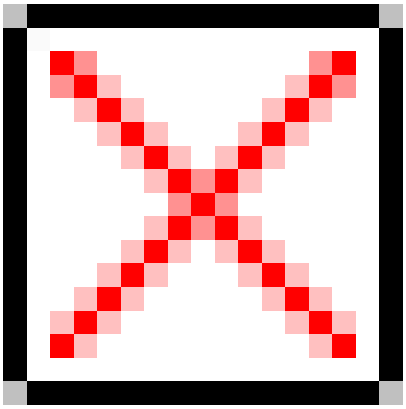
Industria y Comercio
SUPERINTENDENCIA

Radicación	16 172430 0000 0000	2016-06-29 12:39:03	
Trámite	11	PCT-PATENTE DE INVENCION CAPITULOS I Y II	
Evento	378	FASE NACIONAL INCLUIDO CAPITULO I	
Actuación	411	PRESENTACION	Folios: 172
Dependencia	2020	DIRECCION DE NUEVAS CREACIONES	
Pago #1	66865	$ 130000	

DIRECCIÓN DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL - PCT



1	**Titulo de la Invención**(200 caractares o espacios máximos)
	MODULADORES DE TETRAHIDROPIRIDOPIRAZINAS DE GPR6

2	**Datos del Solicitante**			
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Identificación:

- ☐ CEDULA DE CIUDADANIA
- ☐ CEDULA DE EXTRANJERIA
- ☒ EMPRESA EXTRANJERA
- ☐ NIT
- ☐ PASAPORTE

Número: 1044765-

3	**Solicitantes**

	Apellidos - Nombres o Razón Social	Tipo	Identificación
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Identificación:

- ☐ CEDULA DE CIUDADANIA
- ☐ CEDULA DE EXTRANJERIA
- ☐ EMPRESA EXTRANJERA
- ☐ NIT
- ☐ PASAPORTE
- ☒ No Aplica

Número: -

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Identificación:

☒ CEDULA DE CIUDADANIA ☐ CEDULA DE EXTRANJERIA

☐ EMPRESA EXTRANJERA ☐ NIT

☐ PASAPORTE

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10	Reivindicaciones			
Número reivindicaciones:	12	**Pago Reivindicaciones:**	Si	

11 Reducción de tasas.

Declaro que carezco de medios económicos para presentar la solicitud de patente.

☐ SI ☒ NO

Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolucón vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.

☐ Micro, pequeñas y medianas empresas
☐ Universidades públicas o privadas
☐ Entidades sin ánimo de lucro

Debe aportar los documentos que se indican en el numeral 17 de anexos

12 Documentos Anexos

☒ Reivindicaciones
☒ Descripción
☐ Dibujos y/o Figuras
☒ Resumen
☐ Certificado Depósito Material Biológico
☐ Uso de Conocimiento tradicional
☐ Listado de secuencias
☒ Artes finales 12 x 12 cm
☒ Poderes, si fuere el caso
☐ Copia de la primera solicitud si se reivindica prioridad
☐ Traducción simple de la primera solicitud, si se reivindica prioridad
☒ Otros Anexos

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:

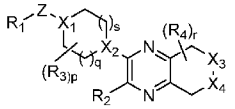
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

WO 2015/095728 A1

(54) Title: TETRAHYDROPYRIDOPYRAZINES MODULATORS OF GPR6



(I)

(57) Abstract: The present invention provides compounds of formula (I): which are useful as modulators of GPR6, pharmaceutical compositions thereof, methods for treatment of conditions associated with GPR6, processes for making the compounds and intermediates thereof.

TETRAHYDROPYRIDOPYRAZINES MODULATORS OF GPR6

FIELD OF THE INVENTION

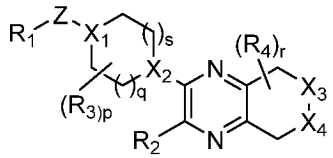
[0001] The present invention relates to medicinal chemistry, pharmacology, and medicine.

BACKGROUND OF THE INVENTION

[0002] The present invention provides compounds that are G-Protein-Coupled Receptor 6 (hereinafter referred to as GPR6) modulators. GPR6 is GPCR that signals via the Gs pathway. GPR6 receptors are highly expression in the central nervous system (CNS), particularly medium spiny neurons (MSNs) of the striatum, with minimal expression in peripheral tissues. The major striatal targets of dopaminergic innervation reside in the medium spiny neurons (MSNs) of the striatopallidal (indirect) and striatonigral (direct) output pathways. The MSNs of the direct output pathway express D1 dopamine receptors whereas those in the indirect pathway express D2 receptors. GPR6 is enriched in D2 receptor expressing MSNs in the striatum where GPR6 activity is functionally opposed to D2 receptor signaling. Antagonism or inverse agonism of Gs coupled GPR6 decreases cAMP in MSNs and provides a functional alternative to dopamine mediated activation of D2 receptors. Therefore, the compounds of the present invention are useful to treat a variety of neurological and psychiatric disorders, including Parkinson's disease.

SUMMARY OF THE INVENTION

[0003] The present invention provides a compound of formula I:



I

wherein

R_1 is selected from the group consisting of optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{3-6} heterocyclyl, optionally substituted C_{6-10} aryl, and optionally substituted C_{1-10} heteroaryl;

X_1 is N and X_2 is CH; or

X_1 is CH and X_2 is N; or

X_1 is N and X_2 is N;

when X_1 is N, Z is selected from the group consisting of C_{1-6} alkylene, C_{1-6} haloalkylene, -C(O)-, and -$S(O)_2$-;

when X_1 is CH, Z is selected from the group consisting of C_{1-6} alkylene, C_{1-6} haloalkylene, -O-, -C(O)-, -NH-, -S-, -S(O)-, and -$S(O)_2$-;

q is 0, 1, or 2;

s is 0, 1, or 2;

R_2 is $–OR_5$ or $–NR_6R_7$;

R_3, each time taken, is independently selected from the group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl, and trifluoromethyl;

p is 0, 1, or 2;

R_4, each time taken, is independently selected from the group consisting of C_{1-6} alkyl, hydroxy, and halo;

r is 0 or 1;

R_5 is selected from the group consisting of C_{1-6} alkyl and C_{3-8} cycloalkyl;

R_6 is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R_7 is selected from the group consisting of optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-10} heteroaryl, and optionally substituted C_{3-6} heterocyclyl;

X_3 is selected from the group consisting of CH and CR_4 and X_4 is NR_8; or

X_3 is NR_8 and X_4 is selected from the group consisting of CH and CR_4;

R_8 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, -$S(O)_2$-R_9, -C(O)-R_{10}, -C(O)-$N(R_{11})(R_{12})$, and -C(O)-OR_{13};

R_9 is selected from the group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl, and optionally substituted phenyl;

R_{10} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-10} heteroaryl, and optionally substituted C_{3-6} heterocyclyl;

R_{11} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R_{12} is selected from the group consisting of hydrogen, C_{1-6} alkyl and C_{3-8} cycloalkyl; or

R_{11} and R_{12} are taken together with the nitrogen to which they are attached form a 4 to 7 membered, saturated, ring optionally having 1 additional ring heteroatom selected from the group N, O, and S and optionally substituted on any of the ring carbon atoms with 1 to 5 substituents independently selected from the group consisting of cyano, halo, hydroxy, amino, optionally substituted C_{3-6} heterocyclyl, C_{1-9} amide, optionally substituted C_{1-6} alkyl, and C_{1-4} alkoxy and substituted on any additional ring nitrogen by a substituent selected from the group consisting of hydrogen, C_{3-8} cycloalkyl, and optionally substituted C_{1-6} alkyl;

R_{13} is selected from the group consisting of C_{1-6} alkyl and C_{3-8} cycloalkyl;
or a pharmaceutically acceptable salt thereof.

[0004] The present invention also provides pharmaceutical compositions, comprising: a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[0005] The compounds of the present invention are modulators of GPR6 and are useful to treat a variety of neurological and psychiatric disorders, for example movement disorders including Parkinson's disease, levodopa induced dyskinesias, and Huntington's disease, drug addiction, eating disorders, cognitive disorders, schizophrenia, bipolar disorders, and depression. Thus, the present invention also provides methods of treating the conditions associated with GPR6 described herein comprising, administering to a patient in need thereof an effective amount of the compounds of the invention. The present invention provides for the use of the compounds of the invention as a medicament, including for treatment of the conditions associated with GPR6 described herein, and including for the manufacture of a medicament for treating the conditions associated with GPR6 described herein.

[0006] The present invention also provides processes from making GPR6 modulators and intermediates thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0007] The term "C_{1-4} alkyl" refers to a straight or branched alkyl chain of one to four carbon atoms.

[0008] The term "optionally substituted C_{1-4} alkyl" refers to a C_{1-4} alkyl optionally substituted with 1 to 6 substituents independently selected from the group consisting of optionally substituted C_{1-4} alkoxy, C_{1-4} thioalkoxy, C_{1-9} amide, C_{1-7} amido, amino, C_{1-8} alkylamino, C_{1-5} oxycarbonyl, C_{1-5} carbonyloxy, C_{1-8} sulfonyl, cyano, optionally substituted C_{3-8} cycloalkyl, C_{3-8} cycloalkoxy, halo, hydroxy, nitro, oxo, optionally substituted C_{3-6} heterocyclyl, optionally substituted C_{1-10} heteroaryl, and optionally substituted C_{6-10} aryl.

[0009] More particularly "optionally substituted C_{1-4} alkyl" refers to a C_{1-4} alkyl optionally substituted with 1 to 6 substituents independently selected from the group consisting of C_{1-4} alkoxy, C_{1-9} amide, amino, C_{1-8} alkylamino, C_{1-5} oxycarbonyl, cyano, C_{3-8} cycloalkyl, halo, hydroxy, C_{3-6} heterocyclyl optionally substituted on any ring nitrogen by C_{1-4} alkyl, C_{1-10} heteroaryl, and optionally substituted phenyl.

[0010] Even more particularly "optionally substituted C_{1-4} alkyl" refers to a C_{1-4} alkyl optionally substituted with 1 to 6 substituents independently selected from the group consisting of C_{1-4} alkoxy, cyano, C_{3-8} cycloalkyl, halo, hydroxy, C_{3-6} heterocyclyl optionally substituted on any ring nitrogen by C_{1-4} alkyl, and optionally substituted phenyl.

[0011] The term "C_{1-6} alkyl" refers to a straight or branched alkyl chain of one to six carbon atoms.

[0012] The term "optionally substituted C_{1-6} alkyl" refers to a C_{1-6} alkyl optionally substituted with 1 to 7 substituents independently selected from the group consisting of amino, C_{1-8} alkylamino, optionally substituted C_{1-4} alkoxy, C_{1-4} thioalkoxy, C_{1-9} amide, C_{1-7} amido, C_{1-5} oxycarbonyl, C_{1-5} carbonyloxy, C_{1-8} sulfonyl, cyano, optionally substituted C_{3-8} cycloalkyl, halo, hydroxy, oxo, optionally substituted C_{1-10} heteroaryl, optionally substituted C_{3-6} heterocyclyl, and optionally substituted C_{6-10} aryl.

[0013] More particularly "optionally substituted C_{1-6} alkyl" refers to a C_{1-6} alkyl optionally substituted with 1 to 7 substituents independently selected from the group consisting of C_{1-4} alkoxy, C_{1-9} amide, amino, C_{1-8} alkylamino, C_{1-5} oxycarbonyl, cyano, C_{3-8} cycloalkyl, halo, hydroxy, C_{3-6} heterocyclyl optionally substituted on any ring nitrogen by C_{1-4} alkyl, C_{1-10} heteroaryl, and optionally substituted phenyl.

[0014] Even more particularly "optionally substituted C_{1-6} alkyl" refers to a C_{1-6} alkyl optionally substituted with 1 to 7 substituents independently selected from the group consisting of C_{1-4} alkoxy, cyano, C_{3-8} cycloalkyl, halo, hydroxy, C_{3-6} heterocyclyl optionally substituted on any ring nitrogen by C_{1-4} alkyl, and optionally substituted phenyl.

[0015] The term "C_{1-6} haloalkyl" refers to a straight or branched alkyl chain of one to six carbon atoms substituted with 1 to 3 halogen atoms. More particularly, the term "C_{1-6} haloalkyl" refers fluoromethyl and difluoromethyl.

[0016] The term "C_{1-8} sulfonyl" refers to a sulfonyl linked to a C_{1-6} alkyl group, C_{3-8} cycloalkyl, or an optionally substituted phenyl.

[0017] The term "C_{1-6} alkylene" refers to a straight or branched, divalent, alkylene chain of one to six carbon atoms.

[0018] The term "C_{1-6} haloalkylene" refers to a straight or branched, divalent, alkylene chain of one to six carbon atoms substituted with 1 to 3 halogen atoms. More particularly, the term "C_{1-6} haloalkylene" refers fluoromethylene and difluoromethylene.

[0019] The term "C_{1-4} alkoxy" refers to a C_{1-4} alkyl attached through an oxygen atom.

[0020] The term "optionally substituted C_{1-4} alkoxy" refers to a C_{1-4} alkoxy optionally substituted with 1 to 6 substituents independently selected from the group consisting of C_{1-4}

alkoxy, C_{1-9} amide, C_{1-5} oxycarbonyl, cyano, optionally substituted C_{3-8} cycloalkyl, halo, hydroxy, optionally substituted C_{1-10} heteroaryl, and optionally substituted C_{6-10} aryl. While it is understood that where the optional substituent is C_{1-4} alkoxy or hydroxy then the substituent is generally not alpha to the alkoxy attachment point, the term "optionally substituted C_{1-4} alkoxy" includes stable moieties and specifically includes trifluoromethoxy, difluoromethoxy, and fluoromethoxy.

[0021] More particularly "optionally substituted C_{1-4} alkoxy" refers to a C_{1-4} alkoxy optionally substituted with 1 to 6 substituents independently selected from the group consisting of C_{1-4} alkoxy, cyano, C_{3-8} cycloalkyl, halo, hydroxy, and optionally substituted phenyl. Even more particularly "optionally substituted C_{1-4} alkoxy" refers to trifluoromethoxy, difluoromethoxy, and fluoromethoxy.

[0022] The term "C_{1-9} amide" refers to a $-C(O)NR_aR_b$ group in which R_a is selected from the group consisting of hydrogen and C_{1-4} alkyl, and R_b is selected from the group consisting of hydrogen, C_{1-3} alkyl, and optionally substituted phenyl.

[0023] The term "C_{1-7} amido" refers to a $-NHC(O)R_c$ group in which R_c is selected from the group consisting of hydrogen, C_{1-6} alkyl, and optionally substituted phenyl.

[0024] The term "C_{1-5} carbamoyl" refers to an O- or N-linked carbamate substituted with a terminal C_{1-4} alkyl.

[0025] The term "C_{1-5} ureido" refers to a urea optionally substituted with a C_{1-4} alkyl.

[0026] The term "C_{1-8} alkylamino" refers to a $-NR_dR_e$ group in which R_d is a C_{1-4} alkyl and R_e is selected from the group consisting of hydrogen and C_{1-4} alkyl.

[0027] The term "C_{6-10} aryl" refers to a monocyclic and polycyclic unsaturated, conjugated hydrocarbon having five to ten carbon atoms, and includes phenyl, and naphthyl.

[0028] More particularly "C_{6-10} aryl" refers to phenyl.

[0029] The term "optionally substituted C_{6-10} aryl" refers to a C_{6-10} aryl optionally substituted with 1 to 5 substituents independently selected from the group consisting of optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} alkoxy, C_{1-4} thioalkoxy, amino, C_{1-8} alkylamino, C_{1-9} amide, C_{1-7} amido, C_{1-5} oxycarbonyl, C_{1-5} carbonyloxy, C_{1-8} sulfonyl, C_{1-5} carbamoyl, C_{1-6} sulfonylamido, aminosulfonyl, C_{1-10} aminosulfonyl, C_{1-5} ureido, cyano, halo, and hydroxyl.

[0030] More particularly "optionally substituted C_{6-10} aryl" refers to a C_{6-10} aryl optionally substituted with 1 to 5 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, cyano, halo, hydroxy, amino, trifluoromethyl, and trifluoromethoxy.

[0031] Even more particularly "optionally substituted C_{6-10} aryl" refers to phenyl optionally substituted with 1 to 5 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, cyano, halo, trifluoromethyl, and trifluoromethoxy.

[0032] The term "C_{1-5} oxycarbonyl" refers to an oxycarbonyl group ($-CO_2H$) and C_{1-4} alkyl ester thereof.

[0033] The term "C_{1-5} carbonyloxy" refers to a carbonyloxy group ($-O_2CR_f$), in which R_f is selected from the group consisting of hydrogen and C_{1-4} alkyl, for example, acetoxy.

[0034] The term "C_{3-8} cycloalkyl" refers to monocyclic or bicyclic, saturated or partially (but not fully) unsaturated alkyl ring of three to eight carbon atoms, and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. It is understood that the term includes benzofused cyclopentyl and cyclohexyl.

[0035] The term "optionally substituted C_{3-8} cycloalkyl" refers to a C_{3-8} cycloalkyl optionally substituted with 1 to 6 substituents independently selected from the group consisting of optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} alkoxy, C_{1-9} amide, C_{1-7} amido, amino, C_{1-8} alkylamino, C_{1-5} oxycarbonyl, cyano, C_{3-8} cycloalkyl, C_{3-8} cycloalkoxy, halo, hydroxy, nitro, oxo, optionally substituted C_{1-10} heteroaryl, and optionally substituted phenyl.

[0036] More particularly "optionally substituted C_{3-8} cycloalkyl" refers to a C_{3-8} cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of C_{1-4} alkoxy, halo, hydroxy, and C_{1-4} alkyl optionally substituted with C_{1-4} alkoxy, halo, and hydroxy.

[0037] The term "C_{3-8} cycloalkoxy" refers to a C_{3-8} cycloalkyl attached through and oxygen.

[0038] The terms "halogen" and "halo" refers to a chloro, fluoro, bromo or iodo atom.

[0039] The term "C_{3-6} heterocyclyl" refers to a 4 to 8 membered monocyclic or bicyclic, saturated or partially (but not fully) unsaturated ring having one or two heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur and the ring optionally includes a carbonyl to form a lactam or lactone. It is understood that where sulfur is included that the sulfur may be either -S-, -SO-, and $-SO_2-$. It is also under that the term includes spirofused bicyclic systems. For example, but not limiting, the term includes azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxetanyl, dioxolanyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuryl, hexahydropyrimidinyl, tetrahydropyrimidinyl, dihydroimidazolyl, and the like. It is understood that a C_{3-6} heterocyclyl can be attached as a substituent through a ring carbon or a ring nitrogen atom.

[0040] More particularly "C_{3-6} heterocyclyl" is selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, oxetanyl, tetrahydropyranyl, tetrahydrothiopyranyl, and tetrahydrofuryl.

[0041] The term "optionally substituted C_{3-6} heterocyclyl" refers to a C_{3-6} heterocyclyl optionally substituted on the ring carbons with 1 to 4 substituents independently selected from the group consisting of optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} alkoxy, C_{1-9} amide, C_{1-7} amido, amino, C_{1-8} alkylamino, C_{1-5} oxycarbonyl, cyano, optionally substituted C_{3-8} cycloalkyl, C_{3-8} cycloalkoxy, halo, hydroxy, nitro, oxo, and optionally substituted phenyl; and optionally substituted on any ring nitrogen with a substituent independently selected from the group consisting of optionally substituted C_{1-4} alkyl, C_{3-8} cycloalkyl, optionally substituted C_{3-6} heterocyclyl, optionally substituted C_{1-10} heteroaryl, and optionally substituted phenyl.

[0042] More particularly "optionally substituted C_{3-6} heterocyclyl" refers to a C_{3-6} heterocyclyl optionally substituted on the ring carbons with 1 to 4 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, and hydroxy and optionally substituted on any ring nitrogen with a C_{1-4} alkyl.

[0043] The term "C_{1-10} heteroaryl" refers to a five to thirteen membered, monocyclic or polycyclic fully unsaturated, ring or ring system with one to ten carbon atoms and one or more, typically one to four, heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. For example, but not limiting, the term includes furyl, thienyl, pyrrolyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, azepinyl, diazepinyl, benzazepinyl, benzodiazepinyl, benzofuryl, benzothienyl, indolyl, isoindolyl, benzimidazolyl, benzisothiazolyl, benzisoxazolyl, benzoxadiazolyl, benzoxazolyl, benzopyrazinyl, benzopyrazolyl, imidazopyridyl, pyrazolopyridyl, pyrrolopyridyl, quinazolyl, thienopyridyl, imidazopyridyl, quinolyl, isoquinolyl benzothiazolyl, and the like. It is understood that a C_{1-10} heteroaryl can be attached as a substituent through a ring carbon or a ring nitrogen atom where such an attachment mode is available, for example for a pyrrolyl, indolyl, imidazolyl, pyrazolyl, azepinyl, triazolyl, pyrazinyl, etc.

[0044] More particularly "C_{1-10} heteroaryl" is selected from the group consisting of furyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, pyridyl, and pyrimidyl.

[0045] The term "optionally substituted C_{1-10} heteroaryl" refers to a C_{1-10} heteroaryl optionally substituted with 1 to 5 substituents on carbon independently selected from the group consisting of amino, C_{1-8} alkylamino, C_{1-9} amide, C_{1-7} amido, C_{1-5} carbamoyl, C_{1-6}

sulfonylamido, aminosulfonyl, C_{1-10} aminosulfonyl,C_{1-5} ureido, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-4} alkoxy, cyano, halo, hydroxyl, oxo, nitro, C_{1-5} carbonyloxy, C_{1-5} oxycarbonyl, and C_{1-8} sulfonyl and optionally substituted with a substituent on each nitrogen independently selected from the group consisting of optionally substituted C_{1-4} alkyl, C_{1-8} sulfonyl, optionally substituted C_{3-6} heterocyclyl, and optionally substituted phenyl.

[0046] More particularly "optionally substituted C_{1-10} heteroaryl" refers to a C_{1-10} heteroaryl optionally substituted with 1 to 3 substituents on carbon independently selected from the group consisting of amino, C_{1-8} alkylamino, C_{1-9} amide, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, halo, hydroxyl, oxo, trifluoromethyl, and trifluoromethoxy and optionally substituted on a ring nitrogen with a C_{1-4} alkyl.

[0047] Even more particularly "optionally substituted C_{1-10} heteroaryl" refers to a C_{1-10} heteroaryl selected from the group consisting of furyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, diazolyl, pyridyl, pyrimidyl, and triazolyl each optionally substituted with 1 to 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, cyano, halo, trifluoromethyl, and trifluoromethoxy and optionally substituted on a ring nitrogen with a methyl.

[0048] The term "oxo" refers to an oxygen atom doubly bonded to the carbon to which it is attached to form the carbonyl of a ketone or aldehyde. For example, a pryidone radical is contemplated as an oxo substituted C_{1-10} heteroaryl.

[0049] The term "optionally substituted phenyl" refers to a phenyl group optionally substituted with 1 to 5 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-9} amide, amino, C_{1-8} alkylamino, C_{1-5} oxycarbonyl, cyano, halo, hydroxyl, nitro, C_{1-8} sulfonyl, and trifluoromethyl.

[0050] More particularly "optionally substituted phenyl" refers to a phenyl group optionally substituted with 1 to 5 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-9} amino, C_{1-8} alkylamino, C_{1-5} oxycarbonyl, cyano, halo, hydroxyl, nitro, and trifluoromethyl.

[0051] The term "C_{1-6} sulfonylamido" refers to a $-NHS(O)_2-R_g$ group wherein R_g is selected from the group consisting of C_{1-6} alkyl and optionally substituted phenyl.

[0052] The term "aminosulfonyl" refers to a $-S(O)_2NH_2$.

[0053] The term "C_{1-10} aminosulfonyl" refers to a $-S(O)_2NR_hR_i$ group wherein R_h is selected from the group consisting of hydrogen and C_{1-4} alkyl and R_i is selected from the group consisting of C_{1-4} alkyl, and optionally substituted phenyl.

[0054] The term "C_{1-4} thioalkoxy" refers to a C_{1-4} alkyl attached through a sulfur atom.

[0055] The term "pharmaceutically acceptable salt" refers to salts of pharmaceutically acceptable organic acids and bases or inorganic acids and bases. Such salts are well known in the art and include those described in Journal of Pharmaceutical Science, 66, 2-19 (1977). An example is the hydrochloride salt.

[0056] The term "substituted," including when used in "optionally substituted" refers to one or more hydrogen radicals of a group are replaced with non-hydrogen radicals (substituent(s)). It is understood that the substituents may be either the same or different at every substituted position. Combinations of groups and substituents envisioned by this invention are those that are stable or chemically feasible.

[0057] The term "stable" refers to compounds that are not substantially altered when subjected to conditions to allow for their production. In a non-limiting example, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for about a week.

[0058] It is understood that, where the terms defined herein mention a number of carbon atoms, the mentioned number refers to the mentioned group and does not include any carbons that may be present in any optional substituent(s) thereon.

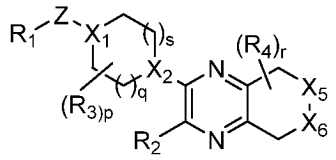
[0059] The skilled artisan will appreciate that certain of the compounds of the present invention exist as isomers. All stereoisomers of the compounds of the invention, including geometric isomers, enantiomers, and diastereomers, in any ratio, are contemplated to be within the scope of the present invention.

[0060] The skilled artisan will appreciate that certain of the compounds of the present invention exist as tautomers. All tautomeric forms the compounds of the invention are contemplated to be within the scope of the present invention.

[0061] Compounds of the invention also include all pharmaceutically acceptable isotopic variations, in which at least one atom is replaced by an atom having the same atomic number, but an atomic mass different from the predominant atomic mass. Isotopes suitable for inclusion in compounds of formula I include radioactive isotopes.

[0062] The terms "compounds of the invention" and "a compound of the invention" and " compounds of the present invention, and the like include the embodiment of formula I and the other more particular embodiments encompassed by formula I described herein and exemplified compounds described herein and a pharmaceutically acceptable salt of each of these embodiments.

[0063] The present invention provides a compound of formula II:



II

wherein

R_1 is selected from the group consisting of optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{3-6} heterocyclyl, optionally substituted C_{6-10} aryl, and optionally substituted C_{1-10} heteroaryl;

X_1 is N and X_2 is CH; or

X_1 is CH and X_2 is N; or

X_1 is N and X_2 is N;

when X_1 is N, Z is selected from the group consisting of C_{1-6} alkylene, C_{1-6} haloalkylene, -C(O)-, and -$S(O)_2$-;

when X_1 is CH, Z is selected from the group consisting of C_{1-6} alkylene, C_{1-6} haloalkylene, -O-, -C(O)-, -NH-, -S-, -S(O)-, and -$S(O)_2$-;

q is 0, 1, or 2;

s is 0, 1, or 2;

R_2 is $-OR_5$ or $-NR_6R_7$;

R_3, each time taken, is independently selected from the group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl, and trifluoromethyl;

p is 0, 1, or 2;

R_4, each time taken, is independently selected from the group consisting of C_{1-6} alkyl, hydroxy, and halo;

r is 0 or 1;

R_5 is selected from the group consisting of C_{1-6} alkyl and C_{3-8} cycloalkyl;

R_6 is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R_7 is selected from the group consisting of optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-10} heteroaryl, and optionally substituted C_{3-6} heterocyclyl;

X_5 is selected from the group consisting of CH and CR_4 and X_6 is selected from the group consisting of NH and N-CH_2-(optionally substituted phenyl); or

X_5 is selected from the group consisting of NH and N-CH_2-(optionally substituted phenyl) and X_6 is selected from the group consisting of CH and CR_4;
or a pharmaceutically acceptable salt thereof.

[0064] (Ia) One embodiment relates to compounds of formula I wherein X_1 is CH and X_2 is N.

[0065] (Ib) One embodiment relates to compounds of formula I wherein X_1 is N and X_2 is N.

[0066] (Ic) One embodiment relates to compounds of formula I and embodiment (Ia) and (Ib) wherein X_3 is selected from the group consisting of CH and CR_4 and X_4 is NR_8.

[0067] (Id) One embodiment relates to compounds of formula I and embodiment (Ia) and (Ib) wherein X_3 is NR_8 and X_4 is selected from the group consisting of CH and CR_4.

[0068] (Ie) One embodiment relates to compounds of formula I and embodiments (Ia), (Ib), (Ic), and (Id) wherein R_1 is optionally substituted C_{6-10} aryl.

[0069] (If) One embodiment relates to compounds of formula I and embodiments (Ia), (Ib), (Ic), and (Id) wherein Z is C_{1-6} alkylene.

[0070] (Ig) One embodiment relates to compounds formula I and embodiments (Ia), (Ib), (Ic), and (Id) wherein Z is C_{1-6} haloalkylene.

[0071] (Ih) One embodiment relates to compounds formula I and embodiments (Ia), (Ic), and (Id) wherein Z is -O-.

[0072] (Ii) One embodiment relates to compounds of formula I and embodiments (Ia), (Ib), (Ic), and (Id) wherein Z is -C(O)-.

[0073] (Ij) One embodiment relates to compounds of formula I and embodiments (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), and (Ii) wherein R_2 -NR_6R_7. In another embodiment within embodiment (Ij), R_6 is hydrogen and R_7 is C_{1-6} alkyl. In yet another embodiment within embodiment (Ij), R_6 is hydrogen and R_7 is C_{3-8} cycloalkyl. In yet another embodiment within embodiment (Ij), R_6 is hydrogen and R_7 is C_{3-6} heterocyclyl.

[0074] (Ik) One embodiment relates to compounds of formula I and embodiments (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), and (Ij) wherein s is 1.

[0075] (Il) One embodiment relates to compounds of formula I and embodiments (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), and (Ik) wherein q is 1.

[0076] (Im) One embodiment relates to compounds of formula I and embodiments (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), and (Il) wherein R_8 is selected from the group consisting -C(O)-R_{10}, -C(O)-N(R_{11})(R_{12}), and -C(O)-OR_{13}.

[0077] (In) One embodiment relates to compounds of formula I and embodiments (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik), and (Il) wherein R_8 is -C(O)-R_{10} and R_{10} is C_{1-6} alkyl.

[0078] (IIa) One embodiment relates to compounds of formula II wherein X_1 is CH and X_2 is N.

[0079] (IIb) One embodiment relates to compounds of formula II wherein X_1 is N and X_2 is N.

[0080] (IIc) One embodiment relates to compounds of formula II and embodiment (IIa) and (IIb) wherein X_3 is NR_8 and X_4 is selected from the group consisting of CH and CR_4.

[0081] (IId) One embodiment relates to compounds of formula II and embodiments (IIa), (IIb), and (IIc) wherein R_1 is optionally substituted C_{6-10} aryl.

[0082] (IIe) One embodiment relates to compounds of formula II and embodiments (IIa), (IIb), (IIc), and (IId) wherein Z is C_{1-6} alkylene.

[0083] (IIf) One embodiment relates to compounds formula II and embodiments (IIa), (IIb), (IIc), and (IId) wherein Z is C_{1-6} haloalkylene.

[0084] (IIg) One embodiment relates to compounds formula II and embodiments (IIa), (IIc), and (IId) wherein Z is -O-.

[0085] (IIh) One embodiment relates to compounds of formula II and embodiments (IIa), (IIb), (IIc), and (IId) wherein Z is -C(O)-.

[0086] (IIi) One embodiment relates to compounds of formula II and embodiments (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), and (IIh) wherein R_2 -NR_6R_7. In another embodiment within embodiment (IIj), R_6 is hydrogen and R_7 is C_{1-6} alkyl. In yet another embodiment within embodiment (IIj), R_6 is hydrogen and R_7 is C_{3-8} cycloalkyl. In yet another embodiment within embodiment (IIj), R_6 is hydrogen and R_7 is C_{3-6} heterocyclyl.

[0087] (IIj) One embodiment relates to compounds of formula II and embodiments (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), and (IIi) wherein s is 1.

[0088] (IIk) One embodiment relates to compounds of formula II and embodiments (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi), and (IIj) wherein q is 1.

[0089] (IIl) One embodiment relates to compounds of formula II and embodiments (IIa), (IIb), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), and (IIk) wherein X_5 is selected from the group consisting of CH and CR_4 and X_6 is NH.

[0090] (IIm) One embodiment relates to compounds of formula II and embodiments (IIa), (IIb), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), and (IIk) wherein X_5 is selected from the group consisting of NH X_6 is selected from the group consisting of CH and CR_4.

[0091] (IIn) One embodiment relates to compounds of formula II and embodiments (IIa), (IIb), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), and (IIk) wherein X_5 is selected from the group consisting of CH and CR_4 and X_6 is N-CH_2-(optionally substituted phenyl).

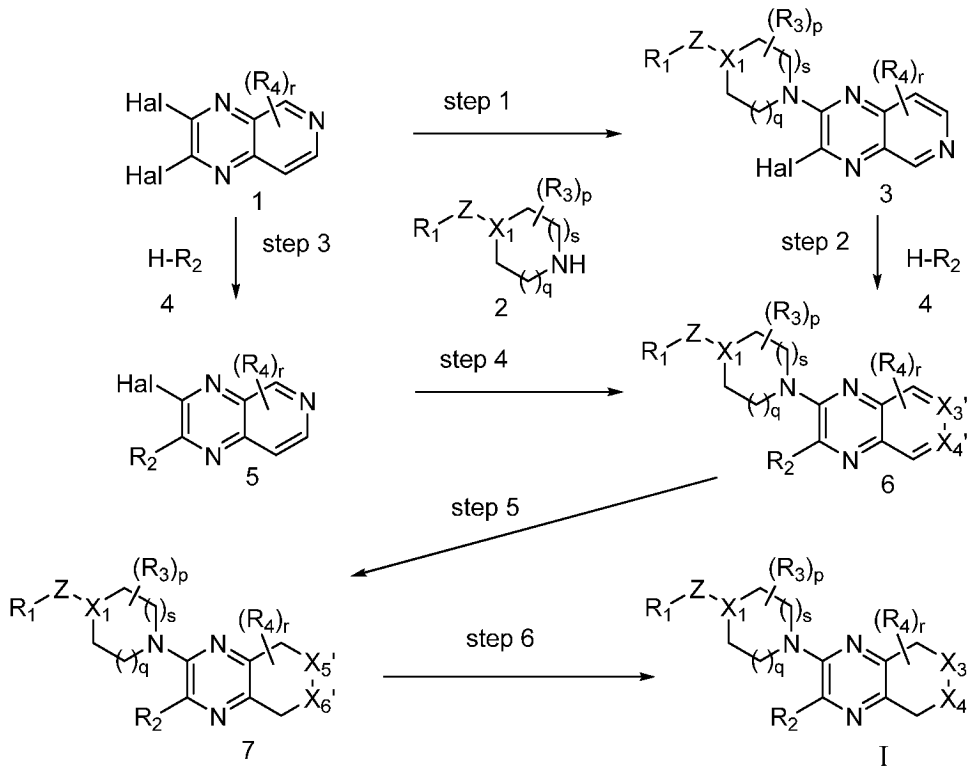
[0092] (IIo) One embodiment relates to compounds of formula II and embodiments (IIa), (IIb), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (IIk), and (III) wherein X_5 is selected from the group consisting of CH and CR_4 and X_6 is N-CH_2-(optionally substituted phenyl).

[0093] (ay) Another embodiment relates to a pharmaceutically acceptable salt of each of the above embodiments.

[0094] (az) Another embodiment relates to a pharmaceutically acceptable salt of each of the exemplified compounds.

[0095] The compounds of the invention can be prepared by a variety of procedures, some of which are described below. All substituents, unless otherwise indicated, are as previously defined. The products of each step can be recovered by conventional methods including extraction, evaporation, precipitation, chromatography, filtration, trituration, crystallization, and the like. The procedures may require protection of certain groups, for example hydroxy, amino, or carboxy groups to minimize unwanted reactions. The selection, use, and removal of protecting groups are well known and appreciated as standard practice, for example T.W. Greene and P. G. M. Wuts in Protective Groups in Organic Chemistry (John Wiley and Sons, 1991). In the schemes below starting materials are either commercially available or can be ready prepared by methods well known in the art.

[0096] Scheme A



[0097] Scheme A depicts the formation of compounds in which X_2 is N.

[0098] In Scheme A, step 1, an appropriate compound of formula 1 is contacted with an appropriate compound of formula 2 to give a compound of formula 3. An appropriate compound of formula 1 is one in which Hal is a halogen and R_4 and r are as desired in the final compound of formula I. An appropriate compound of formula 2 is one in which R_1, Z, R_3, p, s, and q are as desired in the final compound of formula I or give rise to R_1, Z, and R_3 as desired in the final compound of formula I. Compounds of formula 2 are either commercially available or they can be readily prepared by methods well known in the art. For example, compounds of formula 2 where Z is oxygen can be prepared by Mitsunobu reaction between a piperidinol and an aryl alcohol.

[0099] The reaction is carried out in a suitable organic solvent like dioxane, n-butanol, dimethyl sulfoxide and the like with or without base such as diisopropylethylamine and triethylamine. The reaction is generally carried out at a temperature of from 0 to 80 °C.

[00100] It is understood that a compound of formula 1 can also be treated with piperazine to give rise to compounds in which X_1 is N. The piperazine derivative can be further modified by reductive amination, alkylation, arylation, amidation, sulfonylation and the like to

provide a compound of formula 3. Also the piperazine can be protected and elaborated as mentioned above after deprotection in a later step if desired.

[00101] In Scheme A, step 2, a compound of formula 3 is contacted with an appropriate compound of formula 4 to give a compound of formula 6 in which $X_{3'}$ and $X_{4'}$ give rise to X_3 and X_4 as desired in the final product of formula I. An appropriate compound of formula 4 is HOR_5 or HNR_6R_7 in which R_5 or R_6 and R_7 are as desired in the final compound of formula I.

[00102] Where the compound of formula 4 is an amine, HNR_6R_7, the reaction is carried out in a suitable organic solvent like dioxane, ethanol, tetrahydrofuran, dimethyl sulfoxide, N,N-dimethylformamide and the like, with or without a base such as sodium hydroxide, diisopropylethylamine or triethylamine. The reaction is generally carried out at temperature between 20 to 150 °C.

[00103] Where the compound of formula 4 is an alcohol, HOR_5, the reaction is carried out in a suitable organic solvent like dioxane, tetrahydrofuran, dimethyl sulfoxide, N,N-dimethylformamide and the like, with a base such as sodium hydride, lithium hydride, potassium t-butoxide, and the like. The reaction is generally carried out at temperature between 0 to 150 °C.

[00104] Alternatively, as depicted in Scheme A, step 3, using the methodology described above, an appropriate compound of formula 1 can be contacted with an appropriate compound of formula 2 to give a compound of formula 5. As depicted in Scheme A, step 4, a compound of formula 5 can be contacted with a compound of formula 2 to give a compound of formula 6.

[00105] In Scheme A, step 5, a compound of formula 6 is partially reduced to a compound of formula 7 in which the variables are defined above and $X_{5'}$ is selected from the group consisting of CH, CR_4 and NH and $X_{6'}$ is selected from the group consisting of CH, CR_4 and NH provided that one of $X_{5'}$ or $X_{6'}$ is NH and the other is CH or CR_4.

[00106] Such partial reductions are well known in the art. The reaction is carried out in a suitable organic solvent like dioxane, ethanol, methanol, isopropanol, tetrahydrofuran, and the like. The reaction is generally carried out using hydrogen and a catalyst, such as platinum or palladium catalyst.

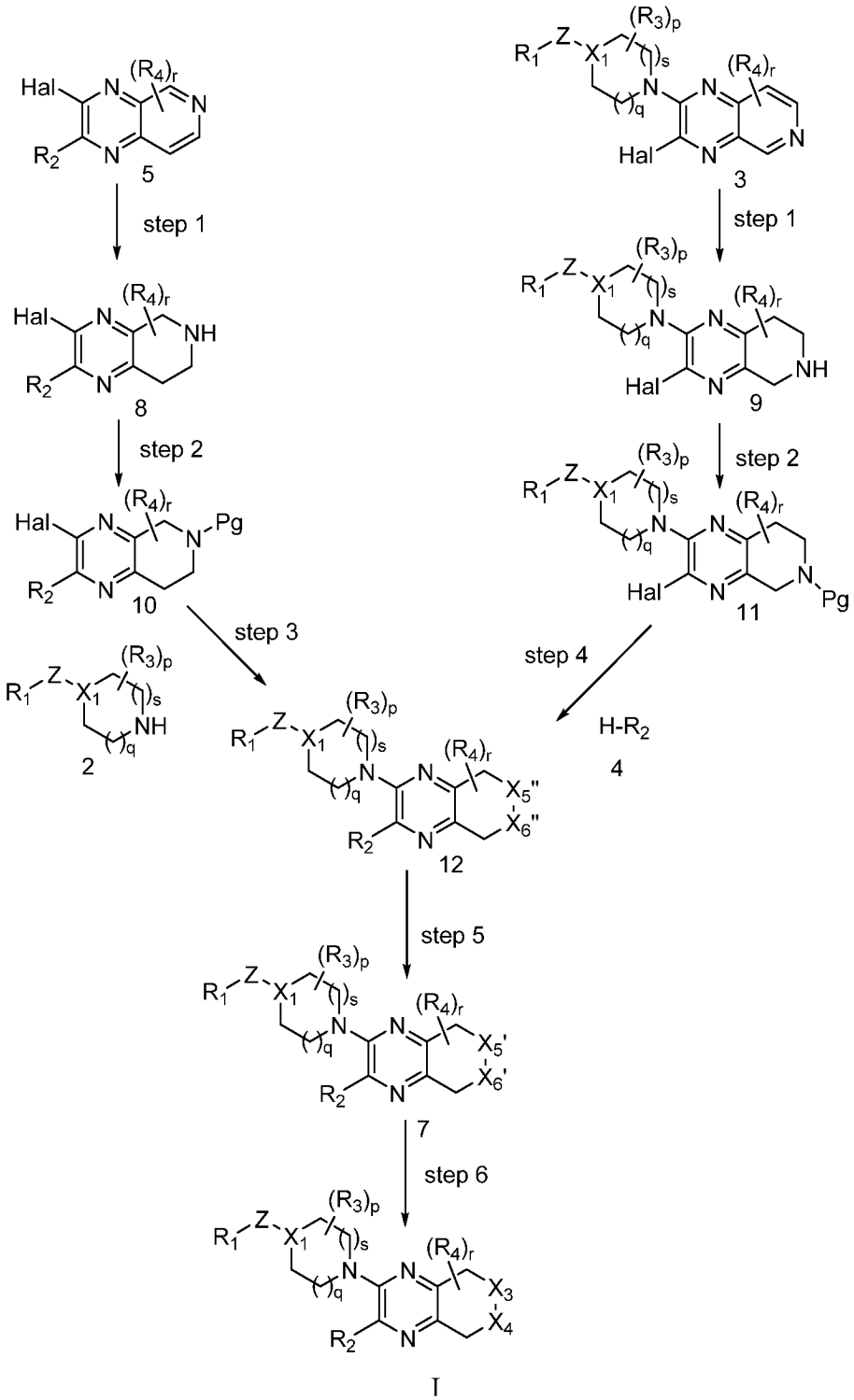
[00107] In Scheme A, step 6, a compound of formula 7 is alkylated, cycloalkylated, sulfonated, acylated, or converted to a urea or carbamate using appropriate reagents that give R_8 being C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, $-S(O)_2-R_9$, $-C(O)-R_{10}$, $-C(O)-N(R_{11})(R_{12})$, or $-C(O)-OR_{13}$ as desired in the final compound of formula I. Such transformation are

readily carried out by reductive amination, alkylation, sulfonylation, amide forming reactions, urea forming reactions, and carbamylation conditions that are well known in the art.

[00108] It will be recognized by one of ordinary skill in the art that the steps in Scheme A may be varied to provide compounds of formula I. In particular, the order of the steps required to produce the compounds of formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties. Other variations are possible and are readily understood by the skilled person.

[00109] An example of a variation of Scheme A is depicted in Scheme B below.

[00110] Scheme B



[00111] Scheme B depicts the formation of compounds in which X_2 is N.

[00112] In Scheme B, step 1, an appropriate compound of formula 5 or 3, as provided above, is partially reduced to a compound of formula 8 or 9, respectively. Such partial reductions

are described above in Scheme A, step 5. In one embodiment the present invention provides compounds of formula 8 in which Hal is halogen and R_2, R_4, and r are as described for formula I. In another embodiment the present invention provides compounds of formula 9 in which Hal is halogen and R_1, Z, R_3, R_4, p, r, q, and s are s described for formula I.

[00113] In Scheme B, step 2, an appropriate compound of formula 8 or 9 is protected to give compounds of formulae 10 or 11, respectively, in which Pg is an amine protecting group. The selection, use, and removal of protecting groups are well known and appreciated as standard practice, for example T.W. Greene and P. G. M. Wuts in Protective Groups in Organic Chemistry (John Wiley and Sons, 1991). In one embodiment the present invention provides compounds of formula 10 in which Pg is -CH_2-(optionally substituted phenyl) and R_2, R_4, and r are as described for formula I. In another embodiment the present invention provides compounds of formula 11 in which Pg is -CH_2-(optionally substituted phenyl) and R_1, Z, R_3, R_4, p, r, q, and s are s described for formula I. In another embodiment of the embodiments of formulae 10 and 11 is one in which Pg is benzyl.

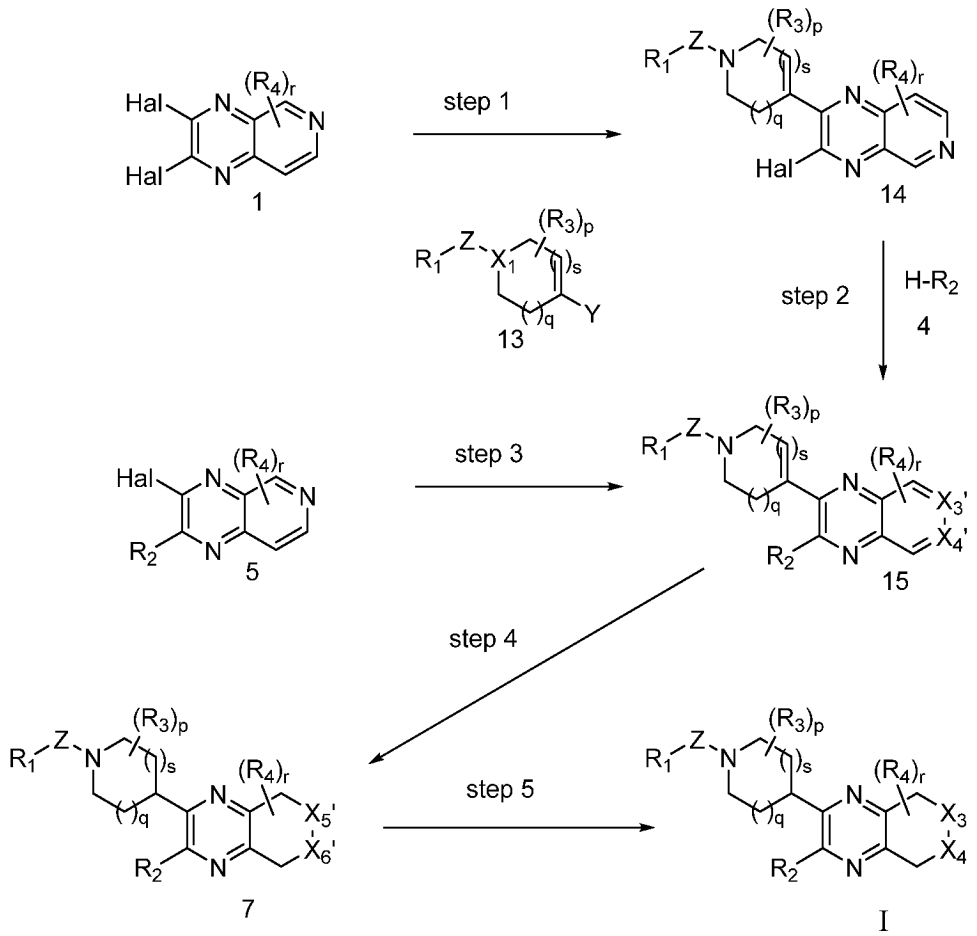
[00114] In Scheme B, step 3, a compound of formula 10 is contacted with an appropriate compound of formula 2, as described above, to give a compound of formula 12 in which $X_{5''}$ is a protected amine and $X_{6''}$ is CH or CR_4. The reaction is carried out as described in Scheme A, step 1.

[00115] In Scheme B, step 4, a compound of formula 11 is contacted with an appropriate compound of formula 4 to give a compound of formula 12 in which $X_{5''}$ is CH or CR_4 and $X_{6''}$ is a protected amine. An appropriate compound of formula 4 as described above. The reaction is carried out as described in Scheme A, step 2.

[00116] In Scheme B, step 5, a compound of formula 12 is deprotected to give a compound of formula 7 as described above.

[00117] In Scheme B, step 6, a compound of formula 7 is alkylated, cycloalkylated, sulfonated, acylated, or converted to a urea or carbamate using appropriate reagents that give R_8 being $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ haloalkyl, $C_{3\text{-}8}$ cycloalkyl, -$S(O)_2$-R_9, -C(O)-R_{10}, -C(O)-N(R_{11})(R_{12}), or -C(O)-OR_{13} as desired in the final compound of formula I as described in Scheme A, step 6, above.

[00118] Scheme C



[00119] Scheme C depicts the formation of compounds in which X_2 is CH.

[00120] In Scheme C, step 1, an appropriate compound of formula 1, as described above, is contacted with an appropriate compound of formula 13 to give a compound of formula 9. An appropriate compound of formula 13 is one in which R_1, Z, R_3, p, s, and q are as desired in the final compound of formula I or give rise to R_1, Z, and R_3 as desired in the final compound of formula I and Y a boronic acid or boronic ester. It is also understood that the group depicted as R_1-Z- can be replaced by an appropriate protecting group, such a methyl, benzyl, t-BOC, or Cbz, subsequent removal of the protecting group and installation of R_1-Z- as desired in the final product of formula I.

[00121] Such reactions are generally known as a Suzuki reaction and are well known in the art. While a Suzuki reaction is depicted in Scheme C it is understood that other carbon-carbon bond forming coupling reactions can be used with compounds of formula 13 having Y other than boronic acid or esters to produce compounds of formula I.

[00122] In Scheme C, step 2, a compound of formula 14 is contacted with an appropriate compound of formula 4 to give a compound of formula 15. An appropriate compound of formula 4 and general reaction conditions are described above in Scheme A, step 2.

[00123] Alternately, Scheme C, step 3, depicts Suzuki reaction with an appropriate compound of formula 13 and an appropriate compound of formula 5 as described above to give a compound of formula 15.

[00124] In Scheme C, step 4, a compound of formula 15 is reduced to a compound of formula 11 in which the variables are defined above and $X_{5'}$ is selected from the group consisting of CH, CR_4 and NH and $X_{6'}$ is selected from the group consisting of CH, CR_4 and NH provided that one of $X_{5'}$ or $X_{6'}$ is NH and the other is CH or CR_4. The conditions are similar to those described above for Scheme A, step 7.

[00125] In Scheme C, step 5, a compound of formula 7 is alkylated, cycloalkylated, sulfonated, acylated, or converted to a urea or carbamate using appropriate reagents that give R_8 being C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl, $-S(O)_2-R_9$, $-C(O)-R_{10}$, $-C(O)-N(R_{11})(R_{12})$, or $-C(O)-OR_{13}$ as desired in the final compound of formula I. Such transformations are readily carried out by reductive amination, alkylation, sulfonylation, amide forming reactions, amidation, and carbamylation conditions that are well known in the art.

[00126] It will be recognized by one of ordinary skill in the art that the steps in Scheme C may be varied to provide compounds of formula I. In particular, the order of the steps required to produce the compounds of formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties. For example, a compound of formula 9 or 5 can undergo step 4 and the NH of $X_{3'}$ or $X_{4'}$ can be protected, followed being contacted with a compound of formula 13 or 4 to give a compound of formula 11 which as depicted above can be elaborated to a compound of formula I. Alternately, the double bond of the ring bearing R_1-Z- may be reduced separately from the partial reduction of the ring ultimately bearing X_3 and X_4. Other variations are possible and are readily understood by the skilled person.

[00127] It is also understood that some compounds of formula I may be elaborated to other compounds of formula I, in an additional steps not shown. Compounds of formula I may be elaborated in a variety of ways. Such reactions include hydrolysis, oxidation, reduction, alkylation, amidations, and the like. Also, in an optional step, not shown in the schemes above, the compounds of formula I can be converted to pharmaceutically acceptable salts by methods well known and appreciated in the art.

[00128] The following examples are intended to be illustrative and non-limiting, and represent specific embodiments of the present invention.

[00129] Proton nuclear magnetic resonance (NMR) spectra were obtained for many of the compounds in the following examples. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks, including s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Other abbreviations have their usual meaning unless otherwise indicated. The mass spectra, unless otherwise indicated, were recorded using either electrospray ionization (ESI) or atmospheric pressure chemical ionization.

[00130] The examples below were carried out in appropriate vessels and were typically stirred. Where indicated, products of certain preparations and examples are purified by HPLC. Where indicated products of the preparations and examples were purified by HPLC.

[00131] HPLC Method A: Pump: Shimadzu LC-8A; UV/Vis: SPD-20A; Software: LCSolution. A Phenomenex Gemini® C18, 5 µm, ID 30 x 100 mm column was used and eluted with gradients of ACN (containing 0.035% TFA) and water (containing 0.005% TFA). A 10% to 100% ACN gradient was used unless otherwise indicated.

[00132] HPLC Method B: Pump: Waters 2525 or 2545; MS: ZQ; Software: MassLynx. A Xbridge™ C18, 5 µm, ID 30 x 75 mm column was used and eluted with gradients of ACN (containing 0.035% TFA) and water (containing 0.005% TFA).

[00133] After isolation by chromatography, the solvent is removed and the product is obtained by evaporating product containing fractions (e.g., GeneVac^{TM}), rotary evaporator, evacuated flask, lyophilization, etc.

[00134] The abbreviations used throughout have their conventional meanings unless indicated otherwise. For example, the following abbreviations are used: ACN (acetonitrile); aq (aqueous); Boc or t-BOC (*tert*-butoxycarbonyl); Cbz (carbobenzyloxy); DCM (dichloromethane); DMSO (dimethyl sulfoxide); TFA (trifluoroacetic acid); HOAc (acetic acid), MeOH (methanol), PE (petroleum ether), EA or EtOAc (ethyl acetate) and the like.

[00135] Preparation 1 (5-chloro-2-fluorophenyl)(piperidin-4-yl)methanone

[00136] A solution of 2-bromo-4-chloro-1-fluorobenzene (175 µL, 1.377 mmol) in THF (4.59 mL) at –78 °C was treated with *n*-BuLi (2.6 M, 741 µL, 1.928 mmol) and the reaction mixture was stirred for 30 min. To this was added *tert*-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (250 mg, 0.918 mmol) in one portion. The cooling bath was removed and the resulting reaction mixture was allowed to warm to rt

and stirred for 1.5 h. Purification by automated flash silica gel chromatography using 10% EtOAc in hexanes afforded *tert*-butyl 4-(5-chloro-2-fluorobenzoyl)piperidine-1-carboxylate (287.9 mg, 92%) as a yellow oil. ESI-MS m/z $[M+Na]^+$ 364.20.

[00137] A solution of *tert*-butyl 4-(5-chloro-2-fluorobenzoyl)piperidine-1-carboxylate (287.9 mg, 0.843 mmol) in dioxane (2.41 mL) was treated with HCl (2.11 mL, 8.43 mmol) at rt and the resulting reaction mixture was stirred overnight. The reaction mixture was diluted with hexanes and filtered by suction to afford (5-chloro-2-fluorophenyl)(piperidin-4-yl)methanone as its HCl salt (146 mg, 62.3%) as a yellow solid. ESI-MS m/z $[M+H]^+$ 242.20.

[00138] Preparation 2 4-(2,4-difluorophenoxy)piperidine

[00139] To a solution of 2,4-difluorophenol (10 g, 77 mmol), PPh_3 (30.2 g, 115 mmol) and *tert*-butyl 4-hydroxypiperidine-1-carboxylate (30.9 g, 154 mmol) in THF (400 mL) was added DEAD (18.3 mL, 115 mmol) at 0 °C dropwise. After the addition was completed, the resulting mixture was allowed to stir at 40 °C for 16 h. The mixture was poured into water and extracted with EtOAc (3 x 400 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give the crude product. Purification by flash silica gel chromatography, eluting with 80:1 PE:EtOAc, gave *tert*-butyl 4-(2,4-difluorophenoxy)piperidine-1-carboxylate as an oil (20 g, 83%).

[00140] A solution of *tert*-butyl 4-(2,4-difluorophenoxy)piperidine-1-carboxylate (20 g, 63.8 mmol) in 4:1 HCl/EtOAc (250 mL) was stirred at 25 °C for 1 h. The mixture was concentrated to give the title compound , as its HCl salt, as a white solid (15.4 g, 97 %). ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 1.84 (m, 2H), 2.08 (m, 2H), 3.05 (m, 2H), 3.20 (m, 2H), 4.57 (m, 1H), 7.04 (m, 1H), 7.31 (m, 2H), 8.95 (br d, 2H).

[00141] Preparation 3 3-fluoro-4-(piperidin-4-yloxy)benzonitrile

[00142] A solution of 3,4-difluorobenzonitrile (28 g, 201 mmol) and *tert*-butyl 4-hydroxypiperidine-1-carboxylate (40.5 g, 201 mmol) in THF (500 mL) was treated with sodium hydride (4 g, 100 mmoL) and stirred at 25 °C for 16 h. The reaction mixture was washed with water, extracted with EtOAc, and the crude product purified by flash silica gel chromatography gave *tert*-butyl 4-(4-cyano-2-fluorophenoxy)piperidine-1-carboxylate (25 g, 39%).

[00143] A solution of *tert*-butyl 4-(4-cyano-2-fluorophenoxy)piperidine-1-carboxylate (42 g, 131 mmol) dissolved in 4:1 HCl/EtOAc (100 mL) was stirred for 5 h. The mixture was concentrated to give the title compound as its HCl salt (12 g, 36%). ^{1}H NMR (400 MHz,

DMSO-*d*6) δ ppm 1.89 (m, 2H), 2.14 (m, 2H); 3.08 (m, 2H), 3.21 (m, 2H), 4.86 (m, 1H), 7.48 (t, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.89 (m, 1H); ESI-MS m/z [M+H]+ 220.7.

[00144] Preparation 4 6 4-((2,4-difluorophenyl)fluoromethyl)piperidine

[00145] To a 0 °C solution of *tert*-butyl 4-(2,4-difluorobenzoyl)piperidine-1-carboxylate (1.28 g, 3.93 mmol) in MeOH (15.7 mL) was added $NaBH_4$ (0.372 g, 9.84 mmol). The ice bath was removed and the reaction mixture stirred for 2 h at room temperature then was quenched with saturated aqueous NH_4Cl. The organic layer was extracted with EtOAc, washed with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure gave *tert*-butyl 4-((2,4-difluorophenyl)(hydroxy)methyl)piperidine-1-carboxylate as a white hygroscopic solid.

[00146] To a –78 °C solution of *tert*-butyl 4-((2,4-difluorophenyl)(hydroxy)methyl)piperidine-1-carboxylate (200 mg, 0.611 mmol) in DCM (3.055 mL) was added DAST (242 µL, 1.833 mmol). The mixture was stirred at –78 °C for 30 min, then quenched with MeOH. Flash silica gel chromatography using a gradient of 0% to 100% EtOAc in hexanes gave *tert*-butyl 4-((2,4-difluorophenyl)fluoromethyl)piperidine-1-carboxylate as a colorless oil.

[00147] To a solution of racemic *tert*-butyl 4-((2,4-difluorophenyl)fluoromethyl)piperidine-1-carboxylate (148 mg, 0.449 mmol) in dioxane (1.50 mL) was added HCl (4 M in dioxane, 337 µL, 1.348 mmol). The mixture was heated at 45 °C for 16 h then concentrated *in vacuo* to give the title compound as its HCl salt (109 mg, 91%) as a white solid.

[00148] Preparation 5 (*R*)-4-((2,4-difluorophenyl)fluoromethyl)piperidine

tert-Butyl 4-((2,4-difluorophenyl)fluoromethyl)piperidine-1-carboxylate as a colorless oil.

tert-Butyl 4-((2,4-difluorophenyl)fluoromethyl)piperidine-1-carboxylate was subjected to chiral SFC separation to give (*R*)-*tert*-butyl 4-((2,4-difluorophenyl)fluoromethyl)piperidine-1-carboxylate.

(*R*)-*tert*-butyl 4-((2,4-difluorophenyl)fluoromethyl)piperidine-1-carboxylate (2.8 g, 8.50 mmol) was dissolved in EtOAc (20 mL) and HCl (4 M in EtOAc, 21 mL) was added. The reaction mixture was stirred at 23 °C for 2 h. Evaporation of the solvent gave the title compound as its HCl salt (2.1 g, 93%). ESI-MS m/z $[M+H]^+$ 229.9.

Preparation 6 (S)- 4-((2,4-difluorophenyl)fluoromethyl)piperidine

tert-Butyl 4-((2,4-difluorophenyl)fluoromethyl)piperidine-1-carboxylate as was subjected to chiral SFC separation to give (R)-tert-butyl 4-((2,4-difluorophenyl)fluoromethyl)piperidine-1-carboxylate.

The HCl salt of the title compound was prepared in similar fashion to Preparation 5a, using (*S*)-*tert*-butyl 4-((2,4-difluorophenyl)fluoromethyl)piperidine-1-carboxylate. ESI-MS m/z $[M+H]^+$ 229.9.

[00149] Preparation 7 4-((2-fluorophenyl)sulfonyl)piperidine

[00150] A mixture of 2-fluorobenzenethiol (0.764 mL, 7.15 mmol), *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (1.816 g, 6.5 mmol), and K_2CO_3 (1.348 g, 9.75 mmol) in ACN (16.25 mL) was heated at 80 °C overnight. The reaction mixture was poured into water and extracted twice with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure gave *tert*-butyl 4-((2-fluorophenyl)thio)piperidine-1-carboxylate as a yellow oil (1.98 g, 98%), which was carried forward without purification.

[00151] A solution of *tert*-butyl 4-((2-fluorophenyl)thio)piperidine-1-carboxylate (1.98 g, 6.36 mmol) in THF (54.5 mL) and MeOH (18.2 mL) at 0 °C was treated with a cold solution of Oxone® (9.77 g, 15.9 mmol) in water (54.5 mL). The reaction mixture was stirred for 5 h, gradually warming to room temperature. The reaction mixture was poured into water and extracted twice with EtOAc. The combined organics were washed with water and then saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using a gradient of 10% to 50% EtOAc with 0.1% triethylamine in heptanes gave *tert*-butyl 4-((2-fluorophenyl)sulfonyl)piperidine-1-carboxylate as a pale yellow oil (1.31 g, 60%).

[00152] A solution of *tert*-butyl 4-((2-fluorophenyl)sulfonyl)piperidine-1-carboxylate (1.31 g, 3.82 mmol) in dioxane (12.7 mL) at room temperature was treated with 4M HCl in dioxane (9.55 ml, 38.2 mmol). The reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The resulting white solid was triturated with hexanes, filtered, collected, and lyophilized overnight to give the title compound , as its HCl salt, as a white solid (815.1 mg, 76%). ESI-MS m/z $[M+H]^+$ 243.95.

[00153] Preparation 8 4-((2-fluoro-4-methoxyphenyl)sulfonyl)piperidine

A mixture of 2,4-difluorobenzenethiol (0.810 mL, 7.15 mmol), *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (1.816 g, 6.5 mmol), and K_2CO_3 (1.348 g, 9.75 mmol) in ACN (16.25 mL) was heated at 80 °C overnight. The reaction mixture was poured into water and extracted twice with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford tert-butyl 4-((2,4-

difluorophenyl)thio)piperidine-1-carboxylate (2.141 g) as a yellow oil, which was carried forward without purification.

[00154] A solution of *tert*-butyl 4-((2,4-difluorophenyl)thio)piperidine-1-carboxylate (2.141 g, 6.50 mmol) in THF/MeOH (3:1, 74 mL) at 0 °C was treated with a cold solution of Oxone® (9.99 g, 16.25 mmol) in water (56 mL). The reaction mixture was allowed to stir overnight, gradually warming to room temperature. The reaction mixture was poured into water and extracted twice with EtOAc. The combined organics were washed with water and then saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using a gradient of 10% to 40% EtOAc with 0.1% triethylamine in heptanes gave *tert*-butyl 4-((2,4-difluorophenyl)sulfonyl)piperidine-1-carboxylate (1.32 g, 56%) as a white solid. ESI-MS m/z $[M+Na]^+$ 383.80.

[00155] To a suspension of *tert*-butyl 4-((2,4-difluorophenyl)sulfonyl)piperidine-1-carboxylate (50 mg, 0.138 mmol) in MeOH (461 µL) was added sodium methoxide (25.6 µL, 0.138 mmol, 5.4 M in MeOH) dropwise. The reaction mixture was allowed to stir at 45 °C for 20 min then concentrated *in vacuo*. Boc deprotection was carried out by addition of HCl (138 µL, 0.553 mmol, 4 M in dioxane) to the crude reaction mixture in 300 µL dioxane. Stirring at 50 °C for 24 h followed by concentration *in vacuo* yielded the title compound as its HCl salt (57 mg) as a white solid (10:1 regioisomeric mixture). ESI-MS m/z $[M+H]^+$ 274.00.

[00156] Preparation 9 4-((3-fluorophenyl)sulfonyl)piperidine

[00157] A mixture of *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (1.0 g, 3.58 mmol), K_2CO_3 (0.742 g, 5.37 mmol), and 3-fluorobenzenethiol (0.363 mL, 4.30 mmol) in ACN (7.5 mL) was stirred at 23 °C for 5 min. The reaction mixture was stirred at 80 °C for 17 h, cooled to 23 °C and partitioned between EtOAc and water. The layers were separated, the organic phase was washed with brine, dried over Na_2SO_4, filtered, rinsed with EtOAc, and dried *in vacuo* gave *tert*-butyl 4-((3-fluorophenyl)thio)piperidine-1-carboxylate (1.115 g, 100 %) as a yellow oil. ESI-MS m/z $[M+H]^+$ 255.9.

[00158] A mixture of basic alumina (3.0 g, 29.4 mmol) in water (0.6 mL) was stirred at 23 °C for 5 min. Next, ACN (12 mL) was added followed by a solution of *tert*-butyl 4-((3-fluorophenyl)thio)piperidine-1-carboxylate (1.115 g, 3.58 mmol) in $CHCl_3$ (8 mL). Next, Oxone® (6.60 g, 10.74 mmol) was added and the reaction mixture was stirred at 60 °C for 19 h. The reaction mixture was cooled to 23 °C, filtered, rinsed with $CHCl_3$, and the filtrate

was washed with water (10 mL). The organic layer was dried over Na_2SO_4, filtered, rinsed with $CHCl_3$, and dried *in vacuo*. The crude residue was dissolved in toluene (5 mL) and purified via medium pressure chromatography using a gradient of 10% to 100% EtOAc with 0.1% triethylamine in heptane on a 80 g silica gel column (Single Step™) gave *tert*-butyl 4-((3-fluorophenyl)sulfonyl)piperidine-1-carboxylate (0.769 g, 62.5%) as a white solid. ESI-MS m/z $[M+Na]^+$ 365.9.

[00159] To a solution of *tert*-butyl 4-((3-fluorophenyl)sulfonyl)piperidine-1-carboxylate (756 mg, 2.201 mmol) in dioxane (5.0 mL) was added HCl (4 M in dioxane, 5.50 mL, 22.01 mmol) at 23 °C. The reaction was stirred at 23 °C for 21 h to furnish a white suspension. The resulting solid was filtered, rinsed with dioxane and dried *in vacuo* to give the title compound as its HCl salt (582.6 mg, 95%) as a white solid. ESI-MS m/z $[M+H]^+$ 243.9.

[00160] Preparation 10 4-((3-methoxyphenyl)sulfonyl)piperidine

[00161] The title compound as its HCl salt was prepared in a similar manner to Preparation 11, with the exception that additional chloroform was used in place of ACN in the second step. ESI-MS m/z $[M+H]^+$ 255.9.

[00162] Preparation 12 4-((4-fluorophenyl)sulfonyl)piperidine

[00163] A mixture of *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (1.42 g, 5.08 mmol), 4-fluorobenzenethiol (0.663 ml, 6.10 mmol) and K_2CO_3 (1.054 g, 7.62 mmol) in ACN (12.71 mL) was stirred at 85 °C overnight. The reaction mixture was filtered by suction and the solvent removed gave *tert*-butyl 4-((4-fluorophenyl)thio)piperidine-1-carboxylate (1.5 g, 95%) as a white solid.

[00164] A solution of *tert*-butyl 4-((4-fluorophenyl)thio)piperidine-1-carboxylate (1.5 g) in water (16.06 mL) and MeOH (16.06 mL) was treated with Oxone® (5.92 g, 9.63 mmol) at room temperature and the resulting reaction mixture was stirred for 6 h. The solution was filtered by suction and the solvent removed gave *tert*-butyl 4-((4-fluorophenyl)sulfonyl)piperidine-1-carboxylate (1.6 g, 4.66 mmol, 97 % yield) as a white solid.

[00165] A solution of *tert*-butyl 4-((4-fluorophenyl)sulfonyl)piperidine-1-carboxylate (32.7 mg, 0.095 mmol) in dioxane (238 µL) at room temperature was treated with HCl (4 M in dioxane, 190 µL, 0.762 mmol) and the resulting reaction mixture was stirred for 4 h. The solvent was removed to give the title compound as its HCl salt (25 mg, 94%) as a white solid. ESI-MS m/z $[M+H]^+$ 243.95.

[00166] Preparation 13 1-(2,4-difluorobenzyl)piperazine

[00167] A mixture of piperazine (26.5 g, 308 mmol) in THF (350 mL) was heated to 70 °C and 1-(chloromethyl)-2,4-difluorobenzene (5 g, 30.8 mmol) was added. The suspension was heated at 70 °C overnight. The solid (piperazine) was filtered off, and the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and water. The organic layer was dried and concentrated to give the title compound (6 g, 92%). ESI-MS m/z $[M+H]^+$ 213.04.

[00168] Preparation 14 4-(2-fluoro-4-methoxyphenoxy)piperidine

[00169] A solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (2.496 g, 12.03 mmol) in THF (33.4 mL) at room temperature was treated with 2-fluoro-4-methoxyphenol (1.181 mL, 10.03 mmol) and triphenylphosphine (3.16 g, 12.03 mmol). The reaction mixture was cooled to 0 °C and DEAD (40 wt % in toluene, 5.95 mL, 15.04 mmol) was added dropwise via syringe. The resulting reaction mixture was stirred at 65 °C for 5 h, then at room temperature overnight. Flash silica gel chromatography using a gradient of 10% to 100% EtOAc in hexanes gave *tert*-butyl 4-(2-fluoro-4-methoxyphenoxy)piperidine-1-carboxylate (2.78 g, 85%) as a light yellow oil. ESI-MS m/z $[M+Na]^+$ 348.2.

[00170] A solution of *tert*-butyl 4-(2-fluoro-4-methoxyphenoxy)piperidine-1-carboxylate (2.78 g, 8.54 mmol) in dioxane (21.36 mL) was treated with HCl (4 M in dioxane, 21.36 mL, 85 mmol) at room temperature and the resulting reaction mixture stirred overnight. Flash silica gel chromatography using a gradient of 5% to 30% MeOH in DCM gave the title compound as its HCl salt (1.7 g, 76%) as a white solid. ESI-MS m/z $[M+H]^+$ 226.20.

[00171] Preparation 15 3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazine

[00172] A solution of 2,3-dichloropyrido[3,4-*b*]pyrazine (492 mg, 2.460 mmol) in DCM (5 mL) at 0 °C was treated with 4-(2,4-difluorophenoxy)piperidine hydrochloride (676 mg, 2.71 mmol) and DIPEA (1.29 mL, 7.38 mmol). The reaction mixture was allowed to stir overnight, gradually warming to room temperature. The reaction mixture was quenched with the addition of saturated aqueous NH_4Cl and was extracted with DCM. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using a gradient of 20% to 60% EtOAc in heptanes to give the title compound as a pale yellow solid (736.2 mg, 79%). ESI-MS m/z $[M+H]^+$ 377.4.

[00173] Preparation 16 4-((1-(3-chloropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile

[00174] To a solution of 2,3-dichloropyrido[3,4-*b*]pyrazine (1.00 g, 5.00 mmol) in DCM (10.0 mL) at 0 °C was added DIPEA (2.62 mL, 15.00 mmol) and 3-fluoro-4-(piperidin-4-yloxy)benzonitrile hydrochloride (1.283 g, 5.00 mmol). The reaction mixture was stirred for 30 min, warming gradually to room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl. The organic layer containing yellow solid was collected and concentrated under reduced pressure. The solid was filtered, washing with water, and was lyophilized overnight to give the title compound as a yellow solid (1.325 g, 69%). ESI-MS m/z $[M+H]^+$ 384.3.

[00175] Preparation 17 (R)-3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)pyrido[3,4-b]pyrazine

[00176] The title compound was prepared in a manner similar to Preparation 18 using (*R*)-4-((2,4-difluorophenyl)fluoromethyl)piperidine hydrochloride in place of 4-(2,4-difluorophenoxy)piperidine hydrochloride. ESI-MS m/z $[M+H]^+$ 393.4.

[00177] Preparation 19 (*S*)-3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)pyrido[3,4-*b*]pyrazine

[00178] The title compound was prepared in a manner similar to Preparation 20 using (*S*)-4-((2,4-difluorophenyl)fluoromethyl)piperidine hydrochloride in place of 4-(2,4-difluorophenoxy)piperidine hydrochloride. ESI-MS m/z $[M+H]^+$ 393.4.

[00179] Preparation 21 3-chloro-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)pyrido[3,4-*b*]pyrazine

[00180] To a mixture of 2,3-dichloropyrido[3,4-*b*]pyrazine (8 g, 40.0 mmol)and 1-(2,4-difluorobenzyl)piperazine (8.49 g, 40.0 mmol) in DCM (100 mL) was added triethylamine (16.72 mL, 120 mmol) at room temperature. Then the mixture was stirred at room temperature for 0.5 h. The reaction mixture was diluted with 30 mL of DCM, washed with brine twice, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography, eluting with a gradient of 50:1 to 5:1 PE:EtOAc to give the title compound (12 g, 80%). ESI-MS m/z $[M+H]^+$ 376.0.

[00181] Preparation 22 3-chloro-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazine

[00182] A mixture of 4-(2-fluoro-4-methoxyphenoxy)piperidine hydrochloride (144 mg, 0.550 mmol), 2,3-dichloropyrido[3,4-*b*]pyrazine (100 mg, 0.500 mmol) and DIPEA (260 µL, 1.500 mmol) in DCM (1.0 mL) was stirred at room temperature for 30 min. The mixture was then partitioned between EtOAc and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was dissolved in

EtOAc and filtered through a silica pad. The filtrate was concentrated to afford the crude title compound (200.7 mg, 100%) as a yellow oil, which was used without further purification. ESI-MS m/z $[M+H]^+$ 389.2.

[00183] Preparation 23 *tert*-butyl 4-(3-chloropyrido[3,4-*b*]pyrazin-2-yl)piperazine-1-carboxylate

[00184] Combine 2,3-dichloropyrido[3,4-*b*]pyrazine (2.0 g, 10.00 mmol), *tert*-butyl piperazine-1-carboxylate (1.955 g, 10.50 mmol) and DCM (25 mL) to furnish a yellow-orange suspension. Next, DIPEA (5.22 mL, 30.0 mmol) was added to the flask over 1 min at 0 °C. The mixture was stirred at 0 °C for 2 h under nitrogen, warmed slowly to 23 °C, and stirred for 17 h. The reaction mixture was partitioned between saturated aqueous NH_4Cl (20 mL) and EtOAc (80 mL) to furnish two layers. The layers were separated, and the aqueous phase was washed with EtOAc (80 mL). The organic extracts were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered, rinsed with EtOAc, and dried *in vacuo* to give the title compound (3.35 g, 96%) as an orange semisolid. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.44 (s, 9H), 3.51-3.58 (m, 4H), 3.62-3.68 (m, 4H), 7.67 (d, J = 1.0 Hz, 1H), 8.66 (d, J = 5.9 Hz, 1H), 9.15 (d, J = 1.0 Hz, 1H); ESI-MS m/z $[M+H]^+$ 350.5.

[00185] Preparation 24 *tert*-butyl 4-(3-(isopropylamino)pyrido[3,4-*b*]pyrazin-2-yl)piperazine-1-carboxylate

[00186] To a flask charged with tert-butyl 4-(3-chloropyrido[3,4-*b*]pyrazin-2-yl)piperazine-1-carboxylate (3.35 g, 9.58 mmol) and potassium fluoride (0.723 g, 12.45 mmol) in DMSO (25 mL) was added DIPEA (3.34 mL, 19.15 mmol) and propan-2-amine (2.468 mL, 28.7 mmol) at 23 °C. The reaction was stirred at 23 °C for 22 hr and diluted with water (100 mL) to furnish an orange, oily sludge. The mixture was cooled to 0 °C to furnish a yellow-orange suspension. The resulting solid was filtered, rinsed with water, and dried *in vacuo*. The crude material was dissolved in EtOAc, adsorbed on NH silica gel (11 g), and purified via medium pressure chromatography using a gradient of 10% to 100% EtOAc in heptane on an NH 60 μM size 400 column (Shoko Scientific Purif-Pack™) to give the title compound (2.105 g, 59.0%) as a light yellow solid. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.26 (d, J = 6.8 Hz, 6H), 1.43 (s, 9H), 3.30-3.33 (m, 4H), 3.52-3.60 (m, 4H), 4.32-4.42 (m, 1H), 6.54 (d, J = 7.8 Hz, 1H), 7.43-7.46 (m, 1H), 8.29 (d, J = 5.4 Hz, 1H), 8.78 (s, 1H); ESI-MS m/z $[M+H]^+$ 373.0.

[00187] Preparation 25 (1*s*,3*s*)-3-((2-(4-(2,4-difluorobenzyl)piperazin-1-yl)pyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutan-1-ol

[00188] Combined 3-chloro-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)pyrido[3,4-*b*]pyrazine (0.75 g, 1.996 mmol), (1*s*,3*s*)-3-aminocyclobutanol hydrochloride (0.740 g, 5.99 mmol), and potassium fluoride (0.151 g, 2.59 mmol) in DMSO (7.5 mL) and added DIPEA (1.738 mL, 9.98 mmol) at 23 °C. The reaction mixture was stirred at 23 °C for 5 days and diluted with water (30 mL) to furnish a yellow-orange suspension. The resulting solid was filtered, rinsed with water, and dried *in vacuo* to give the title compound (690 mg, 81%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.92-2.02 (m, 2H), 2.61-2.70 (m, 6H), 3.38 (br s, 4H), 3.60 (s, 2H), 3.90-3.98 (m, 1H), 3.99-4.07 (m, 1H), 5.08 (d, J = 5.9 Hz, 1H), 6.93-6.98 (m, 1H), 7.09 (td, J = 8.4, 2.7 Hz, 1H), 7.20-7.25 (m, 1H), 7.41-7.45 (m, 1H), 7.47-7.53 (m, 1H), 8.28 (d, J = 5.9 Hz, 1H), 8.75 (s, 1H); ESI-MS m/z $[M+H]^+$ 427.0.

[00189] Preparation 26 (1*s*,3*s*)-3-((2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutan-1-ol

Combined 3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazine (0.75 g, 1.991 mmol), (1*s*,3*s*)-3-aminocyclobutanol hydrochloride (0.738 g, 5.97 mmol), and potassium fluoride (0.150 g, 2.59 mmol) in DMSO (7.5 mL) and added DIPEA (1.734 mL, 9.95 mmol) at 23 °C. The reaction mixture was stirred at 23 °C for 5 days and diluted with water (30 mL) to furnish a yellow-orange suspension. The resulting solid was filtered, rinsed with water, and dried *in vacuo* to give the title compound (784 mg, 92%) as a yellow-orange solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.87-2.03 (m, 4H), 2.07-2.18 (m, 2H), 2.61-2.73 (m, 2H), 3.19-3.29 (m, 2H), 3.63-3.73 (m, 2H), 3.89-3.99 (m, 1H), 3.99-4.10 (m, 1H), 4.62 (tt, J = 7.9, 3.8 Hz, 1H), 5.08 (d, J = 5.9 Hz, 1H), 6.99-7.10 (m, 2H), 7.26-7.38 (m, 2H), 7.44 (d, J = 5.4 Hz, 1H), 8.28 (d, J = 5.4 Hz, 1H), 8.76 (s, 1H); ESI-MS m/z $[M+H]^+$ 427.9.

[00190] Preparation 27 (1*r*,3*r*)-3-((2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutan-1-ol

Combined 3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazine (0.75 g, 1.991 mmol), (1*r*,3*r*)-3-aminocyclobutanol hydrochloride (0.738 g, 5.97 mmol), and potassium fluoride (0.150 g, 2.59 mmol) in DMSO (7.5 mL) and added DIPEA (1.734 mL, 9.95 mmol) at 23 °C. The reaction was stirred at 23 °C for 5 days and diluted with water (30 mL) to furnish a gummy, brown suspension. The suspension was cooled on ice, stirred for 30 min at 0 °C, filtered, rinsed with water, and the resulting solid was dried *in vacuo* to give the title compound (802 mg, 94%) as a light brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.86-1.96 (m, 2H), 2.07-2.15 (m, 2H), 2.23 (ddd, J = 12.6, 7.9, 4.4 Hz, 2H), 2.33-2.40 (m, 2H), 3.23-3.30 (m, 2H), 3.67-3.74 (m, 2H), 4.30-4.37 (m, 1H), 4.56-4.65 (m, 2H), 5.03 (d, J

= 4.9 Hz, 1H), 7.00-7.07 (m, 2H), 7.29-7.37 (m, 2H), 7.44 (d, *J* = 4.9 Hz, 1H), 8.28 (d, *J* = 5.4 Hz, 1H), 8.77 (s, 1H); ESI-MS m/z $[M+H]^+$ 427.9.

[00191] Preparation 28 *N*-cyclobutyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazin-3-amine

[00192] To a solution of 3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazine (10 g, 26.5 mmol) in DMF (150 mL) was added cyclobutanamine (15.10 g, 212 mmol) at rt. Then the mixture was stirred at 70 °C for 15 h. After the reaction was done, the reaction mixture was poured into water/ACN (200 mL, 7:3). The suspension was filtered and rinsed with ACN to give the title compound (8.5 g, 78%). ESI-MS m/z $[M+H]^+$ 412.1.

[00193] Preparation 28 *N*-(3,3-difluorocyclobutyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazin-3-amine

Combined 3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazine (0.46 g, 1.221 mmol), 3,3-difluorocyclobutanamine hydrochloride (0.526 g, 3.66 mmol), and potassium fluoride (0.092 g, 1.587 mmol) in DMSO (5 mL) and added DIPEA (1.063 mL, 6.10 mmol) at 23 °C. The reaction was stirred at 23 °C for 5 days and diluted with water (20 mL) to furnish a yellow-orange suspension. The resulting solid was filtered, rinsed with water, and dried *in vacuo* to give the title compound (516.4 mg, 95%) as a yellow-orange solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.87-1.98 (m, 2H), 2.07-2.18 (m, 2H), 2.77-2.91 (m, 2H), 2.96-3.07 (m, 2H), 3.23-3.32 (m, 2H), 3.69-3.78 (m, 2H), 4.35-4.45 (m, 1H), 4.63 (tt, *J* = 7.9, 3.8 Hz, 1H), 7.00-7.07 (m, 1H), 7.24-7.40 (m, 3H), 7.48 (d, *J* = 5.4 Hz, 1H), 8.33 (d, *J* = 5.4 Hz, 1H), 8.82 (s, 1H); ESI-MS m/z $[M+H]^+$ 447.9.

[00194] Preparation 30 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropylpyrido[3,4-*b*]pyrazin-3-amine

[00195] A solution of 3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazine (2 g, 5.31 mmol), propan-2-amine (1.36 mL, 15.92 mmol) and DIPEA (1.85 mL, 10.62 mmol) in dioxane (10.62 mL) was heated at 95 °C overnight. After concentration, the residue was purified with silica gel column chromatography using a gradient of 0% to 100% EtOAc in heptanes to give the title compound (1.5 g, 71%) as an off-white solid. ESI-MS m/z $[M+H]^+$ 400.00.

[00196] Preparation 31 9 (*S*)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-(tetrahydrofuran-3-yl)pyrido[3,4-*b*]pyrazin-3-amine

[00197] To a mixture of 3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazine (2.5 g, 6.64 mmol) in DMF (30 mL) was added (*S*)-tetrahydrofuran-3-amine hydrochloride (4.10 g, 33.2 mmol) and Et_3N (9.25 mL, 66.4 mmol) at room temperature. The

reaction mixture was stirred at 70 °C for 14 h then cooled to room temperature and diluted with EtOAc (80 mL), washed with water (30 mL) and brine (2 x 30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*, then the residue was purified by column chromatography (petroleum ether:EtOAc from 10:1 to 1:1) on silica gel to give the title compound as a yellow solid (2.0 g). ESI-MS m/z $[M+H]^+$ 428.1.

[00198] Preparation 32 (*R*)-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-(tetrahydrofuran-3-yl)pyrido[3,4-*b*]pyrazin-3-amine

[00199] To a mixture of 3-chloro-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)pyrido[3,4-*b*]pyrazine (5.06 g, 13.46 mmol) in DMSO (40 mL) was added (*R*)-tetrahydrofuran-3-amine hydrochloride (4.16 g, 33.7 mmol) and Et_3N (24.40 mL, 175 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 14 h then cooled to room temperature and diluted with EtOAc (80 mL), washed with water (30 mL) and brine (2 x 30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*, then the residue was purified by column chromatography (petroleum ether:EtOAc from 10:1 to 1:1) on silica gel to give the title compound as a yellow solid (5.0 g). ESI-MS m/z $[M+H]^+$ 427.1.

[00200] Preparation 33 (*S*)-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-(tetrahydrofuran-3-yl)pyrido[3,4-*b*]pyrazin-3-amine

[00201] To a solution of 3-chloro-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)pyrido[3,4-*b*]pyrazine (3.0 g, 7.98 mmol) and Et_3N (10 mL, 71.7 mmol) in DMF (30 mL) was added (*S*)-tetrahydrofuran-3-amine hydrochloride (2.96 g, 23.95 mmol) at room temperature. The mixture was stirred at 60 °C for 16 h then separated between water and EtOAc. The organic layer was washed with brine and water, then dried and concentrated to yield the crude residue, which was purified by column to give the title compound (800 mg) as a yellow oil. ESI-MS m/z $[M+H]^+$ 427.1.

[00202] Preparation 34 2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-isopropylpyrido[3,4-*b*]pyrazin-3-amine

[00203] To a flask charged with 3-chloro-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)pyrido[3,4-*b*]pyrazine (2.34 g, 6.23 mmol) and potassium fluoride (0.470 g, 8.09 mmol) in DMSO (12 mL) was added DIPEA (2.169 mL, 12.45 mmol) and propan-2-amine (1.605 mL, 18.68 mmol) at 23 °C. The reaction was stirred at 23 °C for 22 hr and diluted with water (48 mL) to furnish an orange, oily sludge. The crude product was extracted with EtOAc (25 mL) to furnish a suspension. The resulting solid was filtered, rinsed with EtOAc, and the filtrate was allowed to separate into two layers. The organic phase was washed with brine, dried over Na_2SO_4, filtered, rinsed with EtOAc, and dried *in vacuo*. The crude material was dissolved in

toluene (5 mL) and purified via medium pressure chromatography using a 20% to 100% gradient eluant of EtOAc in heptane on an NH 60 μM, size 400 column (Shoko Scientific Purif-Pack™) to give the title compound (1.489 g, 60.0%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.24 (d, J = 6.4 Hz, 6H), 2.62 (t, J = 4.9 Hz, 4H), 3.34-3.41 (m, 4H), 3.59 (s, 2H), 4.22-4.42 (m, 1H), 6.46 (d, J = 7.8 Hz, 1H), 7.04-7.17 (m, 1H), 7.22 (td, J = 10.0, 2.4 Hz, 1H), 7.40-7.44 (m, 1H), 7.49 (td, J = 8.5, 6.8 Hz, 1H), 8.27 (d, J = 5.9 Hz, 1H), 8.76 (s, 1H); ESI-MS m/z $[M+H]^+$ 399.0.

[00204] Preparation 35 *N*-cyclobutyl-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)pyrido[3,4-*b*]pyrazin-3-amine

[00205] Combined 3-chloro-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)pyrido[3,4-*b*]pyrazine (0.7226 g, 1.923 mmol), cyclobutanamine (0.493 mL, 5.77 mmol), and potassium fluoride (0.145 g, 2.500 mmol) in DMSO (7.2 mL) and DIPEA (0.670 mL, 3.85 mmol) at 23 °C. The reaction was stirred at 23 °C for 16 hr and diluted with water (30 mL) to furnish a yellow-orange suspension. The resulting solid was filtered, rinsed with water, and dried *in vacuo* to give the title compound (0.62 g, 79%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.68-1.77 (m, 2H), 2.12 (quind, J = 9.3, 2.7 Hz, 2H), 2.27-2.35 (m, 2H), 2.56-2.68 (m, 4H), 3.35-3.42 (m, 4H), 3.60 (s, 2H), 4.57 (sextet, J = 8.0 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 7.06-7.12 (m, 1H), 7.22 (td, J = 9.9, 2.7 Hz, 1H), 7.43 (d, J = 5.4 Hz, 1H), 7.46-7.53 (m, 1H), 8.27 (d, J = 5.4 Hz, 1H), 8.76 (s, 1H); ESI-MS m/z $[M+H]^+$ 411.0.

[00206] Preparation 36 6-benzyl-3-chloro-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine

[00207] A mixture of 3-chloro-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazine (93 mg, 0.239 mmol) and (bromomethyl)benzene (29 μL, 0.239 mmol) in ACN (1.2 mL) was heated at 80 °C for 14 h. After the mixture was cooled to room temperature, sodium triacetoxyborohydride (152 mg, 0.718 mmol) was added to the mixture at rt. After 1 h, brine (1 mL) was added to the mixture. After bubbling ceased, the mixture was then purified directly by HPLC Method A to give the title compound as a TFA salt (71.2 mg, 49.9%) as a yellow oil. ESI-MS m/z $[M+H]^+$ 483.3.

[00208] Preparation 37 3-chloro-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine

[00209] The title compound as a TFA salt (30.9 mg, 24.8 %) was prepared in a manner similar to Preparation 38 using iodomethane. ESI-MS m/z $[M+H]^+$ 407.3.

[00210] Preparation 39 6-benzyl-3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine

A mixture of 4-((2,4-difluorophenyl)fluoromethyl)piperidine hydrochloride (247 mg, 0.929 mmol), 2,3-dichloropyrido[3,4-*b*]pyrazine (169 mg, 0.845 mmol) and DIPEA (441 µL, 2.53 mmol) in DCM (1.69 mL) was stirred at 0 °C for 5 min then at rt for 30 min. The mixture was then partitioned between EtOAc and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried over Na_2SO_4, filtrered, and evaporated. The residue was dissolved in EtOAc and filtered through a pad of silica. The filtrate was concentrated to afford 3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)pyrido[3,4-*b*]pyrazine (338.4 mg) as a yellow foam. ESI-MS m/z $[M+H]^+$ 393.2.

[00211] A mixture of 3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)pyrido[3,4-*b*]pyrazine (338.4 mg, 0.861 mmol) benzyl bromide (103 µL, 0.861 mmol) in ACN (4.31 mL) was heated at 80 °C for 14 h. After the mixture was cooled to rt, sodium triacetoxyborohydride (548 mg, 2.58 mmol) was added. After 1 h, brine (1 mL) was added to the mixture. After bubbling ceased, the mixture was then purified directly by HPLC Method A to afford the title compound as its TFA salt (141.7 mg, 27.4%) as an orange oil. ESI-MS m/z $[M+H]^+$ 487.3.

[00212] Preparation 40 6-benzyl-3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine

[00213] Combined 2,3-dichloro-5-methylpyrido[3,4-*b*]pyrazine (1 g, 4.67 mmol), DIPEA (2.04 mL, 11.68 mmol), and 4-(2,4-difluorophenoxy)piperidine hydrochloride (1.225 g, 4.91 mmol) in DCM (9.34 mL) were combined in an ice bath then warmed to room temperature overnight. The reaction mixture was poured into 1 M NaOH, extracted with EtOAc (2x), filtered through $MgSO_4$, concentrated *in vacuo*, and purified by HPLC Method A to give 3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methylpyrido[3,4-*b*]pyrazine as a TFA salt (1.6 g).

[00214] Combined 3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methylpyrido[3,4-*b*]pyrazine (400 mg, 1.024 mmol) and benzyl bromide (122 µL, 1.024 mmol) in ACN (5.12 mL) was heated at 90 °C overnight. The reaction mixture was cooled to RT, sodium triacetoxyborohydride was added (651 mg, 3.07 mmol), and the reaction mixture was stirred overnight. The crude reaction was poured into 1 M NaOH, extracted with EtOAc (2x), filtered through $MgSO_4$, concentrated *in vacuo*, and purified by HPLC Method A to yield the title compound as a TFA salt (150 mg).

[00215] Preparation 41 6-benzyl-3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine

[00216] Benzyl bromide was purified by passage through a plug of basic alumina prior to use. A solution of 3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazine (736.2 mg, 1.954 mmol) in ACN (9.77 mL) was divided into two equal portions. Each solution was treated with a half portion of benzyl bromide (232 µL, 1.954 mmol) and stirred at 80 °C for 3 h. The reaction mixtures were allowed to cool to room temperature, and Each solution was treated with a half portion of sodium triacetoxyborohydride (1.242 g, 5.86 mmol). The reaction mixtures were stirred at room temperature for 1 h, then were quenched with saturated aqueous NaCl. The reaction mixtures were combined and partitioned between EtOAc with Et_2O added to assist in phase separation and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using a 20% to 60% gradient of EtOAc in heptanes gave the title compound (522.2 mg, 56.8%). ESI-MS m/z $[M+H]^+$ 471.4.

[00217] Preparation 42 4-((1-(6-benzyl-3-chloro-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile

[00218] Benzyl bromide was purified by filtration through a plug of basic alumina prior to use. A solution of 4-((1-(3-chloropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile (200 mg, 0.521 mmol) and benzyl bromide (0.062 mL, 0.521 mmol) in ACN (2.60 mL) was heated at 80 °C for 3 h. The reaction mixture was allowed to cool to room temperature and sodium triacetoxyborohydride (331 mg, 1.563 mmol) was added. After stirring for 1 h at room temperature, the reaction mixture was quenched with saturated aqueous NaCl (1 mL). After bubbling ceased, the reaction mixture was purified by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 35% to 70% ACN gradient to give the title compound, as a TFA salt, as a yellow oil (117.9 mg, 38.2%). ESI-MS m/z $[M+H]^+$ 478.5.

[00219] Preparation 43 (*R*)-6-benzyl-3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine

[00220] The title compound was prepared in a manner similar to Preparation 44 using (*R*)-3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)pyrido[3,4-*b*]pyrazine. The product was purified twice by flash silica gel chromatography using a 10% to 60% gradient of EtOAc in heptanes. ESI-MS m/z $[M+H]^+$ 487.4.

[00221] Preparation 45 (*S*)-6-benzyl-3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine

The title compound was prepared in a manner similar to Preparation 46 using (*S*)-3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)pyrido[3,4-*b*]pyrazine. The product was

purified twice by flash silica gel chromatography using a 10% to 50% gradient of EtOAc in heptanes. ESI-MS m/z $[M+H]^+$ 487.3.

[00222] Preparation 47 6-benzyl-*N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00223] A solution of 6-benzyl-3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine (261.1 mg, 0.554 mmol) and 2,2-difluoroethanamine (156 µL, 2.22 mmol) in toluene (1.85 mL) was treated with sodium *tert*-butoxide (107 mg, 1.11 mmol), BINAP (69.0 mg, 0.111 mmol), and $Pd_2(dba)_3$ (50.8 mg, 0.055 mmol). Nitrogen gas (balloon) was bubbled through the reaction mixture for 5 min. The reaction mixture was sealed and stirred at 90 °C overnight. The reaction mixture was allowed to cool to room temperature and was opened to air, and the solution was concentrated under reduced pressure. The residue was taken up in MeOH, filtered, and purified by HPLC Method B using a 35% to 60% ACN gradient to give the title compound, as a TFA salt, as a yellow oil (181.2 mg, 51.9%). ESI-MS m/z $[M+H]^+$ 516.4.

[00224] Preparation 48 6-benzyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00225] To a yellow-orange suspension of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropylpyrido[3,4-*b*]pyrazin-3-amine (5.1 g, 12.77 mmol) in ACN (63.8 mL) was added benzyl bromide (2.184 g, 12.77 mmol) over 1 minute at 23 °C. The mixture was stirred at 80 °C for 4 h to furnish a red-brown solution, cooled to 23 °C, and then concentrated via rotary evaporation to give 6-benzyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)pyrido[3,4-*b*]pyrazin-6-ium bromide (7.30 g) as a red-brown solid, which was used directly in the next step without further purification.

[00226] To a solution of 6-benzyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)pyrido[3,4-*b*]pyrazin-6-ium bromide (7.2 g, 12.62 mmol) in DCM (126 ml) was added $NaBH(OAc)_3$ (16.05 g, 76 mmol).The resulting solution was stirred at room temperature for 3 days. After DCM was removed under vacuum, EtOAc (200 mL) was added to re-dissolve the residue. Then saturated $NaHCO_3$ (150 mL) was added and the mixture was vigorously stirred for 30 min. The organic layer was washed with water (50 mL) and brine (50 mL), and dried with anhydrous Na_2SO_4 overnight. Removal of the solvent gave the title compound (6.43 g) as a yellow solid, which was used without further purification. ESI-MS m/z $[M+H]^+$ 494.10.

[00227] Preparation 50 6-benzyl-*N*-cyclobutyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

The title compound as a TFA salt was prepared in a manner similar to Preparation 51 using cyclobutanamine in place of 2,2-difluoroethanamine and HPLC Method A. ESI-MS m/z $[M+H]^+$ 506.00.

[00228] Preparation 52 (*S*)-6-benzyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-(1-methoxypropan-2-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00229] The title compound as a TFA salt was prepared in a manner similar to Preparation 53 using (*S*)-1-methoxypropan-2-amine in place of 2,2-difluoroethanamine and HPLC Method A. ESI-MS m/z $[M+H]^+$ 524.00.

[00230] Preparation 54 (*R*)-6-benzyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-(1-methoxypropan-2-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00231] The title compound as a TFA salt was prepared in a manner similar to Preparation 55 using (*R*)-1-methoxypropan-2-amine hydrochloride in place of 2,2-difluoroethanamine and HPLC Method A. ESI-MS m/z $[M+H]^+$ 524.00.

[00232] Preparation 56 (*S*)-6-benzyl-*N*-(*sec*-butyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00233] The title compound as a TFA salt was prepared in a manner similar to Preparation 57 using (*S*)-butan-2-amine in place of 2,2-difluoroethanamine and HPLC Method A. ESI-MS m/z $[M+H]^+$ 508.00.

[00234] Preparation 58 (*R*)-6-benzyl-*N*-(*sec*-butyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00235] The title compound as a TFA salt was prepared in a manner similar to Preparation 59 using (*R*)-butan-2-amine in place of 2,2-difluoroethanamine and HPLC Method A. ESI-MS m/z $[M+H]^+$ 508.00.

[00236] Preparation 60 4-((1-(6-benzyl-3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile

[00237] A solution of 4-((1-(6-benzyl-3-chloro-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile TFA salt (213.9 mg, 0.361 mmol) in toluene (1.44 mL) was treated with propan-2-amine (0.118 mL, 1.445 mmol), sodium *tert*-butoxide (69.4 mg, 0.723 mmol), BINAP (22.5 mg, 0.036 mmol), and $Pd_2(dba)_3$ (16.5 mg, 0.018 mmol). Nitrogen gas was bubbled through the solution for 5 min. The reaction mixture was then sealed and the reaction mixture was heated to 90 °C overnight. The reaction mixture was allowed to cool to room temperature. Solvent was removed under reduced pressure and the residue was purified by HPLC Method B, with the exception that a Waters SunFire™ C18, 5

μm, ID 30 x 75 mm column was used, using a 40% to 70% ACN gradient to give the title compound, as a TFA salt, as a yellow oil (105 mg, 47.3%). ESI-MS m/z $[M+H]^+$ 501.5.

[00238] Preparation 61 (*R*)-6-benzyl-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00239] A solution of (*R*)-6-benzyl-3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine (293 mg, 0.602 mmol) and propan-2-amine (197 μL, 2.407 mmol) in toluene (2.01 mL) was treated with sodium *tert*-butoxide (116 mg, 1.203 mmol), BINAP (74.9 mg, 0.120 mmol), and $Pd_2(dba)_3$ (55.1 mg, 0.060 mmol). Nitrogen gas (balloon) was bubbled through the reaction mixture for 5 min. The reaction mixture was sealed and the reaction mixture was stirred at 90 °C overnight. The reaction was opened and the mixture was concentrated under reduced pressure. The residue was taken up in MeOH, filtered, and purified by HPLC Method B using a 40% to 65% ACN gradient to give the title compound as a TFA salt (183.1 mg, 48.8%) as a yellow oil. ESI-MS m/z $[M+H]^+$ 510.4.

[00240] Preparation 62 (*S*)-6-benzyl-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00241] A solution of (*S*)-6-benzyl-3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine (500 mg, 1.027 mmol) and propan-2-amine (350 μL, 4.11 mmol) in toluene (3.42 mL) was treated with sodium *tert*-butoxide (197 mg, 2.054 mmol), BINAP (102 mg, 0.164 mmol), and $Pd_2(dba)_3$ (75 mg, 0.082 mmol). Nitrogen gas (balloon) was bubbled through the reaction mixture for 5 min. The reaction mixture was then sealed and heated at 90 °C for 16 h. The reaction mixture was allowed to cool to room temperature and was opened to air. The reaction mixture was concentrated under reduced pressure and was taken up in MeOH, filtered, and purified by HPLC Method A to give the title compound as a TFA salt (266 mg) as an orange oil. ESI-MS m/z $[M+H]^+$ 510.4.

[00242] Preparation 63 3-fluoro-4-((1-(3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)benzonitrile

[00243] To a solution of 4-((1-(6-benzyl-3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile TFA salt (98.8 mg, 0.161 mmol) in THF (1.61 mL) was added $Pd(OH)_2$ (20 wt %, 33.9 mg, 0.048 mmol). Hydrogen gas (balloon) was bubbled through the reaction mixture for 5 min. The reaction mixture was allowed to stir under hydrogen atmosphere for 6 h. The reaction mixture was filtered through a plug of Celite™, eluting with MeOH. The filtrate was collected and concentrated under

reduced pressure. The residue was purified by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 25% to 60% ACN gradient to give the title compound, as a TFA salt, as a yellow oil (12.8 mg), which was carried forward without additional purification. ESI-MS m/z $[M+H]^+$ 411.5.

[00244] Preparation 64 *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00245] A solution of 6-benzyl-*N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (132.5 mg, 0.210 mmol) in THF (2.1 mL) was treated with $Pd(OH)_2$ (20 wt %, 29.6 mg, 0.042 mmol). Hydrogen gas (balloon) was bubbled through the reaction mixture for 5 min. The vent needle was removed and the reaction was stirred under hydrogen atmosphere for 1 h. The reaction mixture was opened to air and was filtered through a pad of Celite™, eluting with EtOAc and MeOH. The filtrate was concentrated under reduced pressure to give the title compound as a TFA salt (114 mg), which was used without further purification. ESI-MS m/z $[M+H]^+$ 426.5.

[00246] Preparation 65 *N*-cyclobutyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

The title compound as a TFA salt was prepared in a manner similar to Preparation 66, except that the reaction was stirred under hydrogen atmosphere for 2 h. ESI-MS m/z $[M+H]^+$ 416.5.

[00247] Preparation 67 (*R*)-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00248] The title compound as a TFA salt was prepared in a manner similar to Preparation 68, except that the reaction was stirred under hydrogen atmosphere for 2 h. The TFA salt was dissolved in DCM and washed with saturated aqueous K_2CO_3. The organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the title compound as the free base. ESI-MS m/z $[M+H]^+$ 420.5.

[00249] Preparation 69 (*S*)-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00250] The title compound as a TFA salt was prepared in a manner similar to Preparation 70. The TFA salt was dissolved in DCM and washed with saturated aqueous K_2CO_3. The organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the title compound as the free base. ESI-MS m/z $[M+H]^+$ 420.5.

[00251] Preparation 71 *N*-cyclobutyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00252] A mixture of cyclobutanamine (49.9 μL, 0.584 mmol), 6-benzyl-3-chloro-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine TFA salt (116.2 mg, 0.195 mmol), sodium *tert*-butoxide (56.1 mg, 0.584 mmol), BINAP (18.2 mg, 0.029 mmol) and $Pd_2(dba)_3$ (26.7 mg, 0.029 mmol) in toluene (649 μL) was heated at 90 °C in a sealed tube for 16 h. The mixture was directly purified by HPLC Method A to afford 6-benzyl-*N*-cyclobutyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine as its TFA salt (103.4 mg, 84%) as a yellow foam. ESI-MS m/z $[M+H]^+$ 518.4

[00253] A mixture of 6-benzyl-*N*-cyclobutyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (103.4 mg, 0.164 mmol) and $Pd(OH)_2$ on carbon (10 mg, 0.014 mmol) in THF (818 μL) was stirred at rt under an atmosphere of hydrogen gas (balloon) for 4 h. The mixture was filtered through a pad of Celite™, washing with MeOH, and concentrated to afford the title compound as its TFA salt (89 mg, 100%) as a yellow solid. ESI-MS m/z $[M+H]^+$ 428.4.

[00254] Preparation 72 1-(3-(isopropylamino)-2-(piperazin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one

[00255] To a flask charged with *tert*-butyl 4-(6-acetyl-3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperazine-1-carboxylate (1.015 g, 2.425 mmol) was added HCl (4 M in dioxane, 4.85 mL, 19.40 mmol) at 23 °C. The reaction mixture was stirred at 23 °C for 1 h, diluted with dioxane (20 mL), filtered, rinsed with dioxane, and dried *in vacuo* to provide the HCl salt of the title compound (0.861 g, 100%) as a yellow solid. ESI-MS m/z $[M+H]^+$ 319.5.

[00256] Preparation 73 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-N-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-b]pyrazin-3-amine

[00257] Combined 6-benzyl-3-chloro-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine TFA salt (280 mg, 0.467 mmol), isopropylamine (200 μL, 2.337 mmol), $Pd_2(dba)_3$ (42.8 mg, 0.047 mmol), BINAP (58.2 mg, 0.093 mmol), and sodium *tert*-butoxide (112 mg, 1.169 mmol) in toluene (2.34 mL) and heated at 100 °C for 30 min under microwave conditions. The reaction mixture was cooled, concentrated *in vacuo*, and purified by HPLC Method A to give 6-benzyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine as a TFA salt (175 mg) as a brown oil.

[00258] A 50 mL round-bottomed flask containing 6-benzyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-

b]pyrazin-3-amine TFA salt (175 mg, 0.282 mmol) and $Pd(OH)_2$ (20 wt %, 39.5 mg, 0.056 mmol) in THF (2.82 mL) was purged and placed under hydrogen (balloon) for 3 h. Filtration through Celite™ (washed with EtOAc) and concentration *in vacuo* gave the title compound as a TFA salt (150 mg) as a brown oil.

[00259] Preparation 74 *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00260] The title compound (98 mg) was prepared in a manner similar to Preparation 75 using 2,2-difluoroethan-1-amine.

[00261] Preparation 76 (5-chloro-2-fluorophenyl)(1-(3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)methanone

[00262] A mixture of (5-chloro-2-fluorophenyl)(piperidin-4-yl)methanone hydrochloride (153 mg, 0.550 mmol), 2,3-dichloropyrido[3,4-*b*]pyrazine (100 mg, 0.500 mmol) and DIPEA (261 µL, 1.500 mmol) in DCM (1.67 mL) was stirred at rt for 30 min. The mixture was partitioned between aqueous NH_4Cl and EtOAc. The organic layer was filtered through a pad of silica, washing with EtOAc, and the filtrate was concentrated under reduced pressure to give (5-chloro-2-fluorophenyl)(1-(3-chloropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)methanone (205.5 mg) as an orange solid. ESI-MS m/z $[M+H]^+$ 405.2.

[00263] A mixture of (5-chloro-2-fluorophenyl)(1-(3-chloropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)methanone (205.5 mg, 0.507 mmol) and benzyl bromide (63.7 µL, 0.532 mmol) in ACN (1.69 mL) was heated at 80 °C for 4 h. After the mixture was cooled to rt, sodium triacetoxyborohydride (537 mg, 2.54 mmol) was added in one portion. After 1 h, the mixture was quenched with brine, extracted with EtOAc, concentrated and purified by HPLC Method A to afford (1-(6-benzyl-3-chloro-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)(5-chloro-2-fluorophenyl)methanone as its TFA salt (112.4 mg, 36.1%) as a yellow oil. ESI-MS m/z $[M+H]^+$ 499.2.

[00264] A mixture of propan-2-amine (31.5 µL, 0.366 mmol), (1-(6-benzyl-3-chloro-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)(5-chloro-2-fluorophenyl)methanone TFA salt (112.4 mg, 0.183 mmol), sodium *tert*-butoxide (35.2 mg, 0.366 mmol), BINAP (17.1 mg, 0.027 mmol) and $Pd_2(dba)_3$ (8.4 mg, 9.16 µmol) in toluene (611 µL) was heated at 100 °C for 16 h. The mixture was purified by HPLC Method A to afford (1-(6-benzyl-3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)(5-chloro-2-fluorophenyl)methanone as its TFA salt (41.7 mg, 35.8%) as a yellow film. ESI-MS m/z $[M+H]^+$ 522.4.

[00265] A mixture of (1-(6-benzyl-3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)(5-chloro-2-fluorophenyl)methanone TFA salt (41.7 mg, 0.066 mmol) and $Pd(OH)_2$ on carbon (20 wt %, 5 mg, 0.036 mmol) in THF (328 µL) was stirred at rt under an atmosphere of hydrogen gas (balloon). After 3 h, the mixture was diluted with MeOH, filtered through a pad of Celite™, washing with MeOH, and concentrated to afford the title compound as its TFA salt (36 mg, 100%) as a yellow film, which was used without further purification. ESI-MS m/z $[M+H]^+$ 432.3.

[00266] Preparation 77 3-chloro-*N*-isopropylpyrido[3,4-*b*]pyrazin-2-amine

To a solution of 2,3-dichloropyrido[3,4-*b*]pyrazine (2.5 g, 12.50 mmol) and DIPEA (6.53 mL, 37.5 mmol) in DCM (25 mL) was added propan-2-amine (1.065 mL, 12.50 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min, warmed slowly to 23 °C, and stirred for 12 h. The crude mixture was partitioned between EtOAc (100 mL) and saturated aqueous NH_4Cl (100 mL). The layers were separated and the aqueous phase was washed with EtOAc (4 x 100 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered, rinsed with EtOAc, and dried *in vacuo*. The crude material was dissolved in toluene (5 mL) and purified via medium pressure chromatography using a gradient eluant of 50% to 75% EtOAc in heptane on a 80 g silica gel column (Single Step™) to give the title compound (1.828 g, 65.7%) as a yellow-orange solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (d, J = 6.6 Hz, 6H), 4.39-4.49 (m, 1H), 7.49 (dd, J = 5.8, 0.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 8.52 (d, J = 5.6 Hz, 1H), 8.95 (d, J = 0.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 223.1.

[00267] Preparation 78 3-chloro-*N*-cyclopropylpyrido[3,4-*b*]pyrazin-2-amine

[00268] A solution of 2,3-dichloropyrido[3,4-*b*]pyrazine (3.55 g, 17.75 mmol) in dioxane (71.0 mL) at room temperature was treated with cyclopropanamine (1.63 mL, 23.07 mmol), followed by dropwise addition of DIPEA (6.51 mL, 37.3 mmol). The resulting reaction mixture was stirred at room temperature for 12 h. Purification by flash silica gel chromatography using a gradient of 25% to 100% EtOAc in hexanes gave the title compound (3.15 g, 80%) as an orange solid. ESI-MS m/z $[M+H]^+$ 221.1.

[00269] Preparation 79 3-chloro-*N*-(2,2-difluoroethyl)pyrido[3,4-*b*]pyrazin-2-amine

[00270] A solution of 2,3-dichloropyrido[3,4-*b*]pyrazine (50 mg, 0.250 mmol) in dioxane (250 µL) was treated with 2,2-difluoroethanamine (21.0 µL, 0.275 mmol) and DIPEA (131 µL, 0.750 mmol). The resulting reaction mixture was stirred at 70 °C for 1 h then purified by flash silica gel chromatography using a gradient of 0% to 60% EtOAc in hexanes to give the title compound (52 mg, 85%) as a light yellow solid.

[00271] Preparation 80 6-benzyl-3-chloro-*N*-cyclopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00272] A mixture of 3-chloro-*N*-cyclopropylpyrido[3,4-*b*]pyrazin-2-amine (301.8 mg, 1.368 mmol) and (bromomethyl)benzene (170 µL, 1.436 mmol) in ACN (4.5 mL) was heated at 80 °C for 3 h. Sodium triacetoxyborohydride (1449 mg, 6.8 mmol) was added to the mixture at rt. After 30 min, brine was added to the mixture. After stirring for 1 h, the layers were separated and the organic layer was purified by HPLC Method A to give the title compound as a TFA salt (290.6 mg, 49.5%) as a yellow solid. ESI-MS m/z $[M+H]^+$ 315.2.

[00273] Preparation 81 3-chloro-*N*-cyclopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00274] The title compound as a TFA salt (22 mg, 17.2 %) was prepared in a manner similar to Preparation 82 using iodomethane**.** ESI-MS m/z $[M+H]^+$ 239.2.

[00275] Preparation 83 6-benzyl-3-chloro-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00276] The title compound as a TFA salt (240 mg, 41.3%) was prepared in a manner similar to Preparation 84 using 3-chloro-*N*-isopropylpyrido[3,4-*b*]pyrazin-2-amine**.** ESI-MS m/z $[M+H]^+$ 317.3.

[00277] Preparation 85 6-benzyl-3-chloro-*N*-(2,2-difluoroethyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00278] A solution of 3-chloro-*N*-(2,2-difluoroethyl)pyrido[3,4-*b*]pyrazin-2-amine (200 mg, 0.818 mmol) and benzyl bromide (99 µL, 0.818 mmol) in ACN (4.09 mL) was stirred at 80 °C for 3 h, then the reaction mixture was cooled to room temperature and treated with sodium triacetoxyhydroborate (520 mg, 2.453 mmol). After 1 h the solution was poured into 0.5 M NaOH and extracted twice with EtOAc. The extracts were combined, concentrated, diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified by HPLC Method A to give the title compound as a TFA salt (150 mg, 40.5%).

[00279] Preparation 86 6-benzyl-*N*-(*tert*-butyl)-3-chloro-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00280] *N*-(*tert*-butyl)-3-chloropyrido[3,4-*b*]pyrazin-2-amine

[00281] Combined 2,3-dichloropyrido[3,4-*b*]pyrazine (1 g, 5.00 mmol) and DIPEA (1.75 mL, 10.00 mmol) in DCM (10.00 mL) and cooled to 0 °C and added *tert*-butylamine (1.590 mL, 15.00 mmol) and stirred for 48 h. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted twice with EtOAc. The organic extracts were combined,

filtered through $MgSO_4$, and concentrated *in vacuo*. The residue was redissolved in EtOAc, filtered through a one inch plug of silica, washing with EtOAc, and concentrated gave *N*-(*tert*-butyl)-3-chloropyrido[3,4-*b*]pyrazin-2-amine (1.04 g, 88%).

[00282] A solution of *N*-(*tert*-butyl)-3-chloropyrido[3,4-*b*]pyrazin-2-amine (200 mg, 0.845 mmol) and benzyl bromide (145 mg, 0.845 mmol) in ACN (4.22 mL) was heated to 80 °C for 3 h. The reaction was cooled and sodium triacetoxyborohydride (537 mg, 2.53 mmol) was added. After 1 h, the reaction was poured into 0.5 M NaOH and extracted twice with EtOAc. The extracts were combined, concentrated, and purified by HPLC Method A to give the title compound as a TFA salt (125 mg, 33.3%).

[00283] Preparation 87 6-benzyl-3-(4-((2-fluorophenyl)sulfonyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00284] A suspension of 6-benzyl-3-chloro-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine (117.2 mg, 0.370 mmol) and 4-((2-fluorophenyl)sulfonyl)piperidine hydrochloride (124 mg, 0.444 mmol) in toluene (1.85 mL) was treated with sodium *tert*-butoxide (107 mg, 1.110 mmol), BINAP (34.6 mg, 0.055 mmol), and $Pd_2(dba)_3$ (16.9 mg, 0.018 mmol). Nitrogen gas (balloon) was bubbled through the reaction mixture for 5 min. The reaction mixture was then sealed and heated at 90 °C for 18 h. The reaction mixture was opened to air and concentrated under reduced pressure. The residue was taken up in DMF/MeOH, filtered through a 0.45 μm syringe filter, and purified by HPLC Method A to give the title compound (99.7 mg, 42.3%). ESI-MS m/z $[M+H]^+$ 523.90.

[00285] Preparation 88 6-benzyl-*N*-cyclopropyl-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00286] A mixture of 4-(2-fluoro-4-methoxyphenoxy)piperidine hydrochloride (73.2 mg, 0.280 mmol), 6-benzyl-3-chloro-*N*-cyclopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (100 mg, 0.233 mmol), sodium *tert*-butoxide (67.2 mg, 0.700 mmol), BINAP (21.8 mg, 0.035 mmol) and $Pd_2(dba)_3$ (10.7 mg, 0.012 mmol) in toluene (1.2 mL) was heated at 90 °C for 14 h. The mixture was directly purified by HPLC Method A to give the title compound as a TFA salt (114.2 mg, 97%) as a yellow foam. ^1H NMR (400 MHz, methanol-d_4) δ ppm 0.53-0.60 (m, 2H), 0.78-0.85 (m, 2H), 1.84 - 1.95 (m, 2H), 1.99-2.09 (m, 2H), 2.65-2.73 (m, 1H), 2.90-2.98 (m, 1H), 3.08-3.23 (m, 3H), 3.33 - 3.42 (m, 2H), 3.55-3.68 (m, 2H), 3.75 (s, 3H), 4.16-4.24 (m, 1H), 4.28-4.40 (m, 2H), 4.50-4.59 (m, 2H), 6.67 (s, 1H), 6.73 (dd, J = 12.9, 3.0 Hz, 1H), 7.01-7.09 (m, 1H), 7.52-7.61 (m, 5H); ESI-MS m/z $[M+H]^+$ 504.4.

[00287] Preparation 88 6-benzyl-*N*-cyclopropyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00288] A mixture of cyclopropanamine (27.2 mg, 0.477 mmol), 6-benzyl-3-chloro-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine TFA salt (71.2 mg, 0.119 mmol), sodium *tert*-butoxide (22.9 mg, 0.239 mmol), BINAP (11.1 mg, 0.018 mmol) and $Pd_2(dba)_3$ (5.5 mg, 5.96 μmol) in toluene (400 μL) was heated at 90 °C for 14 h. The mixture was directly purified by HPLC Method A to give the title compound as a TFA salt (49.2 mg, 66.8%) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.50-0.55 (m, 2H), 0.76 (dd, J = 7.0, 1.9 Hz, 2H), 1.86-1.96 (m, 2H), 2.01-2.10 (m, 2H), 2.63 (tt, J = 7.0, 3.6 Hz, 1H), 2.93-3.01 (m, 2H), 3.07 (br s, 2H), 3.34-3.41 (m, 2H), 3.56 (br s, 2H), 3.75 (s, 3H), 4.23 (br s, 2H), 4.30-4.37 (m, 1H), 4.53 (br s, 2H,) 6.63-6.68 (m, 1H), 6.73 (dd, J = 12.8, 2.9 Hz, 1H), 7.05 (t, J = 9.2 Hz, 1H), 7.52-7.61 (m, 5H); ESI-MS m/z $[M+H]^+$ 504.4.

[00289] Preparation 90 *N*-cyclopropyl-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00290] A mixture of 6-benzyl-*N*-cyclopropyl-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (5 mg, 8.10 μmol) and $Pd(OH)_2$ on carbon, (20 wt %, 1 mg, 7.12 μmol) in THF (80 μL) was stirred under atmosphere of hydrogen gas (balloon) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (4.6 mg, 100 %) as a yellow film; ESI-MS m/z $[M+H]^+$ 414.4.

[00291] Preparation 91 *N*-cyclopropyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00292] A mixture of 6-benzyl-*N*-cyclopropyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (46.8 mg, 0.076 mmol) and $Pd(OH)_2$ on carbon (20 wt %, 5 mg, 0.036 mmol) in THF (760 μL) was stirred under an atmosphere of hydrogen gas (balloon) at rt. After 2 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (39.6 mg, 99 %) as a yellow oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.52-0.59 (m, 2H), 0.75-0.83 (m, 2H), 1.84-1.97 (m, 2H), 2.02-2.12 (m, 2H), 2.64-2.71 (m, 1H), 2.93-3.16 (m, 4H), 3.35 (s, 2H), 3.52-3.63 (m, 2H), 3.75 (s, 3H), 4.20-4.31 (m, 2H), 4.32-4.40 (m, 1H), 6.63-6.69 (m, 1H), 6.73 (dd, J = 12.9, 3.0 Hz, 1H), 7.03-7.10 (m, 1H); ESI-MS m/z $[M+H]^+$ 414.3.

[00293] Preparation 92 6-benzyl-*N*-cyclopropyl-3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00294] A mixture of 4-((2,4-difluorophenyl)fluoromethyl)piperidine hydrochloride (101 mg, 0.381 mmol), 6-benzyl-3-chloro-*N*-cyclopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine (100 mg, 0.318 mmol), sodium *tert*-butoxide (92 mg, 0.953 mmol), BINAP (29.7 mg, 0.048 mmol) and $Pd_2(dba)_3$ (14.5 mg, 0.016 mmol) in toluene (1.6 mL) was heated at 90 °C for 14 h. The mixture was purified by HPLC Method A to give the title compound as a TFA salt (135.9 mg, 68.8%) as a yellow oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.55 (dt, J = 3.5, 1.4 Hz, 2H), 0.77-0.84 (m, 2H), 1.35-1.43 (m, 1H), 1.50-1.71 (m, 2H), 1.91-2.11 (m, 2H), 2.56-2.72 (m, 3H), 3.06-3.15 (m, 2H), 3.36-3.51 (m, 3H), 3.52-3.76 (m, 1H), 4.17 (br s, 2H), 4.52 (s, 2H), 5.50 (dd, J = 46.2, 7.6 Hz, 1H) 6.96-7.07 (m, 2H), 7.44-7.60 (m, 6H); ESI-MS m/z $[M+H]^+$ 508.4.

[00295] Preparation 93 91 6-benzyl-*N*-cyclopropyl-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00296] A mixture of cyclopropanamine (65 µL, 0.943 mmol), 6-benzyl-3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-b]pyrazine TFA salt (141.7 mg, 0.236 mmol), sodium *tert*-butoxide (45.3 mg, 0.472 mmol), BINAP (22.0 mg, 0.035 mmol), and $Pd_2(dba)_3$ (10.8 mg, 0.012 mmol) in toluene (800 µL) was heated at 90 °C for 14 h. The mixture was directly purified by HPLC Method A to give the title compound as a TFA salt (98.1 mg, 66.9%) as yellow oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.48-0.54 (m, 2H), 0.71-0.78 (m, 2H), 1.36-1.45 (m, 1H), 1.50-1.72 (m, 2H), 1.92-2.12 (m, 2H), 2.57-2.71 (m, 3H), 2.97-3.10 (m, 2H), 3.39-3.55 (m, 3H), 3.75-3.89 (m, 1H), 4.22 (br s, 2H), 4.53 (br s, 2H), 5.50 (dd, J = 46.5, 7.6 Hz, 1H), 6.96-7.07 (m, 2H), 7.45-7.61 (m, 6H); ESI-MS m/z $[M+H]^+$ 508.4.

[00297] Preparation 94 *N*-cyclopropyl-3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00298] A mixture of 6-benzyl-*N*-cyclopropyl-3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (132.1 mg, 0.213 mmol) and $Pd(OH)_2$ (20 wt %, 15 mg, 0.021 mmol) in THF (1.0 mL) was stirred at room temperature under atmosphere of hydrogen gas (balloon). After 2 h, the mixture was directly purified by HPLC Method A to give the title compound as a TFA salt (91.1 mg, 81%) as a yellow oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.55-0.61 (m, 2H), 0.80-0.86 (m, 2H), 1.41 (br d, J = 12.4 Hz, 1H), 1.52-1.73 (m, 2 H), 1.93-2.13 (m, 2H), 2.60-2.73 (m, 3H), 3.05 (t, J = 6.3 Hz, 2H), 3.39-3.52 (m, 2H), 3.55 (t, J = 6.3 Hz, 2H), 3.98 (s, 1H), 4.17 (s, 2H), 5.51 (dd, J = 46.7, 7.6 Hz, 1H), 6.97-7.08 (m, 2H), 7.45-7.54 (m, 1H); ESI-MS m/z $[M+H]^+$ 418.3.

[00299] Preparation 95 *N*-cyclopropyl-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00300] A mixture of 6-benzyl-*N*-cyclopropyl-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (93.5 mg, 0.150 mmol) and $Pd(OH)_2$ (20 wt%, 10 mg, 0.014 mmol) in THF (750 μL) was stirred at room temperature under an atmosphere of hydrogen gas (balloon). After 2 h, the mixture was directly purified by HPLC Method A to give the title compound as a TFA salt (67.7 mg, 85%) as a yellow oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.51-0.57 (m, 2H), 0.75-0.81 (m, 2H), 1.43 (br d, J = 13.1 Hz, 1H), 1.52-1.72 (m, 2H), 1.94-2.13 (m, 2H), 2.59-2.72 (m, 3H), 2.97 (t, J = 6.3 Hz, 2H), 3.40-3.50 (m, 2H), 3.51-3.56 (m, 2H), 3.98 (s, 1H), 4.22 (s, 2H), 5.51 (dd, J = 46.2, 7.3 Hz, 1H), 6.96-7.08 (m, 2H), 7.46-7.54 (m, 1H); ESI-MS m/z $[M+H]^+$ 418.3.

[00301] Preparation 96 6-benzyl-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00302] A mixture of 4-(2-fluoro-4-methoxyphenoxy)piperidine hydrochloride (72.9 mg, 0.279 mmol), 6-benzyl-3-chloro-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (100 mg, 0.232 mmol), sodium *tert*-butoxide (66.9 mg, 0.696 mmol), BINAP (21.7 mg, 0.035 mmol), and $Pd_2(dba)_3$ (10.6 mg, 0.012 mmol) in toluene (1.16 mL) was heated at 100 °C in a sealed tube for 14 h. The mixture was purified by HPLC Method A to give the title compound as a TFA salt (122.1 mg, 85%) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.24 (d, J = 6.6 Hz, 6H), 1.86-1.97 (m, 2H), 2.03-2.12 (m, 2H), 2.95 (br s, 2H), 3.01-3.12 (m, 2H), 3.33-3.38 (m, 2H), 3.53 (br s, 2H), 3.75 (s, 3H), 4.13-4.24 (m, 3H), 4.31-4.38 (m, 1H), 4.52 (s, 2H), 6.63-6.69 (m, 1H), 6.73 (dd, J = 12.8, 2.9 Hz, 1H), 7.06 (t, J = 9.2 Hz, 1H), 7.51-7.60 (m, 5H); ESI-MS m/z $[M+H]^+$ 506.4.

[00303] Preparation 97 6-benzyl-3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00304] A mixture of 4-((2,4-difluorophenyl)fluoromethyl)piperidine hydrochloride (74.0 mg, 0.279 mmol), 6-benzyl-3-chloro-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-b]pyrazin-2-amine TFA salt (100 mg, 0.232 mmol), sodium *tert*-butoxide (66.9 mg, 0.696 mmol), BINAP (21.7 mg, 0.035 mmol) and $Pd_2(dba)_3$ (10.6 mg, 0.012 mmol) in toluene (1.2 mL) was heated at 100 °C in a sealed tube for 14 h. The mixture was purified by HPLC Method A to give the title compound as a TFA salt (108.3 mg, 74.8%) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.23 (dd, J = 6.4, 2.4 Hz, 6H), 1.39-1.47 (m, 1H), 1.51-1.72 (m, 2H), 1.95-2.12 (m, 2H), 2.58-2.70 (m, 2H), 3.04 (br s, 2H), 3.36-3.83 (m, 4H), 4.09-4.21

(m, 3H), 4.51 (br s, 2H), 5.52 (dd, J = 46.2, 7.3 Hz, 1H), 6.97-7.07 (m, 2H), 7.45-7.59 (m, 6H); ESI-MS m/z $[M+H]^+$ 510.4.

[00305] Preparation 98 3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00306] A mixture of 6-benzyl-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (122 mg, 0.197 mmol) and $Pd(OH)_2$ on carbon (20 wt %, 12 mg, 0.017 mmol) in THF (2.0 mL) was stirred under an atmosphere of hydrogen gas (balloon) at rt. After 2 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (83.2 mg, 80%) as a yellow oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.25 (d, J = 6.6 Hz, 6H), 1.88-1.98 (m, 2H), 2.04-2.13 (m, 2H), 2.93-3.03 (m, 4H), 3.35-3.41 (m, 3H), 3.54 (t, J = 6.3 Hz, 2H), 3.76 (s, 3H), 4.14-4.18 (m, 2H), 4.18-4.23 (m, 1H), 4.32-4.40 (m, 1H), 6.67 (ddd, J = 9.0, 3.0, 1.4 Hz, 1H), 6.74 (dd, J = 12.9, 3.0 Hz, 1H), 7.07 (t, J = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 416.3.

[00307] Preparation 99 3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00308] A mixture of 6-benzyl-3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (108.3 mg, 0.174 mmol) and $Pd(OH)_2$ on carbon, (20 wt %, 11 mg, 0.016 mmol) in THF (1.7 mL) was stirred under an atmosphere of hydrogen gas (balloon) at rt. After 2 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (67.5 mg, 72.9%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.24 (dd, J = 6.6, 2.3 Hz, 6H), 1.41-1.48 (br m, 1H), 1.52-1.74 (m, 2H), 1.97-2.14 (m, 2H), 2.61-2.73 (m, 2H), 2.99 (t, J = 6.3 Hz, 2H), 3.38-3.49 (m, 2H), 3.50-3.55 (m, 2H), 4.14 (s, 2H), 4.14-4.21 (m, 1H), 5.53 (dd, J = 46.5, 7.3 Hz, 1H), 6.95-7.10 (m, 2H), 7.46-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 420.3.

[00309] Preparation 100 6-benzyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00310] A mixture of propan-2-amine (71 µL, 0.827 mmol), 6-benzyl-3-chloro-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine TFA salt (123.4 mg, 0.207 mmol), sodium *tert*-butoxide (39.7 mg, 0.413 mmol), BINAP (19.3 mg, 0.031 mmol) and $Pd_2(dba)_3$ (9.5 mg, 10.33 µmol) in toluene (690 µL) was heated at 100 °C for 16 h. The mixture was then purified by HPLC Method A to give the title compound as a TFA salt (54.7 mg, 42.7%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.22 (d, J = 6.6 Hz, 6H), 1.87-2.13 (m, 4H), 2.94-3.10 (m, 4H), 3.35-3.53 (m, 3H), 3.75 (s, 3H), 3.79-3.88 (m, 1H), 4.07-4.27 (m, 3H), 4.31-4.39 (m, 1H), 4.52 (br s, 2H), 6.66 (ddd, J = 8.9,

3.0, 1.5 Hz, 1H), 6.73 (dd, *J* = 12.9, 3.0 Hz, 1H), 7.03-7.10 (m, 1H), 7.51-7.60 (m, 5H); ESI-MS m/z $[M+H]^+$ 506.4.

[00311] Preparation 101 6-benzyl-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00312] A mixture of propan-2-amine (82 µL, 0.954 mmol), 6-benzyl-3-chloro-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine TFA (143.3 mg, 0.238 mmol), sodium *tert*-butoxide (45.8 mg, 0.477 mmol), BINAP (22.3 mg, 0.036 mmol) and $Pd_2(dba)_3$ (10.9 mg, 0.012 mmol) in toluene (800 µL) at 100 °C for 16 h. The mixture was then purified by HPLC Method A to give the title compound as a TFA salt (63.8 mg, 42.9%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.21 (dd, *J* = 6.4, 2.4 Hz, 6H), 1.40-1.48 (m, 1H), 1.51-1.74 (m, 2H), 1.95-2.16 (m, 2H), 2.61-2.73 (m, 2H), 3.00 (br s, 2H), 3.40-3.57 (m, 3H), 4.06-4.13 (m, 2H), 4.15- 4.20 (br m, 1H), 4.51 (br s, 2H), 5.52 (dd, *J* = 46.0, 7.3 Hz, 1H), 6.97-7.08 (m, 2H), 7.46-7.62 (m, 6H); ESI-MS m/z $[M+H]^+$ 510.4.

[00313] Preparation 102 2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00314] A mixture of 6-benzyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (51 mg, 0.082 mmol) and $Pd(OH)_2$ on carbon (20 wt %, 5 mg, 7.12 µmol) in THF (820 µL) was stirred under an atmosphere of hydrogen gas (balloon) at rt. After 2 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (41.2 mg, 95%) as a yellow foam. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.24 (d, *J* = 6.6 Hz, 6H), 1.88-1.98 (m, 2H), 2.05-2.14 (m, 2H), 2.94-3.03 (m, 4H), 3.35-3.43 (m, 2H), 3.54 (t, *J* = 6.3 Hz, 2H), 3.76 (s, 3H), 4.10-4.21 (m, 3H), 4.32-4.39 (m, 1H), 6.67 (ddd, *J* = 8.9, 3.0, 1.5 Hz, 1 H), 6.74 (dd, *J* = 12.8, 2.9 Hz, 1H), 7.07 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 416.3.

[00315] Preparation 103 2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00316] A mixture of 6-benzyl-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (60 mg, 0.096 mmol) and $Pd(OH)_2$ on carbon, (20 wt %, 6 mg, 8.54 µmol) in THF (960 µL) was stirred under an atmosphere of hydrogen gas (balloon) at rt. After 2 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (47.6 mg, 93%) as a yellow foam. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.23 (dd, *J* = 6.4, 2.4 Hz, 6H), 1.41-1.49 (m, 1H), 1.52-1.74 (m, 2H), 1.98-2.14 (m, 2H), 2.68 (qd, *J* = 12.6, 2.5 Hz, 2H), 2.96 (t, *J* = 6.3 Hz,

2H), 3.40-3.51 (m, 2H), 3.52 (t, J = 6.3 Hz, 2H), 4.10-4.16 (m, 1H), 4.16 (s, 2H), 5.53 (dd, J = 46.5, 7.6 Hz, 1H), 6.97-7.08 (m, 2H), 7.47-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 420.3.

[00317] Preparation 104 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00318] A mixture of 6-benzyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-N-isopropyl-5,6,7,8-tetrahydropyrido[3,4-b]pyrazin-3-amine (6.43 g, 13.03 mmol) and 10% Pd/C (640 mg) in MeOH (86 mL) under H_2 in a balloon was stirred at room temperature overnight. Removal of the solvent gave the title compound (4.4 g, 84%) as a yellow oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.24 (d, J = 6.4 Hz, 6H), 1.89-1.99 (m, 2H), 2.09-2.17 (m, 2H), 2.74 (t, J = 5.9 Hz, 2H), 2.95 (ddd, J = 12.3, 8.7, 3.4 Hz, 2H), 3.11 (t, J = 6.1 Hz, 2H), 3.82 (s, 2H), 4.14 (septet, J = 6.4 Hz, 1H), 4.46 (tt, J = 7.7, 3.5 Hz, 1H), 6.85-6.92 (m, 1H), 6.99 (ddd, J = 11.4, 8.4, 3.2 Hz, 1H), 7.18 (td, J = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 404.0.

[00319] Preparation 105 2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine

[00320] To a solution of 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone (0.367 g, 0.826 mmol) in MeOH (4 mL) was added NaOH, 15 % solution (2.201 g, 8.26 mmol) at 23 °C. The reaction mixture was stirred at 65 °C for 16 hr, cooled to 23 °C, and neutralized with 1N HCl (9.5 mL) to furnish a suspension. The crude mixture was concentrated via rotary evaporation, cooled to 23 °C, and stirred overnight. The resulting solid was filtered, rinsed with water, and dried *in vacuo* to give the title compound (253 mg, 76%) as a yellow foam. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.15 (d, J = 6.8 Hz, 6H), 2.42 (br s, 1H), 2.51-2.61 (m, 6H), 2.89-3.00 (m, 6H), 3.58 (s, 2H), 3.63 (s, 2H), 4.00-4.10 (m, 1H), 5.15 (d, J = 8.3 Hz, 1H), 7.04-7.11 (m, 1H), 7.21 (td, J = 10.0, 2.4 Hz, 1H), 7.44-7.52 (m, 1H); ESI-MS m/z $[M+H]^+$ 403.0.

[00321] Preparation 106 4-((1-(6-benzyl-2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile

[00322] A mixture of 6-benzyl-3-chloro-N-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine acetate (2.765 g, 2.93 mmol), 3-fluoro-4-(piperidin-4-yloxy)benzonitrile hydrochloride (0.904 g, 3.52 mmol), sodium *tert*-butoxide (1.128 g, 11.74 mmol), BINAP (0.274 g, 0.440 mmol), and $Pd_2(dba)_3$ (0.134 g, 0.147 mmol) in toluene (25 mL) was stirred at 100 °C for 22 h. Additional portions of BINAP (0.219 g, 0.352 mmol) and $Pd_2(dba)_3$ (0.107 g, 0.117 mmol) were added to the flask and the reaction mixture was stirred for an additional 2 days at 100 °C. The mixture was cooled to 23 °C, filtered through Celite™, rinsed with toluene, and the filtrate was concentrated via rotary evaporation. The crude

material was dissolved in DMSO (10 mL), filtered, rinsed with DMSO, and purified by HPLC Method B, with the exception that a Waters XSelect® CSH C18, 5 μm, ID 4.6 x 50 mm was used, using an ACN gradient of 30% to 70% to give the title compound as a TFA salt (581 mg, 32.2% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05-1.33 (m, 6H), 1.81-1.96 (m, 2H), 2.08-2.18 (m, 2H), 2.84-3.00 (m, 3H), 3.01-3.17 (m, 1H), 3.18-3.32 (m, 2H), 3.33-3.46 (m, 1H), 3.65-3.77 (m, 1H), 3.95-4.06 (m, 1H), 4.08-4.30 (m, 2H), 4.43-4.57 (m, 2H), 4.80-4.87 (m, 1H), 5.91 (d, J = 8.1 Hz, 1H), 7.44-7.60 (m, 6H), 7.66-7.70 (m, 1H), 7.84-7.90 (m, 1H), 10.13 (br s, 1H); ESI-MS m/z $[M+H]^+$ 501.5.

[00323] Preparation 107 3-fluoro-4-((1-(2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile

[00324] A mixture of 4-((1-(6-benzyl-2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile 2,2,2-trifluoroacetate (579 mg, 0.942 mmol) and $Pd(OH)_2$ (20 wt % Pd (dry basis) on carbon, wet, Degussa Type E101 NE/W, 198 mg, 0.283 mmol) in THF (10 mL) was stirred under H_2 (1.899 mg, 0.942 mmol) at 23 °C for 4 h. The mixture was filtered, rinsed with THF, concentrated via rotary evaporation, and dried *in vacuo* to give the title compound as a TFA salt (494 mg, 100%) as a brown oil. ESI-MS m/z $[M+H]^+$ 411.4.

[00325] Preparation 108 (5-chloro-2-fluorophenyl)(1-(2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)methanone

[00326] A mixture of (5-chloro-2-fluorophenyl)(piperidin-4-yl)methanone hydrochloride (69.7 mg, 0.251 mmol), 6-benzyl-3-chloro-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (90 mg, 0.209 mmol), sodium *tert*-butoxide (60.2 mg, 0.627 mmol), BINAP (19.5 mg, 0.031 mmol) and $Pd_2(dba)_3$ (9.6 mg, 10.4 μmol) in toluene (1.04 mL) was heated at 100 °C for 16 h. The mixture was purified by HPLC Method A to afford (1-(6-benzyl-2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)(5-chloro-2-fluorophenyl)methanone as its TFA salt (48.9 mg, 36.8%) as a yellow oil. ESI-MS m/z $[M+H]^+$ 523.4.

[00327] A mixture of (1-(6-benzyl-2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)(5-chloro-2-fluorophenyl)methanone TFA salt (48.9 mg, 0.077 mmol) and $Pd(OH)_2$ on carbon (20 wt %, 5 mg, 0.036 mmol) in THF (384 μL) was stirred at rt under an atmosphere of hydrogen gas (balloon). After 3 h, the mixture was diluted with MeOH, filtered through a pad of Celite™, washing with MeOH, and concentrated to afford he title compound as its TFA salt (37.1 mg, 88%) as a yellow film, which was used without further purification. ESI-MS m/z $[M+H]^+$ 432.3.

[00328] Preparation 109 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00329] A mixture of 4-(2,4-difluorophenoxy)piperidine hydrochloride (62.6 mg, 0.251 mmol), 6-benzyl-3-chloro-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (90 mg, 0.209 mmol), sodium *tert*-butoxide (60.2 mg, 0.627 mmol), BINAP (19.5 mg, 0.031 mmol) and $Pd_2(dba)_3$ (9.6 mg, 10.4 μmol) in toluene (1.04 mL) was heated at 100 °C for 16 h. The mixture was purified by HPLC Method A to afford 6-benzyl-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine as its TFA salt (73.0 mg, 57.5%) as a yellow oil. ESI-MS m/z $[M+H]^+$ 494.4.

[00330] A mixture of 6-benzyl-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (73.0 mg, 0.120 mmol) and $Pd(OH)_2$ on carbon (20 wt %, 7 mg, 9.97 μmol) in THF (601 μL) was stirred at rt under an atmosphere of hydrogen (balloon). After 3 h, the mixture was diluted with MeOH, filtered through a pad of Celite™, washing with MeOH, and concentrated to afford the title compound as its TFA salt (62.3 mg, 100%) as a yellow oil, which was used without further purification. ESI-MS m/z $[M+H]^+$ 404.3.

[00331] Preparation 110 *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00332] A solution of 6-benzyl-3-chloro-*N*-(2,2-difluoroethyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (150 mg, 0.331 mmol), 4-(2,4-difluorophenoxy)piperidine hydrochloride (99 mg, 0.398 mmol), $Pd_2(dba)_3$ (15.2 mg, 0.017 mmol), BINAP (20.63 mg, 0.033 mmol), and sodium *tert*-butoxide (96 mg, 0.994 mmol), in toluene (1104 μL) was stirred at 90 °C overnight. The solvent was removed and the crude product diluted in DMF, filtered through a hydrophilic PTFE 0.45 μm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give 6-benzyl-*N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine as a TFA salt (152 mg).

[00333] A solution of 6-benzyl-*N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (152 mg, 0.241 mmol) and $Pd(OH)_2$ on carbon (33.9 mg, 0.048 mmol) in THF (2.41 mL) was purged with and placed under hydrogen (balloon) atmosphere at room temperature for 2h. The mixture was then filtered through Celite™ and concentrated to give the title compound as a TFA salt (115 mg, 0.213 mmol).

[00334] Preparation 111 *N*-(tert-butyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00335] A solution of sodium *tert*-butoxide (81 mg, 0.843 mmol), 6-benzyl-*N*-(*tert*-butyl)-3-chloro-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (125 mg, 0.281 mmol), $Pd_2(dba)_3$ (12.86 mg, 0.014 mmol), 4-(2,4-difluorophenoxy)piperidine hydrochloride (84 mg, 0.337 mmol), and BINAP (17.50 mg, 0.028 mmol) in toluene (937 µL) was stirred at 90 °C overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give 6-benzyl-*N*-(*tert*-butyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine as a TFA salt (155 mg).

[00336] A solution of 6-benzyl-*N*-(*tert*-butyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (155 mg, 0.249 mmol) and $Pd(OH)_2$ on carbon (35.0 mg, 0.050 mmol) in THF (2.49 mL) was purged and placed under hydrogen (balloon) atmosphere for 2 h. Filtration through Celite™ and concentration gave the title compound as a TFA salt (125 mg).

[00337] Preparation 112 *N*-cyclobutyl-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00338] A mixture of 2,3-dichloropyrido[3,4-*b*]pyrazine (100 mg, 0.500 mmol), cyclobutanamine (47.0 µL, 0.550 mmol) and DIPEA (260 µL, 1.500 mmol) was stirred at 0 °C for 15 min then at rt for 30 min. Saturated aqueous NH_4Cl was added to the mixture and the product was extracted with EtOAc. The combined organic layers were filtered through a pad of silica (EtOAc wash) and the filtrate was concentrated to afford 3-chloro-N-cyclobutylpyrido[3,4-*b*]pyrazin-2-amine (116.1 mg, 99%) as a yellow solid, which was used without further purification. ESI-MS m/z $[M+H]^+$ 235.2.

[00339] A mixture of 3-chloro-*N*-cyclobutylpyrido[3,4-*b*]pyrazin-2-amine (116 mg, 0.494 mmol) and benzyl bromide (59.1 µL, 0.494 mmol) in ACN (2.47 mL) was heated at 80 °C for 3 h. After cooling to rt, the mixture was treated with sodium triacetoxyborohydride (314 mg, 1.483 mmol) at rt. The mixture was purified by HPLC Method A to afford 6-benzyl-3-chloro-*N*-cyclobutyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine as its TFA salt (135.3 mg, 61.8%) as a yellow solid. ESI-MS m/z $[M+H]^+$ 329.3.

[00340] A mixture of 4-(2-fluoro-4-methoxyphenoxy)piperidine hydrochloride (56.7 mg, 0.217 mmol), 6-benzyl-3-chloro-*N*-cyclobutyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (80 mg, 0.181 mmol), sodium *tert*-butoxide (52.1 mg, 0.542 mmol), BINAP (16.9 mg, 0.027 mmol) and $Pd_2(dba)_3$ (24.8 mg, 0.027 mmol) in toluene (602 µL) was

heated at 90 °C in a sealed tube for 16 h. The mixture was purified by HPLC Method A to afford 6-benzyl-*N*-cyclobutyl-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine as its TFA salt (85.2 mg, 74.7%) as a yellow foam. ESI-MS m/z $[M+H]^+$ 518.4.

[00341] A mixture of 6-benzyl-*N*-cyclobutyl-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (85.2 mg, 0.135 mmol) and $Pd(OH)_2$ on carbon (10 mg, 0.071 mmol) in THF (674 µL) was stirred at rt under an atmosphere of hydrogen gas (balloon). After 4 h, the mixture was filtered, washing with MeOH, and concentrated to afford the title compound as its TFA salt (73 mg, 100%) as a yellow solid, which was used without further purification. ESI-MS m/z $[M+H]^+$ 428.4.

[00342] Preparation 113 *N*-cyclopropyl-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00343] 2,3-Dichloro-5-methylpyrido[3,4-*b*]pyrazine (1.700 g, 7.94 mmol) was added to dioxane (15.88 mL), then cyclopropanamine (0.864 mL, 12.71 mmol) and DIPEA (2.24 mL, 13.50 mmol) were added sequentially. The mixture was stirred for 12 h at room temperature then concentrated under reduced pressure. Column chromatography using a gradient of 10% to 75% EtOAc in hexanes provided 3-chloro-*N*-cyclopropyl-5-methylpyrido[3,4-*b*]pyrazin-2-amine (1.3 g) as a brown solid.

[00344] Combined 3-chloro-*N*-cyclopropyl-5-methylpyrido[3,4-*b*]pyrazin-2-amine (350 mg, 1.491 mmol) and benzyl bromide (177 µL, 1.491 mmol) in ACN (5.97 mL) was heated at 80 °C overnight, then cooled to room temperature and sodium triacetoxyborohydride (948 mg, 4.47 mmol) was added. After stirring for 1 h, the reaction mixture was poured into 1 M NaOH, extracted with ethyl acetate (2x), concentrated *in vacuo*, and purified by HPLC Method A gave 6-benzyl-3-chloro-*N*-cyclopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine as a TFA salt (424 mg).

[00345] Combined 6-benzyl-3-chloro-*N*-cyclopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (106 mg, 0.239 mmol), 4-(2,4-difluorophenoxy)piperidine hydrochloride (65.7 mg, 0.263 mmol), $Pd_2(dba)_3$ (21.9 mg, 0.024 mmol), sodium *tert*-butoxide (57.5 mg, 0.598 mmol), and BINAP (29.8 mg, 0.048 mmol) in toluene (798 µL) was heated at 90 °C overnight. Purification by HPLC Method A gave 6-benzyl-*N*-cyclopropyl-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine as a TFA salt (110 mg).

[00346] Combined 6-benzyl-N-cyclopropyl-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (110 mg, 0.178 mmol) and

$Pd(OH)_2$ (20 wt %, 12.5 mg, 0.018 mmol) in THF (888 μL) was purged with hydrogen and allowed to stir under hydrogen (balloon) overnight. The reaction mixture was filtered through Celite™, washed with EtOAc, and concentrated under reduced pressure to give the title compound as a TFA salt (78 mg).

[00347] Preparation 114 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00348] A solution of 6-benzyl-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (150 mg, 0.241 mmol) and $Pd(OH)_2$ on carbon (16.9 mg, 0.024 mmol) in THF (1.21 mL) was purged and placed under hydrogen atmosphere (balloon) overnight. The mixture was then filtered through Celite™ and concentrated to give the title compound as its TFA salt (132 mg).

[00349] Preparation 115 *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00350] A solution of 6-benzyl-*N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (160 mg, 0.249 mmol) and $Pd(OH)_2$ on carbon (17.5 mg, 0.025 mmol) in THF (1.24 mL) was purged and placed under hydrogen atmosphere (balloon) overnight. The mixture was filtered through Celite™ and concentrated to give title compound as its TFA salt (136 mg).

[00351] Preparation 116 *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine

[00352] A solution of 2,3-dichloro-7-methylpyrido[3,4-*b*]pyrazine (125 mg, 0.584 mmol), 2,2-difluoroethanamine (53.6 μL, 0.701 mmol), and DIPEA (306 μL, 1.752 mmol) in DCM (1.17 mL) was stirred at room temperature for 48 h, then poured into a saturated aqueous solution of NH_4Cl and extracted twice with EtOAc. The extracts were combined, filtered through $MgSO_4$, and concentrated to give 3-chloro-*N*-(2,2-difluoroethyl)-7-methylpyrido[3,4-*b*]pyrazin-2-amine (143 mg, 95%).

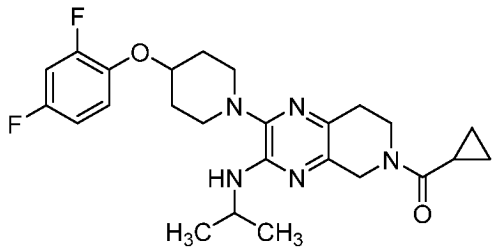
[00353] A solution of 3-chloro-*N*-(2,2-difluoroethyl)-7-methylpyrido[3,4-*b*]pyrazin-2-amine (143 mg, 0.553 mmol) and benzyl bromide (65.8 μL, 0.553 mmol) in ACN (2.76 mL) was stirred at 100 °C overnight, cooled to room temperature, then treated with sodium triacetoxyhydroborate (352 mg, 1.659 mmol) and stirred for 3 h. The mixture was poured into 1 M NaOH, extracted twice with EtOAc, and the EtOAc extracts were combined and concentrated. The crude material was diluted in DMF, filtered through a hydrophilic PTFE 0.45 μm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give 6-

benzyl-*N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine as a TFA salt (120 mg, 46.5%).

[00354] A solution of 6-benzyl-3-chloro-*N*-(2,2-difluoroethyl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (120 mg, 0.257 mmol), 4-(2,4-difluorophenoxy)piperidine hydrochloride (77 mg, 0.308 mmol), $Pd_2(dba)_3$ (23.5 mg, 0.026 mmol), BINAP (32.0 mg, 0.051 mmol), and sodium *tert*-butoxide (74.1 mg, 0.771 mmol), in toluene (1.28 mL) was stirred at 100 °C overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give 6-benzyl-*N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine as a TFA salt (135 mg, 82 %).

[00355] A solution of 6-benzyl-*N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (135 mg, 0.210 mmol) and $Pd(OH)_2$ on carbon (14.7 mg, 0.021 mmol) in THF (1.05 mL) was purged and stirred under hydrogen atmosphere for 3 h. The reaction mixture was filtered through Celite™ and the solvent was removed to give the title compound as a TFA salt (107 mg, 92%).

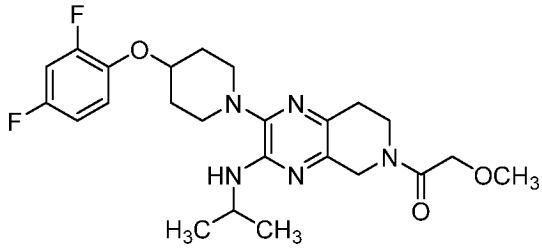
[00356] Example 1 cyclopropyl(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone



[00357] To a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (18.0 mg, 0.035 mmol) in DCM (348 µL) at room temperature was added triethylamine (14.5 µL, 0.104 mmol) and cyclopropanecarbonyl chloride (6.4 µL, 0.070 mmol). The reaction was stirred for 10 min at room temperature. The reaction mixture was concentrated under reduced pressure and was purified by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 50% to 90% ACN gradient to give the title compound, as a TFA salt, as a yellow film (3.3 mg, 16%). ^{1}H NMR (400 MHz, methanol-*d*4, mixture of rotamers) δ ppm 0.81-0.96 (m, 4H), 1.29 (m, 7H), 1.90-2.18 (m, 4H), 2.73 (m, 0.7H), 2,87

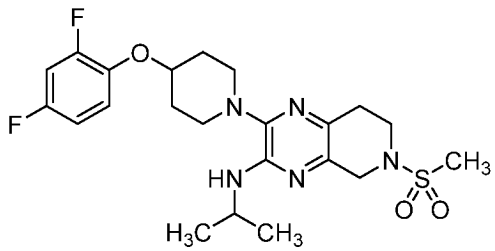
(m, 1.3H), 3.07 (m, 2H), 3.42 (m, 2H), 3.88 (m, 0.7H), 4.06 (t, J = 5.7 Hz, 1.3H), 4.14 (m, 1H), 4.49 (m, 1H), 4.62 (s, 1.3H), 4.80 (s, 0.7H), 6.88 (m, 1H), 6.99 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.18 ppm (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 472.5.

[00358] Example 2 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethan-1-one



[00359] To a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (39.0 mg, 0.075 mmol) in DCM (754 µL) at 0 °C was added triethylamine (31.5 µL, 0.226 mmol) and 2-methoxyacetyl chloride (13.8 µL, 0.151 mmol). The reaction was stirred at 0 °C for 30 min. The reaction mixture was concentrated under reduced pressure and was purified by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 55% to 80% ACN gradient to give the title compound, as a TFA salt, as a yellow oil (14.0 mg, 31.5%). ^{1}H NMR (400 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.30 (m, 6H), 1.96 (m, 2H), 2.13 (m, 2H), 2.75 (t, J = 5.7 Hz, 0.7H), 2.83 (t, J = 5.7 Hz, 1.3H), 3.08 (m, 2H), 3.44 (m, 5H), 3.77 (t, J = 5.8 Hz, 1.3H), 3.88 (t, J = 5.9 Hz, 0.7H), 4.14 (m, 1H), 4.24 (s, 0.7H), 4.28 (s, 1.3H), 4.49 (td, J = 7.1, 3.5 Hz, 1H), 4.56 (s, 0.7H), 4.63 (s, 1.3H), 6.88 (m, 1H), 6.99 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 476.5.

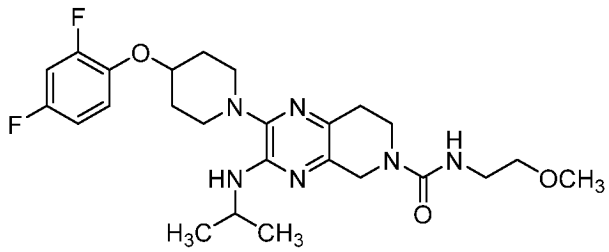
[00360] Example 3 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-N-isopropyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



[00361] A solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-N-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (735.3 mg, 1.421 mmol) in DCM (14.2 mL) at 0 °C was treated with triethylamine (0.594 mL, 4.26 mmol), followed by

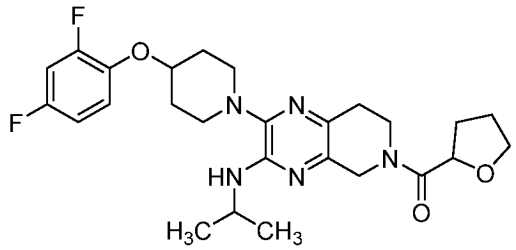
methanesulfonyl chloride (0.221 mL, 2.84 mmol). The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was taken up in MeOH, filtered through a Millipore® 0.45 µm syringe filter, and purified by HPLC Method A. The corresponding fractions were collected and concentrated under reduced pressure. The resulting residue was taken up in DCM and washed with saturated aqueous K_2CO_3 to generate the free base. The organic layer was separated, dried over Na_2SO_4, and filtered. Evaporation of the filtrate and lyophilization gave the title compound as an off-white solid (229.6 mg, 33.6%). ^{1}H NMR (500 MHz, DMSO-*d*6) 1.18 (d, *J* = 6.3 Hz, 6H), 1.88 (m, 2H), 2.07 (m, 2H), 2.75 (t, *J* = 5.9 Hz, 2H), 2.89 (m, 2H), 2.97 (s, 3H), 3.29 (m, 2H), 3.45 (t, *J* = 5.9 Hz, 2H), 4.09 (m, 1H), 4.16 (s, 2H), 4.52 (tt, *J* = 8.1, 3.9 Hz, 1H), 5.57 (d, *J* = 8.3 Hz, 1H), 7.01 (m, 1H), 7.30 (m, 2H); ESI-MS m/z $[M+H]^+$ 481.90.

[00362] Example 4 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-*N*-(2-methoxyethyl)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



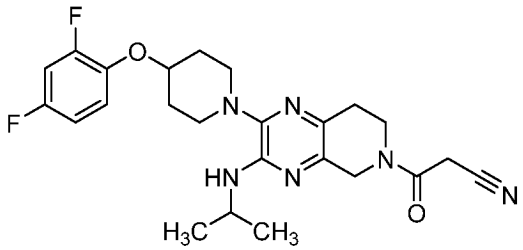
[00363] To a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (39.0 mg, 0.075 mmol) in DCM (754 µL) at 0 °C was added triethylamine (31.5 µL, 0.226 mmol) and 1-isocyanato-2-methoxyethane (11.8 µL, 0.113 mmol). The reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was concentrated under reduced pressure and purified by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 45% to 70% ACN gradient to give the title compound, as a TFA salt, as a yellow oil (24.5 mg, 52.6%). ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm 1.32 (d, *J* = 6.6 Hz, 6H), 1.97 (m, 2H), 2.14 (m, 2H), 2.77 (t, *J* = 5.8 Hz, 2H), 3.12 (m, 2H), 3.37 (m, 5H), 3.46 (m, 4H), 3.71 (t, *J* = 5.8 Hz, 2H), 4.13 (m, 1H), 4.50 (m, 3H), 6.88 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 505.6.

[00364] Example 5 (2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)(tetrahydrofuran-2-yl)methanone



[00365] To a solution of tetrahydrofuran-2-carboxylic acid (10.9 µL, 0.113 mmol) in DMA (0.35 mL) at room temperature was added DIPEA (39.5 µL, 0.226 mmol), followed by HATU (43.0 mg, 0.113 mmol). After stirring for 5 min, the reaction mixture was treated with a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (39.0 mg, 0.075 mmol) in DMA (0.4 mL). The reaction mixture was stirred at 60 °C for 30 min. The reaction mixture was allowed to cool to room temperature and was purified directly by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 55% to 80% ACN gradient to give the title compound, as a TFA salt, as a yellow oil (16.0 mg, 34.5%). ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm 1.31 (m, 6H), 1.97 (m, 4H), 2.16 (m, 4H) 2.82 (m, 2H), 3.10 (m, 2H), 3.45 (m, 2H), 3.89 (m, 4H), 4.14 (m, 1H), 4.44-4.87 (m, 4H), 6.88 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 502.6.

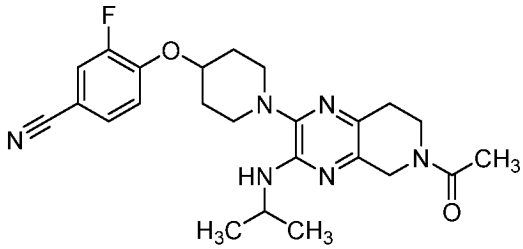
[00366] Example 6 3-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-3-oxopropanenitrile



[00367] To a solution of 2-cyanoacetic acid (8.3 mg, 0.097 mmol) in DMA (0.3 mL) at room temperature was added DIPEA (33.9 µL, 0.194 mmol), followed by HATU (36.9 mg, 0.097 mmol). This mixture was stirred for 5 min, then was treated with a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (33.5 mg, 0.065 mmol) in DMA (0.35 mL). The reaction mixture was heated at 60 °C for 30 min. The reaction mixture was purified directly by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 55% to 80% ACN gradient to give the title compound, as a TFA salt, as a yellow oil (5.5

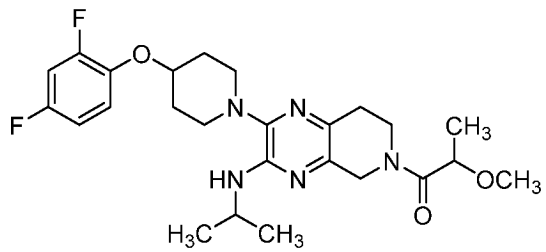
mg, 14%). ^{1}H NMR (400 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.27 (m, 6H), 1.96 (m, 2H), 2.12 (m, 2H), 2.75 (t, *J* = 5.9 Hz, 0.8H), 2.85 (m, 1.2H), 3.01 (m, 2H), 3.39 (m, 2H), 3.75 (t, *J* = 5.8 Hz, 1.2H), 3.89 (t, *J* = 5.9 Hz, 0.8H), 4.00 (m, 2H); 4.14 (m, 1H), 4.48 (m, 1H), 4.50 (s, 0.8H), 4.60 (s, 1.2H), 6.88 (m, 1H), 6.98 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 471.5.

[00368] Example 7 4-((1-(6-acetyl-3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile



[00369] To a solution of 3-fluoro-4-((1-(3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)benzonitrile TFA salt (33.5 mg, 0.064 mmol) in DCM (639 µL) at 0 °C was added pyridine (15.5 µL, 0.192 mmol), followed by acetic anhydride (12.0 µL, 0.128 mmol). The reaction was allowed to stir for 45 min, gradually warming to room temperature. The reaction was concentrated under reduced pressure and purified directly by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 40% to 70% ACN gradient to give the title compound, as a TFA salt, as a yellow solid (7.1 mg, 20%). ^{1}H NMR (400 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.31 (m, 6H), 2.02 (m, 2H), 2.20 (m, 5H), 2.74 (t, *J* = 5.9 Hz, 0.7H), 2.85 (m, 1.3H), 3.14 (m, 2H), 3.43 (m, 2H), 3.83 (t, *J* = 5.9 Hz, 1.3H), 3.87 (t, *J* = 5.9 Hz, 0.7H), 4.14 (m, 1H), 4.60 (s, 0.7H), 4.64 (s, 1.3H), 4.80 (m, 1H), 7.34 (m, 1H), 7.54 (m, 2H); ESI-MS m/z $[M+H]^+$ 453.5.

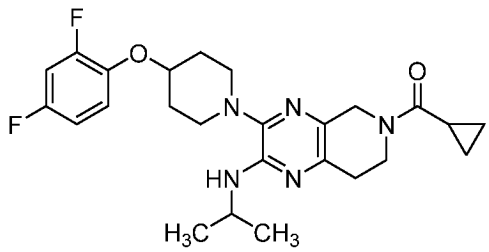
[00370] Example 8 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one



[00371] To a solution of 2-methoxypropanoic acid (10.8 µL, 0.113 mmol) in DMA (0.4 mL) at room temperature was added DIPEA (45.5 µL, 0.261 mmol) and HATU (42.9 mg, 0.113

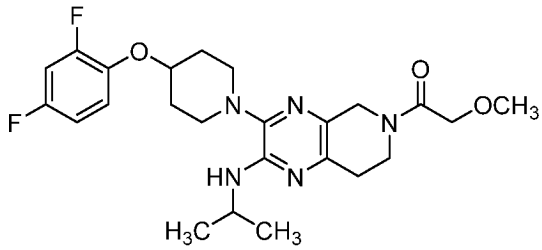
mmol). To this was added a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (45.0 mg, 0.087 mmol) in DMA (0.47 mL). The resulting reaction mixture was stirred at 60 °C for 45 min. The reaction mixture was allowed to cool to room temperature and was purified directly by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 50% to 80% ACN gradient to give the title compound, as a TFA salt, as a pale yellow solid (11.2 mg, 21.4%). ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm 1.36 (m, 9H), 1.98 (m, 2H), 2.14 (m, 2H), 2.83 (m, 2H), 3.16 (m, 2H), 3.35 (s, 3H), 3.49 (m, 2H), 3.90 (m, 1H), 3.93 (t, *J* = 5.8 Hz, 1H), 4.12 (m, 1H), 4.35 (m, 1H), 4.52 (m, 1H), 4.59-4.79 (m, 2H), 6.88 (m, 1H), 6.99 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 490.5.

[00372] Example 9 cyclopropyl(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone



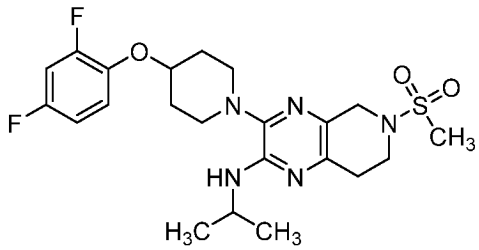
[00373] To a solution of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine 2TFA salt (34.2 mg, 0.059 mmol) and triethylamine (0.025 mL, 0.178 mmol) in DCM (0.5 mL) was added cyclopropanecarboxylic acid chloride (10.8 µL, 0.119 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then concentrated via rotary evaporation. The crude material was diluted with DMSO, filtered, rinsed with DMSO, and purified by HPLC Method B, with the exception that a Waters XSelect® CSH C18, 5 µm, ID 4.6 x 50 mm was used, using an ACN gradient of 30% to 70% to give the title compound as a TFA salt (17.7 mg, 51.0%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers) δ ppm 0.67-0.81 (m, 4H), 1.19 (d, *J* = 6.3 Hz, 6H), 1.80-1.95 (m, 2H), 2.01-2.07 (m, 2H), 2.51-2.56 (m, 1H), 2.57-2.66 (m, 0.9H), 2.72-2.79 (m, 1.1H), 2.84-2.94 (m, 2H), 3.23-3.33 (m, 2H), 3.70-3.79 (m, 0.9H), 3.92-3.98 (m, 1.1H), 4.08-4.18 (m, 1H), 4.42 (br s, 1.1H), 4.48-4.56 (m, 1H), 4.67 (br s, 0.9H), 5.71 (br s, 1H), 6.99-7.05 (m, 1H), 7.26-7.34 (m, 2H); ESI-MS m/z $[M+H]^+$ 472.5.

[00374] Example 10 1-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethan-1-one



[00375] To a solution of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (34.2 mg, 0.059 mmol) and triethylamine (0.025 mL, 0.178 mmol) in DCM (0.5 mL) was added methoxyacetyl chloride (10.8 µL, 0.119 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then concentrated via rotary evaporation. The crude material was diluted with DMSO, rinsed with DMSO, and purified by HPLC Method B, with the exception that a Waters XSelect® CSH C18, 5 µm, ID 4.6 x 50 mm was used, using an ACN gradient of 30% to 70% to give the title compound as a TFA salt (19.0 mg, 54.4%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.18 (d, J = 6.6 Hz, 6H), 1.83-1.93 (m, 2H), 2.03-2.11 (m, 2H), 2.63 (t, J = 5.8 Hz, 0.9H), 2.72 (t, J = 5.3 Hz, 1.1H), 2.84-2.93 (m, 2H), 3.22-3.36 (m, 5H), 3.66 (t, J = 5.8 Hz, 1.1H), 3.74 (t, J = 6.1 Hz, 0.9H), 4.10-4.16 (m, 1H), 4.17 (br s, 0.9H), 4.19 (s, 1.1H), 4.49-4.56 (m, 1H), 5.65-5.72 (m, 1H), 6.99-7.05 (m, 1H), 7.26-7.35 (m, 2H); ESI-MS m/z $[M+H]^+$ 476.5.

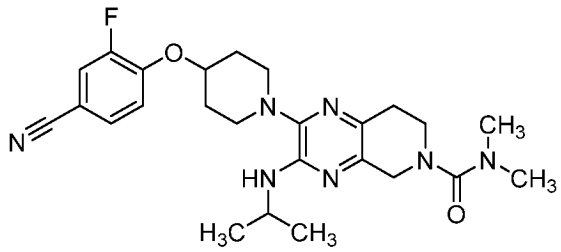
[00376] Example 11 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00377] To a solution of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-N-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (34.2 mg, 0.059 mmol) and triethylamine (0.025 mL, 0.178 mmol) in DCM (0.5 mL) was added methanesulfonyl chloride (6.9 µL, 0.089 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then concentrated via rotary evaporation. The crude material was diluted with DMSO, filtered, rinsed with DMSO, and purified by HPLC Method B, with the exception that a Waters XSelect® CSH C18, 5 µm, ID 4.6 x 50 mm was used, using an ACN gradient of 30% to 70% to give the title compound as a TFA salt (14.7 mg, 41.6%) as a yellow oil. ^{1}H NMR

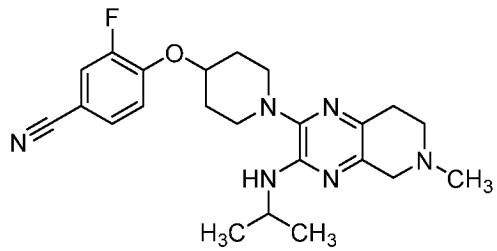
(400 MHz, DMSO-d_6) δ ppm 1.19 (d, J = 6.6 Hz, 6H), 1.82-1.93 (m, 2H), 2.02-2.08 (m, 2H), 2.77 (t, J = 5.7 Hz, 2H), 2.84-2.93 (m, 2H), 2.98 (s, 3H), 3.24-3.32 (m, 2H), 3.45 (t, J = 5.9 Hz, 2H), 4.10-4.18 (m, 3H), 4.50-4.55 (m, 1H), 5.67 (br s, 1H), 6.99-7.04 (m, 1H), 7.26-7.35 (m, 2H); ESI-MS m/z $[M+H]^+$ 482.4.

[00378] Example 12 2-(4-(4-cyano-2-fluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-*N,N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00379] A solution of 3-fluoro-4-((1-(3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)benzonitrile TFA salt (32.5 mg, 0.062 mmol) in DCM (620 µL) at 0 °C was treated with triethylamine (25.9 µL, 0.186 mmol) and dimethylcarbamic chloride (11.4 µL, 0.124 mmol). The reaction mixture was allowed to gradually warm to room temperature and stir for 1 h. The reaction mixture was concentrated under reduced pressure and purified directly by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 40% to 70% ACN gradient to give the title compound in (about 90% purity), as a TFA salt, as a yellow solid (6.8 mg, 18%). ^{1}H NMR (400 MHz, methanol-d4) δ ppm 1.29 (m, 6H), 2.02 (m, 2H), 2.19 (m, 2H), 2.81 (t, J = 5.3 Hz, 2H), 2.91 (s, 5H), 3.17 (m, 3H), 3.43 (m, 2H), 3.56 (t, J = 5.6 Hz, 2H), 4.13 (m, 1H), 4.32 (s, 2H), 4.80 (m, 1H), 7.34 (m, 1H), 7.54 (t, J = 10.9 Hz, 2H); ESI-MS m/z $[M+H]^+$ 482.5.

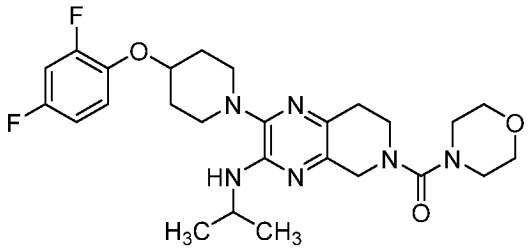
[00380] Example 13 3-fluoro-4-((1-(3-(isopropylamino)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)benzonitrile



[00381] A solution of 3-fluoro-4-((1-(3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)benzonitrile TFA salt (12.8 mg, 0.024 mmol) and formaldehyde (2.2 mg, 0.027 mmol) in MeOH (244 µL) at room temperature was treated

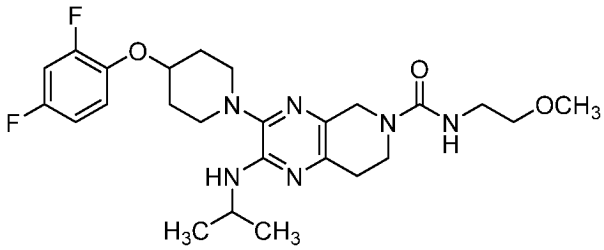
with DIPEA (8.5 µL, 0.049 mmol) and sodium triacetoxyhydroborate (10.3 mg, 0.049 mmol). The reaction mixture was stirred for 45 min at room temperature. The crude reaction mixture was purified directly by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 30% to 55% ACN gradient to give the title compound (about 90% purity), as a TFA salt, as a pale yellow solid. (6.0 mg, 46%). ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm 1.24 (d, *J* = 6.6 Hz, 6H), 1.98 (m, 2H), 2.19 (m, 2H), 3.08 (m, 7H), 3.38 (m, 3H), 3.76 (br s, 1H), 4.16 (m, 1H), 4.29 (m, 2H), 4.79 (m, 1H), 7.34 (m, 1H), 7.53 (m, 2H); ESI-MS m/z $[M+H]^+$ 425.5.

[00382] Example 14 (2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)(morpholino)methanone



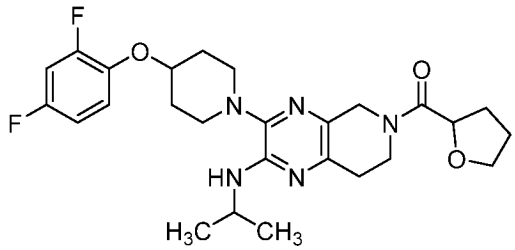
[00383] To a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (38.1 mg, 0.074 mmol) in DCM (736 µL) at 0 °C was added triethylamine (30.8 µL, 0.221 mmol), followed by morpholine-4-carbonyl chloride (17.2 µL, 0.147 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 30 min. The reaction mixture was concentrated under reduced pressure and purified directly by HPLC Method B, with the exception that a Phenomenex Gemini® C18, 5 µm, ID 30 x 75 mm column was used, using a 50% to 75% ACN gradient to give the title compound, as a TFA salt, as a yellow solid (11.9 mg, 25.6%). ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm 1.31 (d, *J* = 6.6 Hz, 6H), 1.96 (m, 2H), 2.13 (m, 2H), 2.81 (t, *J* = 5.8 Hz, 2H), 3.10 (m, 2H), 3.33 (m, 4H), 3.45 (m, 2H), 3.59 (t, *J* = 5.9 Hz, 2H), 3.70 (m, 4H), 4.13 (m, 1H), 4.37 (s, 2H), 4.50 (tt, *J* = 7.2, 3.5 Hz, 1H), 6.88 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 517.5.

[00384] Example 15 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-N-(2-methoxyethyl)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00385] To a solution of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (42.8 mg, 0.070 mmol) and triethylamine (0.029 mL, 0.211 mmol) in DCM (0.75 mL) was added 1-isocyanato-2-methoxyethane (11.0 µL, 0.105 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then concentrated via rotary evaporation. The crude material was diluted with DMSO, filtered, rinsed with DMSO, and purified by HPLC Method B, with the exception that a Waters XSelect® CSH C18, 5 µm, ID 4.6 x 50 mm was used, using an ACN gradient of 30% to 70% to give the title compound as a TFA salt (26.3 mg, 60.5%) as a hygroscopic, yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (d, J = 6.3 Hz, 6H), 1.83-1.93 (m, 2H), 2.02-2.11 (m, 2H), 2.61 (t, J = 5.6 Hz, 2H), 2.82-2.93 (m, 2H), 3.14-3.21 (m, 2H), 3.23 (s, 3H), 3.24-3.31 (m, 2H), 3.31-3.37 (m, 2H), 3.60 (t, J = 5.8 Hz, 2H), 4.08-4.17 (m, 1H), 4.29 (s, 2H), 4.49-4.56 (m, 1H), 5.61-5.70 (m, 1H), 6.66-6.73 (m, 1H), 6.99-7.05 (m, 1H), 7.26-7.34 (m, 2H); ESI-MS m/z $[M+H]^+$ 505.0.

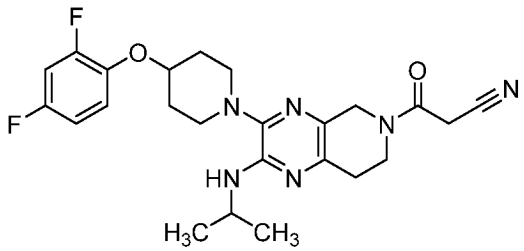
[00386] Example 16 (3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)(tetrahydrofuran-2-yl)methanone



[00387] To a suspension of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (42.8 mg, 0.070 mmol), 2-tetrahydrofuroic acid (10.1 µL, 0.105 mmol), HATU (40.0 mg, 0.105 mmol) in DMA (0.75 mL) was added DIPEA (0.037 mL, 0.211 mmol) at 23 °C. The mixture was stirred at 60 °C for 30 min, cooled to 23 °C, filtered, rinsed with DMSO, and purified by HPLC Method B, with the exception that a Waters XSelect® CSH C18, 5 µm, ID 4.6 x 50 mm was used, using an ACN gradient of 30% to 70% to give the title compound as a TFA salt (20.8 mg, 48.1%) as a hygroscopic, yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.19

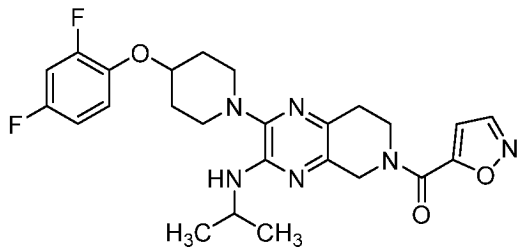
(d, J = 6.3 Hz, 6H), 1.78-1.94 (m, 4H), 1.97-2.13 (m, 4H), 2.63 (t, J = 5.7 Hz, 0.9H), 2.71-2.77 (m, 1.1H), 2.85-2.95 (m, 2H), 3.24-3.33 (m, 2H), 3.69-3.85 (m, 4H), 4.11 (dt, J = 12.9, 6.4 Hz, 1H), 4.38-4.57 (m, 3H), 4.75 (ddd, J = 14.0, 7.8, 5.7 Hz, 1H), 5.81 (br s, 1H), 6.99-7.05 (m, 1H), 7.25-7.34 (m, 2H); ESI-MS m/z $[M+H]^+$ 502.5.

[00388] Example 17 3-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-3-oxopropanenitrile



[00389] To a suspension of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (42.8 mg, 0.070 mmol), cyanoacetic acid (9.0 mg, 0.105 mmol), HATU (40.0 mg, 0.105 mmol) in DMA was added DIPEA (36.7 µL, 0.211 mmol) at 23 °C. The mixture was stirred at 60 °C for 30 min, cooled to 23 °C, filtered, rinsed with DMSO, and purified by HPLC Method B, with the exception that a Waters XSelect® CSH C18, 5 µm, ID 4.6 x 50 mm was used, using an ACN gradient of 30% to 70% to give the title compound as a TFA salt (21.0 mg, 51.2%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.19 (d, J = 6.6 Hz, 6H), 1.80-1.96 (m, 2H), 2.00-2.17 (m, 2H), 2.64 (t, J = 5.6 Hz, 0.9H), 2.76 (t, J = 5.7 Hz, 1.1H), 2.84-2.97 (m, 2H), 3.22-3.34 (m, 2H), 3.64 (t, J = 5.8 Hz, 1.1H), 3.75 (t, J = 5.9 Hz, 0.9H), 4.08-4.14 (m, 1H), 4.16 (s, 0.9H), 4.17 (s, 1.1H), 4.37 (s, 0.9H), 4.43 (s, 1.1H), 4.48-4.57 (m, 1H), 5.76 (br s, 1H), 6.98-7.06 (m, 1H), 7.24-7.36 (m, 2H); ESI-MS m/z $[M+H]^+$ 471.5.

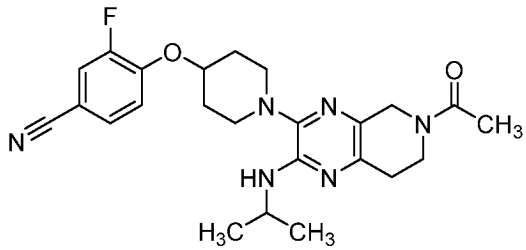
[00390] Example 18 (2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)(isoxazol-5-yl)methanone



[00391] A solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (38.1 mg, 0.074 mmol) in DCM (736 µL) at 0 °C was treated with triethylamine (30.8 µL, 0.221 mmol), followed by isoxazole-5-

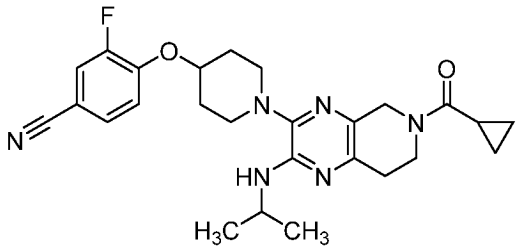
carbonyl chloride (14.2 µL, 0.147 mmol). The reaction mixture was allowed to warm to room temperature and stir for 45 min. The reaction mixture was concentrated under reduced pressure and purified directly by HPLC Method B, with the exception that a Phenomenex Gemini® C18, 5 µm, ID 30 x 75 mm column was used, using a 55% to 90% ACN gradient to give the title compound, as a TFA salt, as a tan oil (18.6 mg, 41.2%). ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm 1.30 (m, 6H), 1.96 (m, 2H), 2.13 (m, 2H), 2.89 (m, 2H), 3.11 (m, 2H), 3.46 (m, 2H), 3.91-4.21 (m, 3H), 4.49 (m, 1H), 4.78 (br s, 2H), 6.87 (m, 1H), 6.92 (s, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H), 8.55 (s, 1H); ESI-MS m/z $[M+H]^+$ 499.5.

[00392] Example 19 4-((1-(6-acetyl-2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile



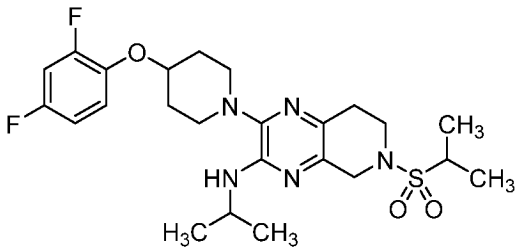
[00393] To a solution of 3-fluoro-4-((1-(2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile TFA salt (98.6 mg, 0.094 mmol) and triethylamine (0.039 mL, 0.283 mmol) in DCM (1.0 mL) was added acetyl chloride (0.013 mL, 0.188 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then concentrated via rotary evaporation. The crude material was diluted with DMSO, filtered, rinsed with DMSO, and purified by HPLC Method B, with the exception that a Waters XSelect® CSH C18, 5 µm, ID 4.6 x 50 mm was used, using an ACN gradient of 30% to 70% to give the title compound as a TFA salt (8.7 mg, 16%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.18 (d, *J* = 6.6 Hz, 6H), 1.86-1.96 (m, 2H), 2.08 (s, 1.3H), 2.09 (s, 1.7H), 2.10-2.21 (m, 2H), 2.61 (t, *J* = 5.6 Hz, 0.9H), 2.73 (t, *J* = 5.2 Hz, 1.1H), 2.88-2.98 (m, 2H), 3.23-3.31 (m, 2H), 3.66-3.76 (m, 2H), 4.09-4.17 (m, 1H), 4.40 (s, 1.1H), 4.43 (s, 0.9H) 4.80-4.87 (m, 1H), 5.59-5.67 (m, 1H), 7.50 (t, *J* = 8.6 Hz, 1H), 7.68 (dq, *J* = 8.6, 1.7 Hz, 1H), 7.86 (dt, *J* = 11.2, 1.7 Hz, 1H); ESI-MS m/z $[M+H]^+$ 453.5.

[00394] Example 20 4-((1-(6-(cyclopropanecarbonyl)-2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile



[00395] To a solution of 3-fluoro-4-((1-(2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile TFA salt (98.6 mg, 0.094 mmol) and triethylamine (0.039 mL, 0.283 mmol) in DCM (0.5 mL) was added cyclopropanecarboxylic acid chloride (0.017 mL, 0.188 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and then concentrated via rotary evaporation. The crude material was diluted with DMSO, filtered, rinsed with DMSO, and purified by HPLC Method B, with the exception that a Waters XSelect® CSH C18, 5 µm, ID 4.6 x 50 mm was used, using an ACN gradient of 30% to 70% to give the title compound as a TFA salt (8.1 mg, 15%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers) δ ppm 0.69-0.79 (m, 4H), 1.18 (d, J = 6.6 Hz, 6H), 1.91 (dd, J = 19.5, 5.6 Hz, 2H), 2.13 (dd, J = 14.3, 6.2 Hz, 2H), 2.52-2.53 (m, 1H), 2.57-2.64 (m, 0.9H), 2.75 (t, J = 6.2 Hz, 1.1H), 2.88-2.99 (m, 2H), 3.22-3.31 (m, 2H), 3.72-3.77 (m, 0.9H), 3.95 (t, J = 5.8 Hz, 1H), 4.10-4.16 (m, 1H), 4.42 (br s, 1.1H), 4.67 (br s, 0.9H), 4.80-4.87 (m, 1H), 5.61-5.67 (m, 1H), 7.50 (t, J = 8.5 Hz, 1H), 7.65-7.70 (m, 1H), 7.86 (dd, J = 11.2, 1.9 Hz, 1H); ESI-MS m/z $[M+H]^+$ 479.5.

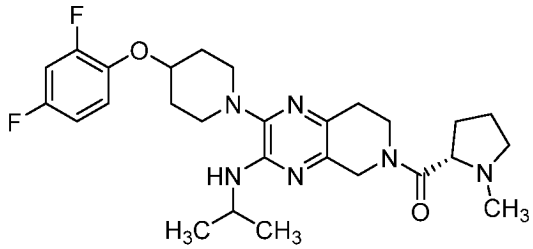
[00396] Example 21 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-6-(isopropylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



[00397] A solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (47 mg, 0.091 mmol) in DCM (908 µL) at 0 °C was treated with triethylamine (38.0 µL, 0.272 mmol), followed by propane-2-sulfonyl chloride (15.3 µL, 0.136 mmol). The reaction mixture was allowed to stir for 45 min, gradually warming to room temperature. The reaction mixture was concentrated under reduced pressure and was purified by HPLC Method B, with the exception that a Waters SunFire™ C18, 5 µm, ID 30 x 75 mm column was used, using a 60% to 95% ACN gradient

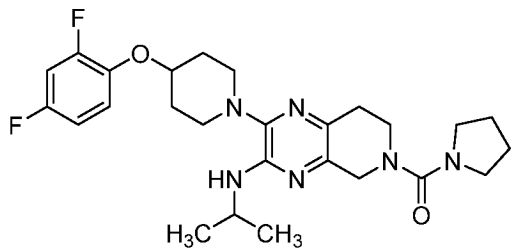
to give the title compound, as a TFA salt, as a yellow oil (16.4 mg, 29.0%). ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm 1.29 (d, *J* = 6.6 Hz, 6H), 1.35 (d, *J* = 6.8 Hz, 6H), 1.95 (m, 2H), 2.13 (m, 2H), 2.82 (t, *J* = 5.9 Hz, 2H), 3.07 (m, 2H), 3.42 (m, 3H), 3.67 (t, *J* = 5.8 Hz, 2H), 4.12 (septet, *J* = 6.5 Hz, 1H), 4.41 (s, 2H), 4.48 (dt, *J* = 7.5, 3.6 Hz, 1H) 6.87 (m, 1H), 6.98 (ddd, *J* = 11.3, 8.5, 2.9 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 510.5.

[00398] Example 22 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-6-(methyl-L-prolyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine



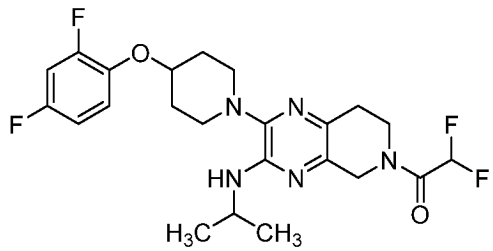
[00399] A solution of (*S*)-1-methylpyrrolidine-2-carboxylic acid (16.8 mg, 0.130 mmol) in DMA (0.4 mL) was treated with HATU (49.6 mg, 0.130 mmol) and DIPEA (45.6 µL, 0.261 mmol) at room temperature. To this was added a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (45 mg, 0.087 mmol) in DMA (0.47 mL). The reaction mixture was stirred at 60 °C for 45 min. The reaction mixture was allowed to cool to room temperature and was purified directly directly by HPLC Method B, with the exception that a Phenomenex Gemini® C18, 5 µm, ID 30 x 75 mm column was used, using a 25% to 60% ACN gradient to give the title compound, as a TFA salt, as a white solid (2.8 mg, 5.1%). ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm 1.26 (dd, *J* = 6.6, 4.5 Hz, 6H), 1.97 (m, 4H), 2.09 (m, 3H), 2.24 (m, 1H), 2.76 (m, 3H), 2.93 (app d, *J* = 7.6 Hz, 3H), 3.03 (m, 2H), 3.20 (m, 1H), 3.40 (m, 2H), 3.69-4.19 (m, 4H), 4.48 (m, 2H), 4.66 (m, 2H), 6.87 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 515.6.

[00400] Example 23 (2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)(pyrrolidin-1-yl)methanone



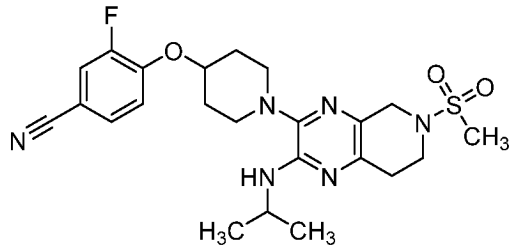
[00401] A solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (45 mg, 0.087 mmol) in DCM (870 µL) at 0 °C was treated with triethylamine (36.4 µL, 0.261 mmol), followed by pyrrolidine-1-carbonyl chloride (19.2 µL, 0.174 mmol). The reaction mixture was allowed to stir for 30 min, gradually warming to room temperature. The reaction mixture was concentrated under reduced pressure and purified directly by HPLC Method B, with the exception that a Phenomenex Gemini® C18, 5 µm, ID 30 x 75 mm column was used, using a 50% to 80% ACN gradient to give the title compound, as a TFA salt, as a pale yellow solid (10.6 mg, 19.8%). ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm 1.33 (d, *J* = 6.3 Hz, 6H), 1.89 (m, 4H), 1.97 (m, 2H), 2.14 (m, 2H), 2.81 (t, *J* = 5.8 Hz, 2H), 3.13 (m, 2H), 3.46 (m, 6H), 3.61 (t, *J* = 5.8 Hz, 2H), 4.12 (septet, *J* = 6.4 Hz, 1H), 4.38 (s, 2H), 4.51 (tt, *J* = 7.2, 3.6 Hz, 1H), 6.88 (m, 1H), 6.99 (ddd, *J* = 11.4, 8.5, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 501.6.

[00402] Example 24 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethan-1-one



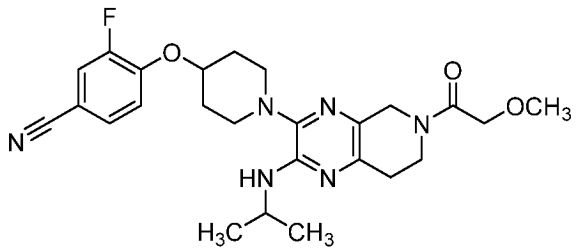
[00403] A solution of 2,2-difluoroacetic acid (8.2 µL, 0.13 mmol) in DMA (0.4 mL) was treated with HATU (49.6 mg, 0.130 mmol) and DIPEA (45.6 µL, 0.261 mmol). To this was added a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (45 mg, 0.087 mmol) in DMA (0.47 mL). The reaction mixture was heated at 60 °C for 50 min. The reaction mixture was allowed to cool to room temperature and was purified directly by HPLC Method B, with the exception that a Phenomenex Gemini® C18, 5 µm, ID 30 x 75 mm column was used, using a 55% to 90% ACN gradient to give the title compound, as a TFA salt, as a yellow solid (10.0 mg, 19.3%). ^{1}H NMR (400 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.28 (m, 6H), 1.96 (m, 2H), 2.12 (m, 2H), 2.79 (t, *J* = 5.9 Hz, 0.7H), 2.85 (t, *J* = 5.8 Hz, 1.3H), 3.05 (m, 2H), 3.42 (m, 2H), 3.92 (dt, *J* = 11.3, 5.8 Hz, 2H), 4.15 (m, 1H), 4.48 (m, 1H), 4.65 (s, 2H), 6.56 (m, 1H), 6.88 (m, 1H), 6.98 (ddd, *J* = 11.3, 8.5, 2.9 Hz, 1H), 7.17 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 482.5.

[00404] Example 25 3-fluoro-4-((1-(2-(isopropylamino)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile



[00405] To a solution of 3-fluoro-4-((1-(2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile TFA salt (98.6 mg, 0.094 mmol) and triethylamine (0.039 mL, 0.283 mmol) in DCM (1.0 mL) was added methanesulfonyl chloride (10.9 µL, 0.141 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and then concentrated via rotary evaporation. The crude material was diluted with DMSO, filtered, rinsed with DMSO, and purified by HPLC Method B, with the exception that a Waters XSelect® CSH C18, 5 µm, ID 4.6 x 50 mm was used, using an ACN gradient of 30% to 70% to give the title compound as a TFA salt (3.5 mg, 6.2%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (d, J = 6.3 Hz, 6H), 1.88-1.96 (m, 2H), 2.09-2.16 (m, 2H), 2.76 (t, J = 5.9 Hz, 2H), 2.89-2.96 (m, 2H), 2.97 (s, 3H), 3.24-3.30 (m, 2H), 3.45 (t, J = 5.9 Hz, 2H), 4.10-4.16 (m, 3H), 4.81-4.85 (m, 1H), 5.66 (d, J = 8.3 Hz, 1H), 7.50 (t, J = 8.7 Hz, 1H), 7.68 (ddd, J = 8.6, 2.0, 1.3 Hz, 1H), 7.86 (dd, J = 11.4, 2.0 Hz, 1H); ESI-MS m/z $[M+H]^+$ 489.5.

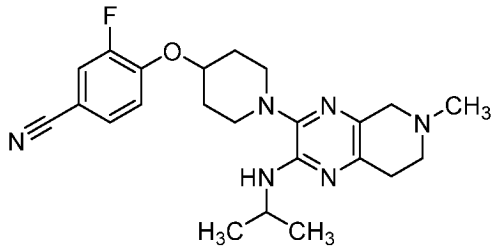
[00406] Example 26 3-fluoro-4-((1-(2-(isopropylamino)-6-(2-methoxyacetyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile



[00407] To a solution of 3-fluoro-4-((1-(2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-b]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile 2,2,2-trifluoroacetate (98.6 mg, 0.094 mmol) and triethylamine (0.039 mL, 0.283 mmol) in DCM (1.0 mL) was added methoxyacetyl chloride (0.017 mL, 0.188 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and then concentrated via rotary evaporation. The crude material was diluted with DMSO, filtered, rinsed with DMSO, and purified by HPLC Method B, with the exception that a

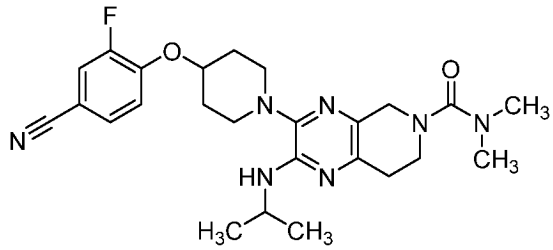
Waters XSelect® CSH C18, 5 μm, ID 4.6 x 50 mm was used, using an ACN gradient of 30% to 70% to give the title compound as a TFA salt (2.9 mg, 5.2%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.18 (d, J = 6.6 Hz, 6H), 1.87-1.97 (m, 2H), 2.08-2.16 (m, 2H), 2.62 (t, J = 5.8 Hz, 0.9H), 2.72 (t, J = 6.1 Hz, 1.1H), 2.89-2.97 (m, 2H), 3.22-3.28 (m, 1H), 3.29 (br s, 1.3H), 3.30 (s, 1.7H), 3.64-3.67 (m, 1.1H), 3.72-3.75 (m, 0.9H), 4.10-4.16 (m, 1H), 4.17 (br s, 0.9H), 4.19 (s, 1.1H), 4.36 (br s, 0.9H), 4.41 (s, 1.1H), 4.80-4.86 (m, 1H), 5.58-5.63 (m, 1H), 7.50 (t, J = 8.7 Hz, 1H), 7.66-7.70 (m, 1H), 7.87 (dd, J =11.2, 1.9 Hz, 1H); ESI-MS m/z $[M+H]^+$ 483.5.

[00408] Example 27 3-fluoro-4-((1-(2-(isopropylamino)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile



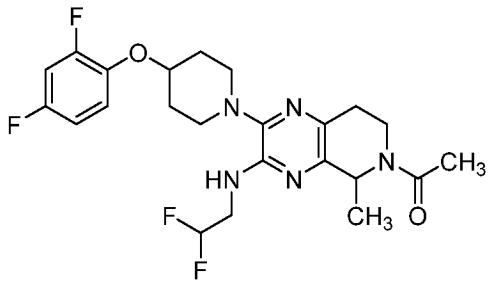
[00409] To a solution of 3-fluoro-4-((1-(2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile TFA salt (20.7 mg, 0.039 mmol) and formaldehyde (3.2 μL, 0.043 mmol) in MeOH (0.5 mL) was added DIPEA (0.014 mL, 0.079 mmol) and sodium triacetoxyborohydride (16.7 mg, 0.079 mmol) at 23 °C. The mixture was stirred at 23 °C for 2 hr and then concentrated via rotary evaporation. The crude material was diluted with DMSO, filtered, rinsed with DMSO, and purified by with the exception that a Waters XSelect® CSH C18, 5 μm, ID 4.6 x 50 mm was used, using a 30% to 40% ACN gradient to give the title compound as a TFA salt (5.3 mg, 25%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.16-1.24 (m, 6H), 1.87-1.96 (m, 2H), 2.08-2.16 (m, 2H), 2.74-2.85 (m, 0.9H), 2.85-2.92 (m, 1.1H), 2.95 (br s, 1.3H), 2.96 br s, 1.7H), 2.97-3.00 (m, 1H), 3.25-3.42 (m, 3H), 3.65-3.71 (m, 1H), 4.12-4.19 (m, 2H), 4.25-4.31 (m, 1H), 4.82-4.88 (m, 1H), 5.89 (d, J = 8.3 Hz, 1H), 7.50 (t, J = 8.6 Hz, 1H), 7.66-7.71 (m, 1H), 7.87 (dd, J = 11.4, 2.0 Hz, 1H), 9.96 (br s, 1H); ESI-MS m/z $[M+H]^+$ 425.5.

[00410] Example 28 3-(4-(4-cyano-2-fluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-N,N-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00411] To a solution of 3-fluoro-4-((1-(2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile TFA salt (20.7 mg, 0.039 mmol) and triethylamine (0.017 mL, 0.118 mmol) in DCM (0.5 mL) was added dimethylcarbamoyl chloride (7.3 µL, 0.079 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and then concentrated via rotary evaporation. The crude material was diluted with DMSO, filtered, rinsed with DMSO, and purified by HPLC Method B, with the exception that a Waters XSelect® CSH C18, 5 µm, ID 4.6 x 50 mm was used, using a 30% to 70% ACN gradient to give the title compound as a TFA salt (11.6 mg, 49.4%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.13-1.26 (m, 6H), 1.87-1.96 (m, 2H), 2.08-2.16 (m, 2H), 2.81-2.99 (m, 6H), 3.25-3.42 (m, 3H), 3.65-3.71 (m, 1H), 4.12-4.19 (m, 2H), 4.25-4.31 (m, 1H), 4.82-4.88 (m, 1H), 5.89 (d, J = 8.3 Hz, 1H), 7.50 (t, J = 8.6 Hz, 1H), 7.66-7.71 (m, 1H), 7.87 (dd, J = 11.4, 2.0 Hz, 1H), 9.96 (br s, 1H); ESI-MS m/z $[M+H]^+$ 482.5.

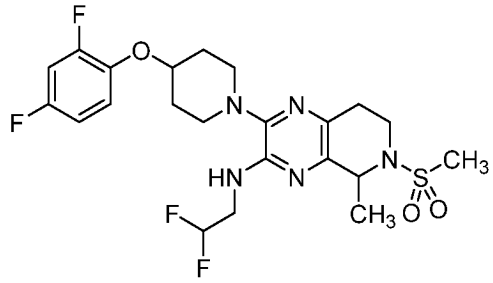
[00412] Example 29 1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00413] A solution of *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (15 mg, 0.027 mmol), DIPEA (14.20 µL, 0.081 mmol), and acetic anhydride (3.8 µL, 0.041 mmol) in DCM (271 µL) was stirred at room temperature overnight. Purification by HPLC Method A gave the title compound as a TFA salt (8.9 mg) as an off-white film. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.45 (d, J = 6.8 Hz, 1.9H), 1.58 (d, J = 6.8 Hz, 1.1H), 1.93-2.02 (m, 2H), 2.14 (dd, J = 12.7, 3.4 Hz, 2H), 2.19-2.23 (m, 3H), 2.62-2.83 (m, 1.5H), 2.87-3.08 (m, 3.2H), 3.35-3.43 (m, 2H), 3.48-3.55 (m, 0.7H), 3.78 (sxtd, J = 14.4, 4.2 Hz, 2H), 4.06 (dd, J = 14.2, 5.4 Hz, 0.6H), 4.46 (dt, J = 7.6, 3.5, Hz, 1H), 4.73 (dd, J = 13.2, 5.4 Hz,

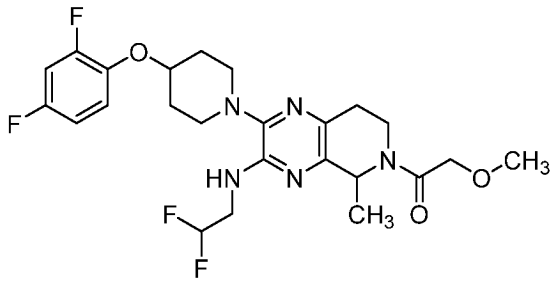
0.4H), 5.34 (q, *J* = 6.8 Hz, 0.6H), 5.92-5.97 (m, 1H), 6.06 (dt, *J* = 9.0, 4.3, Hz, 1H), 6.15-6.20 (m, 1H), 6.86-6.91 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.5, 3.2 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 482.

[00414] Example 30 *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



[00415] A solution of *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (15 mg, 0.027 mmol), DIPEA (14.2 µL, 0.081 mmol), and methanesulfonyl chloride (3.2 µL, 0.041 mmol) in DCM (271 µL) was stirred overnight. Purification by HPLC Method A gave the title compound as a TFA salt (6.4 mg) as a white film. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 1.54 (d, *J* = 6.8 Hz, 3H), 1.91-2.02 (m, 2H), 2.07-2.19 (m, 2H), 2.66 (dd, *J* = 16.8, 3.2 Hz, 1H), 2.91 (s, 3H), 2.93-3.06 (m, 3H), 3.34-3.48 (m, 3H), 3.68-3.88 (m, 2H), 3.98 (dd, *J* = 14.2, 6.4 Hz, 1H), 4.45 (dt, *J* = 7.4, 3.8, Hz, 1H), 4.77 (q, *J* = 6.8 Hz, 1H), 5.87-6.21 (m, 1H), 6.82-6.92 (m, 1H), 6.98 (ddd, *J* = 11.4, 8.7, 2.9 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 518.80.

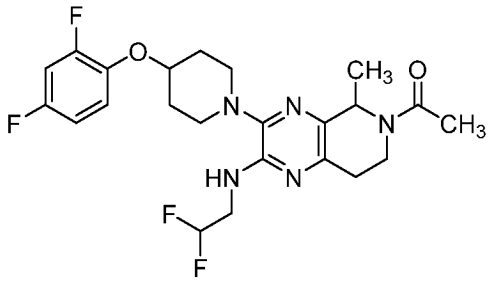
[00416] Example 31 1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethanone



[00417] A solution of 2-methoxyacetic acid (2.4 mg, 0.027 mmol), HATU (10.3 mg, 0.027 mmol), and DIPEA (14.2 µL, 0.081 mmol) in DMF (271 µl) was stirred at room temperature for 10 min. To this was then added *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (15 mg, 0.027 mmol) in DCM (271 µL) and the reaction mixture was stirred

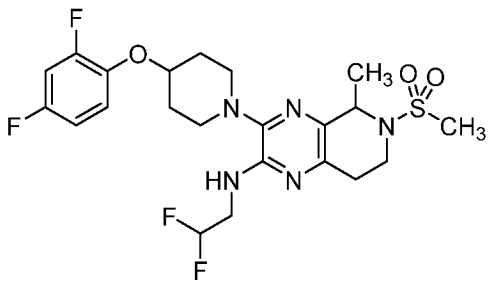
overnight. Purification by HPLC Method A afforded the title compound as a TFA salt (7.4 mg) as an off-white film. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.47 (d, *J* = 6.8 Hz, 2H), 1.58 (d, *J* = 6.8 Hz, 1H), 1.93-2.03 (m, 2H), 2.10-2.18 (m, 2H), 2.63-3.06 (m, 4.1H), 3.12 (td, *J* = 12.9, 3.9 Hz, 0.3H), 3.36-3.51 (m, 5.6H), 3.70-3.88 (m, 2H), 4.02 (dd, *J* = 13.9, 5.6 Hz, 0.7H), 4.18-4.33 (m, 2H), 4.46 (dt, *J* = 7.3, 3.7 Hz, 1H), 4.71 (dd, *J* = 13.4, 5.6 Hz, 0.3H), 4.79-4.84 (m, 0.3H), 5.30 (q, *J* = 6.8 Hz, 0.7H), 5.91-6.21 (m, 1H), 6.85-6.92 (m, 1H), 6.99 (ddd, *J* = 11.3, 8.7, 2.9 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 512.85.

[00418] Example 32 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00419] The title compound was prepared as an off-white film in a manner similar to Example 29 using *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.43 (d, *J* = 6.8 Hz, 1.8H), 1.56 (d, *J* = 6.8 Hz, 1.2H), 1.95-2.03 (m, 2H), 2.10-2.23 (m, 5H), 2.63-2.83 (m, 1.6H), 2.88-3.10 (m, 3.2H), 3.35-3.47 (m, 2H), 3.48-3.57 (m, 0.5H), 3.78 (td, *J* = 14.4, 4.4 Hz, 2H), 4.05 (dd, *J* = 13.9, 5.6 Hz, 0.6H), 4.42-4.51 (m, 1H), 4.73 (dd, *J* = 13.7, 5.9 Hz, 0.6H), 5.35 (q, *J* = 6.7 Hz, 0.5H), 5.92-6.20 (m, 1H), 6.84-6.93 (m, 1H), 6.96-7.04 (m, 1H), 7.14-7.23 (m, 1H); ESI-MS m/z $[M+H]^+$ 482.

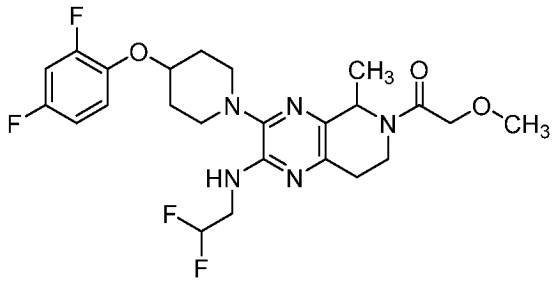
[00420] Example 33 *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00421] The title compound was prepared as a white film in a manner similar to Example 30 using *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-

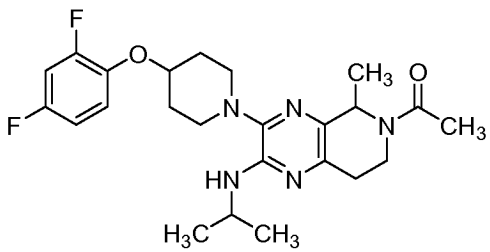
tetrahydropyrido[3,4-*b*]pyrazin-2-amine. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 1.52 (d, *J* = 6.8 Hz, 3H), 1.91-2.01 (m, 2H), 2.08-2.19 (m, 2H), 2.66 (dd, *J* = 17.1, 2.9 Hz, 1H), 2.91 (s, 3H), 2.93-3.08 (m, 3H), 3.34-3.48 (m, 3H), 3.77 (td, *J* = 14.4, 4.4 Hz, 2H), 3.97 (dd, *J* = 14.2, 6.4 Hz, 1H), 4.40-4.51 (m, 1H), 4.78 (q, *J* = 6.7 Hz, 1H), 5.88-6.21 (m, 1H), 6.82-6.92 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.3, 2.9 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 518.80.

[00422] Example 34 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethanone



[00423] The title compound was prepared as an off-white film in a manner similar to Example 31 using *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.45 (d, *J* = 6.8 Hz, 2H), 1.56 (d, *J* = 6.8 Hz, 1H), 1.93-2.02 (m, 2H), 2.11-2.18 (m, 2H), 2.63-3.18 (m, 4.5H), 3.35-3.51 (m, 5.5H), 3.78 (td, *J* = 14.5, 4.1 Hz, 2H), 4.01 (dd, *J* = 13.7, 5.4 Hz, 0.7H), 4.19-4.33 (m, 2H), 4.47 (dd, *J* = 7.3, 3.9 Hz, 1H), 4.70 (dd, *J* = 13.2, 5.9 Hz, 0.3H), 4.80-4.84 (m, 0.3H), 5.31 (q, *J* = 6.7 Hz, 0.7H), 5.93-6.20 (m, 1H), 6.85-6.92 (m, 1 H), 6.99 (ddd, *J* = 11.3, 8.7, 2.9 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 512.80.

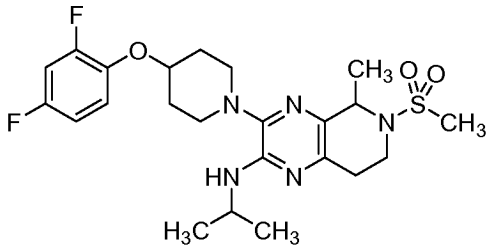
[00424] Example 35 1-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00425] The title compound was prepared as a light yellow film in a manner similar to Example 29 using 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.30-1.36 (m, 6H), 1.45 (d, *J* = 6.8 Hz, 1.8H), 1.58 (d, *J* = 6.8

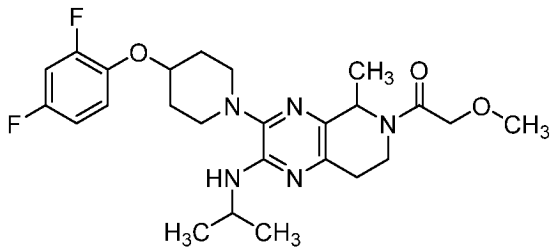
Hz, 1.2H), 1.98 (d, *J* = 6.8 Hz, 2H), 2.15 (dd, *J* = 8.5, 4.6 Hz, 2H), 2.19-2.23 (m, 3H), 2.70-2.85 (m, 1.4H), 2.91-3.17 (m, 3.3H), 3.44-3.57 (m, 2.7H), 4.06-4.19 (m, 1.6H), 4.48-4.55 (m, 1H), 4.76 (dd, *J* = 13.7, 5.4 Hz, 0.4H), 5.35 (q, *J* = 6.8 Hz, 0.6H), 6.86-6.92 (m, 1H), 7.00 (ddd, *J* = 11.3, 8.7, 2.9 Hz, 1H), 7.19 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 460.2.

[00426] Example 36 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00427] The title compound was prepared as an off-white film in a manner similar to Example 30 using 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 1.25-1.31 (m, 6H), 1.52 (d, *J* = 6.4 Hz, 3H), 1.90-2.02 (m, 2H), 2.09-2.19 (m, 2H), 2.70 (dd, *J* = 17.3, 3.2 Hz, 1H), 2.88-3.13 (m, 6H), 3.37-3.50 (m, 3H), 3.98 (dd, *J* = 14.2, 6.4 Hz, 1H), 4.15 (dt, *J* = 13.1, 6.4 Hz, 1H), 4.48 (dt, *J*=7.4, 3.8 Hz, 1H), 4.77 (q, *J* = 7.0 Hz, 1H), 6.84-6.92 (m, 1H), 6.99 (ddd, *J* = 11.4, 8.7, 2.9 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 496.90.

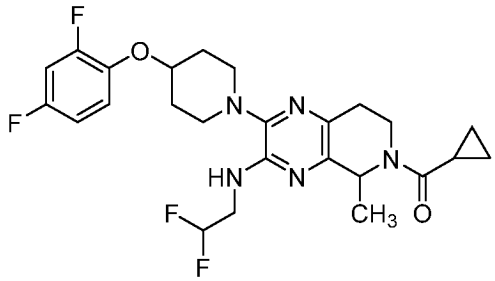
[00428] Example 37 1-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethanone



[00429] The title compound was prepared as an off-white film in a manner similar to Example 31 using *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.29-1.37 (m, 6H), 1.47 (d, *J* = 6.8 Hz, 2H), 1.58 (d, *J* = 6.8 Hz, 1H), 1.98 (d, *J* =9.8 Hz, 2H), 2.14 (br s, 2H), 2.72-2.88 (m, 1.5H), 2.92-3.00 (m, 0.8H), 3.09-3.17 (m, 2.5H), 3.41-3.53 (m, 5.7H), 4.06 (dd, *J* = 14.2, 5.4 Hz, 0.8H), 4.10-4.33 (m,

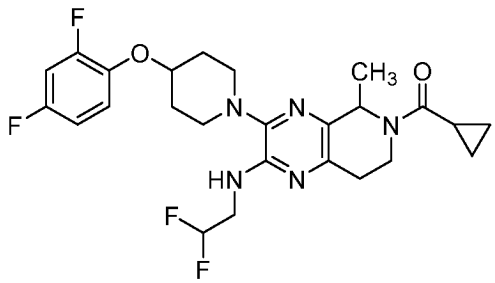
3.2H), 4.52 (d, J = 3.4 Hz, 1H), 4.72 (dd, J = 13.4, 5.6 Hz, 0.4H), 4.80-4.84 (m, 0.4H), 5.31 (q, J = 6.3 Hz, 0.7H), 6.89 (t, J = 8.5 Hz, 1H), 7.00 (ddd, J = 11.2, 8.5, 3.2 Hz, 1H), 7.19 (td, J = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 490.95.

[00430] Example 38 cyclopropyl(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone



[00431] The title compound was prepared as an off-white film in a manner similar to Example 31 using *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 0.81-1.05 (m, 4H), 1.45 (d, J = 6.8 Hz, 1.6H), 1.64 (d, J = 6.8 Hz, 1.4H), 1.94-2.18 (m, 5.4H), 2.61-2.83 (m, 1.6H), 2.89-3.12 (m, 3.2H), 3.35-3.44 (m, 2.1H), 3.51-3.60 (m, 0.6H), 3.71-3.86 (m, 2H), 4.42-4.51 (m, 1.6H), 4.70 (dd, J = 13.2, 4.9 Hz, 0.5H), 5.21-5.37 (m, 1H), 5.91-6.20 (m, 1H), 6.85-6.91 (m, 1H), 6.99 (ddd, J = 11.3, 8.7, 2.9 Hz, 1H), 7.18 (td, J = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 508.85.

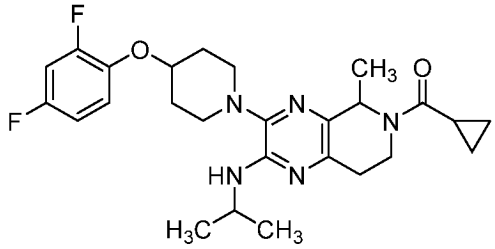
[00432] Example 39 cyclopropyl(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone



[00433] The title compound was prepared as a white film in a manner similar to Example 31 using *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 0.80-1.06 (m, 4H), 1.43 (d, J = 6.8 Hz, 1.5H), 1.62 (d, J = 6.8 Hz, 1.5H), 1.91-2.20 (m, 5.5H), 2.62-2.83 (m, 1.6H), 2.90-3.13 (m, 3.2H), 3.35-3.48 (m,

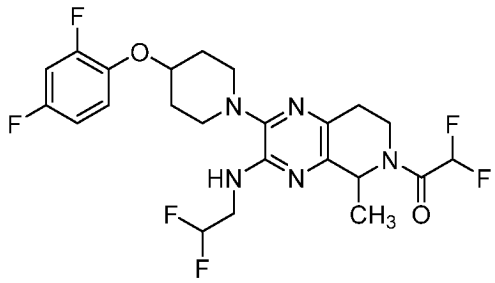
2.1H), 3.52-3.61 (m, 0.5H), 3.78 (td, *J* = 14.4, 3.9 Hz, 2H), 4.46 (dd, *J* = 8.3, 4.4 Hz, 1.6H), 4.69 (dd, *J* = 13.2, 4.9 Hz, 0.5H), 5.21-5.38 (m, 1H), 5.92-6.20 (m, 1H), 6.88 (t, *J* = 8.5 Hz, 1H), 6.96-7.03 (m, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 508.85.

[00434] Example 40 cyclopropyl(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone



[00435] The title compound was prepared as a light yellow film in a manner similar to Example 31 using 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 0.79-1.05 (m, 4H), 1.30 (t, *J* = 6.3 Hz, 6H), 1.44 (d, *J* = 6.8 Hz, 1.5H), 1.63 (d, *J* = 6.8 Hz, 1.5H), 1.92-2.18 (m, 5.1H), 2.67-2.84 (m, 1.5H), 2.91-3.13 (m, 3H), 3.44 (td, *J* = 7.9, 3.7 Hz, 2H), 3.53-3.61 (m, 0.5H), 4.16 (dt, *J* = 11.8, 6.0 Hz, 1H), 4.49 (d, *J* = 7.3 Hz, 1.5H), 4.70 (dd, *J* = 12.9, 5.1 Hz, 0.4H), 5.21-5.37 (m, 1H), 6.89 (t, *J* = 8.3 Hz, 1H), 6.96-7.04 (m, 1H), 7.19 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 486.90.

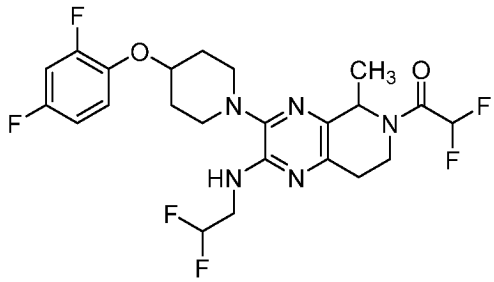
[00436] Example 41 1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone



[00437] A solution of 2,2-difluoroacetic acid (2.86 mg, 0.030 mmol), HATU (11.3 mg, 0.030 mmol), and DIPEA (14.2 μL, 0.081 mmol) in DMF (136 μL) was stirred at room temperature for 10 min. Then, *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (15 mg, 0.027 mmol) was added and stirring was continued overnight. No desired product was detected by LCMS. To this was added 2,2-difluoroacetic anhydride (7.08 mg, 0.041 mmol) and after 1 h, purification by HPLC Method A afforded the title compound as a TFA salt (4.4 mg) as an off-white film. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.51 (d, *J* =

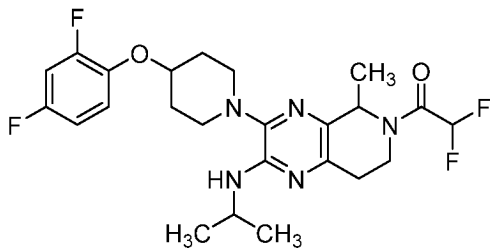
6.8 Hz, 2.1H), 1.62 (d, *J* = 6.8 Hz, 0.9H), 1.94-2.02 (m, 2H), 2.10-2.18 (m, 2H), 2.68-2.78 (m, 1H), 2.82-3.06 (m, 3.2H), 3.36-3.44 (m, 2H), 3.53-3.61 (m, 0.7H), 3.71-3.88 (m, 2.1H), 4.16 (dd, *J* = 14.2, 5.4 Hz, 0.7H), 4.46 (dt, *J* = 7.4, 3.8 Hz, 1H), 4.67 (dd, *J* = 13.2, 5.9 Hz, 0.3H), 4.97 (q, *J* = 6.7 Hz, 0.3H), 5.27 (q, *J* = 6.8 Hz, 0.7H), 5.93-6.20 (m, 1H), 6.43-6.70 (m, 1H), 6.85-6.92 (m, 1H), 6.99 (ddd, *J* = 11.3, 8.4, 3.2 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 518.80.

[00438] Example 42 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone



[00439] T The title compound was prepared as an off-white film in a manner similar to Example 41 using *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.50 (d, *J* = 6.8 Hz, 2.1H), 1.60 (d, *J* = 6.8 Hz, 0.9H), 1.92-2.03 (m, 2H), 2.11-2.18 (m, 2H), 2.68-2.77 (m, 1H), 2.82-3.08 (m, 3H), 3.26 (td, *J* = 12.9, 12.9, 3.9 Hz, 0.4H), 3.36-3.47 (m, 2H), 3.53-3.62 (m, 0.6H), 3.78 (td, *J* = 14.4, 4.4 Hz, 2H), 4.15 (dd, *J* = 13.9, 5.6 Hz, 0.7H), 4.43-4.49 (m, 1H), 4.66 (dd, *J* = 13.2, 5.9 Hz, 0.3H), 4.98 (q, *J* = 6.8 Hz, 0.3H), 5.28 (q, *J* = 6.8 Hz, 0.7H), 5.93-6.19 (m, 1H), 6.43-6.69 (m, 1H), 6.86-6.91 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.3, 2.9 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 518.85.

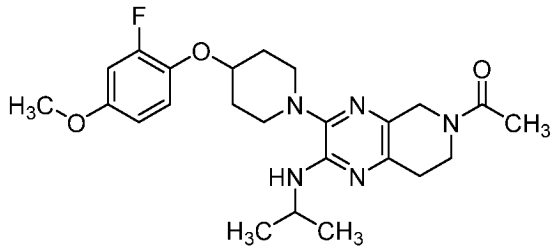
[00440] Example 43 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone



[00441] The title compound was prepared as an off-white film in a manner similar to Example 41 using 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt. ^{1}H NMR (500 MHz, methanol-*d*4,

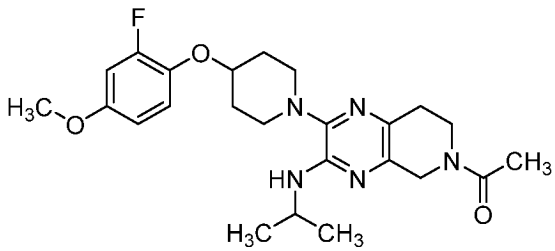
mixture of rotamers) δ ppm 1.25-1.30 (m, 6H), 1.49 (d, *J* = 6.8 Hz, 2H), 1.60 (d, *J* = 6.3 Hz, 1H), 1.91-2.01 (m, 2H), 2.10-2.18 (m, 2H), 2.70-2.80 (m, 1H), 2.81-3.09 (m, 3H), 3.22-3.30 (m, 0.5H), 3.37-3.47 (m, 2H), 3.54-3.62 (m, 0.6H), 4.12-4.21 (m, 1.6H), 4.45-4.52 (m, 1H), 4.66 (dd, *J* = 13.4, 6.1 Hz, 0.3H), 4.93-4.99 (m, 0.3H), 5.26 (q, *J* = 6.5 Hz, 0.7H), 6.43-6.69 (m, 1H), 6.86-6.92 (m, 1H), 7.00 (ddd, *J* = 11.3, 8.7, 2.9 Hz, 1H), 7.19 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 496.90.

[00442] Example 44 1-(3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



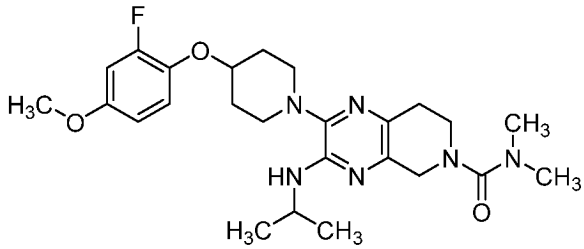
[00443] Acetic anhydride (9 μL, 0.095 mmol) was added to a solution of 3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (25.2 mg, 0.048 mmol) and pyridine (11.5 μL, 0.143 mmol) in DCM (500 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (25.2 mg, 93%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.32 (d, *J* = 6.6 Hz, 6H), 1.89-2.00 (m, 2H), 2.06-2.15 (m, 2H), 2.19 (s, 1.4H), 2.21 (s, 1.6H), 2.77-2.83 (m, 0.9H), 2.87-2.93 (m, 1.1H), 3.04-3.14 (m, 2H), 3.42-3.50 (m, 2H), 3.75 (s, 3H), 3.80-3.85 (m, 1.1H), 3.85-3.90 (m, 0.9H), 4.09-4.19 (m, 1H), 4.35-4.42 (m, 1H), 4.55 (br s, 2H), 6.67 (dt, *J* = 9.0, 1.4 Hz, 1H), 6.74 (dd, *J* = 12.8, 2.9 Hz, 1H), 7.08 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 458.4.

[00444] Example 45 1-(2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



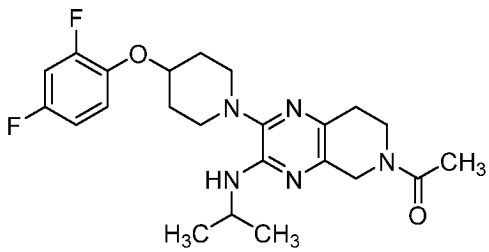
[00445] The title compound was prepared in a manner similar to Example 29 using 2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt. ESI-MS m/z $[M+H]^+$ 458.40.

[00446] Example 46 2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-3-(isopropylamino)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00447] Dimethylcarbamic chloride (4.9 mg, 0.046 mmol) was added to a solution of 2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (12.1 mg, 0.023 mmol) and triethylamine (10 µL, 0.069 mmol) in DCM (230 µL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (12.1 mg, 88%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.27-1.32 (m, 6H), 1.89-1.99 (m, 2H), 2.06-2.15 (m, 2H), 2.81 (s, 2H), 2.91 (s, 6H), 3.00-3.09 (m, 2H), 3.39-3.46 (m, 2H), 3.55 (t, J = 5.8 Hz, 2H), 3.75 (s, 3H), 4.13 (quin, J = 6.4 Hz, 1H), 4.30 (s, 2H), 4.34-4.40 (m, 1H), 6.67 (ddd, J = 8.9, 3.0, 1.5 Hz, 1H), 6.74 (dd, J = 12.8, 2.9 Hz, 1 H), 7.08 (t, J = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 487.4.

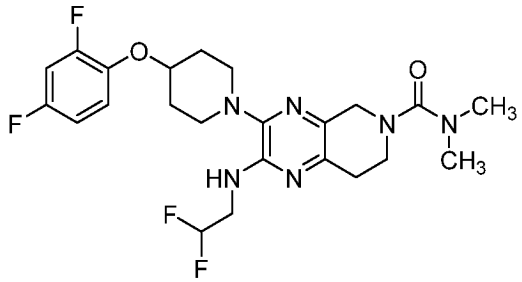
[00448] Example 47 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00449] A mixture of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropylpyrido[3,4-*b*]pyrazin-3-amine (100 mg, 0.250 mmol), acetic anhydride (0.09 mL, 1.00 mmol) and 10% Pd/C (9.0 mg) in a mixture of dioxane (2.5 mL) and acetone (1.5 mL) was stirred at room temperature for 24 h. Then, 4.0 equivalents of acetic anhydride was added and stirring was continued for 2 days. After filtration, the reaction solution was quenched with saturated $NaHCO_3$ and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic phase was dried with anhydrous Na_2SO_4 and concentrated under vacuum. Purification by silica gel column chromatography using a 30% to 100% gradient of EtOAc in heptane gave the title compound (57 mg, 51%) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.23 (d, J = 6.6 Hz, 3.3H), 1.24 (d, J = 6.6 Hz,

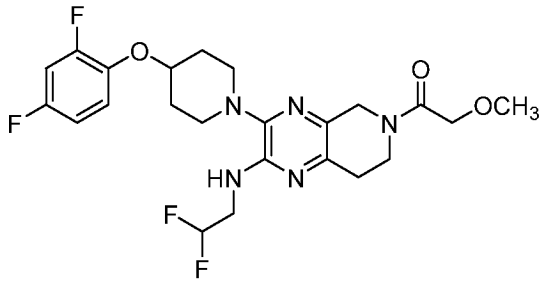
2.7H), 1.93 (m, 2H), 2.11 (m, 2H), 2.18 (s, 1.3H), 2.20 (s, 1.7H), 2.71 (t, J = 6.1 Hz, 0.9H), 2.80 (t, J = 6.1 Hz, 1.1H), 2.95 (m, 2H), 3.34 (m, 2H), 3.79 (t, J = 5.9 Hz, 1.1H), 3.84 (t, J = 6.1 Hz, 0.9H), 4.15 (m, 1H), 4.44 (tt, J = 7.5, 3.7 Hz, 1H), 4.53 (s, 0.9H), 4.54 (s, 1.1H), 6.86 (m, 1H), 6.97 (ddd, J = 11.2, 8.5, 3.2 Hz, 1H), 7.16 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 446.00.

[00450] Example 49 2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00451] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (15 mg, 0.028 mmol) in DCM (278 µL) at room temperature was treated with dimethylcarbamic chloride (3.0 mg, 0.028 mmol) and DIPEA (4.9 µL, 0.028 mmol), and the resulting reaction mixture was stirred overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (7 mg) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.92-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.81-2.86 (m, 2H), 2.90 (s, 6H), 2.96-3.04 (m, 2H), 3.34-3.42 (m, 2H), 3.54 (t, J = 5.9 Hz, 2H), 3.74-3.84 (m, 2H), 4.28 (s, 2H), 4.46 (tt, J = 7.7, 3.9 Hz, 1H), 5.90-6.22 (m, 1H), 6.88 (dddd, J = 9.1, 8.1, 3.2, 1.9 Hz, 1H), 6.99 (ddd, J = 11.4, 8.6, 3.0 Hz, 1 H), 7.18 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 497.4.

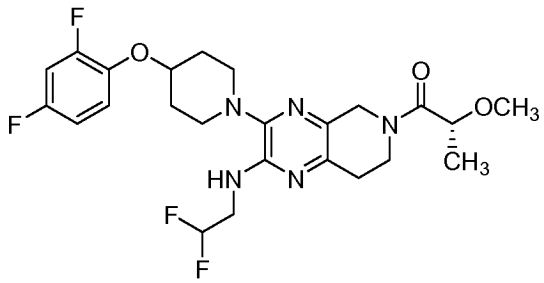
[00452] Example 50 1-(2-((2,2-difluoroethyl)amino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethanone



[00453] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-b]pyrazin-2-amine TFA salt (17 mg, 0.032 mmol), DIPEA

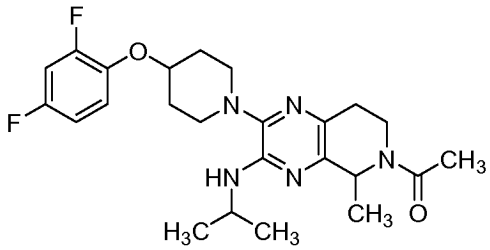
(12.2 mg, 0.095 mmol), and 2-methoxyacetyl chloride (5.1 mg, 0.047 mmol) in DCM (315 µL) was stirred at room temperature overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (7 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.92-2.03 (m, 2H), 2.09-2.18 (m, 2H), 2.77 (t, J = 5.8 Hz, 0.9H), 2.84 (t , J = 5.8 Hz, 1.1H), 2.96-3.04 (m, 2H), 3.37 (d, J = 10.4 Hz, 2H), 3.41 (s, 1.5H), 3.42 (s, 1.5H), 3.73-3.83 (m, 3H), 3.88 (t, J = 5.9 Hz, 1H), 4.24 (s, 0.9H), 4.27 (s, 1.1H), 4.41-4.49 (m, 1H), 4.50 (s, 0.9H), 4.53 (s, 1.1H), 5.89-6.21 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 498.3.

[00454] Example 51 (*R*)-1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one



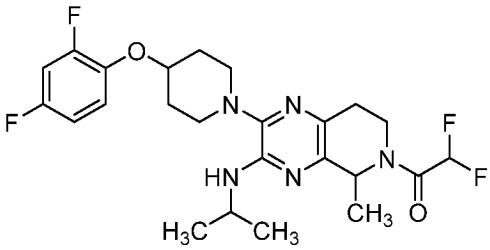
[00455] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (17 mg, 0.032 mmol), DIPEA (12.2 mg, 0.095 mmol), and HATU (13.2 mg, 0.035 mmol) in DMF (158 µL) was stirred for 10 min at rt. To this was added (*R*)-2-methoxypropanoic acid (3.6 mg, 0.035 mmol), and the resulting reaction mixture stirred overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (6 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.32 (d, J = 6.8 Hz, 1.3 H), 1.38 (d, J = 6.6 Hz, 1.7H), 1.92-2.03 (m, 2H), 2.09-2.18 (m, 2H), 2.78 (t, J = 6.2 Hz, 0.9H), 2.86 (m, 1.1H), 2.97-3.06 (m, 2H), 3.33 (s, 3H), 3.35-3.43 (m, 2H), 3.79 (td, J = 14.5, 4.3 Hz, 2H), 3.85-3.97 (m, 2H), 4.36 (dq, J = 12.7, 6.5 Hz, 1H), 4.42-4.49 (m, 1H), 4.58 (m, 0.9H), 4.68 (m, 1.1H), 5.90-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, J = 11.4, 8.5, 3.0 Hz, 1 H), 7.18 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 512.4.

[00456] Example 52 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



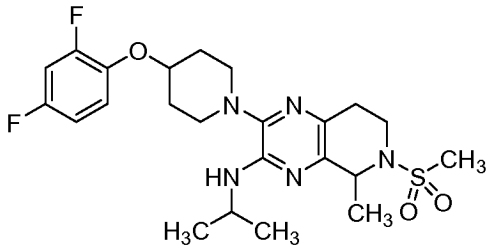
[00457] The title compound was prepared as a yellow film in a manner similar to Example 29 using 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.24-1.31 (m, 6H), 1.46 (d, *J* = 6.8 Hz, 2H), 1.59 (d, *J* = 6.8 Hz, 1H), 1.92-2.00 (m, 2H), 2.09-2.17 (m, 2H), 2.19-2.23 (m, 3H), 2.61-2.82 (m, 1.5H), 2.87-2.96 (m, 0.7H), 2.99-3.09 (m, 2.4H), 3.40 (td, *J* = 7.7, 3.7 Hz, 2H), 3.49-3.57 (m, 0.6H), 4.06 (dd, *J* = 13.9, 5.6 Hz, 0.6H), 4.13-4.20 (m, 1H), 4.48 (td, *J* = 7.2, 3.7 Hz, 1H), 4.73 (dd, *J* = 13.4, 5.6 Hz, 0.4H), 4.84 (br s, 0.2H), 5.39 (q, *J* = 6.5 Hz, 0.6H), 6.85-6.91 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.3, 2.9 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 460.90.

[00458] Example 53 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone



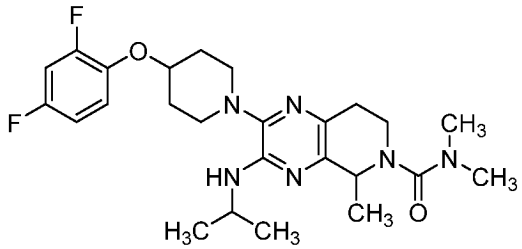
[00459] A solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (15 mg, 0.028 mmol), 2,2-difluoroacetic anhydride (7.4 mg, 0.042 mmol), and DIPEA (10.94 mg, 0.085 mmol) in DCM (141 µL) was stirred at room temperature for 1 h. Purification by HPLC Method A gave the title compound as a TFA salt (8.2 mg) as an off-white film. ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.27 (dd, *J* = 7.6, 6.6 Hz, 6H), 1.51 (d, *J* = 6.8 Hz, 2.1H), 1.62 (d, *J* = 6.8 Hz, 0.9H), 1.90-2.00 (m, 2H), 2.09-2.17 (m, 2H), 2.65-2.75 (m, 1H), 2.80-3.03 (m, 3H), 3.25 (td, *J* = 12.9, 3.9 Hz, 0.3H), 3.34-3.42 (m, 2H), 3.52-3.61 (m, 0.7H), 4.11-4.21 (m, 1.7H), 4.46 (dt, *J* = 7.3, 3.7 Hz, 1H), 4.66 (dd, *J* = 13.4, 5.6 Hz, 0.3H), 4.91-4.98 (m, 0.3H), 5.25 (q, *J* =6.7 Hz, 0.7H), 6.44-6.69 (m, 1H), 6.84-6.92 (m, 1H), 6.99 (ddd, *J* = 11.3, 8.4, 3.2 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 496.90.

[00460] Example 54 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



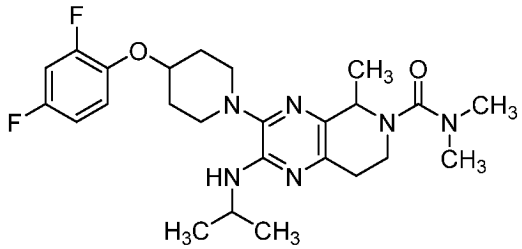
[00461] The title compound was prepared as an off-white film in a manner similar to Example 30 using 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 1.26 (dd, *J* = 10.7, 6.4 Hz, 6H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.88-2.00 (m, 2H), 2.07-2.18 (m, 2H), 2.64 (dd, *J* = 16.6, 2.9 Hz, 1H), 2.89-2.92 (m, 4H), 2.94-3.03 (m, 3H), 3.34-3.48 (m, 3H), 3.97 (dd, *J* = 14.2, 6.4 Hz, 1H), 4.15 (quin, *J* = 6.5 Hz, 1H), 4.46 (dt, *J* = 7.4, 3.8 Hz, 1H), 4.76 (q, *J* = 6.7 Hz, 1H), 6.81-6.92 (m, 1H), 6.98 (ddd, *J* = 11.4, 8.4, 3.2 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 496.95.

[00462] Example 55 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-*N*,*N*,5-trimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



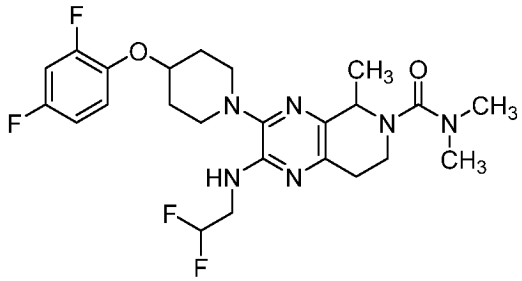
[00463] A solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (15 mg, 0.028 mmol), dimethylcarbamic chloride (6.1 mg, 0.056 mmol), and DIPEA (10.9 mg, 0.085 mmol) in DCM (282 µL) was stirred at room temperature overnight. Purification by HPLC Method A afforded the title compound as a TFA salt (6.1 mg) as an off-white film. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 1.26 (dd, *J* = 9.3, 6.4 Hz, 6H), 1.50 (d, *J* = 6.8 Hz, 3H), 1.89-1.98 (m, 2H), 2.12 (dq, *J* = 13.2, 3.6 Hz, 2H), 2.55-2.64 (m, 1H), 2.88 (s, 6H), 2.94-3.03 (m, 3H), 3.34-3.41 (m, 3H), 3.72-3.82 (m, 1H), 4.14 (quin, *J* = 6.5 Hz, 1H), 4.45 (dt, *J* = 7.4, 3.8 Hz, 1H), 4.67 (q, *J* = 6.8 Hz, 1H), 6.83-6.91 (m, 1H), 6.98 (ddd, *J* =11.4, 8.4, 3.2 Hz, 1H), 7.17 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 489.90.

[00464] Example 56 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-*N*,*N*,5-trimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



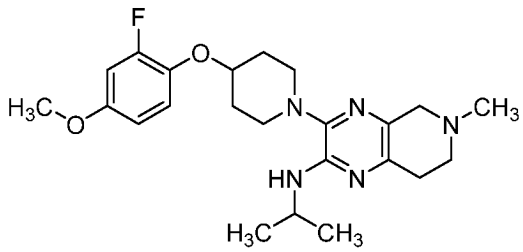
[00465] The title compound was prepared as an light yellow film in a manner similar to Example 55 using 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 1.34 (dd, *J* = 6.4, 5.4 Hz, 6H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.91-2.03 (m, 2H), 2.10-2.18 (m, 2H), 2.70 (dd, *J* = 17.1, 2.9 Hz, 1H), 2.89 (s, 6H), 3.03 (s, 1H), 3.09-3.19 (m, 2H), 3.33-3.39 (m, 1H), 3.43-3.53 (m, 2H), 3.79 (dd, *J* = 14.2, 5.8 Hz, 1H), 4.08-4.18 (m, 1H), 4.46-4.57 (m, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 6.84-6.93 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.3, 2.9 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 489.95.

[00466] Example 57 2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*,*N*,5-trimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



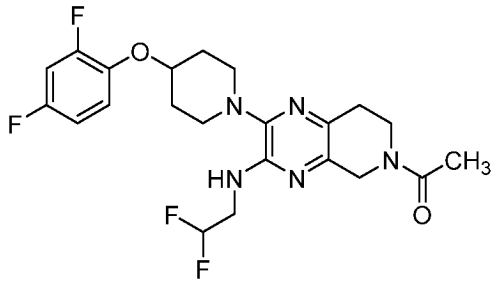
[00467] The title compound was prepared as an off-white film in a manner similar to Example 55 using *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 1.47 (d, *J* = 6.8 Hz, 3H), 1.96 (d, *J* = 8.3 Hz, 2H), 2.12 (d, *J* = 3.4 Hz, 2H), 2.64 (s, 1H), 2.88 (s, 6H), 2.97 (d, *J* = 11.7 Hz, 3H), 3.34-3.45 (m, 3H), 3.71-3.83 (m, 3H), 4.41-4.49 (m, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 6.05 (s, 1H), 6.87 (s, 1H), 6.95-7.02 (m, 1H), 7.13-7.21 (m, 1H); ESI-MS m/z $[M+H]^+$ 511.90.

[00468] Example 58 3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



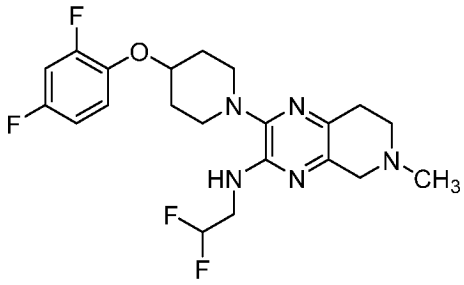
[00469] Sodium triacetoxyborohydride (22.3 mg, 0.105 mmol) was added to a mixture of DIPEA (18 µL, 0.105 mmol), 3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (27.9 mg, 0.053 mmol) and formaldehyde (4 µL, 0.053 mmol) in MeOH (550 µL) at rt. After 30 min, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (27.9 mg, 97%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.25 (d, J = 6.3 Hz, 6H), 1.88-1.98 (m, 2H), 2.04-2.14 (m, 2H), 2.93-3.05 (m, 3H), 3.07 (br s, 4H), 3.33-3.40 (m, 2H), 3.41-3.69 (m, 2H), 3.75 (s, 3H), 4.15-4.32 (m, 3H), 4.32-4.39 (m, 1H), 6.66 (ddd, J = 8.9, 3.0, 1.5 Hz, 1 H), 6.73 (dd, J = 12.8, 2.9 Hz, 1H), 7.07 (t, J = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 430.4.

[00470] Example 59 1-(3-((2,2-difluoroethyl)amino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



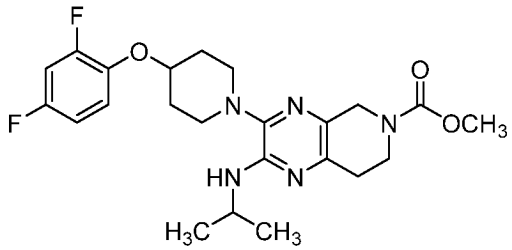
[00471] A solution of *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (114 mg, 0.211 mmol) in DCM (2.11 mL) at 0 °C was treated with pyridine (0.051 mL, 0.63 mmol) and acetic anhydride (0.040 mL, 0.42 mmol). The reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was concentrated under reduced pressure. The residue was taken up in MeOH, filtered, and purified by HPLC Method B, using a 40% to 70% ACN gradient to give the title compound, as a TFA salt, as a yellow solid (39.7 mg, 32.3%). ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.96 (m, 2H), 2.12 (m, 2H), 2.18 (s, 1.3H), 2.20 (s, 1.7H), 2.73 (t, J = 5.9 Hz, 0.8H), 2.83 (t, J = 5.9Hz, 1.2H), 3.01 (m, 2H), 3.39 (m, 2H), 3.80 (m, 4H), 4.45 (dt, J = 7.0, 3.6 Hz, 1H), 4.57 (app d, 2H), 6.05 (m, 1H), 6.86 (m, 1H), 6.96 (ddd, J = 11.2, 8.5, 3.2 Hz, 1H), 7.15 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 468.4.

[00472] Example 60 *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



[00473] A solution of *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (155 mg, 0.287 mmol) in MeOH (2.87 mL) was treated with DIPEA (0.100 mL, 0.575 mmol), formaldehyde (0.021 mL, 0.29 mmol), and after stirring for 5 min, sodium triacetoxyborohydride (122 mg, 0.575 mmol). The reaction mixture was stirred for 30 min at room temperature. The reaction mixture was filtered and purified by HPLC (Pump: Waters 2525 or 2545; MS: ZQ; Software: MassLynx. A Xbridge™ C18, 5 µm, ID 30 x 75 mm column was used and eluted with 40% to 95% of 20/80 (v/v) water/ACN (10 mmol NH_4HCO_3, pH 9.5-10) and water (10 mmol NH_4HCO_3, pH 9.5-10)) to give the title compound as an off-white semisolid (35.4 mg, 28.0%). ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 1.95 (m, 2H), 2.12 (m, 2H), 2.47 (s, 3H), 2.79 (m, 4H), 2.96 (ddd, *J* = 12.4, 8.8, 3.2 Hz, 2H), 3.35 (m, 2H), 3.49 (s, 2H), 3.75 (td, *J* = 14.6, 4.4 Hz, 2H), 4.43 (tt, *J* = 7.7, 3.5 Hz, 1H), 6.03 (m, 1H), 6.86 (m, 1H), 6.97 (ddd, *J* = 11.2, 8.5, 3.2 Hz, 1H), 7.16 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 440.4.

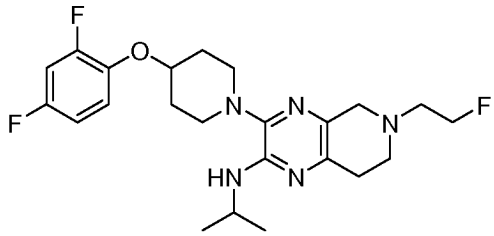
[00474] Example 61 methyl 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxylate



[00475] To a solution of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (50 mg, 0.080 mmol) and triethylamine (0.026 mL, 0.185 mmol) in DCM (0.75 mL) was added methyl carbonochloridate (9.3 µL, 0.121 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr, warmed to 23 °C, and concentrated via rotary evaporation. The resulting crude material was reconstituted in DMSO, rinsed with DMSO, and purified by HPLC Method B using a 30% to 70% ACN

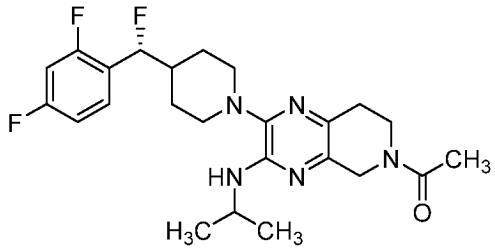
gradient to give the title compound as a TFA salt (11.0 mg, 23.8%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.18 (d, J = 6.8 Hz, 6H), 1.82-1.94 (m, 2H), 2.02-2.12 (m, 2H), 2.65 (t, J = 5.9 Hz, 2H), 2.83-2.93 (m, 2H), 3.21-3.33 (m, 2H), 3.63 (s, 3H), 3.64-3.68 (m, 2H), 4.06-4.17 (m, 1H), 4.34 (br s, 2H), 4.51 (tt, J = 8.1, 3.9 Hz, 1H), 5.51-5.65 (m, 1H), 6.99-7.05 (m, 1H), 7.25-7.35 (m, 2H); ESI-MS m/z $[M+H]^+$ 462.4.

[00476] Example 62 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6-(2-fluoroethyl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



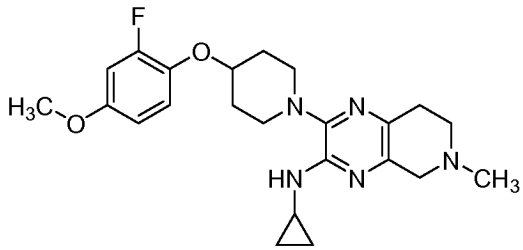
[00477] To a suspension of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (50 mg, 0.080 mmol) and K_2CO_3 (44.4 mg, 0.322 mmol) in acetone (2.0 mL) was added 1-bromo-2-fluoroethane (5.4 µL, 0.072 mmol) at 23 °C. The reaction mixture was stirred at 23 °C for 1 h and then at 50 °C for 3 days. The reaction mixture was cooled to 23 °C, an additional portion of 1-bromo-2-fluoroethane (2.7 µL, 0.036 mmol) was added, and the reaction mixture was heated for an additional 1.5 hr at 50 °C, cooled to 23 °C, and concentrated via rotary evaporation. The resulting crude material was reconstituted in DMSO, filtered, rinsed with DMSO, and purified by HPLC Method B using a 30% to 70% ACN gradient to give the title compound as a TFA salt (10.7 mg, 23.6%) as a yellow film. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.19 (d, J = 6.8 Hz, 6H), 1.83-1.92 (m, 2H), 2.02-2.13 (m, 2H), 2.79-2.96 (m, 3H), 2.96-3.11 (m, 0.9H), 3.24-3.36 (m, 2H), 3.38-3.55 (m, 1.1 H) 3.65 (br s, 1.1H), 3.71 (m, 0.9H), 3.73-3.84 (m, 1H), 4.12-4.19 (m, 1H), 4.28 (br s, 0.9H), 4.30 (br s, 1.1H), 4.54 (ddd, J = 11.7, 7.8, 3.9 Hz, 1H), 4.87 (t, J = 4.4 Hz, 0.9H), 4.88-4.95 (m, 1H), 4.97 (t, J = 4.4 Hz, 1.1H), 5.86 (d, J = 8.3 Hz, 1H), 6.97-7.08 (m, 1H), 7.25-7.37 (m, 2H); ESI-MS m/z $[M+H]^+$ 450.5.

[00478] Example 63 (*R*)-1-(2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00479] Acetic anhydride (14.1 μL, 0.149 mmol) and formic acid (38.1 μL, 0.994 mmol) were combined in THF (99 μL) and stirred at room temperature for 10 min. This solution was cooled to 0 °C and was added to a stirring solution of (*R*)-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine (41.7 mg, 0.099 mmol) in THF (895 μL) at 0 °C. After 10 min, UPLC-MS showed conversion not to the formylated product, but to the acetylated product. The reaction mixture was treated with MeOH, concentrated under reduced pressure, taken up in MeOH, filtered, and purified by HPLC Method B to give the title compound, as a TFA salt, as a pale yellow solid (17.5 mg, 30.6%). ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.28 (m, 6H), 1.45 (d, *J* = 12.7 Hz, 1H), 1.65 (m, 2H), 2.01 (m, 1H), 2.09 (m, 1H), 2.18 (s, 1.1H), 2.20 (s, 1.9H), 2.76 (m, 4H), 3.49 (m, 2H), 3.81 (t, *J* = 6.1 Hz, 1.3H), 3.85 (t, *J* = 5.9 Hz, 0.7H), 4.13 (m, 1H), 4.57 (s, 0.7H), 4.61 (s, 1.3H), 5.52 (m, 1H), 7.02 (m, 2H), 7.50 (m, 1H); ESI-MS m/z $[M+H]^+$ 462.4.

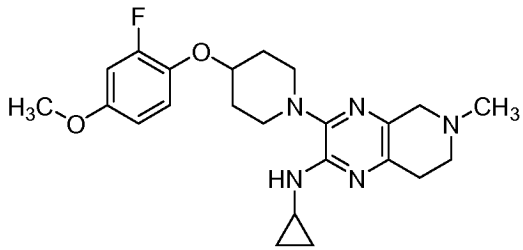
[00480] Example 65 *N*-cyclopropyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



[00481] A mixture of cyclopropanamine (13.6 mg, 0.237 mmol), 3-chloro-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine TFA salt (30.9 mg, 0.059 mmol), sodium *tert*-butoxide (11.4 mg, 0.119 mmol), BINAP (5.5 mg, 8.90 μmol) and $Pd_2(dba)_3$ (2.7 mg, 2.97 μmol) in toluene (200 μL) was heated at 90 °C for 14 h. The mixture was directly purified by HPLC Method A to give the title compound as a TFA salt (12.9 mg, 40.2%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.53-0.58 (m, 2H), 0.75-0.81 (m, 2H), 1.86-1.96 (m, 2H), 2.02-2.12 (m, 2H), 2.64-2.70 (m, 1H), 2.94-3.02 (m, 1H), 3.08-3.12 (m, 3H), 3.17-3.27 (m, 3H), 3.34-3.42 (m, 2H), 3.59-3.68 (m, 2H),

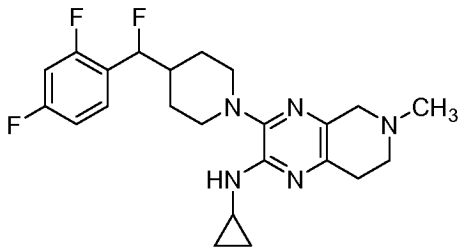
3.75 (s, 3H), 4.25-4.41 (m, 3H), 6.64-6.69 (m, 1H), 6.70-6.76 (m, 1H), 7.03-7.10 (m, 1H); ESI-MS m/z $[M+H]^+$ 428.4.

[00482] Example 66 *N*-cyclopropyl-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00483] A mixture of 4-(2-fluoro-4-methoxyphenoxy)piperidine hydrochloride (15.8 mg, 0.060 mmol), 3-chloro-N-cyclopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-b]pyrazin-2-amine (12 mg, 0.050 mmol), sodium *tert*-butoxide (14.5 mg, 0.151 mmol), BINAP (4.7 mg, 7.54 μmol) and $Pd_2(dba)_3$ (2.3 mg, 2.51 μmol) in toluene (250 μL) was heated at 90 °C for 14 h. The mixture was purified by HPLC Method A to give the title compound as a TFA salt (14.4 mg, 52.9%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.56-0.62 (m, 2H), 0.79-0.87 (m, 2H), 1.85-1.96 (m, 2H), 2.02-2.11 (m, 2H), 2.66-2.75 (m, 1H), 2.94-3.02 (m, 2H), 3.08-3.12 (m, 3H), 3.13-3.27 (m, 2H), 3.33-3.43 (m, 2H), 3.53-3.69 (m, 2H), 3.75 (s, 3H), 4.19-4.42 (m, 3H), 6.63-6.69 (m, 1H) 6.73 (dd, J = 12.9, 3.0 Hz, 1H), 7.02-7.09 (m, 1H); ESI-MS m/z $[M+H]^+$ 428.4.

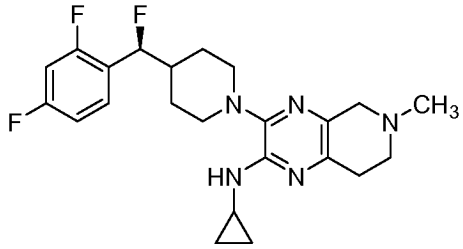
[00484] Example 67 *N*-cyclopropyl-3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00485] A mixture of 4-((2,4-difluorophenyl)fluoromethyl)piperidine hydrochloride (16.0 mg, 0.060 mmol), 3-chloro-*N*-cyclopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine (12 mg, 0.050 mmol), sodium *tert*-butoxide (14.5 mg, 0.151 mmol), BINAP (4.7 mg, 7.54 μmol) and $Pd_2(dba)_3$ (2.3 mg, 2.51 μmol) in toluene (250 μL) was heated at 90 °C for 14 h. The mixture was purified by HPLC Method A to give the title compound as a TFA salt (11.1 mg, 40.5%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.57 (dt, J = 3.5, 1.4 Hz, 2H), 0.78-0.85 (m, 2H), 1.36-1.45 (m, 1H), 1.52-1.73 (m, 2H), 1.93-2.15 (m,

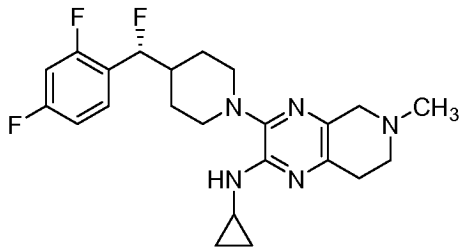
2H), 2.60-2.87 (m, 3H), 3.08 (s, 3H), 3.09 - 3.15 (m, 2H), 3.38-3.74 (m, 4H), 4.26 (br s, 2H), 5.51 (dd, J = 46.2, 7.3 Hz, 1H), 6.96-7.08 (m, 2H), 7.45-7.53 (m, 1H); ESI-MS m/z $[M+H]^+$ 432.4.

[00486] Example 68 (*S*)-*N*-cyclopropyl-3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00487] A mixture of (*S*)-4-((2,4-difluorophenyl)fluoromethyl)piperidine hydrochloride (14.7 mg, 0.055 mmol), 3-chloro-*N*-cyclopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine (11 mg, 0.046 mmol), sodium *tert*-butoxide (13.3 mg, 0.138 mmol), BINAP (4.3 mg, 6.91 μmol), and $Pd_2(dba)_3$ (2.1 mg, 2.30 μmol) in toluene (230 μL) was heated at 90 °C for 14 h. The mixture was purified by HPLC Method A to give the title compound as a TFA salt (11.1 mg, 44.2%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 0.56-0.63 (m, 2H), 0.84 (m, J = 6.8 Hz, 2H), 1.40 (d, J = 12.9 Hz, 1H), 1.52-1.74 (m, 2H), 1.92-2.14 (m, 2H), 2.61-2.75 (m, 3H), 3.08 (s, 3H), 3.09-3.16 (m, 2H), 3.40-3.55 (m, 2H), 3.55-3.80 (m, 2H), 4.31 (br s, 2H), 5.50 (dd, J = 46.0, 7.6 Hz, 1H), 6.96-7.08 (m, 2H), 7.45-7.54 (m, 1H); ESI-MS m/z $[M+H]^+$ 432.4.

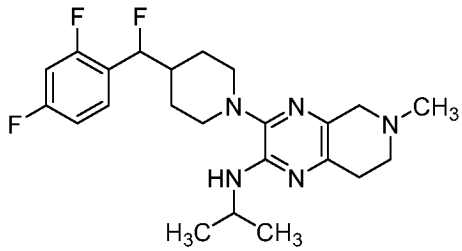
[00488] Example 69 (*R*)-*N*-cyclopropyl-3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00489] A mixture of (*R*)-4-((2,4-difluorophenyl)fluoromethyl)piperidine hydrochloride (14.7 mg, 0.055 mmol), 3-chloro-*N*-cyclopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine (11 mg, 0.046 mmol), sodium *tert*-butoxide (13.3 mg, 0.138 mmol), BINAP (4.3 mg, 6.91 μmol) and $Pd_2(dba)_3$ (2.1 mg, 2.30 μmol) in toluene (230 μL) was heated at 90 °C for 14 h. The mixture was purified by HPLC Method A to give the title compound as a TFA salt (10.5 mg, 41.8%) as a yellow film. ^{1}H NMR (400 MHz, methanol-

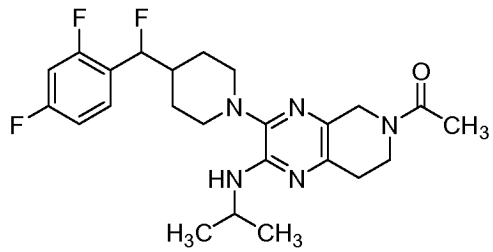
d_4) δ ppm 0.55-0.62 (m, 2H), 0.79-0.87 (m, 2H), 1.40 (br d, J = 12.4 Hz, 1H), 1.52-1.73 (m, 2H), 1.93-2.14 (m, 2H), 2.61-2.74 (m, 3H), 3.08 (s, 3H), 3.10-3.15 (m, 2H), 3.40-3.54 (m, 2H), 3.55-3.81 (m, 2H), 4.26 (br s, 2H), 5.50 (dd, J = 46.2, 7.8 Hz, 1H), 6.97-7.08 (m, 2H), 7.45-7.53 (m, 1H); ESI-MS m/z $[M+H]^+$ 432.3.

[00490] Example 70 3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00491] Sodium triacetoxyborohydride (15.3 mg, 0.072 mmol) was added to a mixture of DIPEA (9.4 mg, 0.072 mmol), 3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-N-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (19.3 mg, 0.036 mmol) and formaldehyde (3 μL, 0.036 mmol) in MeOH (360 μL) at rt. After 30 min, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (19.3 mg, 97%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.24 (dd, J = 6.4, 2.2 Hz, 6H), 1.40-1.48 (m, 1H), 1.53-1.74 (m, 2H), 1.96-2.14 (m, 2H), 2.60-2.73 (m, 2H), 2.93-3.06 (br m, 2H), 3.06 (s, 3H), 3.39-3.54 (m, 3H), 3.69-3.81 (m, 1H), 4.18 (dt, J = 13.1, 6.4 Hz, 2H), 4.16-4.36 (br m, 1H), 5.52 (dd, J = 46.2, 7.6 Hz, 1H), 6.97-7.08 (m, 2H), 7.47-7.54 (m, 1H); ESI-MS m/z $[M+H]^+$ 434.4.

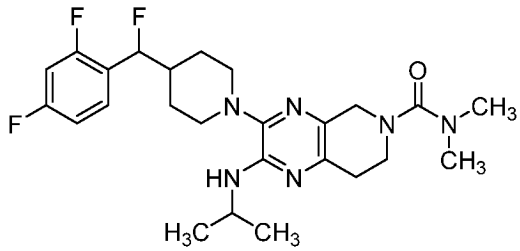
[00492] Example 71 1-(3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00493] Acetic anhydride (7 μL, 0.075 mmol) was added to a solution of 3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (20.1 mg, 0.038 mmol) and pyridine (9 μL, 0.113 mmol) in DCM (380 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (20.1 mg, 93%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4)

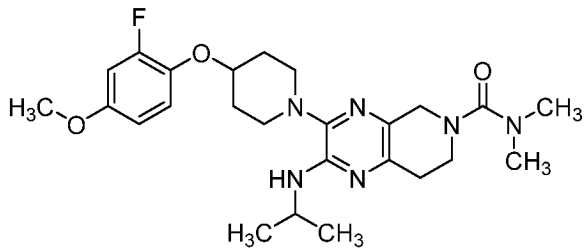
δ ppm 1.29 (dd, *J* = 6.4, 1.9 Hz, 6H), 1.46 (br s, 1H), 1.56-1.77 (m, 2H), 2.00 (d, *J* = 12.9 Hz, 1H), 2.04-2.15 (m, 1H), 2.18 (s, 1.3H), 2.20 (s, 1.7H), 2.76 (qd, *J* = 12.8, 2.4 Hz, 3H), 2.87 (t, *J* = 5.9 Hz, 1H), 3.40-3.56 (m, 2H), 3.78-3.83 (m, 1.1H), 3.83-3.89 (m, 0.9H), 4.09-4.17 (m, 1H), 4.52 (s, 2H), 5.53 (dd, *J* = 46.7, 7.6 Hz, 1H), 6.97-7.08 (m, 2H), 7.47-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 462.4.

[00494] Example 72 3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-2-(isopropylamino)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00495] Dimethylcarbamic chloride (8.4 mg, 0.078 mmol) was added to a solution of 3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (20.8 mg, 0.039 mmol) and triethylamine (16 μL, 0.117 mmol) in DCM (390 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (20.8 mg, 88%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.31 (dd, *J* = 6.6, 1.8 Hz, 6H), 1.40-1.48 (m, 1H), 1.58-1.78 (m, 2H), 1.95-2.03 (m, 1H), 2.03-2.18 (m, 1H), 2.71-2.88 (m, 4H), 2.90 (s, 6H), 3.42-3.52 (m, 2H), 3.54 (t, *J* = 5.7 Hz, 2H), 4.07-4.16 (m, 1H), 4.22-4.27 (m, 2H), 5.53 (dd, *J* = 46.5, 7.3 Hz, 1H), 6.97-7.08 (m, 2H), 7.47-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 491.4.

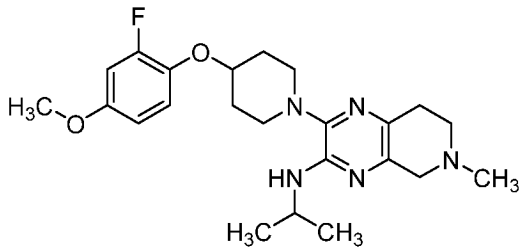
[00496] Example 73 3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-2-(isopropylamino)-N,N-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00497] Dimethylcarbamic chloride (10.5 mg, 0.097 mmol) was added to a solution of 3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (25.8 mg, 0.049 mmol) and triethylamine (20.5 μL, 0.146 mmol) in DCM (500 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (25.8 mg, 88%) as a yellow film. ^{1}H NMR (400 MHz,

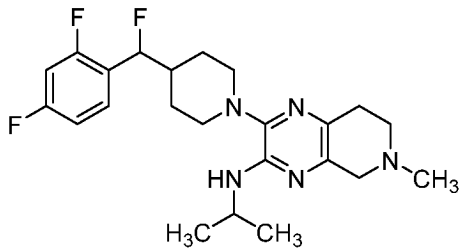
methanol-d_4) δ ppm 1.33 (d, J = 6.3 Hz, 6H), 1.89-2.00 (m, 2H), 2.06-2.16 (m, 2H), 2.85-2.89 (m, 2H), 2.90 (s, 6H), 3.04-3.13 (m, 2H), 3.41-3.50 (m, 2H), 3.55 (t, J = 5.8 Hz, 2H), 3.76 (s, 3H), 4.08-4.18 (m, 1H), 4.27 (s, 2H), 4.35-4.42 (m, 1H), 6.67 (ddd, J = 9.0, 2.9, 1.5 Hz, 1H), 6.74 (dd, J = 12.9, 3.0 Hz, 1H), 7.08 (t, J = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 487.4.

[00498] Example 74 2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



[00499] Sodium triacetoxyhydroborate (9.7 mg, 0.046 mmol) was added to a solution of DIPEA (8 μL, 0.046 mmol), 2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (12.1 mg, 0.023 mmol) and formaldehyde (1.9 μL, 0.023 mmol) in MeOH (229 μL) at rt. After 30 min, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (12.1 mg, 97%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.24 (d, J = 6.3 Hz, 6H), 1.88-1.99 (m, 2H), 2.04-2.14 (m, 2H), 2.93-3.04 (m, 3H), 3.08 (br s, 4H), 3.35-3.53 (m, 3H), 3.76 (br s, 4H), 4.10-4.19 (m, 1H), 4.20-4.40 (m, 3H), 6.64-6.69 (m, 1H), 6.74 (dd, J = 12.8, 2.1 Hz, 1H), 7.07 (t, J = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 430.4.

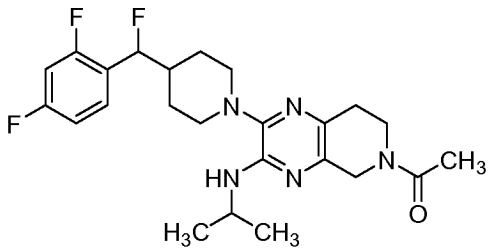
[00500] Example 75 2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



[00501] Sodium triacetoxyhydroborate (11.0 mg, 0.052 mmol) was added to a solution of DIPEA (9 μL, 0.052 mmol), 2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (13.9 mg, 0.026 mmol) and formaldehyde (2 μL, 0.026 mmol) in MeOH (260 μL) at rt. After 30 min, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (13.9 mg, 97%)

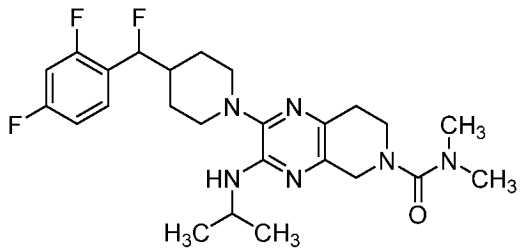
as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.23 (dd, J = 6.4, 2.4 Hz, 6H), 1.41-1.49 (m, 1H), 1.52-1.74 (m, 2H), 1.97-2.15 (m, 2H), 2.61-2.75 (m, 2H), 2.89-3.04 (m, 2H), 3.07 (s, 3H), 3.40-3.56 (m, 3H), 3.75 (br s, 1H), 4.13 (quin, J = 6.5 Hz, 1H), 4.18-4.38 (m, 2H), 5.53 (dd, J = 46.2, 7.6 Hz, 1H), 6.97-7.08 (m, 2H), 7.47-7.54 (m, 1H); ESI-MS m/z $[M+H]^+$ 434.4.

[00502] Example 76 1-(2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00503] Acetic anhydride (5 μL, 0.054 mmol) was added to a solution of 2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (14.3 mg, 0.027 mmol) and pyridine (6.5 μL, 0.080 mmol) in DCM (270 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (14.3 mg, 93%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.23-1.31 (m, 6H), 1.45 (d, J = 12.9 Hz, 1H), 1.53-1.76 (m, 2H), 1.96-2.15 (m, 2H), 2.18 (s, 1.2H), 2.21 (s, 1.8H), 2.67-2.84 (m, 4H), 3.38-3.55 (m, 2H), 3.78-3.83 (m, 1.2H), 3.83-3.87 (m, 0.8H), 4.13 (dq, J = 12.6, 6.3 Hz, 1H), 4.56 (s, 0.8H), 4.59 (s, 1.2H), 5.53 (dd, J = 46.2, 7.6 Hz, 1H), 6.97-7.09 (m, 2H), 7.47-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 462.4.

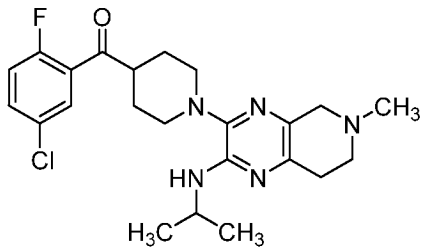
[00504] Example 77 2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00505] Dimethylcarbamic chloride (5.8 mg, 0.054 mmol) was added to a solution of 2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (14.3 mg, 0.027 mmol) and triethylamine (11 μL, 0.080 mmol) in DCM (270 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the

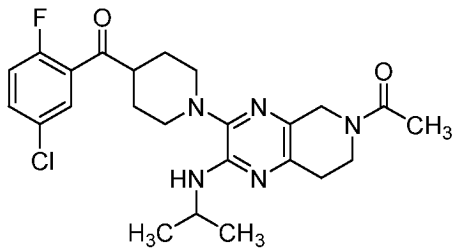
title compound as a TFA salt (14.3 mg, 88%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.29 (dd, J = 6.4, 1.9 Hz, 6H), 1.40-1.49 (m, 1H), 1.55-1.77 (m, 2H), 2.01 (d, J = 13.1 Hz, 2H), 2.70-2.84 (m, 4H), 2.87-2.94 (m, 6H), 3.40-3.52 (m, 2H), 3.53-3.57 (m, 2H), 4.11 (quin, J = 6.4 Hz, 1H) 4.29 (s, 2H) 5.53 (dd, J = 46.2, 7.3 Hz, 1H), 6.97-7.09 (m, 2H), 7.47-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 491.4.

[00506] Example 78 (5-chloro-2-fluorophenyl)(1-(2-(isopropylamino)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)methanone



[00507] Sodium triacetoxyhydroborate (6.9 mg, 0.033 mmol) was added to a solution of DIPEA (6 μL, 0.033 mmol), (5-chloro-2-fluorophenyl)(1-(2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)methanone TFA salt (8.9 mg, 0.016 mmol) and formaldehyde (1.5 μL, 0.016 mmol) in MeOH (160 μL) at rt. After 30 min, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (2.2 mg, 24.1%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.24 (d, J = 6.6 Hz, 6H), 1.81-1.94 (m, 2H), 1.96-2.05 (m, 2H), 2.85 (t, J = 11.5 Hz, 2H), 3.00 (d, J = 6.3 Hz, 2H), 3.07 (s, 3H), 3.44-3.53 (m, 4H), 3.71-3.82 (m, 1H), 4.14-4.23 (m, 2H), 4.28-4.37 (m, 1H), 7.28 (dd, J = 10.6, 8.8 Hz, 1H), 7.61 (ddd, J = 8.8, 4.1, 2.8 Hz, 1H), 7.75 (dd, J = 6.1, 2.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 446.3.

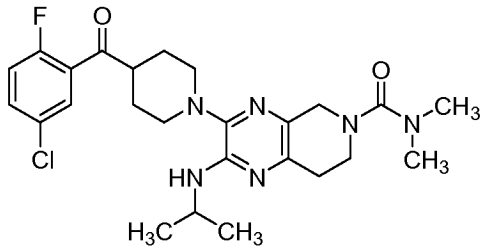
[00508] Example 79 1-(3-(4-(5-chloro-2-fluorobenzoyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00509] Acetic anhydride (3 μL, 0.034 mmol) was added to a solution of (5-chloro-2-fluorophenyl)(1-(2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)methanone TFA salt (9.2 mg, 0.017 mmol) and pyridine (4 μL, 0.051 mmol) in DCM (170 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title

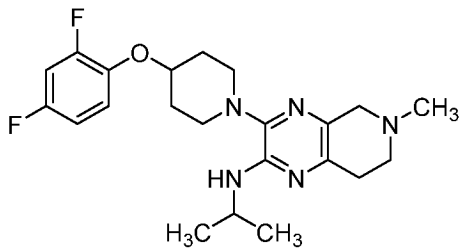
compound as a TFA salt (4.0 mg, 40.4 %) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.30-1.34 (m, 6H), 1.88-2.04 (m, 4H), 2.19 (s, 1.4H), 2.21 (s, 1.6H), 2.77-2.83 (m, 0.9H), 2.87-2.92 (m, 1.1H), 2.93-3.02 (m, 2H), 3.34-3.43 (m, 1H), 3.50-3.59 (m, 2H), 3.80-3.85 (m, 1.1H), 3.85-3.90 (m, 0.9H), 4.08-4.17 (m, 1H), 4.54 (br s, 2H), 7.25-7.32 (m, 1H), 7.59-7.63 (m, 1H), 7.76 (dd, J = 6.1, 2.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 474.3.

[00510] Example 80 3-(4-(5-chloro-2-fluorobenzoyl)piperidin-1-yl)-2-(isopropylamino)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00511] Dimethylcarbamic chloride (3.8 mg, 0.036 mmol) was added to a solution of (5-chloro-2-fluorophenyl)(1-(2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)methanone TFA salt (9.7 mg, 0.018 mmol) and triethylamine (7 µL, 0.053 mmol) in DCM (180 µL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (3.6 mg, 32.8%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.31-1.34 (m, 6H), 1.89-2.06 (m, 4H), 2.85-2.89 (m, 2H), 2.90-2.92 (m, 6H), 2.93-3.02 (m, 2H), 3.35-3.41 (m, 1H), 3.50-3.58 (m, 4H), 4.08-4.16 (m, 1H), 4.27 (s, 2H), 7.29 (dd, J = 10.6, 8.8 Hz, 1H), 7.61 (ddd, J = 8.8, 4.0, 2.8 Hz, 1H), 7.76 (dd, J = 6.1, 2.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 504.4.

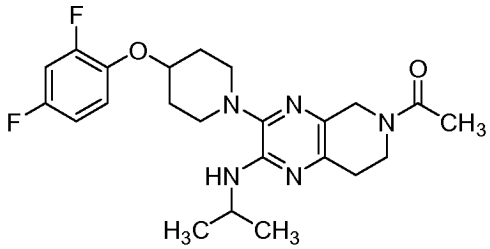
[00512] Example 81 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00513] Sodium triacetoxyhydroborate (12.3 mg, 0.058 mmol) was added to a solution of DIPEA (10 µL, 0.058 mmol), 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (15.0 mg, 0.029 mmol) and formaldehyde (2 µL, 0.029 mmol) in MeOH (290 µL) at rt. After 30 min, the mixture was

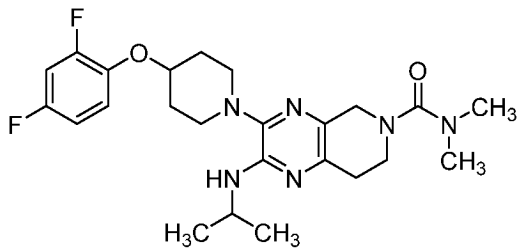
purified by HPLC Method A to give the title compound as a TFA salt (12.3 mg, 80%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.25 (d, J = 6.6 Hz, 6H), 1.90-2.00 (m, 2H), 2.07-2.16 (m, 2H), 2.96-3.05 (m, 3H), 3.08 (br s, 4H), 3.33-3.42 (m, 2H), 3.43-3.85 (m, 2H), 4.14-4.38 (m, 3H), 4.44-4.51 (m, 1H), 6.84-6.91 (m, 1H), 6.95-7.02 (m, 1H), 7.17 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 418.3.

[00514] Example 82 1-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00515] Acetic anhydride (5 μL, 0.058 mmol) was added to a solution of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (15.1 mg, 0.029 mmol) and pyridine (7 μL, 0.088 mmol) in DCM (290 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (12.7 mg, 78%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.33 (d, J = 6.6 Hz, 6H), 1.91-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.19 (s, 1.4H), 2.21 (s, 1.6H), 2.77-2.83 (m, 0.9H), 2.88-2.94 (m, 1.1H), 3.12 (td, J = 8.5, 4.0 Hz, 2H), 3.43-3.51 (m, 2H), 3.80-3.85 (m, 1.1H), 3.86-3.91 (m, 0.9H), 4.10-4.18 (m, 1H), 4.47-4.54 (m, 1H), 4.55 (br s, 2H), 6.85-6.92 (m, 1H), 6.99 (ddd, J = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 446.4.

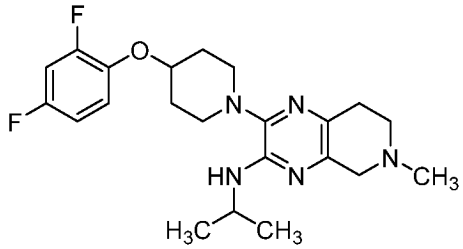
[00516] Example 83 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00517] Dimethylcarbamic chloride (6.4 mg, 0.059 mmol) was added to a solution of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (15.3 mg, 0.030 mmol) and triethylamine (12 μL, 0.089 mmol) in DCM (300 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title

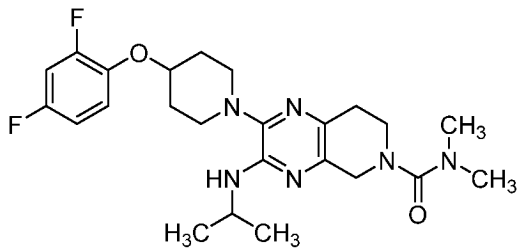
compound as a TFA salt (11.1 mg, 63.8%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.31 (d, J = 6.3 Hz, 6H), 1.91-2.01 (m, 2H), 2.09-2.18 (m, 2H), 2.86 (t, J = 5.7 Hz, 2H), 2.90 (s, 6H), 3.03-3.11 (m, 2H), 3.39-3.47 (m, 2H), 3.55 (t, J = 5.7 Hz, 2H), 4.14 (quin, J = 6.4 Hz, 1H), 4.27 (s, 2H), 4.49 (tt, J = 7.3, 3.6 Hz, 1H), 6.84-6.91 (m, 1H), 6.99 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 475.4.

[00518] Example 84 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



[00519] Sodium triacetoxyhydroborate (9.9 mg, 0.047 mmol) was added to a solution of DIPEA (8 μL, 0.047 mmol), 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (12.1 mg, 0.023 mmol) and formaldehyde (2 μL, 0.023 mmol) in MeOH (230 μL) at rt. After 30 min, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (8.9 mg, 71.6%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.24 (d, J = 6.3 Hz, 6H), 1.90-2.00 (m, 2H), 2.08-2.17 (m, 2H), 2.95-3.06 (m, 3H), 3.12 (br s, 4H), 3.35-3.53 (m, 3H), 3.76 (br s, 1H), 4.15 (dt, J = 13.1, 6.5, 6.5 Hz, 1H), 4.19-4.38 (m, 2H), 4.48 (tt, J = 7.3, 3.7 Hz, 1H), 6.85-6.92 (m, 1H), 6.99 (ddd, J = 11.4, 8.5, 3.0 Hz, 1H), 7.17 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 418.3.

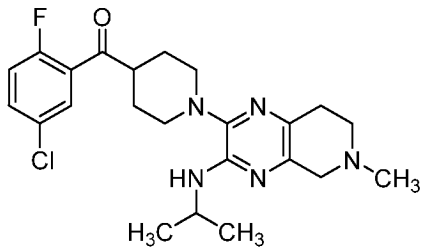
[00520] Example 85 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-N,N-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00521] Dimethylcarbamic chloride (5.2 mg, 0.049 mmol) was added to a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (12.6 mg, 0.024 mmol) and triethylamine (10 μL, 0.073 mmol) in DCM (240 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title

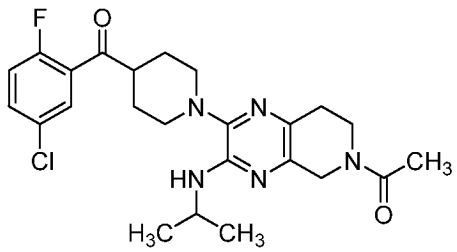
compound as a TFA salt (8.0 mg, 55.8%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.28 (d, J = 6.6 Hz, 6H), 1.90-2.00 (m, 2H), 2.08-2.17 (m, 2H), 2.77-2.84 (m, 2H), 2.91 (s, 6H), 2.99-3.08 (m, 2H), 3.35-3.44 (m, 2H), 3.55 (t, J = 5.8 Hz, 2H), 4.09-4.17 (m, 1H), 4.29 (s, 2H), 4.44-4.51 (m, 1H), 6.84-6.91 (m, 1H), 6.99 (s, 1H), 7.18 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 475.4.

[00522] Example 86 (5-chloro-2-fluorophenyl)(1-(3-(isopropylamino)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)methanone



[00523] Sodium triacetoxyhydroborate (6.5 mg, 0.031 mmol) was added to a solution of DIPEA (5 μL, 0.031 mmol), (5-chloro-2-fluorophenyl)(1-(3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-b]pyrazin-2-yl)piperidin-4-yl)methanone TFA salt (8.4 mg, 0.015 mmol) and formaldehyde (1.5 μL, 0.015 mmol) in MeOH (150 μL) at rt. After 30 min, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (4.7 mg, 54.6%) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.24 (d, J = 6.6 Hz, 6H), 1.82-1.93 (m, 2H), 1.97-2.05 (m, 2H), 2.81-3.05 (m, 4H), 3.08 (s, 3H), 3.35-3.54 (m, 4H), 3.72-3.83 (m, 1H), 4.10-4.18 (m, 1H), 4.19-4.40 (m, 2H), 7.25-7.32 (m, 1H), 7.61 (ddd, J = 8.8, 4.3, 2.8 Hz, 1H), 7.75 (dd, J = 6.1, 2.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 446.3.

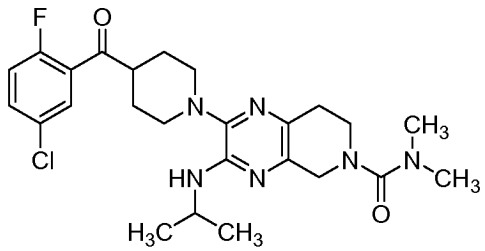
[00524] Example 87 1-(2-(4-(5-chloro-2-fluorobenzoyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00525] Acetic anhydride (3 μL, 0.029 mmol) was added to a solution of (5-chloro-2-fluorophenyl)(1-(3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)methanone TFA salt (8.0 mg, 0.015 mmol) and pyridine (4 μL, 0.044 mmol) in DCM (150 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (3.6 mg, 42%) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4,

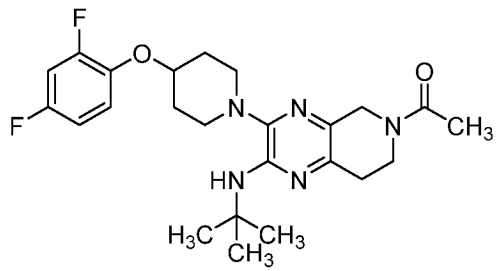
mixture of rotamers) δ ppm 1.26-1.32 (m, 6H), 1.84-1.96 (m, 2H), 1.97-2.06 (m, 2H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.70-2.76 (m, 0.7H), 2.80-2.86 (m, 1.3H), 2.87-3.00 (m, 2H), 3.34-3.41 (m, 1H), 3.46-3.56 (m, 2H), 3.79-3.84 (m, 1.3H), 3.84-3.89 (m, 0.7H), 4.07-4.18 (m, 1H), 4.57 (s, 1.1H), 4.62 (s, 0.9H), 7.28 (dd, J = 10.4, 8.8 Hz, 1H), 7.61 (ddd, J = 8.9, 4.2, 2.9 Hz, 1H), 7.76 (dd, J = 6.1, 2.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 474.3.

[00526] Example 88 2-(4-(5-chloro-2-fluorobenzoyl)piperidin-1-yl)-3-(isopropylamino)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00527] Dimethylcarbamic chloride (3.2 mg, 0.029 mmol) was added to a solution of (5-chloro-2-fluorophenyl)(1-(3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)methanone TFA salt (8.0 mg, 0.015 mmol) and triethylamine (6 μL, 0.044 mmol) in DCM (150 μL) at rt. After 1 h, the mixture was purified by HPLC Method A to give the title compound as a TFA salt (3.9 mg, 43.1%) as a yellow solid. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.31 (d, J = 6.6 Hz, 6H), 1.85-2.05 (m, 4H), 2.77-2.84 (m, 2H), 2.91 (s, 6H), 2.93-3.01 (m, 2H), 3.36-3.41 (m, 1H), 3.51-3.59 (m, 4H), 4.07-4.15 (m, 1H), 4.31 (s, 2H), 7.28 (dd, J = 10.4, 8.8 Hz, 1H), 7.61 (ddd, J = 8.8, 4.3, 2.8 Hz, 1H), 7.76 (dd, J = 6.1, 2.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 504.4.

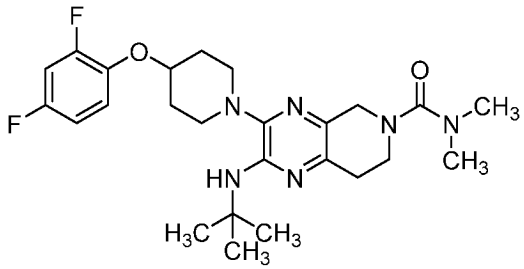
[00528] Example 89 1-(2-(tert-butylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00529] A solution of *N*-(tert-butyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (16 mg, 0.030 mmol), acetic anhydride (5.7 μL, 0.060 mmol), and DIPEA (15.8 μL, 0.090 mmol) in DCM (151 μL) was stirred at room temperature overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 μm filter (Millipore® Millex-LCR), and purified via

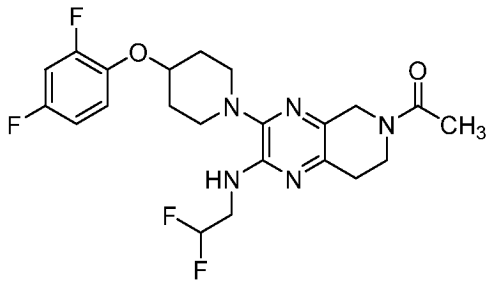
HPLC Method A to give the title compound as a TFA salt (15 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.48 (s, 9H), 1.87-1.98 (m, 2H), 2.07-2.17 (m, 2H), 2.19 (s, 1.3H), 2.21 (s, 1.7H), 2.74 (t, J = 5.9 Hz, 0.9H), 2.84 (t, J = 5.9 Hz, 1.1H), 2.97 (ddd, J = 12.4, 8.6, 3.3 Hz, 2H), 3.33-3.37 (m, 2H), 3.80 (t, J = 5.9 Hz, 1.1H), 3.85 (t, J = 5.9 Hz, 0.9H), 4.43-4.51 (m, 1H), 4.53 (d, J = 1.3 Hz, 2H), 6.88 (ddddd, J = 9.1, 8.1, 2.9, 1.9, 0.8 Hz, 1H), 6.95-7.02 (m, 1H), 7.18 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 460.4.

[00530] Example 90 2-(*tert*-butylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-N,N-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



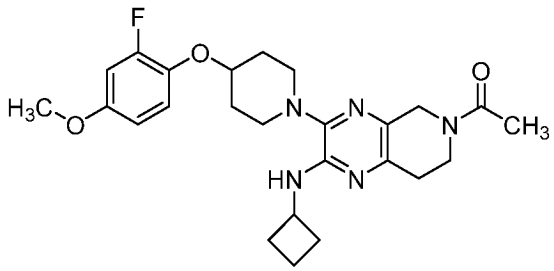
[00531] A solution of *N*-(tert-butyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (16 mg, 0.030 mmol), dimethylcarbamic chloride (3.2 mg, 0.030 mmol), and DIPEA (5.3 µL, 0.030 mmol) in DCM (151 µL) was stirred at room temperature overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (10 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.48 (s, 9H), 1.87-1.97 (m, 2H), 2.07-2.17 (m, 2H), 2.82 (t, J = 5.9 Hz, 2H), 2.90 (s, 6H), 2.95 (ddd, J = 12.2, 8.5, 3.3 Hz, 2H), 3.29-3.35 (m, 2H), 3.53 (t, J = 5.8 Hz, 2H), 4.25 (s, 2H), 4.46 (tt, J = 7.5, 3.8 Hz, 1H), 6.84-6.91 (m, 1H), 6.99 (ddd, J = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, J = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 489.4.

[00532] Example 91 1-(2-((2,2-difluoroethyl)amino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



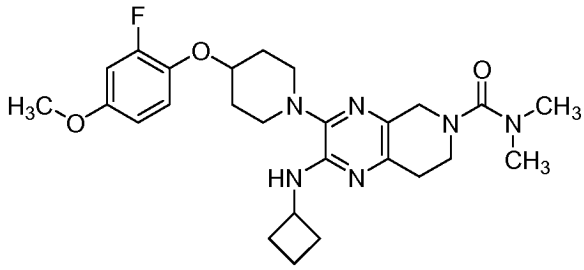
[00533] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (15 mg, 0.028 mmol), acetic anhydride (5.2 μL, 0.056 mmol), and DIPEA (14.6 μL, 0.083 mmol) in DCM (139 μL) was stirred at room temperature overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 μm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (13 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.91-2.03 (m, 2H), 2.09-2.17 (m, 2H), 2.19 (s, 1.3H), 2.21 (s, 1.7H), 2.75 (t, J = 5.9 Hz, 0.9H), 2.85 (t, J = 5.9 Hz, 1.1H), 2.95-3.05 (m, 2H), 3.34-3.42 (m, 2H), 3.73-3.79 (m, 2H), 3.81 (t, J = 5.9 Hz, 1.2H), 3.86 (t, J = 6.1 Hz, 0.8H), 4.46 (tq, J = 7.9, 3.9 Hz, 1H), 4.56 (d, J = 0.8 Hz, 2H), 5.89-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (dddd, J = 11.4, 8.5, 3.0, 1.0 Hz, 1H), 7.17 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 468.3.

[00534] Example 92 1-(2-(cyclobutylamino)-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



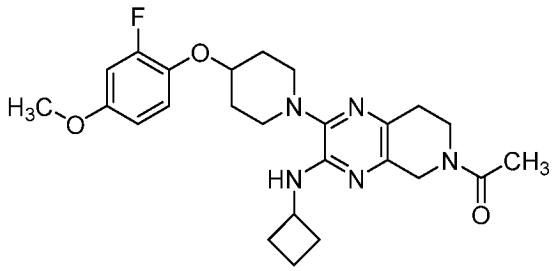
[00535] A mixture of *N*-cyclobutyl-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (10 mg, 0.018 mmol), acetic anhydride (3.8 mg, 0.037 mmol) and pyridine (4.4 mg, 0.055 mmol) in DCM (190 μL) was stirred at room temperature for 30 min. The mixture was purified by HPLC Method A to give the title compound as a TFA salt (6.4 mg, 59%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.76-1.86 (m, 2H), 1.89-2.00 (m, 2H), 2.01-2.15 (m, 4H), 2.19 (s, 1.4H), 2.20 (s, 1.6H), 2.38-2.48 (m, 2H), 2.73-2.79 (m, 0.9H), 2.81-2.88 (m, 1.1H), 2.99-3.08 (m, 2H), 3.38-3.47 (m, 2H), 3.76 (s, 3H), 3.78-3.83 (m, 1.1H), 3.83-3.88 (m, 0.9H), 4.32-4.48 (m, 2H), 4.54 (s, 2H), 6.64-6.70 (m, 1H), 6.74 (dd, J = 12.8, 2.9 Hz, 1H), 7.08 (t, J = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 470.4.

[00536] Example 93 2-(cyclobutylamino)-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



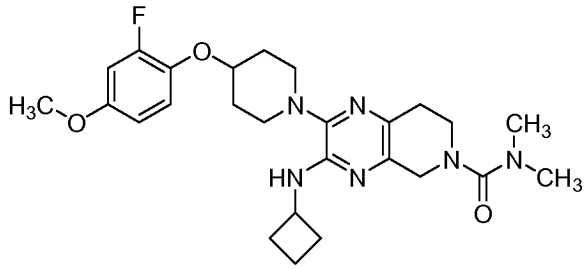
[00537] A mixture of *N*-cyclobutyl-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (10.6 mg, 0.020 mmol), dimethylcarbamic chloride (4.2 mg, 0.039 mmol) and triethylamine (5.9 mg, 0.059 mmol) in DCM (200 µL) was stirred at room temperature for 30 min. The mixture was purified by HPLC Method A to give the title compound as a TFA salt (7.1 mg, 59.2%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.77-1.87 (m, 2H), 1.90-2.00 (m, 2H), 2.03-2.15 (m, 4H), 2.39-2.49 (m, 2H), 2.81-2.87 (m, 2H), 2.90 (s, 6H), 2.98-3.08 (m, 2H), 3.38-3.47 (m, 2H), 3.54 (t, *J* = 5.8 Hz, 2H), 3.76 (s, 3H), 4.26 (s, 2H), 4.33-4.47 (m, 2H), 6.67 (dd, *J* = 9.1, 1.5 Hz, 1H), 6.74 (dd, *J* = 12.8, 2.9 Hz, 1H), 7.08 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 499.4.

[00538] Example 94 1-(3-(cyclobutylamino)-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



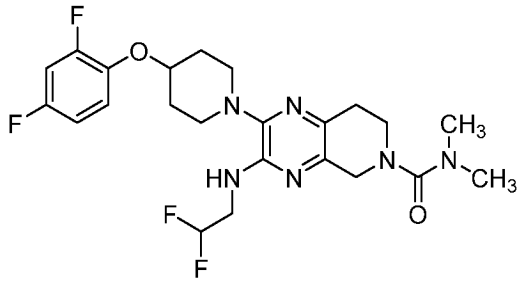
[00539] A mixture of *N*-cyclobutyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (10.1 mg, 0.019 mmol), acetic anhydride (3.8 mg, 0.037 mmol) and pyridine (4 mg, 0.056 mmol) in DCM (190 µL) was stirred at room temperature for 30 min. The mixture was purified by HPLC Method A to give the title compound as a TFA salt (9.7 mg, 89%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.78-1.87 (m, 2H), 1.91-2.01 (m, 2H), 2.03-2.16 (m, 4H), 2.19 (s, 1.2H), 2.21 (s, 1.8H), 2.38-2.50 (m, 2H), 2.70-2.76 (m, 0.8H), 2.80-2.87 (m, 1.2H), 3.00-3.11 (m, 2H), 3.40-3.50 (m, 2H), 3.76 (s, 3H), 3.79-3.83 (m, 1.2H), 3.84-3.88 (m, 0.8H), 4.34-4.48 (m, 2H), 4.57 (s, 0.8H), 4.61 (s, 1.2H), 6.64-6.69 (m, 1H), 6.74 (dd, *J* = 12.8, 2.9 Hz, 1H), 7.08 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 470.4.

[00540] Example 95 3-(cyclobutylamino)-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00541] A mixture of *N*-cyclobutyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (9.1 mg, 0.017 mmol), dimethylcarbamic chloride (3.6 mg, 0.034 mmol) and triethylamine (5.1 mg, 0.050 mmol) in DCM (170 µL) was stirred at room temperature for 30 min. The mixture was purified by HPLC Method A to give the title compound as a TFA salt (6.0 mg, 58.3%) as a yellow film. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.74-1.84 (m, 2H), 1.89-2.04 (m, 4H), 2.06-2.15 (m, 2H), 2.36-2.46 (m, 2H), 2.79 (t, J = 5.7 Hz, 2H), 2.90 (s, 6H), 2.94-3.02 (m, 2H), 3.34-3.43 (m, 2H), 3.51-3.56 (m, 2H), 3.76 (s, 3H), 4.26 (s, 2H), 4.43 (s, 2H), 6.64-6.69 (m, 1H), 6.74 (dd, J = 12.9, 3.0 Hz, 1H), 7.08 (t, J = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 499.4.

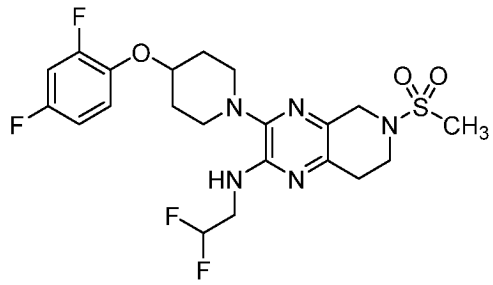
[00542] Example 96 3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



[00543] A solution of *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (15 mg, 0.028 mmol), dimethylcarbamic chloride (3.0 mg, 0.028 mmol), and DIPEA (4.9 µL, 0.028 mmol) in DCM (278 µL) was stirred at room temperature overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method to give the title compound as a TFA salt (5 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.92-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.82 (t, J = 5.8 Hz, 2H), 2.90 (s, 6H), 2.99 (ddd, J = 12.4, 8.6, 3.4 Hz, 2H), 3.34-3.41 (m, 2H), 3.55 (t, J = 5.8 Hz, 2H), 3.77 (td, J = 14.5, 4.3 Hz, 2H), 4.28 (s, 2H), 4.42-4.49 (m,

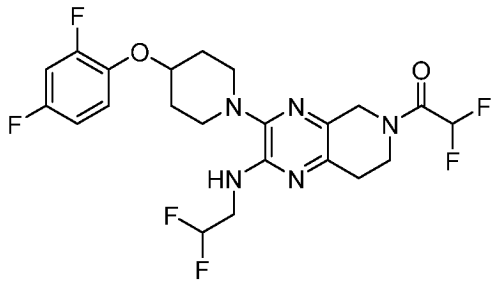
1H), 5.89-6.21 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, J = 11.4, 8.6, 3.0 Hz, 1H), 7.17 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 497.4.

[00544] Example 97 *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00545] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (17 mg, 0.032 mmol), DIPEA (12.2 mg, 0.095 mmol) and methanesulfonyl chloride (4.9 µL, 0.063 mmol) in DCM (315 µL) was stirred at room temperature overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (6 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.92-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.88 (t, J = 5.9 Hz, 2H), 2.93 (s, 3H), 3.00 (ddd, J = 12.4, 8.8, 3.3 Hz, 2H), 3.34-3.42 (m, 2H), 3.57 (t, J = 5.9 Hz, 2H), 3.78 (td, J = 14.5, 4.3 Hz, 2H), 4.28 (s, 2H), 4.46 (tt, J = 7.5, 3.6 Hz, 1H), 5.89-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, J = 11.4, 8.6, 3.0 Hz, 1H), 7.17 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 504.3.

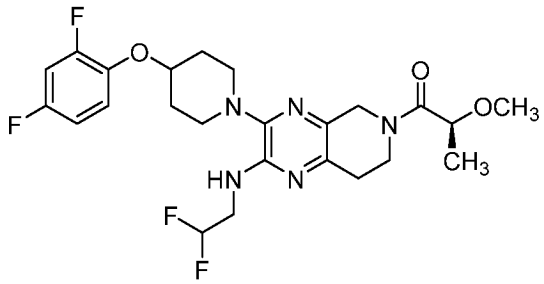
[00546] Example 98 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone



[00547] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (17 mg, 0.032 mmol), DIPEA (12.2 mg, 0.095 mmol), and 2,2-difluoroacetic anhydride (8.2 mg, 0.047 mmol) in DCM (315 µL) was stirred at room temperature overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and

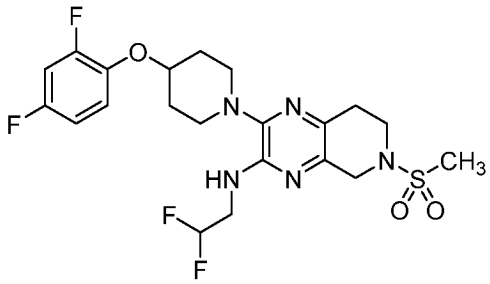
purified via HPLC Method A to give the title compound as a TFA salt (5 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.92-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.81 (t, J = 5.9 Hz, 0.8H), 2.87 (t, J = 5.9 Hz, 1.2H), 2.97-3.05 (m, 2H), 3.35-3.43 (m, 2H), 3.78 (td, J = 14.5, 4.3 Hz, 2H), 3.87-3.96 (m, 2H), 4.42-4.50 (m, 1H), 4.60 (s, 1.2H), 4.62 (s, 0.8H), 5.89-6.22 (m, 1H), 6.41-6.71 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, J = 11.4, 8.6, 3.0 Hz, 1H), 7.17 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 504.3.

[00548] Example 99 (*S*)-1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one



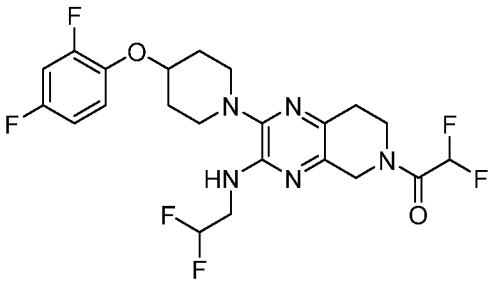
[00549] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (17 mg, 0.032 mmol), HATU (13.2 mg, 0.035 mmol), and DIPEA (12.2 mg, 0.095 mmol) in DMF (158 μL) was stirred for 10 min. Then, (*S*)-2-methoxypropanoic acid (3.6 mg, 0.035 mmol) was added at room temperature and the resulting reaction mixture stirred overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 μm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (6 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.32 (d, J = 6.6 Hz, 1.3H), 1.38 (d, J = 6.6 Hz, 1.7H), 1.91-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.77 (t, J = 5.8 Hz, 0.9H), 2.85 (t, J = 4.9 Hz, 1.1H), 2.96-3.05 (m, 2H), 3.33 (s, 3H), 3.35-3.43 (m, 2H), 3.78 (td, J = 14.5, 4.3 Hz, 2H), 3.84-3.97 (m, 2H), 4.31-4.40 (m, 1H), 4.42-4.49 (m, 1H), 4.59 (m, 0.9H), 4.67 (m, 1.1H), 5.90-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, J = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 512.4.

[00550] Example 100 1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone



[00551] A solution of *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (15 mg, 0.028 mmol), DIPEA (10.8 mg, 0.083 mmol) and methanesulfonyl chloride (4.3 µL, 0.056 mmol) in DCM (280 µL) was stirred at room temperature for 2 h. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (3 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.92-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.87 (t, J = 5.9 Hz, 2H), 2.93 (s, 3H), 2.96-3.04 (m, 2H), 3.34-3.42 (m, 2H), 3.57 (t, J = 5.8 Hz, 2H), 3.76 (td, J = 14.5, 4.3 Hz, 2H), 4.28 (s, 2H), 4.42-4.49 (m, 1H), 5.89-6.21 (m, 1H), 6.85-6.91 (m, 1H), 6.98 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, J =9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 504.4.

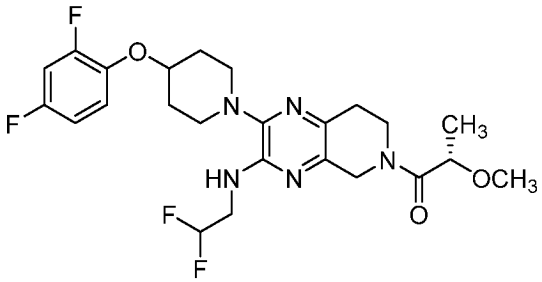
[00552] Example 101 1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone



[00553] A solution of *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (15 mg, 0.028 mmol), DIPEA (10.8 mg, 0.083 mmol), and 2,2-difluoroacetic anhydride (7.3 mg, 0.042 mmol) in DCM (278 µL) was stirred at room temperature for 2 h. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (3 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.92-2.02 (m, 2H), 2.09-2.17 (m, 2H), 2.80 (t, J = 5.9 Hz, 0.8H), 2.86 (t, J = 5.4 Hz, 1.2H), 2.96-3.04 (m, 2H), 3.34-3.43 (m, 2H), 3.77 (td, J = 14.3, 4.0 Hz, 2H), 3.90 (t, J = 5.8 Hz, 1.2H), 3.93 (t, J = 6.1 Hz, 0.8H),

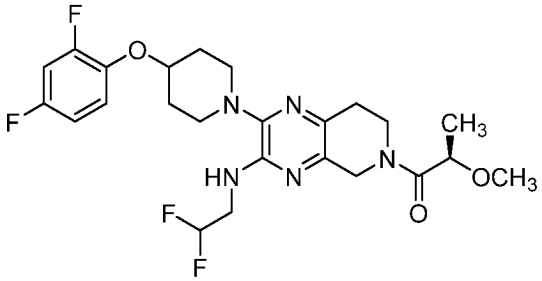
4.46 (tt, J = 7.6, 3.7 Hz, 1H), 4.61 (s, 0.8H), 4.63 (s, 1.2H), 5.89-6.21 (m, 1H), 6.42-6.71 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 504.4.

[00554] Example 102 (*S*)-1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one



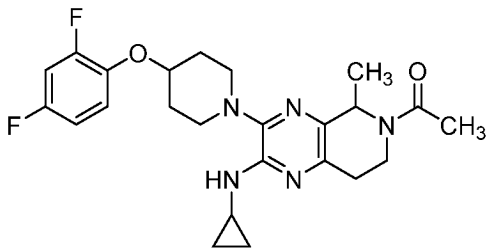
[00555] A solution of (*S*)-2-methoxypropanoic acid (2.9 mg, 0.028 mmol), DIPEA (3.9 mg, 0.028 mmol), and HATU (10.6 mg, 0.028 mmol) in DMF (278 µL) was stirred at room temperature for 10 min then treated with *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (15 mg, 0.028 mmol). Stirring was continued overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (3 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.32 (d, J = 6.6 Hz, 1.3H), 1.38 (d, J = 6.6 Hz, 1.7H), 1.91-2.04 (m, 2H), 2.09-2.19 (m, 2H), 2.76 (t, J = 6.2 Hz, 0.9H), 2.84 (t, J = 5.4 Hz, 1.1H), 2.95-3.05 (m, 2H), 3.33 (s, 3H), 3.35-3.43 (m, 2H), 3.78 (td, J = 14.6, 4.3 Hz, 2H), 3.83-3.98 (m, 2H), 4.32-4.41 (m, 1H), 4.42-4.49 (m, 1H), 4.56 (m, 1.1H), 4.68 (m, 0.9H), 5.89-6.22 (m, 1H), 6.85-6.91 (m, 1H), 6.98 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 512.4.

[00556] Example 103 (*R*)-1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one



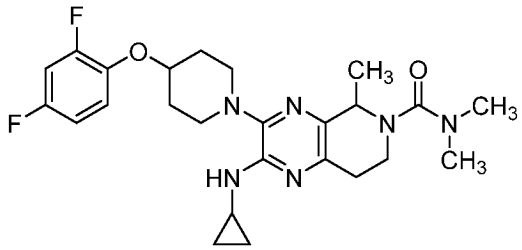
[00557] A solution of (*R*)-2-methoxypropanoic acid (2.9 mg, 0.028 mmol), DIPEA (10.8 mg, 0.083 mmol), and HATU (10.6 mg, 0.028 mmol) in DMF (278 µL) was stirred at room temperature for 10 min followed by the addition of *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (15 mg, 0.028 mmol) and stirring overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (3 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.32 (d, *J* = 6.8 Hz, 1.3H), 1.38 (d, *J* = 6.6 Hz, 1.6H), 1.90-2.04 (m, 2H), 2.09-2.18 (m, 2H), 2.76 (t, *J* = 6.6 Hz, 0.9H), 2.84 (t, *J* = 6.1 Hz, 1.1H), 3.00 (ddd, *J* = 12.3, 8.6, 3.3 Hz, 2H), 3.33 (s, 3H), 3.34-3.43 (m, 2H), 3.72-3.84 (m, 2H), 3.84-3.98 (m, 2H), 4.32-4.41 (m, 1H), 4.42-4.50 (m, 1H), 4.51-4.55 (m, 0.6H), 4.62-4.69 (m, 1.4H), 5.89-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 512.4.

Example 104 1-(2-(cyclopropylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



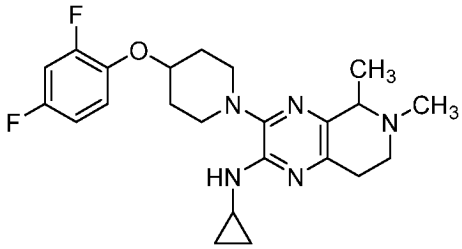
[00558] The title compound was prepared in a manner similar to Example 29 using *N*-cyclopropyl-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt. ^{1}H NMR (400 MHz, methanol-*d*4, mixture of rotamers) δ ppm 0.78-0.84 (m, 2H), 1.01-1.07 (m, 2H), 1.47 (d, *J* = 6.8 Hz, 2H), 1.60 (d, *J* = 6.8 Hz, 1H), 1.90-2.03 (m, 2H), 2.09-2.19 (m, 2H), 2.23 (s, 3H), 2.76 (tt, *J* = 6.9, 3.5 Hz, 1H), 2.85-2.96 (m, 2H), 2.99-3.20 (m, 3H), 3.46-3.60 (m, 3H), 4.14 (dd, *J* = 13.6, 5.6 Hz, 0.5H), 4.52 (td, *J* = 7.4, 3.4 Hz, 1H), 5.38 (q, *J* = 6.6 Hz, 0.5H), 6.86-6.94 (m, 1H), 7.01 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.19 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z [M+H]$^+$ 458.35.

[00559] Example 105 2-(cyclopropylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*,*N*,5-trimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide



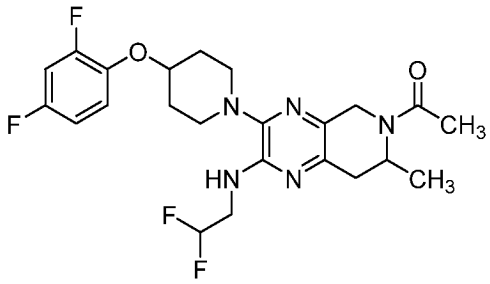
[00560] The title compound was prepared in a manner similar to Example 55 using *N*-cyclopropyl-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt. ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm 0.82-0.89 (m, 1H), 1.05-1.12 (m, 1H), 1.53-1.58 (m, 3H), 1.92-2.04 (m, 2H), 2.10-2.20 (m, 2H), 2.63-2.87 (m, 2H), 2.91-2.94 (m, 5H), 3.02-3.25 (m, 3H), 3.35-3.59 (m, 3H), 3.78-3.86 (m, 1H), 4.49-4.57 (m, 1H), 4.66 (q, *J* = 6.8 Hz, 1H), 6.86-6.94 (m, 1H), 6.97-7.05 (m, 1H), 7.15-7.25 (m, 1H); ESI-MS m/z $[M+H]^+$ 487.40.

[00561] Example 106 *N*-cyclopropyl-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6-dimethyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



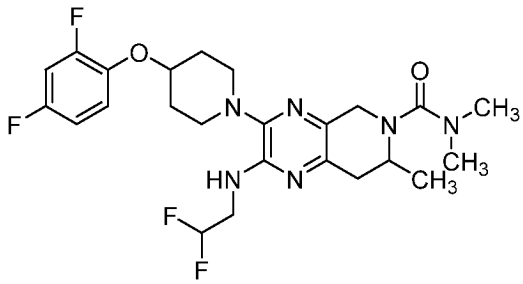
[00562] A solution of *N*-cyclopropyl-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (15 mg, 0.028 mmol), formaldehyde (1.5 μL, 0.057 mmol), and DIPEA (5.0 μL, 0.028 mmol) in DCM (283 μL) was stirred for 10 min. To this was then added sodium triacetoxyborohydride (18.0 mg, 0.085 mmol) and the reaction mixture was stirred overnight. Purification by HPLC Method A afforded the title compound as a TFA salt (4 mg). ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm 0.60-0.67 (m, 2H), 0.83-0.92 (m, 2H), 1.64-1.80 (m, 3H), 1.87-2.04 (m, 2H), 2.05-2.21 (m, 2H), 2.74 (tt, *J* = 7.0, 3.6 Hz, 1H), 2.98-3.21 (m, 7H), 3.35-3.51 (m, 2H), 3.59 (d, *J* = 6.6 Hz, 1H), 3.78 (br s, 1H), 4.42 (br s, 1H), 4.49 (td, *J* = 7.4, 3.7 Hz, 1H), 6.86-6.93 (m, 1H), 6.96-7.05 (m, 1H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H).

[00563] Example 107 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00564] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (15 mg, 0.027 mmol), acetic anhydride (5.1 µL, 0.054 mmol), and DIPEA (14.2 µL, 0.081 mmol) in DCM (136 µL) was stirred at room temperature overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (8 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.13 (d, J = 6.8 Hz, 1.4H), 1.23 (d, J = 6.8 Hz, 1.6H), 1.92-2.03 (m, 2H), 2.09-2.17 (m, 2H), 2.18 (s, 1.4H), 2.22 (s, 1.6H), 2.54-2.67 (m, 1H), 2.95-3.04 (m, 2.4H), 3.13 (dd, J = 16.7, 6.3 Hz, 0.6H), 3.34-3.44 (m, 2H), 3.74-3.83 (m, 2.4H), 3.99 (d, J = 18.2 Hz, 0.6H), 4.40-4.49 (m, 1H), 4.55 (quin, J = 6.6 Hz, 0.5H), 4.66 (d, J = 16.7 Hz, 0.5H), 5.07 (d, J = 17.7 Hz, 0.5H), 5.18 (m, 0.5H), 5.90-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 481.9.

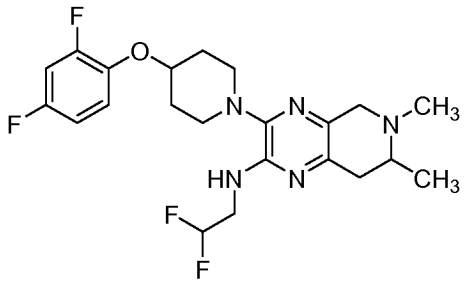
[00565] Example 108 2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*,*N*,7-trimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5H)-carboxamide



[00566] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (15 mg, 0.027 mmol), dimethylcarbamic chloride (5.8 mg, 0.054 mmol), and DIPEA (14.2 µL, 0.081 mmol) in DCM (136 µL) was stirred at room temperature overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (10 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.19 (d, J = 6.8 Hz, 3H), 1.92-2.02 (m,

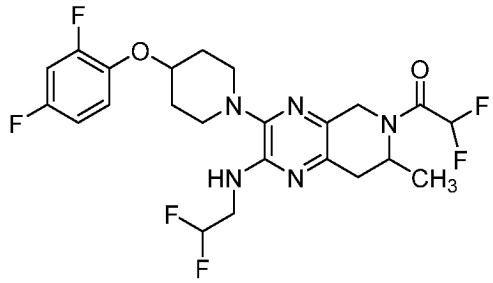
2H), 2.09-2.19 (m, 2H), 2.53 (d, J = 17.2 Hz, 1H), 2.88 (s, 6H), 3.00 (ddd, J = 12.3, 8.6, 3.3 Hz, 2H), 3.15 (dd, J = 16.8, 5.9 Hz, 1H), 3.34-3.42 (m, 2H), 3.73-3.84 (m, 2H), 4.2 -4.34 (m, 3H), 4.46 (tt, J = 7.6, 3.6 Hz, 1H), 5.89-6.22 (m, 1H), 6.85-6.91 (m, 1H), 6.98 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, J =9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 511.1.

[00567] Example 109 *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6,7-dimethyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00568] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (15 mg, 0.027 mmol), formaldehyde (4.0 µL, 0.054 mmol), and DIPEA (4.7 µL, 0.027 mmol) in DCM (136 µL) was stirred for 10 min at room temperature then treated with sodium triacetoxyborohydride (17.2 mg, 0.081 mmol). The resulting reaction mixture was stirred overnight. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (8 mg) as a clear oil. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.39-1.57 (m, 3H), 1.92-2.03 (m, 2H), 2.08-2.18 (m, 2H), 2.82-3.09 (m, 6H), 3.16 (d, J =14.9 Hz, 1H), 3.35-3.44 (m, 2H), 3.67-3.85 (m, 3H), 4.11-4.29 (m, 1H), 4.37-4.44 (m, 1H), 4.44-4.52 (m, 1H), 5.90-6.22 (m, 1H), 6.85-6.91 (m, 1H), 6.98 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 453.9.

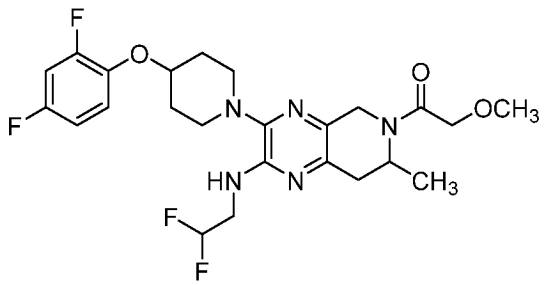
[00569] Example 110 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-7,8-dihydropyrido[4,3-b]pyrazin-6(5H)-yl)-2,2-difluoroethanone



[00570] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (10 mg, 0.018 mmol), 2,2-

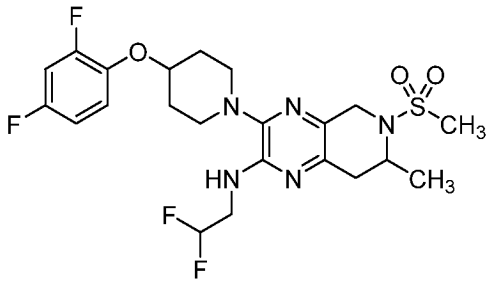
difluoroacetic anhydride (4.7 mg, 0.027 mmol), and DIPEA (7.0 mg, 0.054 mmol) in DCM (90 µL) was stirred at room temperature for 2 h. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (5 mg) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.21 (d, J = 7.1 Hz, 1.2H), 1.29 (d, J = 6.6 Hz, 1.8H), 1.92-2.03 (m, 2H), 2.09-2.19 (m, 2H), 2.58-2.69 (m, 1H), 2.98-3.07 (m, 2.4H), 3.11-3.17 (m, 0.6H), 3.35-3.44 (m, 2H), 3.78 (td, J = 14.5, 4.3 Hz, 2H), 4.11 (d, J = 17.2 Hz, 1H), 4.42-4.51 (m, 1H), 4.60-4.67 (m, 0.6H), 4.73-4.77 (m, 0.4H), 5.05 (d, J = 17.7 Hz, 0.6H), 5.11-5.18 (m, 0.4H), 5.89-6.22 (m, 1H), 6.39-6.73 (m, 1H), 6.85-6.91 (m, 1H), 6.99 (ddd, J = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, J = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 517.9.

[00571] Example 111 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethanone



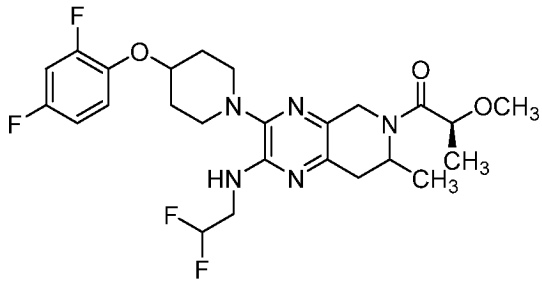
[00572] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (10 mg, 0.018 mmol), 2-methoxyacetyl chloride (2.9 mg, 0.027 mmol), and DIPEA (7.0 mg, 0.054 mmol) in DCM (90 µL) was stirred at room temperature for 2 h. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (4 mg) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.16 (d, J = 6.8 Hz, 1.4H), 1.24 (d, J = 6.6 Hz, 1.6H), 1.91-2.04 (m, 2H), 2.09-2.19 (m, 2H), 2.59 (dd, J = 16.9, 10.6 Hz, 1H), 2.97-3.00 (m, 2.4H), 3.09-3.15 (m, 0.6H), 3.35-3.41 (m, 2H), 3.43 (s, 3H), 3.78 (td, J = 14.6, 4.3 Hz, 2H), 4.03 (d, J = 17.9 Hz, 0.6H), 4.19-4.27 (m, 1.4H), 4.29-4.39 (m, 1H), 4.46-4.52 (m, 1.5H), 4.58-4.62 (m, 0.5H), 5.07 (d, J = 18.8 Hz, 0.5H), 5.18 (t, J = 5.3 Hz, 0.5H), 5.89-6.22 (m, 1H), 6.85-6.91 (m, 1H), 6.99 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 511.9.

[00573] Example 112 *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00574] A solution of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (10 mg, 0.018 mmol), methanesulfonyl chloride (3.1 mg, 0.027 mmol), and DIPEA (7.0 mg, 0.054 mmol) in DCM (181 µL) was stirred at room temperature for 2 h. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (4 mg) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 1.25 (d, J = 6.8 Hz, 3H), 1.92-2.03 (m, 2H), 2.09-2.19 (m, 2H), 2.57 (d, J = 16.9 Hz, 1H), 2.94 (s, 3H), 3.01 (t, J = 10.9 Hz, 2H), 3.14 (dd, J = 16.7, 6.3 Hz, 1H), 3.34-3.43 (m, 2H), 3.78 (td, J = 14.5, 4.3 Hz, 2H), 4.17-4.25 (m, 1H), 4.43-4.55 (m, 3H), 5.89-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.99 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 517.9.

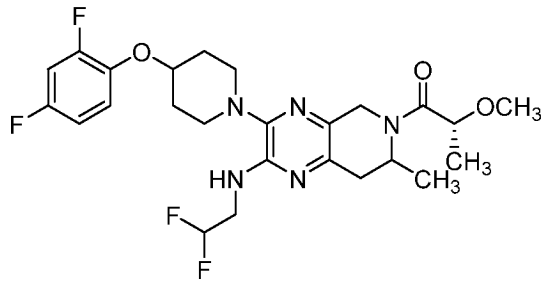
[00575] Example 113 (2*S*)-1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one



[00576] A solution of (*S*)-2-methoxypropanoic acid (1.9 mg, 0.018 mmol), DIPEA (7.0 mg, 0.054 mmol), and HATU (6.9 mg, 0.018 mmol) in DMF (90 µL) was stirred at room temperature for 10 min then treated with *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (10 mg, 0.018 mmol). The resulting reaction mixture was stirred for 2 h. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (5 mg) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ

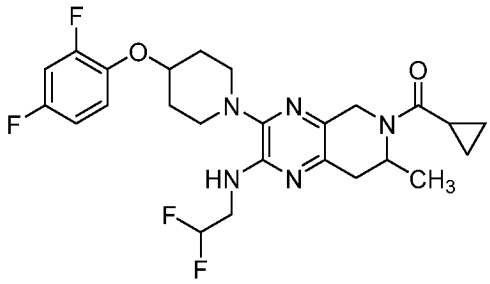
ppm 1.17 (t, J = 6.7 Hz, 1.4H), 1.27 (dd, J = 6.7, 2.7 Hz, 1.6H), 1.33 (dd, J = 11.5, 6.7 Hz, 1.4H), 1.38 (dd, J = 6.7, 2.7 Hz, 1.6H), 1.92-2.03 (m, 2H), 2.09-2.19 (m, 2H), 2.58 (m, 0.6H), 2.64 (m, 0.4H), 2.95-3.05 (m, 2H), 3.08-3.10 (m, 0.5H), 3.12-3.14 (m, 0.5H), 3.35 (s, 3H), 3.37-3.44 (m, 2H), 3.71-3.86 (m, 2H), 4.03 (t, J = 18.3 Hz, 1H), 4.30-4.41 (m, 1H), 4.43-4.50 (m, 1H), 4.70-4.83 (m, 1H), 5.08 (m, 0.5H), 5.21 (m, 0.5H), 5.89-6.21 (m, 1H), 6.84-6.91 (m, 1H), 6.99 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 525.9.

[00577] Example 114 (2*R*)-1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one



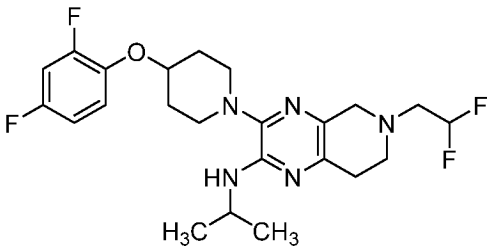
[00578] A solution of (*R*)-2-methoxypropanoic acid (1.9 mg, 0.018 mmol), DIPEA (7.0 mg, 0.054 mmol), and HATU (6.9 mg, 0.018 mmol) in DMF (90 µL) was stirred for 10 min at room temperature then treated with *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (10 mg, 0.018 mmol). The resulting reaction mixture was stirred for 2 h. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (5 mg) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.17 (t, J = 6.6 Hz, 1.4H), 1.27 (dd, J = 6.7, 2.7 Hz, 1.6H), 1.33 (dd, J = 11.6, 6.8 Hz, 1.4H), 1.38 (dd, J = 6.7, 2.7 Hz, 1.6H), 1.92-2.03 (m, 2H), 2.09-2.18 (m, 2H), 2.53-2.68 (m, 1H), 2.94-3.05 (m, 2H), 3.08-3.10 (m, 0.5H), 3.12-3.14 (m, 0.5H), 3.35 (s, 3H), 3.37-3.42 (m, 2H), 3.78 (td, J = 14.5, 4.2 Hz, 2H), 4.03 (t, J = 18.8 Hz, 1H), 4.30-4.41 (m, 1H), 4.43-4.51 (m, 1H), 4.70-4.82 (m, 1H), 5.03-5.14 (m, 0.5H), 5.18-5.23 (m, 0.5H), 5.90-6.22 (m, 1H), 6.85-6.91 (m, 1H), 6.99 (ddd, J = 11.3, 8.5, 2.9 Hz, 1H), 7.18 (td, J = 9.2, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 525.9.

[00579] Example 115 cyclopropyl(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone



[00580] A solution of cyclopropanecarboxylic acid (1.6 mg, 0.018 mmol), DIPEA (7.0 mg, 0.054 mmol), and HATU (6.9 mg, 0.018 mmol) in DMF (181 µL) was stirred at room temperature for 10 min followed by the addition of *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (10 mg, 0.018 mmol). The resulting reaction mixture was stirred for 2 h. The crude reaction mixture was diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give the title compound as a TFA salt (5 mg) as a white solid. ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 0.80-1.01 (m, 4H), 1.13 (d, J = 6.6 Hz, 1.4H), 1.27 (d, J = 6.3 Hz, 1.6H), 1.91-2.04 (m, 2H), 2.06-2.20 (m, 2H), 2.56-2.60 (m, 0.5H), 2.66-2.70 (m, 0.5H), 3.02 (br s, 2H), 3.13-3.15 (m, 0.5H), 3.16-3.20 (m, 0.5H), 3.34-3.46 (m, 2H), 3.72-3.87 (m, 2H), 4.04 (d, J = 18.2 Hz, 1H), 4.41-4.58 (m, 2H), 5.02 (d, J = 17.4 Hz, 1.4H), 5.15-5.19 (m, 0.6H), 5.90-6.23 (m, 1H), 6.84-6.91 (m, 1H), 6.99 (ddd, J = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, J = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 507.9.

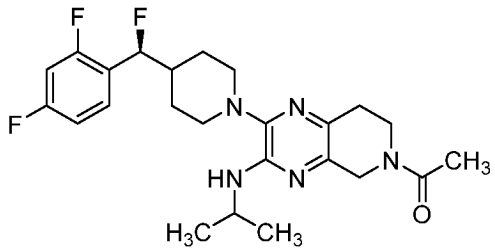
[00581] Example 116 6-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine



[00582] To a suspension of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (50 mg, 0.080 mmol) and Cs_2CO_3 (92 mg, 0.281 mmol) in DMF (0.5 mL) was added 1,1-difluoro-2-iodoethane (0.071 mL, 0.804 mmol) at 23 °C. The reaction mixture was stirred at 80 °C for 18 h. The resulting crude material was filtered, rinsed with DMSO (2 x 0.5 mL), and purified by HPLC Method B using a 30% to 70% ACN gradient to give the title compound as a TFA salt (6.1 mg, 13%) as a yellow film. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.19 (d, J = 6.4 Hz, 6H), 1.82-1.93

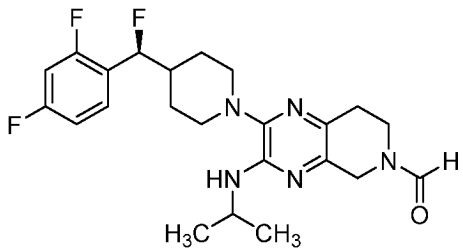
(m, 2H), 2.03-2.10 (m, 2H), 2.79-2.98 (m, 4H), 3.24-3.32 (m, 2H), 3.33-3.75 (m, 4H), 4.05-4.18 (m, 3H), 4.52-4.55 (m, 1H), 5.76-5.82 (m, 1H), 6.39-6.72 (m, 1H), 7.00-7.04 (m, 1H), 7.25-7.34 (m, 2H); ESI-MS m/z $[M+H]^+$ 468.3.

[00583] Example 117 (*S*)-1-(2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



A solution of (*S*)-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (56.0 mg, 0.105 mmol) in DCM (1.05 mL) at 0 °C was treated with acetic anhydride (19.8 µL, 0.210 mmol) and pyridine (25.5 µL, 0.315 mmol). The reaction mixture was concentrated under reduced pressure, taken up in MeOH, filtered, and purified by HPLC Method B. Fractions containing product were concentrated under reduced pressure. The material was repurified by HPLC Method A to give the title compound, as a TFA salt, as a pale yellow solid (5.4 mg, 8.9%). ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.31 (m, 6H), 1.45 (d, *J* = 11.7 Hz, 1H), 1.67 (m, 2H), 2.00 (m, 1H), 2.11 (m, 1H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.80 (m, 4H), 3.53 (m, 2H), 3.82 (t, *J* = 5.9 Hz, 1.3H), 3.86 (t, *J* = 5.9 Hz, 0.7H), 4.11 (m, 1H), 4.60 (s, 0.7H), 4.64 (s, 1.3H), 5.53 (m, 1H), 7.02 (m, 2H), 7.50 (m, 1H); ESI-MS m/z $[M+H]^+$ 462.5.

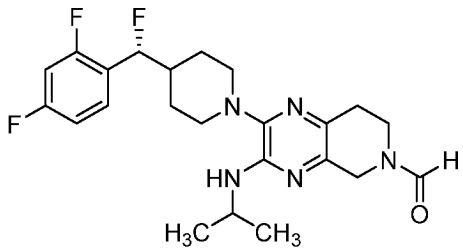
[00584] Example 118 (*S*)-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carbaldehyde



[00585] A solution of (*S*)-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine (30.5 mg, 0.073 mmol) in THF (364 µL) at room temperature was treated with phenyl formate (140 µL, 1.09 mmol). The reaction mixture was stirred at 60 °C for 1 h. The reaction was purified by HPLC Method B using a 50% to 80% ACN gradient to give the title compound, as a TFA salt, as a pale

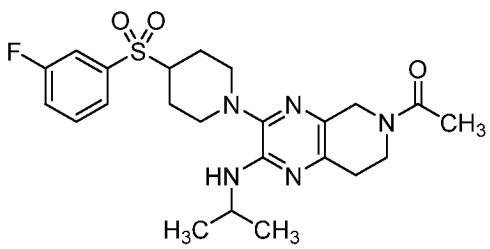
yellow solid (9.4 mg, 23%). ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.29 (m, 6H), 1.45 (d, *J* = 12.7 Hz, 1H), 1.66 (m, 2H), 2.00 (m, 1H), 2.10 (m, 1H), 2.77 (m, 4H), 3.49 (m, 2H), 3.76 (t, *J* = 5.9Hz, 1.4H), 3.82 (t, *J* = 6.1 Hz, 0.6H), 4.12 (m, 1H), 4.48 (s, 0.6H), 4.52 (s, 1.4H), 5.53 (m, 1H), 7.02 (m, 2H), 7.50 (td, *J* = 8.3, 6.3 Hz, 1H), 8.18 (s, 0.7H), 8.24 (s, 0.3H); ESI-MS m/z $[M+H]^+$ 447.90.

Example 119 (*R*)-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carbaldehyde



[00586] A solution of (*R*)-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine (50.5 mg, 0.120 mmol) in THF (602 μL) at room temperature was treated with phenyl formate (232 μL, 1.806 mmol). The reaction mixture was stirred at 60 °C for 15 min. The reaction mixture was removed from heat and allowed to continue stirring at room temperature for 2 h. The reaction was purified by HPLC Method B using a 50% to 80% ACN gradient to give the title compound, as a TFA salt, as a pale yellow solid (6.0 mg, 8.9% yield). ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.30 (m, 7H), 1.45 (d, *J* = 13.2 Hz, 1H), 1.67 (m, 2H), 2.01 (m, 1H), 2.11 (m, 1H), 2.79 (m, 4H), 3.51 (m, 2H), 3.77 (t, *J* = 5.9 Hz, 1.4H), 3.83 (t, *J* = 6.1 Hz, 0.6H), 4.13 (m, 1H), 4.51 (s, 0.6H), 4.56 (s, 1.4H), 5.53 (m, 1H), 7.02 (m, 2H), 7.50 (m, 1H), 8.19 (s, 0.7H), 8.24 (s, 0.3H); ESI-MS m/z $[M+H]^+$ 447.95.

[00587] Example 120 1-(3-(4-(3-fluorophenylsulfonyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



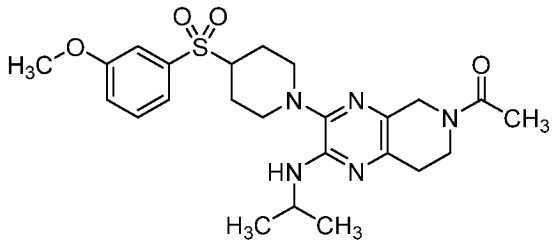
[00588] Combined 6-benzyl-3-chloro-N-isopropyl-5,6,7,8-tetrahydropyrido[3,4-b]pyrazin-2-amine (55 mg, 0.174 mmol), 4-((3-fluorophenyl)sulfonyl)piperidine, HCl (58.3 mg, 0.208 mmol)), $Pd_2(dba)_3$ (8.0 mg, 8.68 μmol), BINAP (16.2 mg, 0.026 mmol) and sodium *tert*-

butoxide (66.7 mg, 0.694 mmol) and toluene (868 µL). The suspension was heated at 100 °C for 3.5 h then diluted in DMF, filtered through a hydrophilic PTFE 0.45 µm filter (Millipore® Millex-LCR), and purified via HPLC Method A to give 6-benzyl-3-(4-((3-fluorophenyl)sulfonyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine as a TFA salt (68 mg) as a yellow film.

[00589] To a solution of 6-benzyl-3-(4-((3-fluorophenyl)sulfonyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (68 mg, 0.107 mmol) in THF (1333 µL) was added $Pd(OH)_2$ (20 wt %, 22.5 mg, 0.032 mmol). The flask was purged with nitrogen then allowed to stir under an atmosphere of hydrogen (balloon) for 2 h. The reaction mixture was filtered through a hydrophilic PTFE 0.45 um filter (Millipore® Millex-LCR) and washed with EtOAc. The crude material was concentrated *in vacuo* to give 3-(4-((3-fluorophenyl)sulfonyl)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine as a TFA salt (58 mg) as a yellow film.

[00590] To a solution of 3-(4-((3-fluorophenyl)sulfonyl)piperidin-1-yl)-N-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (58 mg, 0.106 mmol) in DCM (1059 µL) at 0 °C was added acetic anhydride (20.0 µL, 0.212 mmol) and pyridine (25.7 µL, 0.318 mmol). After stirring at 0 °C for 30 min, the reaction mixture was concentrated *in vacuo*. The resulting crude material was dissolved in DCM and purified via automated flash silica gel chromatography using a gradient of 0% to 100% EtOAc in heptanes to give the title compound (19.2 mg) as a colorless oil. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 0.85-0.94 (m, 3H), 1.21-1.24 (m, 6H), 1.90-1.99 (m, 2H), 2.19 (d, *J* = 13.7 Hz, 3H), 2.67-2.76 (m, 3H), 2.81 (t, *J* = 5.9 Hz, 1 H), 3.34-3.42 (m, 1 H), 3.46-3.55 (m, 2H), 3.78 (t, *J* = 6.1 Hz, 1H), 3.84 (t, *J* = 5.9 Hz, 1 H), 4.16 (td, *J* = 6.5, 3.7 Hz, 1H), 4.49 (d, *J* = 2.4 Hz, 2H), 7.51-7.57 (m, 1H), 7.68-7.75 (m, 2H), 7.76-7.80 (m, 1H); ESI-MS m/z $[M+H]^+$ 476.90.

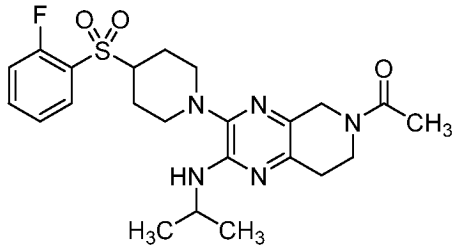
[00591] Example 121 1-(2-(isopropylamino)-3-(4-(3-methoxyphenylsulfonyl)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00592] The title compound was prepared in a manner similar to Example 120 using 4-((3-methoxyphenyl)sulfonyl)piperidine, HCl to give the title compound as a white solid. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 0.82-0.94 (m, 2H), 1.21-1.24 (m, 6H), 1.87-1.98 (m,

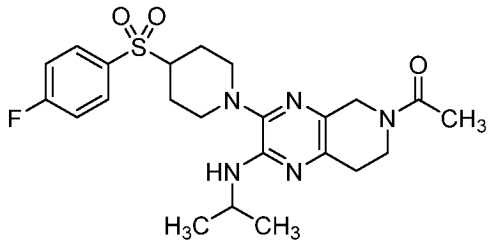
4H), 2.19 (d, *J* = 13.2 Hz, 3H), 2.66-2.75 (m, 3H), 2.81 (t, *J* = 6.1 Hz, 1H), 3.46-3.54 (m, 2H), 3.78 (t, *J* = 5.9 Hz, 1H), 3.84 (t, *J* = 5.9 Hz, 1H), 3.91 (s, 3H), 4.15 (dd, *J* = 10.7, 4.4 Hz, 1H), 4.46-4.50 (m, 2H), 7.29-7.34 (m, 1H), 7.42-7.44 (m, 1H), 7.48-7.52 (m, 1H), 7.56-7.61 (m, 1H); ESI-MS m/z $[M+H]^+$ 488.90.

[00593] Example 122 1-(3-(4-((2-fluorophenyl)sulfonyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



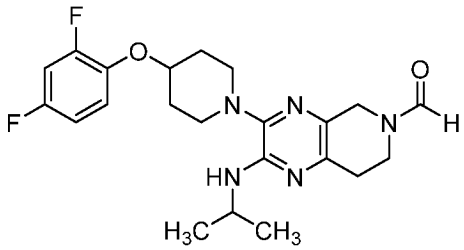
[00594] The title compound was prepared in a manner similar to Example 120 using 4-((2-fluorophenyl)sulfonyl)piperidine to give the title compound, as a TFA salt, as a pale yellow solid (26.6 mg, 28.9% over two steps, mixture of rotamers). ^{1}H NMR (500 MHz, DMSO-*d*6) δ ppm 1.16 (d, *J* = 6.8 Hz, 6H), 1.95 (m, 4H), 2.07 (app d, 3H), 2.65 (m, 4H), 3.49 (m, 3H), 3.69 (m, 2H), 4.13 (m, 1H), 4.37 (app d, 2H), 5.69 (br s, 1H), 7.52 (m, 2H), 7.87 (m, 2H); ESI-MS m/z $[M+H]^+$ 476.00.

[00595] Example 123 1-(3-(4-(4-fluorophenylsulfonyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



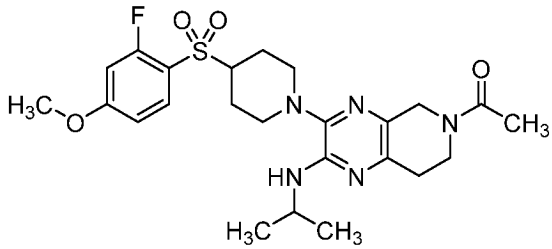
[00596] The title compound was prepared in a manner similar to Example 120 using 4-((4-fluorophenyl)sulfonyl)piperidine, HCl to give the title compound as a colorless oil. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 0.90 (d, *J* = 6.8 Hz, 1H), 1.20-1.24 (m, 6H), 1.90-1.99 (m, 2H), 1.99-2.06 (m, 2H), 2.19 (d, *J* = 13.7 Hz, 3H), 2.67-2.76 (m, 3H), 2.82 (t, *J* = 5.9 Hz, 1H), 3.45-3.55 (m, 2H), 3.79 (t, *J* = 5.9 Hz, 1H), 3.84 (t, *J* = 5.9 Hz, 1H), 4.12-4.20 (m, 1H), 4.49 (s, 2H), 4.58 (s, 1H), 7.42 (td, J = 8.7, 1.7 Hz, 2H), 7.97-8.02 (m, 2H); ESI-MS m/z [M+H]+ 476.90.

[00597] Example 124 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carbaldehyde



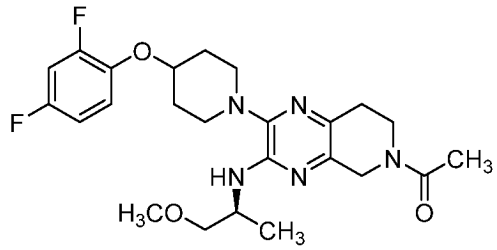
[00598] A mixture of 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine TFA salt (36 mg, 0.058 mmol), Cs_2CO_3 (66.0 mg, 0.203 mmol), and difluoroiodomethane (0.051 mL, 0.579 mmol) in DMA (0.5 mL) was heated in a microwave on high absorbance for 15 min at 50 °C. The resulting crude material was filtered, rinsed with DMSO (2 x 0.5 mL), and purified by HPLC Method B using a 30% to 70% ACN gradient to give the title compound as a TFA salt (11.2 mg, 35.5%) as a yellow solid. ^{1}H NMR (500 MHz, methanol-d_4) δ ppm 1.29 (d, J = 6.4 Hz, 6H), 1.90-2.01 (m, 2H), 2.07-2.18 (m, 2H), 2.78-2.89 (m, 2H), 3.02-3.10 (m, 2H), 3.39-3.45 (m, 2H), 3.76-3.86 (m, 2H), 4.14 (quin, J = 6.4 Hz, 1H), 4.46-4.49 (m, 3H), 6.85-6.91 (m, 1H), 6.95-7.01 (m, 1H), 7.14-7.21 (m, 1H), 8.16-8.27 (m, 1H); ESI-MS m/z $[M+H]^+$ 432.4.

[00599] Example 125 1-(3-(4-(2-fluoro-4-methoxyphenylsulfonyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[4,3-b]pyrazin-6(5H)-yl)ethanone



[00600] The title compound was prepared in a manner similar to Example 120 using 4-((2-fluoro-4-methoxyphenyl)sulfonyl)piperidine, HCl to give the title compound as a colorless oil. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 0.87-0.90 (m, 2H), 1.23 (dd, J = 6.8, 1.0 Hz, 6H), 1.95-2.02 (m, 3H), 2.19 (d, J = 12.2 Hz, 3H), 2.69-2.79 (m, 3H), 2.82 (t, J = 5.9 Hz, 1H), 3.35-3.42 (m, 1H), 3.52 (td, J = 8.3, 4.4 Hz, 2H), 3.79 (t, J = 5.9 Hz, 1H), 3.85 (t, J = 6.1 Hz, 1H), 3.93 (s, 3H), 4.17 (dtt, J = 9.8, 6.4, 3.3 Hz, 1H), 4.50 (s, 2H), 6.95-7.02 (m, 2H), 7.78-7.84 (m, 1H); ESI-MS m/z $[M+H]^+$ 506.90.

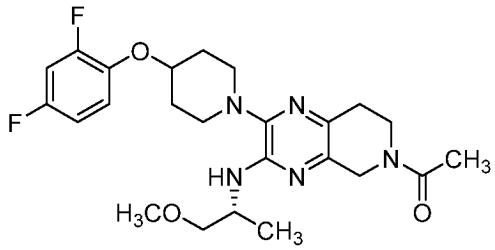
[00601] Example 126 (*S*)-1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-((1-methoxypropan-2-yl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00602] A solution of (*S*)-6-benzyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-N-(1-methoxypropan-2-yl)-5,6,7,8-tetrahydropyrido[3,4-b]pyrazin-3-amine TFA salt (127.7 mg, 0.200 mmol) in THF (2.00 mL) at room temperature was treated with $Pd(OH)_2$ (20 wt %, 42.2 mg, 0.060 mmol). Hydrogen gas (balloon) was bubbled through the reaction mixture for 5 min. The vent needle was removed and the reaction mixture was stirred under hydrogen atmosphere for 1 h. The reaction mixture was opened to air and was filtered through a pad of Celite™, eluting with EtOAc and MeOH. The filtrate was concentrated under reduced pressure to give (*S*)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-(1-methoxypropan-2-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine, as a TFA salt, as a yellow oil, which was carried forward without additional purification. ESI-MS m/z $[M+H]^+$ 434.5.

[00603] A solution of (*S*)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-(1-methoxypropan-2-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt in DCM (2.009 mL) at 0 °C was treated with pyridine (0.049 mL, 0.603 mmol), followed by acetic anhydride (0.038 mL, 0.402 mmol). The reaction mixture was stirred for 1 h 30 min at 0 °C. The reaction mixture was concentrated under reduced pressure and taken up in MeOH, filtered through a Millipore® 0.45 μm syringe filter, and purified by HPLC Method A to give the title compound, as a TFA salt, as a yellow-orange semisolid (46.7 mg, 39.4% over two steps). ^1H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.27 (m, 3H), 1.95 (m, 2H), 2.13 (m, 2H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.79 (app t, 0.7H), 2.84 (app t, 1.3H), 3.05 (m, 2H), 3.39 (m, 3H), 3.43 (m, 2H), 3.51 (dt, J = 5.5, 3.5 Hz, 2H), 3.82 (app t, 1.3H), 3.86 (app t, 0.7H), 4.25 (m, 1H), 4.49 (m, 1H), 4.57 (s, 0.7H), 4.60 (s, 1.3H), 6.88 (m, 1H), 6.99 (ddd, J = 11.2, 8.3, 2.9 Hz, 1H), 7.18 (td, J = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 476.00.

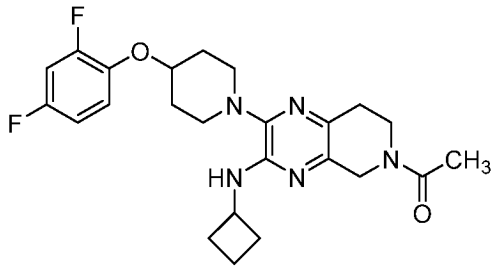
[00604] Example 127 (*R*)-1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-((1-methoxypropan-2-yl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00605] A solution of (*R*)-6-benzyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-(1-methoxypropan-2-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (161.4 mg, 0.253 mmol) in THF (2.53 mL) was treated with $Pd(OH)_2$ (20 wt %, 53.3 mg, 0.076 mmol). Hydrogen gas (balloon) was bubbled through the reaction mixture for 5 min. The vent needle was removed and the reaction mixture was allowed to stir under hydrogen atmosphere at room temperature for 2 h. The reaction mixture was opened to air and filtered through a pad of Celite™, eluting with MeOH and EtOAc. The filtrate was collected and concentrated under reduced pressure to give (*R*)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-(1-methoxypropan-2-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine, as a TFA salt, as a yellow oil, which was carried forward without additional purification. ESI-MS m/z $[M+H]^+$ 434.5.

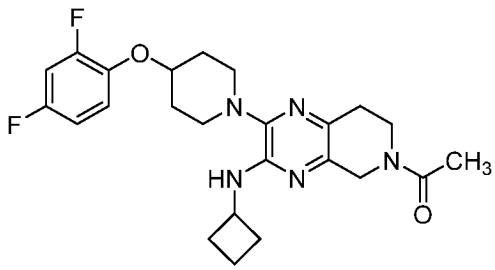
[00606] A solution of (*R*)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-(1-methoxypropan-2-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt in DCM (2.539 mL) at 0 °C was treated with pyridine (0.062 mL, 0.762 mmol), followed by acetic anhydride (0.048 mL, 0.508 mmol). The reaction mixture was stirred at 0 °C for 1 h 30 min. The reaction mixture was concentrated under reduced pressure and taken up in MeOH, filtered through a 0.45 µm Millipore® syringe filter, and purified by HPLC Method A to give the title compound, as a TFA salt, as a yellow semisolid (41.4 mg, 27.7% over two steps). ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.29 (m, 3H), 1.95 (m, 2H), 2.13 (m, 2H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.74 (t, J = 5.9 Hz, 0.7H), 2.84 (app t, 1.3H), 3.09 (m, 2H), 3.38 (m, 3H), 3.47 (m, 4H), 3.82 (t, J = 6.1 Hz, 1.3H), 3.86 (t, J = 5.9 Hz, 0.7H), 4.26 (m, 1H), 4.49 (m, 1H), 4.59 (br s, 0.7H), 4.62 (s, 1.3H), 6.87 (m, 1H), 6.98 (ddd, J = 11.3, 8.7, 2.9 Hz, 1H), 7.27 (td, J = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 476.00.

[00607] Example 128 1-(3-(cyclobutylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00608] A solution of *N*-cyclobutyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (144 mg, 0.272 mmol) in DCM (2.72 mL) at 0 °C was treated with pyridine (66.0 µL, 0.816 mmol), followed by acetic anhydride (51.3 µL, 0.544 mmol). The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was concentrated under reduced pressure and taken up in MeOH, filtered through a 0.45 µm Millipore® syringe filter, and purified via HPLC Method A to give the title compound, as a TFA salt, as a yellow solid (74.9 mg, 48.2%). ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 1.82 (m, 2H), 1.97 (m, 2H), 2.11 (m, 4H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.45 (m, 2H), 2.73 (t, *J* = 5.9 Hz, 0.7H), 2.84 (t, *J* = 5.9 Hz, 1.3H), 3.11 (m, 2H), 3.47 (m, 2H), 3.81 (t, *J* = 5.9 Hz, 1.3 H), 3.85 (t, *J* = 5.9 Hz, 0.7H), 4.40 (m, 1H), 4.49 (m, 1H), 4.59 (s, 0.7H), 4.63 (s, 1.3H), 6.87 (m, 1H), 6.97 (ddd, *J* = 11.2, 8.5, 3.2 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 458.00.

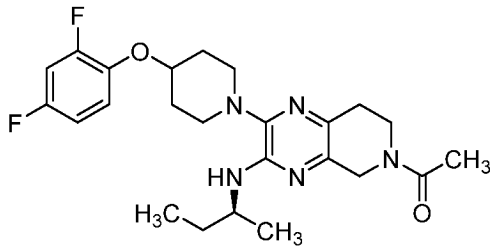
[00609] Example 128A 1-(3-(cyclobutylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00610] To a solution of *N*-cyclobutyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazin-3-amine (12.0 g, 29.2 mmol) in acetone (200 mL) and dioxane (300 mL) was added Ac_2O (30 mL, 318 mmol) and Pd/C (1.80 g, 16.91 mmol). The reaction was then stirred at 60 °C under H_2 atmosphere (345 kPa) for 72 h. Then the mixture was filtered through a pad of Celite™, washing with EtOAc. The reaction solution was diluted with EtOAc (50 mL) and poured into saturated aqueous $NaHCO_3$ (50 mL), then washed with brine (2 x 30 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was recrystallized with PE/EtOAc, lyophilized and washed with PE/EtOAc

(5:1) to give pure title compound (6.1 g). ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.57-1.74 (m, 2H), 1.85-1.95 (m, 2H), 1.97-2.08 (m, 4H), 2.08 (s, 1.3H), 2.09 (s, 1.7H), 2.19-2.30 (m, 2H), 2.58 (t, J = 5.9 Hz, 0.9H), 2.71 (t, J = 5.9 Hz, 1.1H), 2.88 (t, J = 10.5 Hz, 2H), 3.23-3.33 (m, 2H), 3.70 (dt, J = 11.7, 5.9 Hz, 2H), 4.32-4.47 (m, 3H), 4.52 (tt, J = 8.1, 3.8 Hz, 1H), 6.05 (d, J = 7.8 Hz, 0.4H), 6.08 (d, J = 8.3 Hz, 0.6H 6.96-7.07 (m, 1H), 7.24-7.36 (m, 2H); ESI-MS m/z $[M+H]^+$ 458.00.

[00611] Example 129 (*S*)-1-(3-(*sec*-butylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one

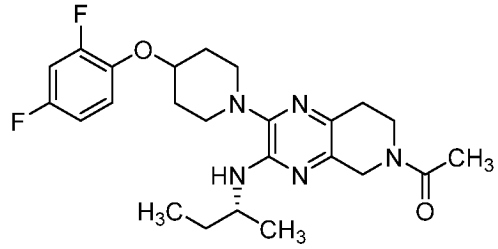


[00612] A solution of (*S*)-6-benzyl-*N*-(*sec*-butyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (212.2 mg, 0.341 mmol) in THF (3.4 mL) was treated with $Pd(OH)_2$ (20 wt %, 71.9 mg, 0.102 mmol). Hydrogen gas (balloon) was bubbled through the reaction mixture for 5 min. The vent needle was removed and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 3 h. The reaction mixture was opened to air and filtered through a pad of Celite™, eluting with EtOAc and MeOH. The filtrate was collected and concentrated under reduced pressure to give (*S*)-*N*-(*sec*-butyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine as a TFA salt (169.0 mg) as a yellow oil, which was carried forward without additional purification. ESI-MS m/z $[M+H]^+$ 418.5.

[00613] A solution of (S)-N-(sec-butyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (169.0 mg) in DCM (3.18 mL) at 0 °C was treated with pyridine (0.077 mL, 0.954 mmol), followed by acetic anhydride (0.060 mL, 0.636 mmol). The reaction mixture was stirred for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was taken up in MeOH, filtered through a Millipore® 0.45 μm syringe filter, and purified by HPLC Method A to give the title compound, as a TFA salt, as a yellow semisolid (84.9 mg, 43.4% over two steps). ^{1}H NMR (500 MHz, methanol-*d*4, mixture of rotamers) δ ppm 0.98 (m, 3H), 1.27 (m, 3H), 1.68 (m, 2H), 1.97 (m, 2H), 2.13 (m, 2H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.74 (td, J = 5.9, 1.5 Hz, 0.7H), 2.84 (td, J = 5.9, 1.5 Hz, 1.3H), 3.11 (m, 2H), 3.45 (m, 2H), 3.82 (t, J = 5.9 Hz,

1.3H), 3.86 (m, 0.7H), 3.97 (m, 1H), 4.50 (m, 1H), 4.61 (d, J = 3.9 Hz, 0.7H), 4.64 (s, 1.3H), 6.87 (m, 1H), 6.97 (ddd, J = 11.3, 8.7, 2.9 Hz, 1H), 7.17 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 460.00.

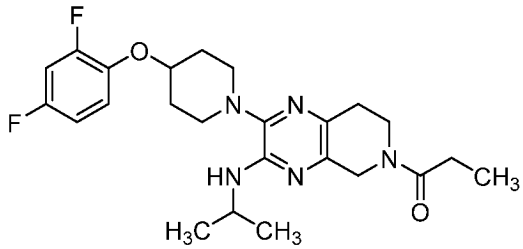
[00614] Example 130 (*R*)-1-(3-(*sec*-butylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00615] A solution of (*R*)-6-benzyl-*N*-(*sec*-butyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (174.6 mg, 0.281 mmol) in THF (2.81 mL) was treated with $Pd(OH)_2$ (20 wt %, 59.2 mg, 0.084 mmol). Hydrogen gas (balloon) was bubbled through the reaction mixture for 5 min. The vent needle was removed and the reaction was allowed to stir at room temperature under hydrogen atmosphere for 1 h. The reaction mixture was opened to air and filtered through a pad of Celite™, eluting with EtOAc/MeOH. The filtrate was collected and concentrated under reduced pressure to give (*R*)-*N*-(*sec*-butyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine as a TFA salt (136.4 mg) as a yellow oil, which was carried forward without additional purification. ESI-MS m/z $[M+H]^+$ 418.5.

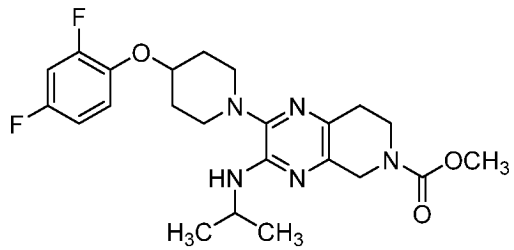
[00616] A solution of (*R*)-*N*-(*sec*-butyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine TFA salt (136.4 mg) in DCM (2.57 mL) at 0 °C was treated with pyridine (0.062 mL, 0.770 mmol), followed by acetic anhydride (0.048 mL, 0.513 mmol). The reaction mixture was stirred for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was taken up in MeOH, filtered through a Millipore® 0.45 μm syringe filter, and purified by HPLC Method A to give title compound, as a TFA salt, as a yellow solid (52.0 mg, 32.2% over two steps). ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 0.98 (m, 3H), 1.26 (m, 3H), 1.67 (m, 2H), 1.96 (m, 2H), 2.13 (m, 2H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.73 (td, J = 5.9, 1.5 Hz, 0.7H), 2.84 (td, J = 5.9, 1.5 Hz, 1.3H), 3.08 (m, 2H), 3.43 (m, 2H), 3.82 (t, J = 5.9 Hz, 1.3H), 3.86 (m, 0.7H), 3.97 (m, 1H), 4.49 (m, 1H), 4.59 (m, 0.7H), 4.63 (s, 1.3H), 6.87 (m, 1H), 6.98 (ddd, J = 11.3, 8.4, 3.2 Hz, 1H), 7.17 (td, J = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 460.0.

[00617] Example 131 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)propan-1-one



[00618] To a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine (50 mg, 0.124 mmol) in DCM (1.24 mL) at 0 °C was added DIPEA (32.5 µL, 0.186 mmol) and propionic anhydride (19.2 µL, 0.149 mmol). The resulting solution was stirred at this temperature for 2 h. Purification by silica gel column chromatography using 0% to 100% EtOAc in heptanes gave the title compound as a white solid (53 mg, 93%). ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm ^{1}H NMR (400 MHz, methanol-d_4, mixture of rotamers) δ ppm 1.10-1.20 (m, 3H), 1.25 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 6.8 Hz, 3H), 1.90-2.00 (m, 2H), 2.09-2.18 (m, 2H), 2.47-2.58 (m, 2H), 2.72 (t, J = 5.9 Hz, 0.8 H), 2.81 (t, J = 5.9 Hz, 1.2H), 2.92-3.01 (m, 2H), 3.81 (t, J = 5.9 Hz, 1.2H), 3.87 (t, J = 6.1 Hz, 0.8H), 4.13-4.21 (m, 1H), 4.46 (tt, J = 7.5, 3.7 Hz, 1H), 4.55 (s, 0.8H), 4.56 (s, 1.2H), 6.85-6.92 (m, 1H), 6.99 (m, 1H), 7.18 (m, 1H); ESI-MS m/z $[M+Na]^+$ 482.9.

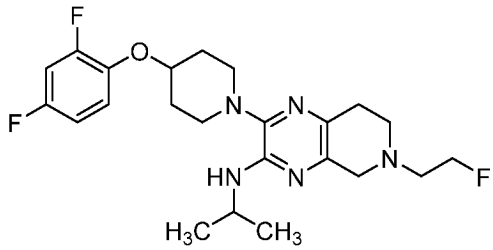
[00619] Example 132 methyl 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxylate



[00620] To a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine (45.6 mg, 0.113 mmol) and triethylamine (0.039 mL, 0.283 mmol) in DCM (0.75 mL) was added methyl carbonochloridate (0.013 mL, 0.170 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr, warmed to 23 °C, and concentrated via rotary evaporation. The resulting crude material was partitioned between EtOAc and H_2O. The organic phase was washed with brine, dried over Na_2SO_4, filtered, rinsed with EtOAc, and concentrated via rotary evaporation. The crude material was

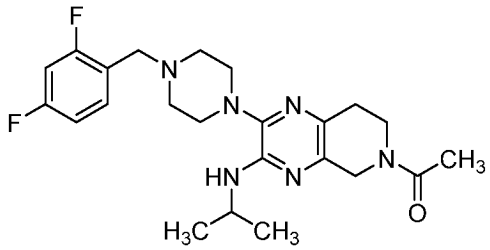
dissolved in toluene (0.5 mL) and purified via medium pressure chromatography using a 2% to 80% gradient eluant of EtOAc in heptane on a 12 g silica gel column (Single Step™) to give the title compound (48.7 mg, 93%) as a white foam. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.17-1.19 (m, 6H), 1.80-1.94 (m, 2H), 2.06 (ddd, J = 9.5, 5.9, 3.2 Hz, 2H), 2.64 (t, J = 5.9 Hz, 2H), 2.82-2.94 (m, 2H), 3.19-3.31 (m, 2H), 3.64 (s, 3H), 3.64-3.69 (m, 2H), 4.07-4.17 (m, 1H), 4.35 (br s, 2H), 4.51 (tt, J = 8.1, 3.9 Hz, 1H), 5.53 (d, J = 8.3 Hz, 1H), 7.01 (dddd, J = 9.3, 8.1, 3.2, 1.5 Hz, 1H), 7.26-7.35 (m, 2H); ESI-MS m/z $[M+H]^+$ 461.9.

[00621] Example 133 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6-(2-fluoroethyl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



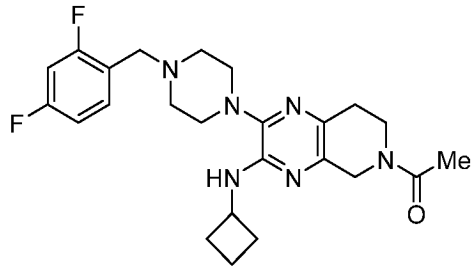
[00622] To a suspension of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine (98.4 mg, 0.244 mmol) and K_2CO_3 (135 mg, 0.976 mmol) in acetone (4.0 mL) was added 1-bromo-2-fluoroethane (0.020 mL, 0.268 mmol) at 23 °C. The reaction mixture was stirred at 50 °C for 1 hr. The reaction mixture was cooled to 23 °C, an additional portion of 1-bromo-2-fluoroethane (8.2 μL, 0.110 mmol) was added, and the reaction mixture was heated for an additional 1.5 hr at 50 °C, cooled to 23 °C, and concentrated via rotary evaporation. The resulting crude material was reconstituted in DMSO, filtered, rinsed with DMSO, and purified by HPLC Method B using a 30% to 70% ACN gradient to give the title compound (42 mg, 38.3%) as a light yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.17 (d, J = 6.8 Hz, 6H), 1.82-1.93 (m, 2H), 2.02-2.11 (m, 2H), 2.62-2.69 (m, 2H), 2.73-2.80 (m, 3H), 2.81-2.91 (m, 3H), 3.20-3.29 (m, 2H), 3.48 (s, 2H), 4.04-4.12 (m, 1H), 4.47-4.54 (m, 1H), 4.56 (t, J = 4.9 Hz, 1H), 4.66 (t, J = 4.9 Hz, 1H), 5.38 (d, J = 7.8 Hz, 1H), 6.98-7.05 (m, 1H), 7.26-7.34 (m, 2H); ESI-MS m/z $[M+H]^+$ 450.0.

[00623] Example 134 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00624] To a pressure reactor charged with a red-orange solution of 2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-N-isopropylpyrido[3,4-*b*]pyrazin-3-amine (0.5 g, 1.255 mmol) in acetone (25 mL) and dioxane (25 mL) was added palladium, 10 wt % on activated carbon (0.053 g, 0.502 mmol) as a slurry in dioxane (3 mL) under nitrogen. Next, acetic anhydride (1.179 mL, 12.55 mmol) was added at 23 °C. The mixture was stirred under hydrogen at 45 °C and 310 kPa for 9.5 hr. The reaction mixture was filtered through Celite™, rinsed with EtOAc, and concentrated via rotary evaporation. The crude material was dissolved in toluene (5 mL) and purified via medium pressure chromatography using a 10% to 100% gradient eluant of EtOAc in heptane on an NH 60 μM size 400 column (Shoko Scientific Purif-Pack™) to give the title compound (341 mg, 61.1%) as an off-white foam. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.14-1.19 (m, 6H), 2.08 (s, 1.2H), 2.09 (s, 1.8H), 2.52-2.65 (m, 5H), 2.70 (t, J = 5.9 Hz, 1H), 2.98 (br s, 4H), 3.58 (s, 2H), 3.70 (dt, J = 12.0, 5.7 Hz, 2H), 4.00-4.15 (m, 1H), 4.40 (s, 0.8H), 4.43 (s, 1.2H), 5.35 (d, J = 7.8 Hz, 0.4H), 5.38 (d, J = 8.3 Hz, 0.6H) 7.08 (td, J = 8.3, 2.4 Hz, 1H), 7.21 (td, J = 10.0, 2.4 Hz, 1H), 7.44-7.51 (m, 1H); ESI-MS m/z $[M+H]^+$ 445.0.

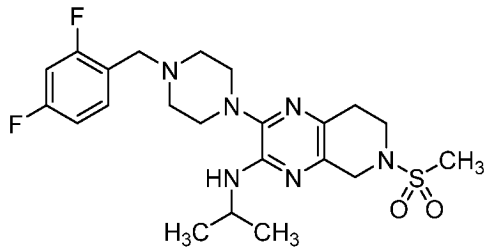
[00625] Example 135 1-(3-(cyclobutylamino)-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00626] To *N*-cyclobutyl-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)pyrido[3,4-*b*]pyrazin-3-amine (0.500 g, 1.218 mmol) in acetone (25 mL) and dioxane (25 mL) was added palladium, 10 wt % on activated carbon (0.052 g, 0.487 mmol) as a slurry in dioxane (3 mL) under nitrogen. Next, acetic anhydride (1.144 mL, 12.18 mmol) was added at 23 °C. The mixture was stirred under hydrogen at 310 kPa for 50 hr at 45 °C. The crude mixture was filtered through Celite™, rinsed with dioxane, and concentrated via rotary evaporation. The crude

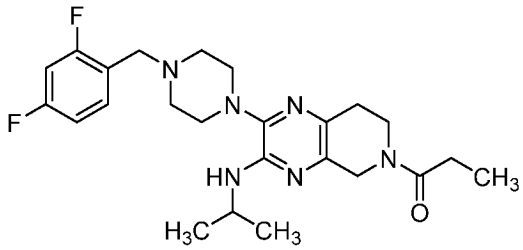
material was purified via medium pressure chromatography using a 10% to 100% gradient eluant of EtOAc in heptanes on an NH 60 μM size 60 column (Shoko Scientific Purif-Pack™) to give the title compound 1-(3-(cyclobutylamino)-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone (284 mg, 51.1%) as a yellow foam. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.56-1.72 (m, 2H), 1.97-2.06 (m, 2H), 2.07 (s, 1.3H), 2.08 (s, 1.7H), 2.18-2.27 (m, 2H), 2.52-2.66 (m, 4.9H), 2.69 (t, J = 5.9 Hz, 1.1H), 2.99 (br s, 4H), 3.59 (s, 2H), 3.69 (dt, J = 11.5, 6.0 Hz, 2H), 4.27-4.46 (m, 3H), 5.89 (d, J = 7.3 Hz, 0.4H), 5.93 (d, J = 7.8 Hz, 0.6H), 7.02-7.13 (m, 1H), 7.17-7.27 (m, 1H), 7.41-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 457.0.

[00627] Example 136 2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-isopropyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



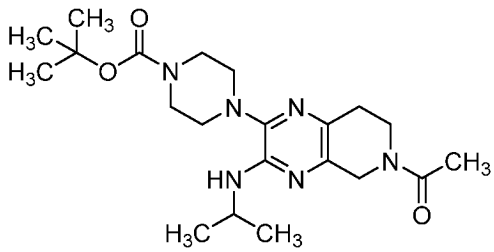
[00628] To a solution of 2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine (50 mg, 0.124 mmol) and DIPEA (0.032 mL, 0.186 mmol) in DCM (1 mL) was added methanesulfonyl chloride (10.6 μL, 0.137 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr and concentrated via rotary evaporation. The resulting crude material was partitioned between EtOAc (2 mL) and water (1 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered, rinsed with EtOAc, and concentrated via rotary evaporation. The crude material was dissolved in EtOAc and MeOH, adsorbed on silica gel (0.75 g), and purified via medium pressure chromatography using a gradient eluant of 50% to 100% EtOAc in heptane on a 4 g silica gel column (Single Step™) to give the title compound (50.6 mg, 85%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.12-1.19 (m, 6H), 2.53-2.61 (m, 4H), 2.74 (t, J = 5.9 Hz, 2H), 2.97 (s, 3H), 3.00 (d, J = 7.3 Hz, 4H), 3.44-3.48 (m, 1H), 3.59 (s, 2H), 4.02-4.10 (m, 1H), 4.16 (s, 2H), 5.41 (d, J = 7.8 Hz, 1H), 7.08 (td, J = 8.4, 2.2 Hz, 1H), 7.22 (td, J = 9.9, 2.7 Hz, 1H), 7.44-7.54 (m, 1H); ESI-MS m/z $[M+H]^+$ 480.9.

[00629] Example 137 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)propan-1-one



[00630] To a solution of 2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine (50 mg, 0.124 mmol) and DIPEA (0.032 mL, 0.186 mmol) in DCM (1 mL) was added propionic anhydride (0.019 mL, 0.149 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hr, warmed to 23 °C, and concentrated via rotary evaporation. The resulting crude material was partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na_2SO_4, filtered, rinsed with EtOAc, and concentrated via rotary evaporation. The crude material was dissolved in EtOAc and MeOH, adsorbed on silica gel (0.75 g), and purified via medium pressure chromatography using a 20% to 100% gradient of EtOAc in heptane on a 4 g silica gel column (Single Step™) to give the title compound (48 mg, 84% yield) as an off-white foam. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 0.94-1.05 (m, 3H), 1.16-1.18 (m, 6H), 2.41 (quin, J = 7.8 Hz, 2H), 2.52-2.65 (m, 5H), 2.69 (t, J = 5.6 Hz, 1H), 2.98 (br s, 3H), 3.58 (s, 2H), 3.70 (t, J = 5.9 Hz, 1.1H), 3.73 (t, J = 5.9 Hz, 0.9H), 4.03 (q, J = 7.2 Hz, 2H), 4.06-4.15 (m, 1H), 4.42 (br s, 2H), 5.34 (d, J = 7.8 Hz, 0.6H), 5.37 (d, J = 8.3 Hz, 0.4H), 7.08 (td, J = 8.5, 2.4 Hz, 1H), 7.21 (td, J = 9.9, 2.7 Hz, 1H), 7.44-7.52 (m, 1 H); ESI-MS m/z $[M+H]^+$ 459.0.

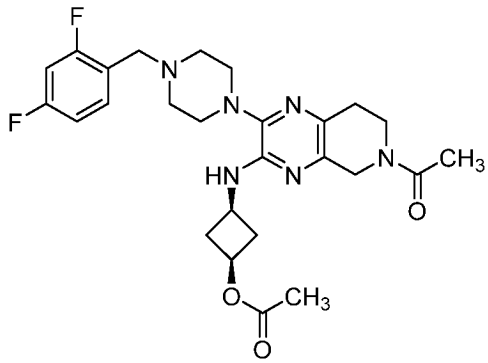
[00631] Example 138 *tert*-butyl 4-(6-acetyl-3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperazine-1-carboxylate



[00632] To a pressure reactor charged with a red-orange solution of tert-butyl 4-(3-(isopropylamino)pyrido[3,4-*b*]pyrazin-2-yl)piperazine-1-carboxylate (2.0 g, 5.37 mmol) in acetone (100 mL) and dioxane (100 mL) was added palladium, 10 wt % on activated carbon (0.229 g, 2.148 mmol) as a slurry in dioxane (3 mL) under nitrogen. Next, acetic anhydride (5.04 mL, 53.7 mmol) was added at 23 °C. The mixture was stirred under hydrogen at 310

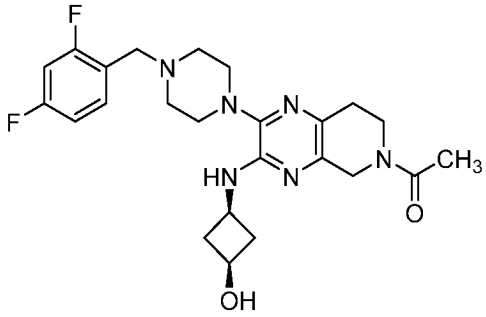
kPa for 17 hr at 45 °C. The reaction mixture was filtered through Celite™, rinsed with dioxane, and concentrated via rotary evaporation. The crude material was purified via medium pressure chromatography using 10% to 100% gradient of EtOAc in heptane on an NH 60 μM size 400 column (Shoko Scientific Purif-Pack™) to give the title compound (1.068 g, 47.5%) as a yellow foam. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.16-1.21 (m, 6H), 1.42 (s, 9H), 2.08 (s, 1.3H), 2.09 (s, 1.7H), 2.58 (t, J = 5.9 Hz, 0.9H), 2.70 (t, J = 5.6 Hz, 1.1H), 2.87-2.98 (m, 4H), 3.51 (br s, 4H), 3.67-3.75 (m, 2H), 4.06-4.15 (m, 1H), 4.41 (s, 1.1H), 4.44 (s, 0.9H), 5.50 (d, J = 7.8 Hz, 1H), 5.53 (d, J = 7.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 419.0.

[00633] Example 139 (1*s*,3*s*)-3-((6-acetyl-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutyl acetate



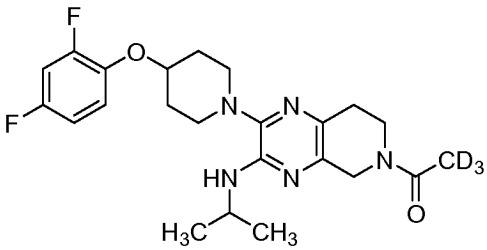
[00634] To a pressure reactor charged with a red-orange solution of (1*s*,3*s*)-3-((2-(4-(2,4-difluorobenzyl)piperazin-1-yl)pyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutanol (0.3 g, 0.703 mmol) in acetone (15 mL) and dioxane (15 mL) was added palladium, 10 wt % on activated carbon (0.030 g, 0.281 mmol) as a slurry in dioxane (3 mL) under nitrogen. Next, acetic anhydride (0.661 mL, 7.03 mmol) was added at 23 °C. The reaction mixture was stirred under hydrogen at 310 kPa for 4 days at 45 °C. The reaction mixture was filtered through Celite™, rinsed with dioxane, and concentrated via rotary evaporation. The crude material was dissolved in toluene (3 mL) and purified via medium pressure chromatography using a gradient eluant of 30% to 100% EtOAc in heptane on a 90 g silica gel column (Single Step™) to give the title compound (119.7 mg, 33.1%) as a yellow foam. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.97-2.00 (m, 3H), 2.07 (s, 1.3H), 2.08 (s, 1.7H), 2.10-2.17 (m, 2H), 2.55-2.63 (m, 5H), 2.67-2.74 (m, 3H), 2.90-3.10 (m, 4H), 3.59 (s, 2H), 3.66-3.74 (m, 2H), 4.02-4.12 (m, 1H), 4.39 (s, 1.1H), 4,42 (s, 0.9H), 4.68 (quind, J = 7.3, 3.4 Hz, 1H), 6.11 (d, J = 7.8 Hz, 0.6H), 6.15 (d, J = 7.8 Hz, 0.4H), 7.08 (td, J = 8.5, 2.4 Hz, 1H), 7.19-7.24 (m, 1H), 7.45-7.51 (m, 1H); ESI-MS m/z $[M+H]^+$ 515.0.

[00635] Example 140 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(((1*s*,3*s*)-3-hydroxycyclobutyl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00636] To a solution of (1*s*,3*s*)-3-((6-acetyl-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutyl acetate (94.8 mg, 0.184 mmol) in MeOH (2 mL) was added sodium methoxide (5.1 µL, 0.028 mmol) at 0 °C. The reaction was stirred at 0 °C for 1 h, concentrated via rotary evaporation at 30 °C, re-constituted with MeOH (2 mL), cooled to 0 °C, and quenched with HOAc (0.005 mL). The reaction mixture was concentrated via rotary evaporation, partitioned between EtOAc (4 mL) and saturated NH_4Cl (1 mL), and the layers were separated. The organic phase was washed with brine (1 mL), dried over Na_2SO_4, filtered, rinsed with EtOAc, and dried *in vacuo* to give the title compound (79.3 mg, 91%) as a yellowish-orange foam. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.80-1.88 (m, 2H), 2.07 (s, 1.3H), 2.08 (s, 1.7H), 2.54-2.64 (m, 7H), 2.69 (t, J = 5.9 Hz, 1H), 2.99 (br s, 4H), 3.59 (s, 2H), 3.69 (dt, J = 11.5, 6.0 Hz, 2H), 3.77-3.91 (m, 2H), 4.38 (s, 1.1H), 4.41 (s, 0.9H), 4.95-5.00 (m, 1H), 5.82 (d, J = 7.3 Hz, 1H), 5.85 (d, J = 7.8 Hz, 1H) 7.08 (td, J = 8.4, 2.2 Hz, 1H), 7.19-7.24 (m, 1H), 7.45-7.51 (m, 1H); ESI-MS m/z $[M+H]^+$ 473.0.

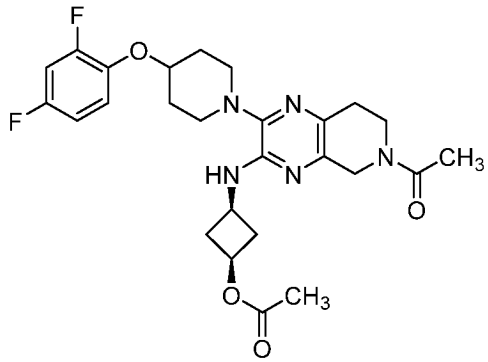
[00637] Example 141 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-*d*3-ethan-1-one



[00638] To a solution of 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine (2.4 g, 5.95 mmol) and DIPEA (1.56 mL, 8.92 mmol) in DCM (59.5 mL) at 0 °C was added acetyl chloride-*d*3 (0.42 mL, 5.95 mmol) dropwise. The resulting solution was stirred at this temperature for 1 h. After concentration,

purification with silica gel column chromatography using 30% to 100% EtOAc in heptanes gave the title compound (1.89 g, 70.8%). ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.19 (d, J = 6.4 Hz, 2.7H), 1.21 (d, J = 6.4 Hz, 3.3H), 1.82-1.92 (m, 2H), 2.03-2.11 (m, 2H), 2.59 (t, J = 5.9 Hz, 0.9H), 2.71 (t, J = 5.9 Hz, 1.1H), 2.87 (m, 2H), 3.22-3.30 (m, 2H), 3.67-3.74 (m, 2H), 4.06-4.16 (m, 1H), 4.41 (s, 1.1H), 4.43 (s, 0.9H), 4.51 (m, 1H), 5.50 (d, J = 8.3 Hz, 1.1H), 5.54 (d, J = 7.8 Hz, 0.9H), 6.92-7.06 (m, 1H), 7.21-7.35 (m, 2H); ESI-MS m/z $[M+H]^+$ 449.0.

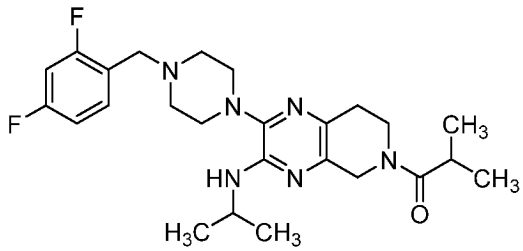
[00639] Example 142 (1*s*,3*s*)-3-((6-acetyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutyl acetate



[00640] To a pressure reactor charged with a red-orange solution of (1*s*,3*s*)-3-((2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutanol (0.355 g, 0.831 mmol) in acetone (15 mL) and dioxane (15 mL) was added palladium, 10 wt % on activated carbon (0.035 g, 0.332 mmol) as a slurry in dioxane (3 mL) under nitrogen. Next, acetic anhydride (0.780 mL, 8.31 mmol) was added at 23 °C. The reaction mixture was stirred under hydrogen at 310 kPa for 48 hr at 45 °C. Additional portions of palladium, 10 wt % on activated carbon and acetic anhydride (0.156 mL, 1.661 mmol) were added to the pressure reactor and the reaction mixture was stirred under hydrogen at 310 kPa for an additional 4 days at 45 °C. The reaction mixture was filtered through Celite™, rinsed with dioxane, and concentrated via rotary evaporation. The crude material was dissolved in toluene (3 mL) and purified via medium pressure chromatography using a gradient eluant of 30% to 100% EtOAc in heptane on a 90 g silica gel column (Single Step™) to give the title compound as a HOAc salt. The HOAc salt was dissolved in MeOH, passed through a 200 mg VariPure™ IPE cartridge (HCO_3MP) to remove HOAc, and the cartridge was rinsed with MeOH. The filtrate was concentrated via rotary evaporation and dried *in vacuo* to give the title compound (165 mg, 38.5%) as a yellow foam. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.86-1.96 (m, 2H), 1.98-2.01 (m, 3H), 2.01-2.08 (m, 2H), 2.08

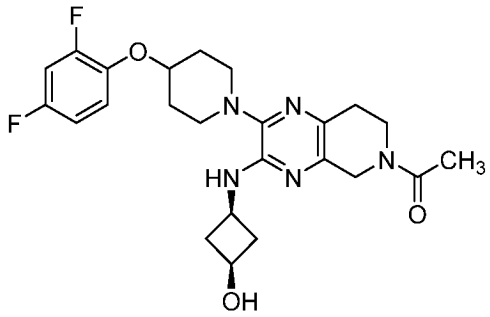
(s, 1.3H), 2.09 (s, 1.7H), 2.11-2.20 (m, 2H), 2.59 (t, *J* = 5.9 Hz, 0.9H), 2.67-2.77 (m, 3.1H), 2.83-2.91 (m, 2H), 3.29 (d, *J* = 10.3 Hz, 2H), 3.70 (dt, *J* = 11.4, 5.8 Hz, 2H), 4.06-4.13 (m, 1H), 4.40 (s, 1H), 4.43 (s, 1H), 4.52 (dt, *J* = 8.2, 4.0 Hz, 1H), 4.69 (td, *J* = 7.3, 2.9 Hz, 1H), 6.24 (d, *J* = 7.3 Hz, 0.6H), 6.28 (d, *J*=7.8 Hz, 0.4H), 6.98-7.05 (m, 1H), 7.26-7.34 (m, 2H); ESI-MS m/z $[M+H]^+$ 516.0.

[00641] Example 143 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methylpropan-1-one



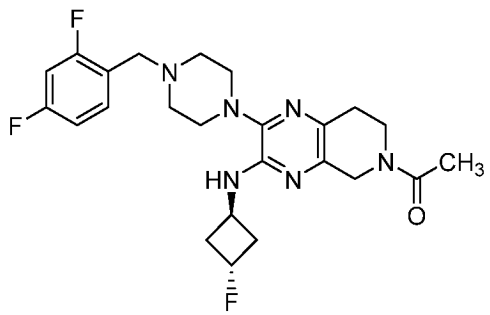
[00642] o a solution of 2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine (50 mg, 0.124 mmol) and DIPEA (0.032 mL, 0.186 mmol) in DCM (1 mL) was added isobutyryl chloride (0.013 mL, 0.124 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, warmed to 23 °C and stirred for an additional 15.5 h. The reaction mixture was concentrated via rotary evaporation and partitioned between EtOAc (4 mL) and NH_4Cl (2 mL). The layers were separated and the organic phase was washed with brine (2 mL), dried over Na_2SO_4, filtered, rinsed with EtOAc, and concentrated via rotary evaporation. The crude material was dissolved in EtOAc and MeOH, adsorbed on silica gel (0.25 g), and purified via medium pressure chromatography using a 50% to 100% gradient of EtOAc in heptane on a 4 g silica gel column (Single Step™) to give the title compound (39.3 mg, 66.9%) as a yellow foam. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 0.99 (d, *J* = 6.8 Hz, 2.7H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.11-1.22 (m, 6H), 2.58 (br s, 3.8H), 2.69 (t, *J* = 5.4 Hz, 1.2H), 2.88-3.13 (m, 5H), 3.58 (s, 2H), 3.75 (dt, *J* = 10.9, 5.6 Hz, 2H), 4.05-4.17 (m, 1H), 4.41 (s, 1.1H), 4.49 (s, 0.9H), 5.29-5.42 (m, 1H), 7.08 (td, *J* = 8.5, 2.4 Hz, 1H), 7.21 (td, *J* = 9.9, 2.7 Hz, 1H), 7.44-7.52 (m, 1H); ESI-MS m/z $[M+H]^+$ 473.0.

[00643] Example 144 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(((1*s*,3*s*)-3-hydroxycyclobutyl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00644] To a solution of (1*s*,3*s*)-3-((6-acetyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutyl acetate (146.5 mg, 0.284 mmol) in MeOH (3 mL) was added sodium methoxide (7.89 μL, 0.043 mmol) at 0 °C. The reaction was stirred at 0 °C for 1 h, concentrated via rotary evaporation at 30 °C, re-constituted with MeOH (2 mL), cooled to 0 °C, and quenched with HOAc (0.005 mL). The reaction mixture was concentrated via rotary evaporation, partitioned between EtOAc (6 mL) and saturated NH_4Cl (4 mL), and the layers were separated. The organic phase was washed with brine (2 mL), dried over Na_2SO_4, filtered, rinsed with EtOAc, and dried *in vacuo* to give the title compound (119.5 mg, 89%) as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.84-1.93 (m, 4H), 2.04-2.11 (m, 5H), 2.56-2.65 (m, 2.9H), 2.71 (t, J = 5.9 Hz, 1.1H), 2.87 (t, J = 10.3 Hz, 2H), 3.27 (dd, J = 8.1, 4.2 Hz, 2H), 3.70 (dt, J = 11.5, 6.0 Hz, 2H), 3.79-3.91 (m, 2H), 4.40 (s, 1.1H), 4.42 (s, 0.9H), 4.51 (tt, J = 8.2, 4.0 Hz, 1H), 4.99-5.04 (m, 1H), 5.99 (d, J = 7.3 Hz, 1.1H), 6.03 (d, J = 7.8 Hz, 1H), 6.99-7.04 (m, 1H), 7.26-7.33 (m, 2H); ESI-MS m/z $[M+H]^+$ 473.9.

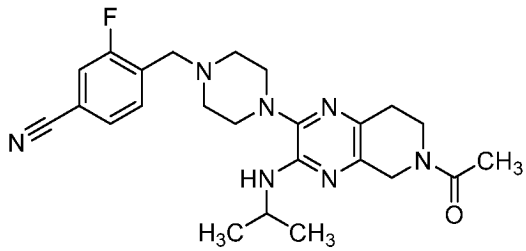
[00645] Example 145 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(((1*r*,3*r*)-3-fluorocyclobutyl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00646] To a solution of 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(((1*s*,3*s*)-3-hydroxycyclobutyl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone (25 mg, 0.053 mmol) in DCM (1 mL) was added DAST (9.1 μL, 0.069 mmol) as a solution in DCM (0.5 mL) at –78 °C during 2 min. The reaction was stirred at –78 °C for 2 h, warmed slowly to 23 °C, and stirred for an additional 14.5 h at 23 °C. The reaction mixture was cooled to –

78 °C and an additional portion of DAST (0.021 mL, 0.159 mmol) was added to the mixture. The reaction mixture was warmed slowly to 23 °C and stirred for an additional 24 hr, cooled to 0 °C and quenched with water (5 mL). The crude product was extracted with EtOAc (2 x 10 mL), the organic extracts were combined, dried over Na_2SO_4, filtered, rinsed with EtOAc, and dried *in vacuo*. The resulting crude material was re-constituted in DMSO (0.5 mL), rinsed with DMSO (2 x 0.25 mL), and purified by HPLC Method B using a 20% to 50% ACN gradient to give the title compound as a TFA salt (1.2 mg, 3.8%) as an off-white solid. ^{1}H NMR (500 MHz, methanol-d_4, mixture of rotamers) δ ppm 2.18-2.23 (m, 3H), 2.36-2.50 (m, 2H), 2.55-2.69 (m, 2H), 2.73 (t, J = 5.4 Hz, 0.9H), 2.80-2.86 (m, 1.1H), 3.26-3.30 (m, 4H), 3.47-3.72 (m, 4H), 3.81 (t, J = 5.6 Hz, 1.1H), 3.87 (t, J = 6.1 Hz, 0.9H), 4.49 (s, 2H), 4.55-4.59 (m, 2H), 4.83 (s, 2H), 5.15-5.21 (m, 0.6H), 5.26-5.33 (m, 0.4H), 7.65-7.71 (m, 1H); ESI-MS m/z $[M+H]^+$ 474.9.

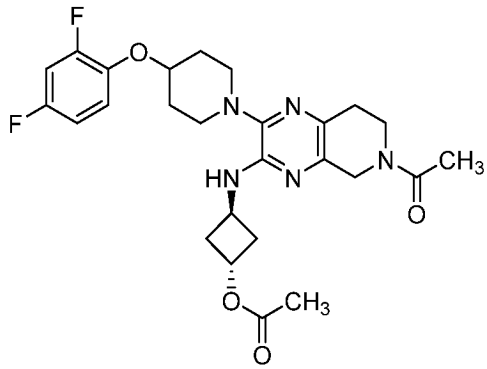
[00647] Example 146 4-((4-(6-acetyl-3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperazin-1-yl)methyl)-3-fluorobenzonitrile



[00648] Combined 1-(3-(isopropylamino)-2-(piperazin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone hydrochloride (132.2 mg, 0.218 mmol) and 3-fluoro-4-formylbenzonitrile (32.6 mg, 0.218 mmol) in DCE (1 mL) and added sodium triacetoxyhydroborate (64.8 mg, 0.306 mmol) at 23 °C. The reaction mixture was stirred at 23 °C for 43 h. An additional portion of sodium triacetoxyhydroborate (64.8 mg, 0.306 mmol) was added to the reaction mixture and the mixture was stirred for an additional 24 h at 23 °C. The resulting residue was diluted with DCE (1 mL), filtered, rinsed with MeOH, and concentrated via rotary evaporation. The resulting crude material was reconstituted in DMSO (1 mL), filtered, rinsed with DMSO (2 x 0.5 mL), and purified by HPLC Method A to give the title compound as a TFA salt (28.0 mg, 22.68%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.13-1.28 (m, 6H), 2.08 (s, 1.3H), 2.09 (s, 1.7H), 2.59 (t, J = 5.9 Hz, 0.9H), 2.67-2.75 (m, 1.1H), 2.90-3.21 (m, 2H), 3.28-3.63 (m, 6H), 3.67-3.77 (m, 2H), 4.06-4.19 (m, 1H), 4.42 (s, 1.1H), 4.45 (s, 0.9H), 4.50 (br s, 2H), 5.68-

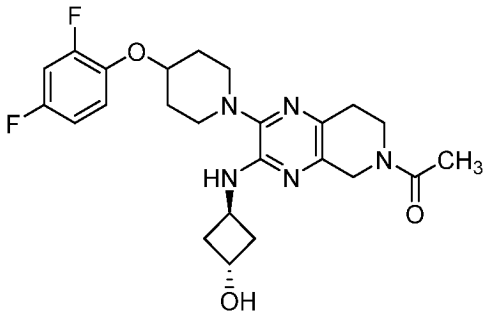
5.77 (m, 1H), 7.83-7.87 (m, 1H), 7.87-7.92 (m, 1H), 8.01-8.22 (m, 1H), 10.22 (br s, 1H); ESI-MS m/z $[M+H]^+$ 452.0.

[00649] Example 147 (1*r*,3*r*)-3-((6-acetyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutyl acetate



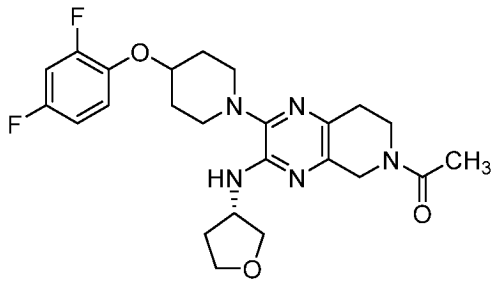
[00650] To a pressure reactor charged with an orange solution of (1*r*,3*r*)-3-((2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutanol (0.8 g, 1.872 mmol) in acetone (30 mL) and dioxane (30 mL) was added palladium, 10 wt % on activated carbon (0.100 g, 0.936 mmol) as a slurry in dioxane (3 mL) under nitrogen. Next, acetic anhydride (1.758 mL, 18.72 mmol) was added at 23 °C. The mixture was stirred under hydrogen at 310 kPa for 3 days at 45 °C. Additional portions of palladium, 10 wt % on activated carbon (0.100 g, 0.936 mmol) and acetic anhydride (0.352 mL, 3.74 mmol) were added to the reactor and the mixture was stirred under hydrogen at 45 kPa for 2 additional days at 45 °C. The reaction mixture was filtered through Celite™, rinsed with dioxane, and concentrated via rotary evaporation. The crude material was dissolved in toluene (2 mL) and purified via medium pressure chromatography using a 30% to 100% gradient of EtOAc in heptane on a 160 g silica gel column (Single Step™) to give the title compound (270 mg, 28.0%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.83-1.97 (m, 2H), 2.03 (s, 3H), 2.04-2.12 (m, 5H), 2.33-2.41 (m, 2H), 2.41-2.49 (m, 2H), 2.59 (t, J = 5.9 Hz, 0.9H), 2.71 (t, J = 5.6 Hz, 1.1H), 2.89 (t, J = 10.0 Hz, 2H), 3.20-3.34 (m, 4H), 3.56-3.79 (m, 2H), 4.40 (s, 1.1H), 4.43 (s, 0.9H), 4.47-4.59 (m, 2H), 5.05 (td, J = 6.9, 3.2 Hz, 1H), 6.24 (d, J = 6.8 Hz, 0.6 H), 6.27 (d, J=6.8 Hz, 0.4H), 6.94-7.11 (m, 1H), 7.22-7.43 (m, 2H); ESI-MS m/z $[M+H]^+$ 515.9.

[00651] Example 148 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(((1*r*,3*r*)-3-hydroxycyclobutyl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00652] To an off-white suspension of (1*r*,3*r*)-3-((6-acetyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutyl acetate (108 mg, 0.209 mmol) in MeOH (2 mL) was added sodium methoxide (5.8 µL, 0.031 mmol) at 23 °C. The reaction was stirred at 23 °C for 15 min, concentrated via rotary evaporation at 30 °C, re-constituted with MeOH (2 mL), cooled to 23 °C, and quenched with HOAc (0.010 mL). The reaction mixture was concentrated via rotary evaporation, partitioned between EtOAc (6 mL) and saturated NH_4Cl (4 mL), and the layers were separated. The organic phase was washed with brine (2 mL), dried over Na_2SO_4, filtered, rinsed with EtOAc, and dried *in vacuo* to give the title compound (99 mg, 100%) as a yellow foam. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.87-1.93 (m, 2H), 2.00-2.12 (m, 5H), 2.12-2.20 (m, 2H), 2.21-2.32 (m, 2H), 2.55-2.62 (m, 0.9H), 2.71 (t, J = 5.1 Hz, 1.1H), 2.88 (t, J = 10.0 Hz, 2H), 3.28 (br s, 2H), 3.63-3.80 (m, 2H), 4.29 (d, J = 3.9 Hz, 1H), 4.40 (s, 1.1H) 4.43 (s, 0.9H), 4.47-4.62 (m, 1H), 4.95 (d, J = 4.9 Hz, 1H), 5.99 (d, J = 6.3 Hz, 1H), 6.03 (d, J = 6.8 Hz, 1H), 6.96-7.08 (m, 1H), 7.23-7.36 (m, 2H); ESI-MS m/z $(M+H)^+$ 474.0.

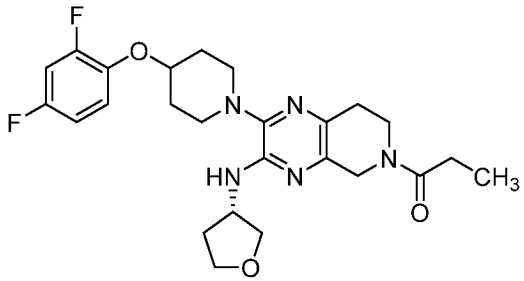
[00653] Example 149 (*S*)-1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(tetrahydrofuran-3-ylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00654] To a solution of (*S*)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-(tetrahydrofuran-3-yl)pyrido[3,4-*b*]pyrazin-3-amine (2.0 g, 4.68 mmol) in dioxane:acetone (50 ml; 1.5:1) was added Ac_2O (4.8 mL, 50.9 mmol) and Pd/C (400 mg, 3.76 mmol); then, the reaction was stirred at 60 °C under H_2 atmosphere (345 kPa) for 72 h. The mixture was filtered through a

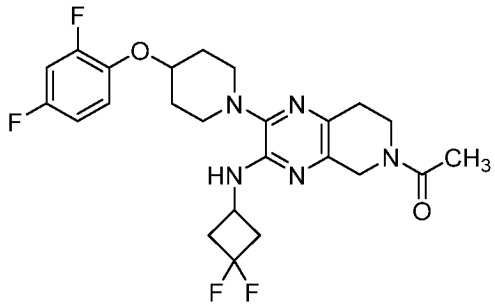
pad of Celite™ and washed with EtOAc. The reaction solution was diluted with EtOAc (50 mL) and poured into sat. aqueous $NaHCO_3$ (50 ml), then washed with brine (2 x 30 mL). The organic layer was dried over Na_2SO_4 and concentrated to give the crude product, which was purified by flash column chromatography to yield the title compound (193.4 mg) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 1.88-1.89 (m, 4H), 2.05-2.09 (m, 4H), 2.60-2.90 (m, 4H), 3.30-3.40 (m, 4H), 3.55-3.57 (m, 1H), 3.68-3.74 (m, 2H), 3.85-3.95 (m, 2H), 4.38-4.51 (m, 4H), 5.91 (dd, *J* = 6.0, 4.4 Hz, 1H), 7.01 (m, 1H), 7.25-7.31 (m, 2H); ESI-MS m/z $[M+H]^+$ 474.3.

[00655] Example 150 (*S*)-1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(tetrahydrofuran-3-ylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)propan-1-one



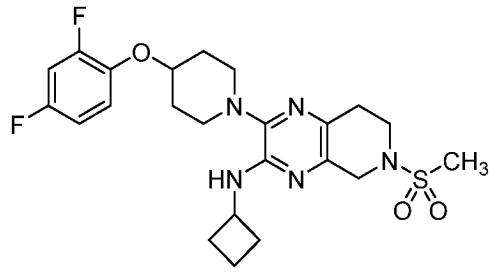
[00656] To a solution of (*S*)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-N-(tetrahydrofuran-3-yl)pyrido[3,4-*b*]pyrazin-3-amine (2.5 g, 5.85 mmol) in dioxane:acetone (105 ml, 1.5:1) was added propionic anhydride (7 mL, 3.76 mmol) and Pd/C (400 mg, 3.76 mmol); then, the reaction was stirred at 60 °C and under H_2 atmosphere (345 kPa) for 72 h. The mixture was filtered through a pad of Celite™ and washed with EtOAc. The reaction solution was diluted with EtOAc (50 mL) and poured into sat. aqueous $NaHCO_3$ (50 mL) then washed with brine (2 x 30 mL). The organic layer was dried over Na_2SO_4 and concentrated to give the crude product, which was purified by flash column chromatography to give the title compound (125 mg) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0.97-1.03 (m, 3H), 1.87-2.04 (m, 6H), 2.15-2.25 (m, 1H), 2.40-2.43 (m, 2H), 2.58-2.60 (m, 1H), 2.69-2.73 (m, 1H), 2.88 (q, *J* = 9.6 Hz, 2H), 3.30-3.34 (m, 2H), 3.50-3.60 (m, 1H), 3.70-3.74 (m, 2H), 3.84-3.90 (m, 2H), 4.35-4.60 (m, 4H), 5.88-5.92 (m, 1H), 6.98-7.02 (m, 1H), 7.27-7.30 (m, 2H); ESI-MS m/z $[M+H]^+$ 488.3.

[00657] Example 151 1-(3-((3,3-difluorocyclobutyl)amino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one



[00658] To a pressure reactor charged with a yellow-orange solution of *N*-(3,3-difluorocyclobutyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)pyrido[3,4-*b*]pyrazin-3-amine (250 mg, 0.559 mmol) in acetone (10 mL) and dioxane (10 mL) was added palladium, 10 wt % on activated carbon (23.8 mg, 0.223 mmol) as a slurry in dioxane (2 mL) under nitrogen. Next, acetic anhydride (0.525 mL, 5.59 mmol) was added at 23 °C. The mixture was stirred under hydrogen at 310 kPa for 45 h at 45 °C. The reaction mixture was filtered through Celite™, rinsed with dioxane, and concentrated via rotary evaporation. The crude material was purified via medium pressure chromatography using a gradient eluant of 30% to 100% EtOAc in heptane on a 80 g silica gel column (Single Step™) to give the title compound (145 mg, 52.6%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers) δ ppm 1.80-1.95 (m, 2H), 2.03-2.08 (m, 2H), 2.0 (s, 1.3H), 2.09 (s, 1.7H), 2.60 (t, J = 5.6 Hz, 0.9H), 2.67-2.80 (m, 3.1H), 2.83-2.98 (m, 4H), 3.31-3.38 (m, 2H), 3.71 (dt, J = 11.2, 5.6 Hz, 2H), 4.14-4.27 (m, 1H), 4.42 (s, 1.1H), 4.45 (s, 0.9H), 4.53 (tt, J = 8.2, 3.8 Hz, 1H), 6.46 (dd, J = 14.6, 6.8 Hz, 1H), 6.98-7.06 (m, 1H), 7.25-7.36 (m, 2H); ESI-MS m/z 493.9 $(M+H)^+$ 493.9.

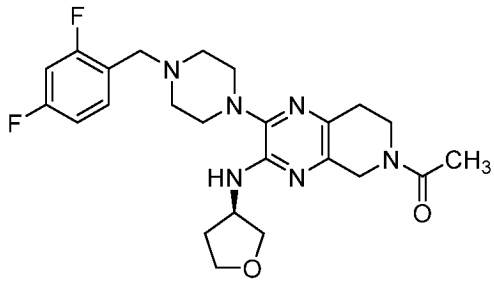
Example 152 *N*-cyclobutyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine



[00659] The title compound was prepared in a manner similar to Example 11 using *N*-cyclobutyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine to give the title compound. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.55-1.75 (m, 2H), 1.84-1.96 (m, 2H), 1.96-2.14 (m, 4H), 2.18-2.32 (m, 2H), 2.75 (t, J = 5.9 Hz, 2H), 2.84-2.95 (m, 2H), 2.95-3.03 (m, 3H), 3.26-3.33 (m, 2H), 3.45 (t, J = 5.9 Hz, 2H), 4.16

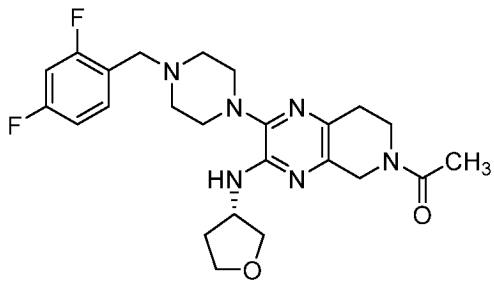
(s, 2H), 4.30-4.44 (m, 1H), 4.52 (tt, J = 8.1, 3.8 Hz, 1H), 6.12 (d, J = 7.8 Hz, 1H), 6.95-7.08 (m, 1H), 7.23-7.37 (m, 2H); ESI-MS m/z $(M+H)^+$ 494.0.

[00660] Example 153 (*R*)-1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(tetrahydrofuran-3-ylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



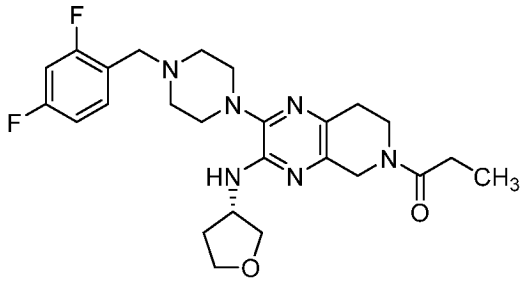
[00661] The title compound was prepared in a manner similar to 149 using (*R*)-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-(tetrahydrofuran-3-yl)pyrido[3,4-*b*]pyrazin-3-amine to give the title compound as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.82-1.86 (m, 1H), 2.20 (s, 3H), 2.33-2.36 (m, 1H), 2.59-2.66 (m, 4H), 2.79 (m, 2H), 3.05-3.15 (m, 4H), 3.63 (s, 1H), 3.69-3.72 (m, 2H), 3.85-3.88 (m, 2H), 3.95-3.99 (m, 2H), 4.46-4.64 (m, 3H), 4.87-4.90 (m, 1H), 6.79-6.90 (m, 2H), 7.39-7.41 (m, 1H); ESI-MS m/z $[M+H]^+$ 473.1.

[00662] Example 154 (*S*)-1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(tetrahydrofuran-3-ylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



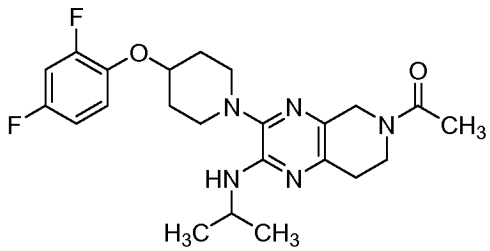
[00663] The title compound was prepared in a manner similar to 149 using (*S*)-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-(tetrahydrofuran-3-yl)pyrido[3,4-*b*]pyrazin-3-amine to give the title compound as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.82-1.86 (m, 1H), 2.20 (s, 3H), 2.33-2.36 (m, 1H), 2.59-2.66 (m, 4H), 2.79 (dt, J = 21.6, 5.6 Hz, 2H), 3.05-3.15 (m, 4H), 3.63 (s, 1H), 3.69-3.72 (m, 2H), 3.85-3.88 (m, 2H), 3.98-4.00 (m, 2H), 4.48-4.64 (m, 3H), 4.88-4.92 (m, 1H), 6.82 (t, J = 9.6 Hz, 1H), 6.84 (t, J = 12.8 Hz, 1H), 7.39 (q, J = 7.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 473.1.

[00664] Example 155 (*S*)-1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(tetrahydrofuran-3-ylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)propan-1-one



[00665] The title compound was prepared in a manner similar Example to 150 using (*S*)-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-(tetrahydrofuran-3-yl)pyrido[3,4-*b*]pyrazin-3-amine to give the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.18 (q, *J* = 7.2 Hz, 3H), 1.75-1.85 (m, 1H), 2.25-2.46 (m, 3H), 2.55-2.65 (m, 4H), 2.75-2.80 (m, 2H), 3.00-3.10 (m, 4H), 3.59-3.70 (m, 4H), 3.87-3.90 (m, 2H), 3.96-3.98 (m, 2H), 4.46-4.62 (m, 3H), 4.85-4.95 (m, 1H), 6.75-6.90 (m, 2H), 7.35-7.45 (m, 1H); ESI-MS m/z $[M+H]^+$ 487.3.

[00666] Example 156 1-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone



[00667] The title compound was prepared in a manner similar to Example 120 using 4-(2,4-difluorophenoxy)piperidine, HCl to give the title compound as a colorless film. ^{1}H NMR (500 MHz, methanol-*d*4) δ ppm 0.85-0.93 (m, 1H), 1.25 (d, *J* = 6.4 Hz, 6H), 1.95 (ddd, *J* = 12.1, 8.2, 3.7 Hz, 2H), 2.09-2.17 (m, 2H), 2.20 (d, *J* = 8.8 Hz, 3H), 2.74 (t, *J* = 5.9 Hz, 1H), 2.84 (t, *J* = 5.6 Hz, 1H), 2.92-3.02 (m, 2H), 3.35 (dd, *J* = 8.3, 3.9 Hz, 2H), 3.81 (t, *J* = 5.6 Hz, 1H), 3.86 (t, *J* = 5.9 Hz, 1H), 4.12-4.21 (m, 1H), 4.46 (dd, *J* = 7.1, 3.7 Hz, 1H), 4.54 (s, 2H), 6.85-6.91 (m, 1H), 6.96-7.02 (m, 1H), 7.18 (td, *J* = 8.8, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 446.90.

[00668] The compounds of the invention can be administered alone or in the form of a pharmaceutical composition. In practice, the compounds of the invention are usually administered in the form of pharmaceutical compositions, that is, in admixture with at least one pharmaceutically acceptable excipient. The proportion and nature of any pharmaceutically acceptable excipient(s) are determined by the properties of the selected

compound of the invention, the chosen route of administration, and standard pharmaceutical practice.

[00669] In another embodiment, the present invention provides pharmaceutical compositions comprising: a compound of invention and at least one pharmaceutically acceptable excipient.

[00670] In effecting treatment of a patient in need of such treatment, a compound of the invention can be administered in any form and route which makes the compound bioavailable. The compounds of the invention can be administered by a variety of routes, including orally, in particularly by tablets and capsules. The compounds of the invention can be administered parenteral routes, more particularly by inhalation, subcutaneously, intramuscularly, intravenously, intraarterially, transdermally, intranasally, rectally, vaginally, occularly, topically, sublingually, and buccally, intraperitoneally, intraadiposally, intrathecally and via local delivery for example by catheter or stent.

[00671] One skilled in the art can readily select the proper form and route of administration depending upon the particular characteristics of the compound selected, the disorder or condition to be treated, the stage of the disorder or condition, and other relevant circumstances. The pharmaceutical compositions of the invention may be administered to the patient, for example, in the form of tablets, capsules, cachets, papers, lozenges, wafers, elixirs, ointments, transdermal patches, aerosols, inhalants, suppositories, solutions, and suspensions.

[00672] The pharmaceutical compositions of the present invention are prepared in a manner well known in the pharmaceutical art and include at least one of the compounds of the invention as the active ingredient. The amount of a compound of the present invention may be varied depending upon its particular form and may conveniently be between 1% to about 50% of the weight of the unit dose form. The term "pharmaceutically acceptable excipient" refers to those typically used in preparing pharmaceutical compositions and should be pharmaceutically pure and non-toxic in the amounts used. They generally are a solid, semi-solid, or liquid material which in the aggregate can serve as a vehicle or medium for the active ingredient. Some examples of pharmaceutically acceptable excipients are found in Remington's Pharmaceutical Sciences and the Handbook of Pharmaceutical Excipients and include diluents, vehicles, carriers, ointment bases, binders, disintegrates, lubricants, glidants, sweetening agents, flavoring agents, gel bases, sustained release matrices, stabilizing agents, preservatives, solvents, suspending agents, buffers, emulsifiers, dyes, propellants, coating agents, and others.

[00673] The present pharmaceutical compositions are preferably formulated in a unit dose form, each dose typically containing from about 0.5 mg to about 100 mg of a compounds of the invention. The term "unit dose form" refers to a physically discrete unit containing a predetermined quantity of active ingredient, in association with a suitable pharmaceutical excipient, by which one or more is used throughout the dosing regimen to produce the desired therapeutic effect. One or more "unit dose form" may be taken to affect the treatment dosage on a daily schedule.

[00674] In one particular variation, the composition is a pharmaceutical composition adapted for oral administration, such as a tablet or a capsule or a liquid formulation, for example, a solution or suspension, adapted for oral administration. In still another particular variation, the pharmaceutical composition is a liquid formulation adapted for parenteral administration.

[00675] Compounds of the present invention are modulators of GPR6, specifically, antagonists or inverse agonists, and as such are useful in the treatment and prevention of conditions associated with GPR6. As mentioned above, the major striatal targets of dopaminergic innervation reside in the medium spiny neurons (MSNs) of the striatopallidal (indirect) and striatonigral (direct) output pathways. The MSNs of the direct output pathway express D1 dopamine receptors whereas those in the indirect pathway express D2 receptors. GPR6 is enriched in D2 receptor expressing MSNs in the striatum where GPR6 activity is functionally opposed to D2 receptor signaling. Antagonism or inverse agonism of Gs coupled GPR6 decreases cAMP in MSNs and provides a functional alternative to dopamine mediated activation of D2 receptors.

[00676] Antagonism or inverse agonism of Gs coupled GPR6 provides a functional alternative to dopamine mediated activation of D2 receptors. As such, compounds that modulate the activity of GPR6 are useful for treating in a variety of neurological and psychiatric disorders. For example movement disorders including Parkinson's disease and Huntington's disease either alone or in combination with other agents are approved for the treatment of Parkinson's disease including L-DOPA, dopaminergic agonists, MAO B inhibitors, DOPA decarboxylase inhibitors and C(O)MT inhibitors. Other disease indications that could be treated by modulation of GPR6 include drug addiction and eating disorders, cognitive disorders, schizophrenia, bipolar disorders, and depression.

[00677] In another embodiment, the invention provides methods of treating conditions associated with GPR6, comprising: administering to a patient in need thereof an effective amount of a compound of the invention. In another embodiment, a compound of the invention is provided for use as a medicament. The invention also provides the use of a

compound of the invention, including the use for the manufacture of a medicament, to treat the conditions associated with GPR6 described herein. The compounds of the present invention are useful as GPR6 modulators for a variety of subjects (*e.g.*, humans, non-human mammals and non-mammals).

[00678] As used herein terms "condition," "disorder," and "disease" relate to any unhealthy or abnormal state. The term "conditions associated with GPR6" includes conditions, disorders, and diseases in which the modulators of GPR6 provides a therapeutic benefit, such as Parkinson's disease, levodopa induced dyskinesias, and Huntington's disease, drug addiction, eating disorders, cognitive disorders, schizophrenia, bipolar disorders, and depression.

[00679] The terms "treat," "treatment," and "treating" include improvement of the conditions described herein. The terms "treat," "treatment," and "treating" include all processes providing slowing, interrupting, arresting, controlling, or stopping of the state or progression of the conditions described herein, but does not necessarily indicate a total elimination of all symptoms or a cure of the condition. The terms "treat," "treatment," and "treating" are intended to include therapeutic treatment of such disorders. The terms "treat," "treatment," and "treating" are intended to include prophylactic treatment of such disorders.

[00680] As used herein the terms "patient" and "subject" includes humans and non-human animals, for example, mammals, such as mice, rats, guinea pigs, dogs, cats, rabbits, cows, horses, sheep, goats, and pigs. The term also includes birds, fish, reptiles, amphibians, and the like. It is understood that a more particular patient is a human. Also, more particular patients and subjects are non-human mammals, such as mice, rats, and dogs.

[00681] As used herein, the term "effective amount" refers to the amount of compound of the invention which treats, upon single or multiple dose administration, a patient suffering from the mentioned condition. An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount, the dose, a number of factors are considered by the attending diagnostician, including, but not limited to, the species of patient, its size, age, and general health; the specific condition, disorder, or disease involved; the degree of or involvement or the severity of the condition, disorder, or disease, the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances. An effective amount of the present invention, the

treatment dosage, is expected to range from 1 mg to 200 mg. Specific amounts can be determined by the skilled person. Although these dosages are based on an average human subject having a mass of about 60 kg to about 70 kg, the physician will be able to determine the appropriate dose for other patients.

[00682] The pathological hallmark of Parkinson disease (PD) is neuronal cell loss within the substantia nigra. Degeneration of the nigrostriatal pathway causes reduction in the striatal concentration of dopamine which results in motor and nonmotor clinical manifestations. Many Parkinson's disease patients are treated with levodopa, a prodrug for dopamine. Levodopa has common serious side effects including induced dyskinesia (LID), impulsive control disorders (ICD), psychotic symptoms and sleep disturbances. LID is progressive (90% of PD patients develop LID within 10yrs). Irreversible adaptations occur in D1 receptor signaling in MSNs in rodent models of LID including reduced desensitization leading to hypersensitivity in the direct pathway. Genetic inactivation of D1 but not D2 receptors abolishes LID in mice. However blockade of D1 receptor signaling does not affect the antiparkinsonian efficacy of L-DOPA.

[00683] In a particular embodiment, the present invention provides a method of treating Parkinson's disease comprising: administering to a patient in need thereof an effective amount of a compound of the invention. That is, the invention also provides the use of a compound of the invention, including the use for the manufacture of a medicament, to treat Parkinson's disease.

[00684] The compounds of the invention may be combined with one or more other pharmacologically active compounds or therapies for the treatment of one or more disorders, diseases or conditions for which GPR6 is indicated may be administered simultaneously, sequentially or separately in combination with one or more compounds or therapies for treating Parkinson's disease, levodopa induced dyskinesias, and Huntington's disease, drug addiction, eating disorders, cognitive disorders, schizophrenia, bipolar disorders, and depression. Such combinations may offer significant therapeutic advantages, including fewer side effects, improved ability to treat underserved patient populations, or synergistic activity. In particular, the compounds of the invention may be administered with levodopa for treating Parkinson's disease. The present invention provides a method treating Parkinson's disease comprising: administering to a patient in need thereof an effective amount of a compound of the invention in combination with levadopa. The invention also provides the use of a compound of the invention in combination with levadopa, including the use for the manufacture of a medicament, to treat Parkinson's disease.

[00685] The activity of compounds as GPR6 modulators may be determined by a variety of methods, including *in vitro* and *in vivo* methods.

[00686] Example A.1

[00687] Inhibition of cAMP activity of GPR6 in vitro assay

[00688] This cell based assay measures the ability of compounds to inhibit the constitutive cAMP activity of GPR6 receptor expressed in CHO-K1 cells. CHO cells were stably expressed with GPR6 receptor, whose expression is controlled by a tetracycline inducable element. The cells were cultured in medium containing F12K, 10% FBS, 1% Penn/Strep, 200ug/mL Hygromycin. GPR6 receptor expression was induced for 20 hrs with 1μg/ml doxycycline (sigma D9891) in growth media. After addition of doxycycline cells were plated at a density of 250-500 cells per well in half-volume black clear bottom plates (Costar) and place in an incubator (37°, 5% $C(O)_2$) for 20 hours prior to cAMP assays.

[00689] Culture media was removed from cells and they were washed with 50 μL of Ringer's Buffer ($MgCl_2$ 0.047 mg/mL, NaH_2PO_4 0.18 mg/mL, Na_2HPO_4 0.1 mg/mL, KCl 0.34 mg/mL, $NaHC(O)_3$ 1.26 mg/mL, D-glucose 1.8 mg/mL, NaCl 7 mg/mL; pH=7.4). Compounds suspended in DMSO were diluted in Ringer's Buffer containing 0.5% fatty acid free BSA and incubated on cells for 45 min at 37° and 5% $C(O)_2$. After incubation cells were incubated for 10 min at room temp with Eu-cAMP tracer solution from a Perkin Elmer Lance HTRF UltracAMP assay kit (TRF0264). Then ULightTM-anti-cAMP solution from the Lance HTRF kit was added and incubated on a shaker at room temp for 1 hour prior to HTRF detection in a BMG PolarStar Omega.

[00690] IC_{50} curves were generated with a four-parameter logistic equation using GraphPad Prism 5.03. Measured IC_{50} value (μM) of example compounds in this assay is provided in the table below.

[00691] Example A.2

[00692] Inhibition of cAMP activity of GPR6 in vitro assay

[00693] This cell based assay measures the ability of compounds to inhibit the constitutive cAMP activity of GPR6 receptor expressed in CHO-K1 cells. CHO cells were stably expressed with GPR6 receptor, whose expression is controlled by a tetracycline inducable element. The cells were cultured in medium containing F12K, 10% FBS, 1% Penn/Strep, 200ug/mL Hygromycin. GPR6 receptor expression was induced for 20 hrs with 2μg/ml doxycycline (sigma D9891) in growth media. After addition of doxycycline cells were

plated at a density of 450-750 cells per well in 96-well half-volume black tissue culture plates (Costar) and placed in an incubator (37°, 5% CO_2) for 20 hours prior to cAMP assays.

[00694] Culture media was removed from cells and they were washed with 50 µL/well of Ringer's Buffer ($MgCl_2$ 0.047 mg/mL, NaH_2PO_4 0.18 mg/mL, Na_2HPO_4 0.1 mg/mL, KCl 0.34 mg/mL, $NaHCO_3$ 1.26 mg/mL, D-glucose 1.8 mg/mL, NaCl 7 mg/mL; pH=7.4). Compounds suspended in DMSO were diluted in Ringer's Buffer containing 0.5% fatty acid free BSA plus 300 µM IBMX and incubated on cells for 45 min at 37° and 5% CO_2. After incubation cells were incubated for 10 min at room temp with Eu-cAMP tracer solution from a Perkin Elmer Lance HTRF Ultra cAMP assay kit (TRF0263). Then ULightTM-anti-cAMP solution from the Lance HTRF kit was added and incubated on a shaker at room temp for 1 hour prior to HTRF detection in a Perkin Elmer Envision plate reader.

[00695] IC_{50} curves were generated with a four-parameter logistic equation using GraphPad Prism 5.03. Measured IC_{50} value (µM) of example compounds in this assay is provided in the Table 1 below.

[00696] Table 1

Ex.	A.1 IC_{50}	A.2 IC_{50}	Ex.	A.1 IC_{50}	A.2 IC_{50}	Ex.	A.1 IC_{50}	A.2 IC_{50}
1		340.2	53		95	105		
2		71.5	54		59.3	106		
3		61.8	55		109.6	107	24.9	
4	29.8		56		179.4	108	31.4	
5	17.9		57		93.5	109	23.2	
6	55.2		58	26.6		110	22.1	
7	86.6		59		49.7	111	23	
8	16.8		60		>1000	112	10.4	
9		210.6	61		131.7	113	20.9	
10	17.3		62		69.2	114	18.5	
11		95.6	63		37.8	115	23.9	
12						116		199.7
13			65			117		27.4
14	62.6		66	145		118		11.4
15	14.9		67	9.4		119		23.6
16	19.5		68	15.2		120		249.8
17	18		69	26.5		121		341.5

18	38.7		70		17.1	122		247
19	105		71	8.5		123		187.7
20	122		72	23.7		124		43.2
21	149		73	16.6		125		200.2
22		78.1	74		140.2	126		107.1
23	391		75		30.3	127		>1000
24		129.2	76	13.4		128		55
25			77	19.7		129		62
26			78	8.8		130		319.3
27			79	9.8		131		27.6
28			80	24.9		132		129.5
29	178		81		59.5	133		74.8
30	87		82		73.7	134		27
31	208		83	13.8		135		43.7
32	76		84		90.1	136		27.9
33	52		85	10.4		137		30.9
34	68		86	13.7		138		>1000
35	88		87	13.8		139		219.8
36	98		88	32.7		140		122
37	91		89			141		33.7
38	85		90			142		113.5
39	126		91	11.5		143		29
40	259		92	12		144		61.5
41		212.2	93	13.8		145		185.9
42		193.3	94	19.9		146		362.9
43		115.5	95	32.5		147		603.9
44		62.5	96	26.9		148		78
45		74.1	97		163	149		58.7
46	35		98		110.6	150		39.2
47		24.6	99	8.3		151		35.9
			100	57.2		152		49.3
49	9.1		101	78.8		153		63.2
50		79.5	102	111		154		97.8
51	6.6		103	64		155		59.1

52		73.2	104			156	9.5	

[00697] Example B

[00698] Haloperidol-induced Catalepsy – in vivo rodent Parkinson's disease model

[00699] The motor symptoms of Parkinson's disease include akinesia, bradykinesia, rigidity, tremor and postural abnormalities and are associated with the loss of nigral dopaminergic cells and a decline in striatal dopamine levels. Administration of haloperidol to rodents leads to a transient parkinsonian-like state that is reversed by the administration of L-Dopa (Duty, S.; Jenner, P. Br. J. Pharmacol. (2011), 164, 1357–1391) and other drugs that have been clinically validated for the treatment of Parkinson's disease. Haloperidol antagonizes dopamine D2 and, to a lesser extent, D1 receptors in medium spiny neurons that comprise the indirect and direct pathways of the motor circuit respectively. The resultant block of striatal dopamine transmission results in abnormal downstream firing within the basal ganglia circuits that is manifest as symptoms of muscle rigidity and catalepsy. Catalepsy has been postulated to reflect the clinical features of Parkinson's disease, whereby patients experience an inability of to initiate movements.

[00700] Male Sprague-Dawley rats (Charles River, Calco, Italy) weighing 175-200 g are used. Alternatively, male C57Bl6 mice weighing 25-35 g were used. The cataleptic state was induced by the subcutaneous administration of the dopamine receptor antagonist haloperidol (0.3 mg/kg, sc), 90 min before testing the animals on the vertical grid test. For this test, the rats or mice were placed on the wire mesh cover of a 25 cm x43 cm plexiglass cage placed at an angle of about 70 degrees with the bench table. The subject was placed on the grid with all four legs abducted and extended ("frog posture"). The use of such an unnatural posture is essential for the specificity of this test for catalepsy. The time span from placement of the paws until the first complete removal of one paw (descent latency) was measured maximally for 120 sec for rats. For mice, the front paws of a mouse was placed on a horizontal metal bar raised 2" above a Plexiglas platform and time was recorded for up to 30 seconds per trial. The test ended when the animal's front paws returned to the platform or after 30 seconds. The test was repeated three times and the average of the three trials was reported as the intensity index of catalepsy.

[00701] Catalepsy was measured 30 min, 120 min, and/or 240 min after dosing the subjects a 0.3 mg/kg i.p. dose of haloperidol along with the GPR6 modulator test compound. Test compound plasma and brain levels were determined by collected tissue samples at the end of the experiment, which was either at the 120 or 240 min time point. A representative number

of compounds of the invention were administered in a dose range from 0.1 to 100 mg/kg i.p, sc or po in conjunction with haloperidol. The A2a antagonist KW6002 (istradefylline) was dosed at 0.6 mg/kg i.p. as a positive control.

[00702] Measured % reversal of example compounds in this assay is provided in the Table 2 below.

[00703] Table 2

Ex.	Species	Dose (mpk)	Route	% reversal	
				30 min	120 min
47	Rat	30	i.p.	75.7*	82.1*
		10	i.p.	83.4*	76.5*
		1	i.p.	39.1	57.9*
		0.1	i.p.	-5.7	27.3

*-significantly different than vehicle contol, one-way ANOVA with Bonferroni's multiple test correction.

[00704] Example C

[00705] 6-Hydroxydopamine Lesion Model – in vivo rodent Parkinson's disease model

[00706] Adult female rats (10) were first assessed for pre-surgery motor activity using an automated activity tracking system that records beam breaks across the testing arena floor. Beam breaks were summed over the first 3 hours after the animals were placed into the arena and recorded as activity counts. To selectively damage dopaminergic nerve terminals in the striatum, 20 µg of the 6-hydroxydopamine was injected directly into the striatum bilaterally (i.e., on both sides of the brain). After 4 weeks of recovery, the rats were again tested for motor activity, and a significant reduction in activity counts was observed. Vehicle and the compound of Example 47 (0.5% methylcellulose) was orally dosed at 0.1, 1.0, or 10 mg/kg in a cross-over study design (5-10 day wash out period), and after dosing activity counts were measured for 3 hours. At the end of the study period, when each animal had received each treatment once, the data were analyzed. The activity counts (standard error of the mean) for the group pre-surgery and post-surgery and for treated and vehicle control were determined and are provide in Table 3 below:

[00707] Table 3

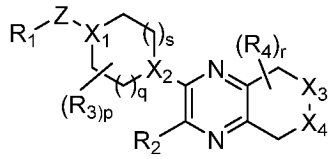
Treatment Group	Mean	S.E.M
Pre-Surgery	12171	1601
Vehicle	7253	768

0.1 mg/kg	11422*	1071
1.0 mg/kg	15334*	2013
10 mg/kg	19368*	1410

*-significantly different than vehicle contol, one-way ANOVA with Bonferroni's multiple test correction.

WHAT IS CLAIMED IS:

1. The compound of formula I



I

wherein

R_1 is selected from the group consisting of optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{3-6} heterocyclyl, optionally substituted C_{6-10} aryl, and optionally substituted C_{1-10} heteroaryl;

X_1 is N and X_2 is CH; or

X_1 is CH and X_2 is N; or

X_1 is N and X_2 is N;

when X_1 is N, Z is selected from the group consisting of C_{1-6} alkylene, C_{1-6} haloalkylene, -C(O)-, and -$S(O)_2$-;

when X_1 is CH, Z is selected from the group consisting of C_{1-6} alkylene, C_{1-6} haloalkylene, -O-, -C(O)-, -NH-, -S-, -S(O)-, and -$S(O)_2$-;

q is 0, 1, or 2;

s is 0, 1, or 2;R_2 is $–OR_5$ or $–NR_6R_7$;

R_3, each time taken, is independently selected from the group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl, and trifluoromethyl;

p is 0, 1, or 2;

R_4, each time taken, is independently selected from the group consisting of C_{1-6} alkyl, hydroxy, and halo;

r is 0 or 1;

R_5 is selected from the group consisting of C_{1-6} alkyl and C_{3-8} cycloalkyl;

R_6 is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R_7 is selected from the group consisting of optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-10} heteroaryl, and optionally substituted C_{3-6} heterocyclyl;

X_3 is selected from the group consisting of CH and CR_4 and X_4 is NR_8; or

X_3 is NR_8 and X_4 is selected from the group consisting of CH and CR_4;

R_8 is selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-8} cycloalkyl,

$-S(O)_2-R_9$, $-C(O)-R_{10}$, $-C(O)-N(R_{11})(R_{12})$, and $-C(O)-OR_{13}$;

R_9 is selected from the group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl, and optionally substituted phenyl;

R_{10} is selected from the group consisting of hydrogen, optionally substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-10} heteroaryl, and optionally substituted C_{3-6} heterocyclyl;

R_{11} is selected from the group consisting of hydrogen and C_{1-6} alkyl;

R_{12} is selected from the group consisting of hydrogen, C_{1-6} alkyl and C_{3-8} cycloalkyl; or

R_{11} and R_{12} are taken together with the nitrogen to which they are attached form a 4 to 7 membered, saturated, ring optionally having 1 additional ring heteroatom selected from the group N, O, and S and optionally substituted on any of the ring carbon atoms with 1 to 5 substituents independently selected from the group consisting of cyano, halo, hydroxy, amino, optionally substituted C_{3-6} heterocyclyl, C_{1-9} amide, optionally substituted C_{1-6} alkyl, and C_{1-4} alkoxy and substituted on any additional ring nitrogen by a substituent selected from the group consisting of hydrogen, C_{3-8} cycloalkyl, and optionally substituted C_{1-6} alkyl;

R_{13} is selected from the group consisting of C_{1-6} alkyl and C_{3-8} cycloalkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein X_1 is CH and X_2 is N or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 wherein X_1 is N and X_2 is N or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 3 wherein X_3 is selected from the group consisting of CH and CR_4 and X_4 is NR_8 or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 4 wherein R_1 is optionally substituted C_{6-10} aryl or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 5 wherein Z is C_{1-6} alkylene or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 5 wherein Z is -O- or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 5 wherein Z is -C(O)- or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 8 wherein R_2 $-NR_6R_7$ or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 selected from the group consisting of:

cyclopropyl(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone; 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethan-1-one; 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-*N*-(2-methoxyethyl)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)(tetrahydrofuran-2-yl)methanone; 3-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-3-oxopropanenitrile; 4-((1-(6-acetyl-3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile; 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one; cyclopropyl(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone; 1-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethan-1-one; 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; 2-(4-(4-cyano-2-fluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-*N,N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 3-fluoro-4-((1-(3-(isopropylamino)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)oxy)benzonitrile; (2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)(morpholino)methanone; 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-N-(2-methoxyethyl)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)(tetrahydrofuran-2-yl)methanone; 3-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-3-oxopropanenitrile; (2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)(isoxazol-5-yl)methanone; 4-((1-(6-acetyl-2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile; 4-((1-(6-(cyclopropanecarbonyl)-2-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)-3-fluorobenzonitrile; 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-6-(isopropylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-6-(methyl-L-prolyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine; (2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-

(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)(pyrrolidin-1-yl)methanone; 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethan-1-one; 3-fluoro-4-((1-(2-(isopropylamino)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile; 3-fluoro-4-((1-(2-(isopropylamino)-6-(2-methoxyacetyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile; 3-fluoro-4-((1-(2-(isopropylamino)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)oxy)benzonitrile; 3-(4-(4-cyano-2-fluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-N,N-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; 1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethanone; 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethanone; 1-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; 1-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethanone; cyclopropyl(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone; cyclopropyl(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone; cyclopropyl(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone; 1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone; 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone; 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone; 1-(3-(4-(2-fluoro-4-

methoxyphenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 1-(2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-3-(isopropylamino)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone ; 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 1-(2-((2,2-difluoroethyl)amino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethanone; (*R*)-1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one; 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone; 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-*N*,*N*,5-trimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-*N*,*N*,5-trimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*,*N*,5-trimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; 1-(3-((2,2-difluoroethyl)amino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; *N*-(2,2-difluoroethyl)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; methyl 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxylate; 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6-(2-fluoroethyl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; (*R*)-1-(2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; 1-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; *N*-cyclopropyl-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; *N*-cyclopropyl-3-(4-(2-fluoro-4-

methoxyphenoxy)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; *N*-cyclopropyl-3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; (*S*)-*N*-cyclopropyl-3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; (*R*)-*N*-cyclopropyl-3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; 3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; 1-(3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 3-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-2-(isopropylamino)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-2-(isopropylamino)-N,N-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; 2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; 1-(2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; (5-chloro-2-fluorophenyl)(1-(2-(isopropylamino)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)piperidin-4-yl)methanone; 1-(3-(4-(5-chloro-2-fluorobenzoyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 3-(4-(5-chloro-2-fluorobenzoyl)piperidin-1-yl)-2-(isopropylamino)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; 1-(3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-N,N-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; (5-chloro-2-fluorophenyl)(1-(3-(isopropylamino)-6-methyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperidin-4-yl)methanone; 1-(2-(4-(5-chloro-2-fluorobenzoyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 2-(4-(5-chloro-2-fluorobenzoyl)piperidin-1-yl)-3-(isopropylamino)-*N*,*N*-

dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 1-(2-(tert-butylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 2-(*tert*-butylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-N,N-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 1-(2-((2,2-difluoroethyl)amino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 1-(2-(cyclobutylamino)-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 2-(cyclobutylamino)-3-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 1-(3-(cyclobutylamino)-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 3-(cyclobutylamino)-2-(4-(2-fluoro-4-methoxyphenoxy)piperidin-1-yl)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; 3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*,*N*-dimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone; (*S*)-1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one; 1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone; 1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2,2-difluoroethanone; (*S*)-1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one ; (*R*)-1-(3-(2,2-difluoroethylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one; 1-(2-(cyclopropylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 2-(cyclopropylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*,*N*,5-trimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxamide; *N*-cyclopropyl-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6-dimethyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*,*N*,7-trimethyl-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5H)-carboxamide; *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6,7-dimethyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-

7,8-dihydropyrido[4,3-b]pyrazin-6(5H)-yl)-2,2-difluoroethanone; 1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxyethanone; *N*-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; (2*S*)-1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one ; (2*R*)-1-(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methoxypropan-1-one; cyclopropyl(2-(2,2-difluoroethylamino)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7-methyl-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)methanone; 6-(2,2-difluoroethyl)-3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-amine; (*S*)-1-(2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; (*S*)-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carbaldehyde; (*R*)-2-(4-((2,4-difluorophenyl)fluoromethyl)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carbaldehyde; 1-(3-(4-(3-fluorophenylsulfonyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 1-(2-(isopropylamino)-3-(4-(3-methoxyphenylsulfonyl)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 1-(3-(4-((2-fluorophenyl)sulfonyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; 1-(3-(4-(4-fluorophenylsulfonyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; 3-(4-(2,4-difluorophenoxy)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carbaldehyde; 1-(3-(4-(2-fluoro-4-methoxyphenylsulfonyl)piperidin-1-yl)-2-(isopropylamino)-7,8-dihydropyrido[4,3-b]pyrazin-6(5H)-yl)ethanone; (*S*)-1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-((1-methoxypropan-2-yl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; (*R*)-1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-((1-methoxypropan-2-yl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; 1-(3-(cyclobutylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; (*S*)-1-(3-(*sec*-butylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; (*R*)-1-(3-(*sec*-butylamino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)propan-1-one; methyl 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-

(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazine-6(5*H*)-carboxylate; 2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6-(2-fluoroethyl)-*N*-isopropyl-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; 1-(3-(cyclobutylamino)-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; 2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-*N*-isopropyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)propan-1-one; *tert*-butyl 4-(6-acetyl-3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperazine-1-carboxylate; (1*s*,3*s*)-3-((6-acetyl-2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutyl acetate; 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(((1*s*,3*s*)-3-hydroxycyclobutyl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-*d*3-ethan-1-one; (1*s*,3*s*)-3-((6-acetyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutyl acetate; 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(isopropylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)-2-methylpropan-1-one; 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(((1*s*,3*s*)-3-hydroxycyclobutyl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; 1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(((1*r*,3*r*)-3-fluorocyclobutyl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; 4-((4-(6-acetyl-3-(isopropylamino)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-2-yl)piperazin-1-yl)methyl)-3-fluorobenzonitrile; (1*r*,3*r*)-3-((6-acetyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-yl)amino)cyclobutyl acetate; 1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(((1*r*,3*r*)-3-hydroxycyclobutyl)amino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; (*S*)-1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(tetrahydrofuran-3-ylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; (*S*)-1-(2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-3-(tetrahydrofuran-3-ylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)propan-1-one; 1-(3-((3,3-difluorocyclobutyl)amino)-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethan-1-one; *N*-cyclobutyl-2-(4-(2,4-difluorophenoxy)piperidin-1-yl)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazin-3-amine; (*R*)-1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(tetrahydrofuran-3-ylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; (*S*)-1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(tetrahydrofuran-3-ylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)ethanone; and

(*S*)-1-(2-(4-(2,4-difluorobenzyl)piperazin-1-yl)-3-(tetrahydrofuran-3-ylamino)-7,8-dihydropyrido[3,4-*b*]pyrazin-6(5*H*)-yl)propan-1-one; or a pharmaceutically acceptable salt of the above-mentioned compounds.

11. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt according to any one of claims 1 to 10 and a pharmaceutically acceptable excipient.

12. The use of a compound or a pharmaceutically acceptable salt according to any one of claims 1 to 10 as a medicament.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/071543

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/4985 A61P25/16
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/62765 A2 (ARENA PHARM INC [US]; BEELEY NIGEL R A [US]; BEHAN DOMINIC P [US]; CHA) 30 August 2001 (2001-08-30) the whole document	1-12
A	WO 2007/122466 A1 (PFIZER PROD INC [US]; HUGHES ROBERT O [US]; BELL ANDREW SIMON [GB]; BR) 1 November 2007 (2007-11-01) the whole document	1-12
A,P	WO 2014/028479 A1 (ENVOY THERAPEUTICS INC [US]; HITCHCOCK STEPHEN [US]; MONENSCHEIN HOLGE) 20 February 2014 (2014-02-20) the whole document	1-12

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 February 2015	26/02/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sotoca Usina, E

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/071543

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0162765 A2	30-08-2001	AU 6453501 A	03-09-2001
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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

STEMERICK, David
Takeda California, Inc.
10410 Science Center Drive
San Diego, California 92121
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing *(day/month/year)*
10 June 2016 (10.06.2016)

Applicant's or agent's file reference
GPR6-5002-WO

IMPORTANT NOTIFICATION

International application No.
PCT/US2014/071543

International filing date *(day/month/year)*
19 December 2014 (19.12.2014)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
MACKLIN, Todd
9700 Blaisell Ave S
Unit 1E
Bloomington, Minnesota 55420
United States of America

State of Nationality: CA
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
MACKLIN, Todd
4709 Marigold Ave N
Brooklyn Park, Minnesota 55443
United States of America

State of Nationality: CA
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address: tsd.docket@takeda.com
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

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Telephone No. +41 22 338 74 04

P2115 PP195
3698COOP
TCB

COLOMBIA

PODER

El (los)

TAKEDA PHARMACEUTICAL COMPANY LIMITED

Domiciliados en **1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, 541-0045, Japón**

Nombran por el presente a **XIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A.** abogadas con oficinas en la Calle 94A No. 7A-09, Bogotá-Colombia para
y para obtener la protección de mi (nuestra) propiedad Industrial e intelectual y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso –administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

a) Obtención de patentes de invención, modelos y dibujos industriales; registro de marcas de fabrica, de servicio, colectivas o defensivas y de denominaciones de origen, depósito de nombres y enseñas comerciales; su renovación, prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos;
b) Para la obtención de registros sanitarios;
c) Para la obtención de registros de derechos de autor.
d) Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso - administrativos que promovamos o se nos promuevan.

Pudiendo en todos los actos y gestiones arriba mencionados sustituir éste mandato entre los apoderados, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extra-judiciales. .

Finalmente, este poder ratifica la validez de todos los actos y solicitudes que, a nombre de la poderdante hubieren realizado los apoderados en relación con las facultades anteriormente enumeradas, antes de la suscripción del presente poder

Dado y firmado hoy 01/06/2011

en Kanagawa, Japón

por Takeda Pharmaceutical Company Limited.

(El notario debe suscribir el documento en la pagina siguiente)
(Se requiere legalización consular o mediante apostilla)

POWER OF ATTORNEY

I (we) the undersigned

TAKEDA PHARMACEUTICAL COMPANY LIMITED

Of **1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, 541-0045, Japan**

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A. and /or MARGARITA CASTELLANOS** a. attorneys residing at Calle 94A No. 7A-09, Bogotá- Colombia, to
and to obtain the protection of my (our) Intellectual Property, for which purpose we authorize the said attorneys to represent us before any authorities, or persons, specially those, administrative, contentious and judicial, in all matters concerning the following:

a) Obtainment of patents, models and designs, registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of trade names and ensigns; its renewal, extension, recordal of assignments, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights;
b) For the obtainment of Sanitary registrations;
c) For the obtainment of copyright registrations
d) Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rights; actions and suits instituted by us or against us;

In all the above matters they may substitute this power of attorney within the appointed attorneys, compromise, cancel, receive, withdraw, renounce, accept notifications and appoint attorneys in fact in or out of court.

Finally, this power of attorney ratifies the validity of all acts and applications made by the representatives in the name of the signatory of this power of attorney, with regard to the faculties above given, before the execution of the present power of attorney.

Given and signed this 01/06/2011

in Kanagawa, Japan

by Yoichi Okumura
General Manager, Intellectual Property Department.
Takeda Pharmaceutical Company Limited

(Notary shall execute on the other side)
(Consular legalization or apostille is required)

CASTELLANOS & Co.
INTELLECTUAL PROPERTY LAW FIRM

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平成２３年登簿第　79　号

認　　証

日本国政府大阪法務局の平成２３年４月１８日発行にかかる履歴事項全部証明書により明らかなところであるが、日本国法律により設立され本店が大阪府大阪市中央区道修町４丁目１番１号に所在する武田薬品工業株式会社の知的財産部長奥村洋一は別紙委任状に署名する権限を付与されており、別紙委任状の証書の署名が自己のものに相違ない旨代理人LEVESQUE SON HYUN REGINAを通じ本公証人に対し自認した。　以上

よって、これを認証する。

平成２３年　６月　１　日、本公証人役場において

藤沢市鵠沼石上2丁目11番2号
横浜地方法務局所属
公証人
Notary

曾我大三郎

DAISABURO SOGA

証　　明

上記署名は、横浜地方法務局所属公証人の署名に相違ないものであり、かつ、その押印は、真実のものであることを証明する。

平成２３年　６月　１　日

横浜地方法務局長　神尾　儀

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Country : JAPAN
   This public document
2. has been signed by DAISABURO SOGA
3. acting in the capacity of Notary of the Yokohama District Legal Affairs Bureau
4. bears the seal/stamp of DAISABURO SOGA , Notary

Certified

5. at Tokyo　　6. JUN. 1.2011
7. by the Ministry of Foreign Affairs
8. 11- No 301579
9. Seal/stamp :　　10.Signature :

MINISTRY OF FOREIGN AFFAIRS JAPAN 日本国 外務省

Kazutoyo OYABE
For the Minister for Foreign Affairs

Registered No. 7 9

NOTARIAL CERTIFICATE

This is to certify that LEVESQUE SON HYUN REGINA, an agent of Yoichi OKUMURA, General Manager, Intellectual Property Department of Takeda Pharmaceutical Company Limited , who has been authorized to grant Power of Attorney on behalf of said company organized and existing according to the law of Japan, located at 1-1 , Doshomachi 4-chome, Chuo-ku Osaka-shi Osaka Japan, has stated in my very presence that said Yoichi OKUMURA has acknowledged himself that the signature on the attached document is his own.

The foregoing was duly evidenced by the certified Register of said company issued by the Certificate of All Registered Items dated 18 April, 2011 from Osaka Legal Affairs Bureau for Corporate Number KU250214 and Title Certificate dated April 14, 2011.

Dated this 1st day of June, 2011.

Daisaburo Soga

YOKOHAMA DISTRICT
LEGAL AFFAIRS BUREAU
NOTARY
2-11-2, KUGENUMAISHIGAMI
FUJISAWA-SHI, KANAGAWA-KEN
JAPAN

Daisaburo Soga

Notary

attached to Yokohama District Legal Affairs Bureau

2-11-2, Kugenuma Ishigami Fujisawa-shi

Kanagawa-ken Japan

----------TRADUCCION OFICIAL No. 11-0607----------

De un documento escrito en INGLES, el cual para su identificación lleva el sello y firma de la Traductora e Intérprete Oficial, Res. 2755/68 y 01144/97 de Minjusticia.----------

(Anexos a un documento de Poder de TAKEDA PHARMACEUTICAL COMPANY LIMITED)

Registro No. 79

CERTIFICADO NOTARIAL

La presente es para certificar que LEVESQUE SON HYUN REGINA, agente de Yoichi OKUMURA, Gerente General, Departamento de Propiedad Intelectual de Takeda Pharmaceutical Company Limited, quien ha sido autorizado para otorgar Poder en nombre de dicha compañía, constituida y existente de acuerdo con la ley de Japón, domiciliada en 1-1, Doshomachi 4-chome, Chuo-ku Osaka-shi, Osaka Japòn ha manifestado en mi propia presencia que la firma en el documento adjunto es de éste.

Lo anterior fue debidamente evidenciado por el Certificado de Registro de dicha compañía expedido por el Certificado de Todos los Items Registrados de fecha abril 18 de 2011 de la Oficina de Asuntos Legales de Osaka para Sociedades No. KU250214 y el Certificado de Título de fecha Abril 14, 2011.

Dado hoy dìa primero de Junio de 2011.

(fdo) ilegible

Daisaburo Soga

Notario

Adjunto a la Oficina de Asuntos Legales del Distrito de Yokohama – 2-11-2, Kugenuma Ishigami Fujisawa-shi Kanagawa-ken, Japón

(Sello Notarial): OFICINA DE ASUNTOS LEGALES

DISTRITO DE YOKOHAMA

NOTARIO

2-11-2, Kugenumaishigami

Fujisawa-shi, Kanagawa-ken – Japón

APOSTILLA

(Convención de La Haya de Octubre 5, 1961)

1. País: JAPON

Este documento público

2. ha sido firmado por: DAISABURO SOGA
3. actuando en su carácter de: Notario Público de la Oficina de Asuntos Legales deL Distrito de Yokohama
4. lleva el sello de DAISURO SOGA - Notario

CERTIFICADO:

5. en Tokyo
6. el día 1° de Junio de 2011
7. por el Ministerio de Relaciones Exteriores
8. 11 No. 301579
9. Sello
10. Firma: (fdo) ilegible

MARIA DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
R.S. 02755/68 Y 01144/97 - MINJUSTICIA
RE. DE COLOMBIA

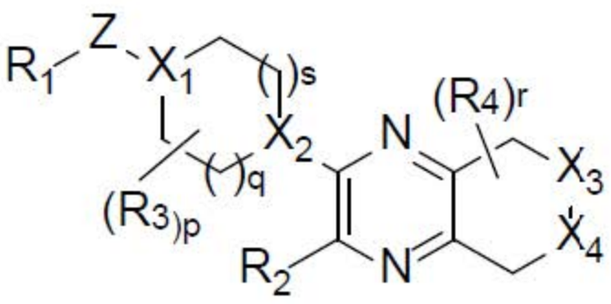
Kazutoyo OYABE

Por el Ministerio de Relaciones Exteriores (Sello)

ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, D. C., Junio 13, 2011

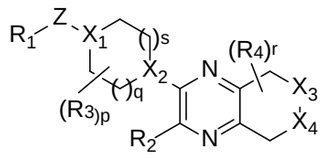
MARIA DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
R.S. 02755/68 Y 01144/97 - MINJUSTICIA
RE. DE COLOMBIA



(I)

RESUMEN

La presente invención proporciona compuestos de fórmula I:



I

que son útiles como moduladores de GPR6, sus composiciones farmacéuticas, los métodos para el tratamiento de afecciones asociadas con GPR6, los procesos para realizar los compuestos y sus intermediarios.

MODULADORES DE TETRAHIDROPIRIDOPIRAZINAS DE GPR6

CAMPO DE LA INVENCIÓN

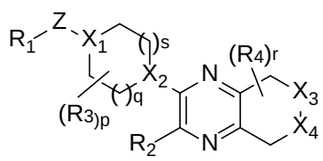
La presente invención se refiere a la química médica, la farmacología y la medicina.

ANTECEDENTES DE LA INVENCIÓN

La presente invención proporciona compuestos que son moduladores del receptor 6 acoplado a la proteína G (en adelante denominados GPR6). El GPR6 es GPCR que se señaliza mediante la senda de las G. Los receptores GPR6 se expresan altamente en el sistema nervioso central (SNC), particularmente neuronas espinales medias (MSN) del estriado, con expresión mínima en los tejidos periféricos. Las dianas estriadas principales de la inervación dopaminérgica residen en las neuronas espinales medias (MSN) de las sendas de salida estriadopalidal (indirectas) y estriadonigral (directas). Las MSN de la senda de salida directa expresan receptores de dopamina D1 mientras que aquellas en la senda indirecta expresan receptores D2. El GPR6 se enriquece en el receptor D2 que expresa las MSN en el estriado en tanto la actividad del GPR6 es funcionalmente opuesta a la señalización del receptor D2. El antagonismo o agonismo inverso del GPR6 acoplado a las G disminuye cAMP en las MSN y proporciona una alternativa funcional para la activación mediada por dopamina de los receptores D2. Por lo tanto, los compuestos de la presente invención son útiles para tratar una variedad de trastornos neurológicos y psiquiátricos, incluida la enfermedad de Parkinson.

SUMARIO DE LA INVENCIÓN

La presente invención proporciona un compuesto de fórmula I:



I

donde

R_1 se selecciona del grupo que consiste en cicloalquilo C_{3-8} opcionalmente sustituido, heterociclilo C_{3-6} opcionalmente sustituido, arilo C_{6-10} opcionalmente sustituido y heteroarilo C_{1-10} opcionalmente sustituido;

X_1 es N y X_2 es CH; o

X_1 es CH y X_2 es N; o

X_1 es N y X_2 es N;

cuando X_1 es N, Z se selecciona del grupo que consiste en alquileno C_{1-6}, haloalquileno C_{1-6},

-C(O)-, y -$S(O)_2$-;

cuando X_1 es CH, Z se selecciona del grupo que consiste en alquileno C_{1-6}, haloalquileno C_{1-6},

-O-, -C(O)-, -NH-, -S-, -S(O)- y -$S(O)_2$-;

q es 0, 1 o 2;

s es 0, 1 o 2;

R_2 es $-OR_5$ o $-NR_6R_7$;

R_3, cada vez que se toma, se selecciona de forma independiente del grupo que consiste en alquilo C_{1-6}, cicloalquilo C_{3-8} y trifluorometilo;

p es 0, 1 o 2;

R_4, cada vez que se toma, se selecciona de forma independiente del grupo que consiste en alquilo C_{1-6}, hidroxi y halo;

r es 0 o 1;

R_5 se selecciona del grupo que consiste en alquilo C_{1-6} y cicloalquilo C_{3-8};

R_6 se selecciona del grupo que consiste en hidrógeno y alquilo C_{1-6};

R_7 se selecciona del grupo que consiste en alquilo C_{1-6} opcionalmente sustituido, cicloalquilo C_{3-8}, arilo C_{6-10} opcionalmente sustituido, heteroarilo C_{1-10} opcionalmente sustituido y heterociclilo C_{3-6} opcionalmente sustituido;

X_3 se selecciona del grupo que consiste en CH y CR_4 y X_4 es NR_8; o

X_3 es NR_8 y X_4 se selecciona del grupo que consiste en CH y CR_4;

R_8 se selecciona del grupo que consiste en alquilo C_{1-6}, haloalquilo C_{1-6}, cicloalquilo C_{3-8},

-$S(O)_2$-R_9, -C(O)-R_{10}, -C(O)-$N(R_{11})(R_{12})$ y -C(O)-OR_{13};

R_9 se selecciona del grupo que consiste en alquilo C_{1-6}, cicloalquilo C_{3-8} y fenilo opcionalmente sustituido;

R_{10} se selecciona del grupo que consiste en hidrógeno, alquilo C_{1-6} opcionalmente sustituido, cicloalquilo C_{3-8}, arilo C_{6-10} opcionalmente sustituido, heteroarilo C_{1-10} opcionalmente sustituido y heterociclilo C_{3-6} opcionalmente sustituido;

R_{11} se selecciona del grupo que consiste en hidrógeno y alquilo C_{1-6};

R_{12} se selecciona del grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8}; o

R_{11} y R_{12} se toman entre sí con el nitrógeno al que se unen para formar un anillo saturado de 4 a 7 miembros que tiene opcionalmente 1 heteroátomo en el anillo adicional que se selecciona del grupo N, O y S y se sustituye opcionalmente sobre cualquiera de los átomos de carbono del anillo con 1 a 5 sustituyentes que se seleccionan de forma independiente del grupo que consiste en ciano, halo, hidroxi, amino, heterociclilo C_{3-6} opcionalmente sustituido, amida C_{1-9}, alquilo C_{1-6} opcionalmente sustituido y alcoxi C_{1-4} y se sustituye sobre cualquier nitrógeno en el anillo adicional por un sustituyente que se selecciona del grupo que consiste en hidrógeno, cicloalquilo C_{3-8} y alquilo C_{1-6} opcionalmente sustituido;

R_{13} se selecciona del grupo que consiste en alquilo C_{1-6} y cicloalquilo C_{3-8};

o su sal farmacéuticamente aceptable.

La presente invención también proporciona composiciones farmacéuticas, que comprenden: un compuesto de fórmula I o su sal farmacéuticamente aceptable y un excipiente farmacéuticamente aceptable.

Los compuestos de la presente invención son moduladores de GPR6 y son útiles para tratar una variedad de trastornos neurológicos y psiquiátricos, por ejemplo, trastornos de movimiento incluidos enfermedad de Parkinson, discinesias inducidas por levodopa y enfermedad de Huntington, adicción a las drogas, trastornos alimenticios, trastornos cognitivos, esquizofrenia, trastornos bipolares y depresión. De este modo, la presente invención también proporciona métodos para tratar afecciones asociadas con el GRP6 descritas en la presente que comprenden administrar a un paciente que lo necesita una cantidad eficaz de los compuestos de la invención. La presente invención proporciona el uso de compuestos de la invención como un medicamento, incluido el tratamiento de las afecciones asociadas con el GPR6 descritas en la presente, e incluida la fabricación de un medicamento para tratar las afecciones asociadas con el GPR6 descritas en la presente.

La presente invención también proporciona procesos para realizar moduladores del GPR6 y sus intermediarios.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

El término “alquilo C_{1-4}” se refiere a una cadena alquilo recta o ramificada de uno a cuatro átomos de carbono.

El término “alquilo C_{1-4} opcionalmente sustituido” se refiere a un alquilo C_{1-4} opcionalmente sustituido con 1 a 6 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alcoxi C_{1-4} opcionalmente sustituido, tioalcoxi C_{1-4}, amida C_{1-9}, amido C_{1-7}, amino, alquilamino C_{1-8}, oxicarbonilo C_{1-5}, carboniloxi C_{1-5}, sulfonilo C_{1-8}, ciano, cicloalquilo C_{3-8} opcionalmente sustituido, cicloalcoxi C_{3-8}, halo, hidroxi, nitro, oxo, heterociclilo C_{3-6} opcionalmente sustituido, heteroarilo C_{1-10} opcionalmente sustituido y arilo C_{6-10} opcionalmente sustituido.

Más particularmente “alquilo C_{1-4} opcionalmente sustituido” se refiere un alquilo C_{1-4} opcionalmente sustituido con 1 a 6 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alcoxi C_{1-4}, amida C_{1-9}, amino, alquilamino C_{1-8}, oxicarbonilo C_{1-5}, ciano, cicloalquilo C_{3-8}, halo, hidroxi, heterociclilo C_{3-6} opcionalmente sustituido sobre cualquier anillo nitrógeno por alquilo C_{1-4}, heteroarilo C_{1-10} y fenilo opcionalmente sustituido.

Aún más particularmente “alquilo C_{1-4} opcionalmente sustituido” se refiere a un alquilo C_{1-4} opcionalmente sustituido con 1 a 6 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alcoxi C_{1-4}, ciano, cicloalquilo C_{3-8}, halo, hidroxi, heterociclilo C_{3-6} opcionalmente sustituido sobre cualquier anillo de nitrógeno por alquilo C_{1-4} y fenilo opcionalmente sustituido.

El término “alquilo C_{1-6}” se refiere a una cadena alquilo recta o ramificada de uno a seis átomos de carbono.

El término “alquilo C_{1-6} opcionalmente sustituido” se refiere a un alquilo C_{1-6} opcionalmente sustituido con 1 a 7 sustituyentes que se seleccionan de forma independiente del grupo que consiste en amino, alquilamino C_{1-8}, alcoxi C_{1-4} opcionalmente sustituido, tioalcoxi C_{1-4}, amida C_{1-9}, amido C_{1-7}, oxicarbonilo C_{1-5} carboniloxi, C_{1-5}, sulfonilo C_{1-8}, ciano, cicloalquilo C_{3-8} opcionalmente sustituido, halo, hidroxi,

oxo, heteroarilo C_{1-10} opcionalmente sustituido, heterociclilo C_{3-6} opcionalmente sustituido y arilo C_{6-10} opcionalmente sustituido.

Más particularmente “alquilo C_{1-6} opcionalmente sustituido” se refiere un alquilo C_{1-6} opcionalmente sustituido con 1 a 7 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alcoxi C_{1-4}, amida C_{1-9}, amino, alquilamino C_{1-8}, oxicarbonilo C_{1-5}, ciano, cicloalquilo C_{3-8}, halo, hidroxi, heterociclilo C_{3-6} opcionalmente sustituido sobre cualquier anillo nitrógeno por alquilo C_{1-4}, heteroarilo C_{1-10} y fenilo opcionalmente sustituido.

Aún más particularmente “alquilo C_{1-6} opcionalmente sustituido” se refiere a un alquilo C_{1-6} opcionalmente sustituido con 1 a 7 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alcoxi C_{1-4}, ciano, cicloalquilo C_{3-8}, halo, hidroxi, heterociclilo C_{3-6} opcionalmente sustituido sobre cualquier anillo de nitrógeno por alquilo C_{1-4} y fenilo opcionalmente sustituido.

El término “haloalquilo C_{1-6}” se refiere a una cadena alquilo recta o ramificada de uno a seis átomos de carbono sustituidos con 1 a 3 átomos de halógeno. Más particularmente, el término “haloalquilo C_{1-6}” se refiere a fluorometilo y difluorometilo.

El término “sulfonilo C_{1-8}” se refiere a un sulfonilo unido a un grupo alquilo C_{1-6}, cicloalquilo C_{3-8} o un fenilo opcionalmente sustituido.

El término “alquileno C_{1-6}” se refiere a una cadena alquileno divalente recta o ramificada de uno a seis átomos de carbono.

El término “haloalquileno C_{1-6}” se refiere a una cadena alquileno divalente recta o ramificada de uno a seis átomos de carbono sustituidos con 1 a 3 átomos de halógeno. Más particularmente, el término “haloalquileno C_{1-6}” se refiere a fluorometileno y difluorometileno.

El término “alcoxi C_{1-4}” se refiere a un alquilo C_{1-4} unido mediante un átomo de oxígeno.

El término “alcoxi C_{1-4} opcionalmente sustituido” se refiere a un alcoxi a C_{1-4} opcionalmente sustituido con 1 a 6 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alcoxi C_{1-4}, amida C_{1-9}, oxicarbonilo C_{1-}

$_{5}$, ciano, cicloalquilo C_{3-8} opcionalmente sustituido, halo, hidroxi, heteroarilo C_{1-10} opcionalmente sustituido y arilo C_{6-10} opcionalmente sustituido. Aunque se entiende que cuando el sustituyente opcional es alcoxi o hidroxi C_{1-4} entonces el sustituyente no es generalmente alfa al punto de unión alcoxi, el término “alcoxi C_{1-4} opcionalmente sustituido” incluye restos estables e incluye específicamente trifluorometoxi, difluorometoxi y fluorometoxi.

Más particularmente, “alcoxi C_{1-4} opcionalmente sustituido” se refiere a un alcoxi C_{1-4} opcionalmente sustituido con 1 a 6 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alcoxi C_{1-4}, ciano, cicloalquilo C_{3-8}, halo, hidroxi y fenilo opcionalmente sustituido. Aún más particularmente, “alcoxi C_{1-4} opcionalmente sustituido” se refiere a trifluorometoxi, difluorometoxi y fluorometoxi.

El término “amida C_{1-9}” se refiere a un grupo $-C(O)NR_aR_b$ donde R_a se selecciona del grupo que consiste en hidrógeno y alquilo C_{1-4} y R_b se selecciona del grupo que consiste en hidrógeno, alquilo C_{1-3} y fenilo opcionalmente sustituido.

El término “amido C_{1-7}” se refiere a un grupo $-NHC(O)R_c$ donde R_c se selecciona del grupo que consiste en hidrógeno, alquilo C_{1-6} y fenilo opcionalmente sustituido.

El término “carbamoílo C_{1-5}” se refiere a un carbamato unido a O o N sustituido con un alquilo C_{1-4} terminal.

El término “ureído C_{1-5}” se refiere a una urea opcionalmente sustituida con un alquilo C_{1-4}.

El término “alquilamino C_{1-8}” se refiere a un grupo $-NR_dR_e$ donde R_d es un alquilo C_{1-4} y R_e se selecciona del grupo que consiste en hidrógeno y alquilo C_{1-4}.

El término “arilo C_{6-10}” se refiere a un hidrocarburo conjugado insaturado monocíclico y policíclico que tiene de cinco a diez átomos de carbono, e incluye fenilo y naftilo.

Más particularmente, “arilo C_{6-10}” se refiere a fenilo.

El término “arilo C_{6-10} opcionalmente sustituido” se refiere a un arilo C_{6-10} opcionalmente sustituido con 1 a 5 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alquilo C_{l-4} opcionalmente sustituido, alcoxi C_{1-4} opcionalmente sustituido, tioalcoxi C_{1-4}, amino, alquilamino C_{1-8}, amida C_{1-9}, amido C_{1-7}, oxicarbonilo C_{1-5}, carboniloxi C_{1-5}, sulfonilo C_{1-8}, carbamoílo C_{1-5},

sulfonilamido C_{1-6}, aminosulfonilo, aminosulfonilo C_{1-10}, ureído C_{1-5}, ciano, halo y hidroxilo.

Más particularmente, "arilo C_{6-10} opcionalmente sustituido" se refiere a un arilo C_{6-10} opcionalmente sustituido con 1 a 5 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alquilo C_{l-4}, alcoxi C_{1-4}, ciano, halo, hidroxi, amino, trifluorometilo y trifluorometoxi.

Aún más particularmente, "arilo C_{6-10} opcionalmente sustituido" se refiere a fenilo opcionalmente sustituido con 1 a 5 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alquilo C_{l-4}, alcoxi C_{1-4}, ciano, halo, trifluorometilo y trifluorometoxi.

El término "oxicarbonilo C_{1-5}" se refiere a un grupo oxicarbonilo (-CO_2H) y su éster de alquilo C_{1-4}.

El término "carboniloxi C_{1-5}" se refiere a un grupo carboniloxi (-O_2CR_f), donde R_f se selecciona del grupo que consiste en hidrógeno y alquilo C_{1-4}, por ejemplo, acetoxi.

El término "cicloalquilo C_{3-8}" se refiere a un anillo alquilo saturado o parcialmente (pero no completamente) insaturado monocíclico o bicíclico de tres a ocho átomos de carbono e incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y similares. Se entiende que el término incluye ciclopentilo y ciclohexilo benzofusionado.

El término "cicloalquilo C_{3-8} opcionalmente sustituido" se refiere a un cicloalquilo C_{3-8} opcionalmente sustituido con 1 a 6 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alquilo C_{1-4} opcionalmente sustituido, alcoxi C_{1-4} opcionalmente sustituido, amida C_{1-9}, amido C_{1-7}, amino, alquilamino C_{1-8}, oxicarbonilo C_{1-5}, ciano, cicloalquilo C_{3-8}, cicloalcoxi C_{3-8}, halo, hidroxi, nitro, oxo, heteroarilo C_{1-10} opcionalmente sustituido y fenilo opcionalmente sustituido.

Más particularmente, "cicloalquilo C_{3-8} opcionalmente sustituido" se refiere a un cicloalquilo C_{3-8} opcionalmente sustituido con 1 a 3 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alcoxi C_{1-4}, halo, hidroxi y alquilo C_{1-4} opcionalmente sustituido con alcoxi C_{1-4}, halo y hidroxi.

El término "cicloalcoxi C_{3-8}" se refiere a un cicloalquilo C_{3-8} unido mediante oxígeno.

Los términos "halógeno" y "halo" se refieren a un átomo de cloro, fluoro, bromo o yodo.

El término “heterociclilo C_{3-6}” se refiere a un anillo saturado o parcialmente (pero no completamente) insaturado monocíclico o bicíclico de 4 a 8 miembros que tiene uno o dos heteroátomos que se seleccionan del grupo que consiste en nitrógeno, oxígeno y azufre y el anillo incluye opcionalmente un carbonilo para formar una lactama o lactona. Se entiende que cuando se incluye azufre, dicho azufre puede ser tanto -S-, -SO- como $-SO_2-$. Dicho término también incluye sistemas bicíclicos espirofusionados. Por ejemplo, a modo no taxativo, el término incluye azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, oxetanilo, dioxolanilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrofurilo, hexahidropirimidinilo, tetrahidropirimidinilo, dihidroimidazolilo y similares. Se entiende que se puede unir un heterociclilo C_{3-6} como un sustituyente mediante un átomo de anillo de carbono o anillo de nitrógeno.

Más particularmente, “heterociclilo C_{3-6}” se selecciona del grupo que consiste en azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, oxetanilo, tetrahidropiranilo, tetrahidrotiopiranilo y tetrahidrofurilo.

El término “heterociclilo C_{3-6} opcionalmente sustituido” se refiere a un heterociclilo C_{3-6} opcionalmente sustituido sobre los anillos de carbono con 1 a 4 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alquilo C_{1-4} opcionalmente sustituido, alcoxi C_{1-4} opcionalmente sustituido, amida C_{1-9}, amido C_{1-7}, amino, alquil C_{1-8}amino, oxicarbonilo C_{1-5}, ciano, cicloalquilo C_{3-8} opcionalmente sustituido, cicloalcoxi C_{3-8}, halo, hidroxi, nitro, oxo y fenilo opcionalmente sustituido; y opcionalmente sustituido sobre cualquier anillo de nitrógeno con un sustituyente que se selecciona de forma independiente del grupo que consiste en alquilo C_{1-4} opcionalmente sustituido, cicloalquilo C_{3-8}, heterociclilo C_{3-6} opcionalmente sustituido, heteroarilo C_{1-10} opcionalmente sustituido y fenilo opcionalmente sustituido.

Más particularmente, “heterociclilo C_{3-6} opcionalmente sustituido” se refiere a un heterociclilo C_{3-6} opcionalmente

sustituido sobre los anillos de carbono con 1 a 4 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alquilo C_{1-4}, alcoxi C_{1-4}, halo e hidroxi y opcionalmente sustituido sobre cualquier anillo de nitrógeno con un alquilo C_{1-4}.

El término “heteroarilo C_{1-10}” se refiere a un anillo o sistema de anillos monocíclico o policíclico completamente insaturado de cinco a trece miembros con uno a diez átomos de carbono y uno o más, típicamente uno a cuatro heteroátomos que se seleccionan del grupo que consiste en nitrógeno, oxígeno y azufre. Por ejemplo, a modo no taxativo, el término incluye furilo, tienilo, pirrolilo, imidazolilo, isotiazolilo, isoxazolilo, oxadiazolilo, oxazolilo, tiazolilo, tiadiazolilo, triazolilo, tetrazolilo, pirazinilo, pirazolilo, piridazinilo, piridilo, pirimidilo, azepinilo, diazepinilo, benzazepinilo, benzodiazepinilo, benzofurilo, benzotienilo, indolilo, isoindolilo, benzimidazolilo, benzisotiazolilo, bencisoxazolilo, benzoxadiazolilo, benzoxazolilo, benzopirazinilo, benzopirazolilo, imidazopiridilo, pirazolopiridilo, pirrolopiridilo, quinazolilo, tienopiridilo, imidazopiridilo, quinolilo, isoquinolilo benzotiazolilo y similares. Se entiende que puede unirse un heteroarilo C_{1-10} como un sustituyente mediante un átomo de anillo de carbono o anillo de nitrógeno donde se encuentra disponible dicho modo de unión, por ejemplo para un pirrolilo, indolilo, imidazolilo, pirazolilo, azepinilo, triazolilo, pirazinilo, etc.

Más particularmente, “heteroarilo C_{1-10}” se selecciona del grupo que consiste en furilo, tienilo, pirrolilo, imidazolilo, oxazolilo, tiazolilo, pirazolilo, triazolilo, piridilo y pirimidilo.

El término “heteroarilo C_{1-10} opcionalmente sustituido” se refiere a un heteroarilo C_{1-10} opcionalmente sustituido con 1 a 5 sustituyentes sobre carbono que se seleccionan de forma independiente del grupo que consiste en amino, alquilamino C_{1-8}, amida C_{1-9}, amido C_{1-7}, carbamoílo C_{1-5}, sulfonil C_{1-6}amido, aminosulfonilo, amino C_{1-10}sulfonilo, ureído C_{1-5}, alquilo C_{l-4} opcionalmente sustituido, alcoxi C_{1-4} opcionalmente sustituido, ciano, halo, hidroxilo, oxo, nitro, carboniloxi C_{1-5}, oxicarbonilo C_{1-5} y sulfonilo C_{1-8} y

opcionalmente sustituido con un sustituyente sobre cada nitrógeno que se selecciona de forma independiente del grupo que consiste en alquilo C_{l-4} opcionalmente sustituido, sulfonilo C_{1-8}, heterociclilo C_{3-6} opcionalmente sustituido y fenilo opcionalmente sustituido.

Más particularmente, “heteroarilo C_{1-10} opcionalmente sustituido” se refiere a un heteroarilo C_{1-10} opcionalmente sustituido con 1 a 3 sustituyentes sobre carbono que se seleccionan de forma independiente del grupo que consiste en amino, alquilamino C_{1-8}, amida C_{1-9}, alquilo C_{l-4}, alcoxi C_{1-4}, ciano, halo, hidroxilo, oxo, trifluorometilo y trifluorometoxi y está opcionalmente sustituido sobre un anillo de nitrógeno con un alquilo C_{l-4}.

Aún más particularmente, “heteroarilo C_{1-10} opcionalmente sustituido” se refiere a un heteroarilo C_{1-10} que se selecciona del grupo que consiste en furilo, tienilo, pirrolilo, imidazolilo, oxazolilo, tiazolilo, pirazolilo, diazolilo, piridilo, pirimidilo y triazolilo cada uno opcionalmente sustituido con 1 a 3 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alquilo C_{l-4}, alcoxi C_{1-4}, ciano, halo, trifluorometilo y trifluorometoxi y está opcionalmente sustituido sobre un anillo de nitrógeno con un metilo.

El término "oxo" se refiere a un átomo de oxígeno unido doblemente al carbono al cual está unido para formar el carbonilo de una cetona o aldehído. Por ejemplo, un radical de pridona está contemplado como un heteroarilo C_{1-10} sustituido con oxo.

El término “fenilo opcionalmente sustituido” se refiere a un grupo fenilo opcionalmente sustituido con 1 a 5 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alquilo C_{l-4}, alcoxi C_{1-4}, amida C_{1-9}, amino, alquilamino C_{1-8}, oxicarbonilo C_{1-5}, ciano, halo, hidroxilo, nitro, sulfonilo C_{1-8} y trifluorometilo.

Más particularmente, “fenilo opcionalmente sustituido” se refiere a un grupo fenilo opcionalmente sustituido con 1 a 5 sustituyentes que se seleccionan de forma independiente del grupo que consiste en alquilo C_{l-4}, alcoxi C_{1-4}, amida C_{1-9}, amino, alquilamino C_{1-8}, oxicarbonilo C_{1-5}, ciano, halo, hidroxilo, nitro y trifluorometilo.

El término “sulfonil C_{1-6} amido” se refiere a un grupo -$NHS(O)_2$-R_g donde R_g se selecciona del grupo que consiste en alquilo C_{1-6} y fenilo opcionalmente sustituido.

El término “aminosulfonilo” se refiere a un -$S(O)_2NH_2$.

El término “aminosulfonilo C_{1-10}” se refiere a un grupo -$S(O)_2NR_hR_i$ donde R_h se selecciona del grupo que consiste en hidrógeno y alquilo C_{1-4} y R_i se selecciona del grupo que consiste en alquilo C_{1-4} y fenilo opcionalmente sustituido.

El término “tioalcoxi C_{1-4}” se refiere a un alquilo C_{1-4} unido mediante un átomo de azufre.

El término "sal farmacéuticamente aceptable" se refiere a sales de ácidos orgánicos y bases o ácidos inorgánicos y bases farmacéuticamente aceptables. Dichas sales se conocen bien en la técnica e incluyen las descritas en *Journal of Pharmaceutical Science*, 66, 2-19 (1977). Un ejemplo es la sal de clorhidrato.

El término "sustituido", incluido cuando se utiliza en "opcionalmente sustituido" se refiere a uno o más radicales de hidrógeno de un grupo se reemplazan con radicales no de hidrógeno (sustituyente(s)). Se entiende que los sustituyentes pueden ser los mismos o diferentes en cada posición de sustitución. Las combinaciones de grupos y sustituyentes previstos por esta invención son aquellas que son estables o posibles químicamente.

El término "estable" se refiere a compuestos que no se alteran sustancialmente cuando son sometidos a condiciones para permitir su producción. En un ejemplo no taxativo, un compuesto estable o compuesto posible químicamente es uno que está alterado sustancialmente cuando se mantiene a una temperatura de 40 °C o menos, en ausencia de humedad u otra condición químicamente reactiva, durante aproximadamente una semana.

Se entiende que, cuando los términos definidos en la presente mencionan un número de átomos de carbono, el número mencionado se refiere al grupo mencionado y no incluye ningún carbono que pueda estar presente sobre cualquier sustituyente(s).

El entendido en la técnica apreciará que determinados compuestos de la presente invención existen como isómeros. Se contempla que todos los estereoisómeros de los compuestos de la invención, incluidos isómeros, enantiómeros y

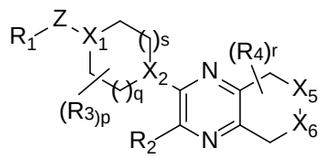
diastereómeros geométricos, en cualquier proporción, se encuentran dentro del alcance de la presente invención.

El entendido en la técnica apreciará que determinados compuestos de la presente invención existen como tautómeros. Se contempla que todas las formas tautoméricas de los compuestos de la invención se encuentran dentro del alcance de la presente invención.

Los compuestos de la invención también incluyen todas las variaciones isotópicas farmacéuticamente aceptables, en las que se reemplaza al menos un átomo por un átomo que tiene el mismo número atómico, pero que tiene una masa atómica diferente de la masa atómica predominante. Los isótopos adecuados para incluir en los compuestos de fórmula I incluyen isótopos radioactivos.

Los términos "compuestos de la invención" y "un compuesto de la invención" y "compuestos de la presente invención" y similares incluyen la realización de la fórmula I y las otras realizaciones más particulares abarcadas por la fórmula I descritas en la presente y ejemplos de compuestos descritos en la presente y una sal farmacéuticamente aceptable de cada una de estas realizaciones.

La presente invención proporciona un compuesto de fórmula II:



II

donde

R_1 se selecciona del grupo que consiste en cicloalquilo C_{3-8} opcionalmente sustituido, heterociclilo C_{3-6} opcionalmente sustituido, arilo C_{6-10} opcionalmente sustituido y heteroarilo C_{1-10} opcionalmente sustituido;

X_1 es N y X_2 es CH; o

X_1 es CH y X_2 es N; o

X_1 es N y X_2 es N;

cuando X_1 es N, Z se selecciona del grupo que consiste en alquileno C_{1-6}, haloalquileno C_{1-6},

-C(O)-, y $-S(O)_2-$;

cuando X_1 es CH, Z se selecciona del grupo que consiste en alquileno C_{1-6}, haloalquileno C_{1-6}, -O-, -C(O)-, -NH-, -S-, -S(O)- y -$S(O)_2$-;

q es 0, 1 o 2;

s es 0, 1 o 2;

R_2 es $-OR_5$ o $-NR_6R_7$;

R_3, cada vez que se toma, se selecciona de forma independiente del grupo que consiste en alquilo C_{1-6}, cicloalquilo C_{3-8} y trifluorometilo;

p es 0, 1 o 2;

R_4, cada vez que se toma, se selecciona de forma independiente del grupo que consiste en alquilo C_{1-6}, hidroxi y halo;

r es 0 o 1;

R_5 se selecciona del grupo que consiste en alquilo C_{1-6} y cicloalquilo C_{3-8};

R_6 se selecciona del grupo que consiste en hidrógeno y alquilo C_{1-6};

R_7 se selecciona del grupo que consiste en alquilo C_{1-6} opcionalmente sustituido, cicloalquilo C_{3-8}, arilo C_{6-10} opcionalmente sustituido, heteroarilo C_{1-10} opcionalmente sustituido y heterociclilo C_{3-6} opcionalmente sustituido

X_5 se selecciona del grupo que consiste en CH y CR_4 y X_6 se selecciona del grupo que consiste en NH y N-CH_2-(fenilo opcionalmente sustituido) o

X_5 se selecciona del grupo que consiste en NH y N-CH_2-(fenilo opcionalmente sustituido) y X_6 se selecciona del grupo que consiste en CH y CR_4;

o su sal farmacéuticamente aceptable.

(Ia) Una realización se refiere a compuestos de fórmula I donde X_1 es CH y X_2 es N.

(Ib) Una realización se refiere a compuestos de fórmula I donde X_1 es N y X_2 es N.

(Ic) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia) y (Ib) donde X_3 se selecciona del grupo que consiste en CH y CR_4 y X_4 es NR_8.

(Id) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia) y (Ib) donde X_3 es NR_8 y X_4 se selecciona del grupo que consiste en CH y CR_4.

(Ie) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia), (Ib), (Ic) y (Id) donde R_1 es arilo C_{6-10} opcionalmente sustituido.

(If) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia), (Ib), (Ic) y (Id) donde Z es alquileno C_{1-6}.

(Ig) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia), (Ib), (Ic) y (Id) donde Z es haloalquileno C_{1-6}.

(Ih) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia), (Ib), (Ic) y (Id) donde Z es -O-.

(Ii) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia), (Ib), (Ic) y (Id) donde Z es -C(O)-.

(Ij) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih) y (Ii) donde R_2 es $-NR_6R_7$. En otra realización dentro de la realización (Ij), R_6 es hidrógeno y R_7 es alquilo C_{1-6}. En aún otra realización dentro de la realización (Ij), R_6 es hidrógeno y R_7 es cicloalquilo C_{3-8}. En aún otra realización dentro de la realización (Ij), R_6 es hidrógeno y R_7 es heterociclilo C_{3-6}.

(Ik) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii) y (Ij) donde s es 1.

(Il) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij) y (Ik) donde q es 1.

(Im) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik) y (Il) donde R_8 se selecciona del grupo que consiste en $-C(O)-R_{10}$, $-C(O)-N(R_{11})(R_{12})$ y $-C(O)-OR_{13}$.

(In) Una realización se refiere a compuestos de fórmula I y realizaciones (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Ik) y (Il) donde R_8 es $-C(O)-R_{10}$ y R_{10} es alquilo C_{1-6}.

(IIa) Una realización se refiere a compuestos de fórmula II donde X_1 es CH y X_2 es N.

(IIb) Una realización se refiere a compuestos de fórmula II donde X_1 es N y X_2 es N.

(IIc) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa) y (IIb) donde X_3 es NR_8 y X_4 se selecciona del grupo que consiste en CH y CR_4.

(IId) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIb) y (IIc) donde R_1 es arilo C_{6-10} opcionalmente sustituido.

(IIe) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIb), (IIc) y (IId) donde Z es alquileno C_{1-6}.

(IIf) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIb), (IIc) y (IId) donde Z es haloalquileno C_{1-6}.

(IIg) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIc) y (IId) donde Z es -O-.

(IIh) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIb), (IIc) y (IId) donde Z es -C(O)-.

(IIi) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg) y (IIh) donde R_2 es $-NR_6R_7$. En otra realización dentro de la realización (IIj), R_6 es hidrógeno y R_7 es alquilo C_{1-6}. En aún otra realización dentro de la realización (IIj), R_6 es hidrógeno y R_7 es cicloalquilo C_{3-8}. En aún otra realización dentro de la realización (IIj), R_6 es hidrógeno y R_7 es heterociclilo C_{3-6}.

(IIj) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh) y (IIi) donde s es 1.

(IIk) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIi) y (IIj) donde q es 1.

(IIl) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIb), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj) y (IIk) donde X_5 se selecciona del grupo que consiste de CH y CR_4 y X_6 es NH.

(IIm) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIb), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj) y (IIk) donde X_5 se selecciona del grupo que consiste en NH X_6 se selecciona del grupo que consiste en CH y CR_4.

(IIn) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIb), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj) y (IIk) donde X_5 se selecciona del grupo que consiste en CH y CR_4 y X_6 es N-CH_2-(fenilo opcionalmente sustituido).

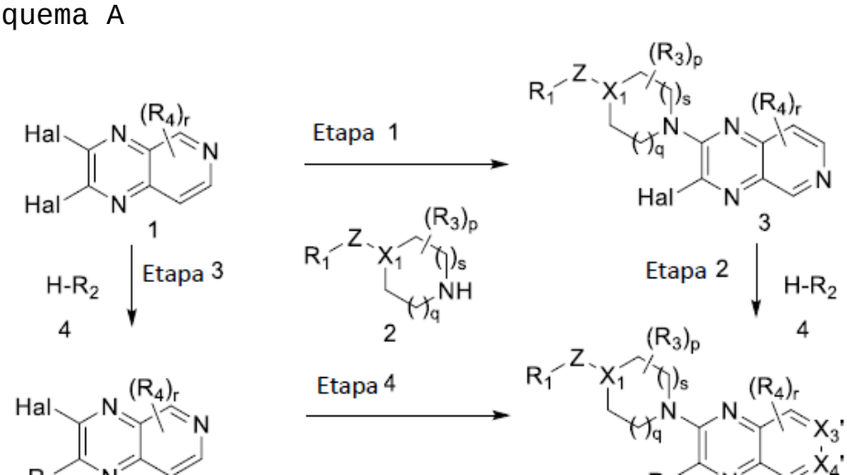
(IIo) Una realización se refiere a compuestos de fórmula II y realizaciones (IIa), (IIb), (IIe), (IIf), (IIg), (IIh), (IIi), (IIj), (IIk) y (IIl) donde X_5 se selecciona del grupo que consiste en CH y CR_4 y X_6 es N-CH_2-(fenilo opcionalmente sustituido).

(ay) Otra realización se refiere a una sal farmacéuticamente aceptable de cada una de las realizaciones anteriores.

(az) Otra realización se refiere a una sal farmacéuticamente aceptable de cada uno de los compuestos ejemplificados.

Los compuestos de la invención pueden prepararse por una variedad de procedimientos, algunos de los cuales se describen a continuación. Todos los sustituyentes, a menos que se indique lo contrario, son como se definen anteriormente. Los productos de cada etapa pueden recuperarse mediante métodos convencionales incluido extracción, evaporación, precipitación, cromatografía, filtración, trituración, cristalización y similares. Los procedimientos pueden requerir la protección de ciertos grupos, por ejemplo, grupos hidroxi, amino o carboxi para minimizar reacciones indeseadas. La selección, el uso y la eliminación de los grupos protectores se conocen bien en la técnica y se aprecian como práctica estándar, por ejemplo, *T.W. Greene and P. G. M. Wuts in Protective Groups in Organic Chemistry* (*John Wiley and Sons*, 1991). En los esquemas a continuación, los materiales de partida se encuentran comercialmente disponibles o pueden estar presentes preparados por métodos bien conocidos en la técnica.

Esquema A



El esquema A representa la formación de compuestos donde X_2 es N.

En el esquema A, etapa 1, un compuesto adecuado de la fórmula 1 se pone en contacto con un compuesto adecuado de la fórmula 2 para dar un compuesto de fórmula 3. Un compuesto adecuado de la fórmula 1 es uno donde Hal es un halógeno y R_4 y r son como se desea en el compuesto final de la fórmula I. Un compuesto adecuado de la fórmula 2 es uno donde R_1, Z, R_3, p, s y q son como se desea en el compuesto final de la fórmula I o dan lugar a R_1, Z y R_3 son como se desea en el compuesto final de la fórmula I. Los compuestos de la fórmula 2 se encuentran comercialmente disponibles o pueden prepararse fácilmente por métodos bien conocidos en la técnica. Por ejemplo, los compuestos de la fórmula 2 donde Z es oxígeno pueden prepararse mediante reacción de Mitsunobu entre un piperidinol y un alcohol de arilo.

La reacción se lleva a cabo en un solvente orgánico adecuado como dioxano, n-butanol, sulfóxido de dimetilo y similares con o sin base tal como diisopropiletilamina y trietilamina. La reacción se lleva a cabo generalmente a una temperatura de 0 a 80 °C.

Se entiende que un compuesto de fórmula 1 también puede tratarse con piperazina para dar lugar a compuestos donde X_1 es N. El derivado de piperazina puede modificarse adicionalmente mediante aminación, alquilación, arilación, amidación, sulfonilación reductiva y similares para proporcionar un compuesto de fórmula 3. Asimismo, la piperazina puede protegerse y elaborarse según se menciona tras la desprotección en una etapa posterior en caso deseado.

En el esquema A, etapa 2, un compuesto de fórmula 3 entra en contacto con un compuesto adecuado de la fórmula 4 para dar un compuesto de fórmula 6 donde X_3' y X_4' da lugar a X_3 y X_4 tal como se desea en el producto final de la fórmula I. Un compuesto adecuado de la fórmula 4 es HOR_5 o HNR_6R_7 donde R_5 o R_6 y R_7 son como se desea en el compuesto final de la fórmula I.

Cuando el compuesto de fórmula 4 es una amina, HNR_6R_7, la reacción se lleva a cabo en un solvente orgánico adecuado como dioxano, etanol, tetrahidrofurano, dimetil sulfóxido, N,N-dimetilformamida y similares, con o sin una base tal como hidróxido de sodio, diisopropiletilamina o trietilamina. La reacción se lleva a cabo generalmente a una temperatura de 20 a 150 °C.

Cuando el compuesto de fórmula 4 es un alcohol, HOR_5, la reacción se lleva a cabo en un solvente orgánico adecuado como dioxano, tetrahidrofurano, dimetil sulfóxido, N,N-dimetilformamida y similares, con una base tales como hidruro de sodio, hidruro de litio, t-butóxido de potasio y similares. La reacción se lleva a cabo generalmente a una temperatura de 0 a 150 °C.

De forma alternativa, tal como se describe en el esquema A, etapa 3, mediante la metodología descrita anteriormente, un compuesto adecuado de fórmula 1 puede ponerse en contacto con un compuesto adecuado de la fórmula 2 para dar un compuesto de fórmula 5. Tal como se describe en el esquema A, etapa 4, puede ponerse en contacto un compuesto de fórmula 5 con un compuesto de fórmula 2 para dar un compuesto de fórmula 6.

En el esquema A, etapa 5, se reduce parcialmente un compuesto de fórmula 6 hasta un compuesto de fórmula 7 donde las variables se definen anteriormente y X_5' se selecciona del grupo que consiste en CH, CR_4 y NH y X_6' se selecciona del grupo que consiste en CH, CR_4 y NH siempre y cuando uno de X_5' o X_6' es NH y el otro es CH o CR_4.

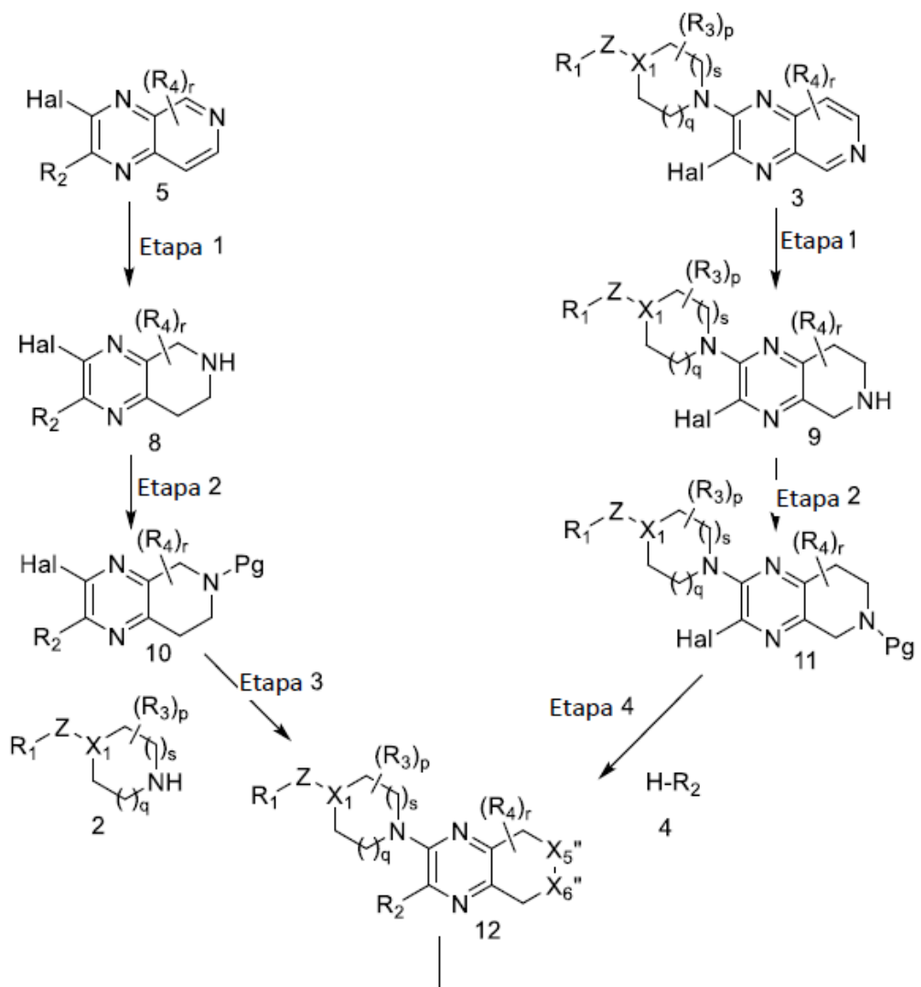
Dichas reducciones parciales se conocen bien en la técnica. La reacción se lleva a cabo en un solvente orgánico adecuado como dioxano, etanol, metanol, isopropanol, tetrahidrofurano y similares. La reacción se lleva a cabo generalmente mediante el uso de hidrógeno y un catalizador, tal como catalizador de platino o paladio.

En el esquema A, etapa 6, un compuesto de fórmula 7 es alquilado, cicloalquilado, sulfonado, acilado o se convierte a una urea o carbamato mediante el uso de reactivos que proporcionan R_8 que son alquilo C_{1-6}, haloalquilo C_{1-6}, cicloalquilo C_{3-8}, $-S(O)_2-R_9$, $-C(O)-R_{10}$, $-C(O)-N(R_{11})(R_{12})$ o $-C(O)-OR_{13}$ según se desea en el compuesto final de la fórmula I. Dicha transformación se lleva a cabo fácilmente mediante aminación, alquilación, sulfonilación reductiva, reacciones que forman amidas, reacciones que forman urea y condiciones de carbamilación que son bien conocidas en la técnica.

El entendido en la técnica reconocerá que las etapas en el esquema A pueden variarse para proporcionar compuestos de fórmula I. En particular, el orden de etapas requeridas para producir los compuestos de fórmula I depende del compuesto particular que se sintetiza, el compuesto de partida y la labilidad relativa de los restos sustituidos. Son posibles otras variaciones y los entendidos en la técnica las entienden con facilidad.

En el esquema B a continuación se describe un ejemplo de una variante del esquema A.

Esquema B



El esquema B representa la formación de compuestos donde X_2 es N.

En el esquema B, etapa 1, un compuesto adecuado de la fórmula 5 o 3, tal como se proporciona anteriormente, se reduce parcialmente hasta un compuesto de fórmula 8 o 9, respectivamente. Dichas reducciones parciales se describen anteriormente en el esquema A, etapa 5. En una realización, la presente invención proporciona compuestos de fórmula 8 donde Hal es halógeno y R_2, R_4 y r son como se describe para la fórmula I. En otra realización, la presente invención proporciona compuestos de fórmula 9 donde Hal es halógeno y R_1, Z, R_3, R_4, p, r, q y s son tal como se describe para la fórmula I.

En el esquema B, etapa 2, un compuesto adecuado de la fórmula 8 o 9 se protege para proporcionar compuestos de fórmulas 10 o 11, respectivamente, donde Pg es un grupo protector amina. La selección, el uso y la eliminación de los grupos protectores se conocen bien en la técnica y se aprecian como práctica estándar, por ejemplo, T.W. Greene y P. G. M. Wuts en *Protective Groups in Organic Chemistry* (*John Wiley and Sons*, 1991). En una realización, la presente invención proporciona compuestos de fórmula 10 donde Pg es -CH_2-(fenilo opcionalmente sustituido) y R_2, R_4 y r son tal como se describe para la fórmula I. En otra realización, la presente invención proporciona los compuestos de la fórmula

11 donde Pg es -CH_2-(fenilo opcionalmente sustituido) y R_1, Z, R_3, R_4, p, r, q y s son tal como se describe para la fórmula I. En otra realización de las realizaciones de las fórmulas 10 y 11 es una donde Pg es bencilo.

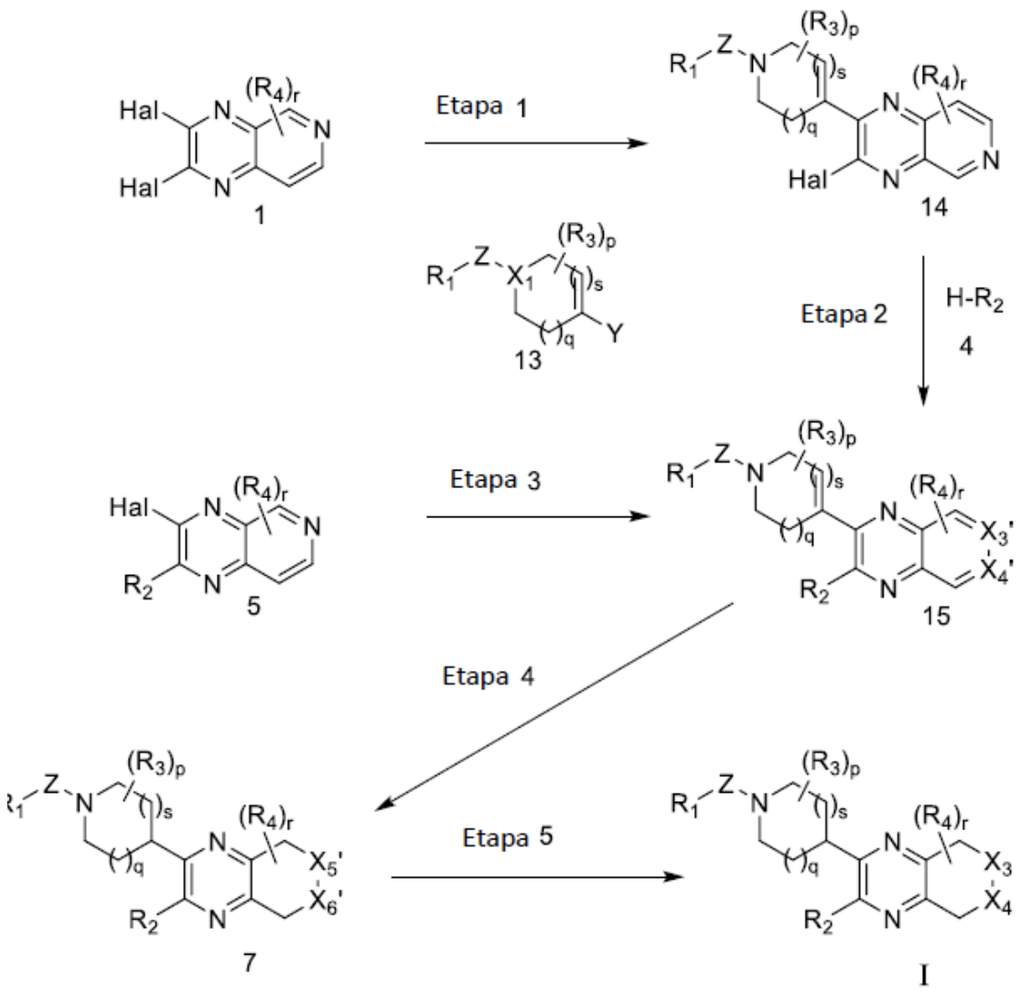
En el esquema B, etapa 3, un compuesto de fórmula 10 entra en contacto con un compuesto adecuado de fórmula 2, tal como se describe anteriormente, para dar un compuesto de fórmula 12 donde $X_{5''}$ es una amina protegida y $X_{6''}$ es CH o CR_4. La reacción se lleva a cabo según se describió en el esquema A, etapa 1.

En el esquema B, etapa 4, un compuesto de fórmula 11 entra en contacto con un compuesto adecuado de fórmula 4 para dar un compuesto de fórmula 12 donde $X_{5''}$ es CH o CR_4 y $X_{6''}$ es una amina protegida. Un compuesto adecuado de fórmula 4 tal como se describió anteriormente. La reacción se lleva a cabo según se describió en el esquema A, etapa 2.

En la esquema B, etapa 5, se desprotege un compuesto de fórmula 12 para proporcionar un compuesto de fórmula 7 tal como se describió anteriormente.

En el esquema B, etapa 6, un compuesto de fórmula 7 es alquilado, cicloalquilado, sulfonado, acilado o se convierte hasta una urea o carbamato mediante el uso de reactivos adecuados que proporcionan R_8 que es alquilo C_{1-6}, haloalquilo C_{1-6}, cicloalquilo C_{3-8}, -$S(O)_2$-R_9, -C(O)-R_{10}, -C(O)-N(R_{11})(R_{12}) o -C(O)-OR_{13} tal como se desea en el compuesto final de fórmula I según se describe en el esquema A, etapa 6, anteriormente.

Esquema C



El esquema C representa la formación de compuestos donde X_2 es CH.

En el esquema C, etapa 1, un compuesto adecuado de fórmula 1, tal como se describe anteriormente, se pone en contacto con un compuesto adecuado de la fórmula 13 para dar un compuesto de fórmula 9. Un compuesto adecuado de la fórmula 13 es uno donde R_1, Z, R_3, p, s y q son tal como se desea en el compuesto final de la fórmula I o da lugar a R_1, Z, y R_3 según se desea en el compuesto final de la fórmula I y Y un ácido borónico o éster borónico. También se entiende que el grupo descrito como R_1-Z- puede reemplazarse por un grupo protector adecuado, tal como un metilo, bencilo, t-BOC o Cbz, la eliminación posterior del grupo protector y la instalación de R_1-Z- según se desea en el producto final de la fórmula I.

Dichas reacciones se conocen generalmente como una reacción de Suzuki y se conocen bien en la técnica. Mientras se describe una reacción de Suzuki en el esquema C se entiende que pueden utilizarse otras reacciones de acoplamiento que forman enlaces carbono-carbono con

compuestos de la fórmula 13 que tienen Y diferente a ésteres o ácidos borónicos para producir compuestos de fórmula I.

En el esquema C, etapa 2, un compuesto de fórmula 14 se pone en contacto con un compuesto adecuado de la fórmula 4 para dar un compuesto de fórmula 15. Un compuesto adecuado de la fórmula 4 y las condiciones de reacción generales se describen anteriormente en el esquema A, etapa 2.

De forma alternativa, el esquema C, etapa 3, describe la reacción de Suzuki con un compuesto adecuado de la fórmula 13 y un compuesto adecuado de la fórmula 5 tal como se describió anteriormente para dar un compuesto de fórmula 15.

En el esquema C, etapa 4, un compuesto de fórmula 15 se reduce hasta un compuesto de fórmula 11 donde las variables se definen anteriormente y $X_{5'}$ se selecciona del grupo que consiste en CH, CR_4 y NH y $X_{6'}$ se selecciona del grupo que consiste en CH, CR_4 y NH siempre y cuando uno de $X_{5'}$ o $X_{6'}$ es NH y el otro es CH o CR_4. Las condiciones son similares a las descritas anteriormente para el esquema A, etapa 7.

En el esquema C, etapa 5, un compuesto de fórmula 7 es alquilado, cicloalquilado, sulfonado, acilado o se convierte a una urea o carbamato mediante el uso de reactivos que proporcionan R_8 que son alquilo C_{1-6}, haloalquilo C_{1-6}, cicloalquilo C_{3-8}, $-S(O)_2-R_9$, $-C(O)-R_{10}$, $-C(O)-N(R_{11})(R_{12})$ o $-C(O)-OR_{13}$ según se desea en el compuesto final de la fórmula I. Dichas transformaciones se llevan a cabo fácilmente mediante aminación, alquilación, sulfonilación reductiva, reacciones que forman amidas, amidación y condiciones de carbamilación que se conocen bien en la técnica.

El entendido en la técnica reconocerá que las etapas en el esquema C pueden variarse para proporcionar compuestos de fórmula I. En particular, el orden de etapas requeridas para producir los compuestos de fórmula I depende del compuesto particular que se sintetiza, el compuesto de partida y la labilidad relativa de los restos sustituidos. Por ejemplo, un compuesto de fórmula 9 o 5 puede someterse a la etapa 4 y el NH de $X_{3'}$ o $X_{4'}$ puede protegerse, después de entrar en contacto con un compuesto de fórmula 13 o 4 para dar un compuesto de fórmula 11 que, tal como se describió anteriormente, puede elaborarse hasta un compuesto de fórmula I. De forma alternativa, el doble enlace del anillo

que porta R_1-Z- puede reducirse individualmente a partir de la reducción parcial del anillo que porta finalmente X_3 y X_4. Son posibles otras variaciones y los entendidos en la técnica las entienden con facilidad.

También se entiende que algunos compuestos de fórmula I pueden elaborarse hasta otros compuestos de fórmula I, en unas etapas adicionales que no se muestran. Los compuestos de fórmula I pueden elaborarse en una variedad de formas. Dichas reacciones incluyen hidrólisis, oxidación, reducción, alquilación, amidaciones y similares. Asimismo, en una etapa opcional, que no se muestra en los esquemas anteriores, los compuestos de fórmula I pueden convertirse en sales farmacéuticamente aceptables mediante métodos bien conocidos y se aprecian en la técnica.

Los siguientes ejemplos pretenden ser ilustrativos y no taxativos, y representan realizaciones específicas de la presente invención.

Los espectros de resonancia magnética nuclear (NMR) de protones se obtuvieron para varios de los compuestos en los siguientes ejemplos. Los cambios químicos característicos (δ) se expresan en partes por millón campo abajo a partir de tetrametilsilano mediante el uso de abreviaturas convencionales para la designación de picos principales, incluidos s (singulete), d (doblete), t (triplete), q (cuarteto), m (multiplete) y br (amplio). Otras abreviaturas tienen su significado usual a menos que se indique lo contrario. Los espectros de masa, a menos que se indique lo contrario, se registraron mediante el uso de ionización de electropulverización (ESI) o ionización química a presión atmosférica.

Los ejemplos a continuación se llevaron a cabo en recipientes adecuados y se agitaron típicamente. Donde se indique, los productos de ciertas preparaciones y ejemplos se purificaron mediante HPLC. Donde se indique, los productos de las preparaciones y ejemplos se purificaron mediante HPLC.

Método A por HPLC: Bomba: Shimadzu LC-8A; UV/Vis: SPD-20A; Software: LCSolution. Se utilizó una columna Phenomenex Gemini® C18, 5 µm, ID 30 x 100 mm y se eluyó con gradientes de ACN (que contiene TFA al 0,035%) y agua (que contiene TFA

al 0,005%). Se utilizó un gradiente de ACN de 10% a 100% ACN a menos que se indique lo contrario.

Método B por HPLC: Bomba: Waters 2525 o 2545; MS: ZQ; Software: MassLynx. Se utilizó una columna Xbridge™ C18, 5 µm, ID 30 x 75 mm y se eluyó con gradientes de ACN (que contienen TFA al 0.035%) y agua (que contiene TFA al 0.005%).

Después del aislamiento mediante cromatografía, se elimina el solvente y el producto se obtiene mediante evaporación de las fracciones que contienen el producto (por ejemplo, GeneVac™), el evaporador giratorio, matraz evacuado, liofilización, etc.

Las abreviaturas utilizadas tienen sus significados convencionales a menos que se indique lo contrario. Por ejemplo, se utilizan las siguientes abreviaturas: ACN (acetonitrilo); aq (acuoso); Boc o t-BOC (*terc*-butoxicarbonilo); Cbz (carbobenciloxi); DCM (diclorometano); DMSO (dimetil sulfóxido); TFA (ácido trifluoroacético); HOAc (ácido acético), MeOH (metanol), PE (éter de petróleo), EA o EtOAc (acetato de etilo) y similares.

Preparación 1 (5-cloro-2-fluorofenil)(piperidin-4-il)metanona

Una solución de 2-bromo-4-cloro-1-fluorobenceno (175 µL, 1.377 mmol) en THF (4,59 mL) a –78 °C se trató con *n*-BuLi (2.6 M, 741 µL, 1.928 mmol) y la mezcla de reacción se agitó durante 30 min. A esto se agregó 4-(metoxi(metil)carbamoil)piperidina-1-carboxilato de terc-butilo (250 mg, 0.918 mmol) en una porción. El baño de enfriamiento se eliminó y la mezcla de reacción resultante se dejó calentar a temperatura ambiente y se agitó durante 1.5 h. La purificación mediante cromatografía ultrarrápida automatizada de gel de sílice utilizando 10% EtOAc en hexanos proporcionó 4-(5-cloro-2-fluorobenzoil)piperidina-1-carboxilato de terc-butilo (287.9 mg, 92%) como un aceite amarillo. ESI-MS m/z $[M+Na]^+$ 364.20.

Una solución de 4-(5-cloro-2-fluorobenzoil)piperidina-1-carboxilato de terc-butilo (287.9 mg, 0.843 mmol) en dioxano (2.41 mL) se trató con HCl (2.11 mL, 8.43 mmol) a temperatura ambiente y la mezcla de reacción resultante se agitó durante la noche. La mezcla de reacción se diluyó con hexanos y se filtró mediante succión para proporcionar (5-cloro-2-

fluorofenil)(piperidin-4-il)metanona como su sal HCl (146 mg, 62.3%) como un sólido amarillo. ESI-MS m/z $[M+H]^+$ 242.20.

Preparación 2 4-(2,4-difluorofenoxi)piperidina

A una solución de 2,4-difluorofenol (10 g, 77 mmol), PPh_3 (30.2 g, 115 mmol) y 4-hidroxipiperidina-1-carboxilato de terc-butilo (30.9 g, 154 mmol) en THF (400 mL) se agregó DEAD (18.3 mL, 115 mmol) a 0 °C por goteo. Después de completarse la adición, la mezcla resultante se dejó en agitación a 40 °C durante 16 h. La mezcla se vertió en agua y se extrajo con EtOAc (3 x 400 mL). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron para proporcionar el producto en bruto. La purificación mediante cromatografía ultrarrápida de gel de sílice, eluyendo con 80:1 PE:EtOAc, proporcionó 4-(2,4-difluorofenoxi)piperidina-1-carboxilato de terc-butilo como un aceite (20 g, 83%).

Una solución de 4-(2,4-difluorofenoxi)piperidina-1-carboxilato de terc-butilo (20 g, 63.8 mmol) en 4:1 HCl/EtOAc (250 mL) se agitó a 25 °C durante 1 h. La mezcla se concentró para proporcionar el compuesto del título, como su sal HCl, como un sólido blanco (15.4 g, 97 %). ^{1}H RMN (400 MHz, DMSO-*d*6) δ ppm 1.84 (m, 2H), 2.08 (m, 2H), 3.05 (m, 2H), 3.20 (m, 2H), 4.57 (m, 1H), 7.04 (m, 1H), 7.31 (m, 2H), 8.95 (d a, 2H).

Preparación 3 3-fluoro-4-(piperidin-4-iloxi)benzonitrilo

Una solución de 3,4-difluorobenzonitrilo (28 g, 201 mmol) y 4-hidroxipiperidina-1-carboxilato de terc-butilo (40.5 g, 201 mmol) en THF (500 mL) se trató con hidruro de sodio (4 g, 100 mmoL) y se agitó a 25 °C durante 16 h. La mezcla de reacción se lavó con agua, se extrajo con EtOAc, y el producto en bruto se purificó mediante cromatografía ultrarrápida de gel de sílice proporcionó 4-(4-ciano-2-fluorofenoxi)piperidina-1-carboxilato de terc-butilo (25 g, 39%).

Una solución de 4-(4-ciano-2-fluorofenoxi)piperidina-1-carboxilato de terc-butilo (42 g, 131 mmol) se disolvió en 4:1 HCl/EtOAc (100 mL) se agitó durante 5 h. La mezcla se concentró para proporcionar el compuesto del título como su sal HCl (12 g, 36%). ^{1}H RMN (400 MHz, DMSO-*d*6) δ ppm 1.89 (m, 2H), 2.14 (m, 2H); 3.08 (m, 2H), 3.21 (m, 2H), 4.86 (m, 1H),

7.48 (t, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.89 (m, 1H); ESI-MS m/z [M+H]+ 220.7.

Preparación 4 6 4-((2,4-difluorofenil)fluorometil)piperidina

A una solución a 0 °C de 4-(2,4-difluorobenzoil)piperidina-1-carboxilato de terc-butilo (1.28 g, 3.93 mmol) en MeOH (15.7 mL) se agregó $NaBH_4$ (0.372 g, 9.84 mmol). El baño de hielo se eliminó y la mezcla de reacción se agitó durante 2 h a temperatura ambiente y se inactivó con NH_4Cl acuoso saturado. La capa orgánica se extrajo con EtOAc, se lavó con H_2O y se secó sobre $MgSO_4$, el solvente se eliminó bajo presión reducida lo que proporcionó 4-((2,4-difluorofenil)(hidroxi)metil)piperidina-1-carboxilato de terc-butilo como un sólido blanco higroscópico.

A una solución a –78 °C de 4-((2,4-difluorofenil)(hidroxi)metil)piperidina-1-carboxilato de terc-butilo (200 mg, 0.611 mmol) en DCM (3.055 mL) se agregó DAST (242 µL, 1.833 mmol). La mezcla se agitó a –78 °C durante 30 min, posteriormente se inactivó con MeOH. La cromatografía ultrarrápida de gel de sílice utilizando un gradiente de 0% a 100% EtOAc en hexanos proporcionó 4-((2,4-difluorofenil)fluorometil)piperidina-1-carboxilato de terc-butilo como un aceite incoloro.

A una solución de racémica 4-((2,4-difluorofenil)fluorometil)piperidina-1-carboxilato de terc-butilo (148 mg, 0.449 mmol) en dioxano (1.50 mL) se agregó HCl (4 M en dioxano, 337 µL, 1.348 mmol). La mezcla se calentó a 45 °C durante 16 h y se concentró al vacío para proporcionar el compuesto del título como su sal HCl (109 mg, 91%) como un sólido blanco.

Preparación 5 (*R*)-4-((2,4-difluorofenil)fluorometil)piperidina

4-((2,4-difluorofenil)fluorometil)piperidina-1-carboxilato de terc-butilo como un aceite incoloro.
Se sometió 4-((2,4-difluorofenil)fluorometil)piperidina-1-carboxilato de terc-butilo a separación quiral SFC para proporcionar 4-((2,4-difluorofenil)fluorometil)piperidina-1-carboxilato de (*R*)-terc-butilo.

4-((2,4-difluorofenil)fluorometil)piperidina-1-carboxilato de (*R*)-terc-butilo (2.8 g, 8.50 mmol) se disolvió en EtOAc (20 mL) y se agregó HCl (4 M en EtOAc, 21 mL). La

mezcla de reacción se agitó a 23 °C durante 2 h. La evaporación del solvente proporcionó el compuesto del título como su sal HCl (2.1 g, 93%). ESI-MS m/z $[M+H]^+$ 229.9.

Preparación 6 (S)- 4-((2,4-difluorofenil)fluorometil)piperidina

4-((2,4-difluorofenil)fluorometil)piperidina-1-carboxilato de terc-butilo se sometió a separación quiral SFC para proporcionar 4-((2,4-difluorofenil)fluorometil)piperidina-1-carboxilato (R)-de terc-butilo.

La sal HCl del compuesto del título se preparó de forma similar a la Preparación 5a, utilizando 4-((2,4-difluorofenil)fluorometil)piperidina-1-carboxilato (*S*)-de terc-butilo. ESI-MS m/z $[M+H]^+$ 229.9.

Preparación 7 4-((2-fluorofenil)sulfonil)piperidina

Una mezcla de 2-fluorobencenotiol (0.764 mL, 7.15 mmol), 4-((metilsulfonil)oxi)piperidina-1-carboxilato de terc-butilo (1.816 g, 6.5 mmol), y K_2CO_3 (1.348 g, 9.75 mmol) en ACN (16.25 mL) se calentó a 80 °C durante la noche. La mezcla de reacción se vertió en agua y se extrajo dos veces con EtOAc. Los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y concentraron bajo presión reducida lo que proporcionó 4-((2-fluorofenil)tio)piperidina-1-carboxilato de terc-butilo como un aceite amarillo (1.98 g, 98%), que se utilizó más adelante sin purificación.

Una solución de 4-((2-fluorofenil)tio)piperidina-1-carboxilato de terc-butilo (1.98 g, 6.36 mmol) en THF (54,5 mL) y MeOH (18.2 mL) a 0 °C se trató con una solución fría de Oxona® (9.77 g, 15.9 mmol) en agua (54,5 mL). La mezcla de reacción se agitó durante 5 h, calentándose gradualmente a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo dos veces con EtOAc. Los extractos orgánicos combinados se lavaron con agua y posteriormente NaCl acuoso saturado, se secó sobre Na_2SO_4, se filtró y concentró bajo presión reducida. El residuo se purificó mediante cromatografía ultrarrápida de gel de sílice utilizando un gradiente de 10% a 50% EtOAc con 0.1% trietilamina en heptanos lo que proporcionó 4-((2-fluorofenil)sulfonil)piperidina-1-carboxilato de terc-butilo como un aceite amarillo claro (1.31 g, 60%).

Una solución de 4-((2-fluorofenil)sulfonil)piperidina-1-carboxilato de terc-butilo (1.31 g, 3.82 mmol) en dioxano

(12.7 mL) a temperatura ambiente se trató con HCl 4M en dioxano (9.55 ml, 38.2 mmol). La mezcla de reacción se dejó en agitación a temperatura ambiente durante la noche. La mezcla de reacción se concentró bajo presión reducida. El sólido resultante blanco se trituró con hexanos, se filtró, recogió, y se liofilizó durante la noche para proporcionar el compuesto del título, como su sal HCl, como un sólido blanco (815.1 mg, 76%). ESI-MS m/z $[M+H]^+$ 243.95.

Preparación 8 4-((2-fluoro-4-metoxifenil)sulfonil)piperidina

Una mezcla de 2,4-difluorobencenotiol (0.810 mL, 7.15 mmol), 4-((metilsulfonil)oxi)piperidina-1-carboxilato de terc-butilo (1.816 g, 6.5 mmol), y K_2CO_3 (1.348 g, 9.75 mmol) en ACN (16.25 mL) se calentó a 80 °C durante la noche. La mezcla de reacción se vertió en agua y se extrajo dos veces con EtOAc. La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró bajo presión reducida para proporcionar 4-((2,4-difluorofenil)tio)piperidina-1-carboxilato de terc-butilo (2.141 g) como un aceite amarillo, que se utilizó más adelante sin purificación.

Una solución de 4-((2,4-difluorofenil)tio)piperidina-1-carboxilato de terc-butilo (2.141 g, 6.50 mmol) en THF/MeOH (3:1, 74 mL) a 0 °C se trató con una solución fría de Oxona® (9.99 g, 16.25 mmol) en agua (56 mL). La mezcla de reacción se dejó en agitación durante la noche, calentándose gradualmente a temperatura ambiente. La mezcla de reacción se vertió en agua y se extrajo dos veces con EtOAc. Los extractos orgánicos combinados se lavaron con agua y posteriormente NaCl acuoso saturado, se secaron sobre Na_2SO_4, se filtraron y concentraron bajo presión reducida. El residuo se purificó mediante cromatografía ultrarrápida de gel de sílice utilizando un gradiente de 10% a 40% EtOAc con 0.1% trietilamina en heptanos proporcionó 4-((2,4-difluorofenil)sulfonil)piperidina-1-carboxilato de terc-butilo (1.32 g, 56%) como un sólido blanco. ESI-MS m/z $[M+Na]^+$ 383.80.

A una suspensión de 4-((2,4-difluorofenil)sulfonil)piperidina-1-carboxilato de terc-butilo (50 mg, 0.138 mmol) en MeOH (461 µL) se agregó metóxido de sodio (25.6 µL, 0.138 mmol, 5.4 M in MeOH) por goteo. La mezcla de reacción se dejó en agitación a 45 °C

durante 20 min y se concentró al vacío. La desprotección Boc se llevó a cabo mediante la adición de HCl (138 µL, 0.553 mmol, 4 M en dioxano) a la mezcla de reacción bruta en 300 µL de dioxano. Se agitó a 50 °C durante 24 h seguido de la concentración al vacío para proporcionar el compuesto del título como su sal HCl (57 mg) como un sólido blanco (10:1 mezcla regioisomérica). ESI-MS m/z $[M+H]^+$ 274,00.

Preparación 9 4-((3-fluorofenil)sulfonil)piperidina

Una mezcla de 4-((metilsulfonil)oxi)piperidina-1-carboxilato de terc-butilo (1.0 g, 3.58 mmol), K_2CO_3 (0.742 g, 5.37 mmol), y 3-fluorobencenotiol (0.363 mL, 4,30 mmol) en ACN (7.5 mL) se agitó a 23 °C durante 5 min. La mezcla de reacción se agitó a 80 °C durante 17 h, se enfrió a 23 °C y se repartió entre EtOAc y agua. Las capas se separaron, la fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró, se lavó con EtOAc, y se secó al vacío lo que proporcionó 4-((3-fluorofenil)tio)piperidina-1-carboxilato de terc-butilo (1.115 g, 100 %) como un aceite amarillo. ESI-MS m/z $[M+H]^+$ 255.9.

Una mezcla de alúmina básica (3.0 g, 29.4 mmol) en agua (0.6 mL) se agitó a 23 °C durante 5 min. Después, se agregó ACN (12 mL) seguido de una solución de 4-((3-fluorofenil)tio)piperidina-1-carboxilato de terc-butilo (1.115 g, 3.58 mmol) en $CHCl_3$ (8 mL). Después, se agregó Oxona® (6.60 g, 10.74 mmol) y la mezcla de reacción se agitó a 60 °C durante 19 h. La mezcla de reacción se enfrió a 23 °C, se filtró, se lavó con $CHCl_3$, y el filtrado se lavó con agua (10 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró, se lavó con $CHCl_3$, y se secó al vacío. El residuo bruto se disolvió en tolueno (5 mL) y se purificó mediante cromatografía de media presión utilizando un gradiente de 10% a 100% EtOAc con 0.1% trietilamina en heptano en una columna de gel de sílice de 80 g (Single Step™) lo que proporcionó 4-((3-fluorofenil)sulfonil)piperidina-1-carboxilato de terc-butilo (0.769 g, 62.5%) como un sólido blanco. ESI-MS m/z $[M+Na]^+$ 365.9.

A una solución de 4-((3-fluorofenil)sulfonil)piperidina-1-carboxilato de terc-butilo (756 mg, 2.201 mmol) en dioxano (5.0 mL) se agregó HCl (4 M en dioxano, 5.50 mL, 22.01 mmol) a 23 °C. La reacción se agitó a 23 °C durante 21 h para proporcionar una suspensión blanca. El sólido resultante se

filtró, se lavó con dioxano y se secó al vacío para proporcionar el compuesto del título como su sal HCl (582.6 mg, 95%) como un sólido blanco. ESI-MS m/z $[M+H]^+$ 243.9.

Preparación 10 4-((3-metoxifenil)sulfonil)piperidina

El compuesto del título como su sal HCl se preparó de una manera similar a la Preparación 11, con la excepción de que cloroformo se usó adicional en lugar de ACN en la segunda etapa. ESI-MS m/z $[M+H]^+$ 255.9.

Preparación 12 4-((4-fluorofenil)sulfonil)piperidina

Una mezcla de 4-((metilsulfonil)oxi)piperidina-1-carboxilato de terc-butilo (1.42 g, 5.08 mmol), 4-fluorobencenotiol (0.663 ml, 6.10 mmol) y K_2CO_3 (1.054 g, 7.62 mmol) en ACN (12.71 mL) se agitó a 85 °C durante la noche. La mezcla de reacción se filtró mediante succión y el solvente se eliminó lo que proporcionó 4-((4-fluorofenil)tio)piperidina-1-carboxilato de terc-butilo (1.5 g, 95%) como un sólido blanco.

Una solución de 4-((4-fluorofenil)tio)piperidina-1-carboxilato de terc-butilo (1.5 g) en agua (16.06 mL) y MeOH (16.06 mL) se trató con Oxona® (5.92 g, 9.63 mmol) a temperatura ambiente y la mezcla de reacción resultante se agitó durante 6 h. La solución se filtró mediante succión y el solvente se eliminó lo que proporcionó 4-((4-fluorofenil)sulfonil)piperidina-1-carboxilato de terc-butilo (1.6 g, 4,66 mmol, 97 % de rendimiento) como un sólido blanco.

Una solución de 4-((4-fluorofenil)sulfonil)piperidina-1-carboxilato de terc-butilo (32.7 mg, 0.095 mmol) en dioxano (238 µL) a temperatura ambiente se trató con HCl (4 M en dioxano, 190 µL, 0.762 mmol) y la mezcla de reacción resultante se agitó durante 4 h. El solvente se eliminó para proporcionar el compuesto del título como su sal HCl (25 mg, 94%) como un sólido blanco. ESI-MS m/z $[M+H]^+$ 243.95.

Preparación 13 1-(2,4-difluorobencil)piperazina

Una mezcla de piperazina (26.5 g, 308 mmol) en THF (350 mL) se calentó hasta 70 °C y 1-(clorometil)-2,4-difluorobenceno (5 g, 30.8 mmol) se agregó. La suspensión se calentó a 70 °C durante la noche. El sólido (piperazina) se filtró, y el solvente se eliminó bajo presión reducida. El residuo se repartió entre EtOAc y agua. La capa orgánica se

secó y se concentró para proporcionar el compuesto del título (6 g, 92%). ESI-MS m/z $[M+H]^+$ 213.04,

Preparación 14 4-(2-fluoro-4-metoxifenoxi)piperidina

Una solución de 4-hidroxipiperidina-1-carboxilato de terc-butilo (2.496 g, 12.03 mmol) en THF (33.4 mL) a temperatura ambiente se trató con 2-fluoro-4-metoxifenol (1.181 mL, 10.03 mmol) y trifenilfosfina (3.16 g, 12.03 mmol). La mezcla de reacción se enfrió a 0 °C y DEAD (40 % p en tolueno, 5.95 mL, 15.04 mmol) se agregó por goteo mediante una jeringa. La mezcla de reacción resultante se agitó a 65 °C durante 5 h, posteriormente a temperatura ambiente durante la noche. La cromatografía ultrarrápida de gel de sílice utilizando un gradiente de 10% a 100% EtOAc en hexanos proporcionó 4-(2-fluoro-4-metoxifenoxi)piperidina-1-carboxilato de terc-butilo (2.78 g, 85%) como un aceite amarillo claro. ESI-MS m/z $[M+Na]^+$ 348.2.

Una solución de 4-(2-fluoro-4-metoxifenoxi)piperidina-1-carboxilato de terc-butilo (2.78 g, 8.54 mmol) en dioxano (21.36 mL) se trató con HCl (4 M en dioxano, 21.36 mL, 85 mmol) a temperatura ambiente y la mezcla de reacción resultante se agitó durante la noche. La cromatografía ultrarrápida de gel de sílice utilizando un gradiente de 5% a 30% MeOH en DCM proporcionó el compuesto del título como su sal HCl (1.7 g, 76%) como un sólido blanco. ESI-MS m/z $[M+H]^+$ 226.20.

Preparación 15 3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazina

Una solución de 2,3-dicloropirido[3,4-*b*]pirazina (492 mg, 2.460 mmol) en DCM (5 mL) a 0 °C se trató con hidrocloruro de 4-(2,4-difluorofenoxi)piperidina (676 mg, 2.71 mmol) y DIPEA (1.29 mL, 7.38 mmol). La mezcla de reacción se dejó en agitación durante la noche, calentándose gradualmente a temperatura ambiente. La mezcla de reacción se inactivó con la adición de acuoso saturado NH_4Cl y se extrajo con DCM. La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró bajo presión reducida. El residuo se purificó mediante cromatografía ultrarrápida de gel de sílice utilizando un gradiente de 20% a 60% EtOAc en heptanos para proporcionar el compuesto del título como un sólido amarillo claro (736.2 mg, 79%). ESI-MS m/z $[M+H]^+$ 377.4,

Preparación 16 4-((1-(3-cloropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo

A una solución de 2,3-dicloropirido[3,4-*b*]pirazina (1.00 g, 5.00 mmol) en DCM (10.0 mL) a 0 °C se agregó DIPEA (2.62 mL, 15.00 mmol) e hidrocloruro de 3-fluoro-4-(piperidin-4-iloxi)benzonitrilo (1.283 g, 5.00 mmol). La mezcla de reacción se agitó durante 30 min y se calentó gradualmente a temperatura ambiente. La mezcla de reacción se trató con acuoso saturado NH_4Cl. La capa orgánica que contenía sólido amarillo se recogió y se concentró bajo presión reducida. El sólido se filtró, se lavó con agua, y se liofilizó durante la noche para proporcionar el compuesto del título como un sólido amarillo (1.325 g, 69%). ESI-MS m/z $[M+H]^+$ 384.3.

Preparación 17 (R)-3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)pirido[3,4-b]pirazina

El compuesto del título se preparó de manera similar a la Preparación 18 utilizando hidrocloruro de (*R*)-4-((2,4-difluorofenil)fluorometil)piperidina en lugar de hidrocloruro de 4-(2,4-difluorofenoxi)piperidina. ESI-MS m/z $[M+H]^+$ 393.4.

Preparación 19 (*S*)-3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)pirido[3,4-*b*]pirazina

El compuesto del título se preparó de manera similar a la Preparación 20 utilizando hidrocloruro de (*S*)-4-((2,4-difluorofenil)fluorometil)piperidina en lugar de hidrocloruro de 4-(2,4-difluorofenoxi)piperidina. ESI-MS m/z $[M+H]^+$ 393.4.

Preparación 21 3-cloro-2-(4-(2,4-difluorobencil)piperazin-1-il)pirido[3,4-*b*]pirazina

A una mezcla de 2,3-dicloropirido[3,4-*b*]pirazina (8 g, 40.0 mmol)and 1-(2,4-difluorobencil)piperazina (8.49 g, 40.0 mmol) en DCM (100 mL) se agregó trietilamina (16.72 mL, 120 mmol) a temperatura ambiente. Posteriormente, la mezcla se agitó a temperatura ambiente durante 0.5 h. La mezcla de reacción se diluyó con 30 mL de DCM, se lavó con salmuera dos veces, se secó sobre Na_2SO_4 anhidro y se concentró. El residuo se purificó mediante cromatografía de gel de sílice, eluyendo con un gradiente de 50:1 to 5:1 PE:EtOAc para proporcionar el compuesto del título (12 g, 80%). ESI-MS m/z $[M+H]^+$ 376.0.

Preparación 22 3-cloro-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)pirido[3,4-*b*]pirazina

Una mezcla de hidrocloruro de 4-(2-fluoro-4-metoxifenoxi)piperidina (144 mg, 0.550 mmol), 2,3-dicloropirido[3,4-*b*]pirazina (100 mg, 0.500 mmol) y DIPEA (260 µL, 1.500 mmol) en DCM (1.0 mL) se agitó a temperatura ambiente durante 30 min. La mezcla se repartió entre EtOAc y acuoso saturado NH_4Cl. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. El residuo se disolvió en EtOAc y se filtró a través de una almohadilla de sílice. El filtrado se concentró para proporcionar el compuesto bruto del título (200.7 mg, 100%) como un aceite amarillo, que se utilizó sin purificación adicional. ESI-MS m/z $[M+H]^+$ 389.2.

Preparación 23 4-(3-cloropirido[3,4-*b*]pirazin-2-il)piperazina-1-carboxilato de terc-butilo

Se combinaron 2,3-dicloropirido[3,4-*b*]pirazina (2.0 g, 10.00 mmol), piperazina-1-carboxilato de terc-butilo (1.955 g, 10.50 mmol) y DCM (25 mL) para proporcionar una suspensión amarilla-anaranjada. Después, DIPEA (5.22 mL, 30.0 mmol) se agregó al recipiente durante 1 min a 0 °C. La mezcla se agitó a 0 °C durante 2 h bajo nitrógeno, se calentó lentamente a 23 °C, y se agitó durante 17 h. La mezcla de reacción se repartió entre NH_4Cl acuoso saturado (20 mL) y EtOAc (80 mL) para proporcionar dos capas. Las capas se separaron, y la fase acuosa se lavó con EtOAc (80 mL). Los extractos orgánicos se combinaron, se lavaron con salmuera (10 mL), se secaron sobre Na_2SO_4, se filtraron, se lavaron con EtOAc, y se secaron al vacío para proporcionar el compuesto del título (3.35 g, 96%) como un semisólido anaranjado. ^1H RMN (500 MHz, DMSO-d_6) δ ppm 1.44 (s, 9H), 3.51-3.58 (m, 4H), 3.62-3.68 (m, 4H), 7.67 (d, *J* = 1.0 Hz, 1H), 8.66 (d, *J* = 5.9 Hz, 1H), 9.15 (d, *J* = 1.0 Hz, 1H); ESI-MS m/z $[M+H]^+$ 350.5.

Preparación 24 4-(3-(isopropilamino)pirido[3,4-*b*]pirazin-2-il)piperazina-1-carboxilato de terc-butilo

A un matraz cargado con 4-(3-cloropirido[3,4-*b*]pirazin-2-il)piperazina-1-carboxilato de terc-butilo (3.35 g, 9.58 mmol) y fluoruro de potasio (0.723 g, 12.45 mmol) en DMSO (25 mL) se agregó DIPEA (3.34 mL, 19.15 mmol) y propan-2-amina (2.468 mL, 28.7 mmol) a 23 °C. La reacción se agitó a 23 °C durante 22 hr y se diluyó con agua (100 mL) para proporcionar un lodo anaranjado aceitoso. La mezcla se enfrió a 0 °C para proporcionar una suspensión amarilla-anaranjada. El sólido

resultante se filtró, se lavó con agua, y se secó al vacío. El material en bruto se disolvió en EtOAc, se absorbió en NH gel de sílice (11 g), y se purificó mediante cromatografía de media presión utilizando un gradiente de 10% a 100% EtOAc en heptano en una columna NH 60 µM, tamaño 400 (Shoko Scientific Purif-Pack™) para proporcionar el compuesto del título (2.105 g, 59.0%) como un sólido amarillo claro. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.26 (d, J = 6.8 Hz, 6H), 1.43 (s, 9H), 3.30-3.33 (m, 4H), 3.52-3.60 (m, 4H), 4.32-4.42 (m, 1H), 6.54 (d, J = 7.8 Hz, 1H), 7.43-7.46 (m, 1H), 8.29 (d, J = 5.4 Hz, 1H), 8.78 (s, 1H); ESI-MS m/z $[M+H]^+$ 373.0.

Preparación 25 (1*s*,3*s*)-3-((2-(4-(2,4-difluorobencil)piperazin-1-il)pirido[3,4-*b*]pirazin-3-il)amino)ciclobutan-1-ol

Se combinaron 3-cloro-2-(4-(2,4-difluorobencil)piperazin-1-il)pirido[3,4-*b*]pirazina (0.75 g, 1.996 mmol), hidrocloruro de (1*s*,3*s*)-3-aminociclobutanol (0.740 g, 5.99 mmol), y fluoruro de potasio (0.151 g, 2.59 mmol) en DMSO (7.5 mL) y se agregó DIPEA (1.738 mL, 9.98 mmol) a 23 °C. La mezcla de reacción se agitó a 23 °C durante 5 días y se diluyó con agua (30 mL) para proporcionar una suspensión amarilla-anaranjada. El sólido resultante se filtró, se lavó con agua, y se secó al vacío para proporcionar el compuesto del título (690 mg, 81%) como un sólido amarillo. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.92-2.02 (m, 2H), 2.61-2.70 (m, 6H), 3.38 (s a, 4H), 3.60 (s, 2H), 3.90-3.98 (m, 1H), 3.99-4.07 (m, 1H), 5.08 (d, J = 5.9 Hz, 1H), 6.93-6.98 (m, 1H), 7.09 (td, J = 8.4, 2.7 Hz, 1H), 7.20-7.25 (m, 1H), 7.41-7.45 (m, 1H), 7.47-7.53 (m, 1H), 8.28 (d, J = 5.9 Hz, 1H), 8.75 (s, 1H); ESI-MS m/z $[M+H]^+$ 427.0.

Preparación 26 (1*s*,3*s*)-3-((2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazin-3-il)amino)ciclobutan-1-ol

Se combinaron 3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazina (0.75 g, 1.991 mmol), hidrocloruro de (1*s*,3*s*)-3-aminociclobutanol (0.738 g, 5.97 mmol), y fluoruro de potasio (0.150 g, 2.59 mmol) en DMSO (7.5 mL) y se agregó DIPEA (1.734 mL, 9.95 mmol) a 23 °C. La mezcla de reacción se agitó a 23 °C durante 5 días y se diluyó con agua (30 mL) para proporcionar una suspensión amarilla-anaranjada. El sólido resultante se

filtró, se lavó con agua, y se secó al vacío para proporcionar el compuesto del título (784 mg, 92%) como un sólido amarillo-anaranjado. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.87-2.03 (m, 4H), 2.07-2.18 (m, 2H), 2.61-2.73 (m, 2H), 3.19-3.29 (m, 2H), 3.63-3.73 (m, 2H), 3.89-3.99 (m, 1H), 3.99-4.10 (m, 1H), 4.62 (tt, *J* = 7.9, 3.8 Hz, 1H), 5.08 (d, *J* = 5.9 Hz, 1H), 6.99-7.10 (m, 2H), 7.26-7.38 (m, 2H), 7.44 (d, *J* = 5.4 Hz, 1H), 8.28 (d, *J* = 5.4 Hz, 1H), 8.76 (s, 1H); ESI-MS m/z $[M+H]^+$ 427.9.

Preparación 27 (1*r*,3*r*)-3-((2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazin-3-il)amino)ciclobutan-1-ol

Se combinaron 3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazina (0.75 g, 1.991 mmol), hidrocloruro de (1*r*,3*r*)-3-aminociclobutanol (0.738 g, 5.97 mmol), y fluoruro de potasio (0.150 g, 2.59 mmol) en DMSO (7.5 mL) y se agregó DIPEA (1.734 mL, 9.95 mmol) a 23 °C. La reacción se agitó a 23 °C durante 5 días y se diluyó con agua (30 mL) para proporcionar una suspensión gomosa marrón. La suspensión se enfrió en hielo, se agitó durante 30 min a 0 °C, se filtró, se lavó con agua, y el sólido resultante se secó al vacío para proporcionar el compuesto del título (802 mg, 94%) como un sólido marrón claro. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.86-1.96 (m, 2H), 2.07-2.15 (m, 2H), 2.23 (ddd, *J* = 12.6, 7.9, 4.4 Hz, 2H), 2.33-2.40 (m, 2H), 3.23-3.30 (m, 2H), 3.67-3.74 (m, 2H), 4.30-4.37 (m, 1H), 4.56-4.65 (m, 2H), 5.03 (d, *J* = 4.9 Hz, 1H), 7.00-7.07 (m, 2H), 7.29-7.37 (m, 2H), 7.44 (d, *J* = 4.9 Hz, 1H), 8.28 (d, *J* = 5.4 Hz, 1H), 8.77 (s, 1H); ESI-MS m/z $[M+H]^+$ 427.9.

Preparación 28 *N*-ciclobutil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazin-3-amina

A una solución de 3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazina (10 g, 26.5 mmol) en DMF (150 mL) se agregó ciclobutanamina (15.10 g, 212 mmol) a temperatura ambiente. Posteriormente, la mezcla se agitó a 70 °C durante 15 h. Después de que la reacción se terminó, la mezcla de reacción se vertió en agua/ACN (200 mL, 7:3). La suspensión se filtró y se lavó con ACN para proporcionar el compuesto del título (8.5 g, 78%). ESI-MS m/z $[M+H]^+$ 412.1.

Preparación 28 *N*-(3,3-difluorociclobutil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazin-3-amina

Se combinaron 3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazina (0.46 g, 1.221 mmol), hidrocloruro de 3,3-difluorociclobutanamina (0.526 g, 3.66 mmol), y fluoruro de potasio (0.092 g, 1.587 mmol) en DMSO (5 mL) y se agregó DIPEA (1.063 mL, 6.10 mmol) a 23 °C. La reacción se agitó a 23 °C durante 5 días y se diluyó con agua (20 mL) para proporcionar una suspensión amarilla-anaranjada. El sólido resultante se filtró, se lavó con agua, y se secó al vacío para proporcionar el compuesto del título (516.4 mg, 95%) como un sólido amarillo-anaranjado. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.87-1.98 (m, 2H), 2.07-2.18 (m, 2H), 2.77-2.91 (m, 2H), 2.96-3.07 (m, 2H), 3.23-3.32 (m, 2H), 3.69-3.78 (m, 2H), 4.35-4.45 (m, 1H), 4.63 (tt, *J* = 7.9, 3.8 Hz, 1H), 7.00-7.07 (m, 1H), 7.24-7.40 (m, 3H), 7.48 (d, *J* = 5.4 Hz, 1H), 8.33 (d, *J* = 5.4 Hz, 1H), 8.82 (s, 1H); ESI-MS m/z $[M+H]^+$ 447.9.

Preparación 30 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropilpirido[3,4-*b*]pirazin-3-amina

Una solución de 3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazina (2 g, 5.31 mmol), propan-2-amina (1.36 mL, 15.92 mmol) y DIPEA (1.85 mL, 10.62 mmol) en dioxano (10.62 mL) se calentó a 95 ºC durante la noche. Después de la concentración, el residuo se purificó sobre cromatografía en columna de gel de sílice utilizando un gradiente de 0% a 100% EtOAc en heptanos para proporcionar el compuesto del título (1.5 g, 71%) como un sólido blancuzco. ESI-MS m/z $[M+H]^+$ 400.00.

Preparación 31 9 (*S*)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-(tetrahidrofurán-3-il)pirido[3,4-*b*]pirazin-3-amina

A una mezcla de 3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazina (2.5 g, 6.64 mmol) en DMF (30 mL) se agregó hidrocloruro de (*S*)-tetrahidrofurán-3-amina (4,10 g, 33.2 mmol) y Et_3N (9.25 mL, 66.4 mmol) a temperatura ambiente. La mezcla de reacción se agitó a 70 °C durante 14 h y se enfrió a temperatura ambiente y se diluyó con EtOAc (80 mL), se lavó con agua (30 mL) y salmuera (2 x 30 mL). La capa orgánica se secó sobre Na_2SO_4 y se concentró al vacío, posteriormente el residuo se purificó mediante cromatografía en columna (éter de petróleo:EtOAc

desde 10:1 a 1:1) sobre gel de sílice para proporcionar el compuesto del título como un sólido amarillo (2.0 g). ESI-MS m/z $[M+H]^+$ 428.1.

Preparación 32 (*R*)-2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-(tetrahidrofurán-3-il)pirido[3,4-*b*]pirazin-3-amina

A una mezcla de 3-cloro-2-(4-(2,4-difluorobencil)piperazin-1-il)pirido[3,4-*b*]pirazina (5.06 g, 13.46 mmol) en DMSO (40 mL) se agregó hidrocloruro de (*R*)-tetrahidrofurán-3-amina (4,16 g, 33.7 mmol) y Et_3N (24,40 mL, 175 mmol) a temperatura ambiente. La mezcla de reacción se agitó a 50 °C durante 14 h, se enfrió a temperatura ambiente y se diluyó con EtOAc (80 mL), se lavó con agua (30 mL) y salmuera (2 x 30 mL). La capa orgánica se secó sobre Na_2SO_4 y se concentró al vacío, posteriormente el residuo se purificó mediante cromatografía en columna (éter de petróleo:EtOAc desde 10:1 a 1:1) sobre gel de sílice para proporcionar el compuesto del título como un sólido amarillo (5.0 g). ESI-MS m/z $[M+H]^+$ 427.1.

Preparación 33 (*S*)-2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-(tetrahidrofurán-3-il)pirido[3,4-*b*]pirazin-3-amina

A una solución de 3-cloro-2-(4-(2,4-difluorobencil)piperazin-1-il)pirido[3,4-*b*]pirazina (3.0 g, 7.98 mmol) y Et_3N (10 mL, 71.7 mmol) en DMF (30 mL) se agregó hidrocloruro de (*S*)-tetrahidrofurán-3-amina (2.96 g, 23.95 mmol) a temperatura ambiente. La mezcla se agitó a 60 °C durante 16 h y se separó entre agua y EtOAc. La capa orgánica se lavó con salmuera y agua, se secó y se concentró para proporcionar el residuo bruto, que se purificó mediante columna para proporcionar el compuesto del título (800 mg) como un aceite amarillo. ESI-MS m/z $[M+H]^+$ 427.1.

Preparación 34 2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-isopropilpirido[3,4-*b*]pirazin-3-amina

A un matraz cargado con 3-cloro-2-(4-(2,4-difluorobencil)piperazin-1-il)pirido[3,4-*b*]pirazina (2.34 g, 6.23 mmol) y fluoruro de potasio (0.470 g, 8.09 mmol) en DMSO (12 mL) se agregó DIPEA (2.169 mL, 12.45 mmol) y propan-2-amina (1.605 mL, 18.68 mmol) a 23 °C. La reacción se agitó a 23 °C durante 22 hr y se diluyó con agua (48 mL) para proporcionar un lodo anaranjado aceitoso. El producto en bruto se extrajo con EtOAc (25 mL) para proporcionar a suspensión. El sólido resultante se filtró, se lavó con

EtOAc, y el filtrado se dejó separar en dos capas. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró, se lavó con EtOAc, y se secó al vacío. El material en bruto se disolvió en tolueno (5 mL) y se purificó mediante cromatografía de media presión utilizando un gradiente de elución de 20% a 100% de EtOAc en heptano en una columna NH 60 µM, tamaño 400 (Shoko Scientific Purif-Pack™) para proporcionar el compuesto del título (1.489 g, 60.0%) como un sólido amarillo. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.24 (d, J = 6.4 Hz, 6H), 2.62 (t, J = 4.9 Hz, 4H), 3.34-3.41 (m, 4H), 3.59 (s, 2H), 4.22-4.42 (m, 1H), 6.46 (d, J = 7.8 Hz, 1H), 7.04-7.17 (m, 1H), 7.22 (td, J = 10.0, 2.4 Hz, 1H), 7.40-7.44 (m, 1H), 7.49 (td, J = 8.5, 6.8 Hz, 1H), 8.27 (d, J = 5.9 Hz, 1H), 8.76 (s, 1H); ESI-MS m/z $[M+H]^+$ 399.0.

Preparación 35 *N*-ciclobutil-2-(4-(2,4-difluorobencil)piperazin-1-il)pirido[3,4-*b*]pirazin-3-amina

Se combinaron 3-cloro-2-(4-(2,4-difluorobencil)piperazin-1-il)pirido[3,4-*b*]pirazina (0.7226 g, 1.923 mmol), ciclobutanamina (0.493 mL, 5.77 mmol), y fluoruro de potasio (0.145 g, 2.500 mmol) en DMSO (7.2 mL) y DIPEA (0.670 mL, 3.85 mmol) a 23 °C. La reacción se agitó a 23 °C durante 16 hr y se diluyó con agua (30 mL) para proporcionar una suspensión amarilla-anaranjada. El sólido resultante se filtró, se lavó con agua, y se secó al vacío para proporcionar el compuesto del título (0.62 g, 79%) como un sólido amarillo. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.68-1.77 (m, 2H), 2.12 (quinteto d, J = 9.3, 2.7 Hz, 2H), 2.27-2.35 (m, 2H), 2.56-2.68 (m, 4H), 3.35-3.42 (m, 4H), 3.60 (s, 2H), 4.57 (sexteto, J = 8.0 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 7.06-7.12 (m, 1H), 7.22 (td, J = 9.9, 2.7 Hz, 1H), 7.43 (d, J = 5.4 Hz, 1H), 7.46-7.53 (m, 1H), 8.27 (d, J = 5.4 Hz, 1H), 8.76 (s, 1H); ESI-MS m/z $[M+H]^+$ 411.0.

Preparación 36 6-bencil-3-cloro-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina

Una mezcla de 3-cloro-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)pirido[3,4-*b*]pirazina (93 mg, 0.239 mmol) y (bromometil)benceno (29 µL, 0.239 mmol) en ACN (1.2 mL) se calentó a 80 °C durante 14 h. Después de que la mezcla se enfrió a temperatura ambiente, se agregó triacetoxiborohidruro de sodio (152 mg, 0.718 mmol) a la

mezcla a temperatura ambiente. Después de 1 h, salmuera (1 mL) se agregó a la mezcla. Después de que cesó el burbujeo, la mezcla se purificó directamente mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (71.2 mg, 49.9%) como un aceite amarillo. ESI-MS m/z $[M+H]^+$ 483.3.

Preparación 37 3-cloro-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina

El compuesto del título como una sal TFA (30.9 mg, 24,8 %) se preparó de manera similar a la Preparación 38 utilizando yodometano. ESI-MS m/z $[M+H]^+$ 407.3.

Preparación 39 6-bencil-3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina

Una mezcla de hidrocloruro de 4-((2,4-difluorofenil)fluorometil)piperidina (247 mg, 0.929 mmol), 2,3-dicloropirido[3,4-*b*]pirazina (169 mg, 0.845 mmol) y DIPEA (441 µL, 2.53 mmol) en DCM (1.69 mL) se agitó a 0 °C durante 5 min y a temperatura ambiente durante 30 min. La mezcla se repartió entre EtOAc y NH_4Cl acuoso saturado. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se evaporó. El residuo se disolvió en EtOAc y se filtró a través de una almohadilla de sílice. El filtrado se concentró para proporcionar 3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)pirido[3,4-*b*]pirazina (338.4 mg) como una espuma amarilla. ESI-MS m/z $[M+H]^+$ 393.2.

Una mezcla de bromuro de 3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)pirido[3,4-*b*]pirazina (338.4 mg, 0.861 mmol)bencilo (103 µL, 0.861 mmol) en ACN (4,31 mL) se calentó a 80 °C durante 14 h. Después de que la mezcla se enfrió a temperatura ambiente, se agregó triacetoxiborohidruro de sodio (548 mg, 2.58 mmol). Después de 1 h, se agregó salmuera (1 mL) a la mezcla. Después de que cesó el burbujeo, la mezcla se purificó directamente mediante HPLC Método A para proporcionar el compuesto del título como su sal TFA (141.7 mg, 27.4%) como un aceite anaranjado. ESI-MS m/z $[M+H]^+$ 487.3.

Preparación 40 6-bencil-3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina

Se combinaron 2,3-dicloro-5-metilpirido[3,4-*b*]pirazina (1 g, 4,67 mmol), DIPEA (2.04 mL, 11.68 mmol), y hidrocloruro de 4-(2,4-difluorofenoxi)piperidina (1.225 g, 4,91 mmol) en DCM (9.34 mL) en un baño de hielo y se calentaron a temperatura ambiente durante la noche. La mezcla de reacción se vertió en NaOH 1 M, se extrajo con EtOAc (2x), se filtró a través $MgSO_4$, se concentró al vacío y se purificó mediante HPLC Método A para proporcionar 3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metilpirido[3,4-*b*]pirazina como una sal TFA (1.6 g).

Se combinaron 3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metilpirido[3,4-*b*]pirazina (400 mg, 1.024 mmol) y bromuro de bencilo (122 µL, 1.024 mmol) en ACN (5.12 mL) y se calentó a 90 °C durante la noche. La mezcla de reacción se enfrió a temperatura ambiente, se agregó triacetoxiborohidruro de sodio (651 mg, 3.07 mmol), y la mezcla de reacción se agitó durante la noche. La reacción en bruto se vertió en NaOH 1 M, se extrajo con EtOAc (2x), se filtró a través $MgSO_4$, se concentró al vacío y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (150 mg).

Preparación 41 6-bencil-3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina

Se purificó bromuro de bencilo mediante el pasaje a través de un tapón de alúmina básica antes de usarse. Una solución de 3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazina (736.2 mg, 1.954 mmol) en ACN (9.77 mL) se dividió en dos porciones iguales. Cada solución se trató con media porción de bromuro de bencilo (232 µL, 1.954 mmol) y se agitó a 80 °C durante 3 h. Las mezclas de reacción se dejaron enfriar a temperatura ambiente, y cada solución se trató con media porción de triacetoxiborohidruro de sodio (1.242 g, 5.86 mmol). Las mezclas de reacción se agitaron a temperatura ambiente durante 1 h, posteriormente se desactivaron con NaCl acuoso saturado. Las mezclas de reacción se combinaron y se repartió entre EtOAc con Et_2O agregado para ayuda en la separación de fases y NaCl acuoso

saturado. La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró bajo presión reducida. El residuo se purificó mediante cromatografía ultrarrápida de gel de sílice utilizando a 20% a 60% gradiente de EtOAc en heptanos proporcionó el compuesto del título (522.2 mg, 56.8%). ESI-MS m/z $[M+H]^+$ 471.4.

Preparación 42 4-((1-(6-bencil-3-cloro-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo

Se purificó bromuro de bencilo mediante filtración a través de un tapón de alúmina básica antes de usarse. Una solución de 4-((1-(3-cloropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo (200 mg, 0.521 mmol) y bromuro de bencilo (0.062 mL, 0.521 mmol) en ACN (2.60 mL) se calentó a 80 °C durante 3 h. La mezcla de reacción se dejó enfriar a temperatura ambiente y se agregó triacetoxiborohidruro de sodio (331 mg, 1.563 mmol). Después de agitarse durante 1 h a temperatura ambiente, la mezcla de reacción se inactivó con NaCl acuoso saturado (1 mL). Después de que cesó el burbujeo, la mezcla de reacción se purificó mediante HPLC Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente de 35% a 70% ACN para proporcionar el compuesto del título, como una sal TFA, como un aceite amarillo (117.9 mg, 38.2%). ESI-MS m/z $[M+H]^+$ 478.5.

Preparación 43 (*R*)-6-bencil-3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina

El compuesto del título se preparó de manera similar a la Preparación 44 utilizando (*R*)-3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)pirido[3,4-*b*]pirazina. El producto se purificó dos veces mediante cromatografía ultrarrápida de gel de sílice utilizando un gradiente de 10% a 60% de EtOAc en heptanos. ESI-MS m/z $[M+H]^+$ 487.4.

Preparación 45 (*S*)-6-bencil-3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina

El compuesto del título se preparó de manera similar a la Preparación 46 utilizando (*S*)-3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)pirido[3,4-

b]pirazina. El producto se purificó dos veces mediante cromatografía ultrarrápida de gel de sílice utilizando un gradiente de 10% a 50% de EtOAc en heptanos. ESI-MS m/z $[M+H]^+$ 487.3.

Preparación 47 6-bencil-*N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una solución de 6-bencil-3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina (261.1 mg, 0.554 mmol) y 2,2-difluoroetanamina (156 µL, 2.22 mmol) en tolueno (1.85 mL) se trató con terc-butóxido de sodio (107 mg, 1.11 mmol), BINAP (69.0 mg, 0.111 mmol), y $Pd_2(dba)_3$ (50.8 mg, 0.055 mmol). Se insufló gas nitrógeno (balón) a través de la mezcla de reacción durante 5 min. La mezcla de reacción se tapó y se agitó at 90 °C durante la noche. La mezcla de reacción se dejó enfriar a temperatura ambiente y se expuso al ambiente, y la solución se concentró bajo presión reducida. El residuo se recogió en MeOH, se filtró, y se purificó mediante HPLC Método B utilizando un gradiente ACN de 35% a 60% para proporcionar el compuesto del título, como una sal TFA, como un aceite amarillo (181.2 mg, 51.9%). ESI-MS m/z $[M+H]^+$ 516.4.

Preparación 48 6-bencil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

A una suspensión amarilla-anaranjada de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropilpirido[3,4-*b*]pirazin-3-amina (5.1 g, 12.77 mmol) en ACN (63.8 mL) se agregó bromuro de bencilo (2.184 g, 12.77 mmol) durante 1 minuto a 23 °C. La mezcla se agitó a 80 °C durante 4 h para proporcionar una solución roja-marrón, se enfrió a 23 °C, y se concentró mediante un evaporador rotatorio para proporcionar 6-bencil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)pirido[3,4-*b*]pirazin-6-io bromuro (7.30 g) como un sólido rojo-marrón, que se utilizó directamente en la siguiente etapa sin purificación adicional.

A una solución de bromuro de 6-bencil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)pirido[3,4-*b*]pirazin-6-io (7.2 g, 12.62 mmol) en DCM (126 ml) se agregó $NaBH(OAc)_3$ (16.05 g, 76 mmol). La solución resultante se agitó a temperatura ambiente durante 3 días. Después de DCM

se eliminó al vacío, se agregó EtOAc (200 mL) para re disolver el residuo. Posteriormente se agregó $NaHCO_3$ saturado (150 mL) y la mezcla se agitó vigorosamente durante 30 min. La capa orgánica se lavó con agua (50 mL) y salmuera (50 mL), y se secó con Na_2SO_4 anhidro durante la noche. La eliminación del solvente proporcionó el compuesto del título (6.43 g) como un sólido amarillo, que se utilizó sin purificación adicional. ESI-MS m/z $[M+H]^+$ 494,10.

Preparación 50 6-bencil-*N*-ciclobutil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

El compuesto del título como una sal TFA se preparó de manera similar a la Preparación 51 utilizando ciclobutanamina en lugar de 2,2-difluoroetanamina y HPLC Método A. ESI-MS m/z $[M+H]^+$ 506.00.

Preparación 52 (*S*)-6-bencil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-(1-metoxipropan-2-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

El compuesto del título como una sal TFA se preparó de manera similar a la Preparación 53 utilizando (*S*)-1-metoxipropan-2-amina en lugar de 2,2-difluoroetanamina y HPLC Método A. ESI-MS m/z $[M+H]^+$ 524.00.

Preparación 54 (*R*)-6-bencil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-(1-metoxipropan-2-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

El compuesto del título como una sal TFA se preparó de manera similar a la Preparación 55 utilizando (*R*)-1-metoxipropan-2-hidrocloruro de amina en lugar de 2,2-difluoroetanamina y HPLC Método A. ESI-MS m/z $[M+H]^+$ 524.00.

Preparación 56 (*S*)-6-bencil-*N*-(*sec*-Butil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

El compuesto del título como una sal TFA se preparó de manera similar a la Preparación 57 utilizando (*S*)-butan-2-amina en lugar de 2,2-difluoroetanamina y HPLC Método A. ESI-MS m/z $[M+H]^+$ 508.00.

Preparación 58 (*R*)-6-bencil-*N*-(*sec*-Butil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

El compuesto del título como una sal TFA se preparó de manera similar a la Preparación 59 utilizando (*R*)-butan-2-

amina en lugar de 2,2-difluoroetanamina y HPLC Método A. ESI-MS m/z $[M+H]^+$ 508.00.

Preparación 60 4-((1-(6-bencil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo

Una solución de sal TFA de 4-((1-(6-bencil-3-cloro-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo (213.9 mg, 0.361 mmol) en tolueno (1.44 mL) se trató con propan-2-amina (0.118 mL, 1.445 mmol), terc-butóxido de sodio (69.4 mg, 0.723 mmol), BINAP (22.5 mg, 0.036 mmol), y $Pd_2(dba)_3$ (16.5 mg, 0.018 mmol). Se insufló gas nitrógeno a través de la solución durante 5 min. La mezcla de reacción se tapó y la mezcla de reacción se calentó hasta 90 °C durante la noche. La mezcla de reacción se dejó enfriar a temperatura ambiente. El solvente se eliminó bajo presión reducida y el residuo se purificó mediante HPLC Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente de 40% a 70% ACN para proporcionar el compuesto del título, como una sal TFA, como un aceite amarillo (105 mg, 47.3%). ESI-MS m/z $[M+H]^+$ 501.5.

Preparación 61 (*R*)-6-bencil-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una solución de (*R*)-6-bencil-3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina (293 mg, 0.602 mmol) y propan-2-amina (197 µL, 2.407 mmol) en tolueno (2.01 mL) se trató con terc-butóxido de sodio (116 mg, 1.203 mmol), BINAP (74,9 mg, 0.120 mmol), y $Pd_2(dba)_3$ (55.1 mg, 0.060 mmol). Se insufló gas nitrógeno (balón) a través de la mezcla de reacción durante 5 min. La mezcla de reacción se tapó y la mezcla de reacción se agitó a 90 °C durante la noche. La reacción se abrió y la mezcla se concentró bajo presión reducida. El residuo se recogió en MeOH, se filtró, y se purificó mediante HPLC Método B utilizando un gradiente de 40% a 65% ACN para proporcionar el compuesto del título como una sal TFA (183.1 mg, 48.8%) como un aceite amarillo. ESI-MS m/z $[M+H]^+$ 510.4.

Preparación 62 (*S*)-6-bencil-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una solución de (*S*)-6-bencil-3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina (500 mg, 1.027 mmol) y propan-2-amina (350 µL, 4,11 mmol) en tolueno (3.42 mL) se trató con terc-butóxido de sodio (197 mg, 2.054 mmol), BINAP (102 mg, 0.164 mmol), y $Pd_2(dba)_3$ (75 mg, 0.082 mmol). Se insufló gas nitrógeno (balón) a través de la mezcla de reacción durante 5 min. La mezcla de reacción se tapó y se calentó a 90 °C durante 16 h. La mezcla de reacción se dejó enfriar a temperatura ambiente y se expuso al ambiente. La mezcla de reacción se concentró bajo presión reducida y se recogió en MeOH, se filtró, y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (266 mg) como un aceite anaranjado. ESI-MS m/z $[M+H]^+$ 510.4.

Preparación 63 3-fluoro-4-((1-(3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)benzonitrilo

A una solución de sal TFA de 4-((1-(6-bencil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo (98.8 mg, 0.161 mmol) en THF (1.61 mL) se agregó $Pd(OH)_2$ (20 % p, 33.9 mg, 0.048 mmol). Se insufló gas hidrógeno (balón) a través de la mezcla de reacción durante 5 min. La mezcla de reacción se dejó en agitación bajo atomósfera de hidrógeno durante 6 h. La mezcla de reacción se filtró a través de un tapón de Celite™, eluyendo con MeOH. El filtrado se recogió y se concentró bajo presión reducida. El residuo se purificó mediante HPLC Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente de 25% a 60% ACN para proporcionar el compuesto del título, como una sal TFA, como un aceite amarillo (12.8 mg), que se utilizó más adelante sin purificación adicional. ESI-MS m/z $[M+H]^+$ 411.5.

Preparación 64 *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una solución de sal TFA de 6-bencil-*N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (132.5 mg, 0.210 mmol) en THF (2.1 mL) se trató con $Pd(OH)_2$ (20 % p, 29.6 mg, 0.042 mmol). Se insufló gas hidrógeno (balón) a través de la mezcla de reacción durante 5 min. Se eliminó la aguja de ventilación y la reacción se agitó bajo atomósfera de hidrógeno durante 1 h. La mezcla de reacción se expuso al ambiente y se filtró a través de una almohadilla de Celite™, eluyendo con EtOAc y MeOH. El filtrado se concentró bajo presión reducida para proporcionar el compuesto del título como una sal TFA (114 mg), que se utilizó sin purificación adicional. ESI-MS m/z $[M+H]^+$ 426.5.

Preparación 65 *N*-ciclobutil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

El compuesto del título como una sal TFA se preparó de manera similar a la Preparación 66, salvo que la reacción se agitó bajo atomósfera de hidrógeno durante 2 h. ESI-MS m/z $[M+H]^+$ 416.5.

Preparación 67 (*R*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

El compuesto del título como una sal TFA se preparó de manera similar a la Preparación 68, salvo que la reacción se agitó bajo atomósfera de hidrógeno durante 2 h. La sal TFA se disolvió en DCM y se lavó con acuoso saturado K_2CO_3. Los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y concentraron bajo presión reducida para obtener el compuesto del título como la base libre. ESI-MS m/z $[M+H]^+$ 420.5.

Preparación 69 (*S*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

El compuesto del título como una sal TFA se preparó de manera similar a la Preparación 70. La sal TFA se disolvió en DCM y se lavó con acuoso saturado K_2CO_3. Los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y concentraron bajo presión reducida para obtener el compuesto del título como la base libre. ESI-MS m/z $[M+H]^+$ 420.5.

Preparación 71 *N*-ciclobutil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una mezcla de ciclobutanamina (49.9 µL, 0.584 mmol), 6-bencil-3-cloro-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina sal TFA de (116.2 mg, 0.195 mmol), terc-butóxido de sodio (56.1 mg, 0.584 mmol), BINAP (18.2 mg, 0.029 mmol) y $Pd_2(dba)_3$ (26.7 mg, 0.029 mmol) en tolueno (649 µL) se calentó a 90 °C en un tubo sellado durante 16 h. La mezcla se purificó directamente mediante HPLC Método A para proporcionar 6-bencil-*N*-ciclobutil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina como su sal TFA (103.4 mg, 84%) como una espuma amarilla. ESI-MS m/z $[M+H]^+$ 518.4

Una mezcla de sal TFA de 6-bencil-*N*-ciclobutil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (103.4 mg, 0.164 mmol) y $Pd(OH)_2$ sobre carbono (10 mg, 0.014 mmol) en THF (818 µL) se agitó a temperatura ambiente bajo una atmósfera de gas hidrógeno (balón) durante 4 h. La mezcla se filtró a través de una almohadilla de Celite™, se lavó con MeOH, y se concentró para proporcionar el compuesto del título como su sal TFA (89 mg, 100%) como un sólido amarillo. ESI-MS m/z $[M+H]^+$ 428.4.

Preparación 72 1-(3-(isopropilamino)-2-(piperazin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona

A un matraz cargado con 4-(6-acetil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperazina-1-carboxilato de terc-butilo (1.015 g, 2.425 mmol) se agregó HCl (4 M en dioxano, 4,85 mL, 19.40 mmol) a 23 °C. La mezcla de reacción se agitó a 23 °C durante 1 h, se diluyó con dioxano (20 mL), se filtró, se lavó con dioxano, y se secó al vacío para proporcionar la sal HCl del compuesto del título (0.861 g, 100%) como un sólido amarillo. ESI-MS m/z $[M+H]^+$ 319.5.

Preparación 73 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-N-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-b]pirazin-3-amina

Se combinaron sal TFA de 6-bencil-3-cloro-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina (280 mg, 0.467 mmol),

isopropilamina (200 µL, 2.337 mmol), $Pd_2(dba)_3$ (42.8 mg, 0.047 mmol), BINAP (58.2 mg, 0.093 mmol), y terc-butóxido de sodio (112 mg, 1.169 mmol) en tolueno (2.34 mL) y calentada a 100 °C durante 30 min bajo condiciones de microondas. La mezcla de reacción se enfrió, se concentró al vacío y se purificó mediante HPLC Método A para proporcionar 6-bencil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina como una sal TFA (175 mg) como un aceite marrón.

Un recipiente de fondo redondo de 50 mL que contenía sal TFA de 6-bencil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (175 mg, 0.282 mmol) y $Pd(OH)_2$ (20 % p, 39.5 mg, 0.056 mmol) en THF (2.82 mL) se purgó y se colocó bajo hidrógeno (balón) durante 3 h. La filtración a través Celite™ (que se lavó con EtOAc) y la concentración al vacío proporcionó el compuesto del título como una sal TFA (150 mg) como un aceite marrón.

Preparación 74 *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

El compuesto del título (98 mg) se preparó de manera similar a la Preparación 75 utilizando 2,2-difluoroetan-1-amina.

Preparación 76 (5-cloro-2-fluorofenil)(1-(3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)metanona

Una mezcla de hidrocloruro de (5-cloro-2-fluorofenil)(piperidin-4-il)metanona (153 mg, 0.550 mmol), 2,3-dicloropirido[3,4-*b*]pirazina (100 mg, 0.500 mmol) y DIPEA (261 µL, 1.500 mmol) en DCM (1.67 mL) se agitó a temperatura ambiente durante 30 min. La mezcla se repartió entre NH_4Cl acuoso y EtOAc. La capa orgánica se filtró a través de una almohadilla de sílice, se lavó con EtOAc, y el filtrado se concentró bajo presión reducida para proporcionar (5-cloro-2-fluorofenil)(1-(3-cloropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)metanona (205.5 mg) como un sólido anaranjado. ESI-MS m/z $[M+H]^+$ 405.2.

Una mezcla de (5-cloro-2-fluorofenil)(1-(3-cloropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)metanona (205.5 mg, 0.507 mmol) y bromuro de bencilo (63.7 µL, 0.532 mmol) en

ACN (1.69 mL) se calentó a 80 °C durante 4 h. Después de que la mezcla se enfrió a temperatura ambiente, triacetoxiborohidruro de sodio (537 mg, 2.54 mmol) se agregó en una porción. Después de 1 h, la mezcla se inactivó con salmuera, se extrajo con EtOAc, se concentró y se purificó mediante HPLC Método A para proporcionar (1-(6-bencil-3-cloro-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)(5-cloro-2-fluorofenil)metanona como su sal TFA (112.4 mg, 36.1%) como un aceite amarillo. ESI-MS m/z $[M+H]^+$ 499.2.

Una mezcla de propan-2-amina (31.5 µL, 0.366 mmol), sal TFA de (1-(6-bencil-3-cloro-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)(5-cloro-2-fluorofenil)metanona (112.4 mg, 0.183 mmol), terc-butóxido de sodio (35.2 mg, 0.366 mmol), BINAP (17.1 mg, 0.027 mmol) y $Pd_2(dba)_3$ (8.4 mg, 9.16 µmol) en tolueno (611 µL) se calentó a 100 °C durante 16 h. La mezcla se purificó mediante HPLC Método A para proporcionar (1-(6-bencil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)(5-cloro-2-fluorofenil)metanona como su sal TFA (41.7 mg, 35.8%) como un película amarilla. ESI-MS m/z $[M+H]^+$ 522.4.

Una mezcla de sal TFA de (1-(6-bencil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)(5-cloro-2-fluorofenil)metanona (41.7 mg, 0.066 mmol) y $Pd(OH)_2$ sobre carbono (20 % p, 5 mg, 0.036 mmol) en THF (328 µL) se agitó a temperatura ambiente bajo una atmósfera de gas hidrógeno (balón). Después de 3 h, la mezcla se diluyó con MeOH, se filtró a través de una almohadilla de Celite™, se lavó con MeOH, y se concentró para proporcionar el compuesto del título como su sal TFA (36 mg, 100%) como un película amarilla, que se utilizó sin purificación adicional. ESI-MS m/z $[M+H]^+$ 432.3.

Preparación 77 3-cloro-*N*-isopropilpirido[3,4-*b*]pirazin-2-amina

A una solución de 2,3-dicloropirido[3,4-*b*]pirazina (2.5 g, 12.50 mmol) y DIPEA (6.53 mL, 37.5 mmol) en DCM (25 mL) se agregó propan-2-amina (1.065 mL, 12.50 mmol) a 0 °C. La mezcla se agitó a 0 °C durante 30 min, se calentó lentamente a 23 °C, y se agitó durante 12 h. La mezcla bruta se repartió entre EtOAc (100 mL) y NH_4Cl acuoso saturado (100 mL). Las capas se separaron y la fase acuosa se lavó con EtOAc (4 x 100 mL). Los extractos orgánicos se combinaron, se lavaron

con salmuera (50 mL), se secó sobre Na_2SO_4, se filtró, se lavó con EtOAc, y se secó al vacío. El material en bruto se disolvió en tolueno (5 mL) y se purificó mediante cromatografía de media presión utilizando un gradiente de elución de 50% a 75% EtOAc en heptano en una columna de gel de sílice de 80 g (Single Step™) para proporcionar el compuesto del título (1.828 g, 65.7%) como un sólido amarillo-anaranjado. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.28 (d, J = 6.6 Hz, 6H), 4.39-4.49 (m, 1H), 7.49 (dd, J = 5.8, 0.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 8.52 (d, J = 5.6 Hz, 1H), 8.95 (d, J = 0.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 223.1.

Preparación 78 3-cloro-*N*-ciclopropilpirido[3,4-*b*]pirazin-2-amina

Una solución de 2,3-dicloropirido[3,4-*b*]pirazina (3.55 g, 17.75 mmol) en dioxano (71.0 mL) a temperatura ambiente se trató con ciclopropanamina (1.63 mL, 23.07 mmol), seguido de la adición por goteo de DIPEA (6.51 mL, 37.3 mmol). La mezcla de reacción resultante se agitó a temperatura ambiente durante 12 h. La purificación mediante cromatografía ultrarrápida de gel de sílice utilizando un gradiente de 25% a 100% EtOAc en hexanos proporcionó el compuesto del título (3.15 g, 80%) como un sólido anaranjado. ESI-MS m/z $[M+H]^+$ 221.1.

Preparación 79 3-cloro-*N*-(2,2-difluoroetil)pirido[3,4-*b*]pirazin-2-amina

Una solución de 2,3-dicloropirido[3,4-*b*]pirazina (50 mg, 0.250 mmol) en dioxano (250 µL) se trató con 2,2-difluoroetanamina (21.0 µL, 0.275 mmol) y DIPEA (131 µL, 0.750 mmol). La mezcla de reacción resultante se agitó a 70 °C durante 1 h y posteriormente se purificó mediante cromatografía ultrarrápida de gel de sílice utilizando un gradiente de 0% a 60% EtOAc en hexanos para proporcionar el compuesto del título (52 mg, 85%) como un sólido amarillo claro.

Preparación 80 6-bencil-3-cloro-*N*-ciclopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una mezcla de 3-cloro-*N*-ciclopropilpirido[3,4-*b*]pirazin-2-amina (301.8 mg, 1.368 mmol) y (bromometil)benceno (170 µL, 1.436 mmol) en ACN (4,5 mL) se calentó a 80 °C durante 3 h. Se agregó triacetoxiborohidruro de sodio (1449 mg, 6.8 mmol) a la mezcla a temperatura ambiente. Después de 30 min,

salmuera se agregó a la mezcla. Después de agitarse durante 1 h. Las capas se separaron y la capa orgánica se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (290.6 mg, 49.5%) como un sólido amarillo. ESI-MS m/z $[M+H]^+$ 315.2.

Preparación 81 3-cloro-*N*-ciclopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

El compuesto del título como una sal TFA (22 mg, 17.2 %) se preparó de manera similar a la Preparación 82 utilizando yodometano. ESI-MS m/z $[M+H]^+$ 239.2.

Preparación 83 6-bencil-3-cloro-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

El compuesto del título como una sal TFA (240 mg, 41.3%) se preparó de manera similar a la Preparación 84 utilizando 3-cloro-*N*-isopropilpirido[3,4-*b*]pirazin-2-amina. ESI-MS m/z $[M+H]^+$ 317.3.

Preparación 85 6-bencil-3-cloro-*N*-(2,2-difluoroetil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una solución de 3-cloro-*N*-(2,2-difluoroetil)pirido[3,4-*b*]pirazin-2-amina (200 mg, 0.818 mmol) y bromuro de bencilo (99 µL, 0.818 mmol) en ACN (4,09 mL) se agitó a 80 °C durante 3 h, posteriormente la mezcla de reacción se enfrió a temperatura ambiente y se trató con triacetoxihidroborato de sodio (520 mg, 2.453 mmol). Después de 1 h, la solución se vertió en NaOH 0.5 M y se extrajo dos veces con EtOAc. Los extractos se combinaron, se concentraron, se diluyeron en DMF, se filtraron a través de un filtro PTFE 0.45 µm hidrófobo (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (150 mg, 40.5%).

Preparación 86 6-bencil-*N*-(terc-butil)-3-cloro-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

N-(terc-butil)-3-cloropirido[3,4-*b*]pirazin-2-amina

Se combinaron 2,3-dicloropirido[3,4-*b*]pirazina (1 g, 5.00 mmol) y DIPEA (1.75 mL, 10.00 mmol) en DCM (10.00 mL) y se enfrió a 0 °C y se agregó terc-butilamina (1.590 mL, 15.00 mmol) y se agitó durante 48 h. La mezcla de reacción se vertió en acuoso saturado NH_4Cl y se extrajo dos veces con EtOAc. Los extractos orgánicos se combinaron, se filtraron a través $MgSO_4$, y se concentraron al vacío. El residuo se re disolvió en EtOAc, se filtró a través de un tapón de una

pulgada de sílice, se lavó con EtOAc, y se concentró lo que proporcionó *N*-(terc-butil)-3-cloropirido[3,4-*b*]pirazin-2-amina (1.04 g, 88%).

Una solución de *N*-(terc-butil)-3-cloropirido[3,4-*b*]pirazin-2-amina (200 mg, 0.845 mmol) y bromuro de bencilo (145 mg, 0.845 mmol) en ACN (4,22 mL) se calentó hasta 80 °C durante 3 h. La reacción se enfrió y se agregó triacetoxiborohidruro de sodio (537 mg, 2.53 mmol). Después de 1 h, la reacción se vertió en NaOH 0.5 M y se extrajo dos veces con EtOAc. Los extractos se combinaron, concentraron, y se purificaron mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (125 mg, 33.3%).

Preparación 87 6-bencil-3-(4-((2-fluorofenil)sulfonil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una suspensión de 6-bencil-3-cloro-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (117.2 mg, 0.370 mmol) e hidrocloruro de 4-((2-fluorofenil)sulfonil)piperidina (124 mg, 0.444 mmol) en tolueno (1.85 mL) se trató con terc-butóxido de sodio (107 mg, 1.110 mmol), BINAP (34,6 mg, 0.055 mmol), y $Pd_2(dba)_3$ (16.9 mg, 0.018 mmol). Se insufló gas nitrógeno (balón) a través de la mezcla de reacción durante 5 min. La mezcla de reacción se tapó y se calentó a 90 °C durante 18 h. La mezcla de reacción se expuso al ambiente y se concentró bajo presión reducida. El residuo se recogió en DMF/MeOH, se filtró a través de un filtro jeringa de 0.45 µm, y se purificó mediante HPLC Método A para proporcionar el compuesto del título (99.7 mg, 42.3%). ESI-MS m/z $[M+H]^+$ 523.90.

Preparación 88 6-bencil-*N*-ciclopropil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una mezcla de hidrocloruro de 4-(2-fluoro-4-metoxifenoxi)piperidina (73.2 mg, 0.280 mmol), sal TFA de 6-bencil-3-cloro-*N*-ciclopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (100 mg, 0.233 mmol), terc-butóxido de sodio (67.2 mg, 0.700 mmol), BINAP (21.8 mg, 0.035 mmol) y $Pd_2(dba)_3$ (10.7 mg, 0.012 mmol) en tolueno (1.2 mL) se calentó a 90 °C durante 14 h. La mezcla se purificó directamente mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (114,2 mg, 97%) como una espuma

amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.53-0.60 (m, 2H), 0.78-0.85 (m, 2H), 1.84 - 1.95 (m, 2H), 1.99-2.09 (m, 2H), 2.65-2.73 (m, 1H), 2.90-2.98 (m, 1H), 3.08-3.23 (m, 3H), 3.33 - 3.42 (m, 2H), 3.55-3.68 (m, 2H), 3.75 (s, 3H), 4.16-4.24 (m, 1H), 4.28-4.40 (m, 2H), 4.50-4.59 (m, 2H), 6.67 (s, 1H), 6.73 (dd, *J* = 12.9, 3.0 Hz, 1H), 7.01-7.09 (m, 1H), 7.52-7.61 (m, 5H); ESI-MS m/z $[M+H]^+$ 504.4.

Preparación 88 6-bencil-*N*-ciclopropil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una mezcla de ciclopropanamina (27.2 mg, 0.477 mmol), sal TFA de 6-bencil-3-cloro-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina (71.2 mg, 0.119 mmol), terc-butóxido de sodio (22.9 mg, 0.239 mmol), BINAP (11.1 mg, 0.018 mmol) y $Pd_2(dba)_3$ (5.5 mg, 5.96 µmol) en tolueno (400 µL) se calentó a 90 °C durante 14 h. La mezcla se purificó directamente mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (49.2 mg, 66.8%) como un sólido amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.50-0.55 (m, 2H), 0.76 (dd, *J* = 7.0, 1.9 Hz, 2H), 1.86-1.96 (m, 2H), 2.01-2.10 (m, 2H), 2.63 (tt, *J* = 7.0, 3.6 Hz, 1H), 2.93-3.01 (m, 2H), 3.07 (s a, 2H), 3.34-3.41 (m, 2H), 3.56 (s a, 2H), 3.75 (s, 3H), 4.23 (s a, 2H), 4.30-4.37 (m, 1H), 4.53 (s a, 2H,) 6.63-6.68 (m, 1H), 6.73 (dd, *J* = 12.8, 2.9 Hz, 1H), 7.05 (t, *J* = 9.2 Hz, 1H), 7.52-7.61 (m, 5H); ESI-MS m/z $[M+H]^+$ 504.4.

Preparación 90 *N*-ciclopropil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una mezcla de 6-bencil-*N*-ciclopropil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina sal TFA de (5 mg, 8.10 µmol) y $Pd(OH)_2$ sobre carbono, (20 % p, 1 mg, 7.12 µmol) en THF (80 µL) se agitó bajo atmósfera de gas hidrógeno (balón) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (4,6 mg, 100 %) como un película amarilla; ESI-MS m/z $[M+H]^+$ 414,4.

Preparación 91 *N*-ciclopropil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una mezcla de 6-bencil-*N*-ciclopropil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina sal TFA de (46.8 mg, 0.076 mmol) y $Pd(OH)_2$ sobre carbono (20 % p, 5 mg, 0.036 mmol) en THF (760 µL) se agitó bajo una atmósfera de gas hidrógeno (balón) a temperatura ambiente. Después de 2 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (39.6 mg, 99 %) como un aceite amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.52-0.59 (m, 2H), 0.75-0.83 (m, 2H), 1.84-1.97 (m, 2H), 2.02-2.12 (m, 2H), 2.64-2.71 (m, 1H), 2.93-3.16 (m, 4H), 3.35 (s, 2H), 3.52-3.63 (m, 2H), 3.75 (s, 3H), 4.20-4.31 (m, 2H), 4.32-4.40 (m, 1H), 6.63-6.69 (m, 1H), 6.73 (dd, *J* = 12.9, 3.0 Hz, 1H), 7.03-7.10 (m, 1H); ESI-MS m/z $[M+H]^+$ 414.3.

Preparación 92 6-bencil-*N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una mezcla de hidrocloruro de 4-((2,4-difluorofenil)fluorometil)piperidina (101 mg, 0.381 mmol), 6-bencil-3-cloro-*N*-ciclopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (100 mg, 0.318 mmol), terc-butóxido de sodio (92 mg, 0.953 mmol), BINAP (29.7 mg, 0.048 mmol) y $Pd_2(dba)_3$ (14,5 mg, 0.016 mmol) en tolueno (1.6 mL) se calentó a 90 °C durante 14 h. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (135.9 mg, 68.8%) como un aceite amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.55 (dt, *J* = 3.5, 1.4 Hz, 2H), 0.77-0.84 (m, 2H), 1.35-1.43 (m, 1H), 1.50-1.71 (m, 2H), 1.91-2.11 (m, 2H), 2.56-2.72 (m, 3H), 3.06-3.15 (m, 2H), 3.36-3.51 (m, 3H), 3.52-3.76 (m, 1H), 4.17 (s a, 2H), 4.52 (s, 2H), 5.50 (dd, *J* = 46.2, 7.6 Hz, 1H) 6.96-7.07 (m, 2H), 7.44-7.60 (m, 6H); ESI-MS m/z $[M+H]^+$ 508.4.

Preparación 93 91 6-bencil-*N*-ciclopropil-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una mezcla de ciclopropanamina (65 µL, 0.943 mmol), sal TFA de 6-bencil-3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-b]pirazina (141.7 mg, 0.236 mmol), terc-butóxido de sodio (45.3 mg, 0.472 mmol), BINAP (22.0 mg, 0.035 mmol), y $Pd_2(dba)_3$ (10.8 mg, 0.012 mmol) en tolueno (800

µL) se calentó a 90 °C durante 14 h. La mezcla se purificó directamente mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (98.1 mg, 66.9%) as aceite amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.48-0.54 (m, 2H), 0.71-0.78 (m, 2H), 1.36-1.45 (m, 1H), 1.50-1.72 (m, 2H), 1.92-2.12 (m, 2H), 2.57-2.71 (m, 3H), 2.97-3.10 (m, 2H), 3.39-3.55 (m, 3H), 3.75-3.89 (m, 1H), 4.22 (s a, 2H), 4.53 (s a, 2H), 5.50 (dd, *J* = 46.5, 7.6 Hz, 1H), 6.96-7.07 (m, 2H), 7.45-7.61 (m, 6H); ESI-MS m/z $[M+H]^+$ 508.4.

Preparación 94 *N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una mezcla de 6-bencil-*N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina sal TFA de (132.1 mg, 0.213 mmol) y $Pd(OH)_2$ (20 % p, 15 mg, 0.021 mmol) en THF (1.0 mL) se agitó a temperatura ambiente bajo atmósfera de gas hidrógeno (balón). Después de 2 h, la mezcla se purificó directamente mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (91.1 mg, 81%) como un aceite amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.55-0.61 (m, 2H), 0.80-0.86 (m, 2H), 1.41 (d a, *J* = 12.4 Hz, 1H), 1.52-1.73 (m, 2 H), 1.93-2.13 (m, 2H), 2.60-2.73 (m, 3H), 3.05 (t, *J* = 6.3 Hz, 2H), 3.39-3.52 (m, 2H), 3.55 (t, *J* = 6.3 Hz, 2H), 3.98 (s, 1H), 4.17 (s, 2H), 5.51 (dd, *J* = 46.7, 7.6 Hz, 1H), 6.97-7.08 (m, 2H), 7.45-7.54 (m, 1H); ESI-MS m/z $[M+H]^+$ 418.3.

Preparación 95 *N*-ciclopropil-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una mezcla de 6-bencil-*N*-ciclopropil-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina sal TFA de (93.5 mg, 0.150 mmol) y $Pd(OH)_2$ (20 %p, 10 mg, 0.014 mmol) en THF (750 µL) se agitó a temperatura ambiente bajo una atmósfera de gas hidrógeno (balón). Después de 2 h, la mezcla se purificó directamente mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (67.7 mg, 85%) como un aceite amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.51-0.57 (m, 2H), 0.75-0.81 (m, 2H), 1.43 (d a, *J* = 13.1 Hz, 1H), 1.52-1.72 (m, 2H), 1.94-2.13 (m, 2H), 2.59-2.72 (m, 3H), 2.97

(t, *J* = 6.3 Hz, 2H), 3.40-3.50 (m, 2H), 3.51-3.56 (m, 2H), 3.98 (s, 1H), 4.22 (s, 2H), 5.51 (dd, *J* = 46.2, 7.3 Hz, 1H), 6.96-7.08 (m, 2H), 7.46-7.54 (m, 1H); ESI-MS m/z $[M+H]^+$ 418.3.

Preparación 96 6-bencil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una mezcla de hidrocloruro de 4-(2-fluoro-4-metoxifenoxi)piperidina (72.9 mg, 0.279 mmol), 6-bencil-3-cloro-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina sal TFA de (100 mg, 0.232 mmol), terc-butóxido de sodio (66.9 mg, 0.696 mmol), BINAP (21.7 mg, 0.035 mmol), y $Pd_2(dba)_3$ (10.6 mg, 0.012 mmol) en tolueno (1.16 mL) se calentó a 100 °C en un tubo sellado durante 14 h. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (122.1 mg, 85%) como un sólido amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.24 (d, *J* = 6.6 Hz, 6H), 1.86-1.97 (m, 2H), 2.03-2.12 (m, 2H), 2.95 (s a, 2H), 3.01-3.12 (m, 2H), 3.33-3.38 (m, 2H), 3.53 (s a, 2H), 3.75 (s, 3H), 4.13-4.24 (m, 3H), 4.31-4.38 (m, 1H), 4.52 (s, 2H), 6.63-6.69 (m, 1H), 6.73 (dd, *J* = 12.8, 2.9 Hz, 1H), 7.06 (t, *J* = 9.2 Hz, 1H), 7.51-7.60 (m, 5H); ESI-MS m/z $[M+H]^+$ 506.4.

Preparación 97 6-bencil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una mezcla de hidrocloruro de 4-((2,4-difluorofenil)fluorometil)piperidina (74,0 mg, 0.279 mmol), 6-bencil-3-cloro-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-b]pirazin-2-amina sal TFA de (100 mg, 0.232 mmol), terc-butóxido de sodio (66.9 mg, 0.696 mmol), BINAP (21.7 mg, 0.035 mmol) y $Pd_2(dba)_3$ (10.6 mg, 0.012 mmol) en tolueno (1.2 mL) se calentó a 100 °C en un tubo sellado durante 14 h. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (108.3 mg, 74,8%) como un sólido amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.23 (dd, *J* = 6.4, 2.4 Hz, 6H), 1.39-1.47 (m, 1H), 1.51-1.72 (m, 2H), 1.95-2.12 (m, 2H), 2.58-2.70 (m, 2H), 3.04 (s a, 2H), 3.36-3.83 (m, 4H), 4.09-4.21 (m, 3H), 4.51 (s a, 2H), 5.52 (dd, *J* = 46.2, 7.3 Hz, 1H), 6.97-7.07 (m, 2H), 7.45-7.59 (m, 6H); ESI-MS m/z $[M+H]^+$ 510.4.

Preparación 98 3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una mezcla de sal TFA de 6-bencil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (122 mg, 0.197 mmol) y $Pd(OH)_2$ sobre carbono (20 % p, 12 mg, 0.017 mmol) en THF (2.0 mL) se agitó bajo una atmósfera de gas hidrógeno (balón) a temperatura ambiente. Después de 2 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (83.2 mg, 80%) como un aceite amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.25 (d, *J* = 6.6 Hz, 6H), 1.88-1.98 (m, 2H), 2.04-2.13 (m, 2H), 2.93-3.03 (m, 4H), 3.35-3.41 (m, 3H), 3.54 (t, *J* = 6.3 Hz, 2H), 3.76 (s, 3H), 4.14-4.18 (m, 2H), 4.18-4.23 (m, 1H), 4.32-4.40 (m, 1H), 6.67 (ddd, *J* = 9.0, 3.0, 1.4 Hz, 1H), 6.74 (dd, *J* = 12.9, 3.0 Hz, 1H), 7.07 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 416.3.

Preparación 99 3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una mezcla de sal TFA de 6-bencil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (108.3 mg, 0.174 mmol) y $Pd(OH)_2$ sobre carbono, (20 % p, 11 mg, 0.016 mmol) en THF (1.7 mL) se agitó bajo una atmósfera de gas hidrógeno (balón) a temperatura ambiente. Después de 2 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (67.5 mg, 72.9%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.24 (dd, *J* = 6.6, 2.3 Hz, 6H), 1.41-1.48 (m a, 1H), 1.52-1.74 (m, 2H), 1.97-2.14 (m, 2H), 2.61-2.73 (m, 2H), 2.99 (t, *J* = 6.3 Hz, 2H), 3.38-3.49 (m, 2H), 3.50-3.55 (m, 2H), 4.14 (s, 2H), 4.14-4.21 (m, 1H), 5.53 (dd, *J* = 46.5, 7.3 Hz, 1H), 6.95-7.10 (m, 2H), 7.46-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 420.3.

Preparación 100 6-bencil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una mezcla de propan-2-amina (71 µL, 0.827 mmol), sal TFA de 6-bencil-3-cloro-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-

b]pirazina (123.4 mg, 0.207 mmol), terc-butóxido de sodio (39.7 mg, 0.413 mmol), BINAP (19.3 mg, 0.031 mmol) y $Pd_2(dba)_3$ (9.5 mg, 10.33 µmol) en tolueno (690 µL) se calentó a 100 °C durante 16 h. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (54,7 mg, 42.7%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.22 (d, *J* = 6.6 Hz, 6H), 1.87-2.13 (m, 4H), 2.94-3.10 (m, 4H), 3.35-3.53 (m, 3H), 3.75 (s, 3H), 3.79-3.88 (m, 1H), 4.07-4.27 (m, 3H), 4.31-4.39 (m, 1H), 4.52 (s a, 2H), 6.66 (ddd, *J* = 8.9, 3.0, 1.5 Hz, 1H), 6.73 (dd, *J* = 12.9, 3.0 Hz, 1H), 7.03-7.10 (m, 1H), 7.51-7.60 (m, 5H); ESI-MS m/z $[M+H]^+$ 506.4.

Preparación 101 6-bencil-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una mezcla de propan-2-amina (82 µL, 0.954 mmol), 6-bencil-3-cloro-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina TFA (143.3 mg, 0.238 mmol), terc-butóxido de sodio (45.8 mg, 0.477 mmol), BINAP (22.3 mg, 0.036 mmol) y $Pd_2(dba)_3$ (10.9 mg, 0.012 mmol) en tolueno (800 µL) a 100 °C durante 16 h. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (63.8 mg, 42.9%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.21 (dd, *J* = 6.4, 2.4 Hz, 6H), 1.40-1.48 (m, 1H), 1.51-1.74 (m, 2H), 1.95-2.16 (m, 2H), 2.61-2.73 (m, 2H), 3.00 (s a, 2H), 3.40-3.57 (m, 3H), 4.06-4.13 (m, 2H), 4.15- 4.20 (m a, 1H), 4.51 (s a, 2H), 5.52 (dd, *J* = 46.0, 7.3 Hz, 1H), 6.97-7.08 (m, 2H), 7.46-7.62 (m, 6H); ESI-MS m/z $[M+H]^+$ 510.4.

Preparación 102 2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una mezcla de sal TFA de 6-bencil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (51 mg, 0.082 mmol) y $Pd(OH)_2$ sobre carbono (20 % p, 5 mg, 7.12 µmol) en THF (820 µL) se agitó bajo una atmósfera de gas hidrógeno (balón) a temperatura ambiente. Después de 2 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (41.2 mg, 95%) como una espuma

amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.24 (d, J = 6.6 Hz, 6H), 1.88-1.98 (m, 2H), 2.05-2.14 (m, 2H), 2.94-3.03 (m, 4H), 3.35-3.43 (m, 2H), 3.54 (t, J = 6.3 Hz, 2H), 3.76 (s, 3H), 4.10-4.21 (m, 3H), 4.32-4.39 (m, 1H), 6.67 (ddd, J = 8.9, 3.0, 1.5 Hz, 1 H), 6.74 (dd, J = 12.8, 2.9 Hz, 1H), 7.07 (t, J = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 416.3.

Preparación 103 2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una mezcla de 6-bencil-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina sal TFA de (60 mg, 0.096 mmol) y $Pd(OH)_2$ sobre carbono, (20 % p, 6 mg, 8.54 µmol) en THF (960 µL) se agitó bajo una atmósfera de gas hidrógeno (balón) a temperatura ambiente. Después de 2 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (47.6 mg, 93%) como una espuma amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.23 (dd, J = 6.4, 2.4 Hz, 6H), 1.41-1.49 (m, 1H), 1.52-1.74 (m, 2H), 1.98-2.14 (m, 2H), 2.68 (cd, J = 12.6, 2.5 Hz, 2H), 2.96 (t, J = 6.3 Hz, 2H), 3.40-3.51 (m, 2H), 3.52 (t, J = 6.3 Hz, 2H), 4.10-4.16 (m, 1H), 4.16 (s, 2H), 5.53 (dd, J = 46.5, 7.6 Hz, 1H), 6.97-7.08 (m, 2H), 7.47-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 420.3.

Preparación 104 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

Una mezcla de 6-bencil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-N-isopropil-5,6,7,8-tetrahidropirido[3,4-b]pirazin-3-amina (6.43 g, 13.03 mmol) y 10% Pd/C (640 mg) en MeOH (86 mL) bajo H_2 en un balón se agitó a temperatura ambiente durante la noche. La eliminación del solvente proporcionó el compuesto del título (4,4 g, 84%) como un aceite amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.24 (d, J = 6.4 Hz, 6H), 1.89-1.99 (m, 2H), 2.09-2.17 (m, 2H), 2.74 (t, J = 5.9 Hz, 2H), 2.95 (ddd, J = 12.3, 8.7, 3.4 Hz, 2H), 3.11 (t, J = 6.1 Hz, 2H), 3.82 (s, 2H), 4.14 (septet, J = 6.4 Hz, 1H), 4.46 (tt, J = 7.7, 3.5 Hz, 1H), 6.85-6.92 (m, 1H), 6.99 (ddd, J = 11.4, 8.4, 3.2 Hz, 1H), 7.18 (td, J = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 404.0.

Preparación 105 2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina

A una solución de 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona (0.367 g, 0.826 mmol) en MeOH (4 mL) se agregó NaOH, solución 15 % (2.201 g, 8.26 mmol) a 23 °C. La mezcla de reacción se agitó a 65 °C durante 16 hr, se enfrió a 23 °C, y se neutralizó con HCl 1N (9.5 mL) para proporcionar a suspensión. La mezcla bruta se concentró mediante un evaporador rotatorio, se enfrió a 23 °C, y se agitó durante la noche. El sólido resultante se filtró, se lavó con agua, y se secó al vacío para proporcionar el compuesto del título (253 mg, 76%) como una espuma amarilla. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.15 (d, *J* = 6.8 Hz, 6H), 2.42 (s a, 1H), 2.51-2.61 (m, 6H), 2.89-3.00 (m, 6H), 3.58 (s, 2H), 3.63 (s, 2H), 4.00-4.10 (m, 1H), 5.15 (d, *J* = 8.3 Hz, 1H), 7.04-7.11 (m, 1H), 7.21 (td, *J* = 10.0, 2.4 Hz, 1H), 7.44-7.52 (m, 1H); ESI-MS m/z $[M+H]^+$ 403.0.

Preparación 106 4-((1-(6-bencil-2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo

Una mezcla de hidrocloruro de 6-bencil-3-cloro-N-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina acetato (2.765 g, 2.93 mmol), 3-fluoro-4-(piperidin-4-iloxi)benzonitrilo (0.904 g, 3.52 mmol), terc-butóxido de sodio (1.128 g, 11.74 mmol), BINAP (0.274 g, 0.440 mmol), y $Pd_2(dba)_3$ (0.134 g, 0.147 mmol) en tolueno (25 mL) se agitó a 100 °C durante 22 h. Se agregaron porciones adicionales de BINAP (0.219 g, 0.352 mmol) y $Pd_2(dba)_3$ (0.107 g, 0.117 mmol) a un recipiente y la mezcla de reacción se agitó durante 2 días adicionales a 100 °C. La mezcla se enfrió a 23 °C, se filtró a través Celite™, se lavó con tolueno, y el filtrado se concentró mediante un evaporador rotatorio. El material en bruto se disolvió en DMSO (10 mL), se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó un Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente ACN de 30% a 70% para proporcionar el compuesto del título como una sal TFA (581 mg, 32.2% de rendimiento) como un aceite amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.05-1.33 (m, 6H), 1.81-1.96 (m,

2H), 2.08-2.18 (m, 2H), 2.84-3.00 (m, 3H), 3.01-3.17 (m, 1H), 3.18-3.32 (m, 2H), 3.33-3.46 (m, 1H), 3.65-3.77 (m, 1H), 3.95-4.06 (m, 1H), 4.08-4.30 (m, 2H), 4.43-4.57 (m, 2H), 4.80-4.87 (m, 1H), 5.91 (d, *J* = 8.1 Hz, 1H), 7.44-7.60 (m, 6H), 7.66-7.70 (m, 1H), 7.84-7.90 (m, 1H), 10.13 (s a, 1H); ESI-MS m/z $[M+H]^+$ 501.5.

Preparación 107 3-fluoro-4-((1-(2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo

Una mezcla de 4-((1-(6-bencil-2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo 2,2,2-trifluoroacetato (579 mg, 0.942 mmol) y $Pd(OH)_2$ (20 % p Pd (base seca) sobre carbono, húmedo, Degussa de tipo E101 NE/W, 198 mg, 0.283 mmol) en THF (10 mL) se agitó bajo H_2 (1.899 mg, 0.942 mmol) a 23 °C durante 4 h. La mezcla se filtró, se lavó con THF, se concentró mediante un evaporador rotatorio, y se secó al vacío para proporcionar el compuesto del título como una sal TFA (494 mg, 100%) como un aceite marrón. ESI-MS m/z $[M+H]^+$ 411.4.

Preparación 108 (5-cloro-2-fluorofenil)(1-(2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)metanona

Una mezcla de hidrocloruro de (5-cloro-2-fluorofenil)(piperidin-4-il)metanona (69.7 mg, 0.251 mmol), sal TFA de 6-bencil-3-cloro-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (90 mg, 0.209 mmol), terc-butóxido de sodio (60.2 mg, 0.627 mmol), BINAP (19.5 mg, 0.031 mmol) y $Pd_2(dba)_3$ (9.6 mg, 10.4 µmol) en tolueno (1.04 mL) se calentó a 100 °C durante 16 h. La mezcla se purificó mediante HPLC Método A para proporcionar (1-(6-bencil-2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)(5-cloro-2-fluorofenil)metanona como su sal TFA (48.9 mg, 36.8%) como un aceite amarillo. ESI-MS m/z $[M+H]^+$ 523.4.

Una mezcla de (1-(6-bencil-2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)(5-cloro-2-fluorofenil)metanona sal TFA de (48.9 mg, 0.077 mmol) y $Pd(OH)_2$ sobre carbono (20 % p, 5 mg, 0.036 mmol) en THF (384 µL) se agitó a temperatura ambiente bajo una atmósfera de gas hidrógeno (balón). Después de 3 h, la mezcla se diluyó con

MeOH, se filtró a través de una almohadilla de Celite™, se lavó con MeOH, y se concentró para proporcionar el compuesto del título como su sal TFA (37.1 mg, 88%) como un película amarilla, que se utilizó sin purificación adicional. ESI-MS m/z $[M+H]^+$ 432.3.

Preparación 109 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una mezcla de sal TFA de hidrocloruro de 4-(2,4-difluorofenoxi)piperidina (62.6 mg, 0.251 mmol), 6-bencil-3-cloro-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (90 mg, 0.209 mmol), terc-butóxido de sodio (60.2 mg, 0.627 mmol), BINAP (19.5 mg, 0.031 mmol) y $Pd_2(dba)_3$ (9.6 mg, 10.4 µmol) en tolueno (1.04 mL) se calentó a 100 °C durante 16 h. La mezcla se purificó mediante HPLC Método A para proporcionar 6-bencil-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina como su sal TFA (73.0 mg, 57.5%) como un aceite amarillo. ESI-MS m/z $[M+H]^+$ 494.4.

Una mezcla de sal TFA de 6-bencil-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (73.0 mg, 0.120 mmol) y $Pd(OH)_2$ sobre carbono (20 % p, 7 mg, 9.97 µmol) en THF (601 µL) se agitó a temperatura ambiente bajo una atmósfera de hidrógeno (balón). Después de 3 h, la mezcla se diluyó con MeOH, se filtró a través de una almohadilla de Celite™, se lavó con MeOH, y se concentró para proporcionar el compuesto del título como su sal TFA (62.3 mg, 100%) como un aceite amarillo, que se utilizó sin purificación adicional. ESI-MS m/z $[M+H]^+$ 404.3.

Preparación 110 *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una solución de sal TFA de 6-bencil-3-cloro-*N*-(2,2-difluoroetil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (150 mg, 0.331 mmol), hidrocloruro de 4-(2,4-difluorofenoxi)piperidina (99 mg, 0.398 mmol), $Pd_2(dba)_3$ (15.2 mg, 0.017 mmol), BINAP (20.63 mg, 0.033 mmol), y terc-butóxido de sodio (96 mg, 0.994 mmol), en tolueno (1104 µL) se agitó a 90 °C durante la noche. El solvente se eliminó y el producto en bruto se diluyó en DMF, se filtró a través de

un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar 6-bencil-*N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina como una sal TFA (152 mg).

Una solución de sal TFA de 6-bencil-*N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (152 mg, 0.241 mmol) y $Pd(OH)_2$ sobre carbono (33.9 mg, 0.048 mmol) en THF (2.41 mL) se purgó con y se colocó bajo atmósfera de hidrógeno (balón) a temperatura ambiente durante 2h. La mezcla se filtró a través Celite™ y se concentró para proporcionar el compuesto del título como una sal TFA (115 mg, 0.213 mmol).

Preparación 111 *N*-(terc-butil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una solución de terc-butóxido de sodio (81 mg, 0.843 mmol), sal TFA de 6-bencil-*N*-(terc-butil)-3-cloro-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (125 mg, 0.281 mmol), $Pd_2(dba)_3$ (12.86 mg, 0.014 mmol), hidrocloruro de 4-(2,4-difluorofenoxi)piperidina (84 mg, 0.337 mmol), y BINAP (17.50 mg, 0.028 mmol) en tolueno (937 µL) se agitó a 90 °C durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar 6-bencil-*N*-(terc-butil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina como una sal TFA (155 mg).

Una solución de sal TFA de 6-bencil-*N*-(terc-butil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (155 mg, 0.249 mmol) y $Pd(OH)_2$ sobre carbono (35.0 mg, 0.050 mmol) en THF (2.49 mL) se purgó y se colocó bajo atmósfera de hidrógeno (balón) durante 2 h. La filtración a través Celite™ y concentración proporcionó el compuesto del título como una sal TFA (125 mg).

Preparación 112 *N*-ciclobutil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una mezcla de 2,3-dicloropirido[3,4-*b*]pirazina (100 mg, 0.500 mmol), ciclobutanamina (47.0 µL, 0.550 mmol) y DIPEA (260 µL, 1.500 mmol) se agitó a 0 °C durante 15 min then a temperatura ambiente durante 30 min. Se agregó NH_4Cl acuoso saturado a la mezcla y el producto se extrajo con EtOAc. Las capas orgánicas combinadas se filtraron a travésuna almohadilla de sílice (lavado EtOAc) y el filtrado se concentró para proporcionar 3-cloro-N-ciclobutilpirido[3,4-*b*]pirazin-2-amina (116.1 mg, 99%) como un sólido amarillo, que se utilizó sin purificación adicional. ESI-MS m/z $[M+H]^+$ 235.2.

Una mezcla de 3-cloro-*N*-ciclobutilpirido[3,4-*b*]pirazin-2-amina (116 mg, 0.494 mmol) y bromuro de bencilo (59.1 µL, 0.494 mmol) en ACN (2.47 mL) se calentó a 80 °C durante 3 h. Después de enfriar a temperatura ambiente, la mezcla se trató con triacetoxiborohidruro de sodio (314 mg, 1.483 mmol) a temperatura ambiente. La mezcla se purificó mediante HPLC Método A para proporcionar 6-bencil-3-cloro-*N*-ciclobutil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina como su sal TFA (135.3 mg, 61.8%) como un sólido amarillo. ESI-MS m/z $[M+H]^+$ 329.3.

Una mezcla de hidrocloruro de 4-(2-fluoro-4-metoxifenoxi)piperidina (56.7 mg, 0.217 mmol), sal TFA de 6-bencil-3-cloro-*N*-ciclobutil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (80 mg, 0.181 mmol), terc-butóxido de sodio (52.1 mg, 0.542 mmol), BINAP (16.9 mg, 0.027 mmol) y $Pd_2(dba)_3$ (24,8 mg, 0.027 mmol) en tolueno (602 µL) se calentó a 90 °C en un tubo sellado durante 16 h. La mezcla se purificó mediante HPLC Método A para proporcionar 6-bencil-*N*-ciclobutil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina como su sal TFA (85.2 mg, 74,7%) como una espuma amarilla. ESI-MS m/z $[M+H]^+$ 518.4.

Una mezcla de 6-bencil-*N*-ciclobutil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina sal TFA de (85.2 mg, 0.135 mmol) y $Pd(OH)_2$ sobre carbono (10 mg, 0.071 mmol) en THF (674 µL) se agitó a temperatura ambiente bajo una atmósfera de gas hidrógeno (balón). Después de 4 h, la mezcla se filtró, se lavó con MeOH, y se concentró para proporcionar el compuesto del título como su sal TFA (73 mg, 100%) como un sólido amarillo,

que se utilizó sin purificación adicional. ESI-MS m/z $[M+H]^+$ 428.4.

Preparación 113 *N*-ciclopropil-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

2,3-Dicloro-5-metilpirido[3,4-*b*]pirazina (1.700 g, 7.94 mmol) se agregó a dioxano (15.88 mL), posteriormente ciclopropanamina (0.864 mL, 12.71 mmol) y DIPEA (2.24 mL, 13.50 mmol) se agregaron secuencialmente. La mezcla se agitó durante 12 h a temperatura ambiente y se concentró bajo presión reducida. La cromatografía en columna utilizando un gradiente de 10% a 75% EtOAc en hexanos provided 3-cloro-*N*-ciclopropil-5-metilpirido[3,4-*b*]pirazin-2-amina (1.3 g) como un sólido marrón.

Se combinaron 3-cloro-*N*-ciclopropil-5-metilpirido[3,4-*b*]pirazin-2-amina (350 mg, 1.491 mmol) y bromuro de bencilo (177 µL, 1.491 mmol) en ACN (5.97 mL) se calentó a 80 °C durante la noche, posteriormente se enfrió a temperatura ambiente y se agregó triacetoxiborohidruro de sodio (948 mg, 4,47 mmol). Después de agitarse durante 1 h, la mezcla de reacción se vertió en NaOH 1 M, se extrajo con acetato de etilo (2x), se concentró al vacío y se purificó mediante HPLC Método A proporcionó 6-bencil-3-cloro-*N*-ciclopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina como una sal TFA (424 mg).

Se combinaron sal TFA de 6-bencil-3-cloro-*N*-ciclopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (106 mg, 0.239 mmol), hidrocloruro de 4-(2,4-difluorofenoxi)piperidina (65.7 mg, 0.263 mmol), $Pd_2(dba)_3$ (21.9 mg, 0.024 mmol), terc-butóxido de sodio (57.5 mg, 0.598 mmol), y BINAP (29.8 mg, 0.048 mmol) en tolueno (798 µL) y se calentó a 90 °C durante la noche. La purificación mediante HPLC Método A proporcionó 6-bencil-*N*-ciclopropil-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina como una sal TFA (110 mg).

Se combinaron 6-bencil-N-ciclopropil-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina sal TFA de (110 mg, 0.178 mmol) y $Pd(OH)_2$ (20 % p, 12.5 mg, 0.018 mmol) en THF (888 µL) se purgó con hidrógeno y se dejó en agitación bajo

hidrógeno (balón) durante la noche. La mezcla de reacción se filtró a través Celite™, se lavó con EtOAc, y se concentró bajo presión reducida para proporcionar el compuesto del título como una sal TFA (78 mg).

Preparación 114 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una solución de sal TFA de 6-bencil-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (150 mg, 0.241 mmol) y $Pd(OH)_2$ sobre carbono (16.9 mg, 0.024 mmol) en THF (1.21 mL) se purgó y se colocó bajo atomósfera de hidrógeno (balón) durante la noche. La mezcla se filtró a través Celite™ y se concentró para proporcionar el compuesto del título como su sal TFA (132 mg).

Preparación 115 *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una solución de 6-bencil-*N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina sal TFA de (160 mg, 0.249 mmol) y $Pd(OH)_2$ sobre carbono (17.5 mg, 0.025 mmol) en THF (1.24 mL) se purgó y se colocó bajo atomósfera de hidrógeno (balón) durante la noche. La mezcla se filtró a través Celite™ y se concentró para proporcionar el compuesto del título como su sal TFA (136 mg).

Preparación 116 *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina

Una solución de 2,3-dicloro-7-metilpirido[3,4-*b*]pirazina (125 mg, 0.584 mmol), 2,2-difluoroetanamina (53.6 µL, 0.701 mmol), y DIPEA (306 µL, 1.752 mmol) en DCM (1.17 mL) se agitó a temperatura ambiente durante 48 h, posteriormente se vertió en una solución saturada acuosa de NH_4Cl y se extrajo dos veces con EtOAc. Los extractos se combinaron, se filtraron a través de $MgSO_4$, y se concentraron para proporcionar 3-cloro-*N*-(2,2-difluoroetil)-7-metilpirido[3,4-*b*]pirazin-2-amina (143 mg, 95%).

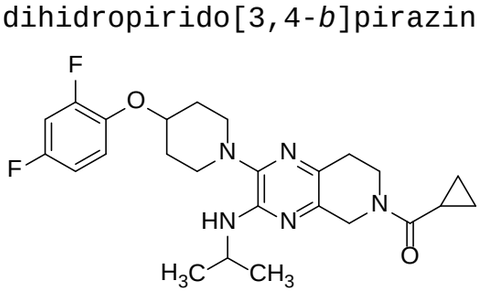
Una solución de 3-cloro-*N*-(2,2-difluoroetil)-7-metilpirido[3,4-*b*]pirazin-2-amina (143 mg, 0.553 mmol) y bromuro de bencilo (65.8 µL, 0.553 mmol) en ACN (2.76 mL) se

agitó a 100 °C durante la noche, se enfrió a temperatura ambiente, posteriormente se trató con triacetoxihidroborato de sodio (352 mg, 1.659 mmol) y se agitó durante 3 h. La mezcla se vertió en NaOH 1 M, se extrajo dos veces con EtOAc y los extractos EtOAc se combinaron y se concentraron. El material en bruto se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar 6-bencil-*N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina como una sal TFA (120 mg, 46.5%).

Una solución de sal TFA de 6-bencil-3-cloro-*N*-(2,2-difluoroetil)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (120 mg, 0.257 mmol), hidrocloruro de 4-(2,4-difluorofenoxi)piperidina (77 mg, 0.308 mmol), $Pd_2(dba)_3$ (23.5 mg, 0.026 mmol), BINAP (32.0 mg, 0.051 mmol), y terc-butóxido de sodio (74,1 mg, 0.771 mmol), en tolueno (1.28 mL) se agitó a 100 °C durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar 6-bencil-*N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina como una sal TFA (135 mg, 82 %).

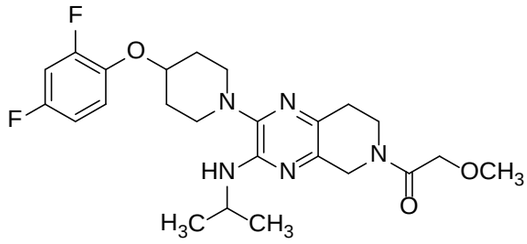
Una solución de 6-bencil-*N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina sal TFA de (135 mg, 0.210 mmol) y $Pd(OH)_2$ sobre carbono (14,7 mg, 0.021 mmol) en THF (1.05 mL) se purgó y se agitó bajo atomósfera de hidrógeno durante 3 h. La mezcla de reacción se filtró a través Celite™ y el solvente se eliminó para proporcionar el compuesto del título como una sal TFA (107 mg, 92%).

Ejemplo 1 Ciclopropil(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona



A una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (18.0 mg, 0.035 mmol) en DCM (348 µL) a temperatura ambiente se agregó trietilamina (14,5 µL, 0.104 mmol) y cloruro de ciclopropanocarbonilo (6.4 µL, 0.070 mmol). La reacción se agitó durante 10 min a temperatura ambiente. La mezcla de reacción se concentró bajo presión reducida y se purificó mediante HPLC Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente de 50% a 90% ACN para proporcionar el compuesto del título, como una sal TFA, como un película amarilla (3.3 mg, 16%). ^{1}H RMN (400 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 0.81-0.96 (m, 4H), 1.29 (m, 7H), 1.90-2.18 (m, 4H), 2.73 (m, 0.7H), 2,87 (m, 1.3H), 3.07 (m, 2H), 3.42 (m, 2H), 3.88 (m, 0.7H), 4.06 (t, *J* = 5.7 Hz, 1.3H), 4.14 (m, 1H), 4.49 (m, 1H), 4.62 (s, 1.3H), 4.80 (s, 0.7H), 6.88 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.18 ppm (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 472.5.

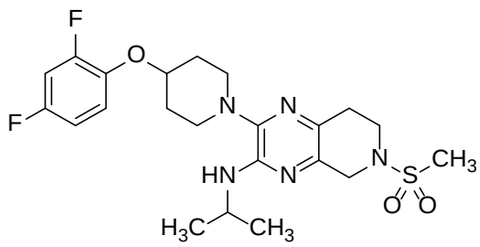
Ejemplo 2 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietan-1-ona



A una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (39.0 mg, 0.075 mmol) en DCM (754 µL) a 0 °C se agregó trietilamina (31.5 µL, 0.226 mmol) y cloruro de 2-metoxiacetilo (13.8 µL, 0.151 mmol). La reacción se agitó a 0 °C durante 30 min. La mezcla de reacción se concentró bajo presión reducida y se purificó mediante HPLC Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente de 55% a 80% ACN para proporcionar el compuesto del título, como una sal TFA, como un aceite amarillo (14,0 mg, 31.5%). ^{1}H RMN (400 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.30 (m, 6H), 1.96 (m, 2H), 2.13 (m, 2H), 2.75 (t, *J* = 5.7 Hz, 0.7H), 2.83 (t, *J* = 5.7 Hz, 1.3H), 3.08 (m, 2H), 3.44

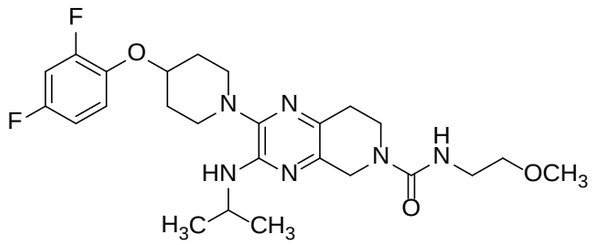
(m, 5H), 3.77 (t, *J* = 5.8 Hz, 1.3H), 3.88 (t, *J* = 5.9 Hz, 0.7H), 4.14 (m, 1H), 4.24 (s, 0.7H), 4.28 (s, 1.3H), 4.49 (td, *J* = 7.1, 3.5 Hz, 1H), 4.56 (s, 0.7H), 4.63 (s, 1.3H), 6.88 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 476.5.

Ejemplo 3 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-N-isopropil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



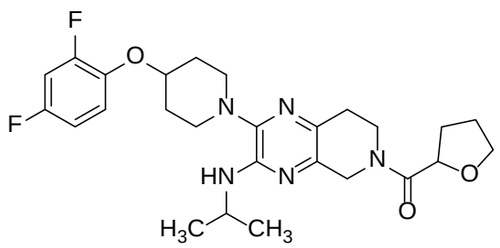
Una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-N-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (735.3 mg, 1.421 mmol) en DCM (14,2 mL) a 0 °C se trató con trietilamina (0.594 mL, 4,26 mmol), seguido de cloruro de metanosulfonilo (0.221 mL, 2.84 mmol). La mezcla de reacción se agitó a 0 °C durante 1 h. La mezcla de reacción se concentró bajo presión reducida. El residuo se recogió en MeOH, se filtró a través de un filtro jeringa Millipore® 0.45 µm, y se purificó mediante HPLC Método A. Las fracciones correspondientes se recogieron y se concentraron bajo presión reducida. El residuo resultante se recogió en DCM y se lavó con acuoso saturado K_2CO_3 para generar la base libre. La capa orgánica se separó, se secó sobre Na_2SO_4, y se filtró. La evaporación del filtrado y liofilización proporcionó el compuesto del título como un sólido blancuzco (229.6 mg, 33.6%). ^{1}H RMN (500 MHz, DMSO-*d*6) 1.18 (d, *J* = 6.3 Hz, 6H), 1.88 (m, 2H), 2.07 (m, 2H), 2.75 (t, *J* = 5.9 Hz, 2H), 2.89 (m, 2H), 2.97 (s, 3H), 3.29 (m, 2H), 3.45 (t, *J* = 5.9 Hz, 2H), 4.09 (m, 1H), 4.16 (s, 2H), 4.52 (tt, *J* = 8.1, 3.9 Hz, 1H), 5.57 (d, *J* = 8.3 Hz, 1H), 7.01 (m, 1H), 7.30 (m, 2H); ESI-MS m/z $[M+H]^+$ 481.90.

Ejemplo 4 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-*N*-(2-metoxietil)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



A una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (39.0 mg, 0.075 mmol) en DCM (754 µL) a 0 °C se agregó trietilamina (31.5 µL, 0.226 mmol) e 1-isocianato-2-metoxietano (11.8 µL, 0.113 mmol). La mezcla de reacción se agitó durante 1 h a 0 °C. La mezcla de reacción se concentró bajo presión reducida y se purificó mediante HPLC Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente de 45% a 70% ACN para proporcionar el compuesto del título, como una sal TFA, como un aceite amarillo (24,5 mg, 52.6%). ^{1}H RMN (400 MHz, metanol-*d*4) δ ppm 1.32 (d, *J* = 6.6 Hz, 6H), 1.97 (m, 2H), 2.14 (m, 2H), 2.77 (t, *J* = 5.8 Hz, 2H), 3.12 (m, 2H), 3.37 (m, 5H), 3.46 (m, 4H), 3.71 (t, *J* = 5.8 Hz, 2H), 4.13 (m, 1H), 4.50 (m, 3H), 6.88 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 505.6.

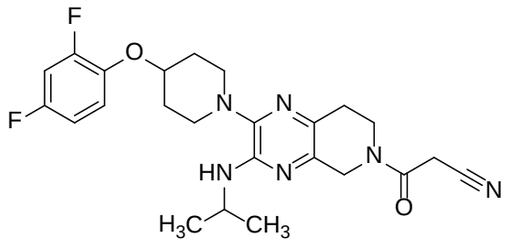
Ejemplo 5 (2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(tetrahidrofurán-2-il)metanona



A una solución de ácido tetrahidrofurán-2-carboxílico (10.9 µL, 0.113 mmol) en DMA (0.35 mL) a temperatura ambiente se agregó DIPEA (39.5 µL, 0.226 mmol), seguido de HATU (43.0 mg, 0.113 mmol). Después de agitar durante 5 min, la mezcla de reacción se trató con una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (39.0 mg, 0.075 mmol) en DMA (0.4 mL). La mezcla de reacción se agitó a 60 °C durante 30 min. La mezcla de reacción se dejó enfriar a temperatura ambiente y se purificó directamente mediante HPLC

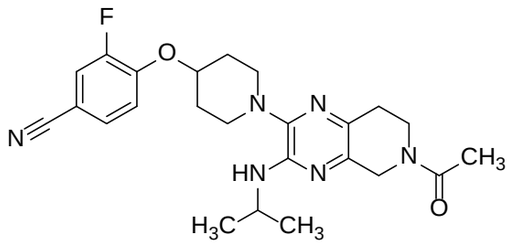
Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente de 55% a 80% ACN para proporcionar el compuesto del título, como una sal TFA, como un aceite amarillo (16.0 mg, 34,5%). ^{1}H RMN (400 MHz, metanol-*d*4) δ ppm 1.31 (m, 6H), 1.97 (m, 4H), 2.16 (m, 4H) 2.82 (m, 2H), 3.10 (m, 2H), 3.45 (m, 2H), 3.89 (m, 4H), 4.14 (m, 1H), 4.44-4.87 (m, 4H), 6.88 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 502.6.

Ejemplo 6 3-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-3-oxopropanonitrilo



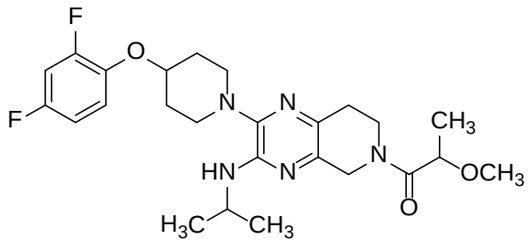
A una solución de ácido 2-cianoacético (8.3 mg, 0.097 mmol) en DMA (0.3 mL) a temperatura ambiente se agregó DIPEA (33.9 µL, 0.194 mmol), seguido de HATU (36.9 mg, 0.097 mmol). Esta mezcla se agitó durante 5 min, posteriormente se trató con una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (33.5 mg, 0.065 mmol) en DMA (0.35 mL). La mezcla de reacción se calentó a 60 °C durante 30 min. La mezcla de reacción se purificó directamente mediante HPLC Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente de 55% a 80% ACN para proporcionar el compuesto del título, como una sal TFA, como un aceite amarillo (5.5 mg, 14%). ^{1}H RMN (400 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.27 (m, 6H), 1.96 (m, 2H), 2.12 (m, 2H), 2.75 (t, *J* = 5.9 Hz, 0.8H), 2.85 (m, 1.2H), 3.01 (m, 2H), 3.39 (m, 2H), 3.75 (t, *J* = 5.8 Hz, 1.2H), 3.89 (t, *J* = 5.9 Hz, 0.8H), 4.00 (m, 2H); 4.14 (m, 1H), 4.48 (m, 1H), 4.50 (s, 0.8H), 4.60 (s, 1.2H), 6.88 (m, 1H), 6.98 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 471.5.

Ejemplo 7 4-((1-(6-acetil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo



A una solución de sal TFA de 3-fluoro-4-((1-(3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)benzonitrilo (33.5 mg, 0.064 mmol) en DCM (639 µL) a 0 °C se agregó piridina (15.5 µL, 0.192 mmol), seguido de anhídrido acético (12.0 µL, 0.128 mmol). La reacción se dejó en agitación durante 45 min, calentándose gradualmente a temperatura ambiente. La reacción se concentró bajo presión reducida y se purificó directamente mediante HPLC Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente 40% a 70% ACN para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo (7.1 mg, 20%). ^{1}H RMN (400 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.31 (m, 6H), 2.02 (m, 2H), 2.20 (m, 5H), 2.74 (t, *J* = 5.9 Hz, 0.7H), 2.85 (m, 1.3H), 3.14 (m, 2H), 3.43 (m, 2H), 3.83 (t, *J* = 5.9 Hz, 1.3H), 3.87 (t, *J* = 5.9 Hz, 0.7H), 4.14 (m, 1H), 4.60 (s, 0.7H), 4.64 (s, 1.3H), 4.80 (m, 1H), 7.34 (m, 1H), 7.54 (m, 2H); ESI-MS m/z [M+H]$^+$ 453.5.

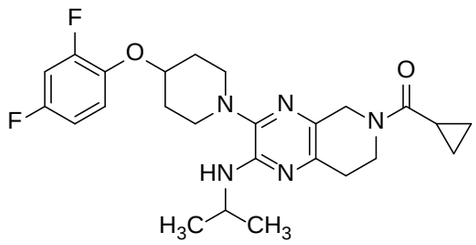
Ejemplo 8 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona



A una solución de ácido 2-metoxipropanoico (10.8 µL, 0.113 mmol) en DMA (0.4 mL) a temperatura ambiente se agregó DIPEA (45.5 µL, 0.261 mmol) y HATU (42.9 mg, 0.113 mmol). A esto se agregó una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (45.0 mg, 0.087 mmol) en DMA (0.47 mL). La mezcla de reacción resultante se agitó a 60 °C durante 45 min. La mezcla de reacción se dejó enfriar a temperatura ambiente y se purificó directamente mediante HPLC

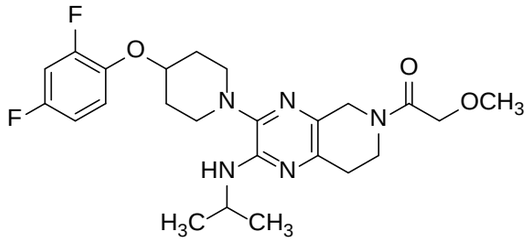
Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente 50% a 80% ACN para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo claro (11.2 mg, 21.4%). ^{1}H RMN (400 MHz, metanol-*d*4) δ ppm 1.36 (m, 9H), 1.98 (m, 2H), 2.14 (m, 2H), 2.83 (m, 2H), 3.16 (m, 2H), 3.35 (s, 3H), 3.49 (m, 2H), 3.90 (m, 1H), 3.93 (t, *J* = 5.8 Hz, 1H), 4.12 (m, 1H), 4.35 (m, 1H), 4.52 (m, 1H), 4.59-4.79 (m, 2H), 6.88 (m, 1H), 6.99 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 490.5.

Ejemplo 9 ciclopropil(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona



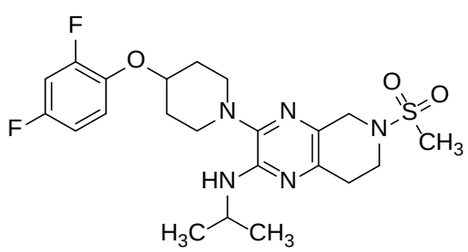
A una solución de sal 2TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (34,2 mg, 0.059 mmol) y trietilamina (0.025 mL, 0.178 mmol) en DCM (0.5 mL) se agregó cloruro de ácido ciclopropanocarboxílico (10.8 µL, 0.119 mmol) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 30 min y se concentró mediante un evaporador rotatorio. El material en bruto se diluyó con DMSO, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente ACN de 30% a 70% para proporcionar el compuesto del título como una sal TFA (17.7 mg, 51.0%) como un aceite amarillo. ^{1}H RMN (400 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 0.67-0.81 (m, 4H), 1.19 (d, *J* = 6.3 Hz, 6H), 1.80-1.95 (m, 2H), 2.01-2.07 (m, 2H), 2.51-2.56 (m, 1H), 2.57-2.66 (m, 0.9H), 2.72-2.79 (m, 1.1H), 2.84-2.94 (m, 2H), 3.23-3.33 (m, 2H), 3.70-3.79 (m, 0.9H), 3.92-3.98 (m, 1.1H), 4.08-4.18 (m, 1H), 4.42 (s a, 1.1H), 4.48-4.56 (m, 1H), 4.67 (s a, 0.9H), 5.71 (s a, 1H), 6.99-7.05 (m, 1H), 7.26-7.34 (m, 2H); ESI-MS m/z $[M+H]^+$ 472.5.

Ejemplo 10 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietan-1-ona



A una solución de sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (34,2 mg, 0.059 mmol) y trietilamina (0.025 mL, 0.178 mmol) en DCM (0.5 mL) se agregó cloruro de metoxiacetilo (10.8 µL, 0.119 mmol) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 30 min y se concentró mediante un evaporador rotatorio. El material en bruto se diluyó con DMSO, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente ACN de 30% a 70% para proporcionar el compuesto del título como una sal TFA (19.0 mg, 54,4%) como un aceite amarillo. ^{1}H RMN (400 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.18 (d, *J* = 6.6 Hz, 6H), 1.83-1.93 (m, 2H), 2.03-2.11 (m, 2H), 2.63 (t, *J* = 5.8 Hz, 0.9H), 2.72 (t, *J* = 5.3 Hz, 1.1H), 2.84-2.93 (m, 2H), 3.22-3.36 (m, 5H), 3.66 (t, *J* = 5.8 Hz, 1.1H), 3.74 (t, *J* = 6.1 Hz, 0.9H), 4.10-4.16 (m, 1H), 4.17 (s a, 0.9H), 4.19 (s, 1.1H), 4.49-4.56 (m, 1H), 5.65-5.72 (m, 1H), 6.99-7.05 (m, 1H), 7.26-7.35 (m, 2H); ESI-MS m/z [M+H]$^+$ 476.5.

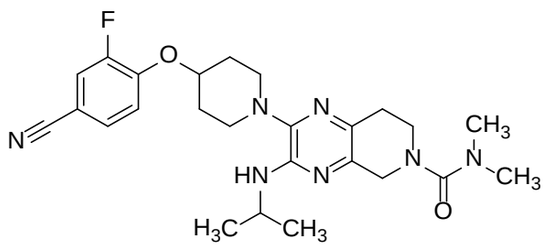
Ejemplo 11 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



A una solución de sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-N-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (34,2 mg, 0.059 mmol) y trietilamina (0.025 mL, 0.178 mmol) en DCM (0.5 mL) se agregó cloruro de metanosulfonilo (6.9 µL, 0.089 mmol) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 30 min y se concentró mediante un evaporador rotatorio. El material en

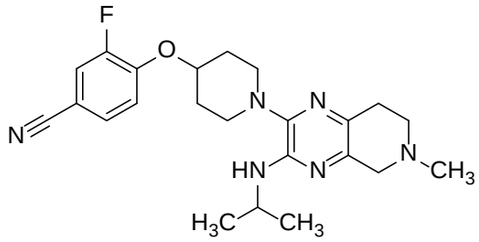
bruto se diluyó con DMSO, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente ACN de 30% a 70% para proporcionar el compuesto del título como una sal TFA (14,7 mg, 41.6%) como un aceite amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.19 (d, J = 6.6 Hz, 6H), 1.82-1.93 (m, 2H), 2.02-2.08 (m, 2H), 2.77 (t, J = 5.7 Hz, 2H), 2.84-2.93 (m, 2H), 2.98 (s, 3H), 3.24-3.32 (m, 2H), 3.45 (t, J = 5.9 Hz, 2H), 4.10-4.18 (m, 3H), 4.50-4.55 (m, 1H), 5.67 (s a, 1H), 6.99-7.04 (m, 1H), 7.26-7.35 (m, 2H); ESI-MS m/z [M+H]$^+$ 482.4.

Ejemplo 12 2-(4-(4-ciano-2-fluorofenoxi)piperidin-1-il)-3-(isopropilamino)-*N,N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



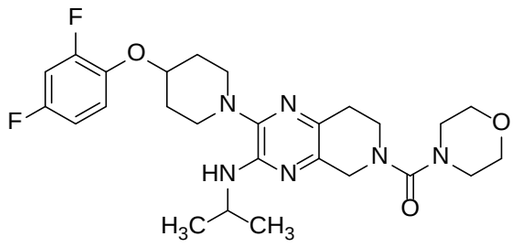
Una solución de sal TFA de 3-fluoro-4-((1-(3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)benzonitrilo (32.5 mg, 0.062 mmol) en DCM (620 µL) a 0 °C se trató con trietilamina (25.9 µL, 0.186 mmol) y cloruro dimetilcarbámico (11.4 µL, 0.124 mmol). La mezcla de reacción se dejó calentar gradualmente a temperatura ambiente y se agitó durante 1 h. La mezcla de reacción se concentró bajo presión reducida y se purificó directamente mediante HPLC Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente 40% a 70% ACN para proporcionar el compuesto del título (aproximadamente 90% de pureza), como una sal TFA, como un sólido amarillo (6.8 mg, 18%). ^{1}H RMN (400 MHz, metanol-d4) δ ppm 1.29 (m, 6H), 2.02 (m, 2H), 2.19 (m, 2H), 2.81 (t, J = 5.3 Hz, 2H), 2.91 (s, 5H), 3.17 (m, 3H), 3.43 (m, 2H), 3.56 (t, J = 5.6 Hz, 2H), 4.13 (m, 1H), 4.32 (s, 2H), 4.80 (m, 1H), 7.34 (m, 1H), 7.54 (t, J = 10.9 Hz, 2H); ESI-MS m/z [M+H]$^+$ 482.5.

Ejemplo 13 3-fluoro-4-((1-(3-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)benzonitrilo



Una solución de sal TFA de 3-fluoro-4-((1-(3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)benzonitrilo (12.8 mg, 0.024 mmol) y formaldehído (2.2 mg, 0.027 mmol) en MeOH (244 µL) a temperatura ambiente se trató con DIPEA (8.5 µL, 0.049 mmol) y triacetoxihidroborato de sodio (10.3 mg, 0.049 mmol). La mezcla de reacción se agitó durante 45 min a temperatura ambiente. La mezcla de reacción bruta se purificó directamente mediante HPLC Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente de 30% a 55% ACN para proporcionar el compuesto del título (aproximadamente 90% de pureza), como una sal TFA, como un sólido amarillo claro. (6.0 mg, 46%). ^{1}H RMN (400 MHz, metanol-*d*4) δ ppm 1.24 (d, *J* = 6.6 Hz, 6H), 1.98 (m, 2H), 2.19 (m, 2H), 3.08 (m, 7H), 3.38 (m, 3H), 3.76 (s a, 1H), 4.16 (m, 1H), 4.29 (m, 2H), 4.79 (m, 1H), 7.34 (m, 1H), 7.53 (m, 2H); ESI-MS m/z $[M+H]^+$ 425.5.

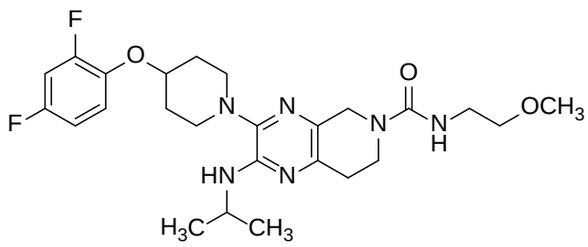
Ejemplo 14 (2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(morfolino)metanona



A una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (38.1 mg, 0.074 mmol) en DCM (736 µL) a 0 °C se agregó trietilamina (30.8 µL, 0.221 mmol), seguido de cloruro de morfolina-4-carbonilo (17.2 µL, 0.147 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 30 min. La mezcla de reacción se concentró bajo presión reducida y se purificó directamente mediante HPLC Método B, con la excepción de que se usó una columna Fenomenex Gemini® C18, 5 µm, ID 30 x 75

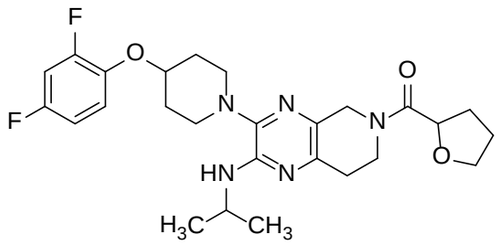
mm, utilizando un gradiente 50% a 75% ACN para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo (11.9 mg, 25.6%). ^{1}H RMN (400 MHz, metanol-*d*4) δ ppm 1.31 (d, *J* = 6.6 Hz, 6H), 1.96 (m, 2H), 2.13 (m, 2H), 2.81 (t, *J* = 5.8 Hz, 2H), 3.10 (m, 2H), 3.33 (m, 4H), 3.45 (m, 2H), 3.59 (t, *J* = 5.9 Hz, 2H), 3.70 (m, 4H), 4.13 (m, 1H), 4.37 (s, 2H), 4.50 (tt, *J* = 7.2, 3.5 Hz, 1H), 6.88 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 517.5.

Ejemplo 15 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-*N*-(2-metoxietil)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



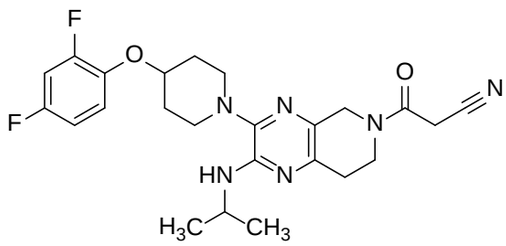
A una solución de sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (42.8 mg, 0.070 mmol) y trietilamina (0.029 mL, 0.211 mmol) en DCM (0.75 mL) se agregó 1-isocianato-2-metoxietano (11.0 µL, 0.105 mmol) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 30 min y se concentró mediante un evaporador rotatorio. El material en bruto se diluyó con DMSO, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente ACN de 30% a 70% para proporcionar el compuesto del título como una sal TFA (26.3 mg, 60.5%) como un higroscópico, sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.18 (d, *J* = 6.3 Hz, 6H), 1.83-1.93 (m, 2H), 2.02-2.11 (m, 2H), 2.61 (t, *J* = 5.6 Hz, 2H), 2.82-2.93 (m, 2H), 3.14-3.21 (m, 2H), 3.23 (s, 3H), 3.24-3.31 (m, 2H), 3.31-3.37 (m, 2H), 3.60 (t, *J* = 5.8 Hz, 2H), 4.08-4.17 (m, 1H), 4.29 (s, 2H), 4.49-4.56 (m, 1H), 5.61-5.70 (m, 1H), 6.66-6.73 (m, 1H), 6.99-7.05 (m, 1H), 7.26-7.34 (m, 2H); ESI-MS m/z $[M+H]^+$ 505.0.

Ejemplo 16 (3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(tetrahidrofurán-2-il)metanona



A una suspensión de sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (42.8 mg, 0.070 mmol), ácido 2-tetrahidrofuroico (10.1 µL, 0.105 mmol), HATU (40.0 mg, 0.105 mmol) en DMA (0.75 mL) se agregó DIPEA (0.037 mL, 0.211 mmol) a 23 °C. La mezcla se agitó a 60 °C durante 30 min, se enfrió a 23 °C, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente ACN de 30% a 70% para proporcionar el compuesto del título como una sal TFA (20.8 mg, 48.1%) como un higroscópico, sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.19 (d, *J* = 6.3 Hz, 6H), 1.78-1.94 (m, 4H), 1.97-2.13 (m, 4H), 2.63 (t, *J* = 5.7 Hz, 0.9H), 2.71-2.77 (m, 1.1H), 2.85-2.95 (m, 2H), 3.24-3.33 (m, 2H), 3.69-3.85 (m, 4H), 4.11 (dt, *J* = 12.9, 6.4 Hz, 1H), 4.38-4.57 (m, 3H), 4.75 (ddd, *J* = 14.0, 7.8, 5.7 Hz, 1H), 5.81 (s a, 1H), 6.99-7.05 (m, 1H), 7.25-7.34 (m, 2H); ESI-MS m/z $[M+H]^+$ 502.5.

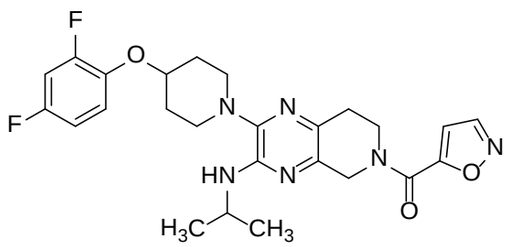
Ejemplo 17 3-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-3-oxopropanonitrilo



A una suspensión de sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (42.8 mg, 0.070 mmol), ácido cianoacético (9.0 mg, 0.105 mmol), HATU (40.0 mg, 0.105 mmol) en DMA se agregó DIPEA (36.7 µL, 0.211 mmol) a 23 °C. La mezcla se agitó a 60 °C durante 30 min, se enfrió a 23 °C, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó Waters XSelect® CSH

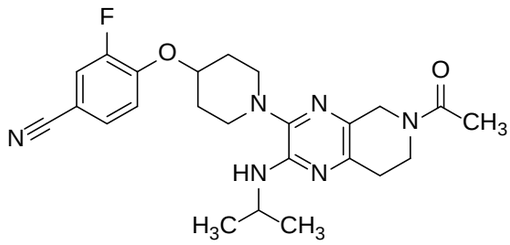
C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente ACN de 30% a 70% para proporcionar el compuesto del título como una sal TFA (21.0 mg, 51.2%) como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.19 (d, J = 6.6 Hz, 6H), 1.80-1.96 (m, 2H), 2.00-2.17 (m, 2H), 2.64 (t, J = 5.6 Hz, 0.9H), 2.76 (t, J = 5.7 Hz, 1.1H), 2.84-2.97 (m, 2H), 3.22-3.34 (m, 2H), 3.64 (t, J = 5.8 Hz, 1.1H), 3.75 (t, J = 5.9 Hz, 0.9H), 4.08-4.14 (m, 1H), 4.16 (s, 0.9H), 4.17 (s, 1.1H), 4.37 (s, 0.9H), 4.43 (s, 1.1H), 4.48-4.57 (m, 1H), 5.76 (s a, 1H), 6.98-7.06 (m, 1H), 7.24-7.36 (m, 2H); ESI-MS m/z $[M+H]^+$ 471.5.

Ejemplo 18 (2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(isoxazol-5-il)metanona



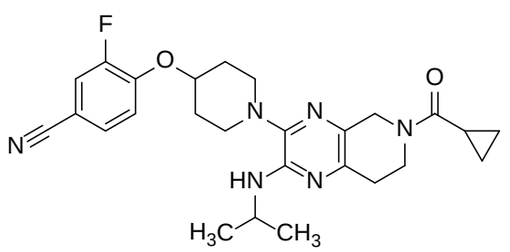
Una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (38.1 mg, 0.074 mmol) en DCM (736 µL) a 0 °C se trató con trietilamina (30.8 µL, 0.221 mmol), seguido de cloruro de isoxazol-5-carbonilo (14,2 µL, 0.147 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 45 min. La mezcla de reacción se concentró bajo presión reducida y se purificó directamente mediante HPLC Método B, con la excepción de que se usó una columna Fenomenex Gemini® C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente 55% a 90% ACN para proporcionar el compuesto del título, como una sal TFA, como un aceite tostado (18.6 mg, 41.2%). ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.30 (m, 6H), 1.96 (m, 2H), 2.13 (m, 2H), 2.89 (m, 2H), 3.11 (m, 2H), 3.46 (m, 2H), 3.91-4.21 (m, 3H), 4.49 (m, 1H), 4.78 (s a, 2H), 6.87 (m, 1H), 6.92 (s, 1H), 6.98 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, J = 9.2, 5.6 Hz, 1H), 8.55 (s, 1H); ESI-MS m/z $[M+H]^+$ 499.5.

Ejemplo 19 4-((1-(6-acetil-2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo



A una solución de sal TFA de 3-fluoro-4-((1-(2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo (98.6 mg, 0.094 mmol) y trietilamina (0.039 mL, 0.283 mmol) en DCM (1.0 mL) se agregó cloruro de acetilo (0.013 mL, 0.188 mmol) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 30 min y se concentró mediante un evaporador rotatorio. El material en bruto se diluyó con DMSO, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente ACN de 30% a 70% para proporcionar el compuesto del título como una sal TFA (8.7 mg, 16%) como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.18 (d, *J* = 6.6 Hz, 6H), 1.86-1.96 (m, 2H), 2.08 (s, 1.3H), 2.09 (s, 1.7H), 2.10-2.21 (m, 2H), 2.61 (t, *J* = 5.6 Hz, 0.9H), 2.73 (t, *J* = 5.2 Hz, 1.1H), 2.88-2.98 (m, 2H), 3.23-3.31 (m, 2H), 3.66-3.76 (m, 2H), 4.09-4.17 (m, 1H), 4.40 (s, 1.1H), 4.43 (s, 0.9H) 4.80-4.87 (m, 1H), 5.59-5.67 (m, 1H), 7.50 (t, *J* = 8.6 Hz, 1H), 7.68 (dc, *J* = 8.6, 1.7 Hz, 1H), 7.86 (dt, *J* = 11.2, 1.7 Hz, 1H); ESI-MS m/z [M+H]$^+$ 453.5.

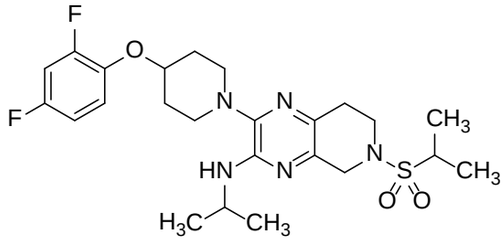
Ejemplo 20 4-((1-(6-(ciclopropanocarbonil)-2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo



A una solución de sal TFA de 3-fluoro-4-((1-(2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo (98.6 mg, 0.094 mmol) y trietilamina (0.039 mL, 0.283 mmol) en DCM (0.5 mL) se agregó cloruro de ácido ciclopropanocarboxílico (0.017 mL, 0.188 mmol) a 0 °C. La mezcla se agitó a 0 °C durante 30 min y se concentró mediante un evaporador rotatorio. El material en

bruto se diluyó con DMSO, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente ACN de 30% a 70% para proporcionar el compuesto del título como una sal TFA (8.1 mg, 15%) como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 0.69-0.79 (m, 4H), 1.18 (d, *J* = 6.6 Hz, 6H), 1.91 (dd, *J* = 19.5, 5.6 Hz, 2H), 2.13 (dd, *J* = 14.3, 6.2 Hz, 2H), 2.52-2.53 (m, 1H), 2.57-2.64 (m, 0.9H), 2.75 (t, *J* = 6.2 Hz, 1.1H), 2.88-2.99 (m, 2H), 3.22-3.31 (m, 2H), 3.72-3.77 (m, 0.9H), 3.95 (t, *J* = 5.8 Hz, 1H), 4.10-4.16 (m, 1H), 4.42 (s a, 1.1H), 4.67 (s a, 0.9H), 4.80-4.87 (m, 1H), 5.61-5.67 (m, 1H), 7.50 (t, *J* = 8.5 Hz, 1H), 7.65-7.70 (m, 1H), 7.86 (dd, *J* = 11.2, 1.9 Hz, 1H); ESI-MS m/z $[M+H]^+$ 479.5.

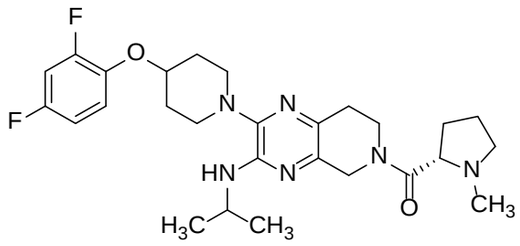
Ejemplo 21 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-(isopropilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



Una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (47 mg, 0.091 mmol) en DCM (908 µL) a 0 °C se trató con trietilamina (38.0 µL, 0.272 mmol), seguido de cloruro de propano-2-sulfonilo (15.3 µL, 0.136 mmol). La mezcla de reacción se dejó en agitación durante 45 min, calentándose gradualmente a temperatura ambiente. La mezcla de reacción se concentró bajo presión reducida y se purificó mediante HPLC Método B, con la excepción de que se usó una columna Waters SunFire™ C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente 60% a 95% ACN para proporcionar el compuesto del título, como una sal TFA, como un aceite amarillo (16.4 mg, 29.0%). ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.29 (d, *J* = 6.6 Hz, 6H), 1.35 (d, *J* = 6.8 Hz, 6H), 1.95 (m, 2H), 2.13 (m, 2H), 2.82 (t, *J* = 5.9 Hz, 2H), 3.07 (m, 2H), 3.42 (m, 3H), 3.67 (t, *J* = 5.8 Hz, 2H), 4.12 (septet, *J* = 6.5 Hz, 1H), 4.41 (s, 2H), 4.48 (dt, *J* = 7.5, 3.6 Hz, 1H) 6.87 (m, 1H), 6.98 (ddd, *J* = 11.3, 8.5, 2.9

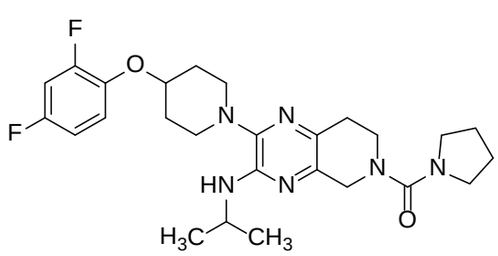
Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 510.5.

Ejemplo 22 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-6-(metil-L-prolil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina



Una solución de ácido (*S*)-1-metilpirrolidina-2-carboxílico (16.8 mg, 0.130 mmol) en DMA (0.4 mL) se trató con HATU (49.6 mg, 0.130 mmol) y DIPEA (45.6 µL, 0.261 mmol) a temperatura ambiente. A esto se agregó una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (45 mg, 0.087 mmol) en DMA (0.47 mL). La mezcla de reacción se agitó a 60 °C durante 45 min. La mezcla de reacción se dejó enfriar a temperatura ambiente y se purificó directamente mediante HPLC Método B, con la excepción de que se usó una columna Fenomenex Gemini® C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente 25% a 60% ACN para proporcionar el compuesto del título, como una sal TFA, como un sólido blanco (2.8 mg, 5.1%). ^{1}H RMN (400 MHz, metanol-*d*4) δ ppm 1.26 (dd, *J* = 6.6, 4.5 Hz, 6H), 1.97 (m, 4H), 2.09 (m, 3H), 2.24 (m, 1H), 2.76 (m, 3H), 2.93 (app d, *J* = 7.6 Hz, 3H), 3.03 (m, 2H), 3.20 (m, 1H), 3.40 (m, 2H), 3.69-4.19 (m, 4H), 4.48 (m, 2H), 4.66 (m, 2H), 6.87 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 515.6.

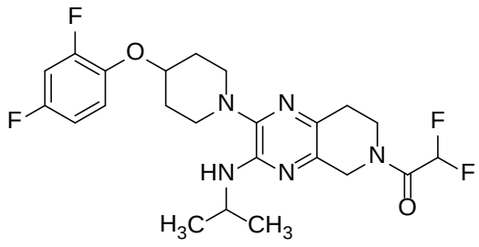
Ejemplo 23 (2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(pirrolidin-1-il)metanona



Una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (45 mg, 0.087 mmol) en

DCM (870 µL) a 0 °C se trató con trietilamina (36.4 µL, 0.261 mmol), seguido de cloruro de pirrolidina-1-carbonilo (19.2 µL, 0.174 mmol). La mezcla de reacción se dejó en agitación durante 30 min, calentándose gradualmente a temperatura ambiente. La mezcla de reacción se concentró bajo presión reducida y se purificó directamente mediante HPLC Método B, con la excepción de que se usó una columna Fenomenex Gemini® C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente 50% a 80% ACN para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo claro (10.6 mg, 19.8%). ^{1}H RMN (400 MHz, metanol-*d*4) δ ppm 1.33 (d, *J* = 6.3 Hz, 6H), 1.89 (m, 4H), 1.97 (m, 2H), 2.14 (m, 2H), 2.81 (t, *J* = 5.8 Hz, 2H), 3.13 (m, 2H), 3.46 (m, 6H), 3.61 (t, *J* = 5.8 Hz, 2H), 4.12 (septet, *J* = 6.4 Hz, 1H), 4.38 (s, 2H), 4.51 (tt, *J* = 7.2, 3.6 Hz, 1H), 6.88 (m, 1H), 6.99 (ddd, *J* = 11.4, 8.5, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 501.6.

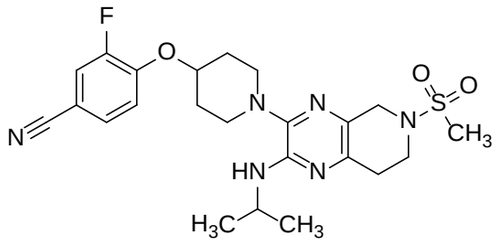
Ejemplo 24 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetan-1-ona



Una solución de ácido 2,2-difluoroacético (8.2 µL, 0.13 mmol) en DMA (0.4 mL) se trató con HATU (49.6 mg, 0.130 mmol) y DIPEA (45.6 µL, 0.261 mmol). A esto se agregó una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (45 mg, 0.087 mmol) en DMA (0.47 mL). La mezcla de reacción se calentó a 60 °C durante 50 min. La mezcla de reacción se dejó enfriar a temperatura ambiente y se purificó directamente mediante HPLC Método B, con la excepción de que se usó una columna Fenomenex Gemini® C18, 5 µm, ID 30 x 75 mm, utilizando un gradiente 55% a 90% ACN para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo (10.0 mg, 19.3%). ^{1}H RMN (400 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.28 (m, 6H), 1.96 (m, 2H), 2.12 (m, 2H), 2.79 (t, *J* = 5.9 Hz, 0.7H), 2.85 (t, *J* = 5.8 Hz, 1.3H), 3.05 (m, 2H), 3.42 (m, 2H), 3.92 (dt, *J* = 11.3, 5.8

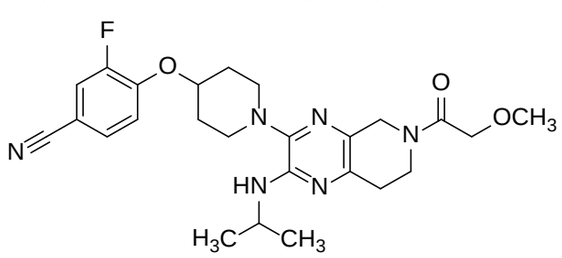
Hz, 2H), 4.15 (m, 1H), 4.48 (m, 1H), 4.65 (s, 2H), 6.56 (m, 1H), 6.88 (m, 1H), 6.98 (ddd, *J* = 11.3, 8.5, 2.9 Hz, 1H), 7.17 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 482.5.

Ejemplo 25 3-fluoro-4-((1-(2-(isopropilamino)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo



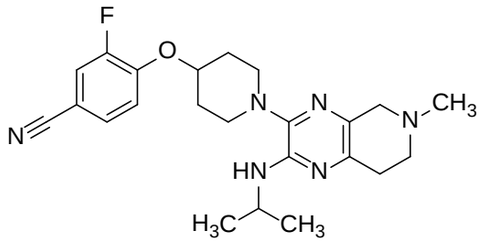
A una solución de sal TFA de 3-fluoro-4-((1-(2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo (98.6 mg, 0.094 mmol) y trietilamina (0.039 mL, 0.283 mmol) en DCM (1.0 mL) se agregó cloruro de metanosulfonilo (10.9 µL, 0.141 mmol) a 0 °C. La mezcla se agitó a 0 °C durante 30 min y se concentró mediante un evaporador rotatorio. El material en bruto se diluyó con DMSO, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente ACN de 30% a 70% para proporcionar el compuesto del título como una sal TFA (3.5 mg, 6.2%) como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.18 (d, *J* = 6.3 Hz, 6H), 1.88-1.96 (m, 2H), 2.09-2.16 (m, 2H), 2.76 (t, *J* = 5.9 Hz, 2H), 2.89-2.96 (m, 2H), 2.97 (s, 3H), 3.24-3.30 (m, 2H), 3.45 (t, *J* = 5.9 Hz, 2H), 4.10-4.16 (m, 3H), 4.81-4.85 (m, 1H), 5.66 (d, *J* = 8.3 Hz, 1H), 7.50 (t, *J* = 8.7 Hz, 1H), 7.68 (ddd, *J* = 8.6, 2.0, 1.3 Hz, 1H), 7.86 (dd, *J* = 11.4, 2.0 Hz, 1H); ESI-MS m/z $[M+H]^+$ 489.5.

Ejemplo 26 3-fluoro-4-((1-(2-(isopropilamino)-6-(2-metoxiacetil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo



A una solución de 2,2,2-trifluoroacetato de 3-fluoro-4-((1-(2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-b]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo (98.6 mg, 0.094 mmol) y trietilamina (0.039 mL, 0.283 mmol) en DCM (1.0 mL) se agregó cloruro de metoxiacetilo (0.017 mL, 0.188 mmol) a 0 °C. La mezcla se agitó a 0 °C durante 30 min y se concentró mediante un evaporador rotatorio. El material en bruto se diluyó con DMSO, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente ACN de 30% a 70% para proporcionar el compuesto del título como una sal TFA (2.9 mg, 5.2%) como un sólido amarillo. ^{1}H RMN (400 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.18 (d, J = 6.6 Hz, 6H), 1.87-1.97 (m, 2H), 2.08-2.16 (m, 2H), 2.62 (t, J = 5.8 Hz, 0.9H), 2.72 (t, J = 6.1 Hz, 1.1H), 2.89-2.97 (m, 2H), 3.22-3.28 (m, 1H), 3.29 (s a, 1.3H), 3.30 (s, 1.7H), 3.64-3.67 (m, 1.1H), 3.72-3.75 (m, 0.9H), 4.10-4.16 (m, 1H), 4.17 (s a, 0.9H), 4.19 (s, 1.1H), 4.36 (s a, 0.9H), 4.41 (s, 1.1H), 4.80-4.86 (m, 1H), 5.58-5.63 (m, 1H), 7.50 (t, J = 8.7 Hz, 1H), 7.66-7.70 (m, 1H), 7.87 (dd, J =11.2, 1.9 Hz, 1H); ESI-MS m/z $[M+H]^+$ 483.5.

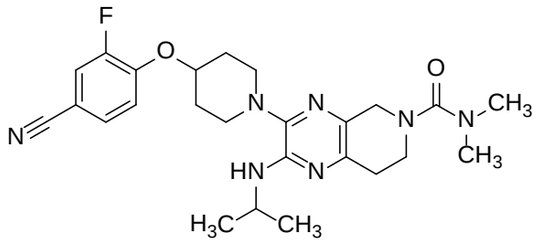
Ejemplo 27 3-fluoro-4-((1-(2-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo



A una solución de sal TFA de 3-fluoro-4-((1-(2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo (20.7 mg, 0.039 mmol) y formaldehído (3.2 µL, 0.043 mmol) en MeOH (0.5 mL) se agregó DIPEA (0.014 mL, 0.079 mmol) y triacetoxiborohidruro de sodio (16.7 mg, 0.079 mmol) a 23 °C. La mezcla se agitó a 23 °C durante 2 hr y se concentró mediante un evaporador rotatorio. El material en bruto se diluyó con DMSO, se filtró, se lavó con DMSO, y se purificó mediante con la excepción de que se usó Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente de 30% a 40% ACN para proporcionar el compuesto del título como una sal TFA (5.3 mg, 25%) como un sólido

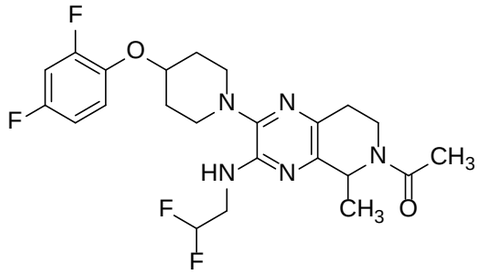
amarillo claro. ^{1}H RMN (400 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.16-1.24 (m, 6H), 1.87-1.96 (m, 2H), 2.08-2.16 (m, 2H), 2.74-2.85 (m, 0.9H), 2.85-2.92 (m, 1.1H), 2.95 (s a, 1.3H), 2.96 s a, 1.7H), 2.97-3.00 (m, 1H), 3.25-3.42 (m, 3H), 3.65-3.71 (m, 1H), 4.12-4.19 (m, 2H), 4.25-4.31 (m, 1H), 4.82-4.88 (m, 1H), 5.89 (d, *J* = 8.3 Hz, 1H), 7.50 (t, *J* = 8.6 Hz, 1H), 7.66-7.71 (m, 1H), 7.87 (dd, *J* = 11.4, 2.0 Hz, 1H), 9.96 (s a, 1H); ESI-MS m/z $[M+H]^+$ 425.5.

Ejemplo 28 3-(4-(4-ciano-2-fluorofenoxi)piperidin-1-il)-2-(isopropilamino)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



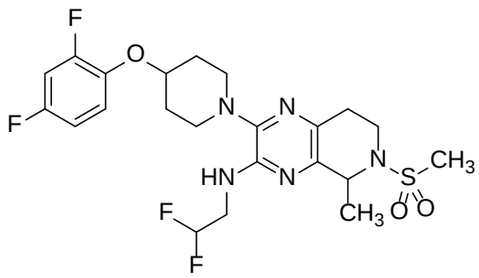
A una solución de sal TFA de 3-fluoro-4-((1-(2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo (20.7 mg, 0.039 mmol) y trietilamina (0.017 mL, 0.118 mmol) en DCM (0.5 mL) se agregó cloruro de dimetilcarbamoilo (7.3 µL, 0.079 mmol) a 0 °C. La mezcla se agitó a 0 °C durante 30 min y se concentró mediante un evaporador rotatorio. El material en bruto se diluyó con DMSO, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B, con la excepción de que se usó Waters XSelect® CSH C18, 5 µm, ID 4,6 x 50 mm, utilizando un gradiente de 30% a 70% ACN para proporcionar el compuesto del título como una sal TFA (11.6 mg, 49.4%) como un sólido amarillo claro. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.13-1.26 (m, 6H), 1.87-1.96 (m, 2H), 2.08-2.16 (m, 2H), 2.81-2.99 (m, 6H), 3.25-3.42 (m, 3H), 3.65-3.71 (m, 1H), 4.12-4.19 (m, 2H), 4.25-4.31 (m, 1H), 4.82-4.88 (m, 1H), 5.89 (d, *J* = 8.3 Hz, 1H), 7.50 (t, *J* = 8.6 Hz, 1H), 7.66-7.71 (m, 1H), 7.87 (dd, *J* = 11.4, 2.0 Hz, 1H), 9.96 (s a, 1H); ESI-MS m/z $[M+H]^+$ 482.5.

Ejemplo 29 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



Una solución de sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (15 mg, 0.027 mmol), DIPEA (14,20 µL, 0.081 mmol), y anhídrido acético (3.8 µL, 0.041 mmol) en DCM (271 µL) se agitó a temperatura ambiente durante la noche. La purificación mediante HPLC Método A proporcionó el compuesto del título como una sal TFA (8.9 mg) una película blancuzca. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.45 (d, *J* = 6.8 Hz, 1.9H), 1.58 (d, *J* = 6.8 Hz, 1.1H), 1.93-2.02 (m, 2H), 2.14 (dd, *J* = 12.7, 3.4 Hz, 2H), 2.19-2.23 (m, 3H), 2.62-2.83 (m, 1.5H), 2.87-3.08 (m, 3.2H), 3.35-3.43 (m, 2H), 3.48-3.55 (m, 0.7H), 3.78 (sxtd, *J* = 14.4, 4.2 Hz, 2H), 4.06 (dd, *J* = 14.2, 5.4 Hz, 0.6H), 4.46 (dt, *J* = 7.6, 3.5, Hz, 1H), 4.73 (dd, *J* = 13.2, 5.4 Hz, 0.4H), 5.34 (c, *J* = 6.8 Hz, 0.6H), 5.92-5.97 (m, 1H), 6.06 (dt, *J* = 9.0, 4.3, Hz, 1H), 6.15-6.20 (m, 1H), 6.86-6.91 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.5, 3.2 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z [M+H]$^+$ 482.

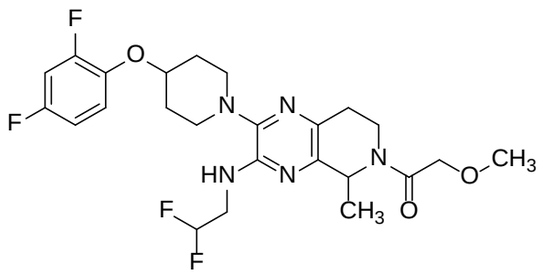
Ejemplo 30 *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



Una solución de sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (15 mg, 0.027 mmol), DIPEA (14,2 µL, 0.081 mmol), y cloruro de metanosulfonilo (3.2 µL, 0.041 mmol) en DCM (271 µL) se agitó durante la noche. La purificación mediante HPLC Método A proporcionó el compuesto del título como una sal TFA (6.4 mg) como una película blanca. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 1.54 (d,

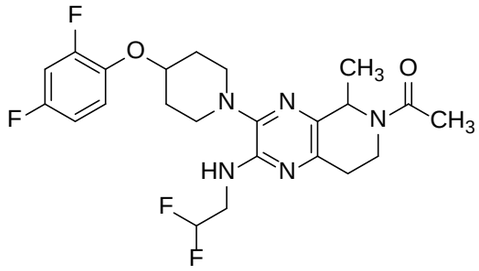
J = 6.8 Hz, 3H), 1.91-2.02 (m, 2H), 2.07-2.19 (m, 2H), 2.66 (dd, *J* = 16.8, 3.2 Hz, 1H), 2.91 (s, 3H), 2.93-3.06 (m, 3H), 3.34-3.48 (m, 3H), 3.68-3.88 (m, 2H), 3.98 (dd, *J* = 14.2, 6.4 Hz, 1H), 4.45 (dt, *J* = 7.4, 3.8, Hz, 1H), 4.77 (c, *J* = 6.8 Hz, 1H), 5.87-6.21 (m, 1H), 6.82-6.92 (m, 1H), 6.98 (ddd, *J* = 11.4, 8.7, 2.9 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 518.80.

Ejemplo 31 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona



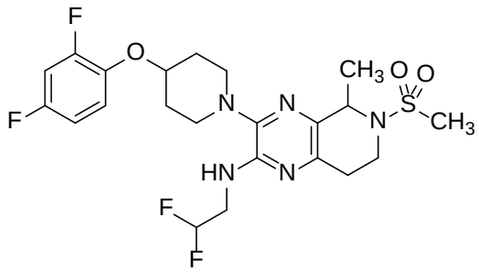
Una solución de ácido 2-metoxiacético (2.4 mg, 0.027 mmol), HATU (10.3 mg, 0.027 mmol), y DIPEA (14,2 µL, 0.081 mmol) en DMF (271 µl) se agitó a temperatura ambiente durante 10 min. A esto se agregó sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (15 mg, 0.027 mmol) en DCM (271 µL) y la mezcla de reacción se agitó durante la noche. La purificación mediante HPLC Método A proporcionó el compuesto del título como una sal TFA (7.4 mg) una película blancuzca. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.47 (d, *J* = 6.8 Hz, 2H), 1.58 (d, *J* = 6.8 Hz, 1H), 1.93-2.03 (m, 2H), 2.10-2.18 (m, 2H), 2.63-3.06 (m, 4.1H), 3.12 (td, *J* = 12.9, 3.9 Hz, 0.3H), 3.36-3.51 (m, 5.6H), 3.70-3.88 (m, 2H), 4.02 (dd, *J* = 13.9, 5.6 Hz, 0.7H), 4.18-4.33 (m, 2H), 4.46 (dt, *J* = 7.3, 3.7 Hz, 1H), 4.71 (dd, *J* = 13.4, 5.6 Hz, 0.3H), 4.79-4.84 (m, 0.3H), 5.30 (c, *J* = 6.8 Hz, 0.7H), 5.91-6.21 (m, 1H), 6.85-6.92 (m, 1H), 6.99 (ddd, *J* = 11.3, 8.7, 2.9 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 512.85.

Ejemplo 32 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



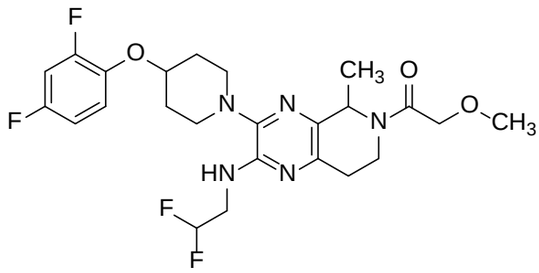
El compuesto del título se preparó una película blancuzca de manera similar al Ejemplo 29 utilizando *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.43 (d, *J* = 6.8 Hz, 1.8H), 1.56 (d, *J* = 6.8 Hz, 1.2H), 1.95-2.03 (m, 2H), 2.10-2.23 (m, 5H), 2.63-2.83 (m, 1.6H), 2.88-3.10 (m, 3.2H), 3.35-3.47 (m, 2H), 3.48-3.57 (m, 0.5H), 3.78 (td, *J* = 14.4, 4.4 Hz, 2H), 4.05 (dd, *J* = 13.9, 5.6 Hz, 0.6H), 4.42-4.51 (m, 1H), 4.73 (dd, *J* = 13.7, 5.9 Hz, 0.6H), 5.35 (c, *J* = 6.7 Hz, 0.5H), 5.92-6.20 (m, 1H), 6.84-6.93 (m, 1H), 6.96-7.04 (m, 1H), 7.14-7.23 (m, 1H); ESI-MS m/z [M+H]$^+$ 482.

Ejemplo 33 *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



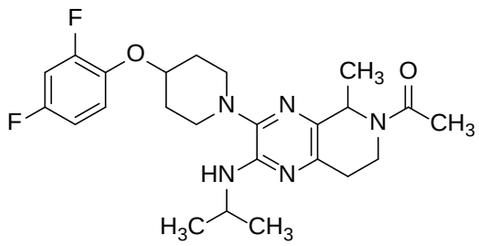
El compuesto del título se preparó como una película blanca de manera similar al Ejemplo 30 utilizando *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 1.52 (d, *J* = 6.8 Hz, 3H), 1.91-2.01 (m, 2H), 2.08-2.19 (m, 2H), 2.66 (dd, *J* = 17.1, 2.9 Hz, 1H), 2.91 (s, 3H), 2.93-3.08 (m, 3H), 3.34-3.48 (m, 3H), 3.77 (td, *J* = 14.4, 4.4 Hz, 2H), 3.97 (dd, *J* = 14.2, 6.4 Hz, 1H), 4.40-4.51 (m, 1H), 4.78 (c, *J* = 6.7 Hz, 1H), 5.88-6.21 (m, 1H), 6.82-6.92 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.3, 2.9 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 518.80.

Ejemplo 34 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona



El compuesto del título se preparó una película blancuzca de manera similar al Ejemplo 31 utilizando *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.45 (d, *J* = 6.8 Hz, 2H), 1.56 (d, *J* = 6.8 Hz, 1H), 1.93-2.02 (m, 2H), 2.11-2.18 (m, 2H), 2.63-3.18 (m, 4.5H), 3.35-3.51 (m, 5.5H), 3.78 (td, *J* = 14.5, 4.1 Hz, 2H), 4.01 (dd, *J* = 13.7, 5.4 Hz, 0.7H), 4.19-4.33 (m, 2H), 4.47 (dd, *J* = 7.3, 3.9 Hz, 1H), 4.70 (dd, *J* = 13.2, 5.9 Hz, 0.3H), 4.80-4.84 (m, 0.3H), 5.31 (c, *J* = 6.7 Hz, 0.7H), 5.93-6.20 (m, 1H), 6.85-6.92 (m, 1 H), 6.99 (ddd, *J* = 11.3, 8.7, 2.9 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 512.80.

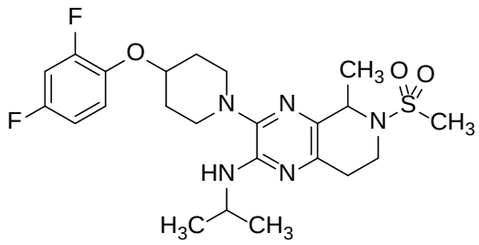
Ejemplo 35 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



El compuesto del título se preparó como una película amarilla claro de manera similar al Ejemplo 29 utilizando sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.30-1.36 (m, 6H), 1.45 (d, *J* = 6.8 Hz, 1.8H), 1.58 (d, *J* = 6.8 Hz, 1.2H), 1.98 (d, *J* = 6.8 Hz, 2H), 2.15 (dd, *J* = 8.5, 4.6 Hz, 2H), 2.19-2.23 (m, 3H), 2.70-2.85 (m, 1.4H), 2.91-3.17 (m, 3.3H), 3.44-3.57 (m, 2.7H), 4.06-4.19 (m, 1.6H), 4.48-4.55 (m, 1H), 4.76 (dd, *J* = 13.7, 5.4 Hz, 0.4H), 5.35 (c, *J* = 6.8 Hz, 0.6H), 6.86-6.92 (m, 1H), 7.00 (ddd, *J* = 11.3, 8.7,

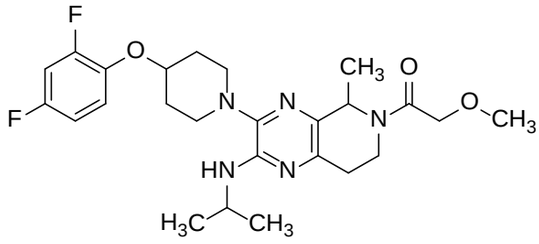
2.9 Hz, 1H), 7.19 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 460.2.

Ejemplo 36 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



El compuesto del título se preparó una película blancuzca de manera similar al Ejemplo 30 utilizando sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 1.25-1.31 (m, 6H), 1.52 (d, *J* = 6.4 Hz, 3H), 1.90-2.02 (m, 2H), 2.09-2.19 (m, 2H), 2.70 (dd, *J* = 17.3, 3.2 Hz, 1H), 2.88-3.13 (m, 6H), 3.37-3.50 (m, 3H), 3.98 (dd, *J* = 14.2, 6.4 Hz, 1H), 4.15 (dt, *J* = 13.1, 6.4 Hz, 1H), 4.48 (dt, *J*=7.4, 3.8 Hz, 1H), 4.77 (c, *J* = 7.0 Hz, 1H), 6.84-6.92 (m, 1H), 6.99 (ddd, *J* = 11.4, 8.7, 2.9 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 496.90.

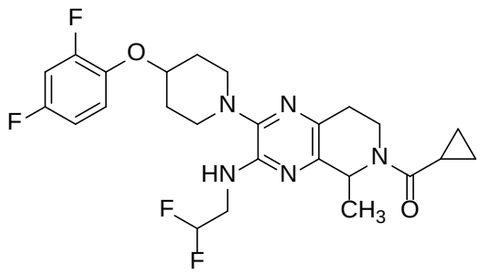
Ejemplo 37 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona



El compuesto del título se preparó una película blancuzca de manera similar al Ejemplo 31 utilizando *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.29-1.37 (m, 6H), 1.47 (d, *J* = 6.8 Hz, 2H), 1.58 (d, *J* = 6.8 Hz, 1H), 1.98 (d, *J* =9.8 Hz, 2H), 2.14 (s a, 2H), 2.72-2.88 (m, 1.5H), 2.92-3.00 (m, 0.8H), 3.09-3.17 (m, 2.5H), 3.41-3.53 (m, 5.7H), 4.06 (dd, *J* = 14.2, 5.4 Hz, 0.8H), 4.10-4.33 (m, 3.2H), 4.52 (d, *J* = 3.4 Hz, 1H), 4.72 (dd, *J* = 13.4, 5.6 Hz, 0.4H), 4.80-4.84 (m, 0.4H), 5.31 (c, *J* = 6.3 Hz, 0.7H), 6.89

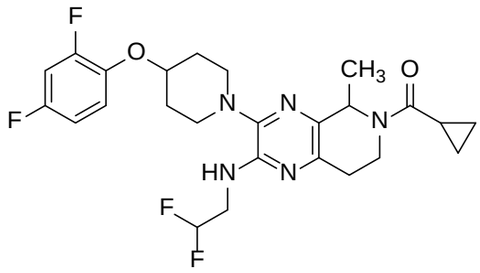
(t, *J* = 8.5 Hz, 1H), 7.00 (ddd, *J* = 11.2, 8.5, 3.2 Hz, 1H), 7.19 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 490.95.

Ejemplo 38 ciclopropil(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona



El compuesto del título se preparó una película blancuzca de manera similar al Ejemplo 31 utilizando sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 0.81-1.05 (m, 4H), 1.45 (d, *J* = 6.8 Hz, 1.6H), 1.64 (d, *J* = 6.8 Hz, 1.4H), 1.94-2.18 (m, 5.4H), 2.61-2.83 (m, 1.6H), 2.89-3.12 (m, 3.2H), 3.35-3.44 (m, 2.1H), 3.51-3.60 (m, 0.6H), 3.71-3.86 (m, 2H), 4.42-4.51 (m, 1.6H), 4.70 (dd, *J* = 13.2, 4.9 Hz, 0.5H), 5.21-5.37 (m, 1H), 5.91-6.20 (m, 1H), 6.85-6.91 (m, 1H), 6.99 (ddd, *J* = 11.3, 8.7, 2.9 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 508.85.

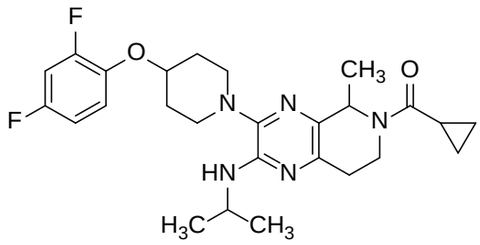
Ejemplo 39 ciclopropil(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona



El compuesto del título se preparó como una película blanca de manera similar al Ejemplo 31 utilizando sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 0.80-1.06 (m, 4H), 1.43 (d, *J* = 6.8 Hz, 1.5H), 1.62 (d, *J* = 6.8 Hz, 1.5H), 1.91-2.20 (m, 5.5H), 2.62-2.83 (m, 1.6H), 2.90-3.13 (m, 3.2H), 3.35-3.48 (m, 2.1H), 3.52-3.61 (m, 0.5H), 3.78 (td, *J* = 14.4, 3.9 Hz, 2H), 4.46 (dd, *J* = 8.3, 4.4 Hz,

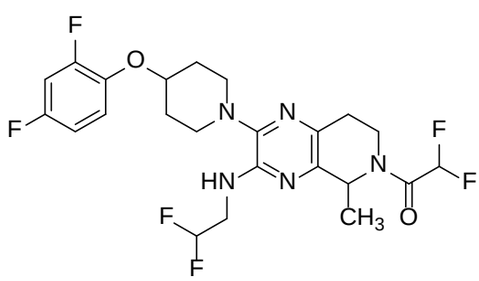
1.6H), 4.69 (dd, *J* = 13.2, 4.9 Hz, 0.5H), 5.21-5.38 (m, 1H), 5.92-6.20 (m, 1H), 6.88 (t, *J* = 8.5 Hz, 1H), 6.96-7.03 (m, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 508.85.

Ejemplo 40 ciclopropil(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona



El compuesto del título se preparó como una película amarilla claro de manera similar al Ejemplo 31 utilizando sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 0.79-1.05 (m, 4H), 1.30 (t, *J* = 6.3 Hz, 6H), 1.44 (d, *J* = 6.8 Hz, 1.5H), 1.63 (d, *J* = 6.8 Hz, 1.5H), 1.92-2.18 (m, 5.1H), 2.67-2.84 (m, 1.5H), 2.91-3.13 (m, 3H), 3.44 (td, *J* = 7.9, 3.7 Hz, 2H), 3.53-3.61 (m, 0.5H), 4.16 (dt, *J* = 11.8, 6.0 Hz, 1H), 4.49 (d, *J* = 7.3 Hz, 1.5H), 4.70 (dd, *J* = 12.9, 5.1 Hz, 0.4H), 5.21-5.37 (m, 1H), 6.89 (t, *J* = 8.3 Hz, 1H), 6.96-7.04 (m, 1H), 7.19 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 486.90.

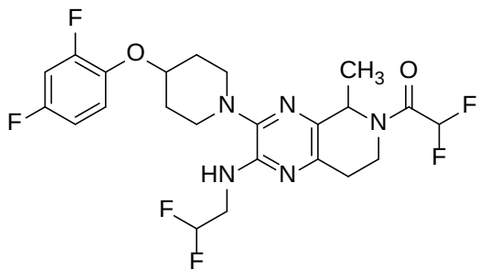
Ejemplo 41 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona



Una solución de ácido 2,2-difluoroacético (2.86 mg, 0.030 mmol), HATU (11.3 mg, 0.030 mmol), y DIPEA (14,2 µL, 0.081 mmol) en DMF (136 µL) se agitó a temperatura ambiente durante 10 min. Posteriormente, sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (15 mg, 0.027 mmol) se agregó y se continuó agitando durante la

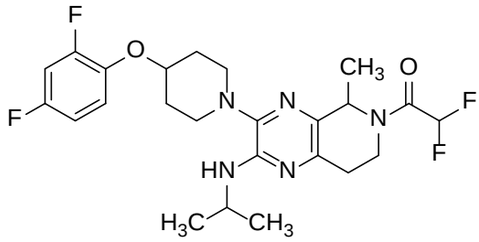
noche. No se detectó producto deseado mediante LCMS. A esto se agregó 2,2-anhídrido difluoroacético (7.08 mg, 0.041 mmol) y después de 1 h, purificación mediante HPLC Método A proporcionó el compuesto del título como una sal TFA (4,4 mg) una película blancuzca. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.51 (d, *J* = 6.8 Hz, 2.1H), 1.62 (d, *J* = 6.8 Hz, 0.9H), 1.94-2.02 (m, 2H), 2.10-2.18 (m, 2H), 2.68-2.78 (m, 1H), 2.82-3.06 (m, 3.2H), 3.36-3.44 (m, 2H), 3.53-3.61 (m, 0.7H), 3.71-3.88 (m, 2.1H), 4.16 (dd, *J* = 14.2, 5.4 Hz, 0.7H), 4.46 (dt, *J* = 7.4, 3.8 Hz, 1H), 4.67 (dd, *J* = 13.2, 5.9 Hz, 0.3H), 4.97 (c, *J* = 6.7 Hz, 0.3H), 5.27 (c, *J* = 6.8 Hz, 0.7H), 5.93-6.20 (m, 1H), 6.43-6.70 (m, 1H), 6.85-6.92 (m, 1H), 6.99 (ddd, *J* = 11.3, 8.4, 3.2 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z [M+H]$^+$ 518.80.

Ejemplo 42 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona



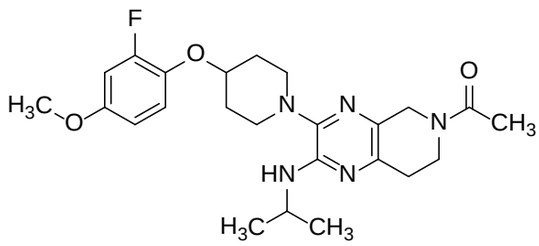
El compuesto del título se preparó una película blancuzca de manera similar al Ejemplo 41 utilizando sal TFA *de N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.50 (d, *J* = 6.8 Hz, 2.1H), 1.60 (d, *J* = 6.8 Hz, 0.9H), 1.92-2.03 (m, 2H), 2.11-2.18 (m, 2H), 2.68-2.77 (m, 1H), 2.82-3.08 (m, 3H), 3.26 (td, *J* = 12.9, 12.9, 3.9 Hz, 0.4H), 3.36-3.47 (m, 2H), 3.53-3.62 (m, 0.6H), 3.78 (td, *J* = 14.4, 4.4 Hz, 2H), 4.15 (dd, *J* = 13.9, 5.6 Hz, 0.7H), 4.43-4.49 (m, 1H), 4.66 (dd, *J* = 13.2, 5.9 Hz, 0.3H), 4.98 (c, *J* = 6.8 Hz, 0.3H), 5.28 (c, *J* = 6.8 Hz, 0.7H), 5.93-6.19 (m, 1H), 6.43-6.69 (m, 1H), 6.86-6.91 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.3, 2.9 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 518.85.

Ejemplo 43 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona



El compuesto del título se preparó una película blancuzca de manera similar al Ejemplo 41 utilizando sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.25-1.30 (m, 6H), 1.49 (d, *J* = 6.8 Hz, 2H), 1.60 (d, *J* = 6.3 Hz, 1H), 1.91-2.01 (m, 2H), 2.10-2.18 (m, 2H), 2.70-2.80 (m, 1H), 2.81-3.09 (m, 3H), 3.22-3.30 (m, 0.5H), 3.37-3.47 (m, 2H), 3.54-3.62 (m, 0.6H), 4.12-4.21 (m, 1.6H), 4.45-4.52 (m, 1H), 4.66 (dd, *J* = 13.4, 6.1 Hz, 0.3H), 4.93-4.99 (m, 0.3H), 5.26 (c, *J* = 6.5 Hz, 0.7H), 6.43-6.69 (m, 1H), 6.86-6.92 (m, 1H), 7.00 (ddd, *J* = 11.3, 8.7, 2.9 Hz, 1H), 7.19 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 496.90.

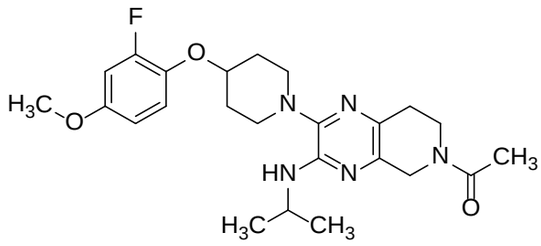
Ejemplo 44 1-(3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



Anhídrido acético (9 µL, 0.095 mmol) se agregó a una solución de sal TFA de 3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (25.2 mg, 0.048 mmol) y piridina (11.5 µL, 0.143 mmol) en DCM (500 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (25.2 mg, 93%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.32 (d, *J* = 6.6 Hz, 6H), 1.89-2.00 (m, 2H), 2.06-2.15 (m, 2H), 2.19 (s, 1.4H), 2.21 (s, 1.6H), 2.77-2.83 (m, 0.9H), 2.87-2.93 (m, 1.1H), 3.04-3.14 (m, 2H), 3.42-3.50 (m, 2H), 3.75 (s, 3H), 3.80-3.85 (m, 1.1H), 3.85-3.90 (m, 0.9H), 4.09-4.19 (m, 1H), 4.35-4.42 (m, 1H), 4.55 (s a, 2H), 6.67 (dt, *J*

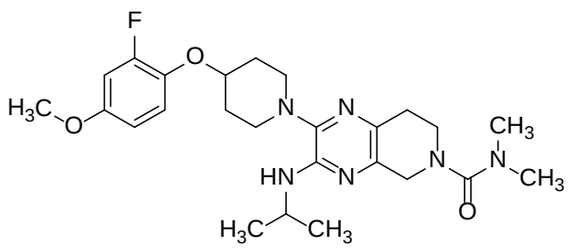
= 9.0, 1.4 Hz, 1H), 6.74 (dd, *J* = 12.8, 2.9 Hz, 1H), 7.08 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 458.4.

Ejemplo 45 1-(2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



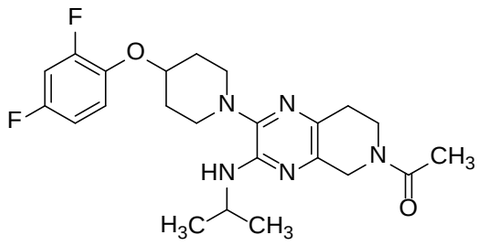
El compuesto del título se preparó de manera similar al Ejemplo 29 utilizando sal TFA de 2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina. ESI-MS m/z $[M+H]^+$ 458.40.

Ejemplo 46 2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-3-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



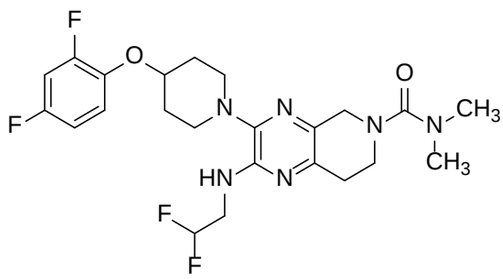
Se agregó cloruro dimetilcarbámico (4,9 mg, 0.046 mmol) a una solución de sal TFA de 2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (12.1 mg, 0.023 mmol) y trietilamina (10 µL, 0.069 mmol) en DCM (230 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (12.1 mg, 88%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.27-1.32 (m, 6H), 1.89-1.99 (m, 2H), 2.06-2.15 (m, 2H), 2.81 (s, 2H), 2.91 (s, 6H), 3.00-3.09 (m, 2H), 3.39-3.46 (m, 2H), 3.55 (t, *J* = 5.8 Hz, 2H), 3.75 (s, 3H), 4.13 (quinteto, *J* = 6.4 Hz, 1H), 4.30 (s, 2H), 4.34-4.40 (m, 1H), 6.67 (ddd, *J* = 8.9, 3.0, 1.5 Hz, 1H), 6.74 (dd, *J* = 12.8, 2.9 Hz, 1 H), 7.08 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 487.4.

Ejemplo 47 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



Una mezcla de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropilpirido[3,4-*b*]pirazin-3-amina (100 mg, 0.250 mmol), anhídrido acético (0.09 mL, 1.00 mmol) y Pd/C 10% (9.0 mg) en una mezcla de dioxano (2.5 mL) y acetona (1.5 mL) se agitó a temperatura ambiente durante 24 h. Posteriormente, 4,0 equivalentes de anhídrido acético se agregó y se continuó agitando durante 2 días. Después del filtrado, la reacción solución se inactivó con $NaHCO_3$ saturado y la capa acuosa se extrajo con acetato de etilo (3 x 5 mL). Las fases orgánicas combinadas se secaron con Na_2SO_4 anhidro y se concentraron al vacío. La purificación mediante cromatografía en columna de gel de sílice utilizando un gradiente de 30% a 100% de EtOAc en heptano proporcionó el compuesto del título (57 mg, 51%) como un sólido blanco. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.23 (d, *J* = 6.6 Hz, 3.3H), 1.24 (d, *J* = 6.6 Hz, 2.7H), 1.93 (m, 2H), 2.11 (m, 2H), 2.18 (s, 1.3H), 2.20 (s, 1.7H), 2.71 (t, *J* = 6.1 Hz, 0.9H), 2.80 (t, *J* = 6.1 Hz, 1.1H), 2.95 (m, 2H), 3.34 (m, 2H), 3.79 (t, *J* = 5.9 Hz, 1.1H), 3.84 (t, *J* = 6.1 Hz, 0.9H), 4.15 (m, 1H), 4.44 (tt, *J* = 7.5, 3.7 Hz, 1H), 4.53 (s, 0.9H), 4.54 (s, 1.1H), 6.86 (m, 1H), 6.97 (ddd, *J* = 11.2, 8.5, 3.2 Hz, 1H), 7.16 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 446.00.

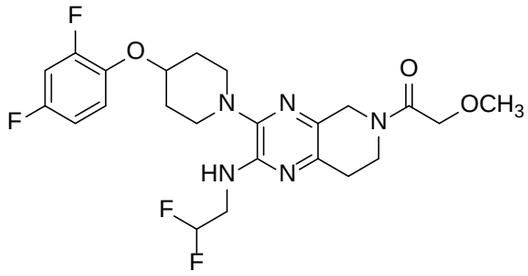
Ejemplo 49 2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-

tetrahidropirido[3,4-*b*]pirazin-2-amina (15 mg, 0.028 mmol) en DCM (278 µL) a temperatura ambiente se trató con cloruro dimetilcarbámico (3.0 mg, 0.028 mmol) y DIPEA (4,9 µL, 0.028 mmol), y la mezcla de reacción resultante se agitó durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (7 mg) como un sólido blanco. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.92-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.81-2.86 (m, 2H), 2.90 (s, 6H), 2.96-3.04 (m, 2H), 3.34-3.42 (m, 2H), 3.54 (t, *J* = 5.9 Hz, 2H), 3.74-3.84 (m, 2H), 4.28 (s, 2H), 4.46 (tt, *J* = 7.7, 3.9 Hz, 1H), 5.90-6.22 (m, 1H), 6.88 (dddd, *J* = 9.1, 8.1, 3.2, 1.9 Hz, 1H), 6.99 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1 H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 497.4.

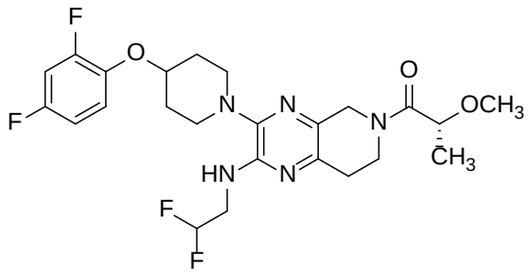
Ejemplo 50 1-(2-((2,2-difluoroetil)amino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona



Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-b]pirazin-2-amina (17 mg, 0.032 mmol), DIPEA (12.2 mg, 0.095 mmol) y cloruro de 2-metoxiacetilo (5.1 mg, 0.047 mmol) en DCM (315 µL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (7 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.92-2.03 (m, 2H), 2.09-2.18 (m, 2H), 2.77 (t, *J* = 5.8 Hz, 0.9H), 2.84 (t, *J* = 5.8 Hz, 1.1H), 2.96-3.04 (m, 2H), 3.37 (d, *J* = 10.4 Hz, 2H), 3.41 (s, 1.5H), 3.42 (s, 1.5H), 3.73-3.83 (m, 3H), 3.88 (t, *J* = 5.9 Hz, 1H), 4.24 (s, 0.9H), 4.27 (s, 1.1H), 4.41-4.49 (m, 1H), 4.50 (s, 0.9H), 4.53 (s, 1.1H), 5.89-6.21 (m, 1H), 6.84-

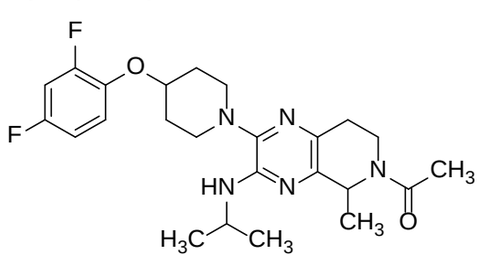
6.91 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 498.3.

Ejemplo 51 (*R*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona



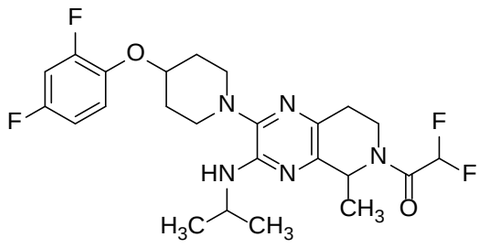
Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (17 mg, 0.032 mmol), DIPEA (12.2 mg, 0.095 mmol), y HATU (13.2 mg, 0.035 mmol) en DMF (158 µL) se agitó durante 10 min a temperatura ambiente. A esto se agregó ácido (R)-2-metoxipropanoico (3.6 mg, 0.035 mmol), y la mezcla de reacción resultante se agitó durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (6 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.32 (d, *J* = 6.8 Hz, 1.3 H), 1.38 (d, *J* = 6.6 Hz, 1.7H), 1.92-2.03 (m, 2H), 2.09-2.18 (m, 2H), 2.78 (t, *J* = 6.2 Hz, 0.9H), 2.86 (m, 1.1H), 2.97-3.06 (m, 2H), 3.33 (s, 3H), 3.35-3.43 (m, 2H), 3.79 (td, *J* = 14.5, 4.3 Hz, 2H), 3.85-3.97 (m, 2H), 4.36 (dc, *J* = 12.7, 6.5 Hz, 1H), 4.42-4.49 (m, 1H), 4.58 (m, 0.9H), 4.68 (m, 1.1H), 5.90-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, *J* = 11.4, 8.5, 3.0 Hz, 1 H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 512.4.

Ejemplo 52 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



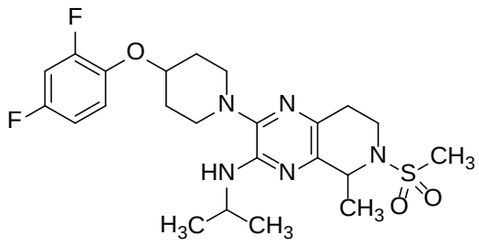
El compuesto del título se preparó como un película amarilla de manera similar al Ejemplo 29 utilizando sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.24-1.31 (m, 6H), 1.46 (d, *J* = 6.8 Hz, 2H), 1.59 (d, *J* = 6.8 Hz, 1H), 1.92-2.00 (m, 2H), 2.09-2.17 (m, 2H), 2.19-2.23 (m, 3H), 2.61-2.82 (m, 1.5H), 2.87-2.96 (m, 0.7H), 2.99-3.09 (m, 2.4H), 3.40 (td, *J* = 7.7, 3.7 Hz, 2H), 3.49-3.57 (m, 0.6H), 4.06 (dd, *J* = 13.9, 5.6 Hz, 0.6H), 4.13-4.20 (m, 1H), 4.48 (td, *J* = 7.2, 3.7 Hz, 1H), 4.73 (dd, *J* = 13.4, 5.6 Hz, 0.4H), 4.84 (s a, 0.2H), 5.39 (c, *J* = 6.5 Hz, 0.6H), 6.85-6.91 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.3, 2.9 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 460.90.

Ejemplo 53 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona



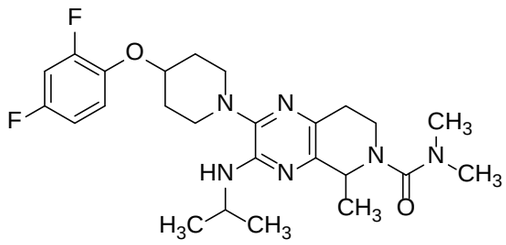
Una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (15 mg, 0.028 mmol), 2,2-anhídrido difluoroacético (7.4 mg, 0.042 mmol), y DIPEA (10.94 mg, 0.085 mmol) en DCM (141 µL) se agitó a temperatura ambiente durante 1 h. La purificación mediante HPLC Método A proporcionó el compuesto del título como una sal TFA (8.2 mg) una película blancuzca. ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.27 (dd, *J* = 7.6, 6.6 Hz, 6H), 1.51 (d, *J* = 6.8 Hz, 2.1H), 1.62 (d, *J* = 6.8 Hz, 0.9H), 1.90-2.00 (m, 2H), 2.09-2.17 (m, 2H), 2.65-2.75 (m, 1H), 2.80-3.03 (m, 3H), 3.25 (td, *J* = 12.9, 3.9 Hz, 0.3H), 3.34-3.42 (m, 2H), 3.52-3.61 (m, 0.7H), 4.11-4.21 (m, 1.7H), 4.46 (dt, *J* = 7.3, 3.7 Hz, 1H), 4.66 (dd, *J* = 13.4, 5.6 Hz, 0.3H), 4.91-4.98 (m, 0.3H), 5.25 (c, *J* =6.7 Hz, 0.7H), 6.44-6.69 (m, 1H), 6.84-6.92 (m, 1H), 6.99 (ddd, *J* = 11.3, 8.4, 3.2 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 496.90.

Ejemplo 54 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



El compuesto del título se preparó una película blancuzca de manera similar al Ejemplo 30 utilizando sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 1.26 (dd, *J* = 10.7, 6.4 Hz, 6H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.88-2.00 (m, 2H), 2.07-2.18 (m, 2H), 2.64 (dd, *J* = 16.6, 2.9 Hz, 1H), 2.89-2.92 (m, 4H), 2.94-3.03 (m, 3H), 3.34-3.48 (m, 3H), 3.97 (dd, *J* = 14.2, 6.4 Hz, 1H), 4.15 (quinteto, *J* = 6.5 Hz, 1H), 4.46 (dt, *J* = 7.4, 3.8 Hz, 1H), 4.76 (c, *J* = 6.7 Hz, 1H), 6.81-6.92 (m, 1H), 6.98 (ddd, *J* = 11.4, 8.4, 3.2 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 496.95.

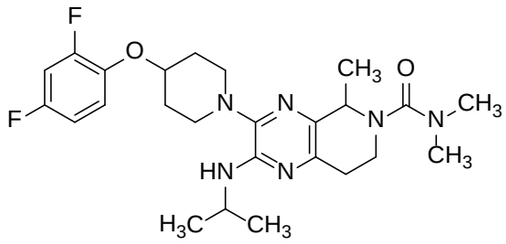
Ejemplo 55 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



Una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (15 mg, 0.028 mmol), cloruro dimetilcarbámico (6.1 mg, 0.056 mmol), y DIPEA (10.9 mg, 0.085 mmol) en DCM (282 µL) se agitó a temperatura ambiente durante la noche. La purificación mediante HPLC Método A proporcionó el compuesto del título como una sal TFA (6.1 mg) una película blancuzca. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 1.26 (dd, *J* = 9.3, 6.4 Hz, 6H), 1.50 (d, *J* = 6.8 Hz, 3H), 1.89-1.98 (m, 2H), 2.12 (dc, *J* = 13.2, 3.6 Hz, 2H), 2.55-2.64 (m, 1H), 2.88 (s, 6H), 2.94-3.03 (m, 3H), 3.34-3.41 (m, 3H), 3.72-3.82 (m, 1H), 4.14 (quinteto, *J* = 6.5 Hz, 1H),

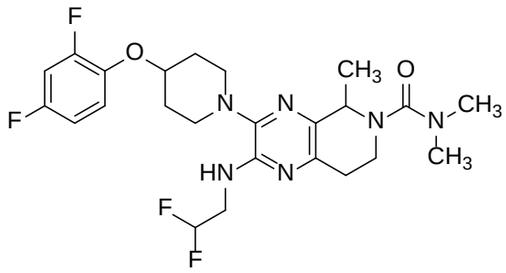
4.45 (dt, *J* = 7.4, 3.8 Hz, 1H), 4.67 (c, *J* = 6.8 Hz, 1H), 6.83-6.91 (m, 1H), 6.98 (ddd, *J* =11.4, 8.4, 3.2 Hz, 1H), 7.17 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 489.90.

Ejemplo 56 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



El compuesto del título se preparó como una película amarilla clara de manera similar al Ejemplo 55 utilizando sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 1.34 (dd, *J* = 6.4, 5.4 Hz, 6H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.91-2.03 (m, 2H), 2.10-2.18 (m, 2H), 2.70 (dd, *J* = 17.1, 2.9 Hz, 1H), 2.89 (s, 6H), 3.03 (s, 1H), 3.09-3.19 (m, 2H), 3.33-3.39 (m, 1H), 3.43-3.53 (m, 2H), 3.79 (dd, *J* = 14.2, 5.8 Hz, 1H), 4.08-4.18 (m, 1H), 4.46-4.57 (m, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 6.84-6.93 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.3, 2.9 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 489.95.

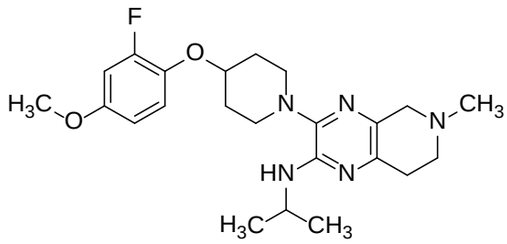
Ejemplo 57 2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



El compuesto del título se preparó una película blancuzca de manera similar al Ejemplo 55 utilizando sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 1.47 (d, *J* = 6.8 Hz, 3H), 1.96 (d, *J* = 8.3 Hz, 2H), 2.12 (d, *J* = 3.4 Hz, 2H), 2.64 (s, 1H), 2.88 (s, 6H), 2.97 (d, *J* = 11.7 Hz, 3H), 3.34-3.45 (m, 3H), 3.71-3.83 (m, 3H), 4.41-4.49 (m, 1H), 4.67 (d, *J* = 6.8

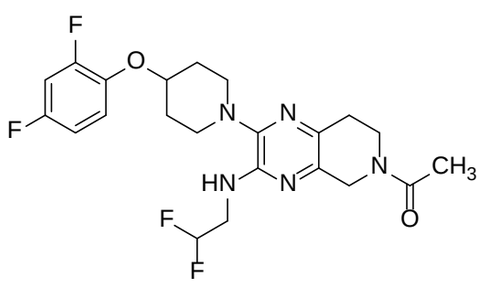
Hz, 1H), 6.05 (s, 1H), 6.87 (s, 1H), 6.95-7.02 (m, 1H), 7.13-7.21 (m, 1H); ESI-MS m/z $[M+H]^+$ 511.90.

Ejemplo 58 3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



Triacetoxiborohidruro de sodio (22.3 mg, 0.105 mmol) se agregó a una mezcla de DIPEA (18 µL, 0.105 mmol), sal TFA de 3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (27.9 mg, 0.053 mmol) y formaldehído (4 µL, 0.053 mmol) en MeOH (550 µL) a temperatura ambiente. Después de 30 min, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (27.9 mg, 97%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.25 (d, *J* = 6.3 Hz, 6H), 1.88-1.98 (m, 2H), 2.04-2.14 (m, 2H), 2.93-3.05 (m, 3H), 3.07 (s a, 4H), 3.33-3.40 (m, 2H), 3.41-3.69 (m, 2H), 3.75 (s, 3H), 4.15-4.32 (m, 3H), 4.32-4.39 (m, 1H), 6.66 (ddd, *J* = 8.9, 3.0, 1.5 Hz, 1 H), 6.73 (dd, *J* = 12.8, 2.9 Hz, 1H), 7.07 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 430.4.

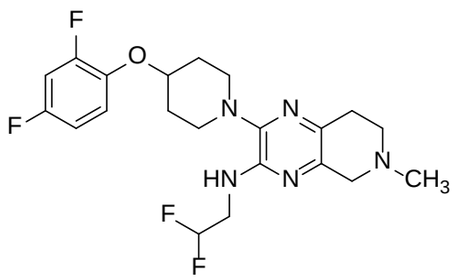
Ejemplo 59 1-(3-((2,2-difluoroetil)amino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



Una solución de sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (114 mg, 0.211 mmol) en DCM (2.11 mL) a 0 °C se trató con piridina (0.051 mL, 0.63 mmol) y anhídrido acético (0.040 mL, 0.42 mmol). La mezcla de reacción se agitó durante 30 min a 0 °C. La mezcla de reacción se concentró bajo presión reducida. El residuo se

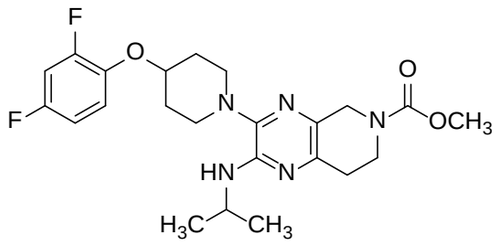
recogió en MeOH, se filtró, y se purificó mediante HPLC Método B, utilizando un gradiente 40% a 70% ACN para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo (39.7 mg, 32.3%). ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.96 (m, 2H), 2.12 (m, 2H), 2.18 (s, 1.3H), 2.20 (s, 1.7H), 2.73 (t, *J* = 5.9 Hz, 0.8H), 2.83 (t, *J* = 5.9Hz, 1.2H), 3.01 (m, 2H), 3.39 (m, 2H), 3.80 (m, 4H), 4.45 (dt, *J* = 7.0, 3.6 Hz, 1H), 4.57 (app d, 2H), 6.05 (m, 1H), 6.86 (m, 1H), 6.96 (ddd, *J* = 11.2, 8.5, 3.2 Hz, 1H), 7.15 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 468.4.

Ejemplo 60 *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



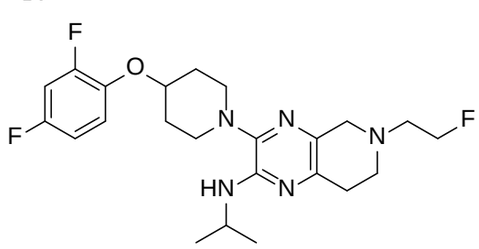
Una solución de sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (155 mg, 0.287 mmol) en MeOH (2.87 mL) se trató con DIPEA (0.100 mL, 0.575 mmol), formaldehído (0.021 mL, 0.29 mmol), y después de agitarse durante 5 min, triacetoxiborohidruro de sodio (122 mg, 0.575 mmol). La mezcla de reacción se agitó durante 30 min a temperatura ambiente. La mezcla de reacción se filtró y se purificó mediante HPLC (Bomba: Waters 2525 o 2545; MS: ZQ; Software: MassLynx. Se usó una columna Xbridge™ C18, 5 µm, ID 30 x 75 mm y se eluyó con 40% a 95% de 20/80 (v/v) agua/ACN (10 mmol NH_4HCO_3, pH 9.5-10) y agua (10 mmol NH_4HCO_3, pH 9.5-10)) para proporcionar el compuesto del título como un semisólido blancuzco (35.4 mg, 28.0%). ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 1.95 (m, 2H), 2.12 (m, 2H), 2.47 (s, 3H), 2.79 (m, 4H), 2.96 (ddd, *J* = 12.4, 8.8, 3.2 Hz, 2H), 3.35 (m, 2H), 3.49 (s, 2H), 3.75 (td, *J* = 14.6, 4.4 Hz, 2H), 4.43 (tt, *J* = 7.7, 3.5 Hz, 1H), 6.03 (m, 1H), 6.86 (m, 1H), 6.97 (ddd, *J* = 11.2, 8.5, 3.2 Hz, 1H), 7.16 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 440.4.

Ejemplo 61 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxilato de metilo



A una solución de sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (50 mg, 0.080 mmol) y trietilamina (0.026 mL, 0.185 mmol) en DCM (0.75 mL) se agregó carbonoclorhidrato de metilo (9.3 µL, 0.121 mmol) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 1 hr, se calentó hasta 23 °C, y se concentró mediante un evaporador rotatorio. El material bruto resultante se reconstituyó en DMSO, se lavó con DMSO, y se purificó mediante HPLC Método B utilizando un gradiente de 30% a 70% ACN para proporcionar el compuesto del título como una sal TFA (11.0 mg, 23.8%) como un sólido amarillo. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.18 (d, *J* = 6.8 Hz, 6H), 1.82-1.94 (m, 2H), 2.02-2.12 (m, 2H), 2.65 (t, *J* = 5.9 Hz, 2H), 2.83-2.93 (m, 2H), 3.21-3.33 (m, 2H), 3.63 (s, 3H), 3.64-3.68 (m, 2H), 4.06-4.17 (m, 1H), 4.34 (s a, 2H), 4.51 (tt, *J* = 8.1, 3.9 Hz, 1H), 5.51-5.65 (m, 1H), 6.99-7.05 (m, 1H), 7.25-7.35 (m, 2H); ESI-MS m/z $[M+H]^+$ 462.4.

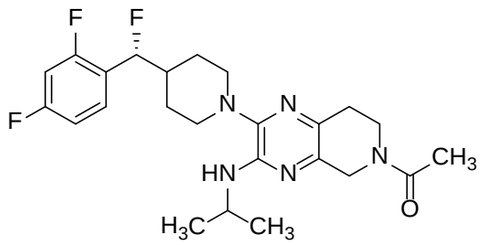
Ejemplo 62 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(2-fluoroetil)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



A una suspensión de sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (50 mg, 0.080 mmol) y K_2CO_3 (44,4 mg, 0.322 mmol) en acetona (2.0 mL) se agregó 1-bromo-2-fluoroetano (5.4 µL, 0.072 mmol) a 23 °C. La mezcla de reacción se agitó a 23 °C durante 1 h y posteriormente at 50 °C durante 3 días. La mezcla de reacción se enfrió a 23 °C, se agregó una porción adicional de 1-bromo-2-fluoroetano

(2.7 µL, 0.036 mmol), y la mezcla de reacción se calentó durante 1.5 hr adicionales a 50 °C, se enfrió a 23 °C, y se concentró mediante un evaporador rotatorio. El material bruto resultante se reconstituyó en DMSO, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B utilizando un gradiente de 30% a 70% ACN para proporcionar el compuesto del título como una sal TFA (10.7 mg, 23.6%) como un película amarilla. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.19 (d, J = 6.8 Hz, 6H), 1.83-1.92 (m, 2H), 2.02-2.13 (m, 2H), 2.79-2.96 (m, 3H), 2.96-3.11 (m, 0.9H), 3.24-3.36 (m, 2H), 3.38-3.55 (m, 1.1 H) 3.65 (s a, 1.1H), 3.71 (m, 0.9H), 3.73-3.84 (m, 1H), 4.12-4.19 (m, 1H), 4.28 (s a, 0.9H), 4.30 (s a, 1.1H), 4.54 (ddd, J = 11.7, 7.8, 3.9 Hz, 1H), 4.87 (t, J = 4.4 Hz, 0.9H), 4.88-4.95 (m, 1H), 4.97 (t, J = 4.4 Hz, 1.1H), 5.86 (d, J = 8.3 Hz, 1H), 6.97-7.08 (m, 1H), 7.25-7.37 (m, 2H); ESI-MS m/z [M+H]$^+$ 450.5.

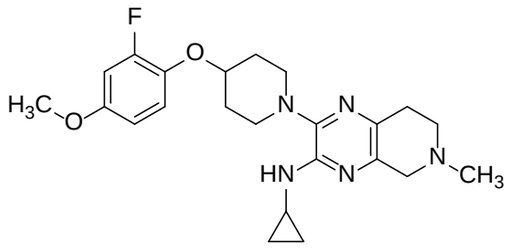
Ejemplo 63 (*R*)-1-(2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



Anhídrido acético (14,1 µL, 0.149 mmol) y ácido fórmico (38.1 µL, 0.994 mmol) se combinaron en THF (99 µL) y se agitó a temperatura ambiente durante 10 min. Esta solución se enfrió a 0 °C y se agregó una solución agitada de (*R*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (41.7 mg, 0.099 mmol) en THF (895 µL) a 0 °C. Después de 10 min, UPLC-MS indicó la conversión al producto acetilatado y no al formilatado. La mezcla de reacción se trató con MeOH, se concentró bajo presión reducida, se recogió en MeOH, se filtró, y se purificó mediante HPLC Método B para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo claro (17.5 mg, 30.6%). ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.28 (m, 6H), 1.45 (d, J = 12.7 Hz, 1H), 1.65 (m, 2H), 2.01 (m, 1H), 2.09 (m, 1H), 2.18 (s, 1.1H), 2.20 (s, 1.9H), 2.76 (m, 4H), 3.49 (m, 2H), 3.81 (t, J = 6.1 Hz, 1.3H), 3.85 (t, J = 5.9 Hz, 0.7H), 4.13

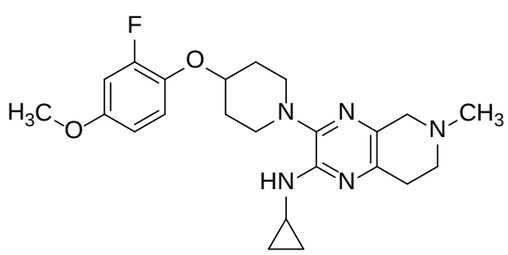
(m, 1H), 4.57 (s, 0.7H), 4.61 (s, 1.3H), 5.52 (m, 1H), 7.02 (m, 2H), 7.50 (m, 1H); ESI-MS m/z $[M+H]^+$ 462.4.

Ejemplo 65 *N*-ciclopropil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



Una mezcla de ciclopropanamina (13.6 mg, 0.237 mmol), sal TFA de 3-cloro-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina (30.9 mg, 0.059 mmol), terc-butóxido de sodio (11.4 mg, 0.119 mmol), BINAP (5.5 mg, 8.90 µmol) y $Pd_2(dba)_3$ (2.7 mg, 2.97 µmol) en tolueno (200 µL) se calentó a 90 °C durante 14 h. La mezcla se purificó directamente mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (12.9 mg, 40.2%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.53-0.58 (m, 2H), 0.75-0.81 (m, 2H), 1.86-1.96 (m, 2H), 2.02-2.12 (m, 2H), 2.64-2.70 (m, 1H), 2.94-3.02 (m, 1H), 3.08-3.12 (m, 3H), 3.17-3.27 (m, 3H), 3.34-3.42 (m, 2H), 3.59-3.68 (m, 2H), 3.75 (s, 3H), 4.25-4.41 (m, 3H), 6.64-6.69 (m, 1H), 6.70-6.76 (m, 1H), 7.03-7.10 (m, 1H); ESI-MS m/z $[M+H]^+$ 428.4.

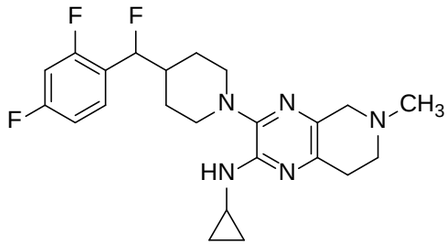
Ejemplo 66 *N*-ciclopropil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



Una mezcla de hidrocloruro de 4-(2-fluoro-4-metoxifenoxi)piperidina (15.8 mg, 0.060 mmol), 3-cloro-N-ciclopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-b]pirazin-2-amina (12 mg, 0.050 mmol), terc-butóxido de sodio (14,5 mg, 0.151 mmol), BINAP (4,7 mg, 7.54 µmol) y $Pd_2(dba)_3$ (2.3 mg, 2.51 µmol) en tolueno (250 µL) se calentó a 90 °C durante 14 h. La mezcla se purificó mediante HPLC Método A para

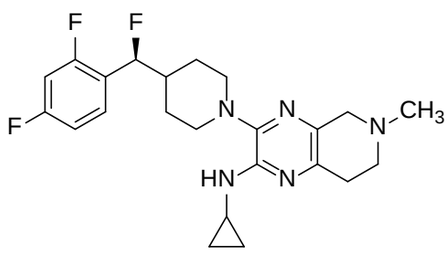
proporcionar el compuesto del título como una sal TFA (14,4 mg, 52.9%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.56-0.62 (m, 2H), 0.79-0.87 (m, 2H), 1.85-1.96 (m, 2H), 2.02-2.11 (m, 2H), 2.66-2.75 (m, 1H), 2.94-3.02 (m, 2H), 3.08-3.12 (m, 3H), 3.13-3.27 (m, 2H), 3.33-3.43 (m, 2H), 3.53-3.69 (m, 2H), 3.75 (s, 3H), 4.19-4.42 (m, 3H), 6.63-6.69 (m, 1H) 6.73 (dd, *J* = 12.9, 3.0 Hz, 1H), 7.02-7.09 (m, 1H); ESI-MS m/z $[M+H]^+$ 428.4.

Ejemplo 67 *N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



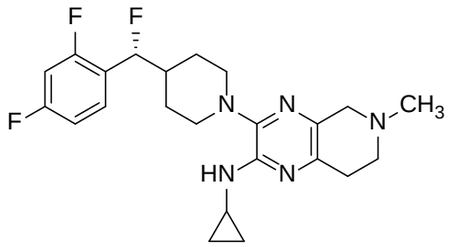
Una mezcla de hidrocloruro de 4-((2,4-difluorofenil)fluorometil)piperidina (16.0 mg, 0.060 mmol), 3-cloro-*N*-ciclopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (12 mg, 0.050 mmol), terc-butóxido de sodio (14,5 mg, 0.151 mmol), BINAP (4,7 mg, 7.54 µmol) y $Pd_2(dba)_3$ (2.3 mg, 2.51 µmol) en tolueno (250 µL) se calentó a 90 °C durante 14 h. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (11.1 mg, 40.5%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.57 (dt, *J* = 3.5, 1.4 Hz, 2H), 0.78-0.85 (m, 2H), 1.36-1.45 (m, 1H), 1.52-1.73 (m, 2H), 1.93-2.15 (m, 2H), 2.60-2.87 (m, 3H), 3.08 (s, 3H), 3.09 - 3.15 (m, 2H), 3.38-3.74 (m, 4H), 4.26 (s a, 2H), 5.51 (dd, *J* = 46.2, 7.3 Hz, 1H), 6.96-7.08 (m, 2H), 7.45-7.53 (m, 1H); ESI-MS m/z $[M+H]^+$ 432.4.

Ejemplo 68 (*S*)-*N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



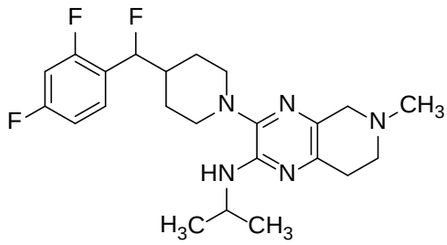
Una mezcla de hidrocloruro de (*S*)-4-((2,4-difluorofenil)fluorometil)piperidina (14,7 mg, 0.055 mmol), 3-cloro-*N*-ciclopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (11 mg, 0.046 mmol), terc-butóxido de sodio (13.3 mg, 0.138 mmol), BINAP (4,3 mg, 6.91 µmol), y $Pd_2(dba)_3$ (2.1 mg, 2.30 µmol) en tolueno (230 µL) se calentó a 90 °C durante 14 h. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (11.1 mg, 44,2%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.56-0.63 (m, 2H), 0.84 (m, *J* = 6.8 Hz, 2H), 1.40 (d, *J* = 12.9 Hz, 1H), 1.52-1.74 (m, 2H), 1.92-2.14 (m, 2H), 2.61-2.75 (m, 3H), 3.08 (s, 3H), 3.09-3.16 (m, 2H), 3.40-3.55 (m, 2H), 3.55-3.80 (m, 2H), 4.31 (s a, 2H), 5.50 (dd, *J* = 46.0, 7.6 Hz, 1H), 6.96-7.08 (m, 2H), 7.45-7.54 (m, 1H); ESI-MS m/z $[M+H]^+$ 432.4.

Ejemplo 69 (*R*)-*N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



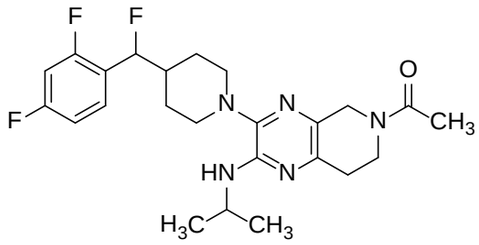
Una mezcla de hidrocloruro de (*R*)-4-((2,4-difluorofenil)fluorometil)piperidina (14,7 mg, 0.055 mmol), 3-cloro-*N*-ciclopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (11 mg, 0.046 mmol), terc-butóxido de sodio (13.3 mg, 0.138 mmol), BINAP (4,3 mg, 6.91 µmol) y $Pd_2(dba)_3$ (2.1 mg, 2.30 µmol) en tolueno (230 µL) se calentó a 90 °C durante 14 h. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (10.5 mg, 41.8%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 0.55-0.62 (m, 2H), 0.79-0.87 (m, 2H), 1.40 (d a, *J* = 12.4 Hz, 1H), 1.52-1.73 (m, 2H), 1.93-2.14 (m, 2H), 2.61-2.74 (m, 3H), 3.08 (s, 3H), 3.10-3.15 (m, 2H), 3.40-3.54 (m, 2H), 3.55-3.81 (m, 2H), 4.26 (s a, 2H), 5.50 (dd, *J* = 46.2, 7.8 Hz, 1H), 6.97-7.08 (m, 2H), 7.45-7.53 (m, 1H); ESI-MS m/z $[M+H]^+$ 432.3.

Ejemplo 70 3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



Se agregó triacetoxiborohidruro de sodio (15.3 mg, 0.072 mmol) a una mezcla de DIPEA (9.4 mg, 0.072 mmol), sal TFA de 3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-N-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (19.3 mg, 0.036 mmol) y formaldehído (3 µL, 0.036 mmol) en MeOH (360 µL) a temperatura ambiente. Después de 30 min, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (19.3 mg, 97%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.24 (dd, *J* = 6.4, 2.2 Hz, 6H), 1.40-1.48 (m, 1H), 1.53-1.74 (m, 2H), 1.96-2.14 (m, 2H), 2.60-2.73 (m, 2H), 2.93-3.06 (m a, 2H), 3.06 (s, 3H), 3.39-3.54 (m, 3H), 3.69-3.81 (m, 1H), 4.18 (dt, *J* = 13.1, 6.4 Hz, 2H), 4.16-4.36 (m a, 1H), 5.52 (dd, *J* = 46.2, 7.6 Hz, 1H), 6.97-7.08 (m, 2H), 7.47-7.54 (m, 1H); ESI-MS m/z [M+H]$^+$ 434.4.

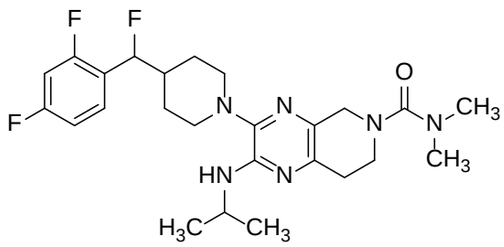
Ejemplo 71 1-(3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



Se agregó anhídrido acético (7 µL, 0.075 mmol) a una solución de sal TFA de 3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (20.1 mg, 0.038 mmol) y piridina (9 µL, 0.113 mmol) en DCM (380 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (20.1 mg, 93%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.29 (dd, *J* = 6.4, 1.9 Hz, 6H), 1.46 (s a, 1H), 1.56-1.77 (m, 2H), 2.00 (d, *J* = 12.9 Hz, 1H), 2.04-2.15 (m, 1H), 2.18 (s, 1.3H), 2.20 (s, 1.7H), 2.76 (cd, *J* = 12.8, 2.4 Hz, 3H), 2.87 (t, *J* = 5.9 Hz,

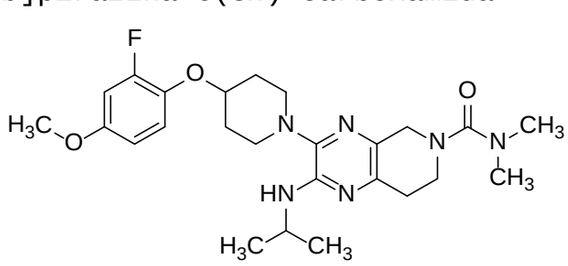
1H), 3.40-3.56 (m, 2H), 3.78-3.83 (m, 1.1H), 3.83-3.89 (m, 0.9H), 4.09-4.17 (m, 1H), 4.52 (s, 2H), 5.53 (dd, *J* = 46.7, 7.6 Hz, 1H), 6.97-7.08 (m, 2H), 7.47-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 462.4.

Ejemplo 72 3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-2-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



Se agregó cloruro dimetilcarbámico (8.4 mg, 0.078 mmol) a una solución de sal TFA de 3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (20.8 mg, 0.039 mmol) y trietilamina (16 µL, 0.117 mmol) en DCM (390 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (20.8 mg, 88%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.31 (dd, *J* = 6.6, 1.8 Hz, 6H), 1.40-1.48 (m, 1H), 1.58-1.78 (m, 2H), 1.95-2.03 (m, 1H), 2.03-2.18 (m, 1H), 2.71-2.88 (m, 4H), 2.90 (s, 6H), 3.42-3.52 (m, 2H), 3.54 (t, *J* = 5.7 Hz, 2H), 4.07-4.16 (m, 1H), 4.22-4.27 (m, 2H), 5.53 (dd, *J* = 46.5, 7.3 Hz, 1H), 6.97-7.08 (m, 2H), 7.47-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 491.4.

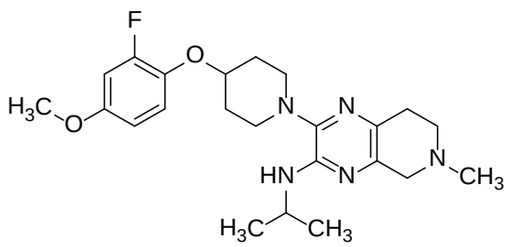
Ejemplo 73 3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-2-(isopropilamino)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



Se agregó cloruro dimetilcarbámico (10.5 mg, 0.097 mmol) a una solución de sal TFA de 3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (25.8 mg, 0.049 mmol)

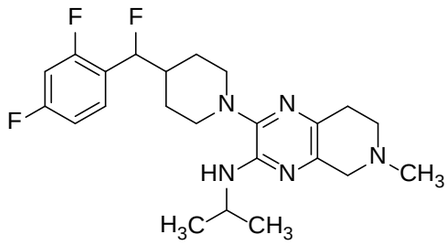
y trietilamina (20.5 µL, 0.146 mmol) en DCM (500 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (25.8 mg, 88%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.33 (d, J = 6.3 Hz, 6H), 1.89-2.00 (m, 2H), 2.06-2.16 (m, 2H), 2.85-2.89 (m, 2H), 2.90 (s, 6H), 3.04-3.13 (m, 2H), 3.41-3.50 (m, 2H), 3.55 (t, J = 5.8 Hz, 2H), 3.76 (s, 3H), 4.08-4.18 (m, 1H), 4.27 (s, 2H), 4.35-4.42 (m, 1H), 6.67 (ddd, J = 9.0, 2.9, 1.5 Hz, 1H), 6.74 (dd, J = 12.9, 3.0 Hz, 1H), 7.08 (t, J = 9.2 Hz, 1H); ESI-MS m/z [M+H]$^+$ 487.4.

Ejemplo 74 2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



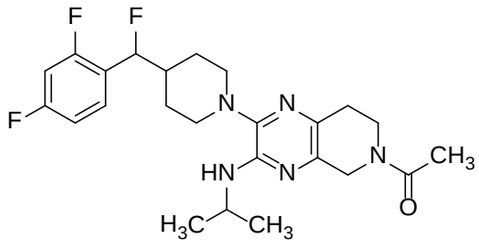
Se agregó triacetoxihidroborato de sodio (9.7 mg, 0.046 mmol) a una solución de DIPEA (8 µL, 0.046 mmol), sal TFA de 2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (12.1 mg, 0.023 mmol) y formaldehído (1.9 µL, 0.023 mmol) en MeOH (229 µL) a temperatura ambiente. Después de 30 min, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (12.1 mg, 97%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.24 (d, J = 6.3 Hz, 6H), 1.88-1.99 (m, 2H), 2.04-2.14 (m, 2H), 2.93-3.04 (m, 3H), 3.08 (s a, 4H), 3.35-3.53 (m, 3H), 3.76 (s a, 4H), 4.10-4.19 (m, 1H), 4.20-4.40 (m, 3H), 6.64-6.69 (m, 1H), 6.74 (dd, J = 12.8, 2.1 Hz, 1H), 7.07 (t, J = 9.2 Hz, 1H); ESI-MS m/z [M+H]$^+$ 430.4.

Ejemplo 75 2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



Se agregó triacetoxihidroborato de sodio (11.0 mg, 0.052 mmol) a una solución de DIPEA (9 µL, 0.052 mmol), sal TFA de 2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (13.9 mg, 0.026 mmol) y formaldehído (2 µL, 0.026 mmol) en MeOH (260 µL) a temperatura ambiente. Después de 30 min, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (13.9 mg, 97%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.23 (dd, *J* = 6.4, 2.4 Hz, 6H), 1.41-1.49 (m, 1H), 1.52-1.74 (m, 2H), 1.97-2.15 (m, 2H), 2.61-2.75 (m, 2H), 2.89-3.04 (m, 2H), 3.07 (s, 3H), 3.40-3.56 (m, 3H), 3.75 (s a, 1H), 4.13 (quinteto, *J* = 6.5 Hz, 1H), 4.18-4.38 (m, 2H), 5.53 (dd, *J* = 46.2, 7.6 Hz, 1H), 6.97-7.08 (m, 2H), 7.47-7.54 (m, 1H); ESI-MS m/z $[M+H]^+$ 434.4.

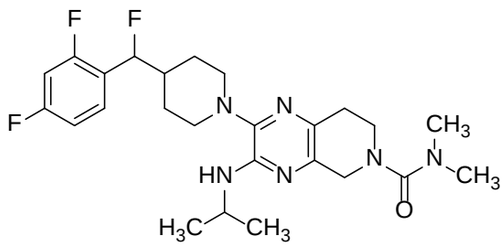
Ejemplo 76 1-(2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



Se agregó anhídrido acético (5 µL, 0.054 mmol) a una solución de sal TFA de 2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (14,3 mg, 0.027 mmol) y piridina (6.5 µL, 0.080 mmol) en DCM (270 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (14,3 mg, 93%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.23-1.31 (m, 6H), 1.45 (d, *J* = 12.9 Hz, 1H), 1.53-1.76 (m, 2H), 1.96-2.15 (m, 2H), 2.18 (s, 1.2H), 2.21 (s, 1.8H), 2.67-2.84 (m, 4H), 3.38-3.55 (m, 2H), 3.78-3.83 (m, 1.2H),

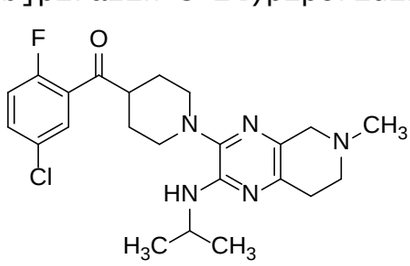
3.83-3.87 (m, 0.8H), 4.13 (dc, *J* = 12.6, 6.3 Hz, 1H), 4.56 (s, 0.8H), 4.59 (s, 1.2H), 5.53 (dd, *J* = 46.2, 7.6 Hz, 1H), 6.97-7.09 (m, 2H), 7.47-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 462.4.

Ejemplo 77 2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



Se agregó cloruro dimetilcarbámico (5.8 mg, 0.054 mmol) a una solución de sal TFA de 2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (14,3 mg, 0.027 mmol) y trietilamina (11 µL, 0.080 mmol) en DCM (270 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (14,3 mg, 88%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.29 (dd, *J* = 6.4, 1.9 Hz, 6H), 1.40-1.49 (m, 1H), 1.55-1.77 (m, 2H), 2.01 (d, *J* = 13.1 Hz, 2H), 2.70-2.84 (m, 4H), 2.87-2.94 (m, 6H), 3.40-3.52 (m, 2H), 3.53-3.57 (m, 2H), 4.11 (quinteto, *J* = 6.4 Hz, 1H) 4.29 (s, 2H) 5.53 (dd, *J* = 46.2, 7.3 Hz, 1H), 6.97-7.09 (m, 2H), 7.47-7.55 (m, 1H); ESI-MS m/z $[M+H]^+$ 491.4.

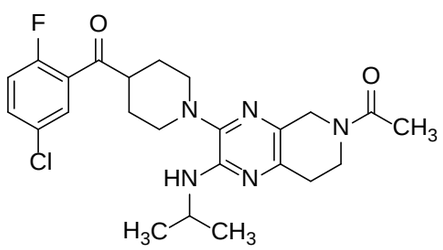
Ejemplo 78 (5-cloro-2-fluorofenil)(1-(2-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)metanona



Se agregó triacetoxihidroborato de sodio (6.9 mg, 0.033 mmol) a una solución de DIPEA (6 µL, 0.033 mmol), sal TFA de (5-cloro-2-fluorofenil)(1-(2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)metanona

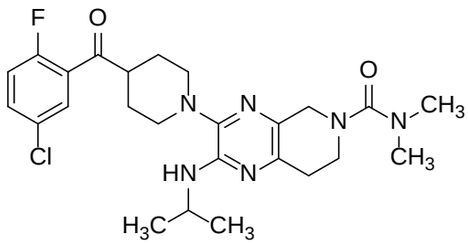
(8.9 mg, 0.016 mmol) y formaldehído (1.5 µL, 0.016 mmol) en MeOH (160 µL) a temperatura ambiente. Después de 30 min, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (2.2 mg, 24,1%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.24 (d, *J* = 6.6 Hz, 6H), 1.81-1.94 (m, 2H), 1.96-2.05 (m, 2H), 2.85 (t, *J* = 11.5 Hz, 2H), 3.00 (d, *J* = 6.3 Hz, 2H), 3.07 (s, 3H), 3.44-3.53 (m, 4H), 3.71-3.82 (m, 1H), 4.14-4.23 (m, 2H), 4.28-4.37 (m, 1H), 7.28 (dd, *J* = 10.6, 8.8 Hz, 1H), 7.61 (ddd, *J* = 8.8, 4.1, 2.8 Hz, 1H), 7.75 (dd, *J* = 6.1, 2.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 446.3.

Ejemplo 79 1-(3-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



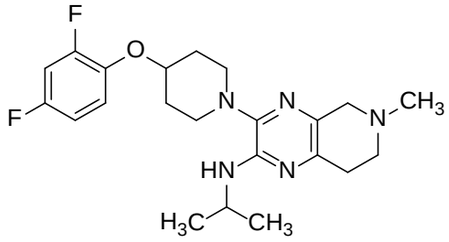
Se agregó anhídrido acético (3 µL, 0.034 mmol) a una solución de sal TFA de (5-cloro-2-fluorofenil)(1-(2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)metanona (9.2 mg, 0.017 mmol) y piridina (4 µL, 0.051 mmol) en DCM (170 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (4,0 mg, 40.4 %) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.30-1.34 (m, 6H), 1.88-2.04 (m, 4H), 2.19 (s, 1.4H), 2.21 (s, 1.6H), 2.77-2.83 (m, 0.9H), 2.87-2.92 (m, 1.1H), 2.93-3.02 (m, 2H), 3.34-3.43 (m, 1H), 3.50-3.59 (m, 2H), 3.80-3.85 (m, 1.1H), 3.85-3.90 (m, 0.9H), 4.08-4.17 (m, 1H), 4.54 (s a, 2H), 7.25-7.32 (m, 1H), 7.59-7.63 (m, 1H), 7.76 (dd, *J* = 6.1, 2.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 474.3.

Ejemplo 80 3-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-2-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



Se agregó cloruro dimetilcarbámico (3.8 mg, 0.036 mmol) a una solución de sal TFA de (5-cloro-2-fluorofenil)(1-(2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)metanona (9.7 mg, 0.018 mmol) y trietilamina (7 µL, 0.053 mmol) en DCM (180 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (3.6 mg, 32.8%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.31-1.34 (m, 6H), 1.89-2.06 (m, 4H), 2.85-2.89 (m, 2H), 2.90-2.92 (m, 6H), 2.93-3.02 (m, 2H), 3.35-3.41 (m, 1H), 3.50-3.58 (m, 4H), 4.08-4.16 (m, 1H), 4.27 (s, 2H), 7.29 (dd, *J* = 10.6, 8.8 Hz, 1H), 7.61 (ddd, *J* = 8.8, 4.0, 2.8 Hz, 1H), 7.76 (dd, *J* = 6.1, 2.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 504.4.

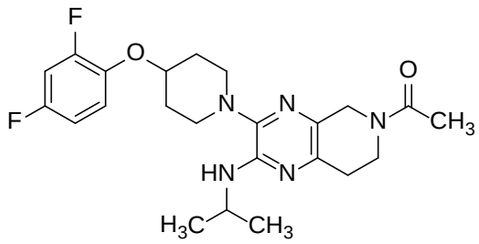
Ejemplo 81 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



Se agregó triacetoxihidroborato de sodio (12.3 mg, 0.058 mmol) a una solución de DIPEA (10 µL, 0.058 mmol), sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (15.0 mg, 0.029 mmol) y formaldehído (2 µL, 0.029 mmol) en MeOH (290 µL) a temperatura ambiente. Después de 30 min, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (12.3 mg, 80%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.25 (d, *J* = 6.6 Hz, 6H), 1.90-2.00 (m, 2H), 2.07-2.16 (m, 2H), 2.96-3.05 (m, 3H), 3.08 (s a, 4H), 3.33-3.42 (m, 2H), 3.43-3.85 (m, 2H), 4.14-4.38 (m, 3H), 4.44-4.51 (m, 1H), 6.84-6.91 (m,

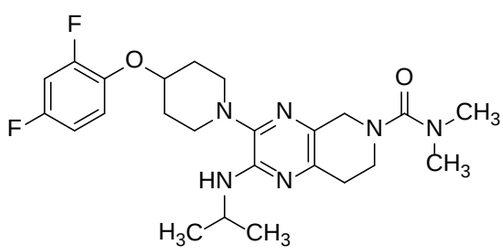
1H), 6.95-7.02 (m, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 418.3.

Ejemplo 82 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



Se agregó anhídrido acético (5 µL, 0.058 mmol) a una solución de sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (15.1 mg, 0.029 mmol) y piridina (7 µL, 0.088 mmol) en DCM (290 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (12.7 mg, 78%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.33 (d, *J* = 6.6 Hz, 6H), 1.91-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.19 (s, 1.4H), 2.21 (s, 1.6H), 2.77-2.83 (m, 0.9H), 2.88-2.94 (m, 1.1H), 3.12 (td, *J* = 8.5, 4.0 Hz, 2H), 3.43-3.51 (m, 2H), 3.80-3.85 (m, 1.1H), 3.86-3.91 (m, 0.9H), 4.10-4.18 (m, 1H), 4.47-4.54 (m, 1H), 4.55 (s a, 2H), 6.85-6.92 (m, 1H), 6.99 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 446.4.

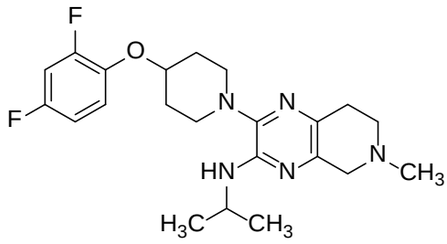
Ejemplo 83 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



Se agregó cloruro dimetilcarbámico (6.4 mg, 0.059 mmol) a una solución de sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (15.3 mg, 0.030 mmol) y trietilamina (12 µL, 0.089 mmol) en DCM (300 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del

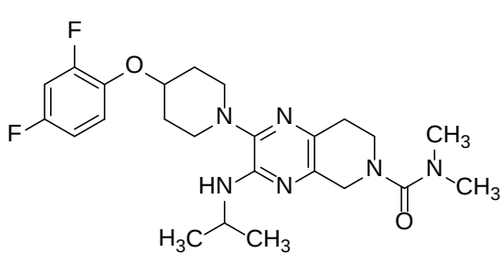
título como una sal TFA (11.1 mg, 63.8%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.31 (d, J = 6.3 Hz, 6H), 1.91-2.01 (m, 2H), 2.09-2.18 (m, 2H), 2.86 (t, J = 5.7 Hz, 2H), 2.90 (s, 6H), 3.03-3.11 (m, 2H), 3.39-3.47 (m, 2H), 3.55 (t, J = 5.7 Hz, 2H), 4.14 (quinteto, J = 6.4 Hz, 1H), 4.27 (s, 2H), 4.49 (tt, J = 7.3, 3.6 Hz, 1H), 6.84-6.91 (m, 1H), 6.99 (ddd, J = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 475.4.

Ejemplo 84 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



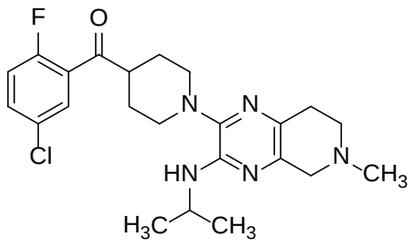
Se agregó triacetoxihidroborato de sodio (9.9 mg, 0.047 mmol) a una solución de DIPEA (8 µL, 0.047 mmol), sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (12.1 mg, 0.023 mmol) y formaldehído (2 µL, 0.023 mmol) en MeOH (230 µL) a temperatura ambiente. Después de 30 min, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (8.9 mg, 71.6%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.24 (d, J = 6.3 Hz, 6H), 1.90-2.00 (m, 2H), 2.08-2.17 (m, 2H), 2.95-3.06 (m, 3H), 3.12 (s a, 4H), 3.35-3.53 (m, 3H), 3.76 (s a, 1H), 4.15 (dt, J = 13.1, 6.5, 6.5 Hz, 1H), 4.19-4.38 (m, 2H), 4.48 (tt, J = 7.3, 3.7 Hz, 1H), 6.85-6.92 (m, 1H), 6.99 (ddd, J = 11.4, 8.5, 3.0 Hz, 1H), 7.17 (td, J = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 418.3.

Ejemplo 85 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



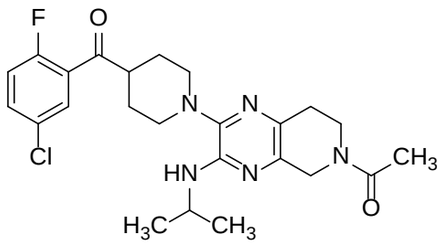
Se agregó cloruro dimetilcarbámico (5.2 mg, 0.049 mmol) a una solución de sal TFA de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (12.6 mg, 0.024 mmol) y trietilamina (10 µL, 0.073 mmol) en DCM (240 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (8.0 mg, 55.8%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.28 (d, *J* = 6.6 Hz, 6H), 1.90-2.00 (m, 2H), 2.08-2.17 (m, 2H), 2.77-2.84 (m, 2H), 2.91 (s, 6H), 2.99-3.08 (m, 2H), 3.35-3.44 (m, 2H), 3.55 (t, *J* = 5.8 Hz, 2H), 4.09-4.17 (m, 1H), 4.29 (s, 2H), 4.44-4.51 (m, 1H), 6.84-6.91 (m, 1H), 6.99 (s, 1H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z [M+H]$^+$ 475.4.

Ejemplo 86 (5-cloro-2-fluorofenil)(1-(3-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)metanona



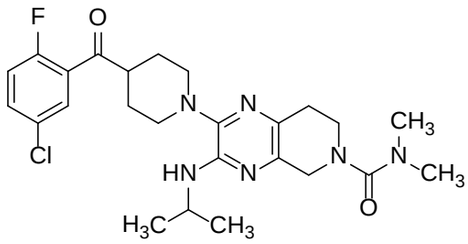
Se agregó triacetoxihidroborato de sodio (6.5 mg, 0.031 mmol) a una solución de DIPEA (5 µL, 0.031 mmol), sal TFA de (5-cloro-2-fluorofenil)(1-(3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-b]pirazin-2-il)piperidin-4-il)metanona (8.4 mg, 0.015 mmol) y formaldehído (1.5 µL, 0.015 mmol) en MeOH (150 µL) a temperatura ambiente. Después de 30 min, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (4,7 mg, 54,6%) como un sólido amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.24 (d, *J* = 6.6 Hz, 6H), 1.82-1.93 (m, 2H), 1.97-2.05 (m, 2H), 2.81-3.05 (m, 4H), 3.08 (s, 3H), 3.35-3.54 (m, 4H), 3.72-3.83 (m, 1H), 4.10-4.18 (m, 1H), 4.19-4.40 (m, 2H), 7.25-7.32 (m, 1H), 7.61 (ddd, *J* = 8.8, 4.3, 2.8 Hz, 1H), 7.75 (dd, *J* = 6.1, 2.8 Hz, 1H); ESI-MS m/z [M+H]$^+$ 446.3.

Ejemplo 87 1-(2-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



Se agregó anhídrido acético (3 µL, 0.029 mmol) a una solución de sal TFA de (5-cloro-2-fluorofenil)(1-(3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)metanona (8.0 mg, 0.015 mmol) y piridina (4 µL, 0.044 mmol) en DCM (150 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (3.6 mg, 42%) como un sólido amarillo. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.26-1.32 (m, 6H), 1.84-1.96 (m, 2H), 1.97-2.06 (m, 2H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.70-2.76 (m, 0.7H), 2.80-2.86 (m, 1.3H), 2.87-3.00 (m, 2H), 3.34-3.41 (m, 1H), 3.46-3.56 (m, 2H), 3.79-3.84 (m, 1.3H), 3.84-3.89 (m, 0.7H), 4.07-4.18 (m, 1H), 4.57 (s, 1.1H), 4.62 (s, 0.9H), 7.28 (dd, *J* = 10.4, 8.8 Hz, 1H), 7.61 (ddd, *J* = 8.9, 4.2, 2.9 Hz, 1H), 7.76 (dd, *J* = 6.1, 2.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 474.3.

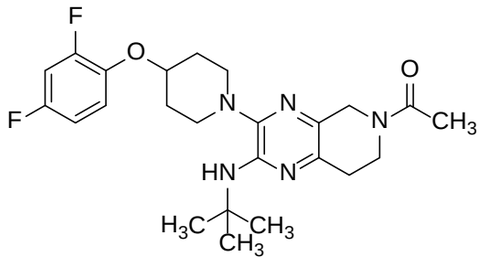
Ejemplo 88 2-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-3-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



Se agregó cloruro dimetilcarbámico (3.2 mg, 0.029 mmol) a una solución de sal TFA de (5-cloro-2-fluorofenil)(1-(3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)metanona (8.0 mg, 0.015 mmol) y trietilamina (6 µL, 0.044 mmol) en DCM (150 µL) a temperatura ambiente. Después de 1 h, la mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (3.9 mg, 43.1%) como un sólido amarillo. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.31 (d, *J* = 6.6 Hz, 6H), 1.85-2.05 (m, 4H), 2.77-2.84 (m, 2H), 2.91 (s, 6H), 2.93-3.01 (m, 2H), 3.36-3.41 (m, 1H), 3.51-3.59 (m, 4H), 4.07-4.15 (m, 1H), 4.31

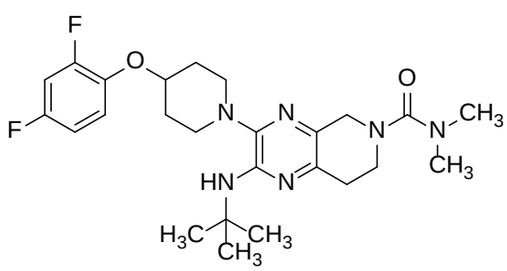
(s, 2H), 7.28 (dd, *J* = 10.4, 8.8 Hz, 1H), 7.61 (ddd, *J* = 8.8, 4.3, 2.8 Hz, 1H), 7.76 (dd, *J* = 6.1, 2.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 504.4.

Ejemplo 89 1-(2-(terc-butilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



Una solución de sal TFA de *N*-(terc-butil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (16 mg, 0.030 mmol), anhídrido acético (5.7 µL, 0.060 mmol), y DIPEA (15.8 µL, 0.090 mmol) en DCM (151 µL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (15 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.48 (s, 9H), 1.87-1.98 (m, 2H), 2.07-2.17 (m, 2H), 2.19 (s, 1.3H), 2.21 (s, 1.7H), 2.74 (t, *J* = 5.9 Hz, 0.9H), 2.84 (t, *J* = 5.9 Hz, 1.1H), 2.97 (ddd, *J* = 12.4, 8.6, 3.3 Hz, 2H), 3.33-3.37 (m, 2H), 3.80 (t, *J* = 5.9 Hz, 1.1H), 3.85 (t, *J* = 5.9 Hz, 0.9H), 4.43-4.51 (m, 1H), 4.53 (d, *J* = 1.3 Hz, 2H), 6.88 (ddddd, *J* = 9.1, 8.1, 2.9, 1.9, 0.8 Hz, 1H), 6.95-7.02 (m, 1H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 460.4.

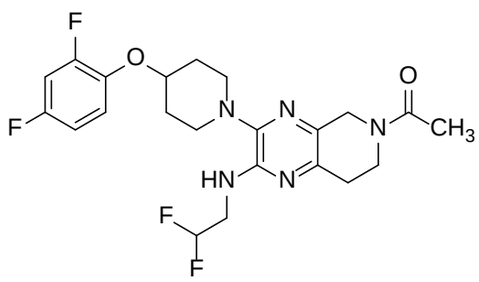
Ejemplo 90 2-(terc-butilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



Una solución de sal TFA de *N*-(terc-butil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (16 mg, 0.030 mmol), cloruro

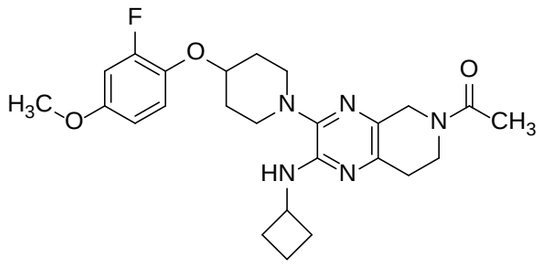
dimetilcarbámico (3.2 mg, 0.030 mmol), y DIPEA (5.3 µL, 0.030 mmol) en DCM (151 µL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (10 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.48 (s, 9H), 1.87-1.97 (m, 2H), 2.07-2.17 (m, 2H), 2.82 (t, *J* = 5.9 Hz, 2H), 2.90 (s, 6H), 2.95 (ddd, *J* = 12.2, 8.5, 3.3 Hz, 2H), 3.29-3.35 (m, 2H), 3.53 (t, *J* = 5.8 Hz, 2H), 4.25 (s, 2H), 4.46 (tt, *J* = 7.5, 3.8 Hz, 1H), 6.84-6.91 (m, 1H), 6.99 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z [M+H]$^+$ 489.4.

Ejemplo 91 1-(2-((2,2-difluoroetil)amino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



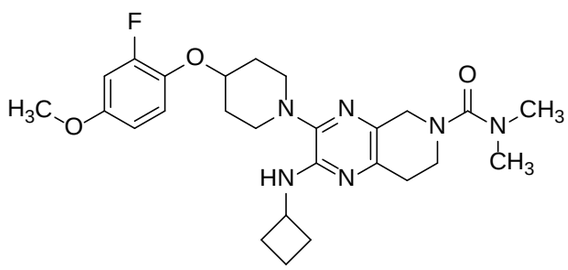
Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (15 mg, 0.028 mmol), anhídrido acético (5.2 µL, 0.056 mmol), y DIPEA (14,6 µL, 0.083 mmol) en DCM (139 µL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR) y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (13 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.91-2.03 (m, 2H), 2.09-2.17 (m, 2H), 2.19 (s, 1.3H), 2.21 (s, 1.7H), 2.75 (t, *J* = 5.9 Hz, 0.9H), 2.85 (t, *J* = 5.9 Hz, 1.1H), 2.95-3.05 (m, 2H), 3.34-3.42 (m, 2H), 3.73-3.79 (m, 2H), 3.81 (t, *J* = 5.9 Hz, 1.2H), 3.86 (t, *J* = 6.1 Hz, 0.8H), 4.46 (tc, *J* = 7.9, 3.9 Hz, 1H), 4.56 (d, *J* = 0.8 Hz, 2H), 5.89-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (dddd, *J* = 11.4, 8.5, 3.0, 1.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z [M+H]$^+$ 468.3.

Ejemplo 92 1-(2-(ciclobutilamino)-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



Una mezcla de sal TFA de *N*-ciclobutil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (10 mg, 0.018 mmol), anhídrido acético (3.8 mg, 0.037 mmol) y piridina (4,4 mg, 0.055 mmol) en DCM (190 µL) se agitó a temperatura ambiente durante 30 min. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (6.4 mg, 59%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.76-1.86 (m, 2H), 1.89-2.00 (m, 2H), 2.01-2.15 (m, 4H), 2.19 (s, 1.4H), 2.20 (s, 1.6H), 2.38-2.48 (m, 2H), 2.73-2.79 (m, 0.9H), 2.81-2.88 (m, 1.1H), 2.99-3.08 (m, 2H), 3.38-3.47 (m, 2H), 3.76 (s, 3H), 3.78-3.83 (m, 1.1H), 3.83-3.88 (m, 0.9H), 4.32-4.48 (m, 2H), 4.54 (s, 2H), 6.64-6.70 (m, 1H), 6.74 (dd, *J* = 12.8, 2.9 Hz, 1H), 7.08 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z [M+H]$^+$ 470.4.

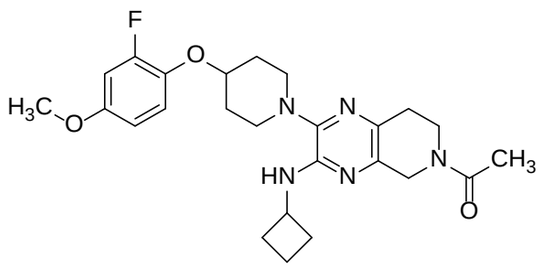
Ejemplo 93 2-(ciclobutilamino)-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



Una mezcla de sal TFA de *N*-ciclobutil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (10.6 mg, 0.020 mmol), cloruro dimetilcarbámico (4,2 mg, 0.039 mmol) y trietilamina (5.9 mg, 0.059 mmol) en DCM (200 µL) se agitó a temperatura ambiente durante 30 min. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (7.1 mg, 59.2%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.77-1.87 (m, 2H), 1.90-2.00 (m, 2H), 2.03-

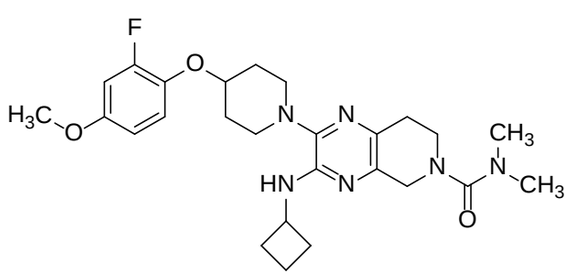
2.15 (m, 4H), 2.39-2.49 (m, 2H), 2.81-2.87 (m, 2H), 2.90 (s, 6H), 2.98-3.08 (m, 2H), 3.38-3.47 (m, 2H), 3.54 (t, *J* = 5.8 Hz, 2H), 3.76 (s, 3H), 4.26 (s, 2H), 4.33-4.47 (m, 2H), 6.67 (dd, *J* = 9.1, 1.5 Hz, 1H), 6.74 (dd, *J* = 12.8, 2.9 Hz, 1H), 7.08 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 499.4.

Ejemplo 94 1-(3-(ciclobutilamino)-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



Una mezcla de sal TFA de *N*-ciclobutil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (10.1 mg, 0.019 mmol), anhídrido acético (3.8 mg, 0.037 mmol) y piridina (4 mg, 0.056 mmol) en DCM (190 µL) se agitó a temperatura ambiente durante 30 min. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (9.7 mg, 89%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.78-1.87 (m, 2H), 1.91-2.01 (m, 2H), 2.03-2.16 (m, 4H), 2.19 (s, 1.2H), 2.21 (s, 1.8H), 2.38-2.50 (m, 2H), 2.70-2.76 (m, 0.8H), 2.80-2.87 (m, 1.2H), 3.00-3.11 (m, 2H), 3.40-3.50 (m, 2H), 3.76 (s, 3H), 3.79-3.83 (m, 1.2H), 3.84-3.88 (m, 0.8H), 4.34-4.48 (m, 2H), 4.57 (s, 0.8H), 4.61 (s, 1.2H), 6.64-6.69 (m, 1H), 6.74 (dd, *J* = 12.8, 2.9 Hz, 1H), 7.08 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 470.4.

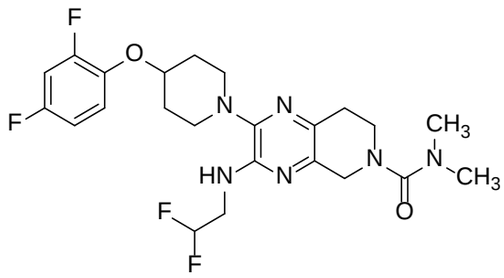
Ejemplo 95 3-(ciclobutilamino)-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



Una mezcla de sal TFA de *N*-ciclobutil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (9.1 mg, 0.017 mmol), cloruro dimetilcarbámico (3.6 mg, 0.034 mmol) y trietilamina (5.1 mg,

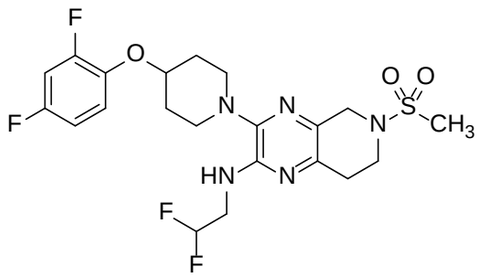
0.050 mmol) en DCM (170 µL) se agitó a temperatura ambiente durante 30 min. La mezcla se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (6.0 mg, 58.3%) como un película amarilla. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.74-1.84 (m, 2H), 1.89-2.04 (m, 4H), 2.06-2.15 (m, 2H), 2.36-2.46 (m, 2H), 2.79 (t, *J* = 5.7 Hz, 2H), 2.90 (s, 6H), 2.94-3.02 (m, 2H), 3.34-3.43 (m, 2H), 3.51-3.56 (m, 2H), 3.76 (s, 3H), 4.26 (s, 2H), 4.43 (s, 2H), 6.64-6.69 (m, 1H), 6.74 (dd, *J* = 12.9, 3.0 Hz, 1H), 7.08 (t, *J* = 9.2 Hz, 1H); ESI-MS m/z [M+H]$^+$ 499.4.

Ejemplo 96 3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



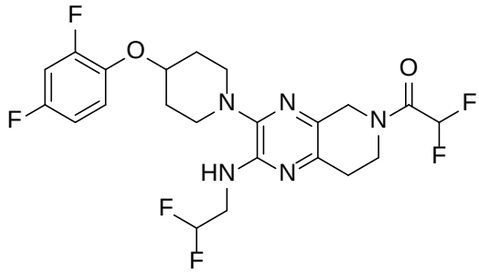
Una solución de sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (15 mg, 0.028 mmol), cloruro dimetilcarbámico (3.0 mg, 0.028 mmol), y DIPEA (4,9 µL, 0.028 mmol) en DCM (278 µL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método para proporcionar el compuesto del título como una sal TFA (5 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.92-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.82 (t, *J* = 5.8 Hz, 2H), 2.90 (s, 6H), 2.99 (ddd, *J* = 12.4, 8.6, 3.4 Hz, 2H), 3.34-3.41 (m, 2H), 3.55 (t, *J* = 5.8 Hz, 2H), 3.77 (td, *J* = 14.5, 4.3 Hz, 2H), 4.28 (s, 2H), 4.42-4.49 (m, 1H), 5.89-6.21 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z [M+H]$^+$ 497.4.

Ejemplo 97 *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (17 mg, 0.032 mmol), DIPEA (12.2 mg, 0.095 mmol) y cloruro de metanosulfonilo (4,9 µL, 0.063 mmol) en DCM (315 µL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (6 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.92-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.88 (t, *J* = 5.9 Hz, 2H), 2.93 (s, 3H), 3.00 (ddd, *J* = 12.4, 8.8, 3.3 Hz, 2H), 3.34-3.42 (m, 2H), 3.57 (t, *J* = 5.9 Hz, 2H), 3.78 (td, *J* = 14.5, 4.3 Hz, 2H), 4.28 (s, 2H), 4.46 (tt, *J* = 7.5, 3.6 Hz, 1H), 5.89-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 504.3.

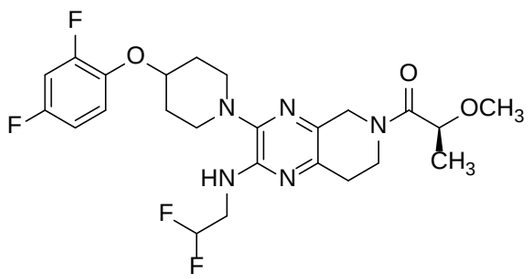
Ejemplo 98 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona



Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (17 mg, 0.032 mmol), DIPEA (12.2 mg, 0.095 mmol), y 2,2-anhídrido difluoroacético (8.2 mg, 0.047 mmol) en DCM (315 µL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una

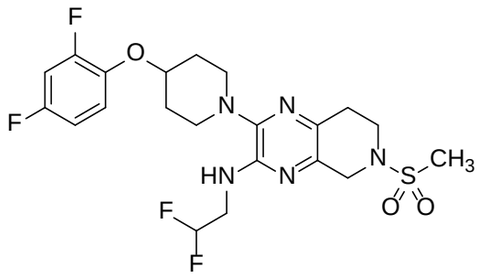
sal TFA (5 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.92-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.81 (t, *J* = 5.9 Hz, 0.8H), 2.87 (t, *J* = 5.9 Hz, 1.2H), 2.97-3.05 (m, 2H), 3.35-3.43 (m, 2H), 3.78 (td, *J* = 14.5, 4.3 Hz, 2H), 3.87-3.96 (m, 2H), 4.42-4.50 (m, 1H), 4.60 (s, 1.2H), 4.62 (s, 0.8H), 5.89-6.22 (m, 1H), 6.41-6.71 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 504.3.

Ejemplo 99 (*S*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona



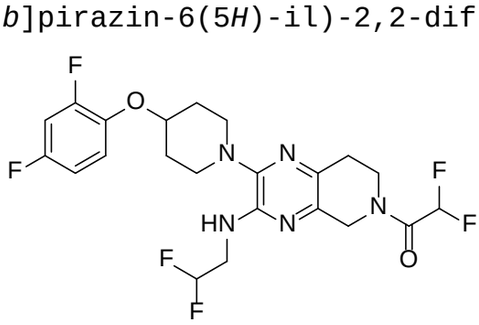
Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (17 mg, 0.032 mmol), HATU (13.2 mg, 0.035 mmol) y DIPEA (12.2 mg, 0.095 mmol) en DMF (158 µL) se agitó durante 10 min. Posteriormente, ácido (*S*)-2-metoxipropanoico (3.6 mg, 0.035 mmol) se agregó a temperatura ambiente y la mezcla de reacción resultante se agitó durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (6 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.32 (d, *J* = 6.6 Hz, 1.3H), 1.38 (d, *J* = 6.6 Hz, 1.7H), 1.91-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.77 (t, *J* = 5.8 Hz, 0.9H), 2.85 (t, *J* = 4.9 Hz, 1.1H), 2.96-3.05 (m, 2H), 3.33 (s, 3H), 3.35-3.43 (m, 2H), 3.78 (td, *J* = 14.5, 4.3 Hz, 2H), 3.84-3.97 (m, 2H), 4.31-4.40 (m, 1H), 4.42-4.49 (m, 1H), 4.59 (m, 0.9H), 4.67 (m, 1.1H), 5.90-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 512.4.

Ejemplo 100 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona



Una solución de sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (15 mg, 0.028 mmol), DIPEA (10.8 mg, 0.083 mmol) y cloruro de metanosulfonilo (4,3 µL, 0.056 mmol) en DCM (280 µL) se agitó a temperatura ambiente durante 2 h. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (3 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.92-2.02 (m, 2H), 2.09-2.18 (m, 2H), 2.87 (t, *J* = 5.9 Hz, 2H), 2.93 (s, 3H), 2.96-3.04 (m, 2H), 3.34-3.42 (m, 2H), 3.57 (t, *J* = 5.8 Hz, 2H), 3.76 (td, *J* = 14.5, 4.3 Hz, 2H), 4.28 (s, 2H), 4.42-4.49 (m, 1H), 5.89-6.21 (m, 1H), 6.85-6.91 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* =9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 504.4.

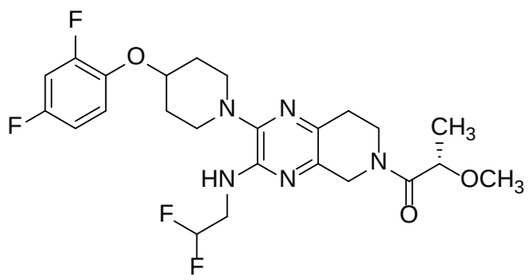
Ejemplo 101 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona



Una solución de sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (15 mg, 0.028 mmol), DIPEA (10.8 mg, 0.083 mmol), y 2,2-anhídrido difluoroacético (7.3 mg, 0.042 mmol) en DCM (278 µL) se agitó a temperatura ambiente durante 2 h. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45

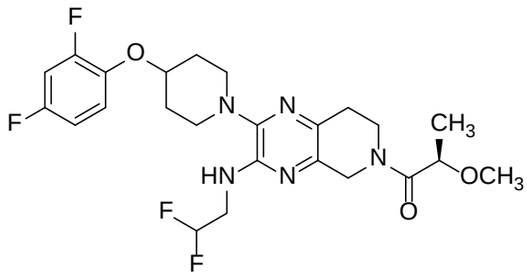
µm (Millipore® Millex-LCR) y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (3 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.92-2.02 (m, 2H), 2.09-2.17 (m, 2H), 2.80 (t, *J* = 5.9 Hz, 0.8H), 2.86 (t, *J* = 5.4 Hz, 1.2H), 2.96-3.04 (m, 2H), 3.34-3.43 (m, 2H), 3.77 (td, *J* = 14.3, 4.0 Hz, 2H), 3.90 (t, *J* = 5.8 Hz, 1.2H), 3.93 (t, *J* = 6.1 Hz, 0.8H), 4.46 (tt, *J* = 7.6, 3.7 Hz, 1H), 4.61 (s, 0.8H), 4.63 (s, 1.2H), 5.89-6.21 (m, 1H), 6.42-6.71 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 504.4.

Ejemplo 102 (*S*)-1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona



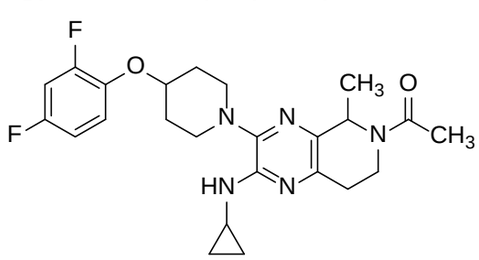
Una solución de ácido (*S*)-2-metoxipropanoico (2.9 mg, 0.028 mmol), DIPEA (3.9 mg, 0.028 mmol), y HATU (10.6 mg, 0.028 mmol) en DMF (278 µL) se agitó a temperatura ambiente durante 10 min y se trató con sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (15 mg, 0.028 mmol). Se continuó agitando durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (3 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.32 (d, *J* = 6.6 Hz, 1.3H), 1.38 (d, *J* = 6.6 Hz, 1.7H), 1.91-2.04 (m, 2H), 2.09-2.19 (m, 2H), 2.76 (t, *J* = 6.2 Hz, 0.9H), 2.84 (t, J = 5.4 Hz, 1.1H), 2.95-3.05 (m, 2H), 3.33 (s, 3H), 3.35-3.43 (m, 2H), 3.78 (td, *J* = 14.6, 4.3 Hz, 2H), 3.83-3.98 (m, 2H), 4.32-4.41 (m, 1H), 4.42-4.49 (m, 1H), 4.56 (m, 1.1H), 4.68 (m, 0.9H), 5.89-6.22 (m, 1H), 6.85-6.91 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 512.4.

Ejemplo 103 (*R*)-1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona



Una solución de ácido (*R*)-2-metoxipropanoico (2.9 mg, 0.028 mmol), DIPEA (10.8 mg, 0.083 mmol), y HATU (10.6 mg, 0.028 mmol) en DMF (278 µL) se agitó a temperatura ambiente durante 10 min seguido por la adición de sal TFA de *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (15 mg, 0.028 mmol) y se agitó durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (3 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotámeros) δ ppm 1.32 (d, *J* = 6.8 Hz, 1.3H), 1.38 (d, *J* = 6.6 Hz, 1.6H), 1.90-2.04 (m, 2H), 2.09-2.18 (m, 2H), 2.76 (t, *J* = 6.6 Hz, 0.9H), 2.84 (t, *J* = 6.1 Hz, 1.1H), 3.00 (ddd, *J* = 12.3, 8.6, 3.3 Hz, 2H), 3.33 (s, 3H), 3.34-3.43 (m, 2H), 3.72-3.84 (m, 2H), 3.84-3.98 (m, 2H), 4.32-4.41 (m, 1H), 4.42-4.50 (m, 1H), 4.51-4.55 (m, 0.6H), 4.62-4.69 (m, 1.4H), 5.89-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 512.4.

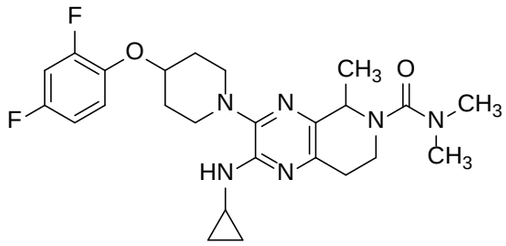
Ejemplo 104 1-(2-(ciclopropilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



El compuesto del título se preparó de manera similar al Ejemplo 29 utilizando sal TFA de *N*-ciclopropil-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (400 MHz,

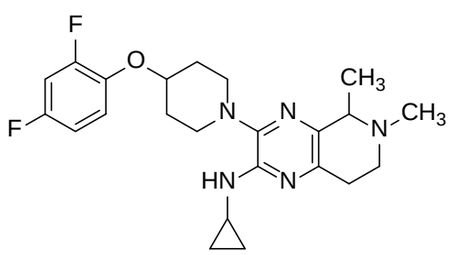
metanol-*d*4, mezcla de rotaméros) δ ppm 0.78-0.84 (m, 2H), 1.01-1.07 (m, 2H), 1.47 (d, *J* = 6.8 Hz, 2H), 1.60 (d, *J* = 6.8 Hz, 1H), 1.90-2.03 (m, 2H), 2.09-2.19 (m, 2H), 2.23 (s, 3H), 2.76 (tt, *J* = 6.9, 3.5 Hz, 1H), 2.85-2.96 (m, 2H), 2.99-3.20 (m, 3H), 3.46-3.60 (m, 3H), 4.14 (dd, *J* = 13.6, 5.6 Hz, 0.5H), 4.52 (td, *J* = 7.4, 3.4 Hz, 1H), 5.38 (c, *J* = 6.6 Hz, 0.5H), 6.86-6.94 (7.01 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.19 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 458.35.

Ejemplo 105 2-(ciclopropilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida



El compuesto del título se preparó de manera similar al Ejemplo 55 utilizando sal TFA de *N*-ciclopropil-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina. ^{1}H RMN (400 MHz, metanol-*d*4) δ ppm 0.82-0.89 (m, 1H), 1.05-1.12 (m, 1H), 1.53-1.58 (m, 3H), 1.92-2.04 (m, 2H), 2.10-2.20 (m, 2H), 2.63-2.87 (m, 2H), 2.91-2.94 (m, 02-3.25 (m, 3H), 3.35-3.59 (m, 3H), 3.78-3.86 (m, 1H), 4.49-4.57 (m, 1H), 4.66 (c, *J* = 6.8 Hz, 1H), 6.86-6.94 (m, 1H), 6.97-7.05 (m, 1H), 7.15-7.25 (m, 1H); ESI-MS m/z $[M+H]^+$ 487.40.

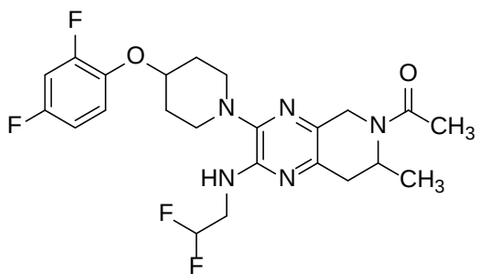
Ejemplo 106 *N*-ciclopropil-3-(4-(2,4-difEjemplonoxi)piperidin-1-il)-5,6-dimetil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



Una solución de sal TFA de *N*-ciclopropil-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (15 mg, 0.028 mmol), formaldehído (1.5 µL, 0.057 mmol) y DIPEA (5.0 µL, 0.028 mmol) en DCM (283 µL) se agitó durante 10 min. A esto se agregó triacetoxiborohidruro de sodio (18.0 mg, 0.085 mmol) y

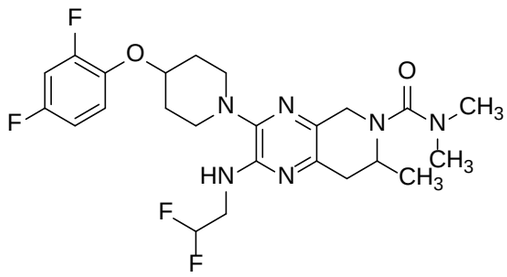
la mezcla de reacción se agitó durante la noche. La purificación mediante HPLC Método A proporcionó el compuesto del título como una sal TFA (4 mg). ^{1}H RMN (400 MHz, metanol-*d*4) δ ppm 0.60-0.67 (m, 2H), 0.83-0.92 (m, 2H), 1.64-1.80 (m, 3H), 1.87-2.04 (m, 2H), 2.05-2.21 (m, 2H), 2.74 (tt, *J* = 7.0, 3.6 Hz, 1H), 2.98-3.21 (m, 7H), 3.35-3.51 (m, 2H), 3.59 (d, *J* = 6.6 Hz, 1H), 3.78 (s a, 1H), 4.42 (s a, 1H), 4.49 (td, *J* = 7.4, 3.7 Hz, 1H), 6.86-6.93 (m, 1H), 6.96-7.05 (m, 1H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H).

Ejemplo 107 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



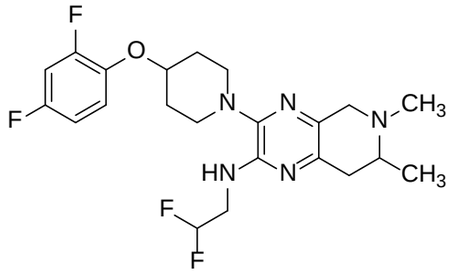
Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (15 mg, 0.027 mmol), anhídrido acético (5.1 µL, 0.054 mmol), y DIPEA (14,2 µL, 0.081 mmol) en DCM (136 µL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófilo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (8 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.13 (d, *J* = 6.8 Hz, 1.4H), 1.23 (d, *J* = 6.8 Hz, 1.6H), 1.92-2.03 (m, 2H), 2.09-2.17 (m, 2H), 2.18 (s, 1.4H), 2.22 (s, 1.6H), 2.54-2.67 (m, 1H), 2.95-3.04 (m, 2.4H), 3.13 (dd, *J* = 16.7, 6.3 Hz, 0.6H), 3.34-3.44 (m, 2H), 3.74-3.83 (m, 2.4H), 3.99 (d, *J* = 18.2 Hz, 0.6H), 4.40-4.49 (m, 1H), 4.55 (quinteto, *J* = 6.6 Hz, 0.5H), 4.66 (d, *J* = 16.7 Hz, 0.5H), 5.07 (d, *J* = 17.7 Hz, 0.5H), 5.18 (m, 0.5H), 5.90-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 481.9.

Ejemplo 108 2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*,7-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5H)-carboxamida



Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (15 mg, 0.027 mmol), cloruro dimetilcarbámico (5.8 mg, 0.054 mmol) y DIPEA (14,2 µL, 0.081 mmol) en DCM (136 µL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR) y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (10 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.19 (d, *J* = 6.8 Hz, 3H), 1.92-2.02 (m, 2H), 2.09-2.19 (m, 2H), 2.53 (d, *J* = 17.2 Hz, 1H), 2.88 (s, 6H), 3.00 (ddd, *J* = 12.3, 8.6, 3.3 Hz, 2H), 3.15 (dd, *J* = 16.8, 5.9 Hz, 1H), 3.34-3.42 (m, 2H), 3.73-3.84 (m, 2H), 4.2 -4.34 (m, 3H), 4.46 (tt, *J* = 7.6, 3.6 Hz, 1H), 5.89-6.22 (m, 1H), 6.85-6.91 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, *J* =9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 511.1.

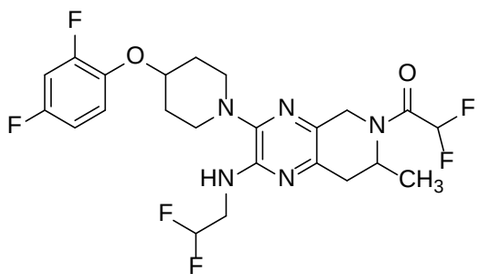
Ejemplo 109 *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-6,7-dimetil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (15 mg, 0.027 mmol), formaldehído (4,0 µL, 0.054 mmol) y DIPEA (4,7 µL, 0.027 mmol) en DCM (136 µL) se agitó durante 10 min a temperatura ambiente y se trató con triacetoxiborohidruro de sodio (17.2 mg, 0.081 mmol). La mezcla de reacción resultante se agitó durante la noche. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm

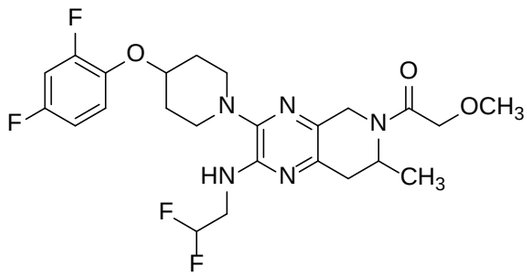
(Millipore® Millex-LCR) y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (8 mg) como un transparente aceite. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.39-1.57 (m, 3H), 1.92-2.03 (m, 2H), 2.08-2.18 (m, 2H), 2.82-3.09 (m, 6H), 3.16 (d, *J* =14.9 Hz, 1H), 3.35-3.44 (m, 2H), 3.67-3.85 (m, 3H), 4.11-4.29 (m, 1H), 4.37-4.44 (m, 1H), 4.44-4.52 (m, 1H), 5.90-6.22 (m, 1H), 6.85-6.91 (m, 1H), 6.98 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.17 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 453.9.

Ejemplo 110 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[4,3-b]pirazin-6(5H)-il)-2,2-difluoroetanona



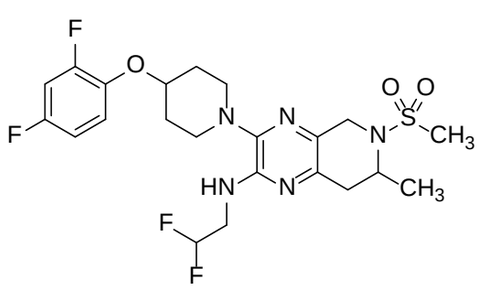
Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (10 mg, 0.018 mmol), 2,2-anhídrido difluoroacético (4,7 mg, 0.027 mmol), y DIPEA (7.0 mg, 0.054 mmol) en DCM (90 µL) se agitó a temperatura ambiente durante 2 h. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (5 mg) como un sólido blanco. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.21 (d, *J* = 7.1 Hz, 1.2H), 1.29 (d, *J* = 6.6 Hz, 1.8H), 1.92-2.03 (m, 2H), 2.09-2.19 (m, 2H), 2.58-2.69 (m, 1H), 2.98-3.07 (m, 2.4H), 3.11-3.17 (m, 0.6H), 3.35-3.44 (m, 2H), 3.78 (td, *J* = 14.5, 4.3 Hz, 2H), 4.11 (d, *J* = 17.2 Hz, 1H), 4.42-4.51 (m, 1H), 4.60-4.67 (m, 0.6H), 4.73-4.77 (m, 0.4H), 5.05 (d, *J* = 17.7 Hz, 0.6H), 5.11-5.18 (m, 0.4H), 5.89-6.22 (m, 1H), 6.39-6.73 (m, 1H), 6.85-6.91 (m, 1H), 6.99 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 517.9.

Ejemplo 111 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona



Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (10 mg, 0.018 mmol), cloruro de 2-metoxiacetilo (2.9 mg, 0.027 mmol), y DIPEA (7.0 mg, 0.054 mmol) en DCM (90 µL) se agitó a temperatura ambiente durante 2 h. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófilo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (4 mg) como un sólido blanco. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.16 (d, *J* = 6.8 Hz, 1.4H), 1.24 (d, *J* = 6.6 Hz, 1.6H), 1.91-2.04 (m, 2H), 2.09-2.19 (m, 2H), 2.59 (dd, *J* = 16.9, 10.6 Hz, 1H), 2.97-3.00 (m, 2.4H), 3.09-3.15 (m, 0.6H), 3.35-3.41 (m, 2H), 3.43 (s, 3H), 3.78 (td, *J* = 14.6, 4.3 Hz, 2H), 4.03 (d, *J* = 17.9 Hz, 0.6H), 4.19-4.27 (m, 1.4H), 4.29-4.39 (m, 1H), 4.46-4.52 (m, 1.5H), 4.58-4.62 (m, 0.5H), 5.07 (d, *J* = 18.8 Hz, 0.5H), 5.18 (t, *J* = 5.3 Hz, 0.5H), 5.89-6.22 (m, 1H), 6.85-6.91 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z [M+H]$^+$ 511.9.

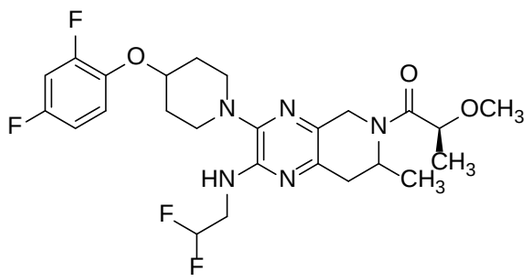
Ejemplo 112 *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



Una solución de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (10 mg, 0.018 mmol), cloruro de metanosulfonilo (3.1 mg, 0.027 mmol), y DIPEA (7.0 mg, 0.054 mmol) en DCM (181 µL) se agitó a temperatura ambiente durante 2 h. La mezcla de reacción bruta se diluyó

en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (4 mg) como un sólido blanco. ^{1}H RMN (400 MHz, metanol-d_4) δ ppm 1.25 (d, *J* = 6.8 Hz, 3H), 1.92-2.03 (m, 2H), 2.09-2.19 (m, 2H), 2.57 (d, *J* = 16.9 Hz, 1H), 2.94 (s, 3H), 3.01 (t, *J* = 10.9 Hz, 2H), 3.14 (dd, *J* = 16.7, 6.3 Hz, 1H), 3.34-3.43 (m, 2H), 3.78 (td, *J* = 14.5, 4.3 Hz, 2H), 4.17-4.25 (m, 1H), 4.43-4.55 (m, 3H), 5.89-6.22 (m, 1H), 6.84-6.91 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z [M+H]$^+$ 517.9.

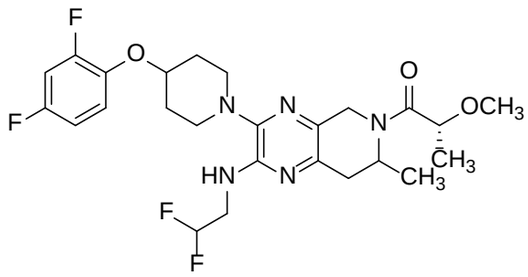
Ejemplo 113 (2*S*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona



Una solución de ácido (*S*)-2-metoxipropanoico (1.9 mg, 0.018 mmol), DIPEA (7.0 mg, 0.054 mmol) y HATU (6.9 mg, 0.018 mmol) en DMF (90 µL) se agitó a temperatura ambiente durante 10 min y se trató con sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (10 mg, 0.Ejemplol). La mezcla de reacción resultante se agitó durante 2 h. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (5 mg) como un sólido blanco. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.17 (t, *J* = 6.7 Hz, 1.4H), 1.27 (dd, *J* = 6.7, 2.7 Hz, 1.6H), 1.33 (dd, *J* = 11.5, 6.7 Hz, 1.4H), 1.38 (dd, *J* = 6.7, 2.7 Hz, 1.6H), 1.92-2.03 (m, 2H), 2.09-2.19 (m, 2H), 2.58 (m, 0.6H), 2.64 (m, 0.4H), 2.95-3.05 (m, 2H), 3.08-3.10 (m, 0.5H), 3.12-3.14 (m, 0.5H), 3.35 (s, 3H), 3.37-3.44 (m, 2H), 3.71-3.86 (m, 2H), 4.03 (t, *J* = 18.3 Hz, 1H), 4.30-4.41 (m, 1H), 4.43-4.50 (m, 1H), 4.70-4.83 (m, 1H), 5.08 (m, 0.5H), 5.21 (m, 0.5H), 5.89-6.21 (m, 1H), 6.84-6.91 (m, 1H), 6.99

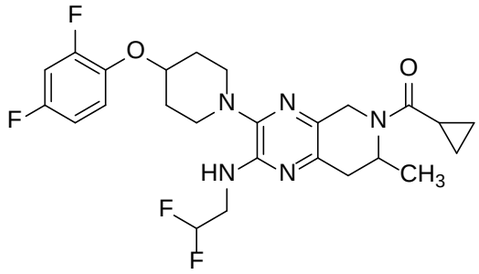
(ddd, *J* = 11.2, 8.5, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z $[M+H]^+$ 525.9.

Ejemplo 114 (2*R*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona



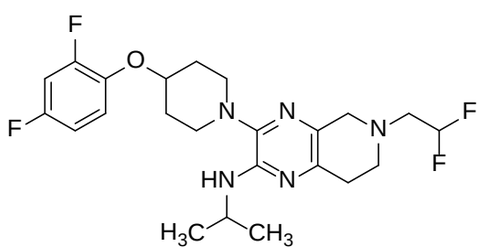
Una solución de ácido (*R*)-2-metoxipropanoico (1.9 mg, 0.018 mmol), DIPEA (7.0 mg, 0.054 mmol), y HATU (6.9 mg, 0.018 mmol) en DMF (90 µL) se agitó durante 10 min a temperatura ambiente y se trató con sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (10 mg, 0.Ejemplol). La mezcla de reacción resultante se agitó durante 2 h. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (5 mg) como un sólido blanco. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.17 (t, *J* = 6.6 Hz, 1.4H), 1.27 (dd, *J* = 6.7, 2.7 Hz, 1.6H), 1.33 (dd, *J* = 11.6, 6.8 Hz, 1.4H), 1.38 (dd, J = 6.7, 2.7 Hz, 1.6H), 1.92-2.03 (m, 2H), 2.09-2.18 (m, 2H), 2.53-2.68 (m, 1H), 2.94-3.05 (m, 2H), 3.08-3.10 (m, 0.5H), 3.12-3.14 (m, 0.5H), 3.35 (s, 3H), 3.37-3.42 (m, 2H), 3.78 (td, *J* = 14.5, 4.2 Hz, 2H), 4.03 (t, *J* = 18.8 Hz, 1H), 4.30-4.41 (m, 1H), 4.43-4.51 (m, 1H), 4.70-4.82 (m, 1H), 5.03-5.14 (m, 0.5H), 5.18-5.23 (m, 0.5H), 5.90-6.22 (m, 1H), 6.85-6.91 (m, 1H), 6.99 (ddd, *J* = 11.3, 8.5, 2.9 Hz, 1H), 7.18 (td, *J* = 9.2, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 525.9.

Ejemplo 115 ciclopropil(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona



Una solución de ácido ciclopropanocarboxílico (1.6 mg, 0.018 mmol), DIPEA (7.0 mg, 0.054 mmol), y HATU (6.9 mg, 0.018 mmol) en DMF (181 µL) se agitó a temperatura ambiente durante 10 min seguido por la adición de sal TFA de *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (10 mg, 0.018 mmol). La mezcla de reacción resultante se agitó durante 2 h. La mezcla de reacción bruta se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR) y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (5 mg) como un sólido blanco. ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 0.80-1.01 (m, 4H), 1.13 (d, *J* = 6.6 Hz, 1.4H), 1.27 (d, *J* = 6.3 Hz, 1.6H), 1.91-2.04 (m, 2H), 2.06-2.20 (m, 2H), 2.56-2.60 (m, 0.5H), 2.66-2.70 (m, 0.5H), 3.02 (s a, 2H), 3.13-3.15 (m, 0.5H), 3.16-3.20 (m, 0.5H), 3.34-3.46 (m, 2H), 3.72-3.87 (m, 2H), 4.04 (d, *J* = 18.2 Hz, 1H), 4.41-4.58 (m, 2H), 5.02 (d, *J* = 17.4 Hz, 1.4H), 5.15-5.19 (m, 0.6H), 5.90-6.23 (m, 1H), 6.84-6.91 (m, 1H), 6.99 (ddd, *J* = 11.4, 8.6, 3.0 Hz, 1H), 7.18 (td, *J* = 9.2, 5.3 Hz, 1H); ESI-MS m/z [M+H]$^+$ 507.9.

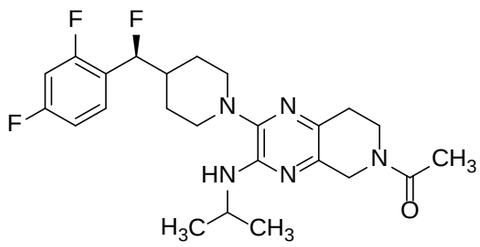
Ejemplo 116 6-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina



A una suspensión de sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (50 mg, 0.080 mmol) y Cs_2CO_3 (92 mg, 0.281 mmol) en DMF (0.5 mL) se agregó 1,1-difluoro-2-yodoetano (0.071 mL, 0.804 mmol) a 23 °C. La mezcla de reacción se agitó a 80 °C durante 18 h. El material

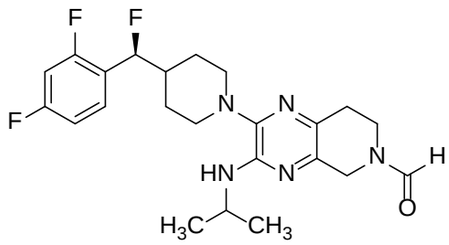
bruto resultante se filtró, se lavó con DMSO (2 x 0.5 mL) y se purificó mediante HPLC Método B utilizando un gradiente de 30% a 70% ACN para proporcionar el compuesto del título como una sal TFA (6.1 mg, 13%) como un película amarilla. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.19 (d, J = 6.4 Hz, 6H), 1.82-1.93 (m, 2H), 2.03-2.10 (m, 2H), 2.79-2.98 (m, 4H), 3.24-3.32 (m, 2H), 3.33-3.75 (m, 4H), 4.05-4.18 (m, 3H), 4.52-4.55 (m, 1H), 5.76-5.82 (m, 1H), 6.39-6.72 (m, 1H), 7.00-7.04 (m, 1H), 7.25-7.34 (m, 2H); ESI-MS m/z [M+H]$^+$ 468.3.

Ejemplo 117 (*S*)-1-(2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



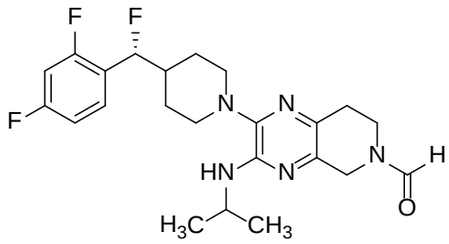
Una solución de sal TFA de (*S*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (56.0 mg, 0.105 mmol) en DCM (1.05 mL) a 0 °C se trató con anhídrido acético (19.8 µL, 0.210 mmol) y piridina (25.5 µL, 0.315 mmol). La mezcla de reacción se concentró bajo presión reducida, se recogió en MeOH, se filtró y se purificó mediante HPLC Método B. Las fracciones que contenían producto se concentraron bajo presión reducida. El material se purificó mediante HPLC Método A para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo claro (5.4 mg, 8.9%). ^{1}H RMN (500 MHz, metanol-d4, mezcla de rotaméros) δ ppm 1.31 (m, 6H), 1.45 (d, J = 11.7 Hz, 1H), 1.67 (m, 2H), 2.00 (m, 1H), 2.11 (m, 1H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.80 (m, 4H), 3.53 (m, 2H), 3.82 (t, J = 5.9 Hz, 1.3H), 3.86 (t, J = 5.9 Hz, 0.7H), 4.11 (m, 1H), 4.60 (s, 0.7H), 4.64 (s, 1.3H), 5.53 (m, 1H), 7.02 (m, 2H), 7.50 (m, 1H); ESI-MS m/z [M+H]$^+$ 462.5.

Ejemplo 118 (*S*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carbaldehído



Una solución de (*S*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (30.5 mg, 0.073 mmol) en THF (364 µL) a temperatura ambiente se trató con formato de fenilo (140 µL, 1.09 mmol). La mezcla de reacción se agitó a 60 °C durante 1 h. La reacción se purificó mediante HPLC Método B utilizando un gradiente 50% a 80%t para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo claro (9.4 mg, 23%). ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.29 (m, 6H), 1.45 (d, *J* = 12.7 Hz, 1H), 1.66 (m, 2H), 2.00 (m, 1H), 2.10 (m, 1H), 2.77 (m, 4H), 3.49 (m, 2H), 3.76 (t, *J* = 5.9Hz, 1.4H), 3.82 (t, *J* = 6.1 Hz, 0.6H), 4.12 (m, 1H), 4.48 (s, 0.6H), 4.52 (s, 1.4H), 5.53 (m, 1H), 7.02 (m, 2H), 7.50 (td, *J* = 8.3, 6.3 Hz, 1H), 8.18 (s, 0.7H), 8.24 (s, 0.3H); ESI-MS m/z [M+H]$^+$ 447.90.

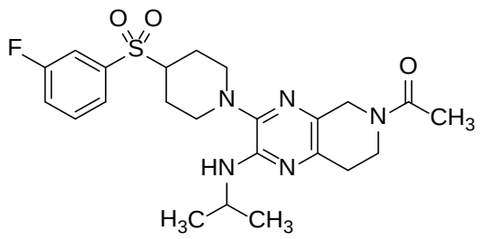
Ejemplo 119 (*R*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carbaldehído



Una solución de (*R*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (50.5 mg, 0.120 mmol) en THF (602 µL) a temperatura ambiente se trató con formato de fenilo (232 µL, 1.806 mmol). La mezcla de reacción se agitó a 60 °C durante 15 min. La mezcla de reacción se retiró del calentamiento y se dejó que continuara en agitación a temperatura ambiente durante 2 h. La reacción se purificó mediante HPLC Método B utilizando un gradiente de 50% a 80% ACN para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo claro (6.0 mg, 8.9% de

rendimiento). ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.30 (m, 7H), 1.45 (d, *J* = 13.2 Hz, 1H), 1.67 (m, 2H), 2.01 (m, 1H), 2.11 (m, 1H), 2.79 (m, 4H), 3.51 (m, 2H), 3.77 (t, *J* = 5.9 Hz, 1.4H), 3.83 (t, *J* = 6.1 Hz, 0.6H), 4.13 (m, 1H), 4.51 (s, 0.6H), 4.56 (s, 1.4H), 5.53 (m, 1H), 7.02 (m, 2H), 7.50 (m, 1H), 8.19 (s, 0.7H), 8.24 (s, 0.3H); ESI-MS m/z $[M+H]^+$ 447.95.

Ejemplo 120 1-(3-(4-(3-fluorofenilsulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



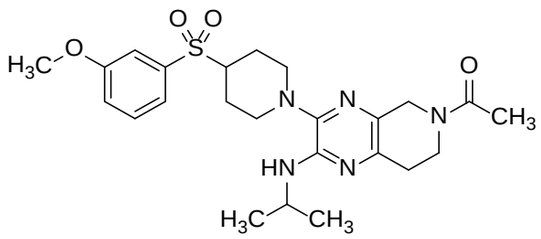
Se combinaron 6-bencil-3-cloro-N-isopropil-5,6,7,8-tetrahidropirido[3,4-b]pirazin-2-amina (55 mg, 0.174 mmol), 4-((3-fluorofenil)sulfonil)piperidina, HCl (58.3 mg, 0.208 mmol)), $Pd_2(dba)_3$ (8.0 mg, 8.68 µmol), BINAP (16.2 mg, 0.026 mmol) y terc-butóxido de sodio (66.7 mg, 0.694 mmol) y tolueno (868 µL). La suspensión se calentó a 100 °C durante 3.5 h y se diluyó en DMF, se filtró a través de un filtro hidrófobo PTFE 0.45 µm (Millipore® Millex-LCR) y se purificó mediante HPLC Método A para proporcionar 6-bencil-3-(4-((3-fluorofenil)sulfonil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina como una sal TFA (68 mg) como un película amarilla.

A una solución de sal TFA de 6-bencil-3-(4-((3-fluorofenil)sulfonil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (68 mg, 0.107 mmol) en THF (1333 µL) se agregó $Pd(OH)_2$ (20 % p, 22.5 mg, 0.032 mmol). El recipiente se purgó con nitrógeno y se dejó en agitación bajo una atmósfera de hidrógeno (balón) durante 2 h. La mezcla de reacción se filtró a través de un filtro hidrófobo PTFE 0.45 um (Millipore® Millex-LCR) y se lavó con EtOAc. El material en bruto se concentró al vacío para proporcionar 3-(4-((3-fluorofenil)sulfonil)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina como una sal TFA (58 mg) como un película amarilla.

A una solución de sal TFA de 3-(4-((3-fluorofenil)sulfonil)piperidin-1-il)-N-isopropil-5,6,7,8-

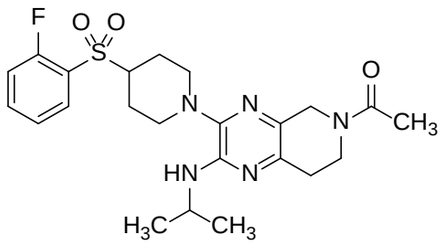
tetrahidropirido[3,4-*b*]pirazin-2-amina (58 mg, 0.106 mmol) en DCM (1059 µL) a 0 °C se agregó anhídrido acético (20.0 µL, 0.212 mmol) y piridina (25.7 µL, 0.318 mmol). Después de agitarse a 0 °C durante 30 min, la mezcla de reacción se concentró al vacío. El material bruto resultante se disolvió en DCM y se purificó mediante cromatografía ultrarrápida automatizada de gel de sílice utilizando un gradiente de 0% a 100% EtOAc en heptanos para proporcionar el compuesto del título (19.2 mg) como un aceite incoloro. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 0.85-0.94 (m, 3H), 1.21-1.24 (m, 6H), 1.90-1.99 (m, 2H), 2.19 (d, *J* = 13.7 Hz, 3H), 2.67-2.76 (m, 3H), 2.81 (t, *J* = 5.9 Hz, 1 H), 3.34-3.42 (m, 1 H), 3.46-3.55 (m, 2H), 3.78 (t, *J* = 6.1 Hz, 1H), 3.84 (t, *J* = 5.9 Hz, 1 H), 4.16 (td, *J* = 6.5, 3.7 Hz, 1H), 4.49 (d, *J* = 2.4 Hz, 2H), 7.51-7.57 (m, 1H), 7.68-7.75 (m, 2H), 7.76-7.80 (m, 1H); ESI-MS m/z $[M+H]^+$ 476.90.

Ejemplo 121 1-(2-(isopropilamino)-3-(4-(3-metoxifenilsulfonil)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



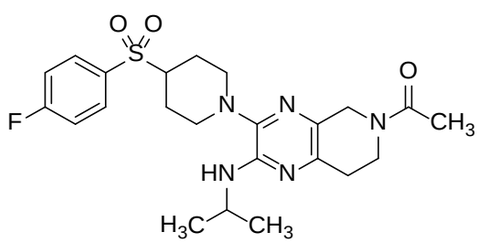
El compuesto del título se preparó de manera similar al Ejemplo 120 utilizando 4-((3-metoxifenil)sulfonil)piperidina, HCl para proporcionar el compuesto del título como un sólido blanco. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 0.82-0.94 (m, 2H), 1.21-1.24 (m, 6H), 1.87-1.98 (m, 4H), 2.19 (d, *J* = 13.2 Hz, 3H), 2.66-2.75 (m, 3H), 2.81 (t, *J* = 6.1 Hz, 1H), 3.46-3.54 (m, 2H), 3.78 (t, *J* = 5.9 Hz, 1H)(t, *J* = 5.9 Hz, 1H), 3.91 (s, 3H), 4.15 (dd, *J* = 10.7, 4.4 Hz, 1H), 4.46-4.50 (m, 2H), 7.29-7.34 (m, 1H), 7.42-7.44 (m, 1H), 7.48-7.52 (m, 1H), 7.56-7.61 (m, 1H); ESI-MS m/z $[M+H]^+$ 488.90.

Ejemplo 122 1-(3-(4-((2-fluororofenil)sulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



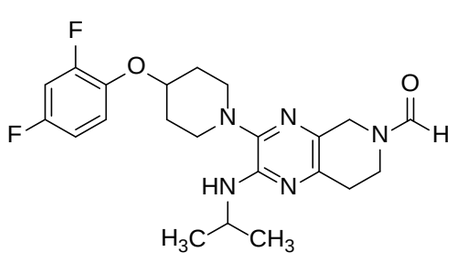
El compuesto del título se preparó de manera similar al Ejemplo 120 utilizando 4-((2-fluorofenil)sulfonil)piperidina para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo claro (26.6 mg, 28.9% en dos etapas, mezcla de rotámeros). ^{1}H RMN (500 MHz, DMSO-*d*6) δ ppm 1.16 (d, *J* = 6.8 Hz, 6H), 1.95 (m, 4H), 2.07 (app d, 3H), 2.65 (m, 4H), 3.49 (m, 3H), 3.69 (m, 2H)(m, 1H), 4.37 (app d, 2H), 5.69 (s a, 1H), 7.52 (m, 2H), 7.87 (m, 2H); ESI-MS m/z $[M+H]^+$ 476.00.

Ejemplo 123 1-(3-(4-(4-fluorofenilsulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



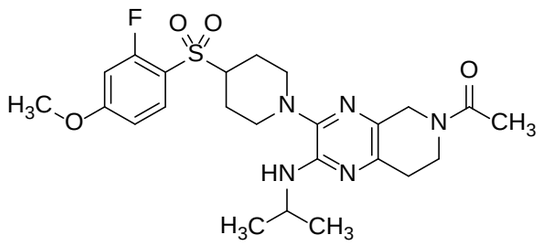
El compuesto del título se preparó de manera similar al Ejemplo 120 utilizando 4-((4-fluorofenil)sulfonil)piperidina, HCl para proporcionar el compuesto del título como un aceite incoloro. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 0.90 (d, *J* = 6.8 Hz, 1H), 1.20-1.24 (m, 6H), 1.90-1.99 (m, 2H), 1.99-2.06 (m, 2H), 2.19 (d, *J* = 13.7 Hz, 3H), 2.67-2.76 (m, 3H), 2.82 (t, *J* = 5.9 Hz, 1H), 3.45-3.55 (m, 79 (t, *J* = 5.9 Hz, 1H), 3.84 (t, *J* = 5.9 Hz, 1H), 4.12-4.20 (m, 1H), 4.49 (s, 2H), 4.58 (s, 1H), 7.42 (td, J = 8.7, 1.7 Hz, 2H), 7.97-8.02 (m, 2H); ESI-MS m/z [M+H]+ 476.90.

Ejemplo 124 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carbaldehído



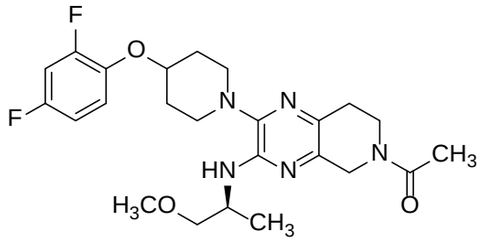
Una mezcla de sal TFA de 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina (36 mg, 0.058 mmol), Cs_2CO_3 (66.0 mg, 0.203 mmol), y difluoroyodometano (0.051 mL, 0.579 mmol) en DMA (0.5 mL) se calentó en un microondas en absorbancia alta durante 15 min a 50 °C. El material bruto resultante se filtró, se lavó con DMSO (2 x 0.5 mL) y se purificó mediante HPLC Método B utilizando un gradiente de 30% a 70% ACN para proporcionar el compuesto del título como una sal TFA (11.2 mg, 35.5%) como un sólido amarillo. ^{1}H RMN (500 MHz, metanol-d_4) δ ppm 1.29 (d, *J* = 6.4 Hz, 6H), 1.90-2.01 (m, 2H), 2.07-2.18 (m, 2H), 2.78-2.89 (m, 2H), 3.02-3.10 (m, 2H), 3.39-3.45 (m, 2H), 3.76-3.86 (m, 2H), 4.14 (c, *J* = 6.4 Hz, 1H), 4.46-4.49 (m, 3H), 6.85-6.91 (m, 1H), 6.95-7.01 (m, 1H), 7.14-7.21 (m, 1H), 8.16-8.27 (m, 1H); ESI-MS m/z $[M+H]^+$ 432.4.

Ejemplo 125 1-(3-(4-(2-fluoro-4-metoxifenilsulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[4,3-b]pirazin-6(5H)-il)etanona



El compuesto del título se preparó de manera similar al Ejemplo 120 utilizando 4-((2-fluoro-4-metoxifenil)sulfonil)piperidina, HCl para proporcionar el compuesto del título como un aceite incoloro. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 0.87-0.90 (m, 2H), 1.23 (dd, *J* = 6.8, 1.0 Hz, 6H), 1.95-2.02 (m, 3H), 2.19 (d, *J* = 12.2 Hz, 3H), 2.69-2.79 (m, 3H), 2.82 (t, *J* = 5.9 Hz, 1H), 3.35-3.42, 3.52 (td, *J* = 8.3, 4.4 Hz, 2H), 3.79 (t, *J* = 5.9 Hz, 1H), 3.85 (t, *J* = 6.1 Hz, 1H), 3.93 (s, 3H), 4.17 (dtt, *J* = 9.8, 6.4, 3.3 Hz, 1H), 4.50 (s, 2H), 6.95-7.02 (m, 2H), 7.78-7.84 (m, 1H); ESI-MS m/z $[M+H]^+$ 506.90.

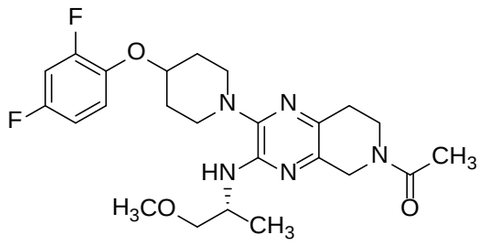
Ejemplo 126 (*S*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-((1-metoxipropan-2-il)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



Una solución de sal TFA de (*S*)-6-bencil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-N-(1-metoxipropan-2-il)-5,6,7,8-tetrahidropirido[3,4-b]pirazin-3-amina (127.7 mg, 0.200 mmol) en THF (2.00 mL) a temperatura ambiente se trató con $Pd(OH)_2$ (20 % p, 42.2 mg, 0.060 mmol). Se insufló gas hidrógeno (balón) a través de la mezcla de reacción durante 5 min. La aguja de ventilación se eliminó y la mezcla de reacción se agitó bajo atomósfera de hidrógeno durante 1 h. La mezcla de reacción se expuso al ambiente y se filtró a través de una almohadilla de Celite™, eluyendo con EtOAc y MeOH. El filtrado se concentró bajo presión reducida para proporcionar (*S*)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-(1-metoxipropan-2-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina, como una sal TFA, como un aceite amarillo, que se utilizó más adelante sin purificación adicional. ESI-MS m/z $[M+H]^+$ 434.5.

Una solución de sal TFA de (*S*)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-(1-metoxipropan-2-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina en DCM (2.009 mL) a 0 °C se trató con piridina (0.049 mL, 0.603 mmol), seguido de anhídrido acético (0.038 mL, 0.402 mmol). La mezcla de reacción se agitó durante 1 h 30 min a 0 °C. La mezcla de reacción se concentró bajo presión reducida y se recogió en MeOH, se filtró a través de un filtro jeringa Millipore® 0.45 µm, y se purificó mediante HPLC Método A para proporcionar el compuesto del título, como una sal TFA, como un semisólido amarillo-anaranjado (46.7 mg, 39.4% en dos etapas). ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.27 (m, 3H), 1.95 (m, 2H), 2.13 (m, 2H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.79 (app t, 0.7H), 2.84 (app t, 1.3H), 3.05 (m, 2H), 3.39 (m, 3H), 3.43 (m, 2H), 3.51 (dt, *J* = 5.5, 3.5 Hz, 2H), 3.82 (app t, 1.3H), 3.86 (app t, 0.7H), 4.25 (m, 1H), 4.49 (m, 1H), 4.57 (s, 0.7H), 4.60 (s, 1.3H), 6.88 (m, 1H), 6.99 (ddd, *J* = 11.2, 8.3, 2.9 Hz, 1H), 7.18 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 476.00.

Ejemplo 127 (*R*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-((1-metoxipropan-2-il)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona

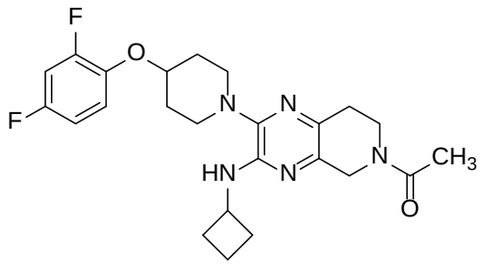


Una solución de sal TFA de (*R*)-6-bencil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-(1-metoxipropan-2-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (161.4 mg, 0.253 mmol) en THF (2.53 mL) se trató con $Pd(OH)_2$ (20 % p, 53.3 mg, 0.076 mmol). Se insufló gas hidrógeno (balón) a través de la mezcla de reacción durante 5 min. La aguja de ventilación se eliminó y la mezcla de reacción se dejó en agitación bajo atomósfera de hidrógeno a temperatura ambiente durante 2 h. La mezcla de reacción se expuso al ambiente y se filtró a través de una almohadilla de Celite™, eluyendo con MeOH y EtOAc. El filtrado se recogió y se concentró bajo presión reducida para proporcionar (*R*)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-(1-metoxipropan-2-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina, como una sal TFA, como un aceite amarillo, que se utilizó más adelante sin purificación adicional . ESI-MS m/z $[M+H]^+$ 434.5.

Una solución de sal TFA de (*R*)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-(1-metoxipropan-2-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina en DCM (2.539 mL) a 0 °C se trató con piridina (0.062 mL, 0.762 mmol), seguido de anhídrido acético (0.048 mL, 0.508 mmol). La mezcla de reacción se agitó a 0 °C durante 1 h 30 min. La mezcla de reacción se concentró bajo presión reducida y se recogió en MeOH, se filtró a través de un filtro jeringa 0.45 µm Millipore®, y se purificó mediante HPLC Método A para proporcionar el compuesto del título, como una sal TFA, como un semisólido amarillo (41.4 mg, 27.7% en dos etapas). ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.29 (m, 3H), 1.95 (m, 2H), 2.13 (m, 2H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.74 (t, *J* = 5.9 Hz, 0.7H), 2.84 (app t, 1.3H), 3.09 (m, 2H), 3.38 (m, 3H), 3.47 (m, 4H), 3.82 (t, *J* = 6.1 Hz, 1.3H), 3.86 (t, *J* = 5.9 Hz, 0.7H), 4.26 (m, 1H), 4.49 (m, 1H), 4.59 (s a, 0.7H), 4.62 (s, 1.3H), 6.87 (m, 1H), 6.98

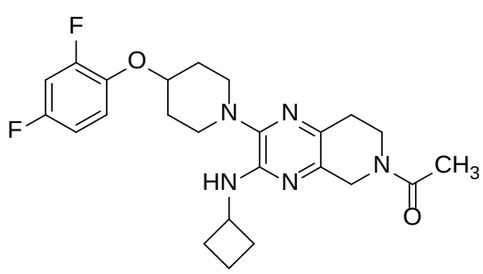
(ddd, *J* = 11.3, 8.7, 2.9 Hz, 1H), 7.27 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 476.00.

Ejemplo 128 1-(3-(ciclobutilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



Una solución de sal TFA de *N*-ciclobutil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (144 mg, 0.272 mmol) en DCM (2.72 mL) a 0 °C se trató con piridina (66.0 µL, 0.816 mmol), seguido de anhídrido acético (51.3 µL, 0.544 mmol). La mezcla de reacción se agitó a 0 °C durante 2 h. La mezcla de reacción se concentró bajo presión reducida y se recogió en MeOH, se filtró a través de un filtro jeringa 0.45 µm Millipore® y se purificó mediante HPLC Método A para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo (74,9 mg, 48.2%). ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 1.82 (m, 2H), 1.97 (m, 2H), 2.11 (m, 4H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.45 (m, 2H), 2.73 (t, *J* = 5.9 Hz, 0.7H), 2.84 (t, *J* = 5.9 Hz, 1.3H), 3.11 (m, 2H), 3.47 (m, 2H), 3.81 (t, *J* = 5.9 Hz, 1.3 H), 3.85 (t, *J* = 5.9 Hz, 0.7H), 4.40 (m, 1H), 4.49 (m, 1H), 4.59 (s, 0.7H), 4.63 (s, 1.3H), 6.87 (m, 1H), 6.97 (ddd, *J* = 11.2, 8.5, 3.2 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 458.00.

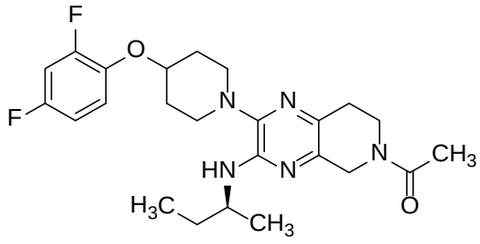
Ejemplo 128A 1-(3-(ciclobutilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



A una solución de *N*-ciclobutil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazin-3-amina (12.0 g, 29.2 mmol) en acetona (200 mL) y dioxano (300 mL) se

agregó Ac_2O (30 mL, 318 mmol) y Pd/C (1.80 g, 16.91 mmol). La reacción se agitó a 60 °C bajo atmósfera de H_2 (345 kPa) durante 72 h. Posteriormente, la mezcla se filtró a través de una almohadilla de Celite™, se lavó con EtOAc. La solución de reacción se diluyó con EtOAc (50 mL) y se vertió en $NaHCO_3$ acuoso saturado (50 mL), posteriormente se lavó con salmuera (2 x 30 mL). La capa orgánica se secó sobre Na_2SO_4 y se concentró al vacío. El producto en bruto se recristalizó con PE/EtOAc, se liofilizó y se lavó con PE/EtOAc (5:1) para proporcionar puro compuesto del título (6.1 g). ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.57-1.74 (m, 2H), 1.85-1.95 (m, 2H), 1.97-2.08 (m, 4H), 2.08 (s, 1.3H), 2.09 (s, 1.7H), 2.19-2.30 (m, 2H), 2.58 (t, *J* = 5.9 Hz, 0.9H), 2.71 (t, *J* = 5.9 Hz, 1.1H), 2.88 (t, *J* = 10.5 Hz, 2H), 3.23-3.33 (m, 2H), 3.70 (dt, *J* = 11.7, 5.9 Hz, 2H), 4.32-4.47 (m, 3H), 4.52 (tt, *J* = 8.1, 3.8 Hz, 1H), 6.05 (d, *J* = 7.8 Hz, 0.4H), 6.08 (d, *J* = 8.3 Hz, 0.6H 6.96-7.07 (m, 1H), 7.24-7.36 (m, 2H); ESI-MS m/z $[M+H]^+$ 458.00.

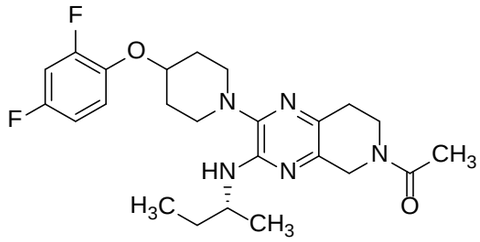
Ejemplo 129 (*S*)-1-(3-(*sec*-Butilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



Una solución de sal TFA de (*S*)-6-bencil-*N*-(*sec*-Butil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (212.2 mg, 0.341 mmol) en THF (3.4 mL) se trató con $Pd(OH)_2$ (20 % p, 71.9 mg, 0.102 mmol). Se insufló gas hidrógeno (balón) a través de la mezcla de reacción durante 5 min. La aguja de ventilación se eliminó y la mezcla de reacción se agitó a temperatura ambiente bajo atomósfera de hidrógeno durante 3 h. La mezcla de reacción se expuso al ambiente y se filtró a través de una almohadilla de Celite™, eluyendo con EtOAc y MeOH. El filtrado se recogió y se concentró bajo presión reducida para proporcionar (*S*)-*N*-(*sec*-Butil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina como una sal TFA (169.0 mg) como un aceite amarillo, que se utilizó más adelante sin purificación adicional. ESI-MS m/z $[M+H]^+$ 418.5.

Una solución de sal TFA de (S)-N-(sec-Butil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (169.0 mg) en DCM (3.18 mL) a 0 °C se trató con piridina (0.077 mL, 0.954 mmol), seguido de anhídrido acético (0.060 mL, 0.636 mmol). La mezcla de reacción se agitó durante 1 h. La mezcla de reacción se concentró bajo presión reducida. El residuo se recogió en MeOH, se filtró a través de un filtro jeringa Millipore® 0.45 µm, y se purificó mediante HPLC Método A para proporcionar el compuesto del título, como una sal TFA, como un semisólido amarillo (84,9 mg, 43.4% en dos etapas). ^{1}H RMN (500 MHz, metanol-*d*4, mezcla de rotaméros) δ ppm 0.98 (m, 3H), 1.27 (m, 3H), 1.68 (m, 2H), 1.97 (m, 2H), 2.13 (m, 2H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.74 (td, *J* = 5.9, 1.5 Hz, 0.7H), 2.84 (td, *J* = 5.9, 1.5 Hz, 1.3H), 3.11 (m, 2H), 3.45 (m, 2H), 3.82 (t, *J* = 5.9 Hz, 1.3H), 3.86 (m, 0.7H), 3.97 (m, 1H), 4.50 (m, 1H), 4.61 (d, *J* = 3.9 Hz, 0.7H), 4.64 (s, 1.3H), 6.87 (m, 1H), 6.97 (ddd, *J* = 11.3, 8.7, 2.9 Hz, 1H), 7.17 (td, *J* = 9.2, 5.6 Hz, 1H); ESI-MS m/z $[M+H]^+$ 460.00.

Ejemplo 130 (*R*)-1-(3-(*sec*-Butilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona

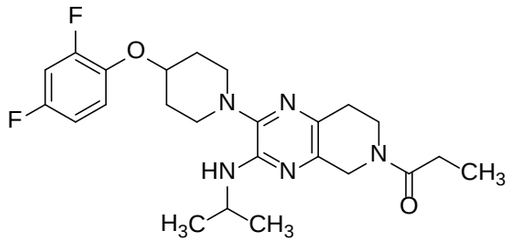


Una solución de sal TFA de (*R*)-6-bencil-*N*-(*sec*-Butil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (174,6 mg, 0.281 mmol) en THF (2.81 mL) se trató con $Pd(OH)_2$ (20 % p, 59.2 mg, 0.084 mmol). Se insufló gas hidrógeno (balón) a través de la mezcla de reacción durante 5 min. La aguja de ventilación se eliminó y la reacción se dejó en agitación a temperatura ambiente bajo atomósfera de hidrógeno durante 1 h. La mezcla de reacción se expuso al ambiente y se filtró a través de una almohadilla de Celite™, eluyendo con EtOAc/MeOH. El filtrado se recogió y se concentró bajo presión reducida para proporcionar (*R*)-*N*-(*sec*-Butil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina como una sal TFA (136.4 mg) como un aceite

amarillo, que se utilizó más adelante sin purificación adicional. ESI-MS m/z $[M+H]^+$ 418.5.

Una solución de sal TFA de (*R*)-*N*-(*sec*-Butil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (136.4 mg) en DCM (2.57 mL) a 0 °C se trató con piridina (0.062 mL, 0.770 mmol), seguido de anhídrido acético (0.048 mL, 0.513 mmol). La mezcla de reacción se agitó durante 1 h. La mezcla de reacción se concentró bajo presión reducida. El residuo se recogió en MeOH, se filtró a través de un filtro jeringa Millipore® 0.45 µm, y se purificó mediante HPLC Método A para proporcionar el compuesto del título, como una sal TFA, como un sólido amarillo (52.0 mg, 32.2% en dos etapas). ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 0.98 (m, 3H), 1.26 (m, 3H), 1.67 (m, 2H), 1.96 (m, 2H), 2.13 (m, 2H), 2.19 (s, 1.1H), 2.21 (s, 1.9H), 2.73 (td, *J* = 5.9, 1.5 Hz, 0.7H), 2.84 (td, *J* = 5.9, 1.5 Hz, 1.3H), 3.08 (m, 2H), 3.43 (m, 2H), 3.82 (t, *J* = 5.9 Hz, 1.3H), 3.86 (m, 0.7H), 3.97 (m, 1H), 4.49 (m, 1H), 4.59 (m, 0.7H), 4.63 (s, 1.3H), 6.87 (m, 1H), 6.98 (ddd, *J* = 11.3, 8.4, 3.2 Hz, 1H), 7.17 (td, *J* = 9.3, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 460.0.

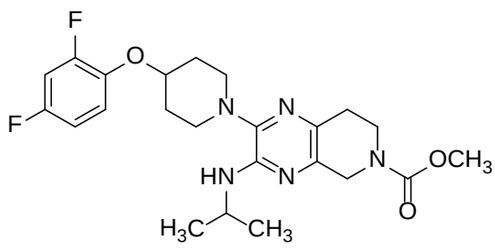
Ejemplo 131 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona



A una solución de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (50 mg, 0.124 mmol) en DCM (1.24 mL) a 0 ºC se agregó DIPEA (32.5 µL, 0.186 mmol) y anhídrido propiónico (19.2 µL, 0.149 mmol). La solución resultante se agitó a esta temperatura durante 2 h. La purificación mediante cromatografía en columna de gel de sílice utilizando 0% a 100% EtOAc en heptanos proporcionó el compuesto del título como un sólido blanco (53 mg, 93%). ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm ^{1}H RMN (400 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 1.10-1.20 (m, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.90-2.00 (m, 2H),

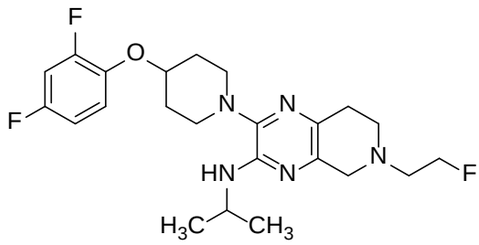
2.09-2.18 (m, 2H), 2.47-2.58 (m, 2H), 2.72 (t, *J* = 5.9 Hz, 0.8 H), 2.81 (t, *J* = 5.9 Hz, 1.2H), 2.92-3.01 (m, 2H), 3.81 (t, *J* = 5.9 Hz, 1.2H), 3.87 (t, *J* = 6.1 Hz, 0.8H), 4.13-4.21 (m, 1H), 4.46 (tt, *J* = 7.5, 3.7 Hz, 1H), 4.55 (s, 0.8H), 4.56 (s, 1.2H), 6.85-6.92 (m, 1H), 6.99 (m, 1H), 7.18 (m, 1H); ESI-MS m/z $[M+Na]^+$ 482.9.

Ejemplo 132 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxilato de metilo



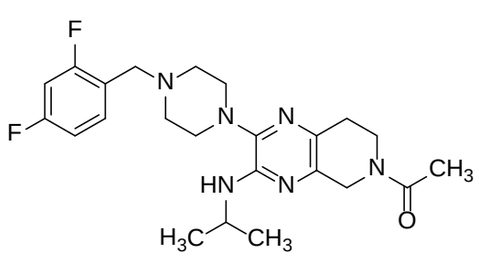
A una solución de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (45.6 mg, 0.113 mmol) y trietilamina (0.039 mL, 0.283 mmol) en DCM (0.75 mL) se agregó carbonoclorhidrato de metilo (0.013 mL, 0.170 mmol) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 1 hr, se calentó hasta 23 °C, y se concentró mediante un evaporador rotatorio. El material resultante se repartió entre EtOAc y H2O. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró, se lavó con EtOAc, y se concentró mediante un evaporador rotatorio. El material en bruto se disolvió en tolueno (0.5 mL) y se purificó mediante cromatografía de media presión utilizando un gradiente de elución de 2% a 80% de EtOAc en heptano en una columna de 12 g de gel de sílice (Single Step™) para proporcionar el compuesto del título (48.7 mg, 93%) como una espuma blanca. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.17-1.19 (m, 6H), 1.80-1.94 (m, 2H), 2.06 (ddd, *J* = 9.5, 5.9, 3.2 Hz, 2H), 2.64 (t, *J* = 5.9 Hz, 2H), 2.82-2.94 (m, 2H), 3.19-3.31 (m, 2H), 3.64 (s, 3H), 3.64-3.69 (m, 2H), 4.07-4.17 (m, 1H), 4.35 (s a, 2H), 4.51 (tt, *J* = 8.1, 3.9 Hz, 1H), 5.53 (d, *J* = 8.3 Hz, 1H), 7.01 (dddd, *J* = 9.3, 8.1, 3.2, 1.5 Hz, 1H), 7.26-7.35 (m, 2H); ESI-MS m/z $[M+H]^+$ 461.9.

Ejemplo 133 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(2-fluoroetil)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



A una suspensión de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (98.4 mg, 0.244 mmol) y K_2CO_3 (135 mg, 0.976 mmol) en acetona (4,0 mL) se agregó 1-bromo-2-fluoroetano (0.020 mL, 0.268 mmol) a 23 °C. La mezcla de reacción se agitó a 50 °C durante 1 hr. La mezcla de reacción se enfrió a 23 °C, se agregó una porción adicional de 1-bromo-2-fluoroetano (8.2 µL, 0.110 mmol), y la mezcla de reacción se calentó durante 1.5 hr adicionales a 50 °C, se enfrió a 23 °C, y se concentró mediante un evaporador rotatorio. El material bruto resultante se reconstituyó en DMSO, se filtró, se lavó con DMSO, y se purificó mediante HPLC Método B utilizando un gradiente de 30% a 70% ACN para proporcionar el compuesto del título (42 mg, 38.3%) como un aceite amarillo claro. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.17 (d, *J* = 6.8 Hz, 6H), 1.82-1.93 (m, 2H), 2.02-2.11 (m, 2H), 2.62-2.69 (m, 2H), 2.73-2.80 (m, 3H), 2.81-2.91 (m, 3H), 3.20-3.29 (m, 2H), 3.48 (s, 2H), 4.04-4.12 (m, 1H), 4.47-4.54 (m, 1H), 4.56 (t, *J* = 4.9 Hz, 1H), 4.66 (t, *J* = 4.9 Hz, 1H), 5.38 (d, *J* = 7.8 Hz, 1H), 6.98-7.05 (m, 1H), 7.26-7.34 (m, 2H); ESI-MS m/z $[M+H]^+$ 450.0.

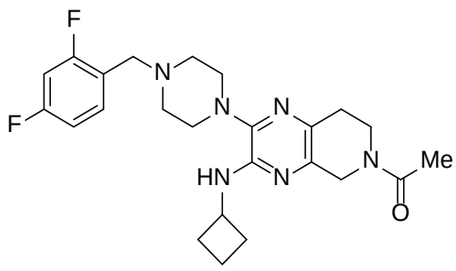
Ejemplo 134 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



A un reactor de presión cargado con una solución roja-anaranjada de 2-(4-(2,4-difluorobencil)piperazin-1-il)-N-isopropilpirido[3,4-*b*]pirazin-3-amina (0.5 g, 1.255 mmol) en acetona (25 mL) y dioxano (25 mL) se agregó paladio, 10 % p sobre carbono activado (0.053 g, 0.502 mmol) como un suspensión en dioxano (3 mL) bajo nitrógeno. Después, se

agregó anhídrido acético (1.179 mL, 12.55 mmol) a 23 °C. La mezcla se agitó bajo hidrógeno a 45 °C y 310 kPa durante 9.5 hr. La mezcla de reacción se filtró a través Celite™, se lavó con EtOAc, y se concentró mediante un evaporador rotatorio. El material en bruto se disolvió en tolueno (5 mL) y se purificó mediante cromatografía de media presión utilizando un gradiente de elución 10% a 100% de EtOAc en heptano en una columna NH 60 μM tamaño 400 (Shoko Scientific Purif-Pack™) para proporcionar el compuesto del título (341 mg, 61.1%) como una espuma blancuzca. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.14-1.19 (m, 6H), 2.08 (s, 1.2H), 2.09 (s, 1.8H), 2.52-2.65 (m, 5H), 2.70 (t, *J* = 5.9 Hz, 1H), 2.98 (s a, 4H), 3.58 (s, 2H), 3.70 (dt, *J* = 12.0, 5.7 Hz, 2H), 4.00-4.15 (m, 1H), 4.40 (s, 0.8H), 4.43 (s, 1.2H), 5.35 (d, *J* = 7.8 Hz, 0.4H), 5.38 (d, *J* = 8.3 Hz, 0.6H) 7.08 (td, *J* = 8.3, 2.4 Hz, 1H), 7.21 (td, *J* = 10.0, 2.4 Hz, 1H), 7.44-7.51 (m, 1H); ESI-MS m/z [M+H]$^+$ 445.0.

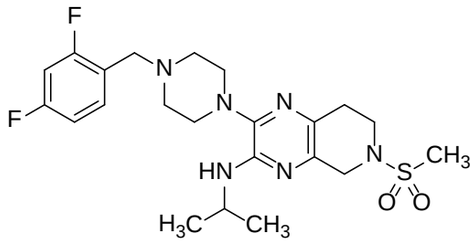
Ejemplo 135 1-(3-(ciclobutilamino)-2-(4-(2,4-difluorobencil)piperazin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



A *N*-ciclobutil-2-(4-(2,4-difluorobencil)piperazin-1-il)pirido[3,4-*b*]pirazin-3-amina (0.500 g, 1.218 mmol) en acetona (25 mL) y dioxano (25 mL) se agregó paladio, 10 % p sobre carbono activado (0.052 g, 0.487 mmol) como un suspensión en dioxano (3 mL) bajo nitrógeno. Después, se agregó anhídrido acético (1.144 mL, 12.18 mmol) a 23 °C. La mezcla se agitó bajo hidrógeno a 310 kPa durante 50 hr a 45 °C. La mezcla bruta se filtró a través Celite™, se lavó con dioxano, y se concentró mediante un evaporador rotatorio. El material en bruto se purificó mediante cromatografía de media presión utilizando un gradiente de elución 10% a 100% de EtOAc en heptanos en una columna NH 60 μM tamaño 60 (Shoko Scientific Purif-Pack™) para proporcionar el compuesto del título 1-(3-(ciclobutilamino)-2-(4-(2,4-difluorobencil)piperazin-1-il)-7,8-dihidropirido[3,4-

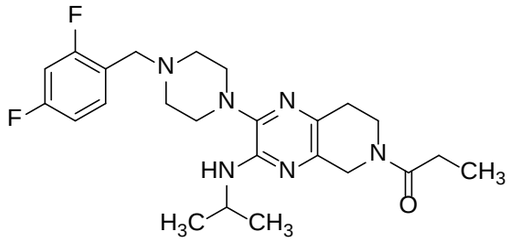
b]pirazin-6(5*H*)-il)etanona (284 mg, 51.1%) como una espuma amarilla. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.56-1.72 (m, 2H), 1.97-2.06 (m, 2H), 2.07 (s, 1.3H), 2.08 (s, 1.7H), 2.18-2.27 (m, 2H), 2.52-2.66 (m, 4.9H), 2.69 (t, *J* = 5.9 Hz, 1.1H), 2.99 (s a, 4H), 3.59 (s, 2H), 3.69 (dt, *J* = 11.5, 6.0 Hz, 2H), 4.27-4.46 (m, 3H), 5.89 (d, *J* = 7.3 Hz, 0.4H), 5.93 (d, *J* = 7.8 Hz, 0.6H), 7.02-7.13 (m, 1H), 7.17-7.27 (m, 1H), 7.41-7.55 (m, 1H); ESI-MS m/z [M+H]$^+$ 457.0.

Ejemplo 136 2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-isopropil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



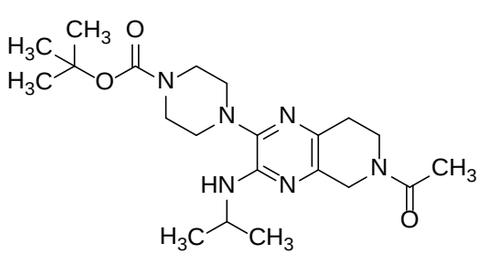
A una solución de 2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (50 mg, 0.124 mmol) y DIPEA (0.032 mL, 0.186 mmol) en DCM (1 mL) se agregó cloruro de metanosulfonilo (10.6 µL, 0.137 mmol) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 1 hr y se concentró mediante un evaporador rotatorio. El material bruto resultante se repartió entre EtOAc (2 mL) y agua (1 mL). La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró, se lavó con EtOAc, y se concentró mediante un evaporador rotatorio. El material en bruto se disolvió en EtOAc y MeOH, se absorbió sobre gel de sílice (0.75 g), y se purificó mediante cromatografía de media presión utilizando un gradiente de elución de 50% a 100% EtOAc en heptano en una columna de 4 g gel de sílice (Single Step™) para proporcionar el compuesto del título (50.6 mg, 85%) como un sólido blancuzco. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.12-1.19 (m, 6H), 2.53-2.61 (m, 4H), 2.74 (t, *J* = 5.9 Hz, 2H), 2.97 (s, 3H), 3.00 (d, *J* = 7.3 Hz, 4H), 3.44-3.48 (m, 1H), 3.59 (s, 2H), 4.02-4.10 (m, 1H), 4.16 (s, 2H), 5.41 (d, *J* = 7.8 Hz, 1H), 7.08 (td, *J* = 8.4, 2.2 Hz, 1H), 7.22 (td, *J* = 9.9, 2.7 Hz, 1H), 7.44-7.54 (m, 1H); ESI-MS m/z [M+H]$^+$ 480.9.

Ejemplo 137 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona



A una solución de 2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (50 mg, 0.124 mmol) y DIPEA (0.032 mL, 0.186 mmol) en DCM (1 mL) se agregó anhídrido propiónico (0.019 mL, 0.149 mmol) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 1 hr, se calentó hasta 23 °C, y se concentró mediante un evaporador rotatorio. El material bruto resultante se repartió entre EtOAc y agua. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró, se lavó con EtOAc, y se concentró mediante un evaporador rotatorio. El material en bruto se disolvió en EtOAc y MeOH, se absorbió sobre gel de sílice (0.75 g) y se purificó mediante cromatografía de media presión utilizando un gradiente de 20% a 100% de EtOAc en heptano en una columna de 4 g gel de sílice (Single Step™) para proporcionar el compuesto del título (48 mg, 84% de rendimiento) como una espuma blancuzca. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 0.94-1.05 (m, 3H), 1.16-1.18 (m, 6H), 2.41 (quinteto, *J* = 7.8 Hz, 2H), 2.52-2.65 (m, 5H), 2.69 (t, *J* = 5.6 Hz, 1H), 2.98 (s a, 3H), 3.58 (s, 2H), 3.70 (t, *J* = 5.9 Hz, 1.1H), 3.73 (t, *J* = 5.9 Hz, 0.9H), 4.03 (c, *J* = 7.2 Hz, 2H), 4.06-4.15 (m, 1H), 4.42 (s a, 2H), 5.34 (d, *J* = 7.8 Hz, 0.6H), 5.37 (d, *J* = 8.3 Hz, 0.4H), 7.08 (td, *J* = 8.5, 2.4 Hz, 1H), 7.21 (td, *J* = 9.9, 2.7 Hz, 1H), 7.44-7.52 (m, 1 H); ESI-MS m/z $[M+H]^+$ 459.0.

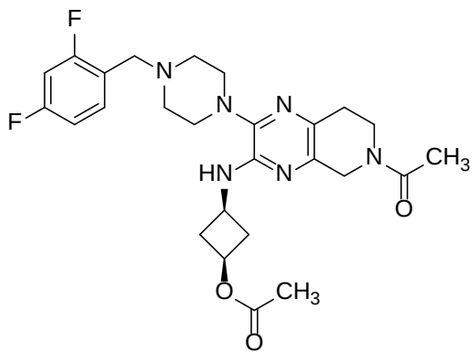
Ejemplo 138 4-(6-acetil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperazina-1-carboxilato de terc-butilo



A un reactor de presión cargado con una solución roja-anaranjada de 4-(3-(isopropilamino)pirido[3,4-*b*]pirazin-2-il)piperazina-1-carboxilato de terc-butilo (2.0 g, 5.37 mmol)

en acetona (100 mL) y dioxano (100 mL) se agregó paladio, 10 % p sobre carbono activado (0.229 g, 2.148 mmol) como un suspensión en dioxano (3 mL) bajo nitrógeno. Después, se agregó a 23°C anhídrido acético (5.04 mL, 53.7 mmol). La mezcla se agitó bajo hidrógeno a 310 kPa durante 17 hr a 45 °C. La mezcla de reacción se filtró a través Celite™, se lavó con dioxano, y se concentró mediante un evaporador rotatorio. El material en bruto se purificó mediante cromatografía de media presión utilizando un gradiente 10% a 100% de EtOAc en heptano en una columna NH 60 µM tamaño 400 (Shoko Scientific Purif-Pack™) para proporcionar el compuesto del título (1.068 g, 47.5%) como una espuma amarilla. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.16-1.21 (m, 6H), 1.42 (s, 9H), 2.08 (s, 1.3H), 2.09 (s, 1.7H), 2.58 (t, *J* = 5.9 Hz, 0.9H), 2.70 (t, *J* = 5.6 Hz, 1.1H), 2.87-2.98 (m, 4H), 3.51 (s a, 4H), 3.67-3.75 (m, 2H), 4.06-4.15 (m, 1H), 4.41 (s, 1.1H), 4.44 (s, 0.9H), 5.50 (d, *J* = 7.8 Hz, 1H), 5.53 (d, *J* = 7.8 Hz, 1H); ESI-MS m/z $[M+H]^+$ 419.0.

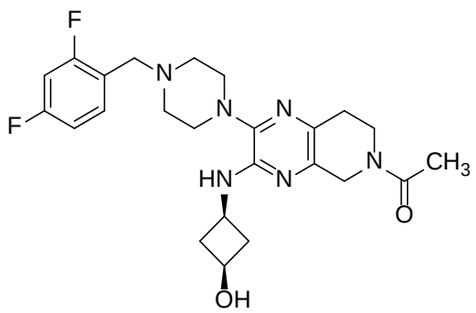
Ejemplo 139 acetato de (1*s*,3*s*)-3-((6-acetil-2-(4-(2,4-difluorobencil)piperazin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo



A un reactor de presión cargado con una solución roja-anaranjada de (1*s*,3*s*)-3-((2-(4-(2,4-difluorobencil)piperazin-1-il)pirido[3,4-*b*]pirazin-3-il)amino)ciclobutanol (0.3 g, 0.703 mmol) en acetona (15 mL) y dioxano (15 mL) se agregó paladio, 10 % p sobre carbono activado (0.030 g, 0.281 mmol) como un suspensión en dioxano (3 mL) bajo nitrógeno. Después, se agregó a 23 °C anhídrido acético (0.661 mL, 7.03 mmol). La mezcla de reacción se agitó bajo hidrógeno a 310 kPa durante 4 días a 45 °C. La mezcla de reacción se filtró a través Celite™, se lavó con dioxano, y se concentró mediante un evaporador rotatorio. El material en bruto se disolvió en tolueno (3 mL) y se purificó mediante cromatografía de media presión utilizando un gradiente de elución de 30% a 100%

EtOAc en heptano en una columna 90 g gel de sílice (Single Step™) para proporcionar el compuesto del título (119.7 mg, 33.1%) como una espuma amarilla. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.97-2.00 (m, 3H), 2.07 (s, 1.3H), 2.08 (s, 1.7H), 2.10-2.17 (m, 2H), 2.55-2.63 (m, 5H), 2.67-2.74 (m, 3H), 2.90-3.10 (m, 4H), 3.59 (s, 2H), 3.66-3.74 (m, 2H), 4.02-4.12 (m, 1H), 4.39 (s, 1.1H), 4,42 (s, 0.9H), 4.68 (quinteto d, J = 7.3, 3.4 Hz, 1H), 6.11 (d, J = 7.8 Hz, 0.6H), 6.15 (d, J = 7.8 Hz, 0.4H), 7.08 (td, J = 8.5, 2.4 Hz, 1H), 7.19-7.24 (m, 1H), 7.45-7.51 (m, 1H); ESI-MS m/z $[M+H]^+$ 515.0.

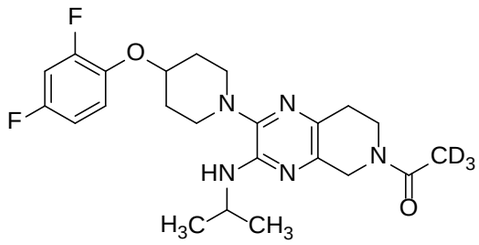
Ejemplo 140 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(((1*s*,3*s*)-3-hidroxiciclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



A una solución de acetato de (1*s*,3*s*)-3-((6-acetil-2-(4-(2,4-difluorobencil)piperazin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo (94,8 mg, 0.184 mmol) en MeOH (2 mL) se agregó metóxido de sodio (5.1 µL, 0.028 mmol) a 0 °C. La reacción se agitó a 0 °C durante 1 h, se concentró mediante un evaporador rotatorio at 30 °C, se reconstituyó con MeOH (2 mL), se enfrió a 0 °C, y se inactivó con HOAc (0.005 mL). La mezcla de reacción se concentró mediante un evaporador rotatorio, se repartió entre EtOAc (4 mL) y NH_4Cl saturado (1 mL), y las capas se separaron. La fase orgánica se lavó con salmuera (1 mL), se secó sobre Na_2SO_4, se filtró, se lavó con EtOAc, y se secó al vacío para proporcionar el compuesto del título (79.3 mg, 91%) como una espuma amarillenta-anaranjada. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.80-1.88 (m, 2H), 2.07 (s, 1.3H), 2.08 (s, 1.7H), 2.54-2.64 (m, 7H), 2.69 (t, J = 5.9 Hz, 1H), 2.99 (s a, 4H), 3.59 (s, 2H), 3.69 (dt, J = 11.5, 6.0 Hz, 2H), 3.77-3.91 (m, 2H), 4.38 (s, 1.1H), 4.41 (s, 0.9H), 4.95-5.00 (m, 1H), 5.82 (d, J = 7.3 Hz, 1H), 5.85

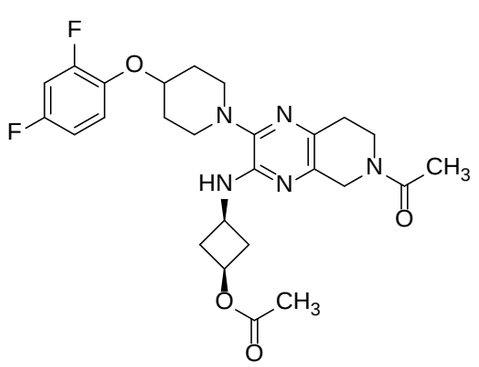
(d, *J* = 7.8 Hz, 1H) 7.08 (td, *J* = 8.4, 2.2 Hz, 1H), 7.19-7.24 (m, 1H), 7.45-7.51 (m, 1H); ESI-MS m/z $[M+H]^+$ 473.0.

Ejemplo 141 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-*d*3-etan-1-ona



A una solución de 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (2.4 g, 5.95 mmol) y DIPEA (1.56 mL, 8.92 mmol) en DCM (59.5 mL) a 0 °C se agregó por goteo cloruro-*d*3 de acetilo (0.42 mL, 5.95 mmol). La solución resultante se agitó a esta temperatura durante 1 h. Después de concentrarse, y purificarse en cromatografía en columna de gel de sílice utilizando 30% a 100% de EtOAc en heptanos proporcionó el compuesto del título (1.89 g, 70.8%). ^{1}H RMN (400 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.19 (d, *J* = 6.4 Hz, 2.7H), 1.21 (d, *J* = 6.4 Hz, 3.3H), 1.82-1.92 (m, 2H), 2.03-2.11 (m, 2H), 2.59 (t, *J* = 5.9 Hz, 0.9H), 2.71 (t, *J* = 5.9 Hz, 1.1H), 2.87 (m, 2H), 3.22-3.30 (m, 2H), 3.67-3.74 (m, 2H), 4.06-4.16 (m, 1H), 4.41 (s, 1.1H), 4.43 (s, 0.9H), 4.51 (m, 1H), 5.50 (d, *J* = 8.3 Hz, 1.1H), 5.54 (d, *J* = 7.8 Hz, 0.9H), 6.92-7.06 (m, 1H), 7.21-7.35 (m, 2H); ESI-MS m/z $[M+H]^+$ 449.0.

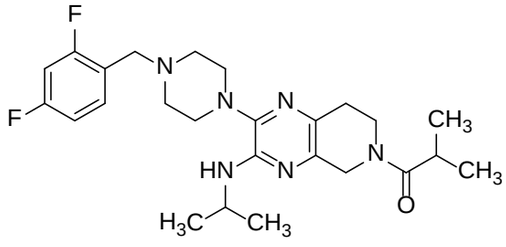
Ejemplo 142 Acetato de (1*s*,3*s*)-3-((6-acetil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo



A un reactor de presión cargado con una solución roja-anaranjada de (1*s*,3*s*)-3-((2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazin-3-il)amino)ciclobutanol (0.355 g, 0.831 mmol) en acetona (15 mL) y dioxano (15 mL) se agregó

paladio, 10 % p sobre carbono activado (0.035 g, 0.332 mmol) como un suspensión en dioxano (3 mL) bajo nitrógeno. Después, se agregó anhídrido acético (0.780 mL, 8.31 mmol) a 23 °C. La mezcla de reacción se agitó bajo hidrógeno a 310 kPa durante 48 hr a 45 °C. Se agregaron porciones adicionales de paladio, 10 % p sobre carbono activado y anhídrido acético (0.156 mL, 1.661 mmol) al reactor de presión y la mezcla de reacción se agitó bajo hidrógeno a 310 kPa durante 4 días adicionales a 45 °C. La mezcla de reacción se filtró a través Celite™, se lavó con dioxano y se concentró mediante un evaporador rotatorio. El material en bruto se disolvió en tolueno (3 mL) y se purificó mediante cromatografía de media presión utilizando un gradiente de elución de 30% a 100% EtOAc en heptano en una columna de 90 g gel de sílice (Single Step™) para proporcionar el compuesto del título como una sal HOAc. La sal HOAc se disolvió en MeOH, se pasó a través de un cartucho de 200 mg VariPure™ IPE (HCO_3MP) para eliminar HOAc, y el cartucho se lavó con MeOH. El filtrado se concentró mediante un evaporador rotatorio y se secó al vacío para proporcionar el compuesto del título (165 mg, 38.5%) como una espuma amarilla. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.86-1.96 (m, 2H), 1.98-2.01 (m, 3H), 2.01-2.08 (m, 2H), 2.08 (s, 1.3H), 2.09 (s, 1.7H), 2.11-2.20 (m, 2H), 2.59 (t, *J* = 5.9 Hz, 0.9H), 2.67-2.77 (m, 3.1H), 2.83-2.91 (m, 2H), 3.29 (d, *J* = 10.3 Hz, 2H), 3.70 (dt, *J* = 11.4, 5.8 Hz, 2H), 4.06-4.13 (m, 1H), 4.40 (s, 1H), 4.43 (s, 1H), 4.52 (dt, *J* = 8.2, 4.0 Hz, 1H), 4.69 (td, *J* = 7.3, 2.9 Hz, 1H), 6.24 (d, *J* = 7.3 Hz, 0.6H), 6.28 (d, *J*=7.8 Hz, 0.4H), 6.98-7.05 (m, 1H), 7.26-7.34 (m, 2H); ESI-MS m/z $[M+H]^+$ 516.0.

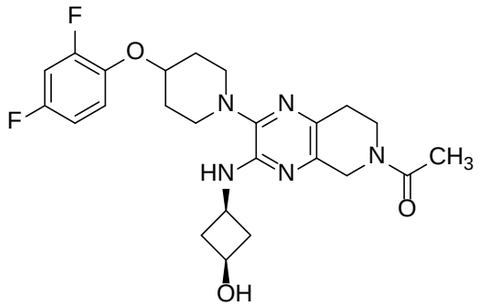
Ejemplo 143 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metilpropan-1-ona



A una solución de 2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina (50 mg, 0.124 mmol) y DIPEA (0.032 mL, 0.186 mmol) en

DCM (1 mL) se agregó cloruro de isobutirilo (0.013 mL, 0.124 mmol) a 0 °C. La mezcla de reacción se agitó a 0 °C durante 1 h, se calentó hasta 23 °C y se agitó durante 15.5 h adicionales. La mezcla de reacción se concentró mediante un evaporador rotatorio y se repartió entre EtOAc (4 mL) y NH_4Cl (2 mL). Las capas se separaron y la fase orgánica se lavó con salmuera (2 mL), se secó sobre Na_2SO_4, se filtró, se lavó con EtOAc, y se concentró mediante un evaporador rotatorio. El material en bruto se disolvió en EtOAc y MeOH, se absorbió sobre gel de sílice (0.25 g), y se purificó mediante cromatografía de media presión utilizando a 50% a 100% gradiente de EtOAc en heptano en una columna de 4 g gel de sílice (Single Step™) para proporcionar el compuesto del título (39.3 mg, 66.9%) como una espuma amarilla. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 0.99 (d, *J* = 6.8 Hz, 2.7H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.11-1.22 (m, 6H), 2.58 (s a, 3.8H), 2.69 (t, *J* = 5.4 Hz, 1.2H), 2.88-3.13 (m, 5H), 3.58 (s, 2H), 3.75 (dt, *J* = 10.9, 5.6 Hz, 2H), 4.05-4.17 (m, 1H), 4.41 (s, 1.1H), 4.49 (s, 0.9H), 5.29-5.42 (m, 1H), 7.08 (td, *J* = 8.5, 2.4 Hz, 1H), 7.21 (td, *J* = 9.9, 2.7 Hz, 1H), 7.44-7.52 (m, 1H); ESI-MS m/z $[M+H]^+$ 473.0.

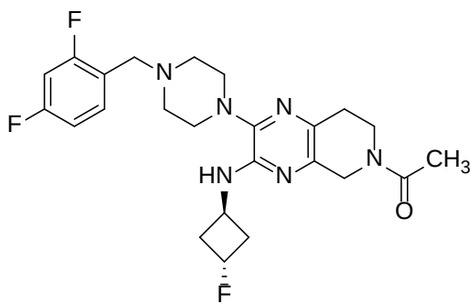
Ejemplo 144 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(((1*s*,3*s*)-3-hidroxiciclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



A una solución de acetato de (1*s*,3*s*)-3-((6-acetil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo (146.5 mg, 0.284 mmol) en MeOH (3 mL) se agregó metóxido de sodio (7.89 µL, 0.043 mmol) a 0 °C. La reacción se agitó a 0 °C durante 1 h, se concentró mediante un evaporador rotatorio at 30 °C, se reconstituyó con MeOH (2 mL), se enfrió a 0 °C, y se inactivó con HOAc (0.005 mL). La mezcla de reacción se concentró mediante un evaporador rotatorio, se repartió entre EtOAc (6 mL) y NH_4Cl saturado (4 mL), y las capas se

separaron. La fase orgánica se lavó con salmuera (2 mL), se secó sobre Na_2SO_4, se filtró, se lavó con EtOAc, y se secó al vacío para proporcionar el compuesto del título (119.5 mg, 89%) como un aceite amarillo. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.84-1.93 (m, 4H), 2.04-2.11 (m, 5H), 2.56-2.65 (m, 2.9H), 2.71 (t, *J* = 5.9 Hz, 1.1H), 2.87 (t, *J* = 10.3 Hz, 2H), 3.27 (dd, *J* = 8.1, 4.2 Hz, 2H), 3.70 (dt, *J* = 11.5, 6.0 Hz, 2H), 3.79-3.91 (m, 2H), 4.40 (s, 1.1H), 4.42 (s, 0.9H), 4.51 (tt, *J* = 8.2, 4.0 Hz, 1H), 4.99-5.04 (m, 1H), 5.99 (d, *J* = 7.3 Hz, 1.1H), 6.03 (d, *J* = 7.8 Hz, 1H), 6.99-7.04 (m, 1H), 7.26-7.33 (m, 2H); ESI-MS m/z $[M+H]^+$ 473.9.

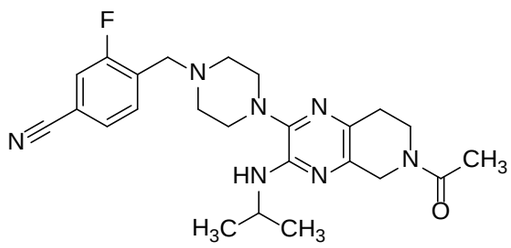
Ejemplo 145 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(((1*r*,3*r*)-3-fluorociclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



A una solución de 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(((1*s*,3*s*)-3-hidroxiciclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona (25 mg, 0.053 mmol) en DCM (1 mL) se agregó DAST (9.1 µL, 0.069 mmol) como una solución en DCM (0.5 mL) a –78 °C durante 2 min. La reacción se agitó a –78 °C durante 2 h, se calentó lentamente a 23 °C, se agitó durante 14,5 h adicionales a 23 °C. La mezcla de reacción se enfrió a –78 °C y se agregó a la mezcla una porción adicional de DAST (0.021 mL, 0.159 mmol). La mezcla de reacción se calentó lentamente a 23 °C y se agitó durante 24 hr adicionales, se enfrió a 0 °C y se inactivó con agua (5 mL). El producto en bruto se extrajo con EtOAc (2 x 10 mL), Los extractos orgánicos se combinaron, se secaron sobre Na_2SO_4, se filtraron, se lavaron con EtOAc, y se secaron al vacío. El material bruto resultante se reconstituyó en DMSO (0.5 mL), se lavó con DMSO (2 x 0.25 mL), y se purificó mediante HPLC Método B utilizando un gradiente de 20% a 50% ACN para proporcionar el compuesto del título como una sal TFA (1.2 mg, 3.8%) como un sólido blancuzco. ^{1}H RMN (500 MHz, metanol-d_4, mezcla de rotaméros) δ ppm 2.18-2.23 (m, 3H),

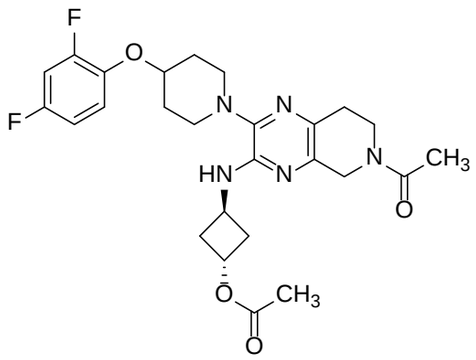
2.36-2.50 (m, 2H), 2.55-2.69 (m, 2H), 2.73 (t, *J* = 5.4 Hz, 0.9H), 2.80-2.86 (m, 1.1H), 3.26-3.30 (m, 4H), 3.47-3.72 (m, 4H), 3.81 (t, *J* = 5.6 Hz, 1.1H), 3.87 (t, *J* = 6.1 Hz, 0.9H), 4.49 (s, 2H), 4.55-4.59 (m, 2H), 4.83 (s, 2H), 5.15-5.21 (m, 0.6H), 5.26-5.33 (m, 0.4H), 7.65-7.71 (m, 1H); ESI-MS m/z $[M+H]^+$ 474.9.

Ejemplo 146 4-((4-(6-acetil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperazin-1-il)metil)-3-fluorobenzonitrilo



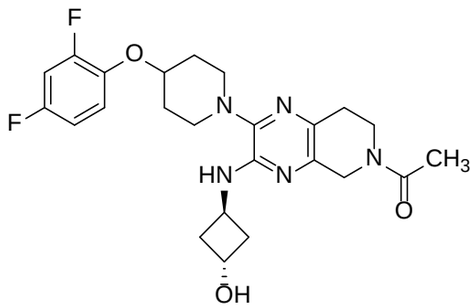
Se combinaron hidrocloruro de 1-(3-(isopropilamino)-2-(piperazin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona (132.2 mg, 0.218 mmol) y 3-fluoro-4-formilbenzonitrilo (32.6 mg, 0.218 mmol) en DCE (1 mL) y se agregó triacetoxihidroborato de sodio (64,8 mg, 0.306 mmol) a 23 °C. La mezcla de reacción se agitó a 23 °C durante 43 h. Se agregó una porción adicional de triacetoxihidroborato de sodio (64,8 mg, 0.306 mmol) a la mezcla de reacción y la mezcla se agitó durante 24 h adicionales a 23 °C. El residuo resultante se diluyó con DCE (1 mL), se filtró, se lavó con MeOH, y se concentró mediante un evaporador rotatorio. El material bruto resultante se reconstituyó en DMSO (1 mL), se filtró, se lavó con DMSO (2 x 0.5 mL), y se purificó mediante HPLC Método A para proporcionar el compuesto del título como una sal TFA (28.0 mg, 22.68%) como un sólido amarillo. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.13-1.28 (m, 6H), 2.08 (s, 1.3H), 2.09 (s, 1.7H), 2.59 (t, *J* = 5.9 Hz, 0.9H), 2.67-2.75 (m, 1.1H), 2.90-3.21 (m, 2H), 3.28-3.63 (m, 6H), 3.67-3.77 (m, 2H), 4.06-4.19 (m, 1H), 4.42 (s, 1.1H), 4.45 (s, 0.9H), 4.50 (s a, 2H), 5.68-5.77 (m, 1H), 7.83-7.87 (m, 1H), 7.87-7.92 (m, 1H), 8.01-8.22 (m, 1H), 10.22 (s a, 1H); ESI-MS m/z $[M+H]^+$ 452.0.

Ejemplo 147 Acetato de (1*r*,3*r*)-3-((6-acetil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo



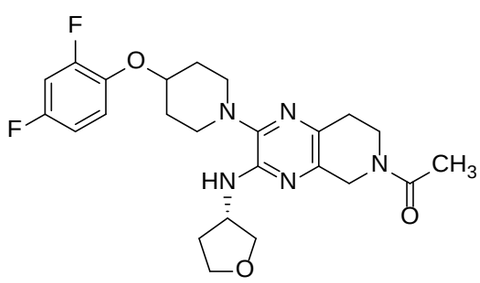
A un reactor de presión cargado con una solución anaranjada de (1*r*,3*r*)-3-((2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazin-3-il)amino)ciclobutanol (0.8 g, 1.872 mmol) en acetona (30 mL) y dioxano (30 mL) se agregó paladio, 10 % p sobre carbono activado (0.100 g, 0.936 mmol) como un suspensión en dioxano (3 mL) bajo nitrógeno. Después, anhídrido acético (1.758 mL, 18.72 mmol) se agregó a 23 °C. La mezcla se agitó bajo hidrógeno a 310 kPa durante 3 días a 45 °C. Se agregaron porciones adicionales de paladio, 10 % p sobre carbono activado (0.100 g, 0.936 mmol) y anhídrido acético (0.352 mL, 3.74 mmol) al reactor y la mezcla se agitó bajo hidrógeno a 45 kPa durante 2 días adicionales a 45 °C. La mezcla de reacción se filtró a través Celite™, se lavó con dioxano, y se concentró mediante un evaporador rotatorio. El material en bruto se disolvió en tolueno (2 mL) y se purificó mediante cromatografía de media presión utilizando un gradiente de 30% a 100% de EtOAc en heptano en una columna de 160 g de gel de sílice (Single Step™) para proporcionar el compuesto del título (270 mg, 28.0%) como un sólido blancuzco. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.83-1.97 (m, 2H), 2.03 (s, 3H), 2.04-2.12 (m, 5H), 2.33-2.41 (m, 2H), 2.41-2.49 (m, 2H), 2.59 (t, *J* = 5.9 Hz, 0.9H), 2.71 (t, *J* = 5.6 Hz, 1.1H), 2.89 (t, *J* = 10.0 Hz, 2H), 3.20-3.34 (m, 4H), 3.56-3.79 (m, 2H), 4.40 (s, 1.1H), 4.43 (s, 0.9H), 4.47-4.59 (m, 2H), 5.05 (td, *J* = 6.9, 3.2 Hz, 1H), 6.24 (d, *J* = 6.8 Hz, 0.6 H), 6.27 (d, *J*=6.8 Hz, 0.4H), 6.94-7.11 (m, 1H), 7.22-7.43 (m, 2H); ESI-MS m/z $[M+H]^+$ 515.9.

Ejemplo 148 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(((1*r*,3*r*)-3-hidroxiciclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



A una suspensión blancuzca de acetato de (1*r*,3*r*)-3-((6-acetil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo (108 mg, 0.209 mmol) en MeOH (2 mL) se agregó metóxido de sodio (5.8 µL, 0.031 mmol) a 23 °C. La reacción se agitó a 23 °C durante 15 min, se concentró mediante un evaporador rotatorio a 30 °C, se reconstituyó con MeOH (2 mL), se enfrió a 23 °C, y se inactivó con HOAc (0.010 mL). La mezcla de reacción se concentró mediante un evaporador rotatorio, se repartió entre EtOAc (6 mL) y NH_4Cl saturado (4 mL), y las capas se separaron. La fase orgánica se lavó con salmuera (2 mL), se secó sobre Na_2SO_4, se filtró, se lavó con EtOAc, y se secó al vacío para proporcionar el compuesto del título (99 mg, 100%) como una espuma amarilla. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.87-1.93 (m, 2H), 2.00-2.12 (m, 5H), 2.12-2.20 (m, 2H), 2.21-2.32 (m, 2H), 2.55-2.62 (m, 0.9H), 2.71 (t, *J* = 5.1 Hz, 1.1H), 2.88 (t, *J* = 10.0 Hz, 2H), 3.28 (s a, 2H), 3.63-3.80 (m, 2H), 4.29 (d, *J* = 3.9 Hz, 1H), 4.40 (s, 1.1H) 4.43 (s, 0.9H), 4.47-4.62 (m, 1H), 4.95 (d, *J* = 4.9 Hz, 1H), 5.99 (d, *J* = 6.3 Hz, 1H), 6.03 (d, *J* = 6.8 Hz, 1H), 6.96-7.08 (m, 1H), 7.23-7.36 (m, 2H); ESI-MS m/z $(M+H)^+$ 474.0.

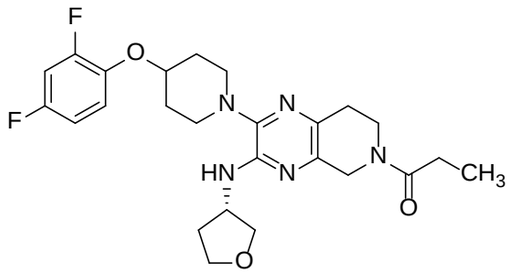
Ejemplo 149 (*S*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(tetrahidrofurán-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



A una solución de (*S*)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-(tetrahidrofurán-3-il)pirido[3,4-*b*]pirazin-3-amina (2.0 g, 4,68 mmol) en dioxano:acetona (50 ml; 1.5:1) se agregó Ac_2O (4,8 mL, 50.9

mmol) y Pd/C (400 mg, 3.76 mmol); posteriormente, la reacción se agitó a 60 °C bajo atmósfera de H_2 (345 kPa) durante 72 h. La mezcla se filtró a través de una almohadilla de Celite™ y se lavó con EtOAc. La reacción solución se diluyó con EtOAc (50 mL) y se vertió en $NaHCO_3$ sat. acuoso (50 ml), posteriormente se lavó con salmuera (2 x 30 mL). La capa orgánica se secó sobre Na_2SO_4 y se concentró para proporcionar el producto en bruto, que se purificó mediante cromatografía ultrarrápida en columna para proporcionar el compuesto del título (193.4 mg) como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-*d*6) δ ppm 1.88-1.89 (m, 4H), 2.05-2.09 (m, 4H), 2.60-2.90 (m, 4H), 3.30-3.40 (m, 4H), 3.55-3.57 (m, 1H), 3.68-3.74 (m, 2H), 3.85-3.95 (m, 2H), 4.38-4.51 (m, 4H), 5.91 (dd, *J* = 6.0, 4.4 Hz, 1H), 7.01 (m, 1H), 7.25-7.31 (m, 2H); ESI-MS m/z $[M+H]^+$ 474.3.

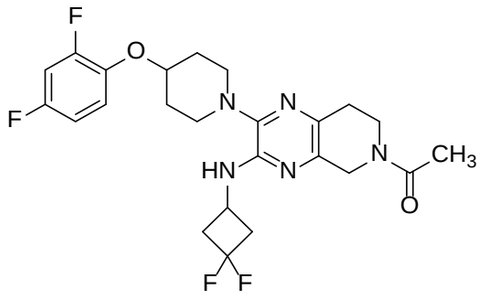
Ejemplo 150 (*S*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(tetrahidrofurán-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona



A una solución de (*S*)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-N-(tetrahidrofurán-3-il)pirido[3,4-*b*]pirazin-3-amina (2.5 g, 5.85 mmol) en dioxano:acetona (105 ml, 1.5:1) se agregó anhídrido propiónico (7 mL, 3.76 mmol) y Pd/C (400 mg, 3.76 mmol); posteriormente, la reacción se agitó a 60 °C y bajo atmósfera de H_2 (345 kPa) durante 72 h. La mezcla se filtró a través de una almohadilla de Celite™ y se lavó con EtOAc. La reacción solución se diluyó con EtOAc (50 mL) y se vertió en $NaHCO_3$ sat. acuoso (50 mL) y se lavó con salmuera (2 x 30 mL). La capa orgánica se secó sobre Na_2SO_4 y se concentró para proporcionar el producto en bruto, que se purificó mediante cromatografía ultrarrápida en columna para proporcionar el compuesto del título (125 mg) como un sólido blancuzco. ^{1}H RMN (400 MHz, DMSO-*d*6) δ ppm 0.97-1.03 (m, 3H), 1.87-2.04 (m, 6H), 2.15-2.25 (m, 1H), 2.40-2.43 (m, 2H), 2.58-2.60 (m, 1H), 2.69-2.73 (m, 1H), 2.88 (c, *J* = 9.6 Hz, 2H), 3.30-3.34 (m,

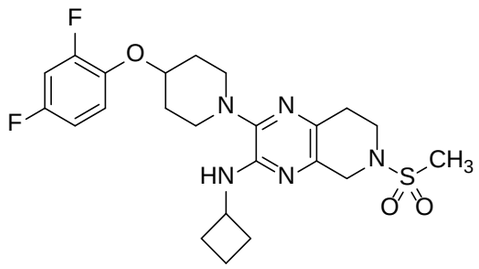
2H), 3.50-3.60 (m, 1H), 3.70-3.74 (m, 2H), 3.84-3.90 (m, 2H), 4.35-4.60 (m, 4H), 5.88-5.92 (m, 1H), 6.98-7.02 (m, 1H), 7.27-7.30 (m, 2H); ESI-MS m/z $[M+H]^+$ 488.3.

Ejemplo 151 1-(3-((3,3-difluorociclobutil)amino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona



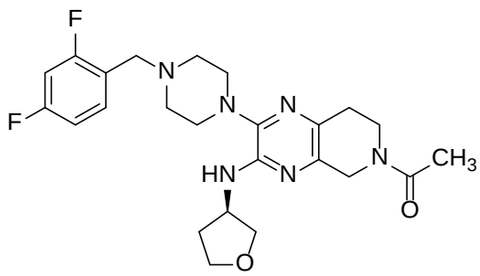
A un reactor de presión cargado con una solución amarilla-anaranjada de *N*-(3,3-difluorociclobutil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)pirido[3,4-*b*]pirazin-3-amina (250 mg, 0.559 mmol) en acetona (10 mL) y dioxano (10 mL) se agregó paladio, 10 % p sobre carbono activado (23.8 mg, 0.223 mmol) como un suspensión en dioxano (2 mL) bajo nitrógeno. Después, se agregó anhídrido acético (0.525 mL, 5.59 mmol) a 23 °C. La mezcla se agitó bajo hidrógeno a 310 kPa durante 45 h a 45 °C. La mezcla de reacción se filtró a través Celite™, se lavó con dioxano, y se concentró mediante un evaporador rotatorio. El material en bruto se purificó mediante cromatografía de media presión utilizando un gradiente de elución de 30% a 100% EtOAc en heptano en una columna de gel de sílice de 80 g (Single Step™) para proporcionar el compuesto del título (145 mg, 52.6%) como un sólido amarillo. ^{1}H RMN (500 MHz, DMSO-d_6, mezcla de rotaméros) δ ppm 1.80-1.95 (m, 2H), 2.03-2.08 (m, 2H), 2.0 (s, 1.3H), 2.09 (s, 1.7H), 2.60 (t, *J* = 5.6 Hz, 0.9H), 2.67-2.80 (m, 3.1H), 2.83-2.98 (m, 4H), 3.31-3.38 (m, 2H), 3.71 (dt, *J* = 11.2, 5.6 Hz, 2H), 4.14-4.27 (m, 1H), 4.42 (s, 1.1H), 4.45 (s, 0.9H), 4.53 (tt, *J* = 8.2, 3.8 Hz, 1H), 6.46 (dd, *J* = 14.6, 6.8 Hz, 1H), 6.98-7.06 (m, 1H), 7.25-7.36 (m, 2H); ESI-MS m/z 493.9 $(M+H)^+$ 493.9.

Ejemplo 152 *N*-ciclobutil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina



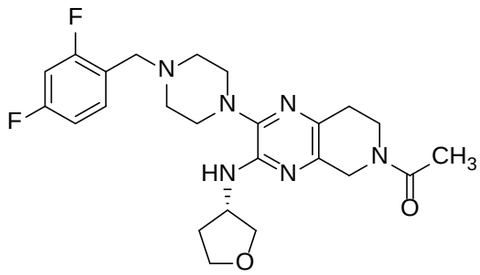
El compuesto del título se preparó de manera similar al Ejemplo 11 utilizando *N*-ciclobutil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina para proporcionar el compuesto del título. ^{1}H RMN (500 MHz, DMSO-d_6) δ ppm 1.55-1.75 (m, 2H), 1.84-1.96 (m, 2H), 1.96-2.14 (m, 4H), 2.18-2.32 (m, 2H), 2.75 (t, *J* = 5.9 Hz, 2H), 2.84-2.95 (m, 2H), 2.95-3.03, 3.26-3.33 (m, 2H), 3.45 (t, *J* = 5.9 Hz, 2H), 4.16 (s, 2H), 4.30-4.44 (m, 1H), 4.52 (tt, *J* = 8.1, 3.8 Hz, 1H), 6.12 (d, *J* = 7.8 Hz, 1H), 6.95-7.08 (m, 1H), 7.23-7.37 (m, 2H); ESI-MS m/z $(M+H)^+$ 494.0.

Ejemplo 153 (*R*)-1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(tetrahidrofurán-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



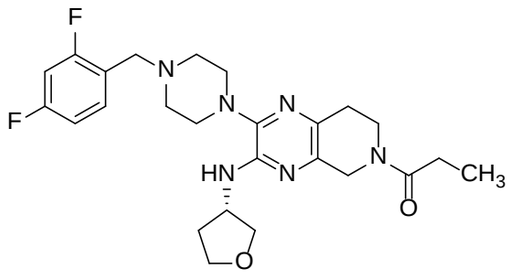
El compuesto del título se preparó de manera similar a 149 utilizando (*R*)-2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-(tetrahidrofurán-3-il)pirido[3,4-*b*]pirazin-3-amina para proporcionar el compuesto del título como un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.82-1.86 (m, 1H), 2.20 (s, 3H), 2.33-2.36 (m, 1H), 2.59-2.66 (m, 4H), 2.79 (m, 2H), 3.05-3.15 (m, 4H), 3.63 (s, 1H),.72 (m, 2H), 3.85-3.88 (m, 2H), 3.95-3.99 (m, 2H), 4.46-4.64 (m, 3H), 4.87-4.90 (m, 1H), 6.79-6.90 (m, 2H), 7.39-7.41 (m, 1H); ESI-MS m/z $[M+H]^+$ 473.1.

Ejemplo 154 (*S*)-1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(tetrahidrofurán-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



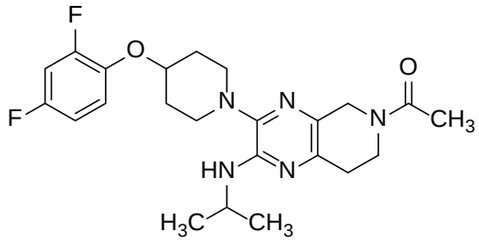
El compuesto del título se preparó de manera similar a 149 utilizando (*S*)-2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-(tetrahidrofurán-3-il)pirido[3,4-*b*]pirazin-3-amina para proporcionar el compuesto del título como un sólido blancuzco. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.82-1.86 (m, 1H), 2.20 (s, 3H), 2.33-2.36 (m, 1H), 2.59-2.66 (m, 4H), 2.79 (dt, *J* = 21.6, 5.6 Hz, 2H), 3.05-3.15), 3.63 (s, 1H), 3.69-3.72 (m, 2H), 3.85-3.88 (m, 2H), 3.98-4.00 (m, 2H), 4.48-4.64 (m, 3H), 4.88-4.92 (m, 1H), 6.82 (t, *J* = 9.6 Hz, 1H), 6.84 (t, *J* = 12.8 Hz, 1H), 7.39 (c, *J* = 7.2 Hz, 1H); ESI-MS m/z $[M+H]^+$ 473.1.

Ejemplo 155 (*S*)-1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(tetrahidrofurán-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona



El compuesto del título se preparó de manera similar al Ejemplo 150 utilizando (*S*)-2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-(tetrahidrofurán-3-il)pirido[3,4-*b*]pirazin-3-amina para proporcionar el compuesto del título como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.18 (c, *J* = 7.2 Hz, 3H), 1.75-1.85 (m, 1H), 2.25-2.46 (m, 3H), 2.55-2.65 (m, 4H), 2.75-2.80 (m, 2H), 3.0(m, 4H), 3.59-3.70 (m, 4H), 3.87-3.90 (m, 2H), 3.96-3.98 (m, 2H), 4.46-4.62 (m, 3H), 4.85-4.95 (m, 1H), 6.75-6.90 (m, 2H), 7.35-7.45 (m, 1H); ESI-MS m/z $[M+H]^+$ 487.3.

Ejemplo 156 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-Ejemploropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona



El compuesto del título se preparó de manera similar al Ejemplo 120 utilizando 4-(2,4-difluorofenoxi)piperidina, HCl para proporcionar el compuesto del título como una película incolora. ^{1}H RMN (500 MHz, metanol-*d*4) δ ppm 0.85-0.93 (m, 1H), 1.25 (d, *J* = 6.4 Hz, 6H), 1.95 (ddd, *J* = 12.1, 8.2, 3.7 Hz, 2H), 2.09-2.17 (m, 2H), 2.20 (d, *J* = 8.8 Hz, 3H), 2.74 (t, *J* = 5.9 Hz, 1H), 2.84 (t, *J* = 5.6 Hz, 12-3.02 (m, 2H), 3.35 (dd, *J* = 8.3, 3.9 Hz, 2H), 3.81 (t, *J* = 5.6 Hz, 1H), 3.86 (t, *J* = 5.9 Hz, 1H), 4.12-4.21 (m, 1H), 4.46 (dd, *J* = 7.1, 3.7 Hz, 1H), 4.54 (s, 2H), 6.85-6.91 (m, 1H), 6.96-7.02 (m, 1H), 7.18 = 8.8, 5.4 Hz, 1H); ESI-MS m/z $[M+H]^+$ 446.90.

Los compuestos de la invención se pueden administrar solos o en la forma de una composición farmacéutica. En la práctica, los compuestos de la invención se administran comúnmente en la forma de composiciones farmacéuticas, esto es, en mezcla con al menos un excipiente farmacéuticamente aceptable. La proporción y naturaleza de cualquier excipiente farmacéuticamente aceptable se determinan en base a las propiedades del compuesto de la invención seleccionado, la ruta de administración elegida y la práctica farmacéutica habitual.

En otra realización, la presente invención proporciona composiciones farmacéuticas que comprenden: un compuesto de la invención y al menos un excipiente farmacéuticamente aceptable.

Para llevar a cabo el tratamiento en un paciente que necesita dicho tratamiento, un compuesto de la invención puede administrarse de cualquier forma y vía que hace que el compuesto se haga biodisponible. Los compuestos de la invención pueden administrarse mediante una variedad de vías, incluido oralmente, en particular mediante comprimidos y cápsulas. Los compuestos de la invención pueden administrarse mediante vías parenterales, más particularmente mediante inhalación, subcutáneamente, intramuscularmente, intravenosamente, intraarterialmente, transdérmicamente, intranasalmente, rectalmente,

vaginalmente, ocularmente, tópicamente, sublingualmente y bucalmente, intraperitonealmente, intraadiposamente, intratecalmente y mediante administración local, por ejemplo, mediante catéter o stent.

El entendido en la técnica puede seleccionar con facilidad la forma y vía adecuadas de administración en función de las características particulares del compuesto seleccionado, el trastorno o afección que se desea tratar, la etapa de trastorno o afección, y otras circunstancias relevantes. Las composiciones farmacéuticas de la invención pueden administrarse al paciente, por ejemplo, en forma de comprimidos, cápsulas, píldoras, papeles, grageas, obleas, elíxires, ungüentos, parches transdérmicos, aerosoles, inhaladores, supositorios, soluciones y suspensiones.

Las composiciones farmacéuticas de la presente invención se preparan de una forma adecuada en la técnica farmacéutica e incluyen al menos uno de los compuestos de la invención como el ingrediente activo. La cantidad de un compuesto de la presente invención puede variar en función de su forma particular y puede encontrarse convenientemente entre un 1% y aproximadamente un 50% del peso de la forma de dosificación unitaria. El término "excipiente farmacéuticamente aceptable" se refiere a aquellos utilizados típicamente en la preparación de composiciones farmacéuticas y deberían ser farmacéuticamente puros y no tóxicos en las cantidades utilizadas. Son generalmente un material sólido, semi sólido o líquido que en el agregado pueden servir como un vehículo o medio para el ingrediente activo. Algunos ejemplos de los excipientes farmacéuticamente aceptables se encuentran en *Remington's Pharmaceutical Sciences* y en el *Handbook of Pharmaceutical Excipients* e incluyen diluyentes, vehículos, portadores, bases de ungüentos, aglutinantes, desintegrantes, lubricantes, deslizantes, agentes endulzantes, agentes saborizantes, bases de gel, matrices de liberación sostenida, agentes estabilizantes, conservantes, solventes, agentes de suspensión, reguladores, emulsionantes, tintes, propelantes, agentes de recubrimiento y otros.

Las presentes composiciones farmacéuticas se formulan preferentemente en una forma de dosificación unitaria, cada dosis contiene típicamente de aproximadamente 0.5 mg a

aproximadamente 100 mg de un compuesto de la invención. El término “forma de dosificación unitaria” se refiere a una unidad físicamente separada que contiene una cantidad predeterminada de ingrediente activo, junto con un excipiente farmacéuticamente adecuado, mediante el cual se utilizan uno o más en todo el régimen de dosificación para producir el efecto terapéutico deseado. Pueden tomarse una o más "formas de dosificación unitaria" para afectar la dosificación del tratamiento a diario.

En una variante particular, la composición es una composición farmacéutica adaptada para administración oral, tal como un comprimido o una cápsula o una formulación líquida, por ejemplo, una solución o suspensión, adaptada para administración oral. Aún en otra variante particular, la composición farmacéutica es una formulación líquida adaptada para administración parenteral.

Los compuestos de la presente invención son moduladores de GPR6, específicamente, antagonistas o agonistas inversos, y como tales son útiles en el tratamiento y la prevención de afecciones asociadas con el GPR6. Tal como se mencionó anteriormente, las dianas estriadas principales de la inervación dopaminérgica residen en las neuronas espinales medias (MSN) de las sendas de salida estriadopalidal (indirectas) y estriadonigral (directas). Las MSN de la senda de salida directa expresan receptores de dopamina D1 mientras que aquellas en la senda indirecta expresan receptores D2. El GPR6 es enriquecido en el receptor D2 que expresa las MSN en el estriado mientras que la actividad del GPR6 es funcionalmente opuesta a la señalización del receptor D2. El antagonismo o agonismo inverso de GPR6 acoplado a las G disminuye cAMP en los MSN y proporciona una alternativa funcional para la activación mediada por dopamina de los receptores D2.

El antagonismo o agonismo inverso del GPR6 acoplado a las G proporciona una alternativa funcional para la activación mediada por dopamina de los receptores D2. Como tales, los compuestos que modulan la actividad de GPR6 son útiles para tratar una variedad de trastornos neurológicos y psiquiátricos. Por ejemplo, los trastornos de movimiento incluidos la enfermedad de Parkinson y la enfermedad de Huntington tanto solas o en combinación con otros agentes

son aprobados para el tratamiento de la enfermedad de Parkinson incluido L-DOPA, agonistas dopaminérgicos, inhibidores de MAO B, inhibidores de descarboxilasa DOPA e inhibidores de C(O)MT. Otras indicaciones de enfermedades que podrían tratarse mediante la modulación del GPR6 incluyen la adicción a fármacos y trastornos alimentarios, trastornos cognitivos, esquizofrenia, trastornos bipolares y depresión.

En otra realización, la invención proporciona métodos para tratar afecciones asociadas con el GPR6, que comprende: administrar a un paciente que lo necesita una cantidad eficaz de un compuesto de la invención. En otra realización, se proporciona un compuesto de la invención para su uso como medicamento. La invención también proporciona el uso de un compuesto de la invención, incluido el uso para la fabricación de un medicamento, para tratar las afecciones asociadas con el GPR6 descritas en la presente. Los compuestos de la presente invención son útiles como moduladores de GPR6 en una variedad de individuos (por ejemplo, humanos, mamíferos no humanos y no mamíferos).

Tal como se utiliza en la presente, los términos "afección", "trastorno" y "enfermedad" se refieren a cualquier estado poco saludable o anormal. El término "afecciones asociadas con el GPR6" incluye afecciones, trastornos y enfermedades en los que los moduladores del GPR6 proporcionan un beneficio terapéutico, tal como enfermedad de Parkinson, discinesias inducidas por levodopa y enfermedad de Huntington, adicción a fármacos, trastornos alimenticios, trastornos cognitivos, esquizofrenia, trastornos bipolares y depresión.

Los términos "tratar", "tratamiento" y "que trata" incluyen la mejora de las afecciones descritas en la presente. Los términos "tratar", "tratamiento" y "que trata" incluyen todos los procesos que proporcionan ralentizar, interrumpir, detener, controlar o parar el estado o avance de las afecciones descritas en la presente, pero no indican necesariamente una eliminación total de todos los síntomas o una cura de la afección. Los términos "tratar", "tratamiento" y "que trata" pretenden incluir el tratamiento terapéutico de dichos trastornos. Los términos "tratar",

"tratamiento" y "que trata" pretenden incluir el tratamiento profiláctico de dichos trastornos.

Tal como se utiliza en la presente, los términos "paciente" e "individuo" incluyen seres humanos y animales no humanos, por ejemplo, mamíferos, tales como ratones, ratas, coballos, perros, gatos, conejos, vacas, caballos, ovejas, cabras y cerdos. El término también incluye pájaros, peces, reptiles, anfibios y similares. Se entiende que un paciente más particular es un ser humano. Además, los pacientes e individuos más particulares son mamíferos no humanos, tales como ratones, ratas y perros.

Tal como se utiliza en la presente, el término "cantidad eficaz" se refiere a la cantidad de compuesto de la invención que trata, tras una administración de dosis única o múltiple, a un paciente que sufre de la afección mencionada. El médico tratante, como un entendido en la técnica, puede determinar fácilmente una cantidad eficaz mediante el uso de técnicas conocidas y mediante observación de los resultados obtenidos en circunstancias análogas. Para determinar la cantidad eficaz, la dosis, una cantidad de factores son considerados por el médico tratante, incluido a modo no taxativo, el tipo de paciente, su tamaño, edad y salud general; la afección, trastorno o enfermedad específica involucrada; el grado de implicancia o la gravedad de la afección, trastorno o enfermedad, la respuesta del paciente individual; el compuesto particular administrado; el modo de administración; las características biodisponibles de la preparación administrada; el régimen de dosificación seleccionado; el uso de medicación concomitante y otras circunstancias relevantes. Se espera que en una cantidad eficaz de la presente invención, la dosificación del tratamiento se encuentre entre 1 mg y 200 mg. El entendido en la técnica puede determinar las cantidades específicas. Aunque estas dosificaciones se basan en un individuo humano promedio que tiene una masa de aproximadamente 60 kg a aproximadamente 70 kg, el médico podrá determinar la dosificación adecuada para otros pacientes.

La característica patológica de la enfermedad de Parkinson (PD) es la pérdida de células neuronales dentro de la sustancia negra. La degeneración del sistema

nigroestriado ocasiona reducción en la concentración estriada de dopamina que resulta en manifestaciones clínicas motoras y no motoras. Varias enfermedades de Parkinson se tratan con levodopa, un profármaco para la dopamina. La levodopa tiene varios efectos colaterales incluida la discinesia inducida (LID), trastornos del control impulsivo (ICD), síntomas psicóticos y alteraciones del sueño. La LID es progresiva (un 90% de pacientes con PD desarrollan LID dentro de 10 años). Las adaptaciones irreversibles ocurren en el receptor D1 que señala en las MSN en modelos de roedores de LID que incluyen desensibilización reducida que conduce a la hipersensibilidad en la senda directa. La inactivación genética de los receptores D1 pero no D2 elimina la LID en ratones. No obstante, el bloqueo de la señalización del receptor D1 no afecta la eficacia antiparkinsoniana de L-DOPA.

En una realización particular, la presente invención proporciona un método para tratar la enfermedad de Parkinson que comprende: administrar a un paciente que lo necesita una cantidad eficaz de un compuesto de la invención. Esto es, la invención también proporciona el uso de un compuesto de la invención, incluido el uso para la fabricación de un medicamento, para tratar la enfermedad de Parkinson.

Los compuestos de la invención pueden combinarse con uno o más compuestos farmacológicamente activos o terapias para el tratamiento de uno o más trastornos, enfermedades o afecciones para los que se indica el GPR6 pueden administrarse simultáneamente, secuencialmente o individualmente en combinación con uno o más compuestos o terapias para tratar la enfermedad de Parkinson, discinesias inducidas por levodopa y enfermedad de Huntington, adicción a los fármacos, trastornos alimenticios, trastornos cognitivos, esquizofrenia, trastornos bipolares y depresión. Dichas combinaciones pueden ofrecer ventajas terapéuticas significativas, incluidos menos efectos colaterales, capacidad mejorada para tratar poblaciones de pacientes subatendidos o actividad sinérgica. En particular, los compuestos de la invención pueden administrarse con levodopa para tratar la enfermedad de Parkinson. La presente invención proporciona un método para tratar la enfermedad de Parkinson que comprende: administrar a un paciente que lo

necesita una cantidad eficaz de un compuesto de la invención en combinación con levodopa. La invención también proporciona el uso de un compuesto de la invención en combinación con levodopa, incluido el uso para la fabricación de un medicamento, para tratar la enfermedad de Parkinson.

La actividad de compuestos como moduladores de GPR6 puede determinarse mediante una variedad de métodos, incluido métodos *in vitro* e *in vivo*.

Ejemplo A.1

Inhibición de la actividad de cAMP de GRP6 en ensayos in vitro

Este ensayo basado en células mide la capacidad de compuestos para inhibir la actividad de cAMP constitutivo del receptor GPR6 expresado en células CHO-K1. Las células CHO se expresaron establemente con el receptor GPR6, cuya expresión se controla mediante un elemento inducible de tetraciclina. Las células se cultivaron en un medio que contiene F12K, FBS al 10%, Pen/Estrep al 1%, 200ug/mL de higromicina. La expresión del receptor GPR6 se indujo durante 20 horas con 1µg/ml de doxiciclina (sigma D9891) en un medio de cultivo. Tras la adición de células de doxiciclina se colocaron en placas a una densidad de 250 a 500 células por pocillo en placas con fondo claro negro con medio volumen (Costar) y se colocaron en un incubador (37°, $C(O)_2$ al 5%) durante 20 horas antes de los ensayos cAMP.

El medio de cultivo se eliminó de las células y se lavaron con 50 µL de regulador de Ringer (0,047 mg/mL de $MgCl_2$, 0,18 mg/mL de NaH_2PO_4, 0.1 mg/mL de Na_2HPO_4, 0.34 mg/mL de KCl, 1.26 mg/mL de $NaHC(O)_3$, 1.8 mg/mL de D-glucosa, 7 mg/mL de NaCl; pH=7,4). Los compuestos suspendidos en DMSO se diluyeron en regulador de Ringer que contiene BSA libre de ácido graso al 0.5% y se incubaron en células durante 45 minutos a 37° y $C(O)_2$ al 5%. Después de la incubación las células se incubaron durante 10 minutos a temperatura ambiente con solución de rastro Eu-cAMP a partir de un kit de ensayo Perkin Elmer Lance HTRF UltracAMP (TRF0264). Después, se agregó la solución ULightTM-anti-cAMP a partir del kit Lance HTRF y se incubó en un agitador a temperatura ambiente durante 1 hora antes de la detección HTRF en un BMG PolarStar Omega.

Las curvas de IC_{50} se generaron con una ecuación logística de cuatro parámetros mediante el uso de GraphPad Prism 5.03. El valor de IC_{50} medido (μM) de ejemplos de compuestos en este ensayo se proporciona en la tabla a continuación.

Ejemplo A.2

Inhibición de la actividad de cAMP de GRP6 en ensayos *in vitro*

Este ensayo basado en células mide la capacidad de compuestos para inhibir la actividad de cAMP constitutivo del receptor GPR6 expresado en células CHO-K1. Las células CHO se expresaron establemente con el receptor GPR6, cuya expresión se controla mediante un elemento inducible de tetraciclina. Las células se cultivaron en un medio que contiene F12K, FBS al 10%, Pen/Estrep al 1%, 200ug/mL de higromicina. La expresión del receptor GPR6 se indujo durante 20 horas con 2μg/ml de doxiciclina (sigma D9891) en un medio de cultivo. Tras la adición de células de doxiciclina se colocaron en placas a una densidad de 450 a 750 células por pocillo en placas de cultivo de tejido negro con medio volumen de 96 pocillos (Costar) y se colocaron en un incubador (37°, CO_2 al 5%) durante 20 horas antes de los ensayos cAMP.

El medio de cultivo se quitó de células y se lavaron con 50 μL/pocillo de regulador de Ringer (0.047 mg/mL de $MgCl_2$, 0.18 mg/mL de NaH_2PO_4, 0.1 mg/mL de Na_2HPO_4, 0.34 mg/mL de KCl, 1.26 mg/mL de $NaHCO_3$, 1.8 mg/mL de D-glucosa, 7 mg/mL de NaCl; pH=7,4). Los compuestos suspendidos en DMSO se diluyeron en regulador de Ringer que contiene BSA libre de ácido graso al 0.5% más 300 μM de IBMX y se incubaron en células durante 45 minutos a 37° y CO_2 al 5%. Después de la incubación las células se incubaron durante 10 minutos a temperatura ambiente con solución de rastro Eu-cAMP a partir de un kit de ensayo Perkin Elmer Lance HTRF Ultra cAMP (TRF0263). Después, se agregó la solución ULightTM-anti-cAMP a partir del kit Lance HTRF y se incubó en un agitador a temperatura ambiente durante 1 hora antes de la detección HTRF en un lector de placa Perkin Elmer Envision.

Las curvas de IC_{50} se generaron con una ecuación logística de cuatro parámetros mediante el uso de GraphPad Prism 5.03. El valor de IC_{50} medido (μM) de ejemplos de

compuestos en este ensayo se proporciona en la tabla 1 a continuación.

Tabla 1

Ejemplo	A.1 IC_{50}	A.2 IC_{50}	Ejemplo	A.1 IC_{50}	A.2 IC_{50}	Ejemplo	A.1 IC_{50}	A.2 IC_{50}
1		340.2	53		95	105		
2		71.5	54		59.3	106		
3		61.8	55		109.6	107	24.9	
4	29.8		56		179.4	108	31.4	
5	17.9		57		93.5	109	23.2	
6	55.2		58	26.6		110	22.1	
7	86.6		59		49.7	111	23	
8	16.8		60		>1000	112	10.4	
9		210.6	61		131.7	113	20.9	
10	17.3		62		69.2	114	18.5	
11		95.6	63		37.8	115	23.9	
12						116		199.7
13			65			117		27.4
14	62.6		66	145		118		11.4
15	14.9		67	9.4		119		23.6
16	19.5		68	15.2		120		249.8
17	18		69	26.5		121		341.5
18	38.7		70		17.1	122		247
19	105		71	8.5		123		187.7
20	122		72	23.7		124		43.2
21	149		73	16.6		125		200.2
22		78.1	74		140.2	126		107.1
23	391		75		30.3	127		>1000
24		129.2	76	13.4		128		55
25			77	19.7		129		62
26			78	8.8		130		319.3
27			79	9.8		131		27.6
28			80	24.9		132		129.5
29	178		81		59.5	133		74.8
30	87		82		73.7	134		27
31	208		83	13.8		135		43.7
32	76		84		90.1	136		27.9
33	52		85	10.4		137		30.9
34	68		86	13.7		138		>1000
35	88		87	13.8		139		219.8

36	98		88	32.7		140		122
37	91		89			141		33.7
38	85		90			142		113.5
39	126		91	11.5		143		29
40	259		92	12		144		61.5
41		212.2	93	13.8		145		185.9
42		193.3	94	19.9		146		362.9
43		115.5	95	32.5		147		603.9
44		62.5	96	26.9		148		78
45		74.1	97		163	149		58.7
46	35		98		110.6	150		39.2
47		24.6	99	8.3		151		35.9
			100	57.2		152		49.3
49	9.1		101	78.8		153		63.2
50		79.5	102	111		154		97.8
51	6.6		103	64		155		59.1
52		73.2	104			156	9.5	

Ejemplo B

Catalepsia inducida por haloperidol - modelo de enfermedad de Parkinson en roedores *in vivo*

Los síntomas motores de la enfermedad de Parkinson incluyen acinesia, bradicinesia, rigidez, temblor y anormalidades en la postura y se asocian con pérdida de células dopaminérgicas de la sustancia negra y una disminución en los niveles de dopamina estriados. La administración de haloperidol a roedores conduce a un estado tipo parkinsoniano transitorio que se revierte por la administración de L-Dopa (*Duty, S.; Jenner, P. Br. J. Pharmacol.* (2011), 164, 1357–1391) y otros fármacos que se validaron clínicamente para el tratamiento de la enfermedad de Parkinson. El haloperidol antagoniza la dopamina D2 y, en menor medida, los receptores de D1 en neuronas espinales medias que comprenden las sendas indirectas y directas del circuito motor, respectivamente. El bloqueo resultante de la transmisión de dopamina estriada resulta en el disparo corriente abajo anormal dentro de los circuitos de los ganglios basales que se manifiestan como síntomas de rigidez del músculo y catalepsia. La catalepsia se postuló para reflejar las características clínicas de la enfermedad de

Parkinson, mediante la cual los pacientes experimentan una incapacidad de iniciar movimientos.

Se utilizan ratas Sprague-Dawley macho (Charles River, Calco, Italia) que pesan entre 175 y 200 g. De forma alternativa, se utilizan ratones C57Bl6 macho que pesan entre 25 y 35 g. El estado cataléptico se indujo mediante la administración subcutánea del antagonista del receptor de dopamina haloperidol (0.3 mg/kg, subcutáneamente), 90 minutos antes de analizar los animales en el análisis de rejilla vertical. Para este análisis, las ratas o los ratones se colocaron sobre la cubierta de tela de alambre de una jaula de plexiglás de 25 cm x43 cm colocada en un ángulo de aproximadamente 70 grados respecto a la mesa de trabajo. El individuo se colocó sobre la rejilla con las cuatro patas sustraídas y extendidas ("postura de rana"). El uso de dicha postura no natural es esencial para la especificidad de este análisis para la catalepsia. El período de tiempo desde la colocación de las patas hasta la primera eliminación completa de una pata (latencia descendente) se midió durante un máximo de 120 segundos para las ratas. Para los ratones, se colocaron las patas delanteras de un ratón sobre una barra de metal horizontal elevada 2” por encima de una plataforma de plexiglás y se registró el tiempo durante hasta 30 segundos por prueba. El análisis finalizó cuando las patas delanteras del animal volvieron a la plataforma o después de 30 segundos. Se repitió el análisis tres veces y el promedio de las tres pruebas se informó como el índice de intensidad de catalepsia.

La catalepsia se midió a los 30 minutos, 120 minutos y/o 240 minutos después de la dosificación a sujetos de una dosis intraperitoneal de 0.3 mg/kg de haloperidol junto con el compuesto de prueba del modulador GPR6. Los niveles cerebrales y plasmáticos del compuesto de prueba se determinaron mediante recolección de las muestras tisulares al final del experimento, que estuvieron en el intervalo de tiempo de 120 o 240 minutos. Se administró una cantidad representativa de compuestos de la invención en un intervalo de dosificación de 0.1 a 100 mg/kg intraperitonealmente, subcutáneamente u oralmente junto con haloperidol. El antagonista A2a KW6002 (istradefilina) se dosificó a 0.6 mg/kg intraperitonealmente como un control positivo.

El porcentaje medido de inversión de los ejemplos de compuestos en este ensayo se proporciona en la tabla 2 a continuación.

Tabla 2

Ejemplo	Tipo	Dosis (mpk)	Vía	% de inversión 30 min	120 min
47	Rata	30	intraperitoneal	75.7*	82.1*
		10	intraperitoneal	83.4*	76.5*
		1	intraperitoneal	39.1	57.9*
		0.1	intraperitoneal	-5.7	27.3

*-significativamente diferente al vehículo de control, ANOVA de una vía con corrección del análisis múltiple de Bonferroni.

Ejemplo C

Modelo de lesión con 6-hidroxidopamina – modelo de enfermedad de Parkinson de roedores *in vivo*

Primero se evaluaron ratas hembra adultas (10) para determinar la actividad motora previa a la cirugía mediante el uso de un sistema de rastreo de actividad automatizada que registra interrupciones de rayos a lo largo del piso de la pista de prueba. Los intervalos de rayos se resumieron durante las primeras 3 horas después de que se colocaron los animales en la pista y se registraron como conteos de actividad. Para dañar selectivamente las terminales nerviosas dopaminérgicas en el estriado, se inyectaron 20 µg de 6-hidroxidopamina directamente en el estriado bilateralmente (es decir, en ambos lados del cerebro). Después de 4 semanas de recuperación, las ratas se analizaron rápidamente para detectar su actividad motora y se observó una reducción significativa en los conteos de actividad. Se dosificaron oralmente el vehículo y el compuesto del ejemplo 47 (metilcelulosa al 0.5%) a 0.1, 1.0 o 10 mg/kg en un diseño de estudio cruzado (5 a 10 días de período de lavado), y después de la dosificación se midieron los conteos de actividad durante 3 horas. Al final del período de estudio, cuando cada animal recibió cada tratamiento una vez, se analizaron los datos. Se determinaron los conteos de actividad (error estándar de la media) para el grupo previo a la cirugía y posterior a la

cirugía y para el control tratado y de vehículo y se proporcionan en la tabla 3 a continuación:

Tabla 3

Grupo de tratamiento	Promedio	S.E.M.
Previo a la cirugía	12171	1601
Vehículo	7253	768
0,1 mg/kg	11422*	1071
1,0 mg/kg	15334*	2013
10 mg/kg	19368*	1410

*-significativamente diferente al vehículo de control, ANOVA de una vía con corrección del análisis múltiple de Bonferroni.

Se hace constar que con relación a esta fecha, el mejor método conocido por la solicitante para llevar a la práctica la citada invención, es el que resulta claro de la presente descripción de la invención.

opcionalmente sustituido, heteroarilo C_{1-10} opcionalmente sustituido y heterociclilo C_{3-6} opcionalmente sustituido;

X_3 se selecciona del grupo que consiste en CH y CR_4 y X_4 es NR_8; o

X_3 es NR_8 y X_4 se selecciona del grupo que consiste en CH y CR_4;

R_8 se selecciona del grupo que consiste en alquilo C_{1-6}, haloalquilo C_{1-6}, cicloalquilo C_{3-8}, $-S(O)_2-R_9$, $-C(O)-R_{10}$, $-C(O)-N(R_{11})(R_{12})$ y $-C(O)-OR_{13}$;

R_9 se selecciona del grupo que consiste en alquilo C_{1-6}, cicloalquilo C_{3-8} y fenilo opcionalmente sustituido;

R_{10} se selecciona del grupo que consiste en hidrógeno, alquilo C_{1-6} opcionalmente sustituido, cicloalquilo C_{3-8}, arilo C_{6-10} opcionalmente sustituido, heteroarilo C_{1-10} opcionalmente sustituido y heterociclilo C_{3-6} opcionalmente sustituido;

R_{11} se selecciona del grupo que consiste en hidrógeno y alquilo C_{1-6};

R_{12} se selecciona del grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8}; o

R_{11} y R_{12} se toman entre sí con el nitrógeno al que se unen para formar un anillo saturado de 4 a 7 miembros que tiene opcionalmente 1 heteroátomo en el anillo adicional que se selecciona del grupo N, O y S y se sustituye opcionalmente sobre cualquiera de los átomos de carbono del anillo con 1 a 5 sustituyentes que se seleccionan de forma independiente del grupo que consiste en ciano, halo, hidroxi, amino, heterociclilo C_{3-6} opcionalmente sustituido, amida C_{1-9}, alquilo C_{1-6} opcionalmente sustituido y alcoxi C_{1-4} y se sustituye sobre cualquier nitrógeno en el anillo adicional por un sustituyente que se selecciona del grupo que consiste en hidrógeno, cicloalquilo C_{3-8} y alquilo C_{1-6} opcionalmente sustituido;

R_{13} se selecciona del grupo que consiste en alquilo C_{1-6} y cicloalquilo C_{3-8};

o su sal farmacéuticamente aceptable.

2. Un compuesto de conformidad con la reivindicación 1 donde X_1 es CH y X_2 es N o su sal farmacéuticamente aceptable.

3. Un compuesto de conformidad con la reivindicación 1 donde X_1 es N y X_2 es N o su sal farmacéuticamente aceptable.

4. Un compuesto de conformidad con la reivindicación 3 donde X_3 se selecciona del grupo que consiste en CH y CR_4 y X_4 es NR_8 o su sal farmacéuticamente aceptable.

5. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 4 donde R_1 es arilo C_{6-10} opcionalmente sustituido o su sal farmacéuticamente aceptable.

6. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5 donde Z es alquileno C_{1-6} o su sal farmacéuticamente aceptable.

7. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5 donde Z es -O- o su sal farmacéuticamente aceptable.

8. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5 donde Z es -C(O)- o su sal farmacéuticamente aceptable.

9. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 8 donde R_2 es $-NR_6R_7$ o su sal farmacéuticamente aceptable.

10. Un compuesto de conformidad con la reivindicación 1 que se selecciona del grupo que consiste en:

ciclopropil(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietan-1-ona; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-*N*-(2-metoxietil)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(tetrahidrofuran-2-il)metanona; 3-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-3-oxopropanonitrilo; 4-((1-(6-acetil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; ciclopropil(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-

(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietan-1-ona; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 2-(4-(4-ciano-2-fluorofenoxi)piperidin-1-il)-3-(isopropilamino)-*N,N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-fluoro-4-((1-(3-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)benzonitrilo; (2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(morfolino)metanona; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-N-(2-metoxietil)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(tetrahidrofuran-2-il)metanona; 3-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-3-oxopropanonitrilo; (2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(isoxazol-5-il)metanona; 4-((1-(6-acetil-2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo; 4-((1-(6-(ciclopropanocarbonil)-2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-(isopropilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-6-(metil-L-prolil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina; (2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(pirrolidin-1-il)metanona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetan-1-ona; 3-fluoro-4-((1-(2-(isopropilamino)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo; 3-fluoro-4-((1-(2-(isopropilamino)-6-(2-metoxiacetil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo; 3-fluoro-4-((1-(2-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo; 3-(4-(4-ciano-2-

fluorofenoxi)piperidin-1-il)-2-(isopropilamino)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona; 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona; ciclopropil(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; ciclopropil(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; ciclopropil(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; 1-(3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-

6(5*H*)-il)etanona; 2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-3-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(2-((2,2-difluoroetil)amino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona; (*R*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(3-((2,2-difluoroetil)amino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; metil 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxilato; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(2-fluoroetil)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; (*R*)-1-(2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-

il)etan-1-ona; 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; *N*-ciclopropil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; *N*-ciclopropil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; *N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; (*S*)-*N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; (*R*)-*N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-2-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-2-(isopropilamino)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 1-(2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; (5-cloro-2-fluorofenil)(1-(2-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)metanona; 1-(3-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-2-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-

dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; (5-cloro-2-fluorofenil)(1-(3-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)metanona; 1-(2-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-3-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(2-(terc-butilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(*terc*-butilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(2-((2,2-difluoroetil)amino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(2-(ciclobutilamino)-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(ciclobutilamino)-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(3-(ciclobutilamino)-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(ciclobutilamino)-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; (*S*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-

difluoroetanona; 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; (*S*)-1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; (*R*)-1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; 1-(2-(ciclopropilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(ciclopropilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; *N*-ciclopropil-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6-dimetil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*,7-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5H)-carboxamida; *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-6,7-dimetil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[4,3-b]pirazin-6(5H)-il)-2,2-difluoroetanona; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona; *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; (2*S*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; (2*R*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; ciclopropil(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; 6-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; (*S*)-1-(2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-

il)etan-1-ona; (*S*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carbaldehído; (*R*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carbaldehído; 1-(3-(4-(3-fluorofenilsulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(2-(isopropilamino)-3-(4-(3-metoxifenilsulfonil)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(3-(4-((2-fluorofenil)sulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(3-(4-(4-fluorofenilsulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carbaldehído; 1-(3-(4-(2-fluoro-4-metoxifenilsulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[4,3-b]pirazin-6(5H)-il)etanona; (*S*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-((1-metoxipropan-2-il)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; (*R*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-((1-metoxipropan-2-il)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(3-(ciclobutilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; (*S*)-1-(3-(*sec*-butilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; (*R*)-1-(3-(*sec*-butilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona; metil 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxilato; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(2-fluoroetil)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(3-(ciclobutilamino)-2-(4-(2,4-difluorobencil)piperazin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-isopropil-6-

(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona; *terc*-butil 4-(6-acetil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperazina-1-carboxilato; acetato de (1*s*,3*s*)-3-((6-acetil-2-(4-(2,4-difluorobencil)piperazin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo; 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(((1*s*,3*s*)-3-hidroxiciclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-*d*3-etan-1-ona; acetato de (1*s*,3*s*)-3-((6-acetil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo; 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metilpropan-1-ona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(((1*s*,3*s*)-3-hidroxiciclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(((1*r*,3*r*)-3-fluorociclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 4-((4-(6-acetil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperazin-1-il)metil)-3-fluorobenzonitrilo; acetato de (1*r*,3*r*)-3-((6-acetil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(((1*r*,3*r*)-3-hidroxiciclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; (*S*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(tetrahidrofuran-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; (*S*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(tetrahidrofuran-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona; 1-(3-((3,3-difluorociclobutil)amino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; *N*-ciclobutil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; (*R*)-1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(tetrahidrofuran-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; (*S*)-1-(2-

(4-(2,4-difluorobencil)piperazin-1-il)-3-(tetrahidrofuran-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona y (*S*)-1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(tetrahidrofuran-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona o una sal farmacéuticamente aceptable de los compuestos mencionados anteriormente.

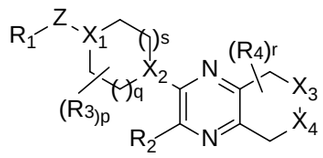
11. Una composición farmacéutica que comprende un compuesto o su sal farmacéuticamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 10 y un excipiente farmacéuticamente aceptable.

12. El uso de un compuesto o su sal farmacéuticamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 10 como un medicamento.

REIVINDICACIONES

Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes reivindicaciones:

1. El compuesto de fórmula I



I

donde

R_1 se selecciona del grupo que consiste en cicloalquilo C_{3-8} opcionalmente sustituido, heterociclilo C_{3-6} opcionalmente sustituido, arilo C_{6-10} opcionalmente sustituido y heteroarilo C_{1-10} opcionalmente sustituido;

X_1 es N y X_2 es CH; o

X_1 es CH y X_2 es N; o

X_1 es N y X_2 es N;

cuando X_1 es N, Z se selecciona del grupo que consiste en alquileno C_{1-6}, haloalquileno C_{1-6},

-C(O)-, y $-S(O)_2-$;

cuando X_1 es CH, Z se selecciona del grupo que consiste en alquileno C_{1-6}, haloalquileno C_{1-6},

-O-, -C(O)-, -NH-, -S-, -S(O)- y $-S(O)_2-$;

q es 0, 1 o 2;

s es 0, 1 o 2; R_2 es $-OR_5$ o $-NR_6R_7$;

R_3, cada vez que se toma, se selecciona de forma independiente del grupo que consiste en alquilo C_{1-6}, cicloalquilo C_{3-8} y trifluorometilo;

p es 0, 1 o 2;

R_4, cada vez que se toma, se selecciona de forma independiente del grupo que consiste en alquilo C_{1-6}, hidroxi y halo;

r es 0 o 1;

R_5 se selecciona del grupo que consiste en alquilo C_{1-6} y cicloalquilo C_{3-8};

R_6 se selecciona del grupo que consiste en hidrógeno y alquilo C_{1-6};

R_7 se selecciona del grupo que consiste en alquilo C_{1-6} opcionalmente sustituido, cicloalquilo C_{3-8}, arilo C_{6-10}

opcionalmente sustituido, heteroarilo C_{1-10} opcionalmente sustituido y heterociclilo C_{3-6} opcionalmente sustituido;

X_3 se selecciona del grupo que consiste en CH y CR_4 y X_4 es NR_8; o

X_3 es NR_8 y X_4 se selecciona del grupo que consiste en CH y CR_4;

R_8 se selecciona del grupo que consiste en alquilo C_{1-6}, haloalquilo C_{1-6}, cicloalquilo C_{3-8}, $-S(O)_2-R_9$, $-C(O)-R_{10}$, $-C(O)-N(R_{11})(R_{12})$ y $-C(O)-OR_{13}$;

R_9 se selecciona del grupo que consiste en alquilo C_{1-6}, cicloalquilo C_{3-8} y fenilo opcionalmente sustituido;

R_{10} se selecciona del grupo que consiste en hidrógeno, alquilo C_{1-6} opcionalmente sustituido, cicloalquilo C_{3-8}, arilo C_{6-10} opcionalmente sustituido, heteroarilo C_{1-10} opcionalmente sustituido y heterociclilo C_{3-6} opcionalmente sustituido;

R_{11} se selecciona del grupo que consiste en hidrógeno y alquilo C_{1-6};

R_{12} se selecciona del grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8}; o

R_{11} y R_{12} se toman entre sí con el nitrógeno al que se unen para formar un anillo saturado de 4 a 7 miembros que tiene opcionalmente 1 heteroátomo en el anillo adicional que se selecciona del grupo N, O y S y se sustituye opcionalmente sobre cualquiera de los átomos de carbono del anillo con 1 a 5 sustituyentes que se seleccionan de forma independiente del grupo que consiste en ciano, halo, hidroxi, amino, heterociclilo C_{3-6} opcionalmente sustituido, amida C_{1-9}, alquilo C_{1-6} opcionalmente sustituido y alcoxi C_{1-4} y se sustituye sobre cualquier nitrógeno en el anillo adicional por un sustituyente que se selecciona del grupo que consiste en hidrógeno, cicloalquilo C_{3-8} y alquilo C_{1-6} opcionalmente sustituido;

R_{13} se selecciona del grupo que consiste en alquilo C_{1-6} y cicloalquilo C_{3-8};

o su sal farmacéuticamente aceptable.

2. Un compuesto de conformidad con la reivindicación 1 donde X_1 es CH y X_2 es N o su sal farmacéuticamente aceptable.

3. Un compuesto de conformidad con la reivindicación 1 donde X_1 es N y X_2 es N o su sal farmacéuticamente aceptable.

4. Un compuesto de conformidad con la reivindicación 3 donde X_3 se selecciona del grupo que consiste en CH y CR_4 y X_4 es NR_8 o su sal farmacéuticamente aceptable.

5. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 4 donde R_1 es arilo C_{6-10} opcionalmente sustituido o su sal farmacéuticamente aceptable.

6. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5 donde Z es alquileno C_{1-6} o su sal farmacéuticamente aceptable.

7. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5 donde Z es -O- o su sal farmacéuticamente aceptable.

8. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5 donde Z es -C(O)- o su sal farmacéuticamente aceptable.

9. Un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 8 donde R_2 es $-NR_6R_7$ o su sal farmacéuticamente aceptable.

10. Un compuesto de conformidad con la reivindicación 1 que se selecciona del grupo que consiste en:

ciclopropil(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietan-1-ona; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-*N*-(2-metoxietil)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(tetrahidrofuran-2-il)metanona; 3-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-3-oxopropanonitrilo; 4-((1-(6-acetil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; ciclopropil(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-

(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietan-1-ona; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 2-(4-(4-ciano-2-fluorofenoxi)piperidin-1-il)-3-(isopropilamino)-*N,N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-fluoro-4-((1-(3-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)oxi)benzonitrilo; (2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(morfolino)metanona; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-N-(2-metoxietil)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(tetrahidrofuran-2-il)metanona; 3-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-3-oxopropanonitrilo; (2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(isoxazol-5-il)metanona; 4-((1-(6-acetil-2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo; 4-((1-(6-(ciclopropanocarbonil)-2-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)-3-fluorobenzonitrilo; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-(isopropilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-6-(metil-L-prolil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazina; (2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)(pirrolidin-1-il)metanona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetan-1-ona; 3-fluoro-4-((1-(2-(isopropilamino)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo; 3-fluoro-4-((1-(2-(isopropilamino)-6-(2-metoxiacetil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo; 3-fluoro-4-((1-(2-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)oxi)benzonitrilo; 3-(4-(4-ciano-2-

fluorofenoxi)piperidin-1-il)-2-(isopropilamino)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona; 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona; ciclopropil(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; ciclopropil(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; ciclopropil(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; 1-(3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-

6(5*H*)-il)etanona; 2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-3-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(2-((2,2-difluoroetil)amino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona; (*R*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(3-((2,2-difluoroetil)amino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; *N*-(2,2-difluoroetil)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; metil 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxilato; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(2-fluoroetil)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; (*R*)-1-(2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-

il)etan-1-ona; 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; *N*-ciclopropil-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; *N*-ciclopropil-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; *N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; (*S*)-*N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; (*R*)-*N*-ciclopropil-3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-2-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-2-(isopropilamino)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 1-(2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; (5-cloro-2-fluorofenil)(1-(2-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)piperidin-4-il)metanona; 1-(3-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-2-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-

dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; (5-cloro-2-fluorofenil)(1-(3-(isopropilamino)-6-metil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperidin-4-il)metanona; 1-(2-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(4-(5-cloro-2-fluorobenzoil)piperidin-1-il)-3-(isopropilamino)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(2-(terc-butilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(*terc*-butilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-N,N-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(2-((2,2-difluoroetil)amino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(2-(ciclobutilamino)-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(ciclobutilamino)-3-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 1-(3-(ciclobutilamino)-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(ciclobutilamino)-2-(4-(2-fluoro-4-metoxifenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; 3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*-dimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; (*S*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-

difluoroetanona; 1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2,2-difluoroetanona; (*S*)-1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; (*R*)-1-(3-(2,2-difluoroetilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; 1-(2-(ciclopropilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(ciclopropilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*,5-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxamida; *N*-ciclopropil-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6-dimetil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*,*N*,7-trimetil-7,8-dihidropirido[3,4-*b*]pirazina-6(5H)-carboxamida; *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-6,7-dimetil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[4,3-b]pirazin-6(5H)-il)-2,2-difluoroetanona; 1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxietanona; *N*-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; (2*S*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; (2*R*)-1-(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metoxipropan-1-ona; ciclopropil(2-(2,2-difluoroetilamino)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-7-metil-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)metanona; 6-(2,2-difluoroetil)-3-(4-(2,4-difluorofenoxi)piperidin-1-il)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-amina; (*S*)-1-(2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-

il)etan-1-ona; (*S*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carbaldehído; (*R*)-2-(4-((2,4-difluorofenil)fluorometil)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carbaldehído; 1-(3-(4-(3-fluorofenilsulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(2-(isopropilamino)-3-(4-(3-metoxifenilsulfonil)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 1-(3-(4-((2-fluorofenil)sulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(3-(4-(4-fluorofenilsulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; 3-(4-(2,4-difluorofenoxi)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carbaldehído; 1-(3-(4-(2-fluoro-4-metoxifenilsulfonil)piperidin-1-il)-2-(isopropilamino)-7,8-dihidropirido[4,3-b]pirazin-6(5H)-il)etanona; (*S*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-((1-metoxipropan-2-il)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; (*R*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-((1-metoxipropan-2-il)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(3-(ciclobutilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; (*S*)-1-(3-(*sec*-butilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; (*R*)-1-(3-(*sec*-butilamino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona; metil 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazina-6(5*H*)-carboxilato; 2-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(2-fluoroetil)-*N*-isopropil-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(3-(ciclobutilamino)-2-(4-(2,4-difluorobencil)piperazin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 2-(4-(2,4-difluorobencil)piperazin-1-il)-*N*-isopropil-6-

(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona; *terc*-butil 4-(6-acetil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperazina-1-carboxilato; acetato de (1*s*,3*s*)-3-((6-acetil-2-(4-(2,4-difluorobencil)piperazin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo; 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(((1*s*,3*s*)-3-hidroxiciclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-*d*3-etan-1-ona; acetato de (1*s*,3*s*)-3-((6-acetil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo; 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(isopropilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)-2-metilpropan-1-ona; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(((1*s*,3*s*)-3-hidroxiciclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(((1*r*,3*r*)-3-fluorociclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; 4-((4-(6-acetil-3-(isopropilamino)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-2-il)piperazin-1-il)metil)-3-fluorobenzonitrilo; acetato de (1*r*,3*r*)-3-((6-acetil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-il)amino)ciclobutilo; 1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(((1*r*,3*r*)-3-hidroxiciclobutil)amino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; (*S*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(tetrahidrofuran-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; (*S*)-1-(2-(4-(2,4-difluorofenoxi)piperidin-1-il)-3-(tetrahidrofuran-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona; 1-(3-((3,3-difluorociclobutil)amino)-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etan-1-ona; *N*-ciclobutil-2-(4-(2,4-difluorofenoxi)piperidin-1-il)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-*b*]pirazin-3-amina; (*R*)-1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(tetrahidrofuran-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona; (*S*)-1-(2-

(4-(2,4-difluorobencil)piperazin-1-il)-3-(tetrahidrofuran-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)etanona y (*S*)-1-(2-(4-(2,4-difluorobencil)piperazin-1-il)-3-(tetrahidrofuran-3-ilamino)-7,8-dihidropirido[3,4-*b*]pirazin-6(5*H*)-il)propan-1-ona o una sal farmacéuticamente aceptable de los compuestos mencionados anteriormente.

11. Una composición farmacéutica que comprende un compuesto o su sal farmacéuticamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 10 y un excipiente farmacéuticamente aceptable.

12. El uso de un compuesto o su sal farmacéuticamente aceptable de conformidad con cualquiera de las reivindicaciones 1 a 10 como un medicamento.