 mg tert-butyl 3-((3,5-difluoro-6-(methylamino)pyridin-2-yl)oxy)azetidine-1-carboxylate as light-yellow solid. Yield: 81.8%. LC-MS (m/z) 317.1 [M+H]⁺.

[0384] Step 3. Tert-butyl 3-((3,5-difluoro-6-(methylamino)pyridin-2-yl)oxy)azetidine-1-carboxylate (100 mg, 0.316 mmol) was dissolved in 2 mL DCM. 2 mL DCM/TFA(1/1) was added slowly to the solution at 0°C. Let it stir r.t for 1h. The solvent was evaporated to dryness and used for next step without further purification. LC-MS (m/z) 217.2 [M+H]⁺.

[0385] Step 4. The above residue was dissolved in 2mL THF. 0.2 mL of TEA was added. (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (87 mg, 0.315 mmol) was added. Let it stir at 70°C for 16 hrs. The solvent was evaporated to

dryness and purified by Prep-TLC (PE/EA = 1/1) to give 80 mg of the titled compound **262** as light-yellow solid. Yield: 59.8%. ^1H NMR (400 MHz, CDCl_3) δ (ppm): δ 7.11 (t, J = 8.8 Hz, 1H), 6.74-6.79 (m, 3H), 6.66-6.71 (m, 1H), 5.32-5.37 (m, 1H), 5.28 (dd, J = 6.4, 12.0 Hz, 1H), 4.51-4.59 (m, 2H), 4.31 (dd, J = 4.8, 10.4 Hz, 1H), 4.22 (dd, J = 4.0, 10.4 Hz, 1H), 3.34 (ddd, J = 2.0, 12.4, 14.0 Hz, 1H), 2.94 (s, 3H), 2.69 (ddd, J = 2.0, 6.8, 8.4 Hz, 1H). LC-MS (ESI): m/z calcd for $\text{C}_{19}\text{H}_{17}\text{F}_4\text{N}_5\text{O}_2$ 423.4, found 424.3 $[\text{M}+\text{H}]^+$.

[0386] Compound 263 : (S)-(3-((6-amino-3,5-difluoropyridin-2-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



[0387] Setp 1: tert-butyl 3-((3,5,6-trifluoropyridin-2-yl)oxy)azetidine-1-carboxylate

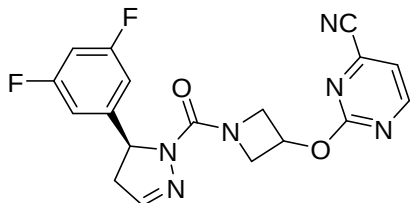
To a solution of 2,3,5-trifluoropyridine (795 mg, 5.2 mmol) and tert-butyl 3-hydroxyazetidine-1-carboxylate (1.0 g, 5.8 mmol) in 1,4-dioxane (200 mL) was added t-BuOK (882 mg, 7.8 mmol). The mixture was stirred to at room temperature for overnight. The reaction mixture was concentrated in vacuo to a residue. The crude product was purified by silica gel chromatography (petrol ether/EtOAc =5/1) to give the titled compound (1.1 g, 45% yield) as a white solid. LCMS (ES, m/z):305.3 $[\text{M}+\text{H}]^+$.

[0388] Step 2: tert-butyl 3-((6-amino-3,5-difluoropyridin-2-yl)oxy)azetidine-1-carboxylate To a solution of tert-butyl 3-((3,5,6-trifluoropyridin-2-yl)oxy)azetidine-1-carboxylate (3.4 g, 11.2 mmol) in DMSO (30mL) was added NH_3 in MeOH (20 mL, 7M). The mixture was stirred to 150°C for overnight. The mixture was extracted with DCM, washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the titled compound (2.0 g, 62 %) as a yellow Solid. (ES, m/s): 302.1 $[\text{M}+\text{H}]^+$.

[0389] Step 3 and 4: The titled compound **72** was prepared in 5% yield (two steps) from 6-(azetidin-3-yloxy)-3,5-difluoropyridin-2-amine TFA salt and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according the

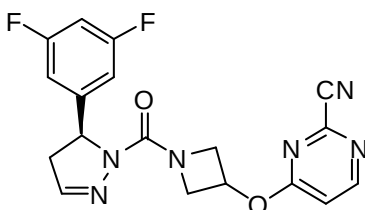
produce outlined for compound **62**. ^1H NMR (400 MHz, Chloroform- d) δ 7.15 (t, J = 8.8 Hz, 1H), 6.80 – 6.62 (m, 4H), 5.31 – 5.23 (m, 2H), 4.56-4.49 (m, 2H), 4.27-4.17 (m, 2H), 3.76 (brs, 2H), 3.34 (ddd, J = 18.6, 12.2, 1.5 Hz, 1H), 2.68 (ddd, J = 18.5, 6.5, 1.6 Hz, 1H).
Yield: 5% (5 mg), LCMS (ES, m/z):410.1[M+H] $^+$

[0390] Compound 264: (S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)pyrimidine-4-carbonitrile



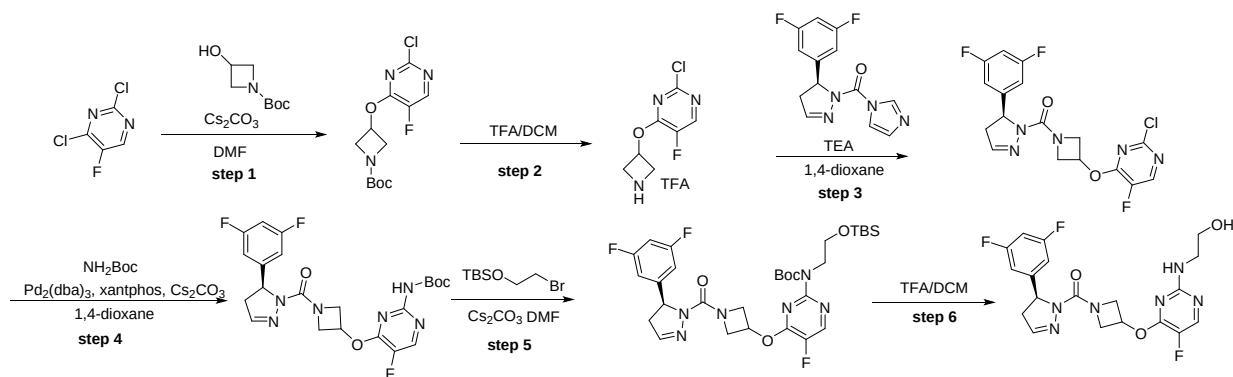
The titled compound **264** was synthesized in an analogous manner to the preparation of compound **256**. ^1H NMR (400 MHz, Chloroform- d) δ 8.77 (d, J = 4.7 Hz, 1H), 7.33 (d, J = 4.8 Hz, 1H), 6.79 (t, J = 1.7 Hz, 1H), 6.77 – 6.73 (m, 2H), 6.69 (tt, J = 8.9, 2.3 Hz, 1H), 5.39 (tt, J = 6.6, 4.2 Hz, 1H), 5.28 (dd, J = 12.2, 6.5 Hz, 1H), 4.66 – 4.52 (m, 2H), 4.34 – 4.19 (m, 2H), 3.35 (ddd, J = 18.6, 12.2, 1.7 Hz, 1H), 2.69 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H).
LC-MS (m/z): 385.2[M+H] $^+$.

[0391] Compound 265 : (S)-4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)pyrimidine-2-carbonitrile



The titled compound **265** was synthesized in an analogous manner to the preparation of compound **256**. ^1H NMR (400 MHz, Chloroform- d) δ 8.57 (d, J = 5.8 Hz, 1H), 7.00 (d, J = 5.8 Hz, 1H), 6.82 (t, J = 1.7 Hz, 1H), 6.76 – 6.73 (m, 2H), 6.70 (tt, J = 8.9, 2.3 Hz, 1H), 5.45 (tt, J = 6.6, 4.1 Hz, 1H), 5.28 (dd, J = 12.2, 6.3 Hz, 1H), 4.71 – 4.55 (m, 2H), 4.28 – 4.17 (m, 2H), 3.36 (ddd, J = 18.7, 12.2, 1.7 Hz, 1H), 2.71 (ddd, J = 18.6, 6.4, 1.7 Hz, 1H).
LC-MS (m/z): 385.2[M+H] $^+$.

[0392] Compound 266: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-((2-hydroxyethyl)amino)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone



[0393] Step 1. Preparation of tert-butyl 3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidine-1-carboxylate. 2,4-dichloro-5-fluoropyrimidine (5g, 29.9mmol) was added to a solution of Cs_2CO_3 (19.5g, 59.9mmol) in DMF (100mL), and tert-butyl 3-hydroxyazetidine-1-carboxylate (5.7g, 32.9mmol) was added. The mixture was stirred at 100°C for 2hrs. The reaction mixture was then extracted by EtOAc/H₂O (50mL/50mL) 3 times. The organic layer was combined, washed with brine, dried over Na_2SO_4 , concentrated and further purified by silica gel column chromatography (PE/EA=5/1) to give tert-butyl 3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidine-1-carboxylate (3.9g) as a colorless oil (43%). LC-MS (ESI) m/z $[\text{M}+\text{H}]^+$: 304.1.

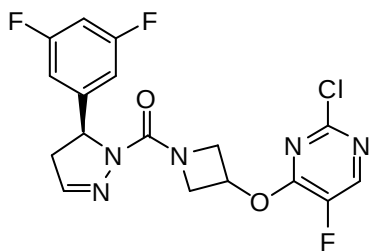
[0394] Step 2. Preparation of 4-(azetidin-3-yloxy)-2-chloro-5-fluoropyrimidine. TFA(5mL) was added to a solution of tert-butyl 3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidine-1-carboxylate (3.9g, 12.9mmol) in DCM (10 mL). the reaction mixture was stirred at room temperature for 0.5hr. then the solvent was evaporated in vacuo to give 5.2g of 4-(azetidin-3-yloxy)-2-chloro-5-fluoropyrimidine as a colorless oil (crude). LC-MS (ESI) m/z $[\text{M}+\text{H}]^+$:204.1.

[0395] Step 3. Preparation of (S)-3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone. (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(1H-imidazol-1-yl)methanone (3.23g, 11.7mmol) was added to a solution of 4-(azetidin-3-yloxy)-2-chloro-5-fluoropyrimidine and TEA (3.55g, 35.1mmol) in 1,4-dioxane (30mL). The reaction mixture was stirred at room temperature overnight. Then the solvent was evaporated in vacuo. The oil residue was purified by silica gel column chromatography(PE/EA=1/1) to give 4.35g of (S)-3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone as a yellow oil (90%). LC-MS (ESI) m/z $[\text{M}+\text{H}]^+$:412.1.

[0396] Step 4. Preparation of tert-butyl (S)-(2-((tert-butyldimethylsilyl)oxy)ethyl)(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)carbamate. (2-bromoethoxy)(tert-butyl)dimethylsilane (29.1mg, 0.122mmol) was added to a solution of Cs₂CO₃ (66.5mg, 0.204mmol) in DMF (1mL), and **(3-01)** (50mg, 0.102mmol) was added. The mixture was stirred at 100°C for 1hr. The reaction mixture was then extracted by EtOAc/H₂O (50mL/50mL) 3 times. The organic layer was combined, washed with brine, dried over Na₂SO₄, concentrated to give tert-butyl (S)-(2-((tert-butyldimethylsilyl)oxy)ethyl)(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)carbamate (60 mg) as a yellow oil.

[0397] Step 5. Preparation of (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-((2-hydroxyethyl)amino)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone. TFA(5 mL) was added to a solution of tert-butyl (S)-(2-((tert-butyldimethylsilyl)oxy)ethyl)(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)carbamate (60mg, 0.092mmol) in DCM (10mL). the reaction mixture was stirred at room temperature for 0.5hr. The reaction mixture was concentrated and purified by pre-HPLC to give 16mg of the titled compound **266** : (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-((2-hydroxyethyl)amino)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (40%). LC-MS (ESI) *m/z* [M+H]⁺:437.2 ¹H NMR (400 MHz, CDCl₃): δ 7.82 (d, *J* = 3.4 Hz, 1H), 6.85 – 6.64 (m, 4H), 5.50 (s, 1H), 5.27 (dd, *J* = 12.1, 6.4 Hz, 1H), 4.60 (br, 2H), 4.38-4.26 ((m, 2H), 3.85 (s, 2H), 3.55 (s, 2H), 3.41-3.33 (m, 1H), 2.77 – 2.66 (m, 1H).

[0398] Compound 267: (S)-(3-((2-chloropyrimidin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone

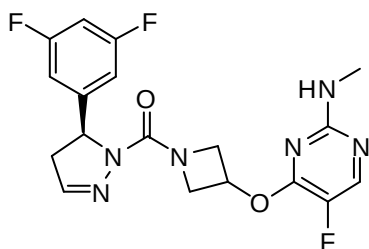


The titled compound **267** was synthesized in the manner to the preparation of compound **75**. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 2.1 Hz, 1H), 6.79 (t, *J* = 1.7 Hz, 1H),

6.78 – 6.73 (m, 2H), 6.69 (tt, $J = 8.9, 2.3$ Hz, 1H), 5.50 (tt, $J = 6.7, 4.1$ Hz, 1H), 5.27 (dd, $J = 12.2, 6.5$ Hz, 1H), 4.69 – 4.54 (m, 2H), 4.34 – 4.22 (m, 2H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.70 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H). LC-MS (m/z): 412.1[M+H]⁺.

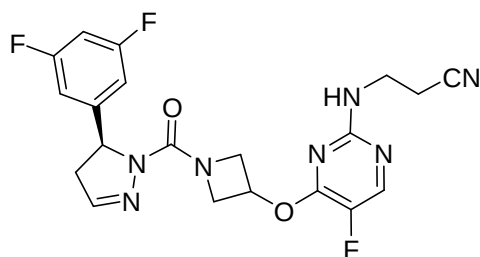
[0399] Compound 268: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(methylamino)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone

The titled compound **268** was synthesized in 68% yield from compound **267** and methylamine according to the similar manner to the preparation of compound **266**



¹H NMR (400 MHz, Chloroform-*d*) δ 10.25 – 10.01 (br, 1H), 7.80 (d, $J = 3.7$ Hz, 1H), 6.82 (t, $J = 1.7$ Hz, 1H), 6.78 – 6.73 (m, 2H), 6.70 (tt, $J = 8.8, 2.3$ Hz, 1H), 5.54 (tt, $J = 6.7, 4.1$ Hz, 1H), 5.28 (dd, $J = 12.2, 6.4$ Hz, 1H), 4.68 – 4.55 (m, 2H), 4.42 – 4.33 (m, 1H), 4.33 – 4.25 (m, 1H), 3.37 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 3.00 (s, 3H), 2.72 (ddd, $J = 18.7, 6.4, 1.7$ Hz, 1H). LC-MS (m/z): 407.2[M+H]⁺.

[0400] Compound 269 : (S)-3-((4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)amino)propanenitrile

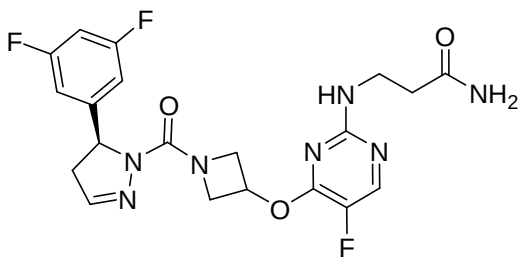


The titled compound **269** was prepared in an analogous manner to the preparation of **266**

¹H NMR (400 MHz, Chloroform-*d*) δ 10.29 (s, 1H), 8.00 (s, 1H), 6.88 (s, 1H), 6.80 – 6.61 (m, 3H), 5.68 – 5.57 (m, 1H), 5.30 (dd, $J = 12.4, 6.0$ Hz, 1H), 4.76–4.62 (m, 2H), 4.51 – 4.30 (m, 2H), 3.84–3.77 (m, 2H), 3.45–3.30 (m, 1H), 2.81 – 2.64 (m, 3H).

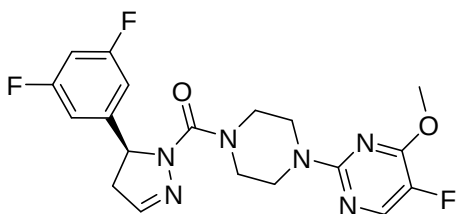
LC-MS (m/z) 446.3(M+H⁺), Yield 12.4 %

[0401] Compound 270 : (S)-3-((4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)amino)propanamide



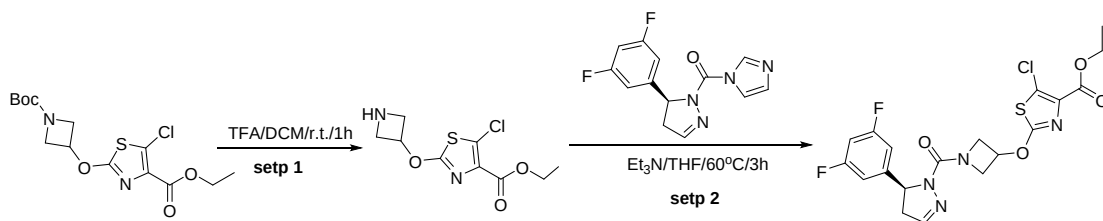
The titled compound **270** was prepared from compound **269** by hydrolysis reaction using 1 N NaOH solution. Yield 48.2%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.95 (s, 1H), 6.78 (t, *J* = 1.6 Hz, 1H), 6.77-6.71 (m, 2H), 6.71 – 6.65 (m, 1H), 5.74 (s, 1H), 5.60 (s, 2H), 5.39-5.32 (m, 1H), 5.27 (dd, *J* = 12.4, 6.4 Hz, 1H), 4.61-4.47 (m, 2H), 4.36 – 4.09 (m, 2H), 3.64 (q, *J* = 6.0 Hz, 2H), 3.40-3.29(m, 1H), 2.73-2.64(m, 1H), 2.50 (t, *J* = 6.0 Hz, 2H). LC-MS (*m/z*) 464.3 (*M*+*H*⁺).

[0402] Compound 271: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-(5-fluoro-4-methoxypyrimidin-2-yl)piperazin-1-yl)methanone



(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone (100 mg, 0.34 mmol) and 2-chloro-5-fluoro-4-methoxypyrimidine (60.8 mg, 0.37 mmol) were dissolved in 2 mL 1,4-dioxane. *p*-Toluenesulfonic acid (11.7 mg, 0.068 mmol) was added. Let it stir at 100°C under sealed tube for 16 hrs. The solvent was evaporated to dryness and purified by prep-TLC (PE/EA = 1/2) to give 35 mg of the titled compound as a white solid. Yield: 24.5%. ¹H NMR (400 MHz, CDCl₃) δ (ppm): δ 7.96 (s, 1H), 6.81-6.85 (m, 3H), 6.69 (t, *J* = 8.8 Hz, 1H), 5.33 (t, *J* = 10.8 Hz, 1H), 3.98 (s, 3H), 3.70-3.87 (m, 6H), 3.58-3.64 (m, 2H), 3.32 (dd, *J* = 12.0, 18.4 Hz, 1H), 2.68 (dd, *J* = 10.4, 18.4 Hz, 1H). Mass (ESI): *m/z* calcd for C₁₉H₁₉F₃N₆O₂ 420.4, found 421.5 [*M*+*H*]⁺.

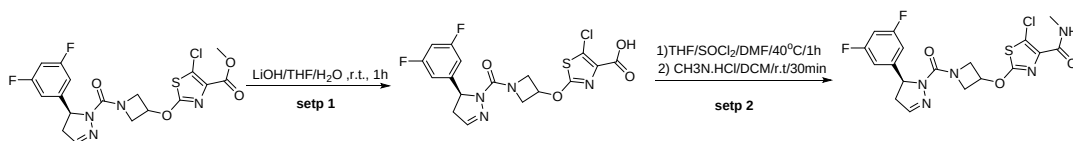
[0403] Compound 272: ethyl (S)-5-chloro-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-4-carboxylate



[0404] Step1: A solution of ethyl 2-((1-(tert-butoxycarbonyl)azetidin-3-yl)oxy)-5-chlorothiazole-4-carboxylate (240 mg, 0.7 mmol) in DCM (5 mL) was added TFA (1 mL). The resulting mixture was stirred at room temperature for 2 h, then concentrated in vacuo to give ethyl 2-(azetidin-3-yloxy)-5-chlorothiazole-4-carboxylate (174 mg crude) as TFA salt. which was used for next step directly.

[0405] Step 2: To a solution of (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(1H-imidazol-1-yl)methanone (183 mg, 0.7 mmol) and ethyl 2-(azetidin-3-yloxy)-5-chlorothiazole-4-carboxylate (174 g crude, 0.7 mmol) in THF (5 mL) was added Et₃N (0.5 mL, 2.0 mmol). The mixture was stirred at 70°C for 3 h. When the reaction was completed, the reaction mixture was concentrated in vacuo to a residue. The crude product was purified by pre-TLC (petrol ether/EtOAc =1/1) to give the titled compound (220 mg, 74% yield) as a white solid. LCMS (ES, m/z): 471.1[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.84 – 6.55 (m, 4H), 5.53-5.51 (m, 1H), 5.33 (dd, *J* = 5.2, 16.4 Hz, 1H), 4.63-4.47 (m, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.33 – 4.06 (m, 2H), 3.34 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.69 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H), 1.39 (t, *J* = 7.2 Hz, 3H).

[0406] Compound 273: (S)-5-chloro-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-N-methylthiazole-4-carboxamide



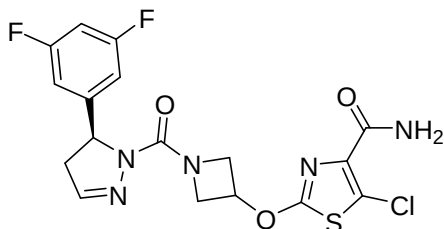
[0407] Step1: To a solution of ethyl (S)-5-chloro-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-4-carboxylate (180 mg, 0.4 mmol) in THF (3 mL) was added a solution of LiOH (17 g, 0.4 mmol) in water (3 mL). The resulting mixture was stirred at room temperature for 2 h. TLC analysis showed the reaction was completed. THF was evaporated in vacuo and 1N HCl was added to adjust pH<5, The mixture was poured into water (20 ml) and then extracted with DCM(3x10 ml). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and

concentrated under vacuum to give (S)-5-chloro-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-4-carboxylic acid as a white solid (170 mg, crude).

[0408] Step 2: To a solution of (S)-5-chloro-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-4-carboxylic acid (50 mg, 0.11mmol) was dissolved in 10 ml of dry THF and DMF(cat.) was added. SO_2Cl_2 (0.738g, 6.42 mmol) and added slowly to the above solution at 0°C. The mixture was stirred for 1h, then concentrated in vacuo give crude as a residue. The residue was dissolved in DCM (100 mL), methylamine hydrochloride (13.5 mg, 0.2 mmol) was added and the mixture was stirred at room temperature for 1 h. then concentrated in vacuo to give crude product. The crude product was purified by pre-TLC (petrol ether/EtOAc =1/1) to give the titled compound **273** (12 mg, 24%). ^1H NMR (400 MHz, Chloroform-d) δ 6.90 (brs, 1H), 6.80 (t, J = 1.6 Hz, 1H), 6.78 – 6.66 (m, 3H), 5.42-5.36 (m, 1H), 5.28 (dd, J = 6.4, 12.4 Hz, 1H), 4.57-4.52 (m, 2H), 4.32-4.20 (m, 2H), 3.36 (ddd, J = 18.4, 12.2, 1.6 Hz, 1H), 2.94 (d, J = 3.6 Hz, 3H), 2.71 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H). LCMS (ES, m/z):456.9 $[\text{M}+\text{H}]^+$.

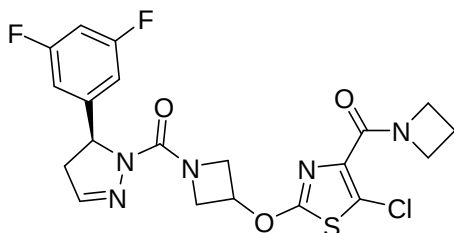
[0409] Compound 274: (S)-5-chloro-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-4-carboxamide

SN-115-14



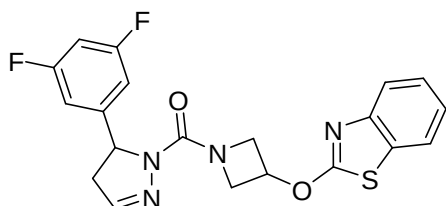
The titled compound **274** was prepared in an analogous manner to the preparation of compound **273**. Yield: 30%. ^1H NMR (400 MHz, Chloroform-d) δ 6.83 – 6.63 (m, 4H), 5.68 (brs, 1H), 5.42-5.36 (m, 1H), 5.33 (dd, J = 6.4, 12.4 Hz, 1H), 4.68 – 4.45 (m, 2H), 4.39 – 4.11 (m, 2H), 3.36 (ddd, J = 18.4, 12.4, 1.6 Hz, 1H), 2.70 (ddd, J = 18.4, 6.4, 1.6 Hz, 1H). LCMS (ES, m/z): 442.8 $[\text{M}+\text{H}]^+$.

[0410] Compound 275:



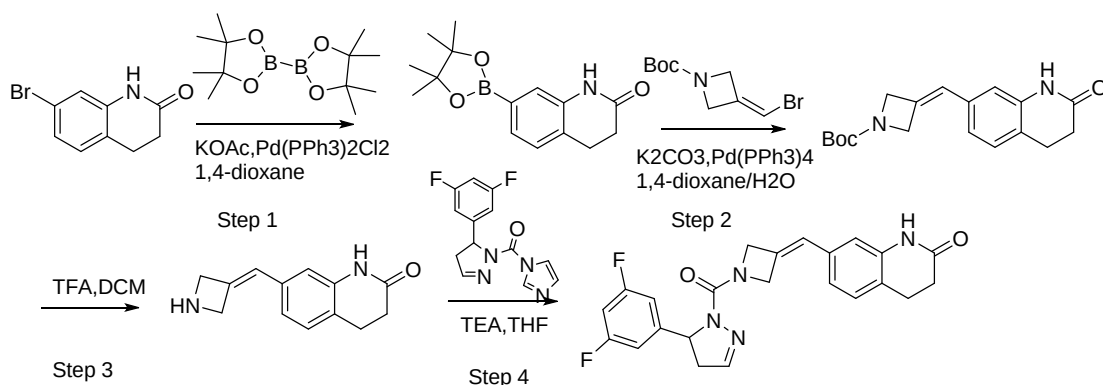
The titled compound **275** was prepared in an analogous manner to the preparation of compound **273**. ^1H NMR (400 MHz, cdcl_3) δ 6.87 – 6.65 (m, 4H), 5.38-5.33 (m, 1H), 5.27 (dd, J = 6.4, 12.0 Hz, 1H), 4.61 – 4.47 (m, 2H), 4.47 – 4.36 (m, 2H), 4.31-4.27 (m, 1H), 4.25 – 4.10 (m, 3H), 3.36 (dd, J = 17.3, 12.3 Hz, 1H), 2.71 (ddd, J = 18.6, 6.5, 1.7 Hz, 1H), 2.35-2.27 (m, 2H). Yield: 45% (12.1 mg). LCMS (ES, m/z): 482.1 $[\text{M}+\text{H}]^+$.

[0411] Compound 276: (3-(benzo[d]thiazol-2-yloxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **276** was synthesized in an analogous manner to the preparation of compound **203**. ^1H NMR (400 MHz, Chloroform- d) δ 7.67 (dddd, J = 7.9, 7.4, 1.2, 0.6 Hz, 2H), 7.40 – 7.34 (m, 1H), 7.24-7.28 (m, 1H), 6.80 – 6.73 (m, 3H), 6.73 – 6.65 (m, 1H), 5.59 (dt, J = 6.6, 2.8 Hz, 1H), 5.37 – 5.19 (m, 1H), 4.62 (s, 2H), 4.46 – 4.23 (m, 2H), 3.43 – 3.25 (m, 1H), 2.70 (dd, J = 18.5, 6.1 Hz, 1H). LC-MS (m/z) 414.6 $[\text{M}+\text{H}]^+$.

[0412] Compound 277: 7-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)-3,4-dihydroquinolin-2(1H)-one



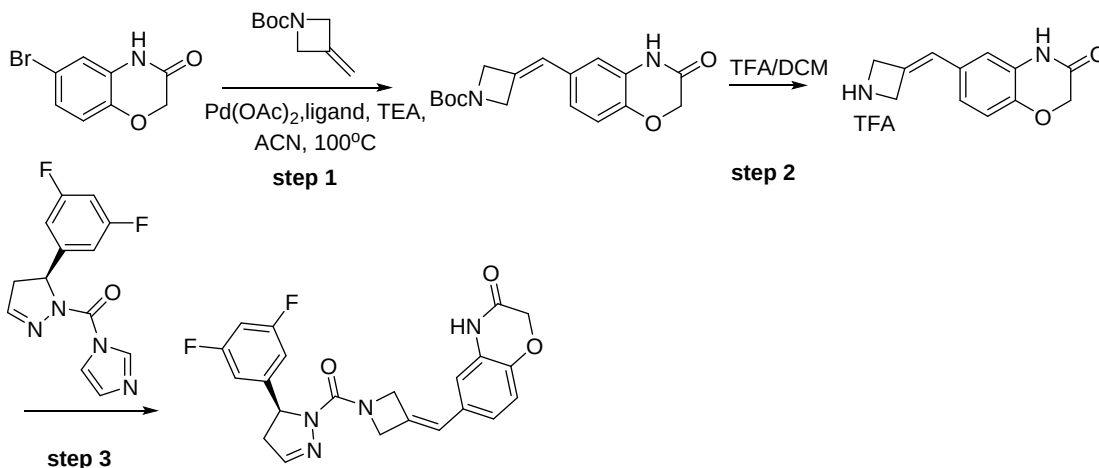
[0413] Step 1: 7-bromo-3,4-dihydroquinolin-2(1H)-one(100 mg, 0.44 mmol) was dissolved in 5ml of dry 1,4-dioxane, 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane)(223 mg, 0.88 mmol) KOAc (130 mg, 1.32 mmol) Pd(PPh₃)₂Cl₂(32 mg, 0.04 mmol) was added, The mixture was stirred at 80°C for overnight. The mixture was filtered, the filtrate was concentrated to give 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one, which was used for next step without further purification. LC-MS (m/z) 274.15(M+H⁺).

[0414] Step 2: 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one (120 mg) was dissolved in 5ml of 1,4-dioxane/H₂O, tert-butyl 3-(bromomethylene)azetidine-1-carboxylate(90 mg, 0.36 mmol) K₂CO₃ (150 mg, 1.08 mmol) Pd(PPh₃)₄(83 mg, 0.072 mmol) was added, The mixture was stirred at 80°C for 2h, The mixture was filtered, the filtrate was concentrated in vacuo. Purification by silica gel chromatography (EA/PE = 1:1) to give tert-butyl 3-((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methylene)azetidine-1-carboxylate (58mg) as a yellow solid. LC-MS (m/z) 315.16(M+H⁺)

[0415] Step 3: tert-butyl 3-((2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methylene)azetidine-1-carboxylate (58 mg, 0.18 mmol) was dissolved in 3ml of DCM, trifluoroacetic acid(210 mg, 1.8 mmol) was added, The mixture was stirred at r.t. for 4 h. The mixture was concentrated to give 7-(azetidin-3-ylidenemethyl)-3,4-dihydroquinolin-2(1H)-one trifluoroacetic acid salt, which was used for next step without further purification. LC-MS (m/z) 215.15 (M+H⁺).

[0416] Step 4: 7-(azetidin-3-ylidenemethyl)-3,4-dihydroquinolin-2(1H)-one and (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone(45 mg, 0.16 mmol) and TEA(0.4 ml) were dissolved in THF(5 mL) and stirred at 65°C for 6h. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by Pre-HPLC to give the titled compound **277** (0.6mg, 0.8% yield in two steps). LC-MS (m/z)423.16(M+H⁺). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 6.84 (s, 1H), 6.80 – 6.64 (m, 3H), 6.50 (s, 1H), 6.21 (s, 1H), 5.37 – 5.30 (m, 1H), 5.11-5.10 (m, 2H), 4.90-4.80 (m, 2H), 3.38 (dd, *J* = 18.6, 11.7 Hz, 1H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.72 (dd, *J* = 18.6, 5.8 Hz, 1H), 2.65 (m, *J* = 7.5 Hz, 2H).

[0417] Compound 278: 6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one



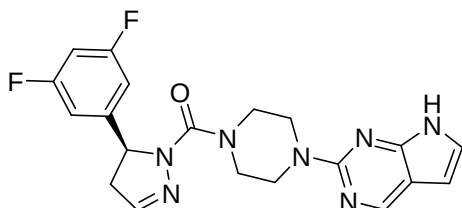
[0418] Step 1: 6-bromo-2H-benzo[b][1,4]oxazin-3(4H)-one (100 mg, 0.44 mmol) was dissolved in 5 ml of ACN, tert-butyl 3-methyleneazetidine-1-carboxylate (149 mg, 0.88 mmol) Pd(OAc)₂ (10 mg, 0.044 mmol), tris(2-methylphenyl)phosphine (27 mg, 0.08 mmol) and TEA (133 mg, 1.32 mmol) were added, The mixture was stirred at 100°C for 3h. The mixture was extracted with EA, washed with brine, dried with (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography (EA/PE = 1:1) to give tert-butyl 3-((3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)methylene)azetidine-1-carboxylate (100 mg). LC-MS (m/z) 316.14(M+H⁺)

[0419] Step 2: tert-butyl 3-((3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)methylene)azetidine-1-carboxylate (100 mg, 0.32 mmol) was dissolved in 6 ml of DCM, trifluoroacetic acid (1.5 ml) was added, The mixture was stirred at r.t. for 4 h. The mixture was concentrated to give 6-(azetidin-3-ylidenemethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one trifluoroacetic acid, which was used for next step without further purification. LC-MS (m/z) 216.15(M+H⁺)

[0420] Step 3: 6-(azetidin-3-ylidenemethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one and (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone (73 mg) and TEA (0.4 mL) were dissolved in THF (10 ml) and stirred at 65°C for 6h. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **278** (15 mg, 8% yield in three steps). LC-MS (m/z) 425.13(M+H⁺). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.68 (s, 1H), 7.11 (tt, *J* =

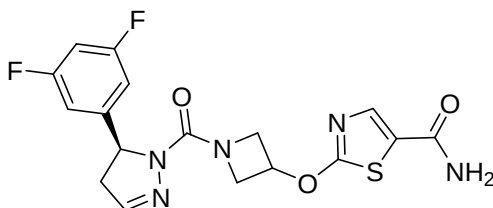
9.4, 2.4 Hz, 1H), 7.05 (brs, 1H), 6.97 – 6.90 (m, 3H), 6.76-6.74 (m, 2H), 6.25 (brs, 1H), 5.28 (dd, $J = 12.2, 6.6$ Hz, 1H), 4.90 (bs, 2H), 4.73 (brs, 2H), 4.56 (s, 2H), 3.46 – 3.36 (m, 1H), 2.66 – 2.60 (m, 1H).

[0421] Compound 279: (S)-(4-(7H-pyrrolo[2,3-d]pyrimidin-2-yl)piperazin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **279** was prepared in 3.9% yield from 2-chloro-7H-pyrrolo[2,3-d]pyrimidine and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone according to the procedure outlined for compound **271**. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.93(brs, 1H), 8.62 (s, 1H), 6.91 (dd, $J = 2.0, 3.6$ Hz, 1H), 6.80-6.86 (m, 3H), 6.66-6.72 (m, 1H), 6.37 (dd, $J = 1.6, 4.0$ Hz, 1H), 5.35 (dd, $J = 10.0, 11.6$ Hz, 1H), 3.90-3.96 (m, 2H), 3.78-3.86 (m, 4H), 3.65-3.71 (m, 2H), 3.31 (ddd, $J = 2, 11.6, 13.6$ Hz, 1H), 2.68 (ddd, $J = 1.6, 10.0, 11.6$ Hz, 1H). Mass (ESI): m/z calcd for $\text{C}_{20}\text{H}_{19}\text{F}_2\text{N}_7\text{O}$ 411.4, found 412.3 $[\text{M}+\text{H}]^+$.

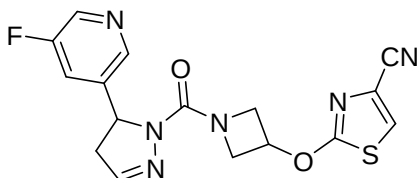
[0422] Compound 280: (S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-5-carboxamide



The titled compound **280** was prepared from 2-(azetidin-3-yloxy)thiazole-5-carboxamide trifluoroacetic acid salt and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according the produce outlined for compound **203**. LC-MS (m/z) 408.4 ($\text{M}+\text{H}^+$) ^1H NMR (400 MHz, Chloroform- d) δ 7.54 (s, 1H), 6.78 (t, $J = 1.7$ Hz, 1H), 6.77 – 6.73 (m, 2H), 6.72-6.66 (m, 1H), 5.45-5.40 (m, 1H), 5.27 (dd, $J = 12.1, 6.4$ Hz, 1H),

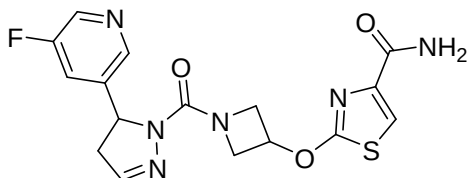
4.62 – 4.49 (m, 2H), 4.31-4.22 (m, 2H), 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.70 (ddd, $J = 18.6, 6.5, 1.8$ Hz, 1H).

[0423] Compound 281 : 2-((1-(5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-4-carbonitrile



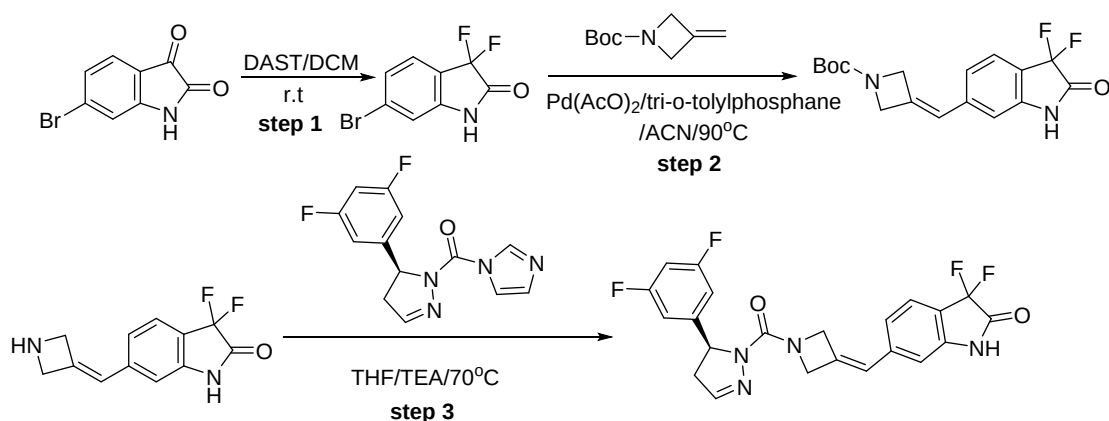
The titled compound **90** was prepared from 2-(azetidin-3-yloxy)thiazole-4-carbonitrile trifluoroacetic acid salt and (5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according to the procedure outlined for compound **203**. LC-MS (m/z) 373.4 ($M+H^+$) LC-MS (m/z) 395.5 ($M+H^+$) ^1H NMR (400 MHz, Chloroform- d) δ 8.43 (d, $J = 8.0$ Hz, 2H), 7.50 – 7.45 (m, 1H), 7.43 (brs, 1H), 6.86 – 6.84 (m, 1H), 5.45 – 5.40 (m, 1H), 5.40 – 5.35 (m, 1H), 4.57 (brs, 2H), 4.27-4.22 (m, 2H), 3.44 (ddd, $J = 18.7, 12.3, 1.7$ Hz, 1H), 2.76 (ddd, $J = 18.7, 6.8, 1.7$ Hz, 1H).

[0424] Compound 282: (S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)thiazole-4-carboxamide



The titled compound **282** was prepared from compound **281** by hydrolysis reaction using 1N NaOH. LC-MS (m/z) 391.4 ($M+H^+$). ^1H NMR (400 MHz, Chloroform- d) δ 7.65 (s, 1H), 6.81 (t, $J = 1.7$ Hz, 1H), 6.77 – 6.73 (m, 2H), 6.70 (tt, $J = 8.8, 2.3$ Hz, 1H), 5.46 – 5.39 (m, 1H), 5.29 (dd, $J = 12.2, 6.3$ Hz, 1H), 4.62-4.54 (m, 2H), 4.37 – 4.23 (m, 2H), 3.37 (ddd, $J = 18.7, 12.2, 1.7$ Hz, 1H), 2.71 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H).

[0425] Compound 283: (S)-6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)-3,3-difluoroindolin-2-one



[0426] Step 1. 6-bromoindoline-2,3-dione (1 g, 4.44 mmol) was dissolved in 2 mL DCM. DAST (1.78 g, 11.04 mmol) was added slowly to the suspension at 0°C . Let it stir at r.t. under nitrogen for 16 hrs. Water was added to quench the reaction and extracted with DCM (50 mL X 3). The organic layers were combined and evaporated to dryness and purified by column chromatography (PE/EA = 4/1) to give 0.5 g of 6-bromo-3,3-difluoroindolin-2-one as red solid. Yield: 45.6%. LC-MS (m/z) 249.1 $[\text{M}+\text{H}]^+$.

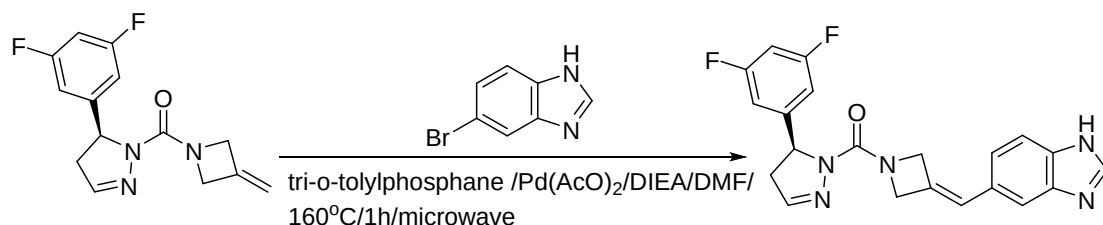
[0427] Step 2. 6-bromo-3,3-difluoroindolin-2-one (140 mg, 0.57 mmol) and tert-butyl 3-methyleneazetidine-1-carboxylate (115 mg, 0.68 mmol) and DIEA (0.19 mL) were dissolved in 5 mL CH_3CN . $\text{Pd}(\text{AcO})_2$ (12.8 mg, 0.057 mmol) and tri-*o*-tolylphosphane (35 mg, 0.115 mmol) were added. Let it stir at 100°C under nitrogen for 16 hrs. The solvent was evaporated to dryness and purified by column chromatography (PE/EA = 7/1) to give 100 mg tert-butyl 3-((3,3-difluoro-2-oxoindolin-6-yl)methylene)azetidine-1-carboxylate as light-yellow solid. Yield: 43.8%. LC-MS (m/z) 337.2 $[\text{M}+\text{H}]^+$.

[0428] Step 3. tert-butyl 3-((3,3-difluoro-2-oxoindolin-6-yl)methylene)azetidine-1-carboxylate (35 mg, 0.104 mmol) was dissolved in 2 mL DCM. 2 mL DCM/TFA (1/1) was added slowly to the solution at 0°C . Let it stir r.t. for 1h. The solvent was evaporated to dryness and used for next step without further purification. LC-MS (m/z) 237.1 $[\text{M}+\text{H}]^+$.

[0429] Step 4. The above residue was dissolved in 2 mL THF. 0.2 mL of TEA was added. (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (28.7 mg, 0.104 mmol) was added. Let it stir at 70°C for 16 hrs. The solvent was evaporated to dryness and purified by Prep-TLC (PE/EA = 1/1) to give 25 mg of the titled compound **283** as a white solid. Yield: 53%. ^1H NMR (400 MHz, CDCl_3) δ (ppm): δ 8.86 (brs, 1H), 7.46 (d, J = 7.6 Hz, 1H), 6.83-6.88 (m, 2 H), 6.73-6.79 (m, 2H), 6.61-6.67 (m,

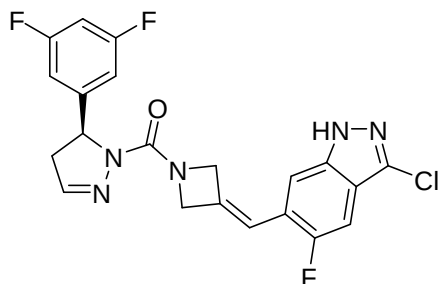
2H), 6.25(s, 1H), 5.43 (dd, $J = 6.0, 12.0$ Hz, 1H), 4.94-5.09 (m, 4H), 3.41 (ddd, $J = 1.6, 12.4, 13.6$ Hz, 1H), 2.70 (ddd, $J = 1.6, 6.4, 7.6$ Hz, 1H). LC-MS (ESI): m/z calcd for $C_{22}H_{16}F_4N_4O_2$ 444.4, found 445.3 $[M+H]^+$.

[0430] Compound 284: (S)-(3-((1H-benzo[d]imidazol-5-yl)methylene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



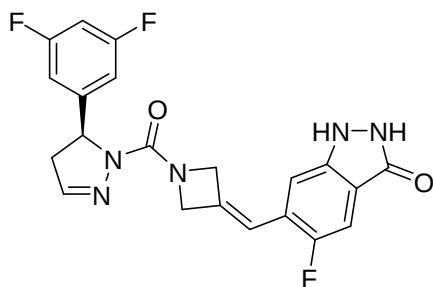
6-bromo-1H-benzimidazole (8.5 mg, 0.043 mmol) and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-methyleneazetidin-1-yl)methanone (10 mg, 0.036 mmol). $Pd(AcO)_2$ (5 mg) and tri-o-tolylphosphane (1.8 mg, 0.006 mmol) were added. 0.2 mL DIEA was added. Let it stir at 160°C under microwave for 1h. The solvent was evaporated to dryness and purified by column chromatography (DCM/MeOH = 92/8) to give the titled compound **284** as orange solid (6mg, 42.4%). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 8.64 (s, 1H), 7.61 (d, $J = 7.6$ Hz, 1H), 7.45 (s, 1H), 7.10 (d, $J = 7.6$ Hz, 1H), 6.84 (s, 1H), 6.78 (d, $J = 5.6$ Hz, 2H), 6.64-6.70 (m, 1 H), 6.34 (s, 1H), 5.35 (dd, $J = 6.4, 8.4$ Hz, 1H), 5.09 (s, 2H), 4.90 (s, 2H), 3.39 (dd, $J = 12.8, 18.0$ Hz, 1H), 2.71 (dd, $J = 6.8, 18.0$ Hz, 1H). LC-MS (ESI): m/z calcd for $C_{21}H_{17}F_2N_5O$ 393.4, found 394.3 $[M+H]^+$.

[0431] Compound 285 : (S)-(3-((3-chloro-5-fluoro-1H-indazol-6-yl)methylene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



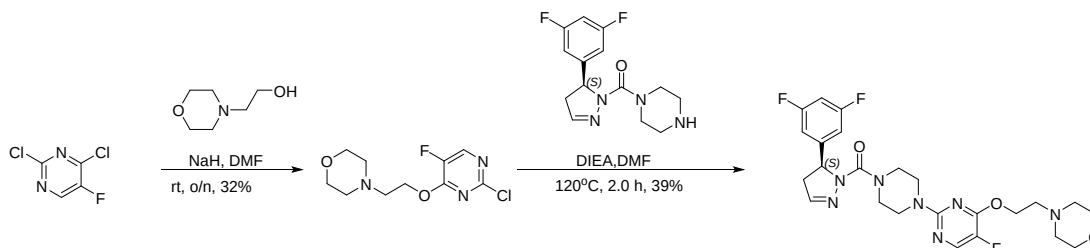
The titled compound **285** was synthesized in an analogous manner to the preparation of compound **284**. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.71-7.68 (m, 1H), 7.61-7.58 (m, 1H), 7.33 – 7.26 (m, 1H), 6.96 (s, 1H), 6.85 – 6.79 (m, 2H), 6.59 (s, 1H), 5.30 (dd, *J* = 12.0, 8.0 Hz, 1H), 5.07 (s, 2H), 4.89 (s, 2H), 3.48 – 3.40 (m, 1H), 2.74-2.68 (m, 1H).

[0432] Compound 286: (S)-6-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)-5-fluoro-1H-3l5-indazol-3-one



The titled compound **286** was synthesized in an analogous manner to the preparation of compound **284**. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.37 (d, *J* = 12.0 Hz, 1H), 7.06 (d, *J* = 4.0 Hz, 1H), 6.96 (d, *J* = 4.0 Hz, 1H), 6.85 – 6.79 (m, 3H), 6.58 (s, 1H), 5.30 (dd, *J* = 12.0, 4.0 Hz, 1H), 5.06 (s, 2H), 4.89 (s, 2H), 3.48 – 3.40 (m, 1H), 2.74-2.67 (m, 1H).

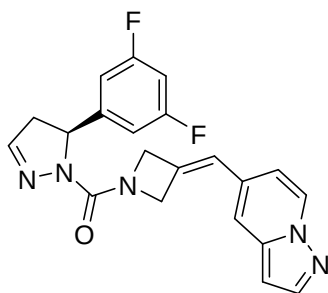
[0433] Compound 287: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-(5-fluoro-4-(2-morpholinoethoxy)pyrimidin-2-yl)piperazin-1-yl)methanone



[0434] Step 1 : 4-(2-((2-chloro-5-fluoropyrimidin-4-yl)oxy)ethyl)morpholine. 2-morpholinoethan-1-ol (863 mg, 7.13 mmol) was dissolved in 20 ml of dry DMF. NaH(263 mg, 6.57 mmol) was added to the above solution under nitrogen at 0 degrees C. The mixture was stirred for 0.5 hour at 0 degrees C. To this was added 2,4-dichloro-5-fluoropyrimidine (1.0g, 5.98 mmol), the mixture was stirred for another 1 overnight at room temperature. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound (500 mg, 32%) as ayellow oil. (ES, m/s): 262.1 [M+H]⁺

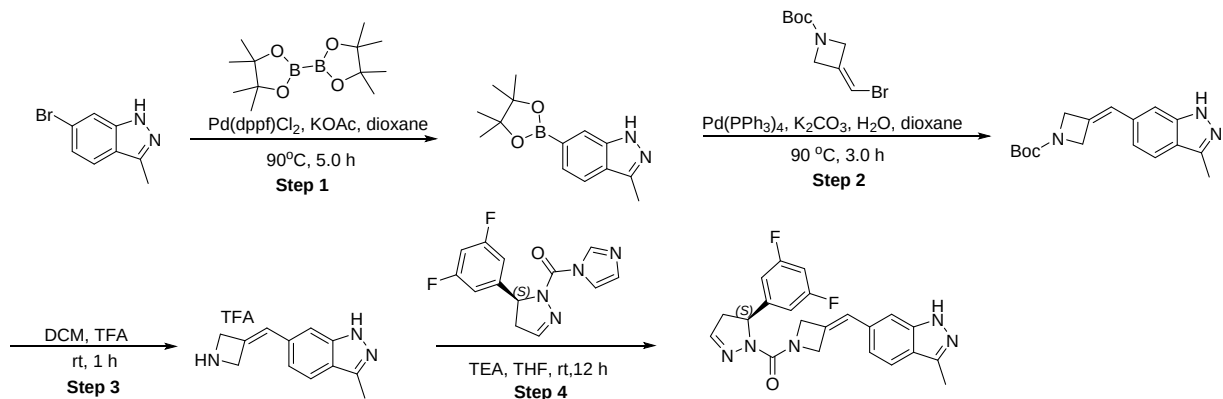
[0435] Step 2: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-(5-fluoro-4-(2-morpholinoethoxy)pyrimidin-2-yl)piperazin-1-yl)methanone. (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone (295 mg, 1.00 mmol) was dissolved in 5 ml of dry DMF. 4-(2-((2-chloro-5-fluoropyrimidin-4-yl)oxy)ethyl)morpholine (261mg, 1.00 mmol) and DIEA(260 mg, 2.00 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 2.0 hours at 120 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **287** (200 mg, 39%) as a white solid. (ES, m/s): 520.2[M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17 (d, *J* = 3.2 Hz, 1H), 7.13 – 7.05 (m, 2H), 7.01 – 6.94 (m, 2H), 5.28 – 5.18 (m, 1H), 4.47 (t, *J* = 5.8 Hz, 2H), 3.73 – 3.65 (m, 2H), 3.64 – 3.56 (m, 4H), 3.55 – 3.46 (m, 6H), 3.39 – 3.32 (m, 1H), 2.68 (t, *J* = 5.8 Hz, 2H), 2.65 – 2.56 (m, 1H), 2.45–2.41 (m, 4H).

[0436] Compound 288: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(pyrazolo[1,5-a]pyridin-5-ylmethylene)azetidin-1-yl)methanone



The titled compound **288** was prepared in 50% yield from 5-bromopyrazolo[1,5-a]pyridine and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-methyleneazetidin-1-yl)methanone according to the procedure outlined for compound **284**. ¹H NMR (400 MHz, CDCl₃) δ (ppm): δ 8.39 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 2.4 Hz, 1H), 7.25 (s, 1H), 6.83 (t, *J* = 1.6 Hz, 1H), 6.75-6.80 (m, 2H), 6.66-6.72 (m, 1 H), 6.53 (dd, *J* = 1.6, 7.2 Hz, 1H), 6.49 (d, *J* = 2.0 Hz, 1H), 6.25 (t, *J* = 2.0 Hz, 1H), 5.31 (dd, *J* = 6.4, 12.0 Hz, 1H), 5.12 (q, *J* = 14.0 Hz, 2H), 4.86 (q, *J* = 14.0 Hz, 2H), 3.37 (ddd, *J* = 1.6, 12.0, 13.6 Hz, 1H), 2.71 (ddd, *J* = 1.6, 6.8, 8.0 Hz, 1H). LC-MS (ESI): m/z calcd for C₂₁H₁₇F₂N₅O 393.4, found 394.3 [M+H]⁺.

[0437] Compound 289: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-methyl-1H-indazol-6-yl)methylene)azetidin-1-yl)methanone



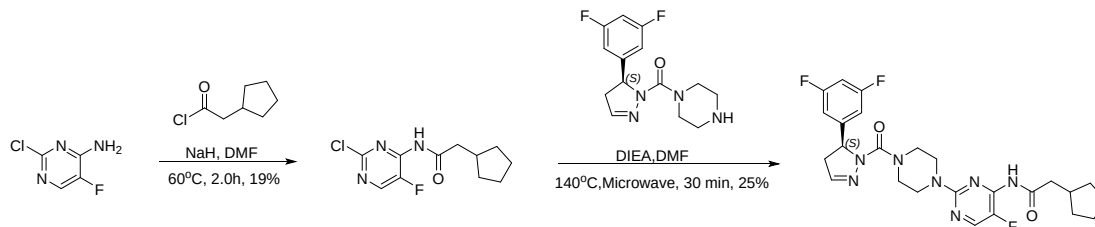
[0438] Step 1: 6-bromo-3-methyl-1H-indazole (100 mg, 0.47 mmol) was dissolved in 10 ml of dry dioxane. 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (241 mg, 0.95 mmol), Pd(dppf)Cl₂ (52 mg, 0.07 mmol), AcOK (140 mg, 1.01 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 5.0 hour at 90 °C. The mixture was filtered and concentrated in vacuo to give 3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (400 mg, crude) as brown oil which was used for next step without further purification. LC-MS (m/z): 259.2[M+H]⁺.

[0439] Step 2: 3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (400 mg, crude) was dissolved in 15 ml dioxane and 4 ml H₂O. Pd(PPh₃)₄ (82 mg, 0.07 mmol), K₂CO₃ (197 mg, 1.43 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 3.0 hour at 90 °C. The resulting solution was added H₂O and extracted with EA. The organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by silica gel chromatography to afford 20 mg of tert-butyl 3-((3-methyl-1H-indazol-6-yl)methylene)azetidine-1-carboxylate as a yellow solid. (Two-step yield: 14 %) LC-MS (m/z): 300.2[M+H]⁺.

[0440] Step 3: tert-butyl 3-((3-methyl-1H-indazol-6-yl)methylene)azetidine-1-carboxylate (20 mg, 0.07 mmol) was dissolved in 10 ml dry DCM. TFA (1 mL) was added to the above solution at room temperature. The mixture was stirred for 1 hour at room temperature. The mixture was concentrated in vacuo to give 6-(azetidin-3-ylidenemethyl)-3-methyl-1H-indazole as TFA salt (30 mg, crude) as brown oil which was used for next step without further purification. LC-MS (m/z): 200.2[M+H]⁺.

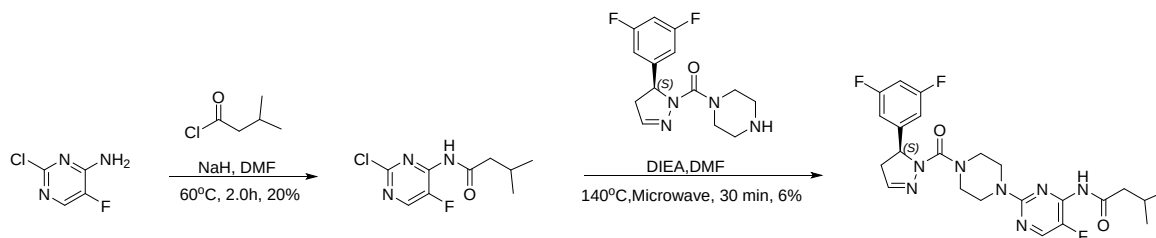
[0441] Step 4: 6-(azetidin-3-ylidenemethyl)-3-methyl-1H-indazole (20 mg, crude) was dissolved in 10 ml dry THF. TEA (0.5 mL), 3-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (22 mg, 0.08 mmol) was added to the above solution at room temperature. The mixture was stirred for 12 h at room temperature. The resulting solution was concentrated in vacuo. Purification by Prep-HPLC to give 1 mg of the titled compound **289** (yield:4 %)as a white solid. LC-MS (m/z): 408.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.13 (s, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 6.85 – 6.72 (m, 4H), 6.61 (s, 1H), 6.26 – 6.18 (m, 1H), 5.34 (dd, *J* = 12.2, 6.5 Hz, 1H), 5.13 - 4.95 (m, 2H), 4.94 - 4.76 (m, 2H), 3.52 (s, 3H), 3.44 - 3.30 (m, 1H), 2.78 - 2.64 (m, 1H).

[0442] Compound 290: (S)-2-cyclopentyl-N-(2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)-5-fluoropyrimidin-4-yl)acetamide



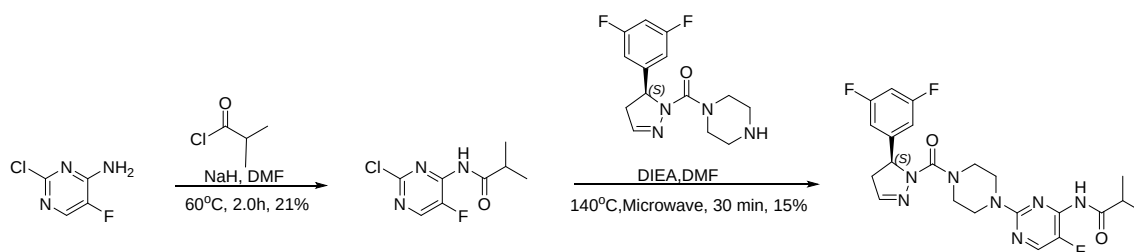
The titled compound **290** as a gray solid(21.8 mg, 25 %) was prepare from (S)-2-cyclopentyl-N-(2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)-5-fluoropyrimidin-4-yl)acetamide and N-(2-chloro-5-fluoropyrimidin-4-yl)-2-cyclopentylacetamide according to the procedure outlined for compound **225** (ES, m/s): 416.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.27 (brs, 1H), 8.30 (d, *J* = 3.0 Hz, 1H), 7.12–7.04 (m, 2H), 7.00–6.93 (m, 2H), 5.23 (m, 1H), 3.72–3.64 (m, 2H), 3.62–3.58 (m, 4H), 3.54–3.44 (m, 2H), 3.38–3.34 (m, 1H), 2.66–2.57 (m, 1H), 2.41 (d, *J* = 7.6 Hz, 2H), 2.21–2.12 (m, 1H), 1.76–1.67 (m, 2H), 1.60–1.52 (m, 1H), 1.51–1.43 (m, 1H), 1.23–1.19 (m, 2H), 1.17–1.10 (m, 2H).

[0443] Compound 291: (S)-N-(2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)-5-fluoropyrimidin-4-yl)-3-methylbutanamide



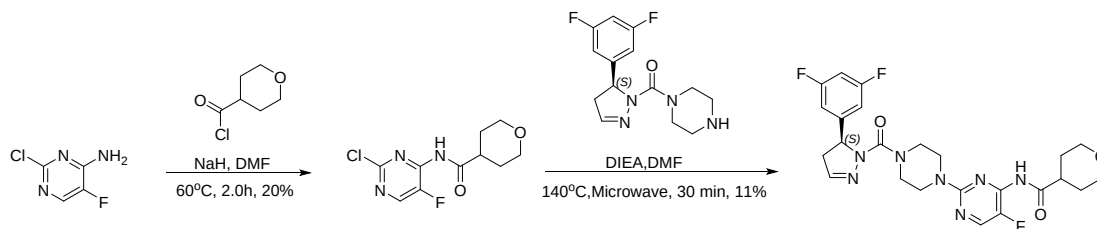
The titled compound **291** as a gray solid (5.4 mg, 6 %) was prepared from (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone and N-(2-chloro-5-fluoropyrimidin-4-yl)-3-methylbutanamide according to the procedure outlined for compound **225** (ES, m/s): 490.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.46 (brs, 1H), 8.48 (d, *J* = 3.0 Hz, 1H), 7.28–7.20 (m, 2H), 7.18–7.10 (m, 2H), 5.43–5.39 (m, 1H), 3.90–3.59 (m, 8H), 3.38–3.34 (m, 1H), 2.84–2.72 (m, 1H), 2.47–2.41 (m, 2H), 2.16–2.07 (m, 1H), 1.40–1.34 (m, 3H), 1.10–1.03 (m, 3H)

[0444] Compound 292: (S)-N-(2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)-5-fluoropyrimidin-4-yl)isobutyramide



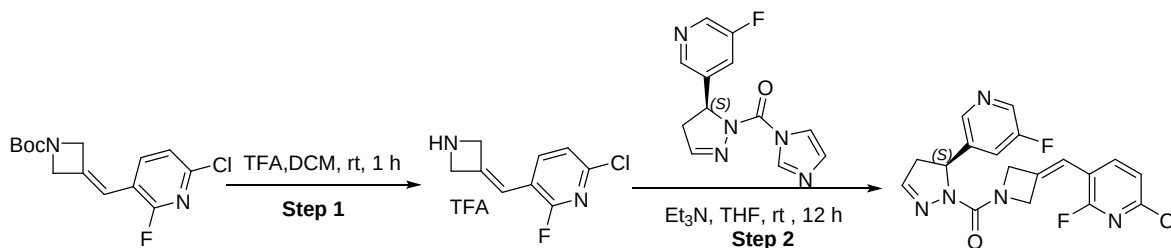
The titled compound **205** as a white solid (13.0 mg, 15 %) was prepared from (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone and N-(2-chloro-5-fluoropyrimidin-4-yl)isobutyramide according to the procedure outlined for compound **199** (ES, m/s): 476.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.26 (brs, 1H), 8.31 (d, *J* = 3.0 Hz, 1H), 7.13–7.05 (m, 2H), 7.00–6.93 (m, 2H), 5.28–5.18 (m, 1H), 3.73–3.65 (m, 2H), 3.64–3.56 (m, 4H), 3.53–3.45 (m, 2H), 3.38–3.34 (m, 1H), 2.77–2.70 (m, 1H), 2.66–2.57 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 6H).

[0445] Compound 293: (S)-N-(2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)-5-fluoropyrimidin-4-yl)tetrahydro-2H-pyran-4-carboxamide



The titled compound **293** as a white solid (10.0 mg, 11 %) was prepared from (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone and N-(2-chloro-5-fluoropyrimidin-4-yl)tetrahydro-2H-pyran-4-carboxamide according to the procedure outlined for compound **225** (ES, m/s): 518.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.31 (brs, 1H), 8.32 (d, *J* = 3.0 Hz, 1H), 7.12–7.05 (m, 2H), 7.00–6.94 (m, 2H), 5.26–5.19 (m, 1H), 3.90–3.82 (m, 2H), 3.73–3.65 (m, 2H), 3.64–3.56 (m, 2H), 3.53–3.44 (m, 2H), 3.39–3.34 (m, 1H), 2.81–2.73 (m, 1H), 2.66–2.57 (m, 1H), 1.74–1.65 (m, 4H), 1.64–1.52 (m, 4H),

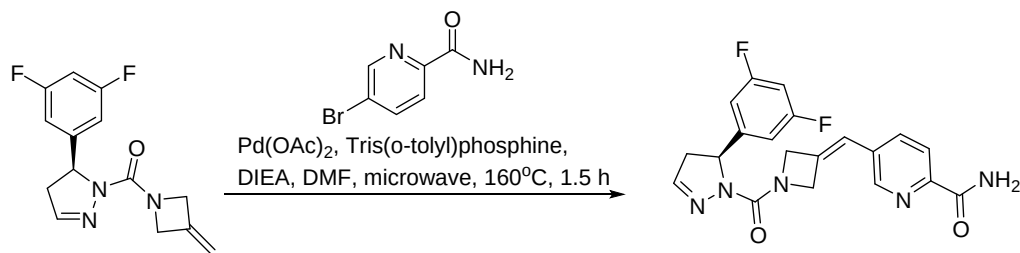
[0446] Compound 294: (S)-(3-((6-chloro-2-fluoropyridin-3-yl)methylene)azetidin-1-yl)(5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



[0447] Step 1: tert-butyl 3-((6-chloro-2-fluoropyridin-3-yl)methylene)azetidine-1-carboxylate (135 mg, 0.45 mmol) was dissolved in 10 ml dry DCM. TFA (2 mL) was added to the above solution at room temperature. The mixture was stirred for 1 hour at room temperature. The mixture was concentrated in vacuo to give 3-(azetidin-3-ylidenemethyl)-6-chloro-2-fluoropyridine (200 mg, crude) as TFA salt, which was used for next step without further purification.

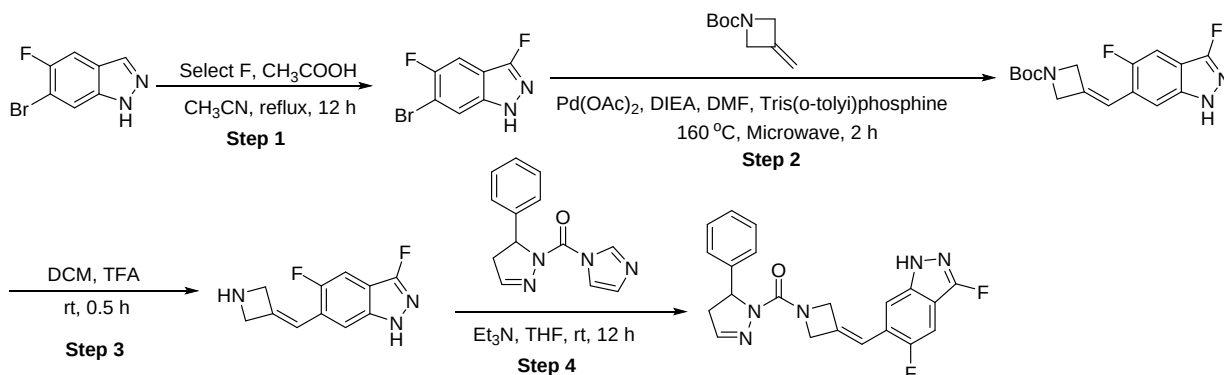
[0448] Step 2: 3-(azetidin-3-ylidenemethyl)-6-chloro-2-fluoropyridine (200 mg, crude) was dissolved in 10 ml dry THF. TEA (1 mL), SM2 (98 mg, 0.38 mmol) was added to the above solution at room temperature. The mixture was stirred for 12 h at room temperature. The resulting solution was concentrated in vacuo. Purification by silica gel chromatography to afford 85 mg of **294**: (S)-(3-((6-chloro-2-fluoropyridin-3-yl)methylene)azetidin-1-yl)(5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (yield: 58 %) as a white solid. LC-MS (m/z): 390.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.44–8.35 (m, 2H), 7.49–7.39 (m, 1H), 7.34–7.28 (m, 1H), 7.24–7.18 (m, 1H), 6.89–6.85 (m, 1H), 6.37–6.31 (m, 1H), 5.39 (dd, *J* = 12.3, 6.7 Hz, 1H), 5.10–4.76 (m, 4H), 3.44 (ddd, *J* = 18.6, 12.2, 1.8 Hz, 1H), 2.78 (ddd, *J* = 18.5, 6.7, 1.8 Hz, 1H).

[0449] Compound 295: (S)-5-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)picolinamide



(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-methyleneazetidin-1-yl)methanone (45 mg, 0.16 mmol) was dissolved in 2.5 ml DMF. 5-bromopicolinamide (30 mg, 0.15 mmol), Pd(OAc)₂ (7 mg, 0.03 mmol), DIEA (38 mg, 0.29 mmol), Tris(o-tolyl)phosphine (18 mg, 0.06 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 1.5 hour at 160 °C under Microwave. The resulting solution was added H₂O and extracted with EA. The organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by prep-HPLC to afford the titled compound (3.6 mg, 6%) as an yellow solid. LC-MS (m/z): 398.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.40 (s, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 8.02 (s, 1H), 7.63 – 7.54 (m, 1H), 6.92 – 6.86 (m, 1H), 6.82 – 6.66 (m, 2H), 6.37 (s, 1H), 5.33 (dd, *J* = 12.0, 6.2 Hz, 1H), 5.23 – 5.06 (m, 2H), 5.02 – 4.84 (m, 2H), 3.40 (ddd, *J* = 18.5, 12.2, 1.8 Hz, 1H), 2.75 (ddd, *J* = 18.6, 6.2, 1.8 Hz, 1H).

[0450] Compound 296 : (3-((3,5-difluoro-1H-indazol-6-yl)methylene)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



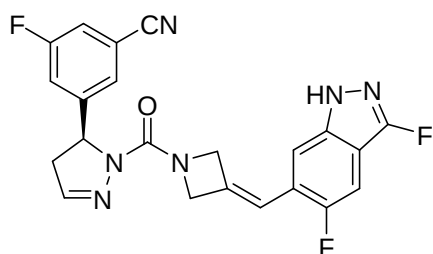
[0451] Step 1: 6-bromo-5-fluoro-1H-indazole (6.5 g, 30 mmol) was dissolved in 130 ml dry CH₃CN. Select F(16 g, 45 mmol), CH₃COOH (6.5 ml) was added to the above solution at room temperature under nitrogen protection. The mixture was heated to reflux for 12 h.

The resulting solution was concentrated in vacuo, added H₂O and extracted with EA. The organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by silica gel chromatography to afford 2.67 g of 6-bromo-3,5-difluoro-1H-indazole (yield: 38 %) as a yellow solid. LC-MS (m/z): 234.2[M+H]⁺.

[0452] Step 2: 6-bromo-3,5-difluoro-1H-indazole (300 mg, 1.29 mmol) was dissolved in 20 ml DMF. tert-butyl 3-methyleneazetidine-1-carboxylate (436 mg, 2.58 mmol), Pd(OAc)₂ (58 mg, 0.26 mmol), DIEA (332 mg, 2.57 mmol), Tris(o-tolyl)phosphine (158 mg, 0.51 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 2 hour at 160 °C under Microwave. The resulting solution was added H₂O and extracted with EA. The organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by silica gel chromatography to afford 200 mg of tert-butyl 3-((3,5-difluoro-1H-indazol-6-yl)methylene)azetidine-1-carboxylate (yield: 48%) as a light yellow solid. LC-MS (m/z): 322.3[M+H]⁺

[0453] Step 3 and 4: The title compound **105** was prepared in a yield of 19.5% as white solid from tert-butyl 3-((3,5-difluoro-1H-indazol-6-yl)methylene)azetidine-1-carboxylate and (1H-imidazol-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone according to the procedure outlined for **203**. LC-MS (m/z): 394.2[M+H]⁺. ¹H NMR (400 MHz, Methanol-d₄) δ 7.36 – 7.28 (m, 3H), 7.25 – 7.16 (m, 4H), 6.95 (t, *J* = 1.7 Hz, 1H), 6.60 – 6.56 (m, 1H), 5.30 (dd, *J* = 12.0, 5.8 Hz, 1H), 5.08 – 5.02 (m, 2H), 4.93 – 4.81 (m, 2H), 3.43 (ddd, *J* = 18.6, 12.1, 1.7 Hz, 1H), 2.70 (ddd, *J* = 18.7, 5.8, 1.8 Hz, 1H).

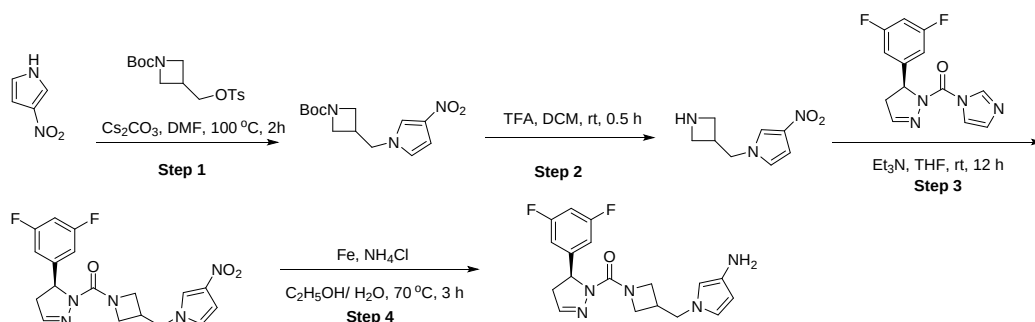
[0454] Compound 297 : (S)-3-(1-(3-((3,5-difluoro-1H-indazol-6-yl)methylene)azetidine-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)-5-fluorobenzonitrile



The titled compound **297** was prepared in 55% yield as white solid from tert-butyl 3-((3,5-difluoro-1H-indazol-6-yl)methylene)azetidine-1-carboxylate and (S)-3-(1-(1H-imidazole-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)-5-fluorobenzonitrile according to the procedure for

296. LC-MS (m/z): 437.2[M+H]⁺. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.51 – 7.43 (m, 2H), 7.39 – 7.32 (m, 2H), 7.23 – 7.18 (m, 1H), 7.01 – 6.97 (m, 1H), 6.62 – 6.57 (m, 1H), 5.39 – 5.31 (m, 1H), 5.14 – 5.04 (m, 2H), 4.95 – 4.81 (m, 2H), 3.53 – 3.43 (m, 1H), 2.80 – 2.70 (m, 1H).

[0455] Compound 298 : (S)-(3-((3-amino-1H-pyrrol-1-yl)methyl)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



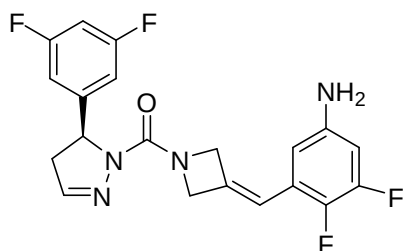
[0456] Step 1: 3-nitro-1H-pyrrole (270 mg, 0.79 mmol) was dissolved in 13 ml dry DMF. tert-butyl 3-((tosyloxy)methyl)azetidine-1-carboxylate (108 g, 0.96 mmol), Cs₂CO₃ (515 mg, 1.58 mmol) was added to the above solution at room temperature under nitrogen protection. The mixture was heated to 100 °C for 2 h. The resulting solution was added H₂O and extracted with EA. The organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified by silica gel chromatography to afford 203 mg of tert-butyl 3-((3-nitro-1H-pyrrol-1-yl)methyl)azetidine-1-carboxylate (yield: 91 %) as a white solid. LC-MS (m/z): 282.2[M+H]⁺.

[0457] Step 2 and Step 3: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-nitro-1H-pyrrol-1-yl)methyl)azetidin-1-yl)methanone (218 mg) was prepared in 78% yield as white solid from tert-butyl 3-((3-nitro-1H-pyrrol-1-yl)methyl)azetidine-1-carboxylate and (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone according to the procedure outlined for **203**.

[0458] Step 4: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-nitro-1H-pyrrol-1-yl)methyl)azetidin-1-yl)methanone (30 mg, 0.08 mmol) in EtOH/H₂O (12 ml v:v=5:1) was added Fe (52mg, 0.93mmol), NH₄Cl (42mg, 0.79mmol) under nitrogen protection at rt. The mixture was stirred at 70°C for 3 h, the resulting solution was filtrated and evaporated to give 100 mg crude product. The crude product was purified by pre-

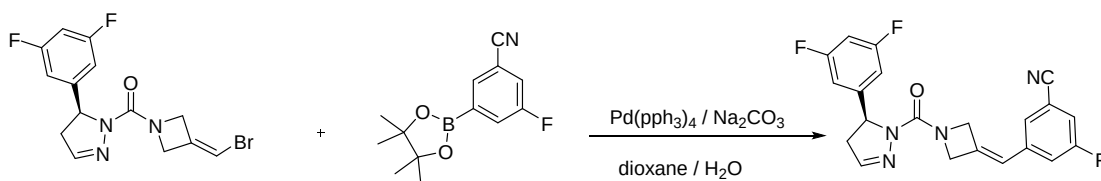
HPLC to afford the titled compound **298** (6.2 mg, 22%) as an yellow solid. LC-MS (m/z): 360.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.84 – 6.58 (m, 5H), 6.56 – 6.42 (m, 1H), 6.09 – 5.94 (m, 1H), 5.31 – 5.13 (m, 1H), 4.34 – 4.10 (m, 2H), 4.06 – 3.92 (m, 2H), 3.91 – 3.70 (m, 2H), 3.40 – 3.24 (m, 1H), 2.88 (s, 1H), 2.75 – 2.56 (m, 1H).

[0459] Compound 299: (S)-(3-(5-amino-2,3-difluorobenzylidene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



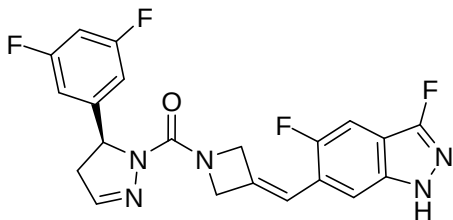
The title compound **299** was prepared in a yield of 4.5% as gray solid from (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-methyleneazetidin-1-yl)methanone and 3-bromo-4,5-difluoroaniline according to the procedure outlined for **294**. LC-MS (m/z): 405.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.81 (t, *J* = 1.7 Hz, 1H), 6.80 – 6.73 (m, 2H), 6.69 (tt, *J* = 8.9, 2.3 Hz, 1H), 6.41 – 6.33 (m, 2H), 6.12 – 6.08 (m, 1H), 5.31 (dd, *J* = 12.1, 6.5 Hz, 1H), 5.06 – 4.93 (m, 2H), 4.89 – 4.77 (m, 2H), 3.37 (ddd, *J* = 18.5, 12.2, 1.7 Hz, 1H), 2.71 (ddd, *J* = 18.5, 6.5, 1.7 Hz, 1H).

[0460] Compound 300: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(3-fluoro-5-isocyanobenzylidene)azetidin-1-yl)methanone



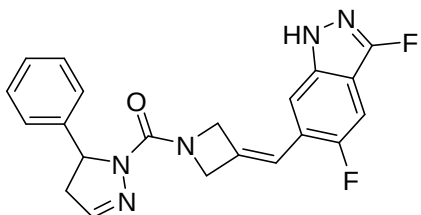
The titled compound **300** was prepared in an analogous manner to the preparation of compound **244** yield:54.5% ¹H NMR (400 MHz, Chloroform-*d*) δ 7.39(dd, *J* = 9.0, 1.6 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.91 – 6.58 (m, 4H), 6.49 (s, 1H), 5.31 (dd, *J* = 12.0, 6.4 Hz, 1H), 5.13-4.65 (m, 4H), 3.45-3.32 (m, 1H), 2.738-2.68(m, 1H). LC-MS (m/z) 397.2(M+H⁺).

[0461] Compound 301 : (S)-(3-((3,5-difluoro-1H-indazol-6-yl)methylene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



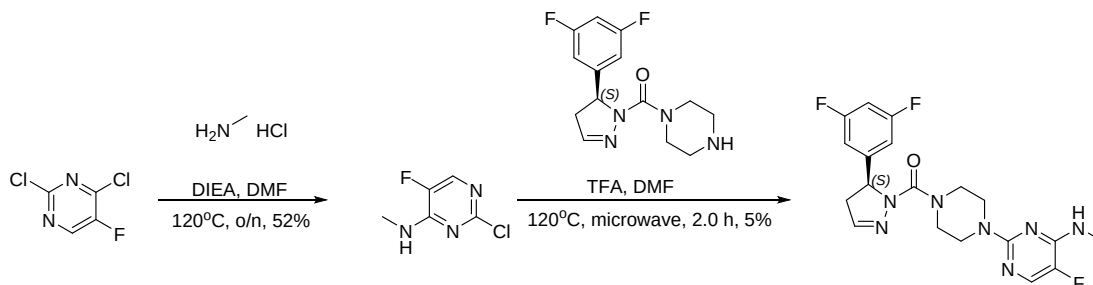
The titled compound **301** was prepared in an analogous manner to the preparation of compound **296**. yield:38.7%. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.37 (s, 1H), 7.34–7.29 (m, 1H), 7.04 (d, J = 5.6 Hz, 1H), 6.83 (d, J = 1.7 Hz, 1H), 6.81 – 6.73 (m, 2H), 6.72–6.63 (m, 1H), 6.57 (s, 1H), 5.41 – 5.30 (m, 1H), 5.13–4.85 (m 4H), 3.44–3.34 (m, 1H), 2.79–2.66 (m, 1H). LC-MS (m/z) 430.2($\text{M}+\text{H}^+$).

[0462] Compound 302: (3-((3,5-difluoro-1H-indazol-6-yl)methylene)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **302** was prepared in an analogous manner to the preparation of **296**. LC-MS (m/z): 394.2[$\text{M}+\text{H}$] $^+$. ^1H NMR (400 MHz, Methanol-*d*₄) δ 7.36 – 7.28 (m, 3H), 7.25 – 7.16 (m, 4H), 6.95 (t, J = 1.7 Hz, 1H), 6.60 – 6.56 (m, 1H), 5.30 (dd, J = 12.0, 5.8 Hz, 1H), 5.08 – 5.02 (m, 2H), 4.93 – 4.81 (m, 2H), 3.43 (ddd, J = 18.6, 12.1, 1.7 Hz, 1H), 2.70 (ddd, J = 18.7, 5.8, 1.8 Hz, 1H).

[0463] Compound 303 : (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-(5-fluoro-4-(methylamino)pyrimidin-2-yl)piperazin-1-yl)methanone

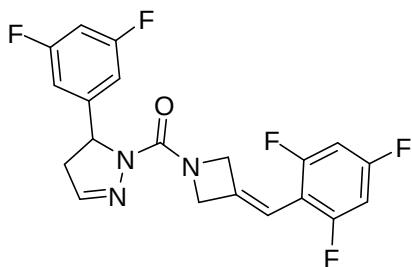


[0464] Step 1 : 2-chloro-5-fluoro-N-methylpyrimidin-4-amine. 2,4-dichloro-5-fluoropyrimidine (1.0 g, 5.98 mmol) was dissolved in 20 ml of dry DMF. DIEA (1.8 g, 13.95 mmol) and Methylamine hydrochloride (474 mg, 7.18 mmol) were added to the

above solution under nitrogen at room temperature. The mixture was stirred for 1 overnight at 120 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound (500 mg, 52%) as a white solid . (ES, m/s): 162.1 [M+H]⁺

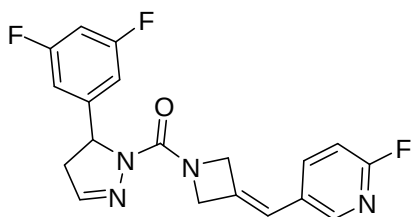
[0465] Step 2: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-(5-fluoro-4-(methylamino)pyrimidin-2-yl)piperazin-1-yl)methanone. (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone (295 mg, 1.00 mmol) was dissolved in 5 ml of dry DMF. 2-chloro-5-fluoro-N-methylpyrimidin-4-amine (161mg, 1.00 mmol) and TFA(1 mL) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 1.0 hours at 120 degrees C under microwave . The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **303**(21.8 mg, 5%) as a white solid. (ES, m/s): 420.4[M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.74 (d, *J* = 4.0 Hz, 1H), 7.25 (d, *J* = 5.2 Hz, 1H), 7.13 – 7.05 (m, 2H), 6.99–6.96 (m, 2H), 5.27 – 5.18 (m, 1H), 3.70 – 3.62 (m, 2H), 3.61 – 3.52 (m, 4H), 3.51 – 3.41 (m, 2H), 3.37–3.32 (m, 1H), 2.81 (d, *J* = 4.6 Hz, 3H), 2.66–2.58 (m, 1H).

[0466] Compound 304 : (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(2,4,6-trifluorobenzylidene) azetidin-1-yl)methanone



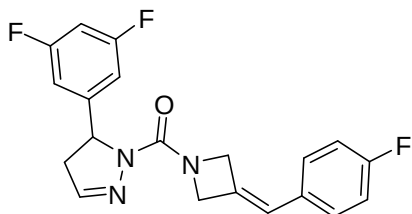
The titled compound **304** was prepared in an analogous manner to the preparation of **296** yield:14.8%. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.86 – 6.73 (m, 3H), 6.72 – 6.54 (m, 3H), 6.24 – 6.19 (m, 1H), 5.30 (dd, *J* = 12.0, 6.4Hz, 1H), 4.95-4.68 (m, 4H), 3.44-3.30(m, 1H), 2.77-2.63 (m, 1H). LC-MS (m/z) 408.3 (M+H⁺).

[0467] Compound 305: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((6-fluoropyridin-3-yl)methylene)azetidin-1-yl)methanone



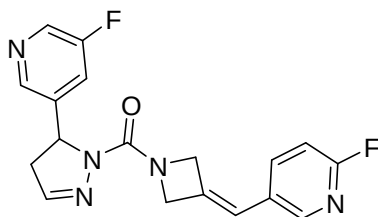
The titled compound **305** was prepared in an analogous manner to the preparation of **296** yield: 97.0%. ^1H NMR (400 MHz, DMSO- d_6) δ 8.11 (d, J = 2.4 Hz, 1H), 7.81-7.7 (m, 1H), 7.19 (dd, J = 8.4, 2.8 Hz, 1H), 7.14-7.07 (m, 1H), 7.08 – 7.02 (m, 1H), 6.99 – 6.88 (m, 2H), 6.42 (t, J = 2.4 Hz, 1H), 5.27 (dd, J = 12.0, 6.4 Hz, 1H), 5.09-4.90 (m, 2H), 4.83-7.66 (m, 2H), 3.47 – 3.35 (m, 1H), 2.70-2.60 (m, 1H). LC-MS (m/z) 373.3($M+H^+$).

[0468] Compound 306: (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(4-fluorobenzylidene)azetidin-1-yl)methanone



The titled compound **306** was prepared in an analogous manner to the preparation of **296**. yield: 22.8%. ^1H NMR (400 MHz, Chloroform- d) δ 7.15 – 6.91 (m, 4H), 6.85 – 6.72 (m, 3H), 6.72 – 6.63 (m, 1H), 6.24 (s, 1H), 5.32 (dd, J = 12.4, 6.4 Hz, 1H), 5.13-4.98 (m, 2H), 4.90-4.75 (m, 2H), 3.37 (dd, J = 18.4, 11.6 Hz, 1H), 2.72 (dd, J = 18.4, 5.8 Hz, 1H). LC-MS (m/z) 372.3($M+H^+$).

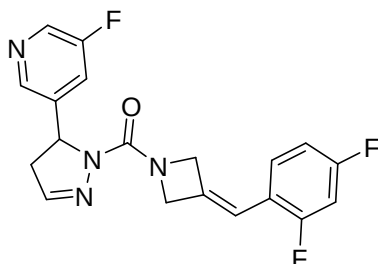
[0469] Compound 307: (5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((6-fluoropyridin-3-yl)methylene)azetidin-1-yl)methanone



The titled compound **307** was prepared in an analogous manner to the preparation of **296** yield: 25.5%. ^1H NMR (400 MHz, Chloroform- d) δ 8.60-8.33 (m, 2H), 8.03 (d, J = 2.4 Hz, 1H), 7.63 – 7.46 (m, 2H), 6.97 – 6.85 (m, 2H), 6.28 (t, J = 2.3 Hz, 1H), 5.45 (dd, J = 12.0,

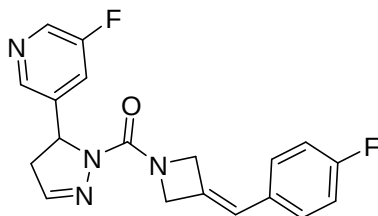
6.0 Hz, 1H), 5.15-4.99(m, 2H), 4.93-4.77(m, 2H), 3.56 – 3.41 (m, 1H), 2.87 – 2.73 (m, 1H). LC-MS (m/z) 3563(M+H⁺).

[0470] Compound 308: (3-(2,4-difluorobenzylidene)azetidin-1-yl)(5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



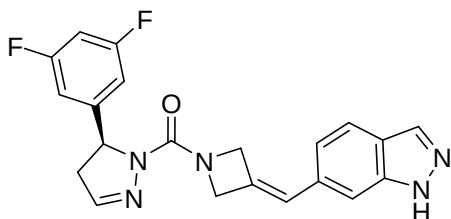
The titled compound **308** was prepared in an analogous manner to the preparation of **296** yield:30.8%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.59-8.31(m, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.05 (q, *J* = 8.4 Hz, 1H), 6.92 – 6.68 (m, 3H), 6.40 (s, 1H), 5.50-5.39 (m, 1H), 5.12-4.72(m, 4H), 3.47 (dd, *J* = 18.4, 12.0 Hz, 1H), 2.80 (dd, *J* = 18.0, 6.4 Hz, 1H). LC-MS (m/z) 373.3(M+H⁺).

[0471] Compound 309: (3-(4-fluorobenzylidene)azetidin-1-yl)(5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



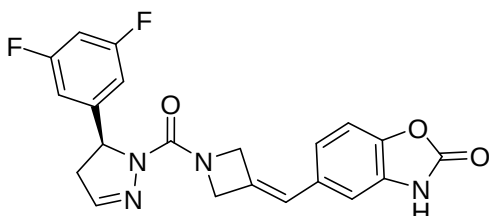
The titled compound **309** was prepared in an analogous manner to the preparation of **296** . yield:23.1%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.59-8.30 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.06 – 6.96 (m, 2H), 6.87 (s, 1H), 6.24 (t, *J* = 2.4 Hz, 1H), 5.41 (dd, *J* = 12.0, 6.4 Hz, 1H), 5.09-4.94(m, 2H), 4.90-4.74 (m, 2H), 3.51 – 3.35 (m, 1H), 2.82-2.73 (m, 1H). LC-MS (m/z) 355.2(M+H⁺).

[0472] Compound 310: (S)-(3-((1H-indazol-6-yl)methylene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



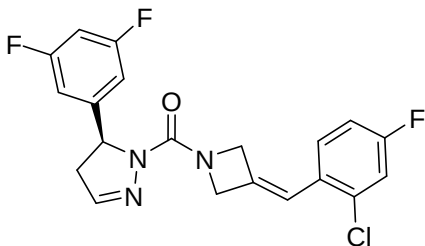
The titled compound **310** was prepared in an analogous manner to the preparation of **296**.
 yield:32.1%. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.87 (s, 1H), 7.58 (dd, J = 8.4, 3.1 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.17-7.09 (m, 1H), 6.92 – 6.71 (m, 2H), 6.70 – 6.54 (m, 2H), 6.35 – 6.21 (m, 1H), 5.18 (dd, J = 12.0, 6.0 Hz, 1H), 5.08-4.90 (m, 2H), 4.87-4.70 (m, 2H), 3.37–3.14 (m, 2H), 2.70–2.52 (m, 1H). LC-MS $[\text{M}+\text{H}]^+$:394.2

[0473] Compound 311: (S)-5-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)benzo[d]oxazol-2(3H)-one



The titled compound **311** was prepared in an analogous manner to the preparation of **296**.
 yield:54.2%. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.05 (d, J = 8.3 Hz, 1H), 6.81 – 6.75 (m, 2H), 6.74 – 6.66 (m, 3H), 6.66 – 6.56 (m, 1H), 6.19 (t, J = 2.4 Hz, 1H), 5.26 – 5.18 (m, 1H), 5.02-4.70 (m, 4H), 3.38 – 3.26 (m, 1H), 2.70-2.60 (m, 1H). LC-MS (m/z) 411.2($\text{M}+\text{H}^+$).

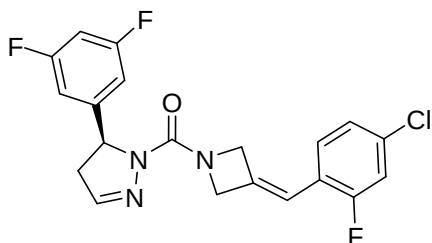
[0474] Compound 312: (S)-(3-(2-chloro-4-fluorobenzylidene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **312** was prepared in an analogous manner to the preparation of **296**.
 yield:31.3%. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.14 (dd, J = 8.4, 2.4 Hz, 1H), 7.10 (dd, J = 8.8, 6.0 Hz, 1H), 7.00 – 6.92 (m, 1H), 6.81 (t, J = 1.7 Hz, 1H), 6.77 (dt, J = 6.5, 2.1 Hz,

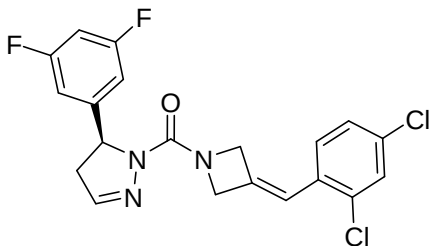
2H), 6.72 – 6.65 (m, 1H), 6.62 – 6.56 (m, 1H), 5.31 (q, $J = 6.4$ Hz, 1H), 5.09-4.67(m, 4H), 3.44-3.30 (m, 1H), 2.76-2.65 (m, 1H). LC-MS (m/z) 406.2($M+H^+$).

[0475] Compound 313: (S)-(3-(2,4-dichlorobenzylidene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



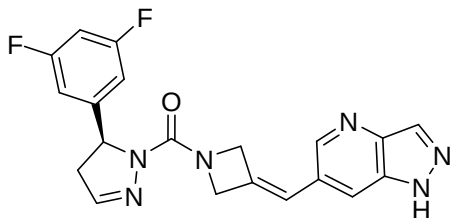
The titled compound **313** was prepared in an analogous manner to the preparation of **296** yield:25.1%. ^1H NMR (400 MHz, Chloroform- d) δ 7.13 – 7.06 (m, 2H), 7.05 – 6.97 (m, 1H), 6.82 (t, $J = 1.7$ Hz, 1H), 6.80 – 6.73 (m, 2H), 6.73 – 6.63 (m, 1H), 6.40 (t, $J = 2.4$ Hz, 1H), 5.31 (q, $J = 6.0$ Hz, 1H), 5.10-4.76 (m, 4H), 3.42-3.32 (m, 1H), 2.75-2.67 (m, 1H). LC-MS (m/z) 406.2($M+H^+$).

[0476] Compound 314: (S)-(3-(2,4-dichlorobenzylidene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



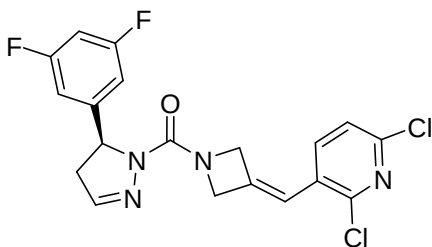
The titled compound **314** was prepared in an analogous manner to the preparation of **296** yield:65.6%. ^1H NMR (400 MHz, Chloroform- d) δ 7.40 (d, $J = 2.2$ Hz, 1H), 7.24-7.19 (m, 1H), 7.05 (d, $J = 8.4$ Hz, 1H), 6.82 (t, $J = 1.6$ Hz, 1H), 6.79 – 6.73 (m, 2H), 6.72 – 6.65 (m, 1H), 6.61 (t, $J = 2.4$ Hz, 1H), 5.34 – 5.26 (q, $J = 6.0$ Hz, 1H, 1H), 5.10-4.78 (m, 4H), 3.42-3.32 (m, 1H), 2.76-2.67 (m, 1H). LC-MS [$M+H$] $^+$:422.1

[0477] Compound 315: (S)-(3-((1H-pyrazolo[4,3-b]pyridin-6-yl)methylene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



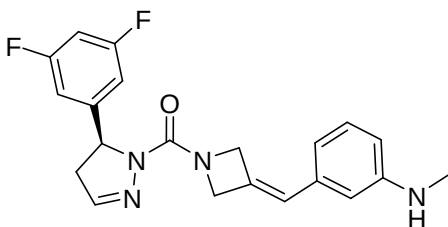
The titled compound **315** was prepared in an analogous manner to the preparation of **296** .
 yield:27.9%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.34 (s, 2H), 7.53 (s 1H), 6.84 (t, *J* = 1.6 Hz, 1H), 6.80 – 6.71 (m, 2H), 6.71 – 6.63 (m, 1H), 6.46-6.40(m, 1H), 5.30 (q *J* = 6.0Hz, 1H), 5.21 – 4.73 (m, 4H), 3.46 – 3.32 (m, 1H), 2.76-2.67(m, 1H). LC-MS (*m/z*) 395.2(M+H⁺).

[0478] Compound 316: (S)-3-((2,6-dichloropyridin-3-yl)methylene)azetidin-1-yl(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **316** was prepared in an analogous manner to the preparation of **296** .
 yield:30.4%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 8.0 Hz, 1H), 7.27-7.25 (m, 1H), 6.83 (t, *J* = 1.6 Hz, 1H), 6.80 – 6.72 (m, 2H), 6.72-6.67 (m, 1H), 6.57 (p, *J* = 2.4 Hz, 1H), 5.30 (dd, *J* = 12.0, 6.4 Hz, 1H), 5.05-4.82 (m, 4H), 3.43-3.34 (m, 1H), 2.77-2.68(m, 1H). LC-MS (*m/z*) 423.2(M+H⁺).

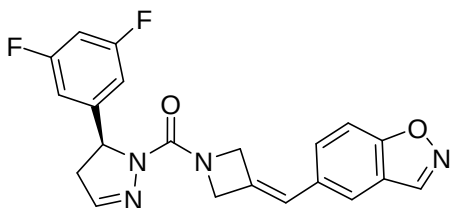
[0479] Compound 317: (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-(3-(methylamino)benzylidene)azetidin-1-yl)methanone



The titled compound **317** was prepared in an analogous manner to the preparation of **296** .
 yield:12.7%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.06 – 6.99 (m, 2H), 6.87 – 6.72 (m, 3H), 6.68 (t, *J* = 8.8 Hz, 1H),

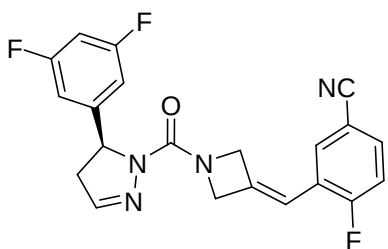
6.23 (s, 1H), 5.36-5.31 (m, 1H), 5.05 – 4.79 (m, 4H), 3.43-3.31 (m, 1H), 2.99 (s, 3H), 2.76-2.67 (m, 1H). LC-MS (m/z) 383.2(M+H⁺).

[0480] Compound 318: (S)-3-(benzo[d]isoxazol-5-ylmethylene)azetidin-1-yl(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **318** was prepared in an analogous manner to the preparation of **296** yield:27.3%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.18 (s, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.31 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.15 – 7.07 (m, 1H), 7.07 – 7.04 (m, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.98 – 6.89 (m, 2H), 6.29 – 6.22 (m, 1H), 5.27 (dd, *J* = 12.0, 6.8 Hz, 1H), 4.95 (s, 2H), 4.71 (s, 2H), 3.45-3.36 (m, 1H), 2.69-2.61 (m, 1H). LC-MS (m/z) 395.3(M+H⁺).

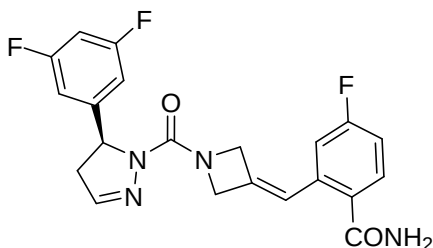
[0481] Compound 319: (S)-3-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)-4-fluorobenzonitrile



The titled compound **319** was prepared in an analogous manner to the preparation of **296** yield:77.3%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.55-7.50 (m, 1H), 7.39 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.17 (dd, *J* = 9.6, 8.4 Hz, 1H), 6.86 (t, *J* = 1.6 Hz, 1H), 6.82 – 6.74 (m, 2H), 6.73-6.66 (m, 1H), 6.44 (q, *J* = 2.4 Hz, 1H), 5.38 – 5.26 (m, 1H), 5.05 (q, *J* = 15.6, 15.1 Hz, 2H), 4.84 (q, *J* = 15.2 Hz, 2H), 3.44-3.33 (m, 1H), 2.78-2.69m, 1H).

LC-MS (m/z) 397.3(M+H⁺).

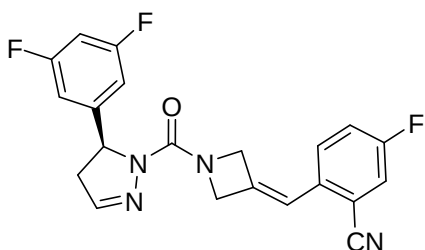
[0482] Compound 320 (S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)-4-fluorobenzamide



The titled compound **320** was prepared in an analogous manner to the preparation of **296** .
 yield:34.5%. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.22 (m, 1H), 7.18-7.10 (, 2H), 6.81 (t, J = 1.6 Hz, 1H), 6.79 – 6.73 (m, 2H), 6.73 – 6.64 (m, 2H), 5.86 (brs, 2H), 5.38 – 5.22 (m, 1H), 5.05-4.95 (m, 4H), 3.45 – 3.26 (m, 1H), 2.76-2.66 (m, 1H).

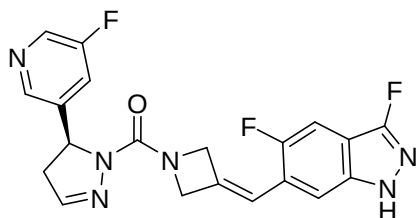
LC-MS (m/z) 415.2(M+H⁺).

[0483] Compound 321: (S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)-5-fluorobenzonitrile



The titled compound **321** was prepared in an analogous manner to the preparation of **296**
 yield: 9.0%. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.35 (dd, J = 8.0, 2.8 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.18 (dd, J = 8.8, 5.2 Hz, 1H), 6.83 (t, J = 1.6 Hz, 1H), 6.80-6.74 (m, 2H), 6.73 – 6.61 (m, 2H), 5.34-5.28 (m, 1H), 5.11 – 4.78 (m, 4H), 3.44-3.33 (m, 1H), 2.77-2.67(m, 1H). LC-MS (m/z) 397.2(M+H⁺).

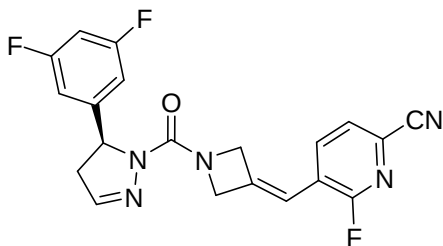
[0484] Compound 322: (S)-3-((3,5-difluoro-1H-indazol-6-yl)methylene)azetidin-1-yl)(5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **322** was prepared in an analogous manner to the preparation of **296**
 yield: 19.0%. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.45 (brs, 1H), 8.47 – 8.33 (m, 2H), 7.39 (d, J = 8.8 Hz, 1H), 7.42-7.36 (m 1H), 7.03 (dd, J = 5.6, 2.4 Hz, 1H), 6.91 – 6.85 (m,

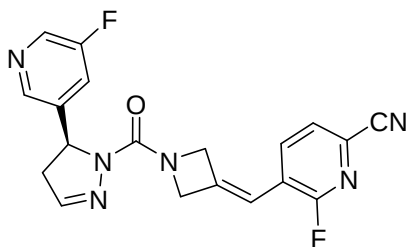
1H), 6.60-6.55 (m, 1H), 5.45 (dd, $J = 12.4, 6.4$ Hz, 1H), 5.15-4.79(m, 4H), 3.53-3.41 (m, 1H), 2.85-2.74 (m, 1H). LC-MS (m/z) 413.2(M+H⁺).

[0485] Compound 323 : (S)-5-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)-6-fluoropicolinonitrile



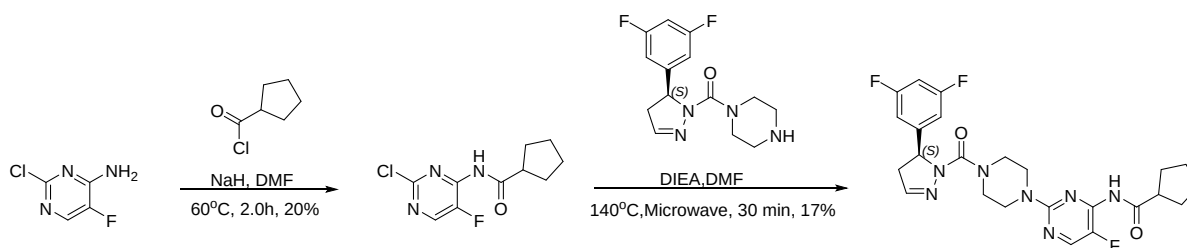
The titled compound **323** was prepared in an analogous manner to the preparation of **296** yield:27.3%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 7.55 (m, 2H), 6.84 (t, $J = 1.6$ Hz, 1H), 6.80 – 6.64 (m, 3H), 6.44 (p, $J = 2.4$ Hz, 1H), 5.36-5.28 (m, 1H), 5.18 – 4.71 (m, 4H), 3.45-3.34 (m, 1H), 2.79-2.69 (m, 1H). LC-MS (m/z) 389.2(M+H⁺).

[0486] Compound 324 : (S)-6-fluoro-5-((1-(5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)picolinonitrile



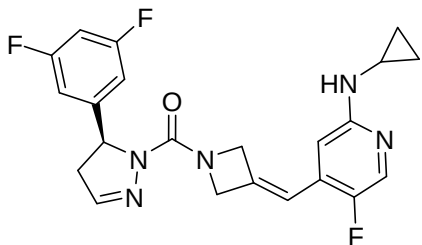
The titled compound **324** was prepared in an analogous manner to the preparation of **296** yield:21.4%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.89-8.24 (m, 2H), 7.72 – 7.53 (m, 3H), 6.95 (d, $J = 1.6$ Hz, 1H), 6.46 (t, $J = 2.4$ Hz, 1H), 5.48 (dd, $J = 12.4, 6.8$ Hz, 1H), 5.54-5.43 (m, 4H), 3.60-3.43 (m, 1H), 2.95 – 2.80 (m, 1H). LC-MS (m/z) 381.2(M+H⁺).

[0487] Compound 325: (S)-N-(2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)-5-fluoropyrimidin-4-yl)cyclopentanecarboxamide



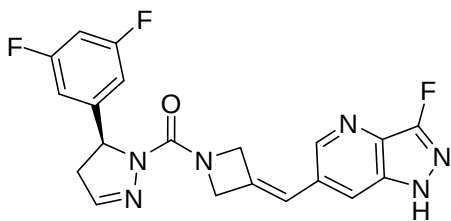
The titled compound **325** as a white solid(14.4 mg, 17 %) was prepare from (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone and N-(2-chloro-5-fluoropyrimidin-4-yl)cyclopentanecarboxamide according to the procedure outlined for compound **225** (ES, m/s): 502.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.27 (brs, 1H), 8.31 (d, *J* = 3.0 Hz, 1H), 7.12–7.02 (m, 2H), 7.02–6.91 (m, 2H), 5.24 (m, 1H), 3.73–3.65 (m, 2H), 3.64–3.56 (m, 4H), 3.54–3.43 (m, 2H), 3.39–3.33 (m, 1H), 2.87–2.95(m, 1H), 2.65–2.58 (m, 1H), 1.88–1.74 (m, 2H), 1.71–1.57 (m, 4H), 1.55–1.47(m, 2H).

[0488] Compound 326 : (S)-(3-((2-(cyclopropylamino)-5-fluoropyridin-4-yl)methylene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



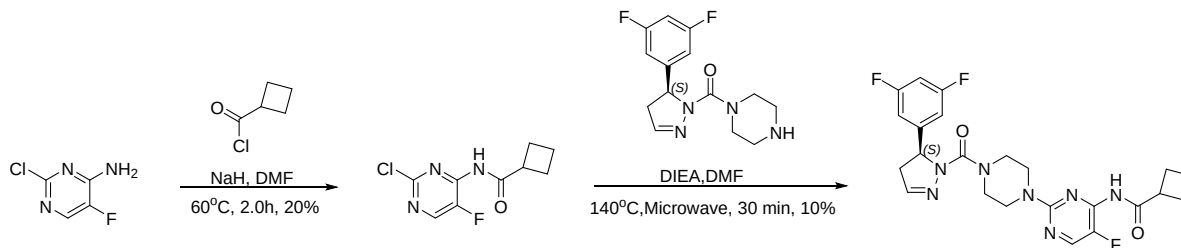
The titled compound **326** was prepared in an analogous manner to the preparation of **105**. yield:23.4%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.69 (s, 1H), 7.24 – 7.16 (m, 1H), 6.85 (s, 1H), 6.81 – 6.62 (m, 3H), 6.11 (s, 1H), 5.31 (dd, *J* = 12.0, 6.4 Hz, 1H), 5.14-4.70 (m, 4H), 3.47 – 3.32 (m, 1H), 3.01-2.93 (m, 1H), 2.79-2.68 (m, 1H), 0.99-0.90 (m, 2H), 0.78-0.68 (m, 2H). LC-MS (m/z) 428.4(M+H⁺).

[0489] Compound 327 : (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((3-fluoro-1H-pyrazolo[4,3-b]pyridin-6-yl)methylene)azetidin-1-yl)methanone



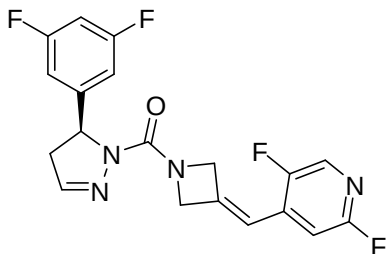
The titled compound **327** was prepared in an analogous manner to the preparation of **296** yield:6.8%. ¹H NMR (400 MHz, Chloroform-*d*) δ 10.09 (brs, 1H), 8.45 (s, 1H), 7.39 (s, 1H), 6.86 (s, 1H), 6.82 – 6.72 (m, 2H), 6.72-6.62 (m, 1H), 6.44 (s, 1H), 5.37 (dd, *J* = 12.4, 6.4 Hz, 1H), 5.21 – 4.78 (m, 4H), 3.47-3.35 (dd, *J* = 18.4, 12.0 Hz, 1H), 2.74 (dd, *J* = 18.4, 6.0 Hz, 1H). LC-MS (m/z) 413.3(M+H⁺).

[0490] Compound 328: (S)-N-(2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)-5-fluoropyrimidin-4-yl)cyclobutanecarboxamide



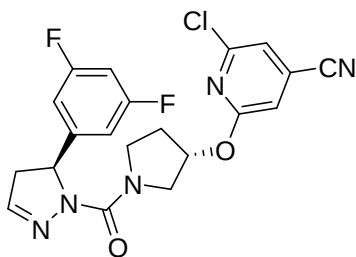
The titled compound **328** as a white solid (9.8 mg, 10 %) was prepared from (S)-1-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-oxo-1H-pyrazol-5-yl)piperazine-1-carboxamide and N-(2-chloro-5-fluoropyrimidin-4-yl)cyclobutanecarboxamide according to the procedure outlined for compound **225** (ES, m/s): 488.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.17 (brs, 1H), 8.31 (d, *J* = 3.0 Hz, 1H), 7.13–7.05 (m, 2H), 7.01–6.93 (m, 2H), 5.27–5.17 (m, 1H), 3.73–3.45 (m, 8H), 3.42–3.36 (m, 1H), 3.35–3.33 (m, 1H), 2.66–2.57 (m, 1H), 2.20–2.04 (m, 2H), 2.00–1.86 (m, 2H), 1.82–1.71 (m, 2H).

[0491] Compound 329 : (S)-1-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-oxo-1H-pyrazol-5-yl)-3-(2,5-difluoropyridin-4-yl)methyleneazetidin-2-ylmethanone



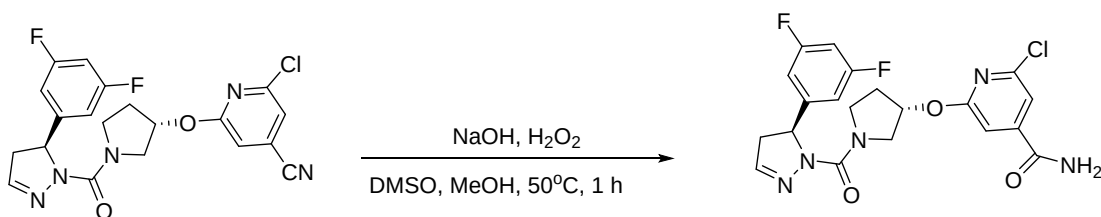
The titled compound **329** was prepared in an analogous manner to the preparation of **296** ¹H NMR (400 MHz, Chloroform-*d*) δ 6.95–6.91 (m, 1H), 6.84–6.66 (m, 4H), 6.58–6.56 (m, 1H), 6.43 (s, 1H), 5.29 (dd, *J* = 16.0, 8.0 Hz, 1H), 5.07–5.06 (m, 2H), 4.88–4.84 (m, 2H), 3.42–3.33 (m, 1H), 2.76–2.69 (m, 1H).

[0492] Compound 330 : 2-chloro-6-(((S)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)isonicotinonitrile



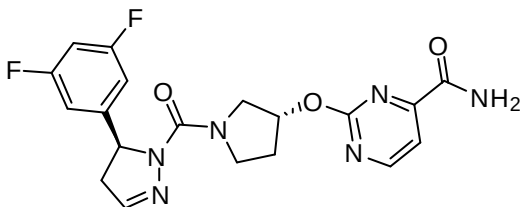
The titled compound **330** was prepared in an analogous manner to the preparation of compound **203**. LC-MS (m/z): 432.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 7.14 – 7.11 (m, 1H), 6.92 – 6.88 (m, 1H), 6.84 – 6.76 (m, 3H), 6.74 – 6.65 (m, 1H), 5.61 (s, 1H), 5.36 – 5.27 (m, 1H), 4.03 – 3.94 (m, 1H), 3.91 – 3.80 (m, 1H), 3.73 (d, J = 12.7 Hz, 2H), 3.38 – 3.27 (m, 1H), 2.73 – 2.62 (m, 1H), 2.26 – 2.11 (m, 2H).

[0493] Compound 331: 2-chloro-6-(((S)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)isonicotinamide



The titled compound **331** was prepared from 2-chloro-6-(((S)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)isonicotinonitrile by hydrolysis reaction using NaOH and H_2O_2 . LC-MS (m/z): 450.1 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 7.30 – 7.28 (m, 1H), 6.93 (d, J = 1.2 Hz, 1H), 6.83 – 6.76 (m, 3H), 6.68 (tt, J = 8.9, 2.3 Hz, 1H), 5.65 – 5.61 (m, 1H), 5.32 (dd, J = 11.9, 9.1 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.91 – 3.81 (m, 1H), 3.79 – 3.65 (m, 2H), 3.33 (ddd, J = 18.4, 12.1, 1.8 Hz, 1H), 2.67 (ddd, J = 18.3, 9.3, 1.7 Hz, 1H), 2.28 – 2.09 (m, 2H).

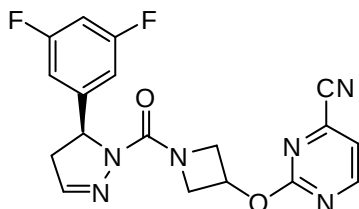
[0494] Compound 332 :2-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyrimidine-4-carboxamide



The titled compound **332** was prepared in an analogous manner to the preparation of **256**. LC-MS (m/z): 417.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.58 (s, 1H), 7.80 (s,

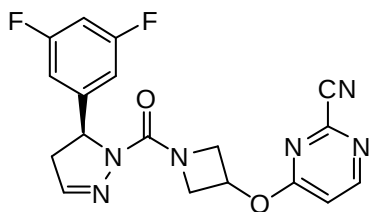
1H), 6.91 – 6.85 (m, 1H), 6.84 – 6.75 (m, 3H), 6.69 (tt, $J = 8.9, 2.2$ Hz, 1H), 6.30 (s, 1H), 5.86 (s, 1H), 5.33 (dd, $J = 12.0, 9.0$ Hz, 1H), 4.09 – 3.99 (m, 1H), 3.93 – 3.70 (m, 3H), 3.40 – 3.27 (m, 1H), 2.73 – 2.64 (m, 1H), 2.38 – 2.17 (m, 2H).

[0495] Compound 333: (S)-2-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)pyrimidine-4-carbonitrile



The titled compound **333** was prepared in an analogous manner to the preparation of **256**
LC-MS (m/z): 385.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.77 (d, $J = 4.7$ Hz, 1H), 7.33 (d, $J = 4.8$ Hz, 1H), 6.79 (t, $J = 1.7$ Hz, 1H), 6.77 – 6.73 (m, 2H), 6.69 (tt, $J = 8.9, 2.3$ Hz, 1H), 5.39 (tt, $J = 6.6, 4.2$ Hz, 1H), 5.28 (dd, $J = 12.2, 6.5$ Hz, 1H), 4.66 – 4.52 (m, 2H), 4.34 – 4.19 (m, 2H), 3.35 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.69 (ddd, $J = 18.6, 6.5, 1.7$ Hz, 1H).

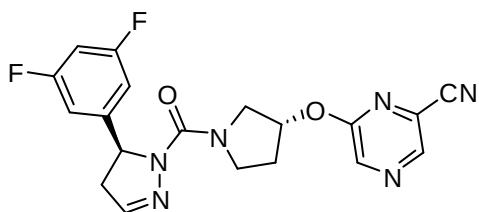
[0496] Compound 334 : (S)-4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)pyrimidine-2-carbonitrile



The titled compound **334** was prepared in an analogous manner to the preparation of **256**
LC-MS (m/z): 385.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.57 (d, $J = 5.8$ Hz, 1H), 7.00 (d, $J = 5.8$ Hz, 1H), 6.82 (t, $J = 1.7$ Hz, 1H), 6.76 – 6.73 (m, 2H), 6.70 (tt, $J = 8.9, 2.3$ Hz, 1H), 5.45 (tt, $J = 6.6, 4.1$ Hz, 1H), 5.28 (dd, $J = 12.2, 6.3$ Hz, 1H), 4.71 – 4.55 (m, 2H), 4.28 – 4.17 (m, 2H), 3.36 (ddd, $J = 18.7, 12.2, 1.7$ Hz, 1H), 2.71 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H).

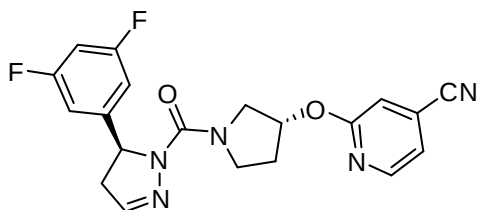
[0497] Compound 335 : 6-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyrazine-2-carbonitrile

The titled compound **335** was prepared in an analogous manner to the preparation of **256**



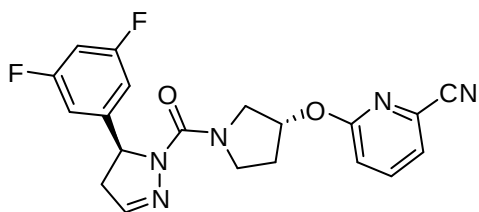
LC-MS (m/z): 399.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.49 (d, *J* = 0.6 Hz, 1H), 8.39 (d, *J* = 0.6 Hz, 1H), 6.85 – 6.74 (m, 3H), 6.68 (tt, *J* = 8.9, 2.3 Hz, 1H), 5.63 – 5.58 (m, 1H), 5.32 (dd, *J* = 12.0, 9.0 Hz, 1H), 4.03 (dd, *J* = 13.5, 4.3 Hz, 1H), 3.92 – 3.82 (m, 1H), 3.81 – 3.70 (m, 2H), 3.33 (ddd, *J* = 18.4, 12.0, 1.8 Hz, 1H), 2.68 (ddd, *J* = 18.4, 9.1, 1.6 Hz, 1H), 2.25 – 2.20 (m, 2H).

[0498] Compound 336 :2-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)isonicotinonitrile



The titled compound **336** was prepared in an analogous manner to the preparation of **256**
 LC-MS (m/z): 398.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.30 – 8.27 (m, 1H), 7.09 – 7.07 (m, 1H), 6.99 – 6.97 (m, 1H), 6.82 – 6.76 (m, 3H), 6.69 (tt, *J* = 8.9, 2.3 Hz, 1H), 5.61 (t, *J* = 4.3 Hz, 1H), 5.32 (dd, *J* = 12.0, 9.1 Hz, 1H), 3.98 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.87 (td, *J* = 11.0, 6.9 Hz, 1H), 3.73 (d, *J* = 12.5 Hz, 2H), 3.32 (ddd, *J* = 18.4, 12.0, 1.8 Hz, 1H), 2.67 (ddd, *J* = 18.3, 9.1, 1.6 Hz, 1H), 2.25 – 2.10 (m, 2H).

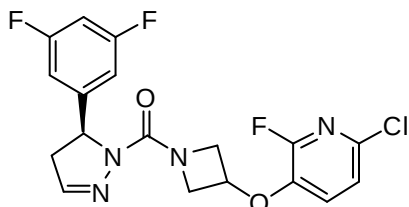
[0499] Compound 337 :6-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)picolinonitrile



The titled compound **337** was prepared in an analogous manner to the preparation of **256**
 LC-MS (m/z): 398.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.67 (dd, *J* = 8.5, 7.2 Hz, 1H), 7.31 (dd, *J* = 7.2, 0.8 Hz, 1H), 6.94 (dd, *J* = 8.5, 0.8 Hz, 1H), 6.82 – 6.76 (m, 3H),

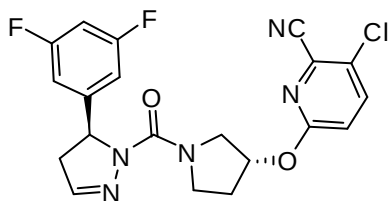
6.67 (tt, $J = 8.9, 2.3$ Hz, 1H), 5.62 (t, $J = 4.2$ Hz, 1H), 5.32 (dd, $J = 12.0, 9.2$ Hz, 1H), 4.00 (dd, $J = 13.3, 4.3$ Hz, 1H), 3.85 (td, $J = 11.0, 7.0$ Hz, 1H), 3.79 – 3.65 (m, 2H), 3.32 (ddd, $J = 18.3, 12.0, 1.8$ Hz, 1H), 2.67 (ddd, $J = 18.3, 9.2, 1.6$ Hz, 1H), 2.27 – 2.10 (m, 2H).

[0500] Compound 338: (S)-((6-chloro-2-fluoropyridin-3-yl)oxy)azetidin-1-yl)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



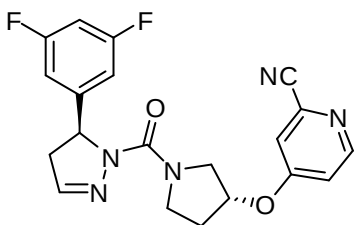
The titled compound **338** was prepared in an analogous manner to the preparation of **256**
 LC-MS (m/z): 411.1[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.14 (d, $J = 8.2$ Hz, 1H), 7.06 (dd, $J = 9.5, 8.2$ Hz, 1H), 6.80 (t, $J = 1.7$ Hz, 1H), 6.78 – 6.71 (m, 2H), 6.69 (tt, $J = 8.8, 2.3$ Hz, 1H), 5.27 (dd, $J = 12.2, 6.4$ Hz, 1H), 4.99 – 4.92 (m, 1H), 4.54 (q, $J = 8.8, 8.3$ Hz, 2H), 4.35 – 4.19 (m, 2H), 3.36 (ddd, $J = 18.6, 12.2, 1.7$ Hz, 1H), 2.71 (ddd, $J = 18.6, 6.4, 1.7$ Hz, 1H).

[0501] Compound 339 :3-chloro-6-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)picolinonitrile



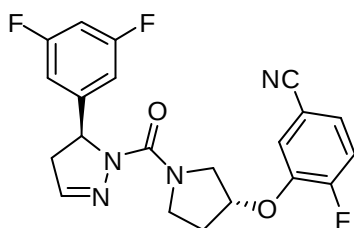
The titled compound **339** was prepared in an analogous manner to the preparation of **256**
 LC-MS (m/z): 432.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.67 (d, $J = 8.9$ Hz, 1H), 6.91 (d, $J = 9.0$ Hz, 1H), 6.82 – 6.75 (m, 3H), 6.67 (tt, $J = 8.9, 2.3$ Hz, 1H), 5.60 – 5.55 (m, 1H), 5.31 (dd, $J = 12.0, 9.2$ Hz, 1H), 4.00 (dd, $J = 13.4, 4.3$ Hz, 1H), 3.88 – 3.78 (m, 1H), 3.78 – 3.64 (m, 2H), 3.32 (ddd, $J = 18.4, 12.0, 1.8$ Hz, 1H), 2.67 (ddd, $J = 18.3, 9.2, 1.6$ Hz, 1H), 2.26 – 2.10 (m, 2H).

[0502] Compound 340 :4-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)picolinonitrile



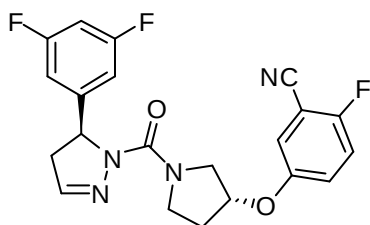
The titled compound **340** was prepared in an analogous manner to the preparation of compound **203** LC-MS (m/z): 398.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 5.8 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 6.97 (dd, *J* = 5.8, 2.5 Hz, 1H), 6.82 – 6.75 (m, 3H), 6.69 (tt, *J* = 8.9, 2.3 Hz, 1H), 5.31 (dd, *J* = 12.0, 9.1 Hz, 1H), 5.00 (t, *J* = 4.3 Hz, 1H), 4.02 (dd, *J* = 13.3, 4.2 Hz, 1H), 3.90 – 3.81 (m, 1H), 3.81 – 3.72 (m, 2H), 3.33 (ddd, *J* = 18.4, 12.0, 1.8 Hz, 1H), 2.68 (ddd, *J* = 18.4, 9.1, 1.6 Hz, 1H), 2.29 – 2.13 (m, 2H).

[0503] Compound 341 :3-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)-4-fluorobenzonitrile.



The titled compound **341** was prepared in an analogous manner to the preparation of compound **203** LC-MS (m/z): 415.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.27 (m, 1H), 7.23 – 7.17 (m, 2H), 6.81 – 6.75 (m, 3H), 6.68 (tt, *J* = 8.9, 2.3 Hz, 1H), 5.31 (dd, *J* = 11.9, 7.5 Hz, 1H), 4.98 – 4.92 (m, 1H), 4.09 – 4.03 (m, 1H), 4.02 – 3.93 (m, 1H), 3.87 (dd, *J* = 13.0, 4.8 Hz, 1H), 3.76 – 3.66 (m, 1H), 3.32 (ddd, *J* = 18.3, 11.9, 1.7 Hz, 1H), 2.67 (ddd, *J* = 18.3, 7.6, 1.7 Hz, 1H), 2.29 – 2.13 (m, 2H).

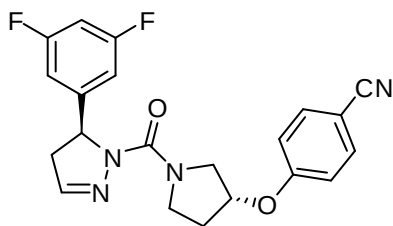
[0504] Compound 342 :5-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)-2-fluorobenzonitrile



The titled compound **343** was prepared in an analogous manner to the preparation of **203** LC-MS (m/z): 415.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.14 – 7.08 (m, 2H),

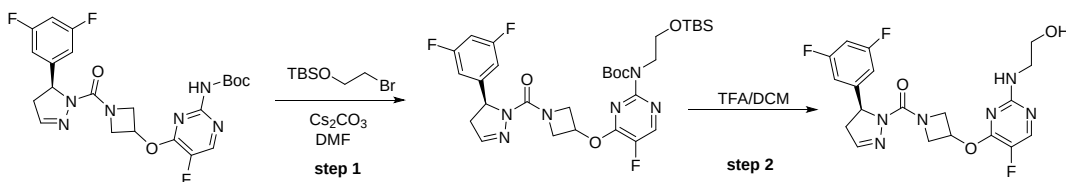
7.06 – 7.03 (m, 1H), 6.81 – 6.74 (m, 3H), 6.69 (tt, $J = 8.9, 2.3$ Hz, 1H), 5.30 (dd, $J = 11.9, 7.7$ Hz, 1H), 4.88 – 4.81 (m, 1H), 4.04 – 3.91 (m, 2H), 3.84 (dd, $J = 12.7, 4.9$ Hz, 1H), 3.67 (dt, $J = 11.2, 8.2$ Hz, 1H), 3.31 (ddd, $J = 18.3, 12.0, 1.8$ Hz, 1H), 2.67 (ddd, $J = 18.3, 7.7, 1.7$ Hz, 1H), 2.20 – 2.13 (m, 2H).

[0505] Compound 343 :4-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)benzonitrile



The titled compound **343** was prepared in an analogous manner to the preparation of **203**. LC-MS (m/z): 397.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 7.63 – 7.55 (m, 2H), 6.97 – 6.89 (m, 2H), 6.81 – 3.74 (m, 3H), 6.68 (tt, $J = 8.9, 2.3$ Hz, 1H), 5.30 (dd, $J = 11.9, 7.5$ Hz, 1H), 4.99 – 4.92 (m, 1H), 4.05 – 3.85 (m, 3H), 3.68 (dt, $J = 11.2, 8.2$ Hz, 1H), 3.31 (ddd, $J = 18.3, 12.0, 1.8$ Hz, 1H), 2.66 (ddd, $J = 18.3, 7.6, 1.7$ Hz, 1H), 2.23 - 2.16 (m, 2H).

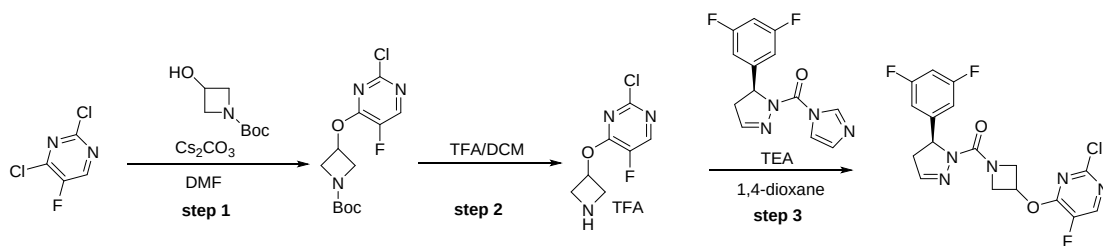
[0506] Compound 344: (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-((2-hydroxyethyl)amino)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone (SIR-1495D):



[0507] Step 1. (2-bromoethoxy)(tert-butyl)dimethylsilane (29.1mg, 0.122mmol) was added to a solution of Cs_2CO_3 (66.5mg, 0.204mmol) in DMF (1mL), and (S)-(3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (50mg, 0.102mmol) was added. The mixture was stirred at 100°C for 1hr. The reaction mixture was then extracted by EtOAc/ H_2O (50mL/50mL) 3 times. The organic layer was combined, washed with brine, dried over Na_2SO_4 , concentrated to give tert-butyl (S)-(2-((tert-butyldimethylsilyl)oxy)ethyl)(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)carbamate (60mg) as a yellow oil.

[0508] Step 2. TFA(5mL) was added to a solution of tert-butyl (S)-2-((tert-butyltrimethylsilyl)oxy)ethyl(4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)carbamate (60mg, 0.092mmol) in DCM (10mL). the reaction mixture was stirred at room temperature for 0.5hr. The reaction mixture was concentrated and purified by pre-HPLC to give 16mg of (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-((2-hydroxyethyl)amino)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone **344** (40%). LC-MS (ESI) m/z $[M+H]^+$: 437.2 ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 3.4 Hz, 1H), 6.85 – 6.64 (m, 4H), 5.50 (s, 1H), 5.27 (dd, J = 12.1, 6.4 Hz, 1H), 4.60 (br, 2H), 4.38-4.26 ((m, 2H), 3.85 (s, 2H), 3.55 (s, 2H), 3.41-3.33 (m, 1H), 2.77 – 2.66 (m, 1H).

[0509] Compound 345: (S)-(3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



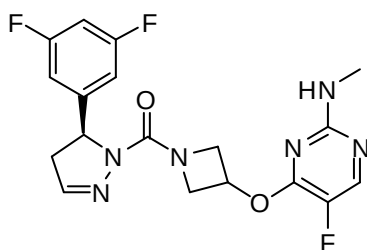
[0510] Step 1. Preparation of tert-butyl 3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidine-1-carboxylate 2,4-dichloro-5-fluoropyrimidine (5g, 29.9mmol) was added to a solution of Cs_2CO_3 (19.5g, 59.9mmol) in DMF (100mL), and tert-butyl 3-hydroxyazetidine-1-carboxylate (5.7g, 32.9mmol) was added. The mixture was stirred at 100°C for 2hrs. The reaction mixture was then extracted by EtOAc/ H_2O (50mL/50mL) 3 times. The organic layer was combined, washed with brine, dried over Na_2SO_4 , concentrated and further purified by silica gel column chromatography (PE/EA=5/1) to give tert-butyl 3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidine-1-carboxylate (3.9g) as a colorless oil (43%). LC-MS (ESI) m/z $[M+H]^+$:304.1.

[0511] Step 2. Preparation of 4-(azetidin-3-yloxy)-2-chloro-5-fluoropyrimidine. TFA (5mL) was added to a solution of tert-butyl 3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidine-1-carboxylate (3.9g, 12.9mmol) in DCM (10mL). the reaction mixture was stirred at room temperature for 0.5hr. then the solvent was evaporated in vacuo to give 5.2g of 4-(azetidin-3-yloxy)-2-chloro-5-fluoropyrimidine as a colorless oil (crude). LC-MS (ESI) m/z $[M+H]^+$:204.1.

[0512] Step 3. Preparation of (S)-3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone. (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone (3.23g, 11.7mmol) was added to a solution of 4-(azetidin-3-yloxy)-2-chloro-5-fluoropyrimidine and TEA (3.55g, 35.1mmol) in 1,4-dioxane (30mL). The reaction mixture was stirred at room temperature overnight. Then the solvent was evaporated in vacuo. The oil residue was purified by silica gel column chromatography (PE/EA=1/1) to give 4.35g of (S)-3-((2-chloro-5-fluoropyrimidin-4-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone **154** as a yellow oil (yield =90%). LC-MS (ESI) *m/z*

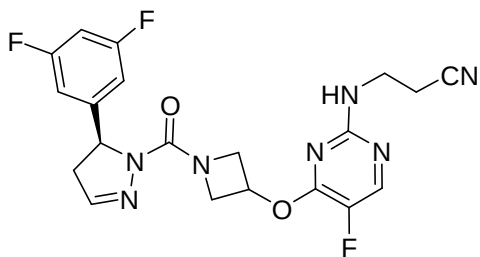
[M+H]⁺:412.1. LC-MS (*m/z*): 412.1[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 2.1 Hz, 1H), 6.79 (t, *J* = 1.7 Hz, 1H), 6.78 – 6.73 (m, 2H), 6.69 (tt, *J* = 8.9, 2.3 Hz, 1H), 5.50 (tt, *J* = 6.7, 4.1 Hz, 1H), 5.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 4.69 – 4.54 (m, 2H), 4.34 – 4.22 (m, 2H), 3.36 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.70 (ddd, *J* = 18.6, 6.5, 1.7 Hz, 1H).

[0513] Compound 346 : (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-((5-fluoro-2-(methylamino)pyrimidin-4-yl)oxy)azetidin-1-yl)methanone



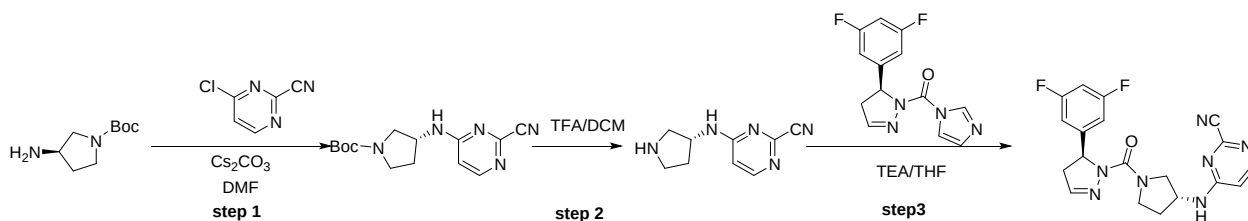
The titled compound **346** was prepared from compound 345 by reacting with methylamine, hydrochloride. LC-MS (*m/z*): 407.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 10.25 – 10.01 (br, 1H), 7.80 (d, *J* = 3.7 Hz, 1H), 6.82 (t, *J* = 1.7 Hz, 1H), 6.78 – 6.73 (m, 2H), 6.70 (tt, *J* = 8.8, 2.3 Hz, 1H), 5.54 (tt, *J* = 6.7, 4.1 Hz, 1H), 5.28 (dd, *J* = 12.2, 6.4 Hz, 1H), 4.68 – 4.55 (m, 2H), 4.42 – 4.33 (m, 1H), 4.33 – 4.25 (m, 1H), 3.37 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 3.00 (s, 3H), 2.72 (ddd, *J* = 18.7, 6.4, 1.7 Hz, 1H).

[0514] Compound 347: (S)-3-((4-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-5-fluoropyrimidin-2-yl)amino)propanenitrile



The titled compound **347** was prepared in an analogous manner to the preparation of **347**
Yield 12.4 % . ^1H NMR (400 MHz, Chloroform-*d*) δ 10.29 (s, 1H), 8.00 (s, 1H), 6.88 (s, 1H), 6.80 – 6.61 (m, 3H), 5.68 – 5.57 (m, 1H), 5.30 (dd, $J = 12.4, 6.0$ Hz, 1H), 4.76-4.62 (m, 2H), 4.51 – 4.30 (m, 2H), 3.84-3.77 (m, 2H), 3.45-3.30 (m, 1H), 2.81 – 2.64 (m, 3H). LC-MS (m/z) 446.3($M+H^+$)

[0515] Compound 348: 4-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)amino)pyrimidine-2-carbonitrile

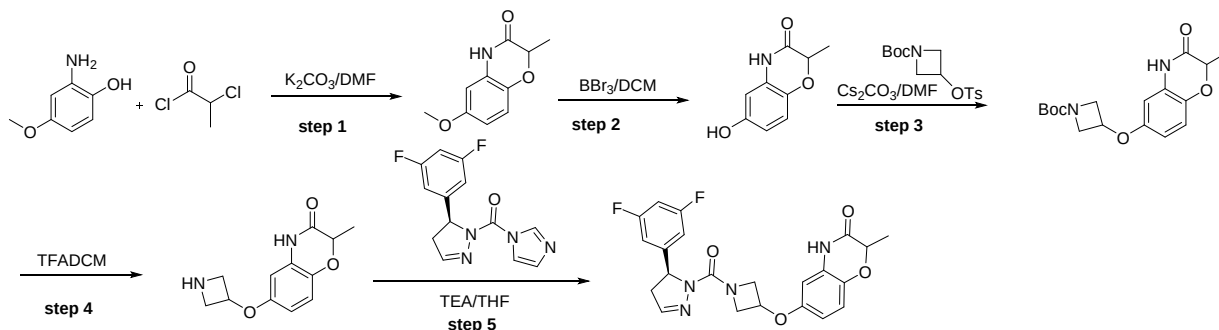


[0516] Step 1. Preparation of tert-butyl (R)-3-((2-cyanopyrimidin-4-yl)amino)pyrrolidine-1-carboxylate. 100mL dry single-necked flask tert-butyl (R)-3-aminopyrrolidine-1-carboxylate(187mg, 1.0mmol), 4-chloropyrimidine-2-carbonitrile(140mg, 1.0mmol), Cs_2CO_3 (978mg, 3.0mmol) and DMF (5ml). The reaction system was stirred at 100°C for 3 hours. The residue was diluted with water (500mL) and extracted with ethyl acetate (3x500mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum to afford the tert-butyl (R)-3-((2-cyanopyrimidin-4-yl)amino)pyrrolidine-1-carboxylate (yellow solid, 280mg, Yield: 96.8percent). LC-MS (ESI) m/z : $[M+H]=290.2$

[0517] Step 2. Preparation of (R)-4-(pyrrolidin-3-ylamino)pyrimidine-2-carbonitrile. To a vigorously stirring mixture of tert-butyl (R)-3-((2-cyanopyrimidin-4-yl)amino)pyrrolidine-1-carboxylate (280mg, 0.97mmol) in DCM (10mL) was added TFA (5mL) dropwise. The resulting mixture was stirred at room temperature for 0.5 hour and concentrated under vacuum to afford the (R)-4-(pyrrolidin-3-ylamino)pyrimidine-2-carbonitrile (180mg crude) as a yellow solid. LC-MS (ESI) m/z : $[M+H]=190.2$

[0518] Step 3. Preparation of 4-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)amino)pyrimidine-2-carbonitrile. 50 mL dry single-necked flask (R)-4-(pyrrolidin-3-ylamino)pyrimidine-2-carbonitrile (180mg, 0.95mmol), (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(1H-imidazol-1-yl)methanone(193mg, 0.7mmol) and TEA(7mL) in THF (15ml). The reaction system was refluxed for 2 hours and then concentrated. Crude product Column chromatography (eluent: petroleum ether / ethyl acetate volume ratio:100/1 to 55/45) to give 4-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)amino)pyrimidine-2-carbonitrile **348** (white solid, 51mg, Yield: 18.3percent). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 5.5 Hz, 1H), 6.87 (d, *J* = 1.7 Hz, 1H), 6.76 – 6.65 (m, 3H), 6.49 (d, *J* = 6.0 Hz, 1H), 5.88 (d, *J* = 7.2 Hz, 1H), 5.30 (dd, *J* = 12.0, 8.5 Hz, 1H), 4.79 (d, *J* = 74.7 Hz, 1H), 3.96 (dd, *J* = 12.5, 4.9 Hz, 1H), 3.80-3.69 (m, 1H), 3.65 (d, *J* = 11.5 Hz, 2H), 3.37 (ddd, *J* = 18.6, 12.0, 1.8 Hz, 1H), 2.72 (ddd, *J* = 18.6, 8.5, 1.6 Hz, 1H), 2.25-2.12 (m, 1H), 2.06 – 1.97 (m, 1H). LC-MS (ESI) *m/z*: [M+H]=398.2

[0519] Compound 349 : 6-(((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one



[0520] Step1: 2-amino-4-methoxyphenol(800 mg,5.76mmol), 2-chloropropanoyl chloride(731 mg,5.76mmol) and K₂CO₃(1.59 g, 11.5mmol) were dissolved in DMF(15 mL).The mixture was stirred at 100°C overnight. The solvent was evaporated to dryness and purified by flash chromatography (PE/EA=5/1) to give 6-methoxy-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one as a yellow solid (850mg) .Yield 76.6%. LC-MS (*m/z*) 194.2 (M+H⁺).

[0521] Step2: BBr₃(1.6 mL,1.66 mmol) was added to the solution of 6-methoxy-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one (160 mg, 0.83 mmol) in DCM(5 mL) at -78°C.The

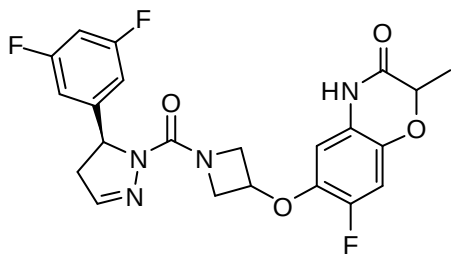
mixture was stirred at r.t. for 3hrs. H₂O was added and 90 mg of 6-hydroxy-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one as a gray solid was obtained. Yield 60.4%

[0522] Step3 : 6-hydroxy-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one(90 mg,0.5 mmol), tert-butyl 3-(tosyloxy)azetidine-1-carboxylate(181 mg,0.55 mmol) and CS₂CO₃(326 mg, 1.0 mmol) were dissolved in DMF(3 mL). The mixture was stirred at 100°C for 3hrs. The solvent was evaporated to dryness and purified by flash chromatography (PE/EA=5/1) to give tert-butyl 3-((2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)azetidine-1-carboxylate as an colorless oil (15 mg). Yield 9.0% LC-MS (m/z) 333.2 (M-H⁺).

[0523] Step 4 ad 5: The titled compound **349** was prepared in an analogous manner to the preparation of **192** . Yield 23.1% ¹H NMR (400 MHz, Chloroform-*d*) δ 8.33 (brs, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.81 – 6.71 (m, 3H), 6.71 – 6.59 (m, 1H), 6.33 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.25 (d, *J* = 2.8 Hz, 1H), 5.37 – 5.31 (m, 1H), 4.89-4.78 (m, 1H), 4.65 – 4.43 (m, 3H), 4.30 – 4.05 (m, 2H), 3.41-3.31 (m, 1H), 2.74-2.62 m, 1H), 1.56 (dd, *J* = 6.8, 1.6 Hz, 3H). LC-MS (m/z) 443.2 (M+H⁺).

[0524] Compound 350: 6-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-7-fluoro-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one

The titled compound **350** was prepared in an analogous manner to the preparation of **349** . After Chiral HPLC separation to yield two unknown single- enantiomer 350-A and 350-B:

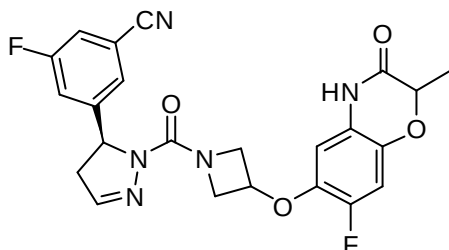


[0525] (350-B)LC-MS (m/z): 461.3[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.33 (s, 1H), 6.81 – 6.73 (m, 4H), 6.67 (tt, *J* = 8.8, 2.3 Hz, 1H), 6.22 (d, *J* = 7.8 Hz, 1H), 5.41 (dd, *J* = 12.2, 6.3 Hz, 1H), 4.88 – 4.80 (m, 1H), 4.59 (q, *J* = 6.8 Hz, 1H), 4.55 – 4.44 (m, 2H), 4.40 – 4.31 (m, 1H), 4.21 – 4.11 (m, 1H), 3.38 (ddd, *J* = 18.6, 12.1, 1.7 Hz, 1H), 2.69 (ddd, *J* = 18.6, 6.3, 1.8 Hz, 1H), 1.54 (d, *J* = 6.8 Hz, 3H).

[0526] (350-A)LC-MS (m/z): 461.3[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 6.82 – 6.70 (m, 4H), 6.71 – 6.64 (m, 1H), 6.23 (d, *J* = 7.8 Hz, 1H), 5.41 (dd, *J* = 12.1, 6.2 Hz, 1H), 4.88 – 4.80 (m, 1H), 4.57 (q, *J* = 6.8 Hz, 1H), 4.53 – 4.45 (m, 2H), 4.40 – 4.32

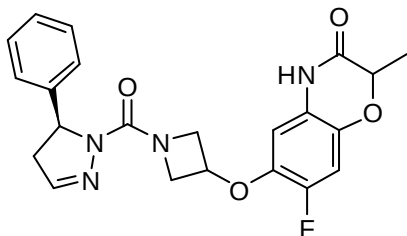
(m, 1H), 4.20 – 4.11 (m, 1H), 3.37 (ddd, $J = 18.5, 12.1, 1.7$ Hz, 1H), 2.69 (ddd, $J = 18.5, 6.2, 1.8$ Hz, 1H), 1.56 (d, $J = 6.8$ Hz, 3H).

[0527] Compound 351: 3-fluoro-5-((5S)-1-(3-((7-fluoro-2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)azetidine-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)benzonitrile



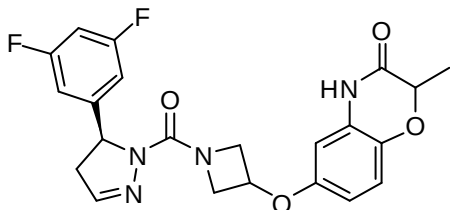
The titled compound **351** was prepared in an analogous manner to the preparation of compound **349**. LC-MS (m/z): 468.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.01 (s, 1H), 7.32 (s, 1H), 7.25 – 7.17 (m, 2H), 6.86 – 6.84 (m, 1H), 6.78 (d, $J = 11.1$ Hz, 1H), 6.26 (d, $J = 7.4$ Hz, 1H), 5.52 – 5.42 (m, 1H), 4.90 – 4.83 (m, 1H), 4.66 – 4.56 (m, 1H), 4.55 – 4.45 (m, 2H), 4.43 – 4.33 (m, 1H), 4.25 – 4.12 (m, 1H), 3.43 (ddd, $J = 18.7, 12.2, 1.7$ Hz, 1H), 2.70 (ddd, $J = 18.7, 6.4, 1.7$ Hz, 1H), 1.57 – 1.53 (m, 3H).

[0528] Compound 352: 7-fluoro-2-methyl-6-((1-((S)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-3(4H)-one



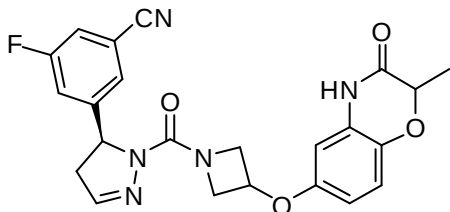
The titled compound **352** was prepared in an analogous manner to the preparation of compound **349**. LC-MS (m/z): 425.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, $J = 10.7$ Hz, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 6.81 (t, $J = 1.7$ Hz, 1H), 6.76 (d, $J = 11.2$ Hz, 1H), 6.21 (d, $J = 7.8$ Hz, 1H), 5.45 – 5.38 (m, 1H), 4.84 – 4.76 (m, 1H), 4.58 (qd, $J = 6.8, 4.3$ Hz, 1H), 4.52 – 4.42 (m, 2H), 4.36 – 4.28 (m, 1H), 4.19 – 4.12 (m, 1H), 3.37 (ddd, $J = 18.6, 12.1, 1.7$ Hz, 1H), 2.74 (ddd, $J = 18.6, 6.0, 1.7$ Hz, 1H), 1.55 (dd, $J = 6.8, 1.3$ Hz, 3H).

[0529] Compound 353: 6-((1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2-methyl-2H-benzo[b][1,4]oxazin-3(4H)-one



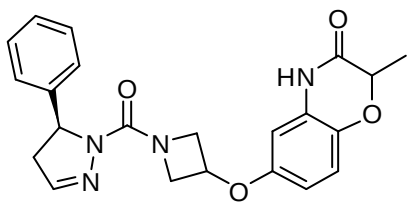
The titled compound **353** was prepared in an analogous manner to the preparation of compound **349**. LC-MS (m/z): 443.2[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.99 (s, 1H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.79 – 6.77 (m, 1H), 6.77 – 6.72 (m, 2H), 6.68 (tt, *J* = 8.8, 2.3 Hz, 1H), 6.33 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.24 (d, *J* = 2.8 Hz, 1H), 5.36 – 5.28 (m, 1H), 4.88 – 4.81 (m, 1H), 4.58 (qd, *J* = 6.8, 2.2 Hz, 1H), 4.54 – 4.45 (m, 2H), 4.28 – 4.21 (m, 1H), 4.17 – 4.10 (m, 1H), 3.35 (ddd, *J* = 18.6, 12.2, 1.7 Hz, 1H), 2.69 (ddd, *J* = 18.6, 6.4, 1.7 Hz, 1H), 1.56 (dd, *J* = 6.8, 1.4 Hz, 3H).

[0530] Compound 354: 3-fluoro-5-((5S)-1-(3-((2-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)azetidine-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)benzonitrile



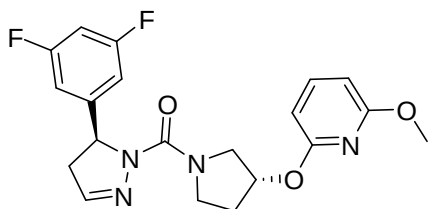
The titled compound **354** was prepared in an analogous manner to the preparation of compound **349**. LC-MS (m/z): 450.4[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.85 (s, 1H), 7.33 (s, 1H), 7.25 – 7.16 (m, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.82 (s, 1H), 6.36 – 6.30 (m, 1H), 6.28 – 6.22 (m, 1H), 5.47 – 5.36 (m, 1H), 4.89 – 4.79 (m, 1H), 4.62 – 4.44 (m, 3H), 4.34 – 4.21 (m, 1H), 4.20 – 4.08 (m, 1H), 3.46 – 3.33 (m, 1H), 2.68 (ddd, *J* = 18.5, 6.5, 1.7 Hz, 1H), 1.58 – 1.52 (m, 3H).

[0531] Compound 355: 2-methyl-6-((1-((S)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-3(4H)-one



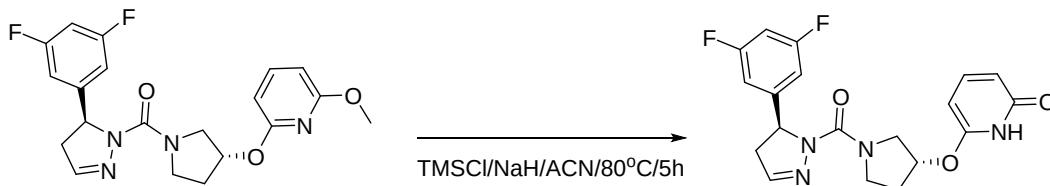
The titled compound **355** was prepared in an analogous manner to the preparation of compound **349**. LC-MS (m/z): 407.2 $[M+H]^+$. ^1H NMR (400 MHz, Chloroform- d) δ 8.85 – 8.78 (br, 1H), 7.33 – 7.28 (m, 2H), 7.25 – 7.19 (m, 3H), 6.86 (d, J = 8.8 Hz, 1H), 6.80 (t, J = 1.7 Hz, 1H), 6.32 (dd, J = 8.8, 2.8 Hz, 1H), 6.25 (d, J = 2.8 Hz, 1H), 5.38 (ddd, J = 12.1, 6.1, 1.9 Hz, 1H), 4.80 (tt, J = 6.4, 4.1 Hz, 1H), 4.57 (qd, J = 6.8, 1.8 Hz, 1H), 4.49 (q, J = 8.3 Hz, 2H), 4.27 – 4.20 (m, 1H), 4.15 – 4.08 (m, 1H), 3.36 (ddd, J = 18.6, 12.1, 1.7 Hz, 2H), 2.74 (ddd, J = 18.6, 6.1, 1.8 Hz, 1H), 1.55 (d, J = 6.8 Hz, 3H).

[0532] Compound 356: ((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((R)-3-((6-methoxypyridin-2-yl)oxy)pyrrolidin-1-yl)methanone



The titled compound **356** was prepared in an analogous manner to the preparation of **256** yield:46.3%. ^1H NMR (400 MHz, Chloroform- d) δ 7.48 (t, J = 8.0 Hz, 1H), 6.85 – 6.75 (m, 2H), 6.71-6.64 (m, 1H), 6.29 (dd, J = 9.6, 8.0 Hz, 2H), 5.55 (t, J = 4.0 Hz, 1H), 5.32 (dd, J = 12.0, 8.8 Hz, 1H), 3.98 (dd, J = 13.2, 4.4 Hz, 1H), 3.88 (s, 3H), 3.80 – 3.59 (m, 2H), 3.36-3.25 (m, 1H), 2.74 – 2.44 (m, 3H), 2.28-2.19 (m, 1H), 2.17-2.05 (m, 1H). LC-MS (m/z) 403.2($M+H^+$).

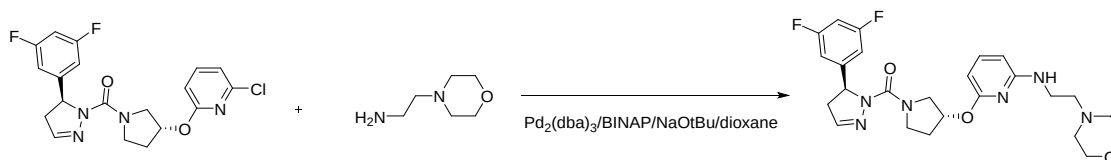
[0533] Compound 357: 6-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyridin-2(1H)-one



To a solution of ((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((R)-3-((6-methoxypyridin-2-yl)oxy)pyrrolidin-1-yl)methanone (10 mg, 0.025 mmol) and NaI(11 mg,

0.075 mmol) in ACN (3 mL) TMSCl(8 mg, 0.075mmol) was added. The mixture was stirred at 80°C for 5hrs. concentrated and the residue was purified by TLC(PE/EA=1/1) to give 6-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyridin-2(1H)-one **357** as a colorless oil(6 mg., 61.9%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.43 (s, 1H), 6.82 – 6.75 (m, 2H), 6.72 – 6.53 (m, 1H), 6.23 (s, 1H), 5.89 (d, *J* = 7.4 Hz, 1H), 5.36 – 5.25 (m, 1H), 5.18 (s, 1H), 4.07 – 3.80 (m, 2H), 3.73 (d, *J* = 12.0 Hz, 3H), 3.31 (dd, *J* = 18.4, 11.9 Hz, 1H), 2.65 (dd, *J* = 18.3, 8.9 Hz, 1H), 2.30 – 2.05 (m, 2H). LC-MS (*m/z*) 389.3(M+H⁺).

[0534] Compound 358 : ((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((R)-3-(((6-((2-morpholinoethyl)amino)pyridin-2-yl)oxy)pyrrolidin-1-yl)methanone



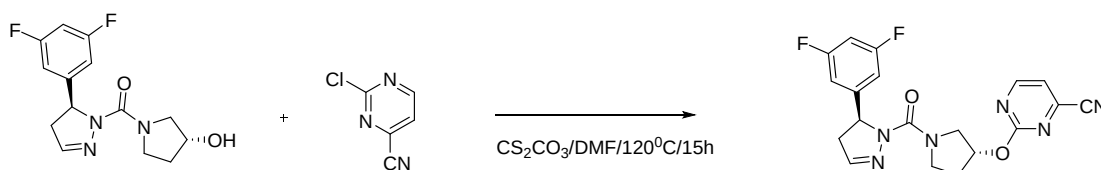
((R)-3-(((6-chloropyridin-2-yl)oxy)pyrrolidin-1-yl)((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (20 mg,0.05mmol),2-morpholinoethan-1-amine(13 mg, 0.1 mmol), NaOtBu(7.2 mg, 0.075mmol), Pd₂(dba)₃ (4.5 mg, 0.005 mmol) and BINAP(3 mg, 0.005mmol) were added to dioxane (3 mL) under N₂ atmosphere. The mixture was stirred at 90°C for overnight. concentrated and the residue was purified by

TLC(DCM/MeOH=20/1) to give the title compound **358** as brown oil (5 mg, 20.0%)

¹H NMR (400 MHz, Chloroform-*d*) δ 7.43 (t, *J* = 7.6 Hz, 1H), 7.35 – 7.17(m, 1H). 6.80 (d, *J* = 6.4 Hz, 2H), 6.68 (t, *J* = 8.4 Hz, 1H), 6.16 (d, *J* = 8.0 Hz, 1H), 6.03 (d, *J* = 7.6 Hz, 1H), 5.37-5.30 (m, 1H), 4.31 – 3.67 (m, 9H), 3.66-3.42 (m, 3H), 3.41 – 3.15 (m, 3H), 3.10-2.77 (m, 3H), 2.72 – 2.58 (m, 1H), 2.30 – 2.04 (m, 2H).

LC-MS (*m/z*) 501.3(M+H⁺).

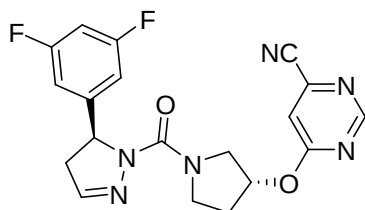
[0535] Compound 359 : 2-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyrimidine-4-carbonitrile



((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((R)-3-hydroxypyrrrolidin-1-yl)methanone (70 mg,0.24 mmol), 2-chloropyrimidine-4-carbonitrile(40 mg, 0.29 mmol)

and CS_2CO_3 (156 mg, 0.48 mmol) were dissolved in DMF (3 mL). the mixture was stirred at 120°C overnight. concentrated and purified by TLC (DCM/MeOH=25/1) to give the titled compound **359** as colorless oil (12 mg, 12.6%) ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, J = 5.6 Hz, 1H), 6.90 (d, J = 5.6 Hz, 1H), 6.83 – 6.62 (m, 3H), 5.75-5.65 (m, 1H), 5.32 (dd, J = 12.0, 8.8 Hz, 1H), 4.13 – 3.92 (m, 2H), 3.89 – 3.63 (m, 3H), 3.42-3.24 (m, 1H), 2.74-2.61 (m, 1H), 2.30-2.12 (m, 2H). LC-MS $[\text{M}+\text{H}]^+$:399.2. LC-MS (m/z) 399.2($\text{M}+\text{H}^+$).

[0536] Compound 360: 6-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyrimidine-4-carbonitrile

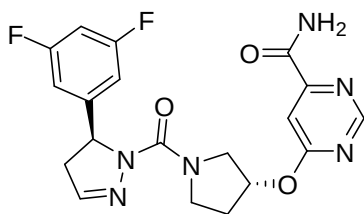


[0537]

The titled compound **360** was prepared in an analogous manner to the preparation of **256**. Yield:12.6%. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.84 (d, J = 1.1 Hz, 1H), 7.09 (d, J = 1.2 Hz, 1H), 6.84 – 6.66 (m, 3H), 5.71 (t, J = 4.6 Hz, 1H), 5.32 (dd, J = 12.0, 8.8 Hz, 1H), 4.01 (dd, J = 13.6, 4.4 Hz, 1H), 3.93 – 3.71 (m, 2H), 3.60-3.42 (m, 2H), 3.40-3.26 (m, 1H), 2.73-2.62 (m, 1H), 2.29-2.13(m, 2H).

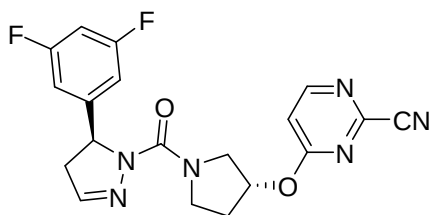
LC-MS (m/z) 399.2($\text{M}+\text{H}^+$).

[0538] Compound 361: 6-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyrimidine-4-carboxamide



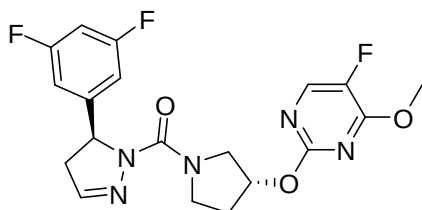
The titled compound **361** was prepared in an analogous manner to the preparation of **360**. yield 14.0% ^1H NMR (400 MHz, Chloroform-*d*) δ 8.78 (s, 1H), 7.92 (s, 1H), 7.51 (s, 1H), 6.86 – 6.59 (m, 4H), 5.70 (t, J = 4.4 Hz, 1H), 5.40 – 5.26 (m, 1H), 4.12 – 3.85 (m, 2H), 3.83-3.55 (m, 3H), 3.44 – 3.25 (m, 1H), 2.75-2.63 (m, 1H), 2.33–2.11(m, 2H). LC-MS (m/z) 417.2($\text{M}+\text{H}^+$).

[0539] Compound 362: 4-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyrimidine-2-carbonitrile



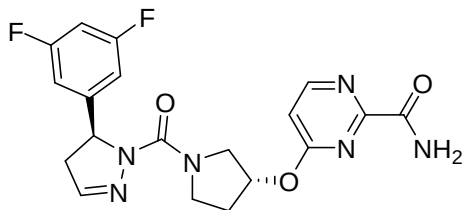
The titled compound **362** was prepared in an analogous manner to the preparation of **256**. yield: 22.2 % ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, J = 6.0 Hz, 1H), 6.90 (d, J = 6.0 Hz, 1H), 6.85 – 6.72 (m, 2H), 6.72 – 6.56 (m, 1H), 5.73-5.67 (m, 1H), 5.40 – 5.24 (m, 1H), 4.03 (dd, J = 13.6, 4.4 Hz, 1H), 3.92 – 3.64 (m, 3H), 3.63-2.3.43 (m, 1H), 3.41-3.28 (m, 1H), 2.714-3.63 (m, 1H), 2.31 – 2.03 (m, 2H). LC-MS (m/z) 399.2 ($\text{M}+\text{H}^+$).

[0540] Compound 363: ((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((R)-3-((5-fluoro-4-methoxypyrimidin-2-yl)oxy)pyrrolidin-1-yl)methanone



The titled compound **363** was prepared in an analogous manner to the preparation of **256**. Yield 3.0%. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.07 (d, J = 2.4 Hz, 1H), 6.83 – 6.73 (m, 2H), 6.72 – 6.60 (m, 1H), 5.46 (t, J = 4.4 Hz, 1H), 5.35 – 5.27 (m, 1H), 4.05 (s, 3H), 3.95-3.85 (m, 1H), 3.82-3.70 (m, 2H), 3.60-3.43 (m, 2H), 3.37-3.26 (m, 1H), 2.72-2.61 (m, 1H), 2.35 – 2.05 (m, 2H). LC-MS (m/z) 442.3 ($\text{M}+\text{H}^+$).

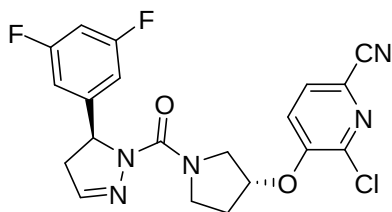
[0541] Compound 364 : 4-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyrimidine-2-carboxamide



The titled compound **364** was prepared in 50% yield from compound **363** by hydrolyzed using 1N NaOH in MeOH. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.56 (d, J = 5.6 Hz, 1H), 7.69 (s, 1H), 6.93 – 6.72 (m, 3H), 6.71 – 6.54 (m, 1H), 6.08 (s, 1H), 5.87 (s, 1H), 5.36 – 5.25 (m, 1H), 4.03 (dd, J = 13.2, 4.2 Hz, 1H), 3.93 – 3.76 (m, 2H), 3.76-3.58 (dd, J = 17.2,

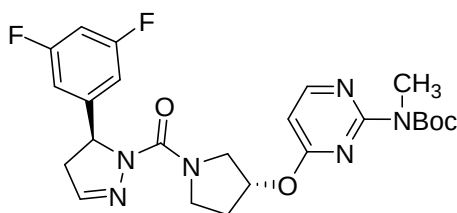
8.0 Hz, 2H), 3.39-3.26 (m, 1H), 2.72-2.60 (m, 1H), 2.30-2.11 m, 2H). LC-MS (m/z) 417.2 (M+H⁺).

[0542] Compound 365 :6-chloro-5-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)picolinonitrile



The titled compound **365** was prepared in an analogous manner to the preparation of **256**. Yield 9.3%. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.62 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), 6.88 – 6.74 (m, 2H), 6.73-6.63 (m, 1H), 5.31 (dd, *J* = 12.0, 8.8 Hz, 1H), 5.01 (t, *J* = 4.4 Hz, 1H), 4.14-3.89 (m, 2H), 3.88-3.58 (m, 3H), 3.39-3.28 (m, 1H), 2.74-2.62 (m, 1H), 2.37 – 2.10 (m, 2H). LC-MS (m/z) 432.2 (M+H⁺).

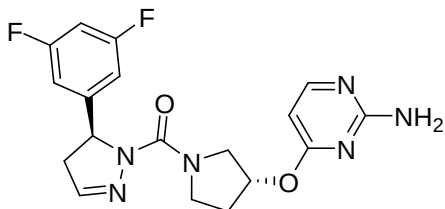
[0543] Compound 366 :tert-butyl (4-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyrimidin-2-yl)(methyl)carbamate



The titled compound **366** was prepared in an analogous manner to the preparation of **256**. Yield 66.7% ¹H NMR (400 MHz, Chloroform-*d*) δ 8.35 (dd, *J* = 5.6, 0.8 Hz, 1H), 6.89 – 6.74 (m, 2H), 6.72 – 6.62 (m, 1H), 6.40 (dd, *J* = 5.6, 0.8 Hz, 1H), 5.65 (t, *J* = 4.4 Hz, 1H), 5.31 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.98 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.93 – 3.78 (m, 2H), 3.76 – 3.61 (m, 2H), 3.38 (s, 3H), 3.35 – 3.26 (m, 1H), 2.72-2.62 (m, 1H), 2.28 – 2.05 (m, 2H), 1.53 (s, 9H).

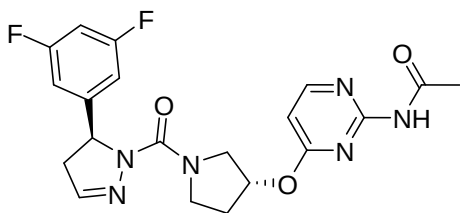
LC-MS (m/z) 503.3 (M+H⁺)

[0544] Compound 367 : ((R)-3-((2-aminopyrimidin-4-yl)oxy)pyrrolidin-1-yl)((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



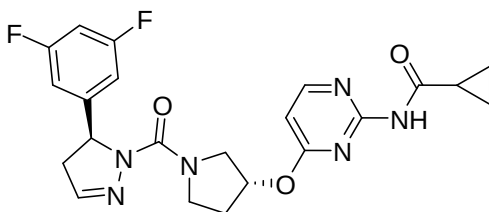
The titled compound **367** was prepared in an analogous manner to the preparation of **256**. Yield 94.1%. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.79 (s, 1H), 7.87 (s, 1H), 6.79 (d, $J = 8.4$ Hz, 2H), 6.69 (t, $J = 8.8$ Hz, 1H), 6.26 (s, 1H), 6.06 (s, 1H), 5.68 (s, 1H), 5.31 (t, $J = 10.4$ Hz, 1H), 4.07-3.96 (m, 1H), 3.94-3.79 (m, 2H), 3.78-3.64 (m, 2H), 3.34 (dd, $J = 18.4$, 11.6 Hz, 1H), 2.70 (dd, $J = 18.4$, 8.4 Hz, 1H), 2.29-2.13 (m, 2H). LC-MS (m/z) 389.2 ($M+H^+$)

[0545] Compound 368 :N-(4-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyrimidin-2-yl)acetamide



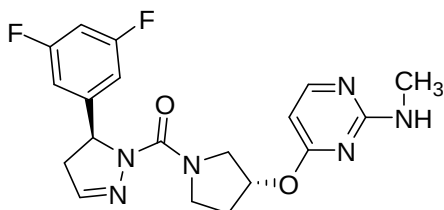
The titled compound **368** was prepared in 40% yield from compound **367** by acetylation reaction. LC-MS (m/z) 431.3 ($M+H^+$)

[0546] Compound 369 :N-(4-(((R)-1-((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)pyrrolidin-3-yl)oxy)pyrimidin-2-yl)cyclopropanecarboxamide



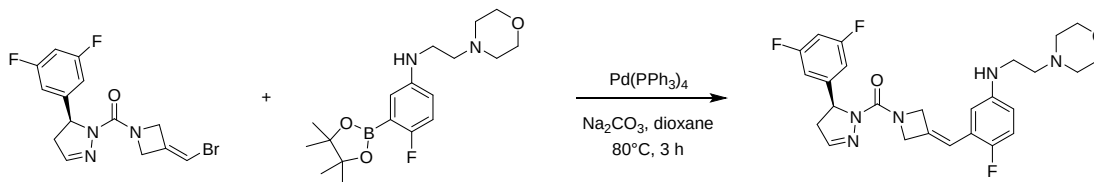
The titled compound **369** was prepared in 67.6% yield from compound **367** by acylation reaction. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 8.25 (d, $J = 5.8$ Hz, 1H), 6.87 – 6.74 (m, 2H), 6.72-6.62 (m, 1H), 6.40 (d, $J = 5.8$ Hz, 1H), 5.62 (t, $J = 4.4$ Hz, 1H), 5.31 (dd, $J = 12.0, 9.6$ Hz, 1H), 3.97 (dd, $J = 13.3$, 4.4 Hz, 1H), 3.90 – 3.76 (m, 2H), 3.75 – 3.55 (m, 2H), 3.37-3.27 (m, 1H), 2.71-2.63 (m, 1H), 2.29 – 2.05 (m, 2H), 1.67 – 1.57 (m, 1H), 1.20-1.14 (m, 2H), 0.98 – 0.83 (m, 2H). LC-MS (m/z) 457.3 ($M+H^+$)

[0547] Compound 370 : ((S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)((R)-3-((2-(methylamino)pyrimidin-4-yl)oxy)pyrrolidin-1-yl)methanone



The titled compound **370** was prepared in an analogous manner to the preparation of **256**. Yield 88.2%. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.85 (s, 1H), 7.83 (d, *J* = 6.4 Hz, 1H), 6.86 – 6.75 (m, 2H), 6.72-6.64 (m, 1H), 6.15 (d, *J* = 6.0 Hz, 1H), 5.72 (s, 1H), 5.32 (dd, *J* = 12.0, 8.8 Hz, 1H), 4.10 – 3.99 (m, 1H), 3.95 – 3.80 (m, 2H), 3.79-3.62 (m, 2H), 3.34 (dd, *J* = 18.4, 11.9 Hz, 1H), 3.07 (d, *J* = 4.0 Hz, 3H), 2.70 (dd, *J* = 18.4, 8.8 Hz, 1H), 2.35 – 2.16 (m, 2H). LC-MS (*m/z*) 403.2 (*M*+*H*⁺)

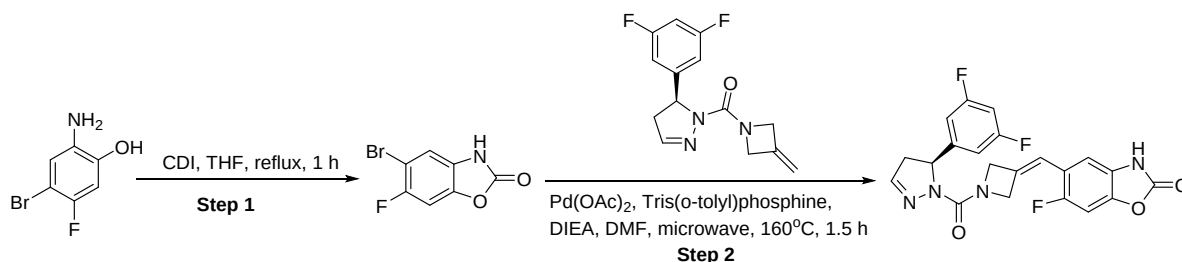
[0548] Compound 371 : (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(3-(2-fluoro-5-((2-morpholinoethyl)amino)benzylidene)azetidin-1-yl)methanone



(S)-(3-(bromomethylene)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (51 mg, 0.142 mmol) was dissolved in dioxane (3 mL) and water (1.5 mL). Followed by the addition of 4-fluoro-N-(2-morpholinoethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (50 mg, 0.142 mmol) and Na₂CO₃ (30 mg, 0.285 mmol), then the reaction mixture was degassed with argon for three times and stirred at 80 °C for 3 h. EtOAc (150 mL) was added and stirred at 20 °C. Followed by NaHCO₃ aqueous solution (150 mL). The organic layers were washed with water (100 mL x 3) and brine (100 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. The crude purified by Pre-HPLC to give 10 mg of the titled compound **371** as a white solid. Yield: 14.3%. Mass (ESI): *m/z* calcd for C₂₆H₂₈F₃N₅O₂ 499.2, found 500.1 [*M*+*H*]⁺. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.67 (d, *J* = 1.9 Hz, 1H), 6.99 (dd, *J* = 11.5, 1.9 Hz, 1H), 6.83 – 6.80 (m, 1H), 6.78-6.62 (m, 3H), 6.10 (s, 1H), 5.30 (dd, *J* = 12.1, 6.4 Hz, 1H), 3.97 (t, *J* = 4.9 Hz,

8H), 3.65-3.46 (m, 1H), 3.44-3.28 (m, 3H), 3.11-2.92 (m, 1H), 2.74-2.67 (m, 1H), 1.24 (s, 6H).

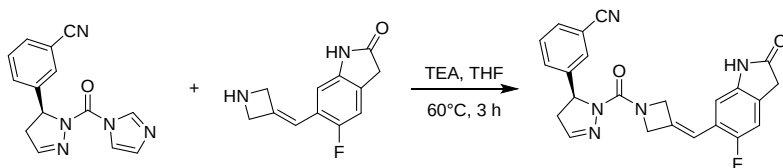
[0549] Compound 372 : (S)-5-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)-6-fluorobenzo[d]oxazol-2(3H)-one



[0550] Step 1: 2-amino-4-bromo-5-fluorophenol (300 mg, 1.46 mmol) was dissolved in 12 ml dry THF. CDI (283 mg, 1.75 mmol) was added to the above solution at room temperature. The mixture was heated to reflux for 1 hour. The resulting solution was concentrated in vacuo, purified by silica gel chromatography to afford 300 mg of 5-bromo-6-fluorobenzo[d]oxazol-2(3H)-one as a yellow solid. yield: 89 %.

[0551] Step 2: The title compound (S)-5-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)-6-fluorobenzo[d]oxazol-2(3H)-one (10 mg) was prepared in a yield of 18% as white solid from 5-bromo-6-fluorobenzo[d]oxazol-2(3H)-one and (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-methyleneazetidin-1-yl)methanone according to the procedure outlined for **372**. LC-MS (m/z): 429.1[M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.99 – 9.63 (br, 1H), 6.97 (d, *J* = 9.2 Hz, 1H), 6.88 (s, 1H), 6.82 – 6.74 (m, 2H), 6.72 – 6.63 (m, 2H), 6.49 (s, 1H), 5.66 – 5.48 (m, 1H), 5.16 – 4.81 (m, 4H), 3.54 – 3.36 (m, 1H), 2.82 – 2.66 (m, 1H).

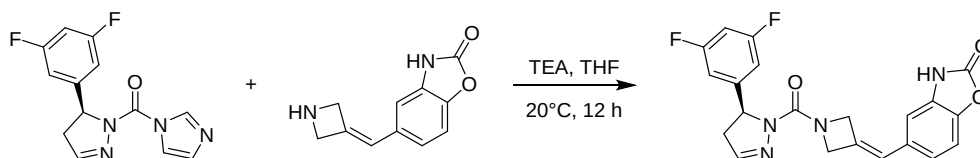
[0552] Compound 373 : (S)-3-(1-(3-((5-fluoro-2-oxoindolin-6-yl)methylene)azetidine-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)benzonitrile



The titled compound **373** was prepared in 28.1% yield from 6-(azetidin-3-ylidenemethyl)-5-fluoroindolin-2-one according to the procedure outlined for compound **203**. Mass (ESI): m/z calcd for C₂₃H₁₈FN₅O₂ 415.1, found 416.0 [M+H]⁺.

^1H NMR (400 MHz, CDCl_3) δ (ppm): 9.77 (s, 1H), 7.60-7.44 (m, 3H), 6.98-6.83 (m, 3H), 6.58 (d, J = 6.1 Hz, 1H), 6.43 (s, 1H), 5.39-5.34 (dd, J = 12.2, 6.5 Hz, 1H), 4.97-4.85 (m, 2H), 3.66-3.63 (m, 1H), 3.47-3.40 (m, 1H), 2.88-2.70 (m, 2H), 1.47-1.02 (m, 2H).

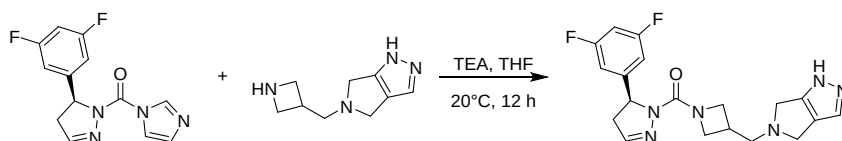
[0553] Compound 374: (S)-5-((1-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)azetidin-3-ylidene)methyl)benzo[d]oxazol-2(3H)-one



The titled compound **374** was prepared in 47.3% yield from 5-(azetidin-3-ylidenemethyl)benzo[d]oxazol-2(3H)-one according to the procedure outlined for compound **203**. Mass (ESI): m/z calcd for $\text{C}_{21}\text{H}_{16}\text{F}_2\text{N}_4\text{O}_3$ 410.1, found 411.0 $[\text{M}+\text{H}]^+$.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 11.57 (s, 1H), 7.25 (d, J = 8.3 Hz, 1H), 7.13-7.02 (m, 2H), 6.97-6.85 (m, 3H), 6.83 (d, J = 1.7 Hz, 1H), 6.36-6.34 (m, 1H), 5.26 (dd, J = 12.1, 6.7 Hz, 1H), 4.96 (s, 2H), 4.71 (s, 2H), 3.39 (ddd, J = 18.7, 12.2, 1.7 Hz, 1H), 2.64 (ddd, J = 18.6, 6.7, 1.8 Hz, 1H).

[0554] Compound 375 : (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(3-((4,6-dihydropyrrolo[3,4-c]pyrazol-5(1H)-yl)methyl)azetidin-1-yl)methanone

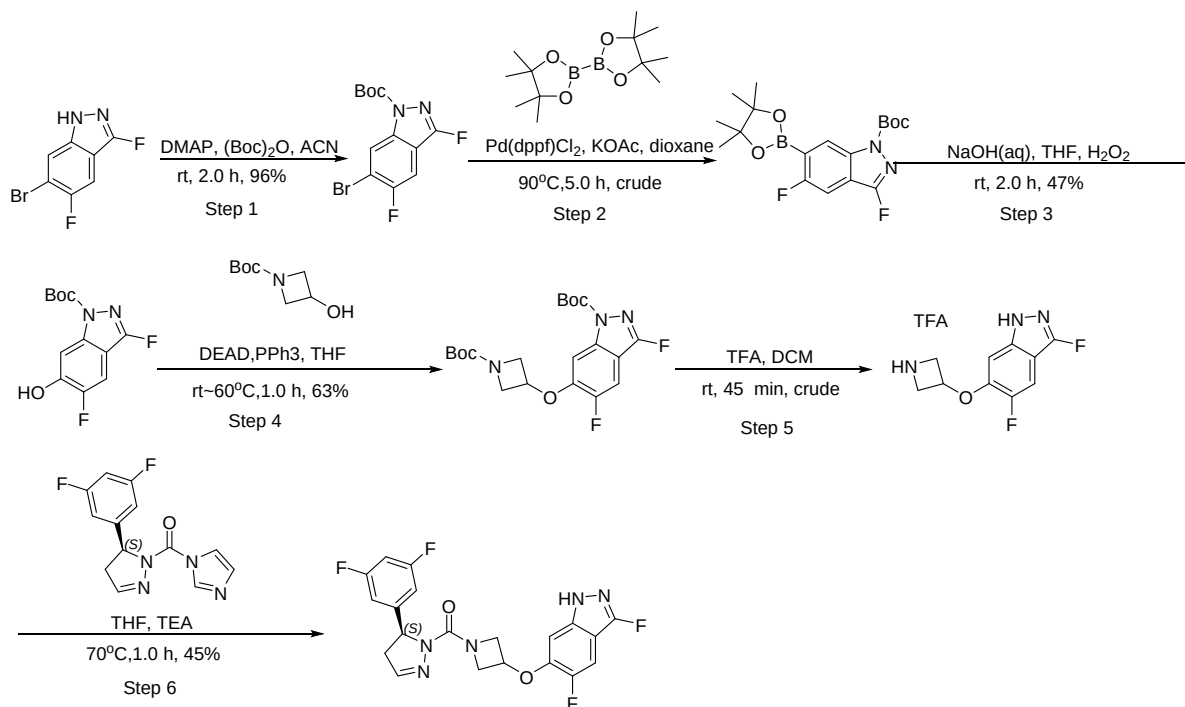


The titled compound **375** was prepared in 45.2% yield from 5-(azetidin-3-ylmethyl)-1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole according to the procedure outlined for compound **203**.

Mass (ESI): m/z calcd for $\text{C}_{19}\text{H}_{20}\text{F}_2\text{N}_6\text{O}$ 386.2, found 386.1 $[\text{M}+\text{H}]^+$.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 12.75 (s, 1H), 7.53 (s, 1H), 7.10 (tt, J = 9.3, 2.4 Hz, 1H), 7.05-6.94 (m, 1H), 6.94-6.75 (m, 2H), 5.20 (dd, J = 12.1, 6.6 Hz, 1H), 4.14 (d, J = 7.5 Hz, 6H), 3.85-3.76 (m, 2H), 3.50-3.18 (m, 2H), 3.08 (q, J = 7.3 Hz, 2H), 2.95-2.88 (m, 1H), 2.62 (ddd, J = 18.7, 6.6, 1.8 Hz, 1H).

[0555] Compound 376 : (S)-3-((3,5-difluoro-1H-indazol-6-yl)oxy)azetidin-1-yl(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



[0556] Step 1: tert-butyl 6-bromo-3,5-difluoro-1H-indazole-1-carboxylate. 6-bromo-3,5-difluoro-1H-indazole (4.0 g, 17.16 mmol) was dissolved in 40 ml of dry ACN. (Boc)₂O (5.6 g, 25.57mmol), DMAP(208 mg, 1.71 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 1 hour at room temperature. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound (5.5 g, 96%) as a yellow solids. (ES, m/s): 333.1 [M+H]⁺

[0557] Step 2 : tert-butyl 3,5-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole-1-carboxylate tert-butyl 6-bromo-3,5-difluoro-1H-indazole-1-carboxylate(5.0 g, 15.01 mmol) was dissolved in 100 ml of dry dioxane. 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.7 g, 22.53 mmol), Pd(dppf)Cl₂ (1.09 g, 1.49 mmol) ,KOAc (3.0 g, 30.61 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 5.0 hours at 90 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give the desired compound (9 g, crude) as brown oil which was used for next step without further purification. (ES, m/s): 281.1 [M+H]⁺

[0558] Step 3 : tert-butyl 3,5-difluoro-6-hydroxy-1H-indazole-1-carboxylate. tert-butyl 3,5-difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole-1-carboxylate

(9.0 g, crude) was dissolved in 100 ml of dry THF and NaOH(aq) (50 mL, 1 N). H₂O₂ (50 mL, 3% in H₂O) was added to the above solution at room temperature. The mixture was stirred for 2.0 hours at room temperature. The pH of resulting mixture was adjusted to 3-4 with HCl(aq, 1N). The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound (1.9 g, 47%) as a yellow oil. (ES, m/s): 271.2[M+H]⁺

[0559] Step 4 : tert-butyl 6-((1-(tert-butoxycarbonyl)azetidin-3-yl)oxy)-3,5-difluoro-1H-indazole-1-carboxylate tert-butyl 3,5-difluoro-6-hydroxy-1H-indazole-1-

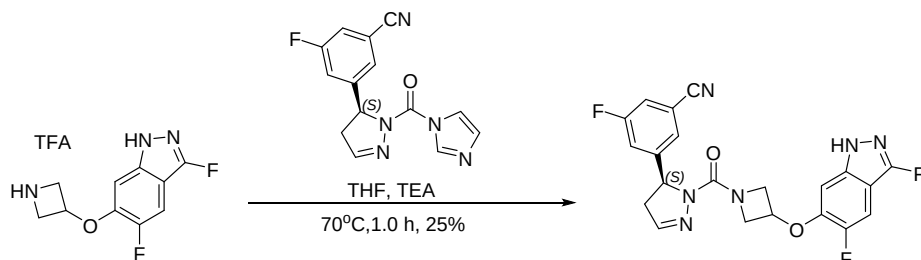
carboxylate (1.5 g, 5.55 mmol) was dissolved in 30 ml of dry THF. DEAD (1.45 g, 8.33 mmol), tert-butyl 3-hydroxyazetidine-1-carboxylate (1.15 g, 6.65 mmol), PPh₃ (2.18 g, 8.32 mmol) was added to the above solution at 0 degrees C under nitrogen. The mixture was stirred for 45 minutes at 60 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound (1.5 g, 63 %) as a white solid. (ES, m/s): 426.3[M+H]⁺

[0560] Step 5 : 6-(azetidin-3-yloxy)-3,5-difluoro-1H-indazole trifluoroacetate tert-butyl 6-((1-(tert-butoxycarbonyl)azetidin-3-yl)oxy)-3,5-difluoro-1H-indazole-1-carboxylate (150 mg, 0.35 mmol) was dissolved in 5 ml of dry DCM. TFA (2 mL) was added to the above solution at room temperature. The mixture was stirred for 45 minutes at room temperature. The mixture was concentrated in vacuo to give the desired compound (300 mg, crude) as brown oil which was used for next step without further purification. (ES, m/s): 225.3[M-H]⁻

[0561] Step 6: (S)-(3-((3,5-difluoro-1H-indazol-6-yl)oxy)azetidin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone (S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(1H-imidazol-1-yl)methanone was dissolved in 5 ml of dry THF and 2 mL of TEA. 6-(azetidin-3-yloxy)-3,5-difluoro-1H-indazole trifluoroacetate (300 mg, crude) in 5 mL of THF was added to the above solution at room temperature. The mixture was stirred for 1.0 hour at 70 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **376** (69 mg, 45%) as a white solid. (ES, m/s): 434.3[M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.41 (brs, 1H), 7.60 (d, *J* = 10.4 Hz, 1H), 7.11 (tt, *J* = 9.4, 2.4 Hz, 1H), 7.03 – 7.00 (m, 1H), 6.95 – 6.87 (m, 2H), 6.83 (dd, *J* = 6.8,

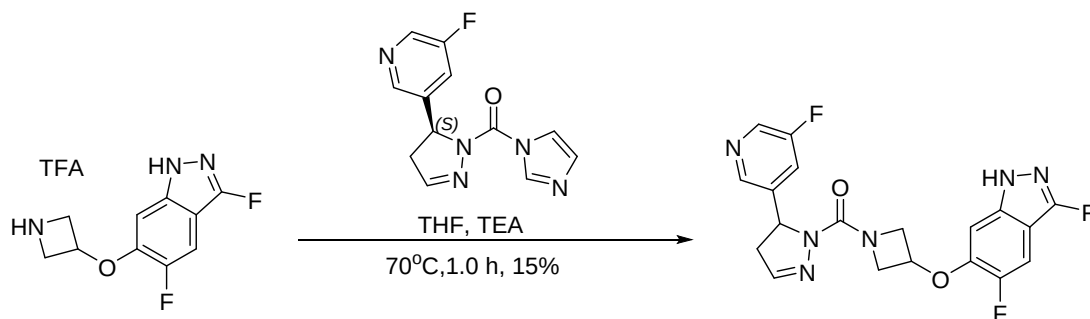
2.4 Hz, 1H), 5.24 (dd, $J = 12.2, 6.6$ Hz, 1H), 5.20-5.13 (m, 1H), 4.53 (brs, 2H), 4.05 (brs, 2H), 3.43 – 3.37 (m, 1H), 2.69 – 2.59 (m, 1H).

[0562] Compound 377 : (S)-3-(1-(3-((3,5-difluoro-1H-indazol-6-yl)oxy)azetidine-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)-5-fluorobenzonitrile



The titled compound **377** as a white solid (13 mg, 25 %) was prepared from (S)-3-(1-(1H-imidazole-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)-5-fluorobenzonitrile and 6-(azetidin-3-yloxy)-3,5-difluoro-1H-indazole trifluoroacetate according to the procedure outlined for compound **376** (ES, m/s): 441.4 $[M+H]^+$ ^1H NMR (400 MHz, DMSO- d_6) δ 12.41 (brs, 1H), 7.75 (ddd, $J = 8.6, 2.6, 1.4$ Hz, 1H), 7.63 – 7.52 (m, 2H), 7.51 – 7.37 (m, 1H), 7.08 – 6.98 (m, 1H), 6.82 (dd, $J = 6.8, 2.2$ Hz, 1H), 5.27 (dd, $J = 12.2, 6.8$ Hz, 1H), 5.20 – 5.12 (m, 1H), 4.53 (brs, 2H), 4.02 (brs, 2H), 3.44 – 3.37 (m, 1H), 2.70 (ddd, $J = 18.8, 7.0, 1.6$ Hz, 1H).

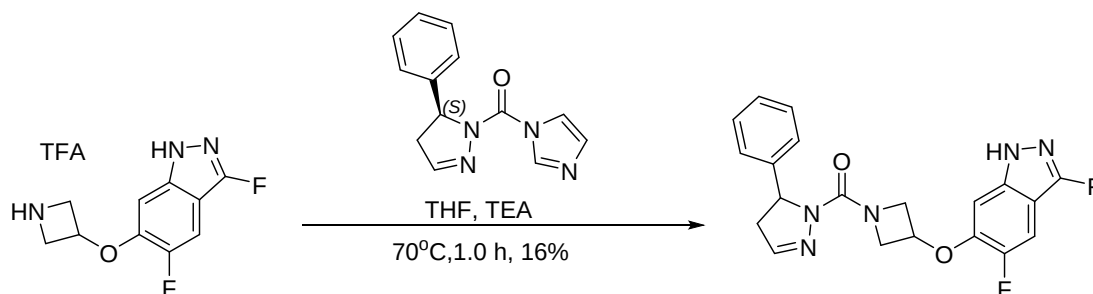
[0563] Compound 378 : (3-((3,5-difluoro-1H-indazol-6-yl)oxy)azetidin-1-yl)(5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **378** as a white solid (10 mg, 15 %) was prepared from (S)-5-(5-fluoropyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)methanone and 6-(azetidin-3-yloxy)-3,5-difluoro-1H-indazole trifluoroacetate according to the procedure outlined for compound **376** (ES, m/s): 417.4 $[M+H]^+$ ^1H NMR (400 MHz, DMSO- d_6) δ 12.40 (brs, 1H), 8.46 (d, $J = 2.8$ Hz, 1H), 8.34 (t, $J = 1.8$ Hz, 1H), 7.59 (d, $J = 10.4$ Hz, 1H), 7.54 (dt, $J = 9.8, 2.4$ Hz, 1H), 7.06 – 7.03 (m, 1H), 6.81 (dd, $J = 6.8, 2.4$ Hz, 1H), 5.29 (dd,

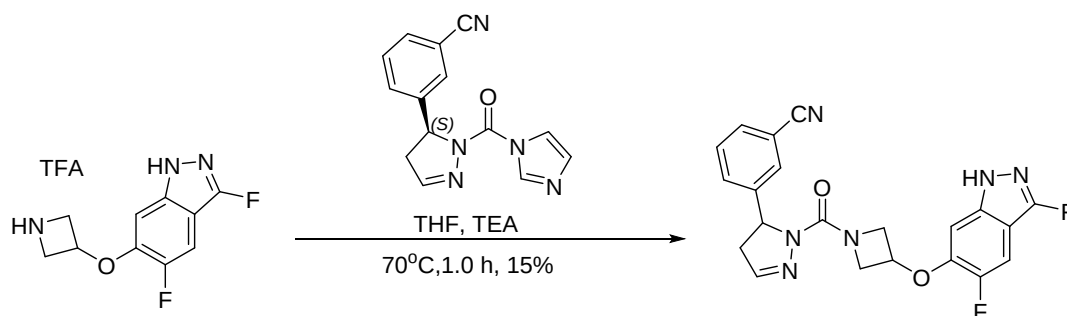
$J = 12.2, 6.8$ Hz, 1H), 5.18 – 5.10 (m, 1H), 4.51 (brs, 2H), 4.03 (brs, 2H), 3.45-3.36 (m, 1H), 2.76 – 2.63 (m, 1H).

[0564] Compound 379 : (3-((3,5-difluoro-1H-indazol-6-yl)oxy)azetidin-1-yl)(5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone



The titled compound **379** as a white solid (10 mg, 16 %) was prepared from (S)-3-(1-(1H-imidazol-1-yl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)methanone and 6-(azetidin-3-yloxy)-3,5-difluoro-1H-indazole trifluoroacetate according to the procedure outlined for compound **376**. (ES, m/s): 398.4 $[M+H]^+$ ^1H NMR (400 MHz, DMSO- d_6) δ 12.40 (brs, 1H), 7.59 (d, $J = 10.4$ Hz, 1H), 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.18 – 7.13 (m, 2H), 7.01 – 6.99 (m, 1H), 6.82 (dd, $J = 6.8, 2.4$ Hz, 1H), 5.20 (dd, $J = 12.0, 6.0$ Hz, 1H), 5.17-5.12 (m, 1H), 4.50 (brs, 2H), 4.00 (brs, 2H), 3.44 – 3.35 (m, 1H), 2.61 – 2.53 (m, 1H).

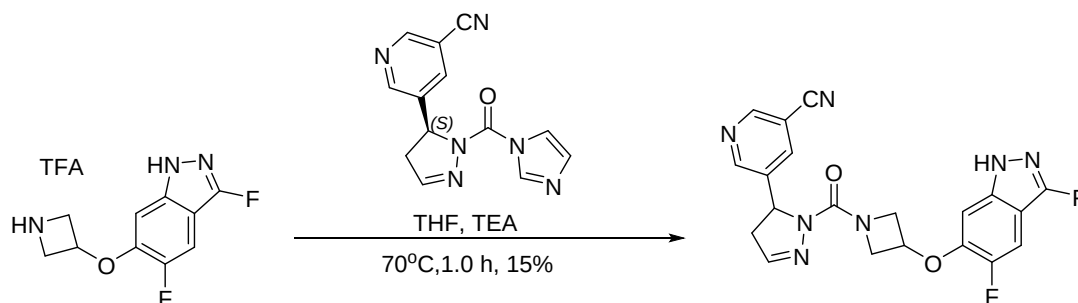
[0565] Compound 380 : 3-(1-(3-((3,5-difluoro-1H-indazol-6-yl)oxy)azetidine-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)benzonitrile



The titled compound **380** as a white solid (10 mg, 15 %) was prepared from (S)-3-(1-(1H-imidazole-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)benzonitrile and 6-(azetidin-3-yloxy)-3,5-difluoro-1H-indazole trifluoroacetate according to the procedure outlined for compound **376**. (ES, m/s): 423.4 $[M+H]^+$ ^1H NMR (400 MHz, DMSO- d_6) δ 12.40 (brs, 1H), 7.74-7.70 (m, 1H), 7.64 (brs, 1H), 7.59 (d, $J = 10.4$ Hz, 1H), 7.55 – 7.51 (m, 2H), 7.05

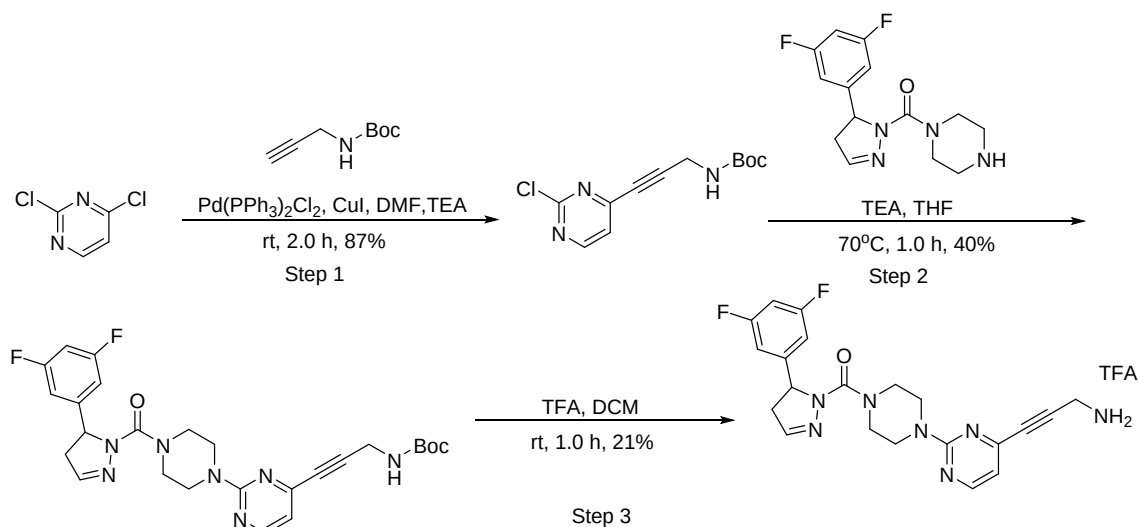
– 6.99 (m, 1H), 6.81 (dd, $J = 6.8, 2.2$ Hz, 1H), 5.26 (dd, $J = 12.2, 6.6$ Hz, 1H), 5.18-5.12(m, 1H), 4.51 (brs, 2H), 4.01 (brs, 1H), 3.44 – 3.34 (m, 1H), 2.69-2.61 (m, 1H).

[0566] Compound 381 :5-(1-(3-((3,5-difluoro-1H-indazol-6-yl)oxy)azetidine-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)nicotinonitrile



The titled compound **381** as a white solid (10 mg, 15 %) was prepared from (S)-5-(1-(1H-imidazole-1-carbonyl)-4,5-dihydro-1H-pyrazol-5-yl)nicotinonitrile and 6-(azetidin-3-yloxy)-3,5-difluoro-1H-indazole trifluoroacetate according to the procedure outlined for compound **376** (ES, m/z): 423.4 $[M+H]^+$ ^1H NMR (400 MHz, $DMSO-d_6$) δ 12.40 (brs, 1H), 8.91 (d, $J = 2.0$ Hz, 1H), 8.73 (d, $J = 2.2$ Hz, 1H), 8.16 (t, $J = 2.0$ Hz, 1H), 7.59 (d, $J = 10.6$ Hz, 1H), 7.07 – 7.03 (m, 1H), 6.81 (dd, $J = 6.8, 2.2$ Hz, 1H), 5.30 (dd, $J = 12.2, 7.2$ Hz, 1H), 5.18-5.11 (m, 1H), 4.51 (brs, 2H), 4.04 (brs, 2H), 3.46 – 3.38 (m, 1H), 2.69-2.61 (m, 1H).

[0567] Compound 382: (4-(4-(3-aminoprop-1-yn-1-yl)pyrimidin-2-yl)piperazin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone trifluoroacetate

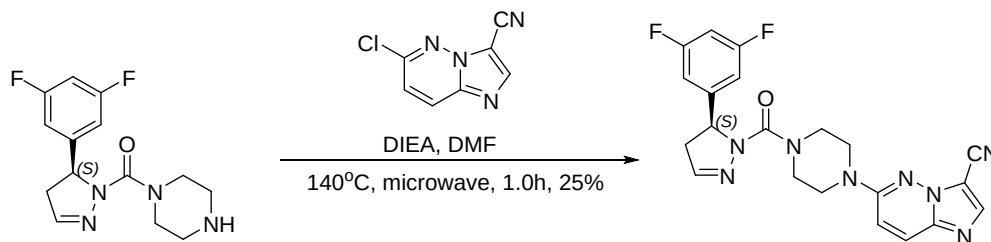


[0568] Step 1: tert-butyl (3-(2-chloropyrimidin-4-yl)prop-2-yn-1-yl)carbamate. 2,4-dichloropyrimidine (444 mg, 3.00 mmol) was dissolved in 20 ml of dry DMF and TEA (2 mL). tert-butyl prop-2-yn-1-ylcarbamate (930 mg, 6.00 mmol), Pd(PPh₃)₂Cl₂ (210 mg, 0.30 mmol), CuI (114 mg, 0.60 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 2.0 hours at room temperature. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give the desired compound (700 mg, 87%) as brown solids which was used for next step without further purification. (ES, m/s): 268.5 [M+H]⁺

[0569] Step 2: tert-butyl (3-(2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)pyrimidin-4-yl)prop-2-yn-1-yl)carbamate (5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone (300 mg, 1.12 mmol) was dissolved in 5 ml of dry THF. tert-butyl (3-(2-chloropyrimidin-4-yl)prop-2-yn-1-yl)carbamate (331 mg, 1.12 mmol), TEA (227 mg, 2.24 mmol) was added to the above solution at room temperature. The mixture was stirred for 1.0 hour at 70 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound (200 mg, 40%) as a brown solid. (ES, m/s): 526.5 [M+H]⁺

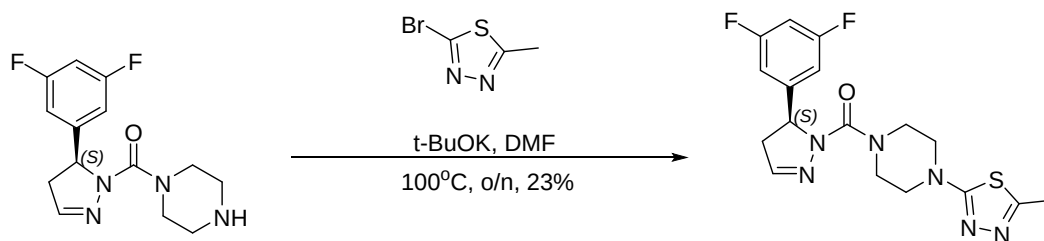
[0570] Step 3: (4-(4-(3-aminoprop-1-yn-1-yl)pyrimidin-2-yl)piperazin-1-yl)(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)methanone trifluoroacetate. tert-butyl (3-(2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)pyrimidin-4-yl)prop-2-yn-1-yl)carbamate (50 mg, 0.09 mmol) was dissolved in 4 ml of dry DCM. TFA (1 mL) was added to the above solution at room temperature. The mixture was stirred for 1.0 hour at room temperature. The mixture was concentrated in vacuo. Purification by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18 silica gel; mobile phase, H₂O (0.05% TFA) / ACN = 100:0 increasing to H₂O (0.05% TFA) / ACN = 60:40 within 25 min; Detector, UV 254 nm. to give the titled compound **382** (10 mg, 21%) as a yellow solid. (ES, m/s): 426.2 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.45 (d, *J* = 5.0 Hz, 1H), 8.36 (brs, 2H), 7.15-7.07 (m, 2H), 7.00 (d, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 4.8 Hz, 1H), 5.26 (t, *J* = 10.8 Hz, 1H), 4.07 (brs, 2H), 3.81 – 3.49 (m, 8H), 3.44 – 3.34 (m, 1H), 2.70-2.61 (m, 1H).

[0571] Compound 383: (S)-6-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)imidazo[1,2-b]pyridazine-3-carbonitrile



(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(piperazin-1-yl)methanone (165 mg, 0.56 mmol) was dissolved in 4 ml of dry DMF. 6-chloroimidazo[1,2-b]pyridazine-3-carbonitrile (100 mg, 0.56 mmol) and DIEA (145 mg, 1.12 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 1.0 hour at 140 degrees C under microwave. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **383** (60 mg, 25%) as a white solid. (ES, m/s): 437.4 $[\text{M}+\text{H}]^+$ ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.26 (d, $J = 0.8$ Hz, 1H), 8.07 (d, $J = 10.0$ Hz, 1H), 7.46 (d, $J = 10.2$ Hz, 1H), 7.13–7.06 (m, 2H), 7.02–6.96 (m, 2H), 5.28–5.20 (m, 1H), 3.61 (m, 8H), 3.39–3.32 (m, 1H), 2.68–2.58 (m, 1H).

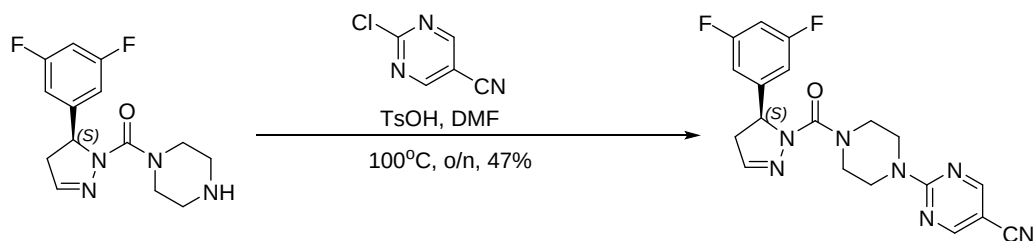
[0572] Compound 384 : (S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(4-(5-methyl-1,3,4-thiadiazol-2-yl)piperazin-1-yl)methanone



(S)-5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl(piperazin-1-yl)methanone (100 mg, 0.34 mmol) was dissolved in 10 ml of dry DMF. 2-bromo-5-methyl-1,3,4-thiadiazole (91 mg, 0.51 mmol) and t-BuOK (77 mg, 0.68 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 1 overnight at 100 degrees C. The mixture was extracted with EA, washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **384** (30 mg, 23%) as a yellow solid. (ES, m/s): 393.2 $[\text{M}+\text{H}]^+$ ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.13–7.06 (m, 2H), 6.98 (dt, $J = 8.7, 2.0$ Hz, 2H), 5.24 (dd, $J = 11.6, 9.8$

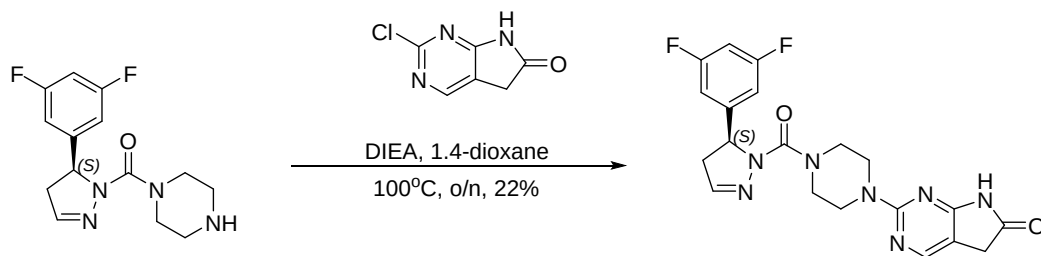
Hz, 1H), 3.73–3.65 (m, 2H), 3.53–3.47(m, 2H), 3.45 –3.37 (m, 4H), 3.37–3.33 (m, 1H), 2.68–2.58 (m, 1H), 2.50 (s, 3H).

[0573] Compound 385: (S)-2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)pyrimidine-5-carbonitrile



(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone (200 mg, 0.68 mmol) was dissolved in 10 ml of dry DMF. 2-chloropyrimidine-5-carbonitrile (95 mg, 0.68 mmol) and TsOH(39 mg, 0.20 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 1 overnight at 100 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **385** (126 mg, 47%) as a white solid. (ES, m/s): 398.2[M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.55 – 8.53 (m, 2H), 6.91 – 6.82 (m, 2H), 6.80 – 6.71 (m, 2H), 5.01 (t, *J* = 10.8 Hz, 1H), 3.73 – 3.52 (m, 4H), 3.48 – 3.23 (m, 4H), 3.18–3.10 (m, 1H), 2.46 – 2.36 (m, 1H).

[0574] Compound 386 : (S)-2-(4-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)piperazin-1-yl)-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one



(S)-(5-(3,5-difluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(piperazin-1-yl)methanone (100 mg, 0.34 mmol) was dissolved in 10 ml of dry 1,4-dioxane. 2-chloro-5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one (86 mg, 0.51 mmol) and DIEA(88 mg, 0.68 mmol) were added to the above solution under nitrogen at room temperature. The mixture was stirred for 1 overnight at 100 degrees C. The mixture was extracted with EA, washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Purification by silica gel chromatography to give the titled compound **386** (32 mg, 22%) as a pink solid. (ES, m/s): 428.2[M+H]⁺ ¹H

NMR (400 MHz, DMSO- d_6) δ 11.10 (brs, 1H), 7.93 (brs, 1H), 7.13 – 7.05 (m, 2H), 7.02 – 6.93 (m, 2H), 5.24 (t, J = 10.8 Hz, 1H), 3.77 – 3.44 (m, 8H), 3.40 (s, 2H), 3.39 – 3.34 (m, 1H), 2.67–2.58 (m, 1H).

