

CDK2 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to and the benefit of U.S. Provisional Patent Application No. 63/496,146, filed on April 14, 2023, U.S. Provisional Patent Application No. 63/591,862, filed on October 20, 2023, and U.S. Provisional Patent Application No. 63/564,604, filed on March 13, 2024, the entire contents of each of which are incorporated herein by reference.

BACKGROUND

[002] Cyclin-Dependent Kinase (CDK) are serine/threonine protein kinases that have a central role in cell cycle progression. CDK levels remain relatively constant throughout the cell cycle, and it is the selective activation of specific CDKs allows for the proper ordering of the steps in cell cycle progression. Activation of CDKs requires heterodimerization with regulatory subunits known as cyclins. Cell cycle deregulation is a common feature of human cancer.

[003] Cyclin-dependent kinase 2 (Cdk2) participates in a range of biological activities. CDK2 is a key cell cycle regulator, active from the late G₁-phase and throughout the S-phase. CDK2 is involved in DNA damage response (DDR) through the homologous recombination (HR) pathway. CDK2 also regulates aspects of apoptotic pathways. Cyclin E1 (CCNE1), cyclin E2 (CCNE2), cyclin A1 (CCNA1), and cyclin A2 (CCNA2), along with p21Cip1/Waf1, p27Kip1 and p57Kip2 (the cyclin dependent kinase inhibitors of the cyclin-CDK2 complex) are the main regulators of CDK2 activity. In cancer, dysregulation of the binding of CDK2 by cyclin E1, E2, A1, or A2 or the activity of the cyclin-dependent kinase inhibitor proteins may occur. (See S. Tadesse *et al.*, Drug Discovery Today, Volume 25, Number 2 February 2020)

[004] The dysregulation of CDK2 can occur through several mechanisms. Amplification and/or overexpression of CCNE1 has been identified occurring in ovarian and breast cancer (See Scaltriti, M. *et al.*, Proc. Natl Acad. Sci. USA 108, 3761–3766 (2011) and Etemadmoghadam, D. *et al.* Proc. Natl Acad. Sci. USA 110, 19489–19494 (2013). Poor outcomes in gastric, endometrial, and other cancers have been associated with overexpression and/or amplification of CCNE1 (See Ooi *et al.* Hum Pathol. (2017) 61:58-67, and Noske *et al.* Oncotarget (2017) 8: 14794-14805).

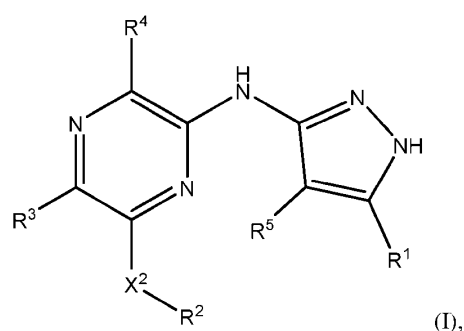
[005] While these findings indicate CDK2 is a potential target for cancers with deregulated CDK2 activity, no agents selectively targeting CDK2 have been approved to date. Therefore, there is a need to develop new CDK2 inhibitors.

SUMMARY

[006] The applicant has discovered novel compounds which are effective inhibitors of CDK2 (*see*, e.g., Examples 1-258). In particular, it has been demonstrated that the compounds of the present

disclosure effectively inhibit CDK2. Compounds of the disclosure (also referred to herein as the “disclosed compounds”) or pharmaceutically acceptable salts thereof effectively inhibit CDK2 (*see* Biological Example 1) and can be used treat various cancers. Importantly, the disclosed compounds are selective CDK2 inhibitors, *i.e.*, the disclosed compounds have no or low activity against CDK-family kinases, most notably CDK1. Advantages associated with such selectivity may include facilitating efficacious dosing and reducing CDK1-mediated on-target toxicities. Some of the disclosed compounds also have the advantage of having high microsomal stability. Compounds of the disclosure also may have favorable toxicity profiles related to other non-kinase targets.

[007] In one aspect, the present disclosure provides a compound represented by the following structural Formula (I):



or a pharmaceutically acceptable salt thereof, wherein the definition of each variable is provided below.

[008] In another aspect, the present disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof (a “pharmaceutical composition of the disclosure”).

[009] The present disclosure provides a method of treating a subject with cancer, comprising administering to the subject an effective amount of a compound of the disclosure (*e.g.*, a compound of Formula (I)) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the disclosure. In one embodiment, the cancer is uterine cancer (including uterine carcinosarcoma (UCS), uterine corpus endometrial carcinoma (UCEC)), endometrial cancer, breast cancer (including breast invasive carcinoma (BRCA), TNBC (triple negative breast cancer), HR+ breast cancer (hormone receptor positive breast cancer), ER+ breast cancer (estrogen receptor positive breast cancer), HR+HER2- breast cancer (hormone receptor positive, human epidermal growth factor 2 negative breast cancer), ER+HER2- breast cancer (estrogen receptor positive, human epidermal growth factor 2 negative breast cancer), HER2- breast cancer (human epidermal growth factor 2 negative breast cancer), HER2-low breast cancer (human epidermal growth factor 2 low breast cancer), and HER2+ breast cancer (human epidermal growth factor 2 positive breast cancer), ovarian cancer (*e.g.* ovarian serous cystadenocarcinoma (OV)), stomach cancer (including stomach adenocarcinoma (STAD)), gastric cancer (including gastrointestinal stromal tumor), colorectal cancer, pancreatic cancer (including pancreatic adenocarcinoma (PAAD) and pancreatic ductal adenocarcinoma (PDAC)), kidney cancer, head and neck cancer, liver cancer, prostate

cancer, skin cancer, leukemia (including AML (acute myeloid leukemia)), lymphoma (including B-cell lymphoma), myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), sarcoma (SARC), esophageal cancer (including esophageal carcinoma (ESCA)), bladder cancer (including bladder urothelial carcinoma), lung cancer (including lung squamous carcinoma and non-small cell lung cancer, e.g., EGFRm (epidermal growth factor receptor mutant)+ non-small cell lung cancer), cholangiocarcinoma, adrenocortical carcinoma (ACC), or mesothelioma. In some embodiments, the cancer is breast cancer. In one embodiment, the subject has CCNE1 amplified advanced/relapsed tumors. In one embodiment, the subject has CCNE1 amplified platinum-resistant or platinum-refractory ovarian cancer. In one embodiment, the subject has endometrial cancer (with prior platinum therapy, e.g., wherein the patient has been previously treated with a platinum therapy) that has progressed following 2 or more lines of therapies (including the platinum therapy). In one embodiment, the subject has CCNE1 amplified endometrial cancer that has failed 2 or more lines of therapies (which may include a prior platinum therapy). In one embodiment, the subject has gastric cancer (with prior platinum therapy e.g., wherein the patient has been previously treated with a platinum therapy) that has progressed following 2 or more lines of therapies (including the platinum therapy). In one embodiment, the subject has ER+ HER- breast cancer that has progressed despite treatment with one or more CDK4/6 inhibitors.

[0010] In one embodiment, the cancer as described herein to be treated (e.g., the cancer as described in paragraphs [009], [0019], [00119]-[00130], and [00132]-[00148], e.g., breast cancer) has CCNE1 amplification and/or overexpression.

[0011] In one embodiment, the cancer as described herein to be treated (e.g., the cancer as described in paragraphs [009], [0019], [00119]-[00130], and [00132]-[00148], e.g., breast cancer) does not have a CCNE1 amplification and/or overexpression.

[0012] In some embodiments, the treatment method disclosed herein further comprises administering to the subject an effective amount of palbociclib (e.g., ibrance®), ribociclib, abemaciclib, tamoxifen, letrozole, olaparib (e.g., lynparza®), niraparib, carboplatin, cisplatin, paclitaxel, gemcitabine, megestrol acetate, medroxyprogesterone acetate, capecitabine (e.g., xeloda®), regorafenib (e.g., stivarga®), afatinib (e.g., gilotrif®), osimertinib (e.g., tagrisso®), gefitinib (e.g., irtessa®), erlotinib (e.g., tarceva®), ramucirumab (e.g., cyramza®), an EGFR inhibitor, pralsetinib, ABT-263 (navitoclax), MK-1775 (adavosertib), BAY-1895344, berzosertib, ceralasertib, SRA-737, LY2603618 (rabusertib), or trastuzumab (e.g., herceptin®), or combinations thereof. The EGFR inhibitor may be selected from afatinib, osimertinib, lapatinib, erlotinib, dacomitinib, poziotinib, neratinib, gefitinib JBJ-04-125-02, alflutinin (AST 2818), aumolertinib (formerly almonertinib) (HS10296), BBT-176, BI-4020, BPI-361175, BPI-D0316, CH7233163, gilitertinib, icotinib, JND-3229, lazertinib, nazartinib (EGF 816), avitinib, PCC-0208027, rezivertinib (BPI-7711), TQB3804, zorifertinib (AZ-3759), or DZD9008; an EGFR antibody such as cetuximab, panitumumab, necitumumab, HLX07, JMT101; or a bispecific EGFR and MET antibody (e.g., amivantamab (JNJ-61186372, JNJ-372)).

[0013] The present disclosure also provides a method of inhibiting CDK2 in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the disclosure (*e.g.*, a compound of Formula (I)) or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the disclosure.

[0014] The present disclosure also provides the use of an effective amount of a compound of the disclosure (*e.g.*, a compound of Formula (I)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the disclosure, for the preparation of a medicament for the treatment of cancers.

[0015] In another aspect, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the disclosure for use in treating cancers.

[0016] In one aspect, the present disclosure provides a method of treating a subject having, or at risk of developing, a disease or disorder associated with CDK2, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, wherein the subject has an amplification of the CCNE1 gene and/or have an expression level of CCNE1 higher than a control expression level of CCNE1. In some embodiments, the disease or disorder associated with CDK2 is cancer.

[0017] The present disclosure also provides a method of treating a subject having, or at risk of developing, a disease or disorder associated with CDK2, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, wherein the subject has an amplification of the CCNE1 gene and/or have an expression level of CCNE1 similar to a control expression level of CCNE1. In some embodiments, the disease or disorder associated with CDK2 is cancer.

[0018] Also provided herein is a method of treating a patient having an amplified expression level of CCNE1 and suffering from, or at risk of developing, a solid tumor cancer, comprising administering to the patient a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein.

[0019] The contemplated solid tumor cancer may be at least one of: uterine cancer (including uterine carcinosarcoma, uterine corpus endometrial carcinoma (UCEC)), endometrial cancer, breast cancer (including breast invasive carcinoma, TNBC (triple negative breast cancer), ER (estrogen receptor)+HER2 (human epidermal growth factor 2)- breast cancer, HR (hormone receptor)+HER2 (human epidermal growth factor 2)- breast cancer, HER2- breast cancer and HER2+ breast cancer), ovarian cancer (*e.g.* ovarian serous cystadenocarcinoma), stomach cancer (including stomach adenocarcinoma), gastric cancer (including gastrointestinal stromal tumor), colorectal cancer, pancreatic cancer, kidney cancer, head and neck cancer, liver cancer, prostate cancer, skin cancer, lymphoma (including B-cell lymphoma), sarcoma, esophageal cancer (including esophageal carcinoma and esophageal adenocarcinoma), bladder cancer (including bladder urothelial carcinoma (BLCA)), lung cancer (including lung squamous carcinoma and non-small cell lung cancer, *e.g.*, EGFRm (epidermal

growth factor receptor mutant)+ non-small cell lung cancer), cholangiocarcinoma, adrenocortical carcinoma, or mesothelioma.

DETAILED DESCRIPTION

Definitions

[0020] The term “halo” as used herein means halogen and includes chloro, fluoro, bromo and iodo.

[0021] The term “alkyl” used alone or as part of a larger moiety, such as “alkoxy” or “haloalkyl” and the like, means saturated aliphatic straight-chain or branched monovalent hydrocarbon radical. Unless otherwise specified, an alkyl group typically has 1-4 carbon atoms, *i.e.* (C₁-C₄)alkyl. As used herein, a “(C₁-C₄)alkyl” group means a radical having from 1 to 4 carbon atoms in a linear or branched arrangement. Examples include methyl, ethyl, *n*-propyl, *iso*-propyl, and the like.

[0022] The term “alkoxy” means an alkyl radical attached through an oxygen linking atom, represented by -O-alkyl. For example, “(C₁-C₄)alkoxy” includes methoxy, ethoxy, propoxy, and butoxy.

[0023] The term “aromatic ring system” is art-recognized and refers to a monocyclic, bicyclic or polycyclic hydrocarbon ring system, wherein at least one ring is aromatic.

[0024] The term “aryl” refers to a monovalent radical of an aromatic ring system. Representative aryl groups include fully aromatic ring systems, such as phenyl, cyclooctatetraene, indene, and naphthyl, and ring systems where an aromatic carbon ring is fused to one or more non-aromatic carbon rings, such as indanyl, phthalimidyl, naphthimidyl, or tetrahydronaphthyl, and the like. The number of ring members designates the number of ring members in the fused ring system. An aryl group may be described as, *e.g.*, a 6-10-membered aryl, wherein the term “membered” refers to the non-hydrogen ring atoms within the moiety.

[0025] The term “cycloalkyl” refers to a saturated hydrocarbon ring system. Unless otherwise specified, cycloalkyl has from 3-10 carbon atoms. In some embodiments, cycloalkyl has from 3-6 carbon atoms. For example, a C₃-C₁₀ cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentane, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[3.2.1]octane, bicyclo[4.1.1]octane, spiro[2.2]pentane, spiro[2.3]hexane, spiro[2.4]heptane, spiro[2.5]octane, spiro[2.6]nonane, spiro[2.7]decane, spiro[3.3]heptane, spiro[3.4]octane, spiro[3.5]nonane, spiro[3.6]decane, spiro[4.4]nonane, spiro[4.5]decane, and the like. Unless otherwise described, a “cycloalkyl” has from three to ten carbon atoms.

[0026] The term “cycloalkoxy” refers to a -O-cycloalkyl group.

[0027] The term “heterocyclyl” or “heterocyclic” refers to a radical of a 4- to 12-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, quaternary nitrogen, oxidized nitrogen (*e.g.*, NO), oxygen, and sulfur, including sulfoxide and sulfone (“4-12 membered heterocyclyl”). In some embodiments, heterocyclyl is a 3- to 6- membered or 4- to 6- membered non-aromatic ring system having ring carbon

atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, quaternary nitrogen, oxidized nitrogen (*e.g.*, NO), oxygen, and sulfur, including sulfoxide and sulfone. In some embodiments, heterocyclyl has 1 to 2 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, quaternary nitrogen, oxidized nitrogen (*e.g.*, NO), oxygen, and sulfur, including sulfoxide and sulfone. In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Exemplary heterocyclyl groups include azetidiny, oxetanyl, thietanyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, tetrahydropyranyl, piperazinyl, morpholinyl, azepanyl, oxepanyl, thiepanyl, tetrahydropyridinyl, 2-oxabicyclo[2.1.1]hexane, 5-oxabicyclo[2.1.1]hexane, 3-oxabicyclo[3.1.0]hexane, 2-oxabicyclo[2.1.1]heptane, 7-oxabicyclo[2.2.1]heptane, 3-oxabicyclo[3.1.1]heptane, 6-oxabicyclo[3.1.1]heptane, 2-oxabicyclo[2.2.2]octane, 7-oxabicyclo[4.1.1]octane, 8-oxabicyclo[3.2.1]octane, and the like.

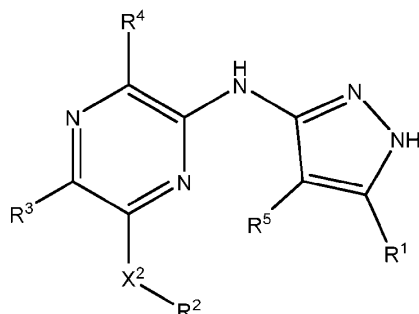
[0028] The term “heteroaryl” refers to a radical of a 4-12 membered monocyclic or bicyclic $4n+2$ aromatic ring system (*e.g.*, having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–10 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinoliny, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl). A heteroaryl group may be described as, *e.g.*, a 6-10-membered heteroaryl, wherein the term “membered” refers to the non-hydrogen ring atoms within the moiety.

[0029] It will be apparent to one skilled in the art that certain compounds disclosed herein may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure. The term “tautomers” refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H).

Compounds of the Present Disclosure

[0030] Disclosed herein are embodiments of compounds having a general structure of Formula (I). The present invention provides a compound of the present invention or a pharmaceutically acceptable salt thereof for use in the treatment of cancer. These compounds are selective inhibitors of CDK2.

[0031] In a first embodiment, the present disclosure provides a compound represented by the following structural Formula (I):



(I), or a pharmaceutically acceptable salt thereof, wherein

R¹ is selected from the group consisting of CN, C₁-C₄alkyl, C₁-C₄alkoxy, -(C(R^d)₂)_p-C₃-C₁₀cycloalkyl, -O(C(R^d)₂)_p-C₃-C₁₀cycloalkyl, -(C(R^d)₂)_p-4 to 12-membered heterocyclyl, -O(C(R^d)₂)_p-4 to 12-membered heterocyclyl, -(C(R^d)₂)_p-6 to 12-membered aryl, and -(C(R^d)₂)_p-4 to 12-membered heteroaryl, wherein the C₁-C₄alkyl, C₁-C₄alkoxy, C₃-C₁₀cycloalkyl, C₃-C₁₀cycloalkoxy, 6 to 12-membered aryl are each optionally substituted with 1 to 4 R^a, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then are optionally substituted on a ring carbon with 1 to 4 R^a;

X² is selected from the group consisting of -O-, -(C(R^d)₂)_n-, -NR^b-, -NR^b-(C(R^c)₂)_m-, -O(C(R^c)₂)_m-, and -(C(R^d)₂)_n-O-;

R² is selected from C₁-C₄alkyl and Ring A, wherein the C₁-C₄alkyl is optionally substituted with 1 to 4 groups each independently selected from the group consisting of D, halo, CN, and OH and/or 1 group of 5 to 6 membered heteroaryl having 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b; or

X² and R² together form Ring B bonded to the pyrazine, wherein Ring B is C₃-C₁₀cycloalkyl or 4 to 12-membered heterocyclyl, wherein the C₃-C₁₀cycloalkyl is optionally substituted with 1 to 4 R^a, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b, and then is optionally substituted on a ring carbon with 1 to 4 R^a;

Ring A is selected from the group consisting of C₃-C₁₀cycloalkyl, 4 to 12-membered heterocyclyl, 6 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C₃-C₁₀cycloalkyl and 6 to 12-membered aryl are each optionally substituted with 1 to 4 R^a, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon with 1 to 4 R^a;

R³ is selected from the group consisting of H, D, halo, OH, CN, C₁-C₄alkyl, -SO₂C₁-C₄alkyl, and -S(O)NR^b-C₁-C₄alkyl;

R^4 is selected from the group consisting of H, D, C_1 - C_4 alkyl, and C_3 - C_{10} cycloalkyl;

R^5 is selected from the group consisting of H, D, and C_1 - C_4 alkyl;

Each R^a is independently selected from the group consisting of D, halo, OH, CN, $N(R^b)_2$, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy, or two R^a attached to the same atom, form a $=O$, wherein the C_1 - C_4 alkyl and C_1 - C_4 alkoxy are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of D, halo, OH, and CN;

Each R^b is independently selected from the group consisting of H, D, and C_1 - C_4 alkyl, wherein the C_1 - C_4 alkyl is optionally substituted with 1 to 4 D;

Each R^c is independently selected from the group consisting of H, D, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_3 - C_{10} cycloalkyl, and 4 to 12-membered heterocyclyl, wherein the C_1 - C_4 alkyl, C_1 - C_4 alkoxy, and C_3 - C_{10} cycloalkyl are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH, and CN, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon with 1 to 4 groups each independently selected from the group consisting of halo, OH, and CN;

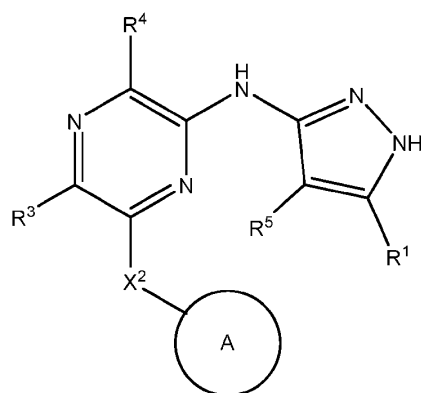
Each R^d is independently selected from the group consisting of H, D, and C_1 - C_4 alkyl;

m is 1 to 4;

n is 1 to 4; and

p is 0 to 3.

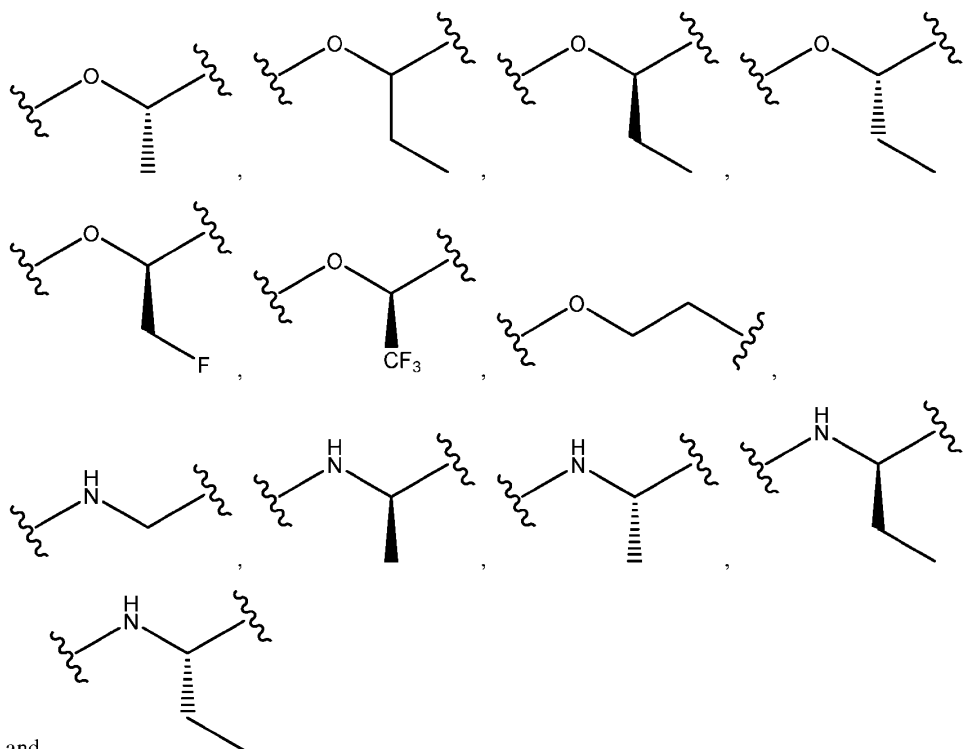
[0032] In some embodiments, the compound is of Formula (II):



(II), or a pharmaceutically acceptable salt thereof.

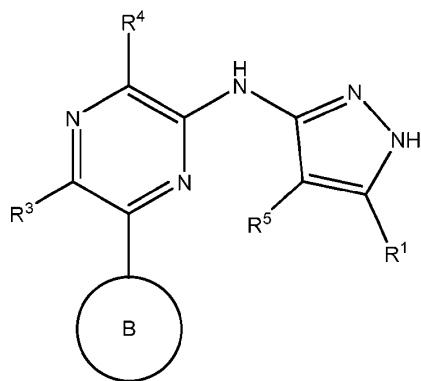
[0033] In some embodiments, X_2 is selected from the group consisting of $-O-$, $-(CHR^d)_n-$, $-NR^b-$, $-NR^b-(CHR^c)_m-$, and $-O-(CHR^c)_m-$.

[0034] In some embodiments, X^2 is selected from the group consisting of $-O-$, $-(CHR^d)-$, $-NR^b-$, $-(CHR^c)-$, and $-O-(CHR^c)-$.



[0037] In certain embodiments, X_2 is -O-.

[0038] In some embodiments, the compound is of Formula (III):



(III), or a pharmaceutically acceptable salt thereof.

[0039] In some embodiments, Ring B is C_3 - C_8 cycloalkyl or 4 to 10-membered heterocyclyl, wherein the C_3 - C_8 cycloalkyl is optionally substituted with 1 to 4 R^a , wherein the 4 to 10-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b , and then is optionally substituted on a ring carbon by 1 to 4 R^a .

[0040] In some embodiments, Ring B is C_3 - C_8 cycloalkyl or 4 to 10-membered heterocyclyl, wherein the C_3 - C_8 cycloalkyl is optionally substituted with 1 to 4 groups selected from the group

consisting of -NH_2 , OH , and =O , wherein the 4 to 10-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b , and then is optionally substituted on a ring carbon by 1 to 4 groups selected from the group consisting of -NH_2 , OH , and =O .

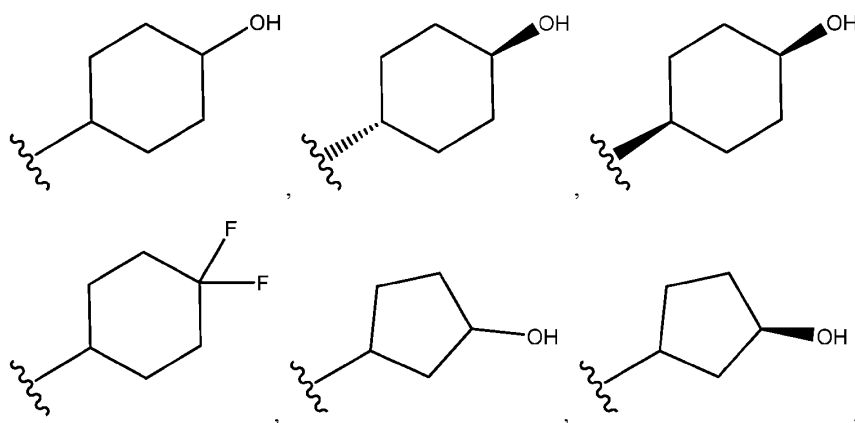
[0041] In some embodiments, Ring B is $\text{C}_4\text{-C}_6$ cycloalkyl or 4 to 8-membered heterocyclyl, wherein the $\text{C}_4\text{-C}_6$ cycloalkyl is optionally substituted with 1 to 4 R^a , wherein the 4 to 8-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b , and then is optionally substituted on a ring carbon by 1 to 4 R^a .

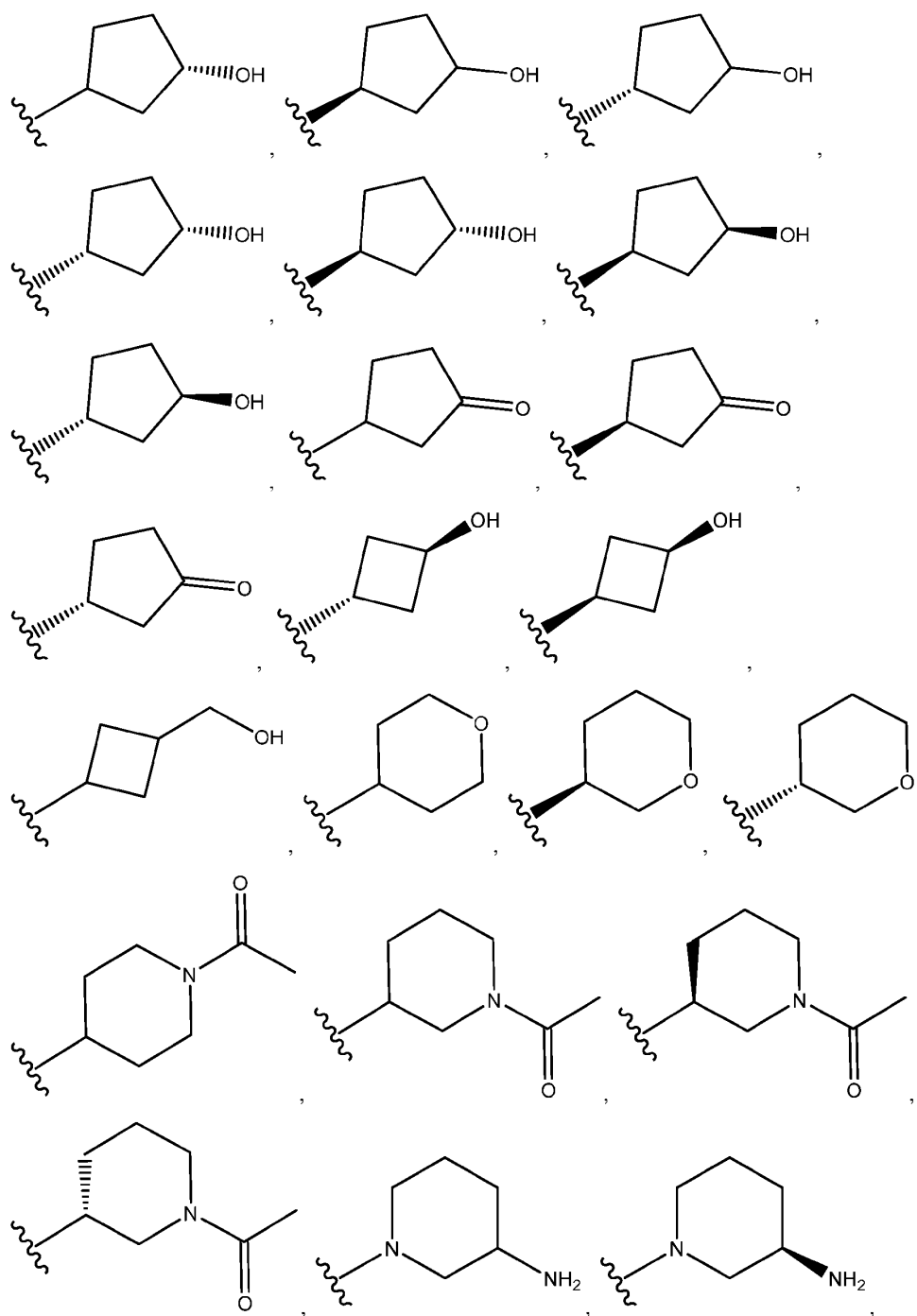
[0042] In some embodiments, Ring B is $\text{C}_4\text{-C}_6$ cycloalkyl or 4 to 8-membered heterocyclyl, wherein the $\text{C}_4\text{-C}_6$ cycloalkyl is optionally substituted with 1 to 4 groups selected from the group consisting of -NH_2 , OH , and =O , wherein the 4 to 8-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b , and then is optionally substituted on a ring carbon by 1 to 4 groups selected from the group consisting of -NH_2 , OH , and =O .

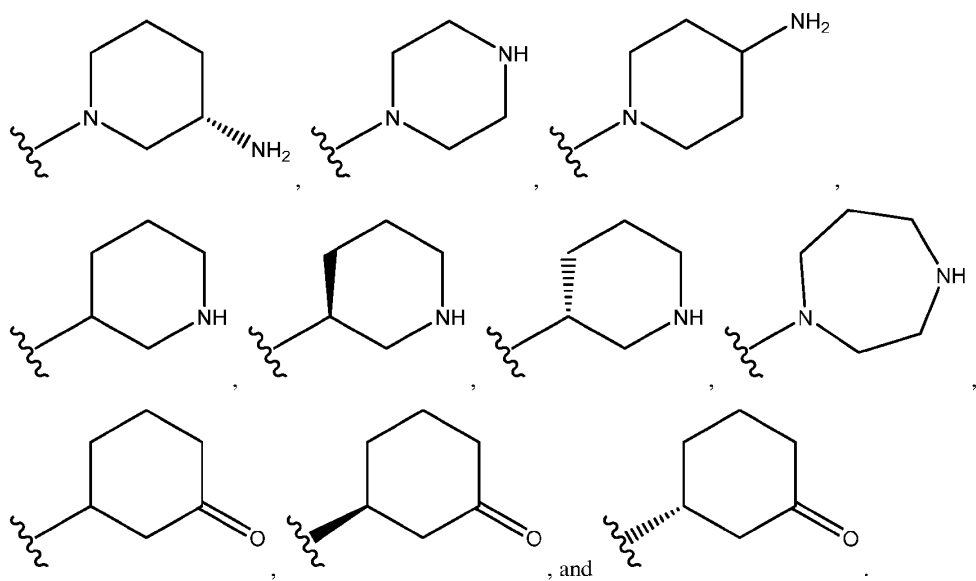
[0043] In some embodiments, Ring B is selected from the group consisting of cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, and 1,4-diazepanyl, wherein the cyclopentyl and cyclohexyl are optionally substituted with 1 to 4 R^a , wherein the piperidinyl, piperazinyl, and 1,4-diazepanyl are optionally substituted on their N atom(s) with R^b and then are optionally substituted on a ring carbon by 1 to 4 R^a .

[0044] In some embodiments, Ring B is selected from the group consisting of cyclopentyl, cyclohexyl, piperidinyl, piperazinyl, and 1,4-diazepanyl, wherein the cyclopentyl and cyclohexyl are optionally substituted with 1 to 4 groups selected from the group consisting of -NH_2 , OH , and =O , wherein the piperidinyl, piperazinyl, and 1,4-diazepanyl are optionally substituted on their N atom(s) with R^b and then are optionally substituted on a ring carbon by 1 to 4 groups selected from the group consisting of -NH_2 , OH , and =O .

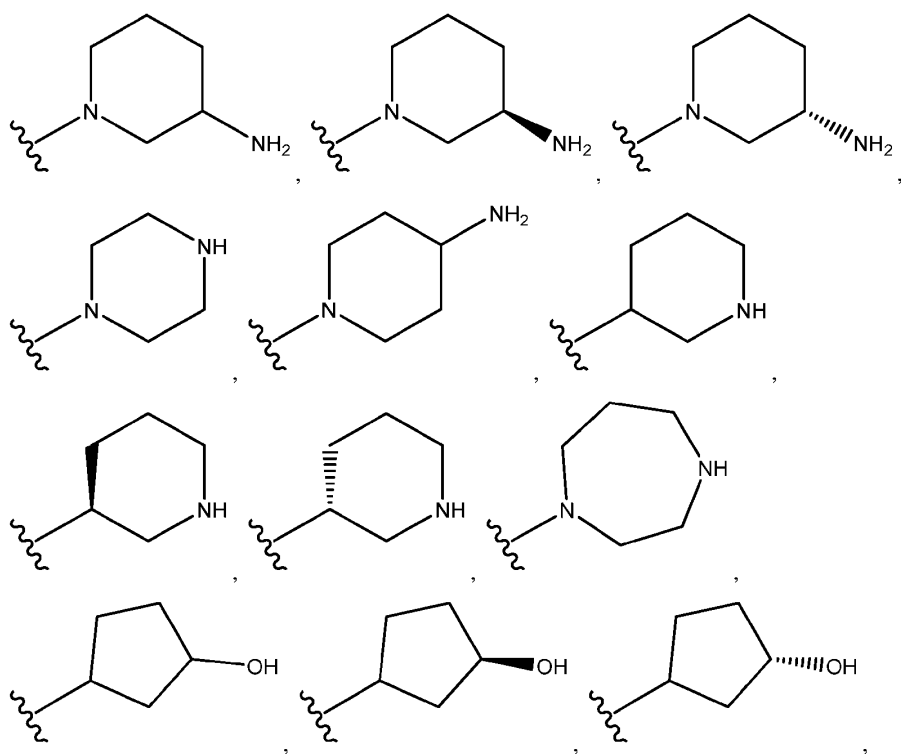
[0045] In some embodiments, Ring B is selected from the group consisting of

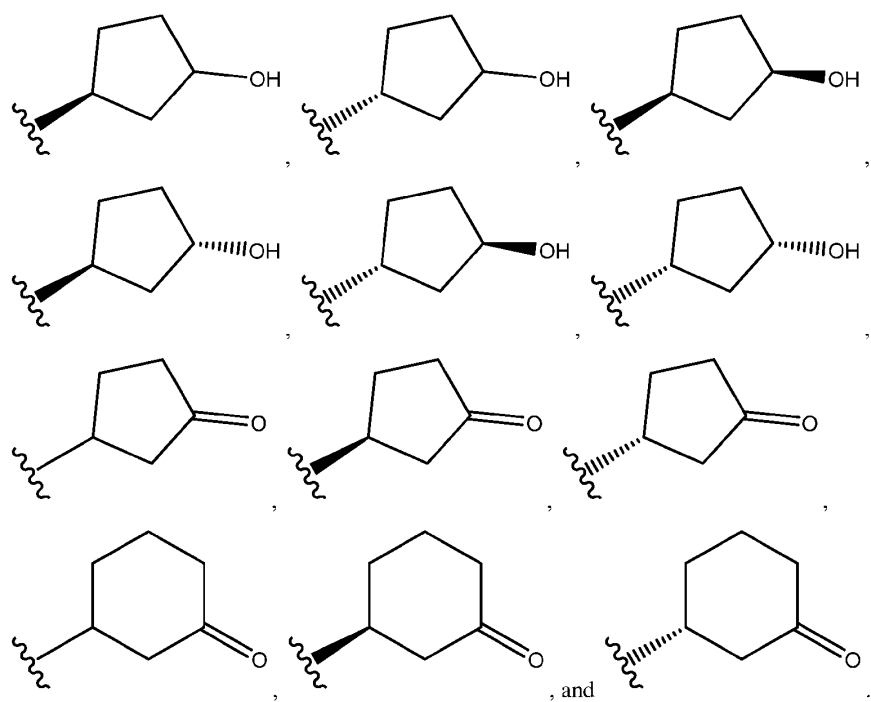




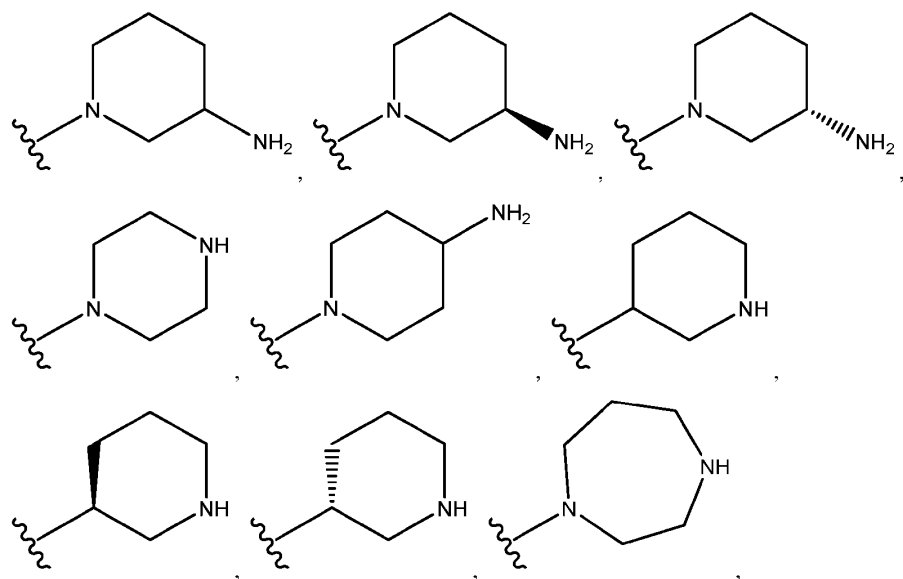


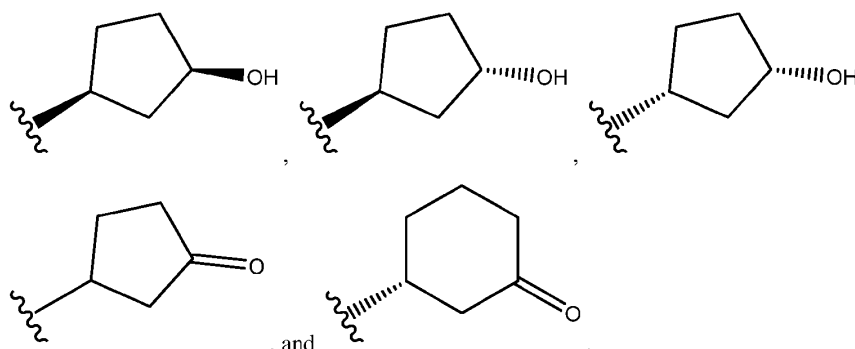
[0046] In some embodiments, Ring B is selected from the group consisting of





[0047] In some embodiments, Ring B is selected from the group consisting of





[0048] In some embodiments, R^3 is selected from the group consisting of H, C_1 - C_4 alkyl, CN, $-SO_2C_1-C_4$ alkyl, and $-S(O)NH-C_1-C_4$ alkyl.

[0049] In some embodiments, R^3 is selected from the group consisting of H, methyl, ethyl, CN, $-S(O)_2CH_3$, and $-S(O)NHCH_3$. In certain embodiments, R^3 is H.

[0050] In some embodiments, R^4 is selected from the group consisting of H, C_1 - C_4 alkyl, and C_3 - C_6 cycloalkyl.

[0051] In some embodiments, R^4 is selected from the group consisting of H, methyl, ethyl, and cyclopropyl. In certain embodiments, R^4 is H.

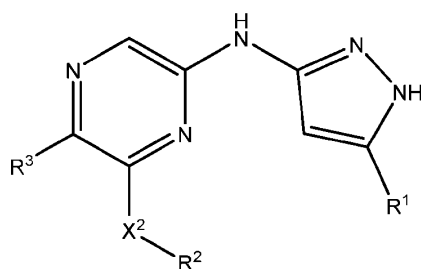
[0052] In some embodiments, R^5 is H.

[0053] In some embodiments, R^6 is selected from H and C_1 - C_4 alkyl optionally substituted with 1 to 4 halo.

[0054] In some embodiments, R^6 is selected from the group consisting of H, methyl, ethyl, $-CH_2F$, and $-CF_3$.

[0055] In some embodiments, m is 1 or 2.

[0056] In some embodiments, the compound is of Formula (IVa):



(IVa), or a pharmaceutically acceptable salt thereof,

wherein

R^1 is selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_3 - C_8 cycloalkyl, and 4 to 10-membered heterocyclyl, wherein the C_1 - C_4 alkyl, C_1 - C_4 alkoxy, and C_3 - C_8 cycloalkyl are each optionally substituted with 1 to 3 R^a , wherein the 4 to 10-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a ;

X^2 is selected from the group consisting of $-O-$, $-O(C(R^c)_2)_m-$, and $-(C(R^d)_2)_n-O-$;

R^2 is selected from C_1-C_4 alkyl and Ring A, wherein the C_1-C_4 alkyl is optionally substituted with 1 to 3 groups each independently selected from the group consisting of halo, CN, and OH;

Ring A is selected from the group consisting of C_3-C_8 cycloalkyl, 4 to 10-membered heterocyclyl, 6 to 10-membered aryl, and 4 to 10-membered heteroaryl, wherein the C_3-C_8 cycloalkyl and 6 to 10-membered aryl are each optionally substituted with 1 to 3 R^a , wherein the 4 to 10-membered heterocyclyl and 4 to 10-membered heteroaryl have 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a ;

R^3 is H or C_1-C_4 alkyl;

Each R^a is independently selected from the group consisting of halo, OH, CN, C_1-C_4 alkyl, and C_1-C_4 alkoxy, or two R^a , attached to the same atom, form a $=O$, wherein the C_1-C_4 alkyl and C_1-C_4 alkoxy are each optionally substituted with 1 to 3 groups each independently selected from the group consisting of halo, OH and CN;

Each R^b is independently H or C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is optionally substituted with 1 to 4 D;

Each R^c is independently H or C_1-C_4 alkyl;

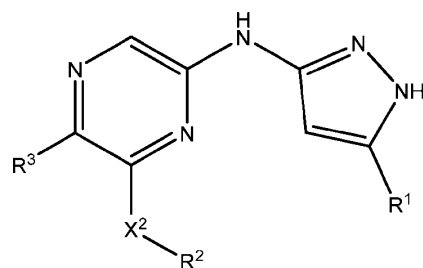
Each R^d is independently H or C_1-C_4 alkyl;

m is 1 or 2; and

n is 1 or 2.

[0057] In some embodiments, R^d is selected from H and methyl.

[0058] In some embodiments, the compound is of Formula (IVb):



(IVb), or a pharmaceutically acceptable salt thereof,

wherein

R^1 is selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, C_3-C_8 cycloalkyl, and 4 to 10-membered heterocyclyl, wherein the C_1-C_4 alkyl, C_1-C_4 alkoxy, and C_3-C_8 cycloalkyl are each optionally substituted with 1 to 3 R^a , wherein the 4 to 10-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a ;

X^2 is $-NR^b-$ or $-NR^b-(C(R^c)_2)_m-$;

R^2 is selected from C_1-C_4 alkyl and Ring A, wherein the C_1-C_4 alkyl is optionally substituted with 1 to 3 groups each independently selected from the group consisting of halo, CN, and OH;

Ring A is selected from the group consisting of C₃-C₈cycloalkyl, 4 to 10-membered heterocyclyl, 6 to 10-membered aryl, and 4 to 10-membered heteroaryl, wherein the C₃-C₈cycloalkyl and 6 to 10-membered aryl are each optionally substituted with 1 to 3 R^a, wherein the 4 to 10-membered heterocyclyl and 4 to 10-membered heteroaryl have 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a;

R³ is H or C₁-C₄ alkyl;

Each R^a is independently selected from the group consisting of halo, OH, CN, C₁-C₄alkyl, and C₁-C₄alkoxy, or two R^a, attached to the same atom, form a =O, wherein the C₁-C₄alkyl and C₁-C₄alkoxy are each optionally substituted with 1 to 3 groups each independently selected from the group consisting of halo, OH and CN;

Each R^b is independently H or C₁-C₄alkyl, wherein the C₁-C₄alkyl is optionally substituted with 1 to 4 D;

Each R^c is independently H or C₁-C₄alkyl; and

m is 1 or 2.

[0059] In some embodiments, R¹ is selected from the group consisting of CN, C₁-C₄alkyl, C₁-C₄alkoxy, -C₃-C₆cycloalkyl, -(CH₂)-C₃-C₆cycloalkyl, -O(CH₂)-C₃-C₆cycloalkyl, 4 to 6-membered heterocyclyl, -O-(4 to 6-membered heterocyclyl), -O(CH₂)-(4 to 6-membered heterocyclyl), and -(CH₂)-phenyl, wherein the C₁-C₄alkyl, C₁-C₄alkoxy, C₃-C₆cycloalkyl, and phenyl are each optionally substituted with 1 to 3 R^a, wherein the 4 to 6-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a.

[0060] In some embodiments, R¹ is selected from the group consisting of CN, C₁-C₄alkyl, C₁-C₄alkoxy, -C₃-C₆cycloalkyl, -(CH₂)-C₃-C₆cycloalkyl, -O(CH₂)-C₃-C₆cycloalkyl, 4 to 6-membered heterocyclyl, -O-(4 to 6-membered heterocyclyl), -O(CH₂)-(4 to 6-membered heterocyclyl), and -(CH₂)-phenyl, wherein the C₁-C₄alkyl, C₁-C₄alkoxy, C₃-C₆cycloalkyl, and phenyl are each optionally substituted with 1 to 3 groups selected from the group consisting of fluoro, OH, CN, methyl, and methoxy, wherein the 4 to 6-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N and NR^b and then is optionally substituted on a ring carbon with 1 to 3 groups selected from the group consisting of fluoro, OH, CN, methyl, and methoxy.

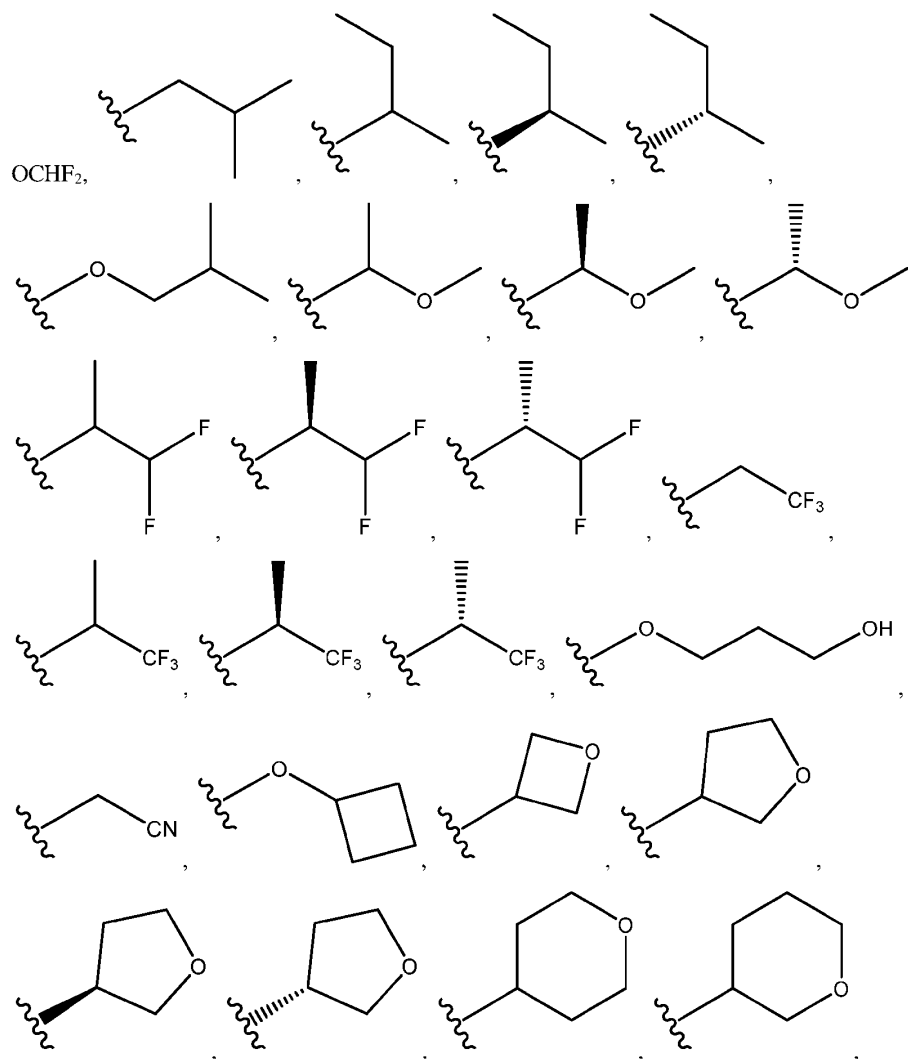
[0061] In some embodiments, R¹ is selected from the group consisting of CN, C₁-C₄alkyl, C₁-C₄alkoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, -(CH₂)-cyclopropyl, -O(CH₂)-cyclopropyl, -O(CH₂)-tetrahydrofuranyl, -O-tetrahydropyranyl, and -(CH₂)-phenyl, wherein the C₁-C₄alkyl, C₁-C₄alkoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and phenyl are optionally substituted on a ring carbon with 1 to 3 R^a.

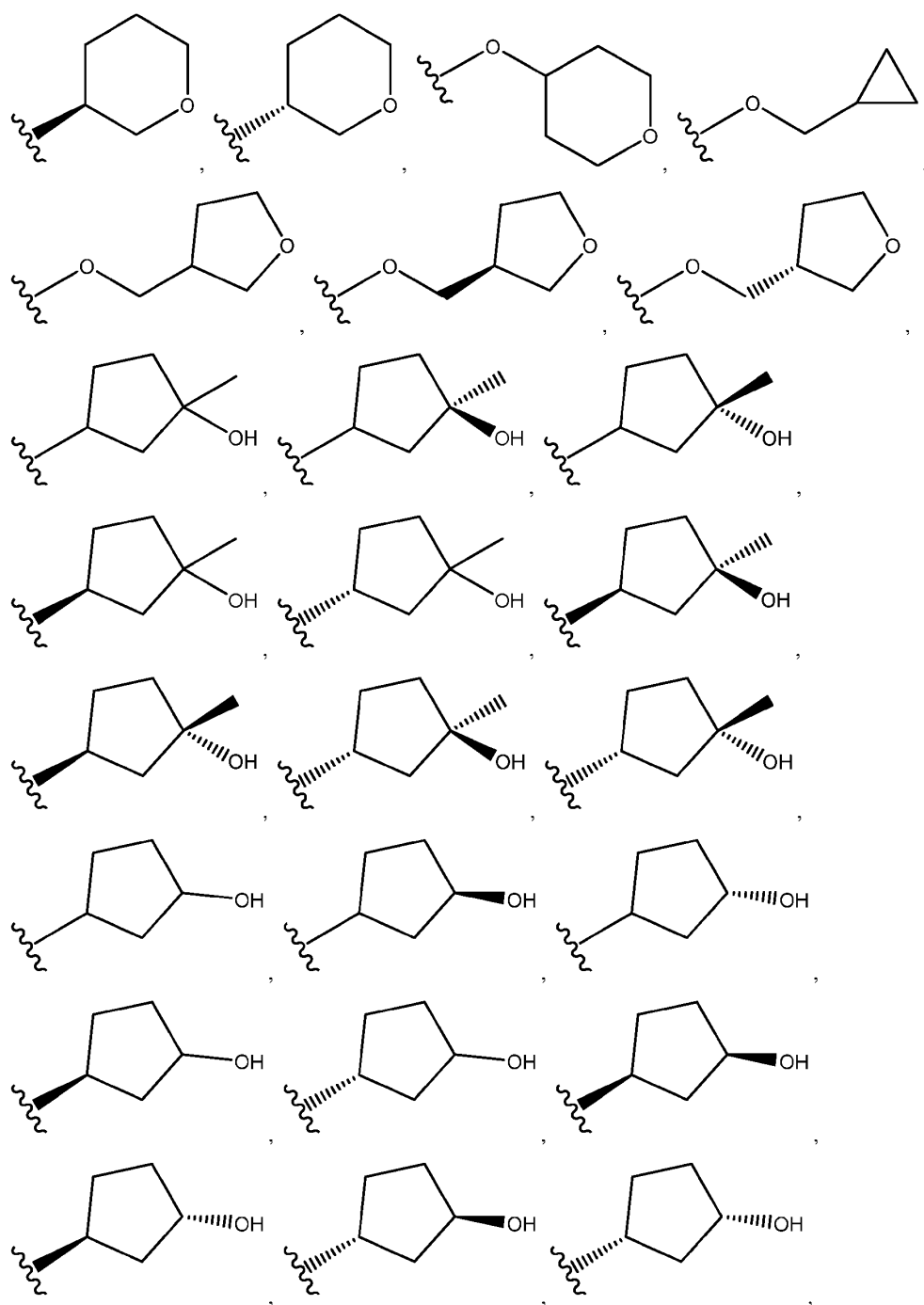
[0062] In some embodiments, R¹ is selected from the group consisting of CN, C₁-C₄alkyl, C₁-C₄alkoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl,

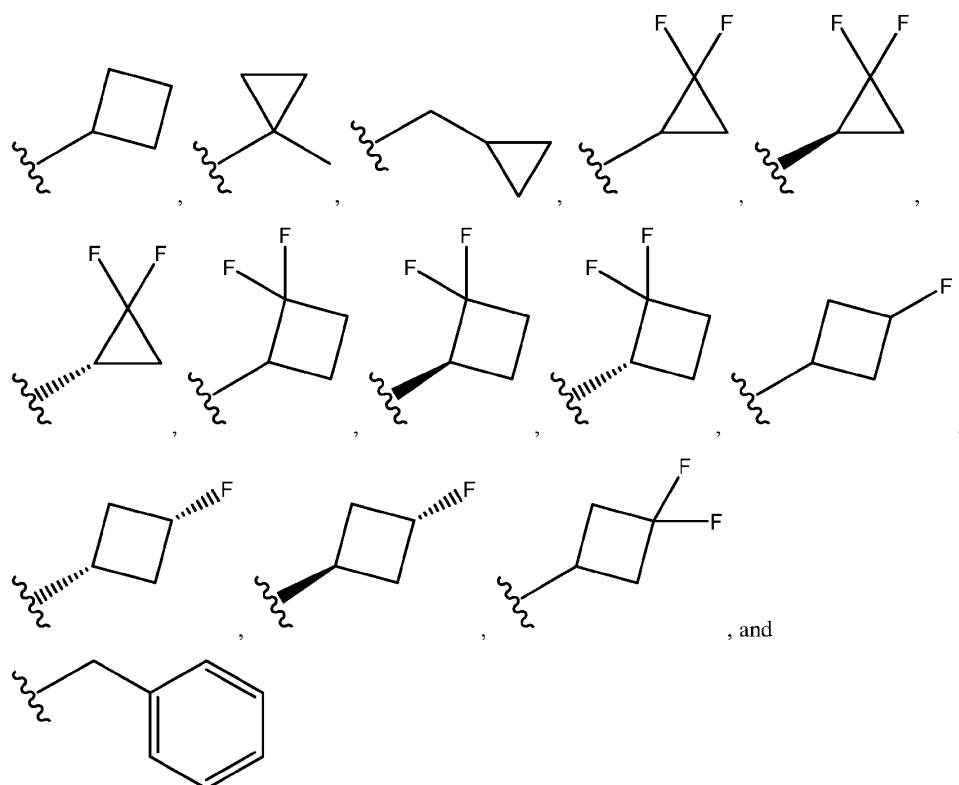
tetrahydropyran-2-yl, -(CH₂)₁₋₄-cyclopropyl, -O(CH₂)₁₋₄-cyclopropyl, -O(CH₂)₁₋₄-tetrahydrofuran-2-yl, -O-tetrahydropyran-2-yl, and -(CH₂)₁₋₄-phenyl, wherein the C₁-C₄alkyl, C₁-C₄alkoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuran-2-yl, tetrahydropyran-2-yl, and phenyl are optionally substituted on a ring carbon with 1 to 3 groups selected from the group consisting of fluoro, OH, CN, methyl, and methoxy.

[0063] In some embodiments, R¹ is C₁-C₄alkoxy substituted with 1 to 3 halo. In some embodiments, R¹ is C₁-C₄alkoxy substituted with 1 to 3 fluoro. In some embodiments, R¹ is -OCHF₂.

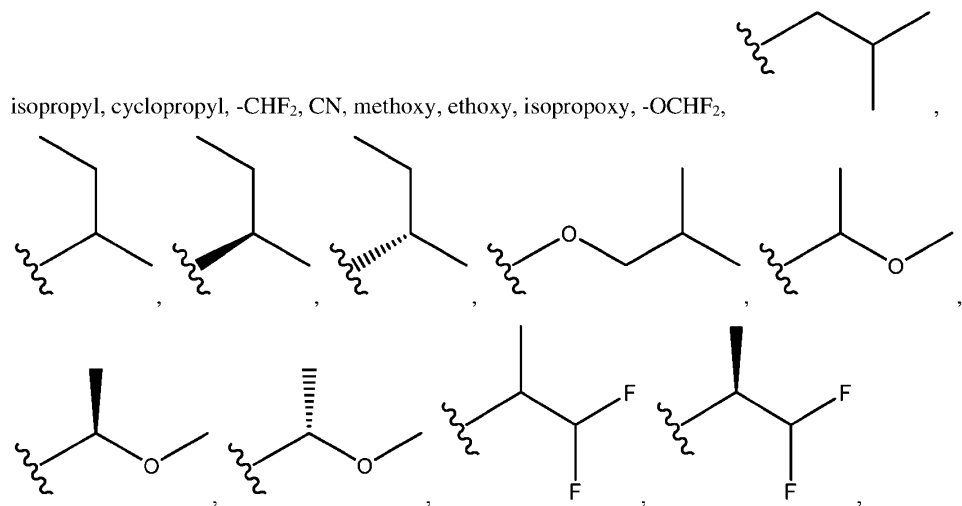
[0064] In some embodiments, R¹ is selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, -CD₃, -CD₂H, -CDH₂, -CF₃, -CH₂F, -CHF₂, CN, methoxy, ethoxy, isopropoxy, -

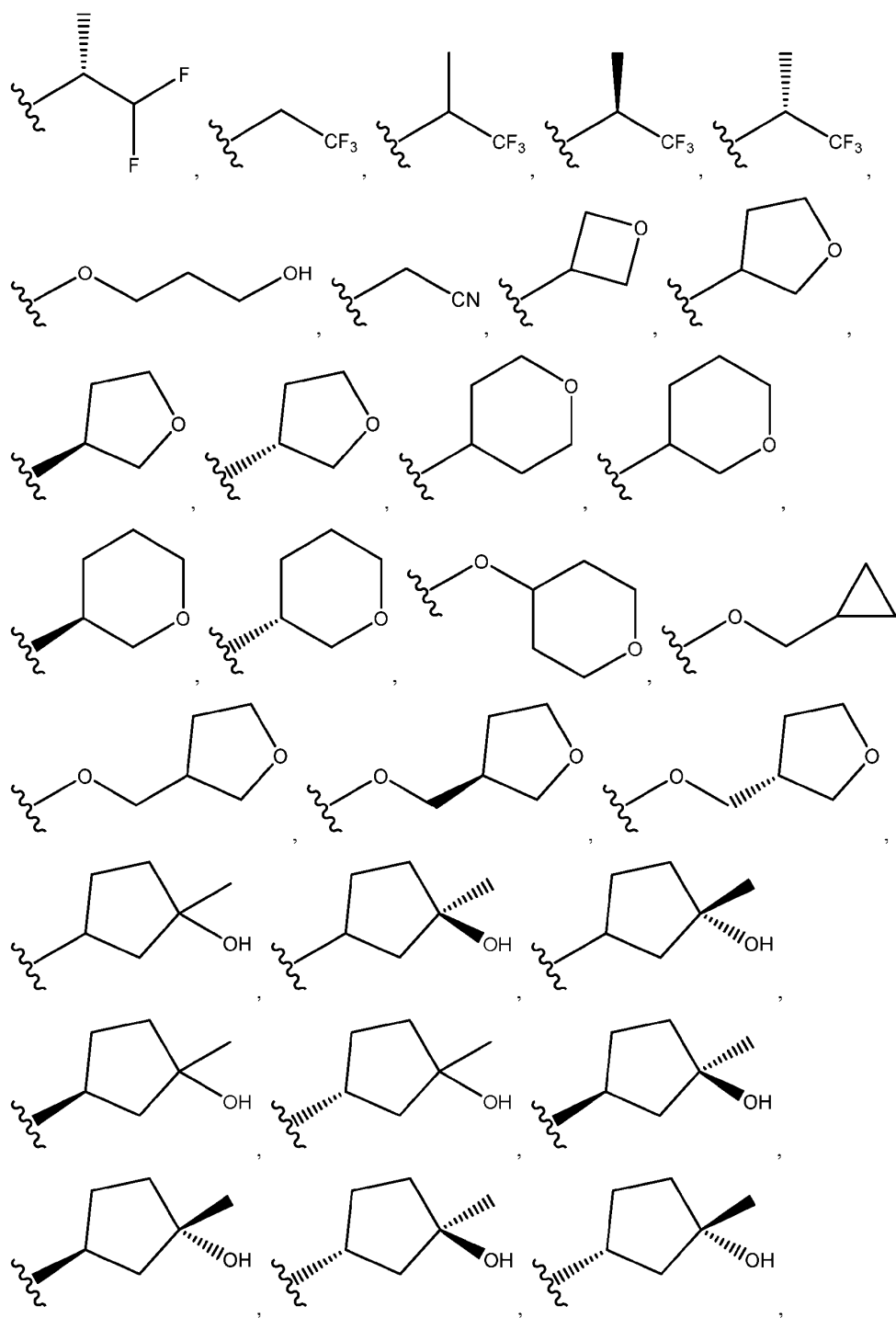


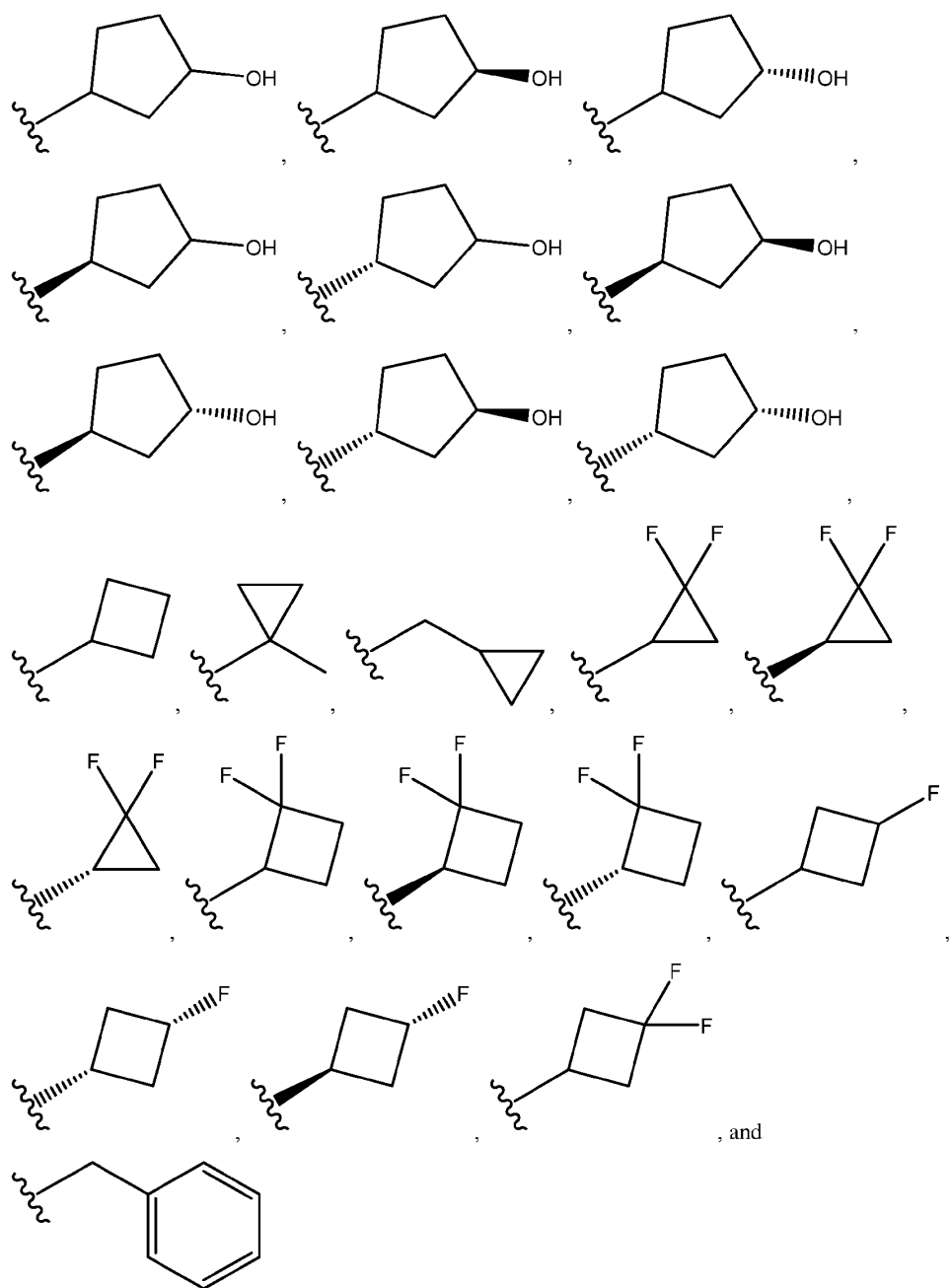




[0065] In some embodiments, R¹ is selected from the group consisting of methyl, ethyl, *n*-propyl,

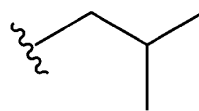




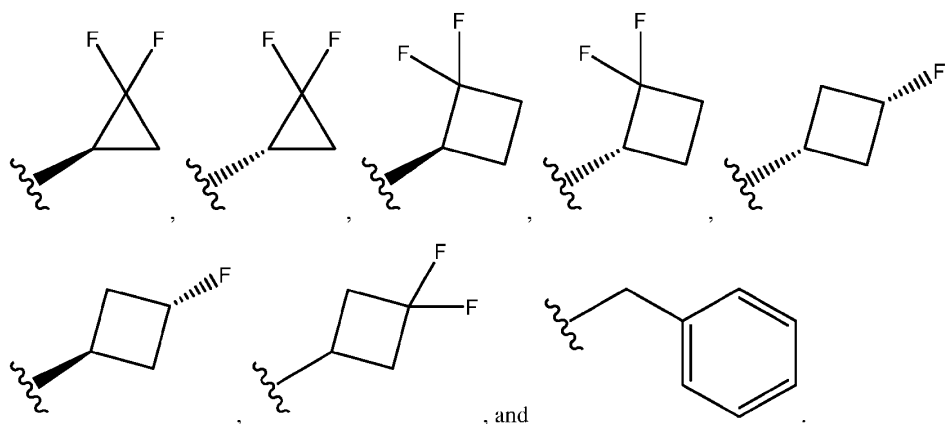


[0066] In some embodiments, R^1 is selected from the group consisting of methyl, ethyl, *n*-propyl,

isopropyl, cyclopropyl, $-\text{CHF}_2$, CN, methoxy, ethoxy, isopropoxy, $-\text{OCHF}_2$,





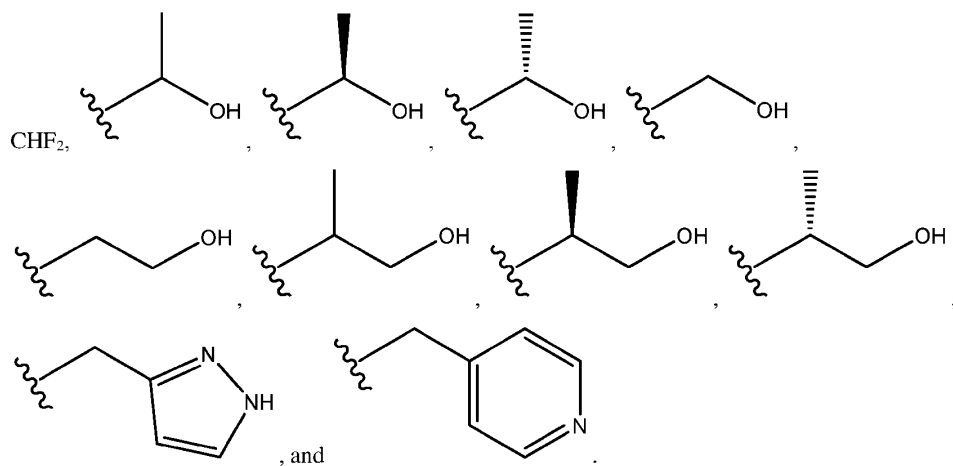


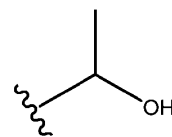
[0067] In some embodiments, R² is C₁-C₄alkyl optionally substituted with 1 to 4 groups each independently selected from the group consisting of D, halo, CN, and OH.

[0068] In some embodiments, R² is C₁-C₄alkyl optionally substituted with 1 to 4 OH. In some embodiments, R² is C₁-C₄alkyl optionally substituted with OH.

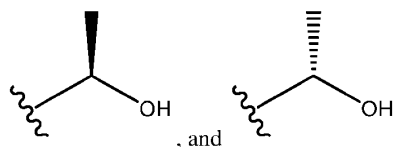
[0069] In some embodiments, R² is ethyl optionally substituted with OH.

[0070] In some embodiments, R² is selected from the group consisting of methyl, ethyl, -CH₂F, -

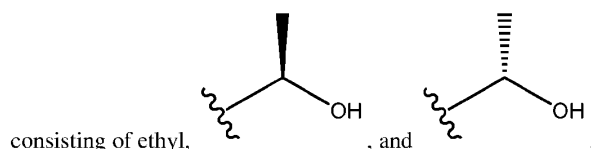




[0071] In some embodiments, R^2 is selected from the group consisting of ethyl,



, and . In some embodiments, R^2 is selected from the group



consisting of ethyl,

[0072] In some embodiments, Ring A is 4 to 10-membered heterocyclyl having 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a .

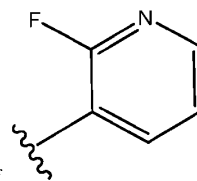
[0073] In some embodiments, Ring A is selected from the group consisting of C_3 - C_6 cycloalkyl, 4 to 10-membered heterocyclyl, and 4 to 10-membered heteroaryl, wherein the C_3 - C_6 cycloalkyl is optionally substituted with 1 to 3 R^a , wherein the 4 to 10-membered heterocyclyl and 4 to 10-membered heteroaryl have 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a .

[0074] In some embodiments, Ring A is selected from the group consisting of C_3 - C_6 cycloalkyl, 4 to 10-membered heterocyclyl, and 4 to 10-membered heteroaryl, wherein the C_3 - C_6 cycloalkyl is optionally substituted with 1 to 3 groups selected from the group consisting of fluoro, CN, methyl, ethyl, isopropyl, methoxy, and oxo, wherein the 4 to 10-membered heterocyclyl and the 4 to 10-membered heteroaryl have 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then are optionally substituted on a ring carbon with 1 to 3 groups selected from the group consisting of fluoro, CN, methyl, ethyl, isopropyl, methoxy, and oxo.

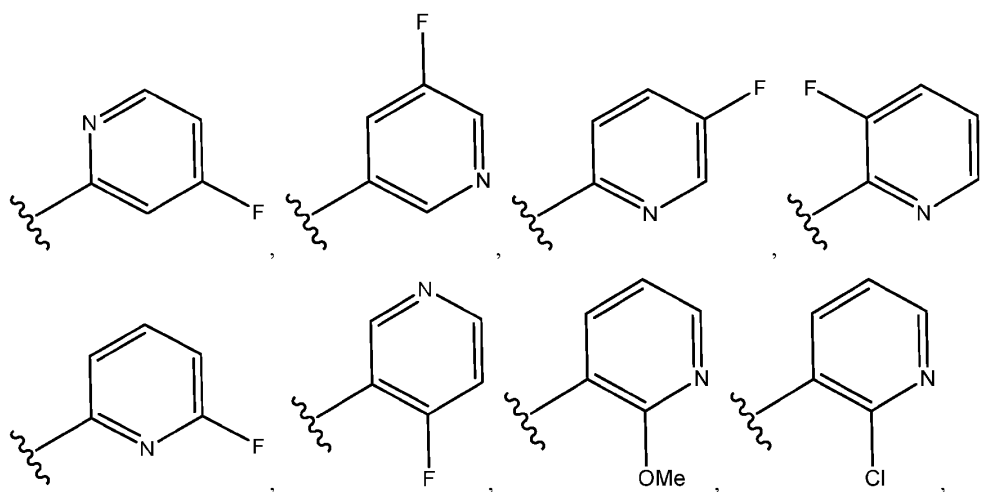
[0075] In some embodiments, Ring A is selected from the group consisting of cyclopropyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrrolidinyl, piperidinyl, 5-azaspiro[2.5]octanyl, 1-azabicyclo[2.2.1]heptanyl, quinuclidinyl, 3-azabicyclo[3.1.1]heptanyl, 8-azabicyclo[3.2.1]octanyl, azepanyl, 9-azabicyclo[3.3.1]nonanyl, 2-azaspiro[3.3]heptanyl, 3-azabicyclo[3.2.0]heptanyl, quinolyl, oxazolyl, phenyl, pyridyl, and pyridazyl, wherein the cyclopropyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, quinolyl, oxazolyl, phenyl, pyridyl, and pyridazyl are optionally substituted on a ring carbon with 1 to 4 R^a , wherein the pyrrolidinyl, piperidinyl, 5-azaspiro[2.5]octanyl, 1-azabicyclo[2.2.1]heptanyl, quinuclidinyl, 3-azabicyclo[3.1.1]heptanyl, 8-azabicyclo[3.2.1]octanyl, azepanyl, 9-azabicyclo[3.3.1]nonanyl, 2-azaspiro[3.3]heptanyl, and 3-azabicyclo[3.2.0]heptanyl are optionally substituted on their N atom with R^b and then are optionally substituted on a ring carbon with 1 to 4 R^a .

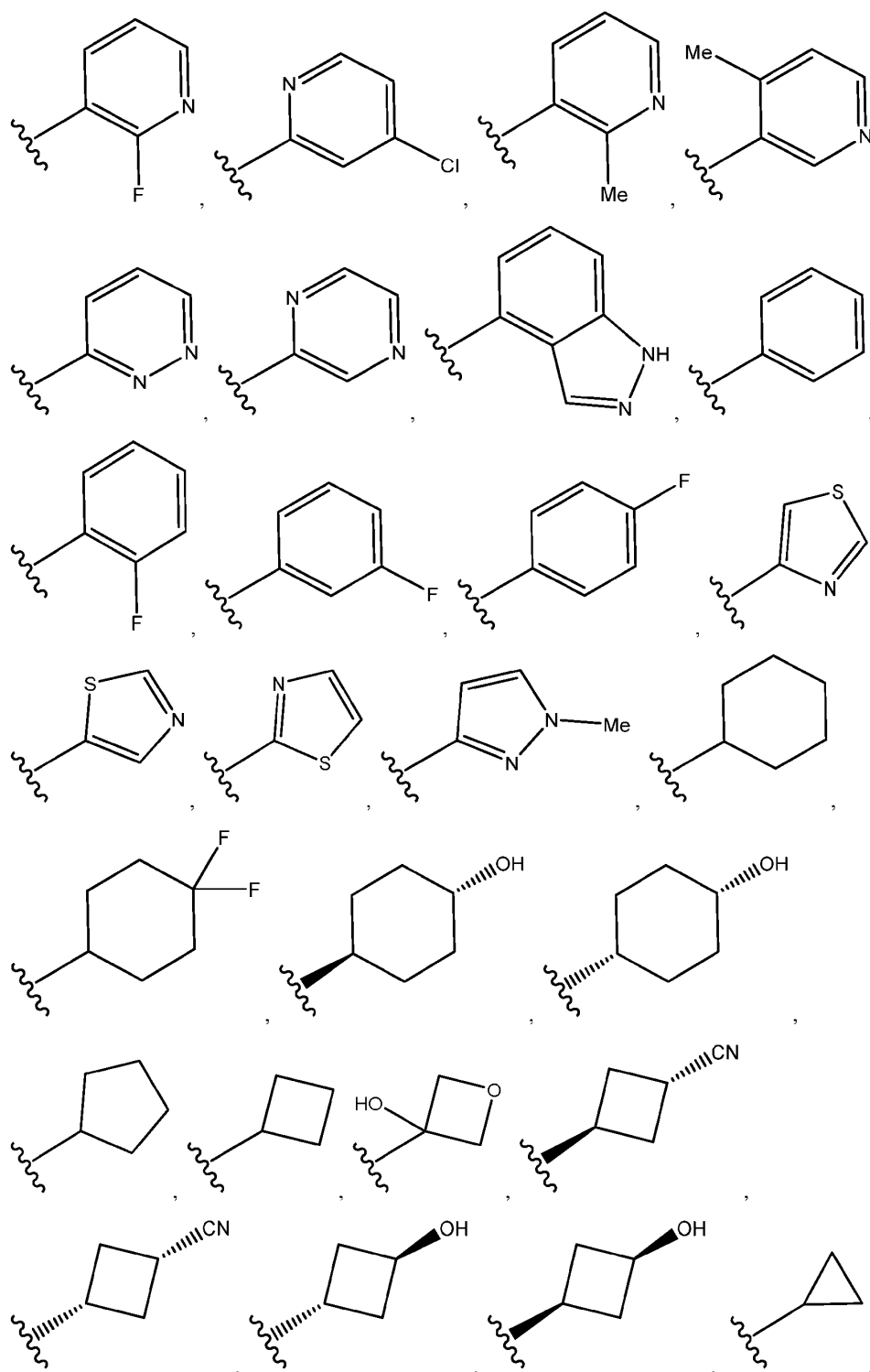
[0076] In some embodiments, Ring A is selected from the group consisting of cyclopropyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, pyrrolidinyl, piperidinyl, 5-azaspiro[2.5]octanyl, 1-azabicyclo[2.2.1]heptanyl, quinuclidinyl, 3-azabicyclo[3.1.1]heptanyl, 8-azabicyclo[3.2.1]octanyl, azepanyl, 9-azabicyclo[3.3.1]nonanyl, 2-azaspiro[3.3]heptanyl, 3-azabicyclo[3.2.0]heptanyl, quinolyl, oxazolyl, phenyl, pyridyl, and pyridazyl, wherein the cyclopropyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, quinolyl, oxazolyl, phenyl, pyridyl, and pyridazyl are optionally substituted on a ring carbon with 1 to 4 groups selected from the group consisting of fluoro, CN, methyl, ethyl, isopropyl, methoxy, and oxo, wherein the pyrrolidinyl, piperidinyl, 5-azaspiro[2.5]octanyl, 1-azabicyclo[2.2.1]heptanyl, quinuclidinyl, 3-azabicyclo[3.1.1]heptanyl, 8-azabicyclo[3.2.1]octanyl, azepanyl, 9-azabicyclo[3.3.1]nonanyl, 2-azaspiro[3.3]heptanyl, and 3-azabicyclo[3.2.0]heptanyl are optionally substituted on their N atom with R^b and then are optionally substituted on a ring carbon with 1 to 4 groups selected from the group consisting of fluoro, CN, methyl, ethyl, isopropyl, methoxy, and oxo.

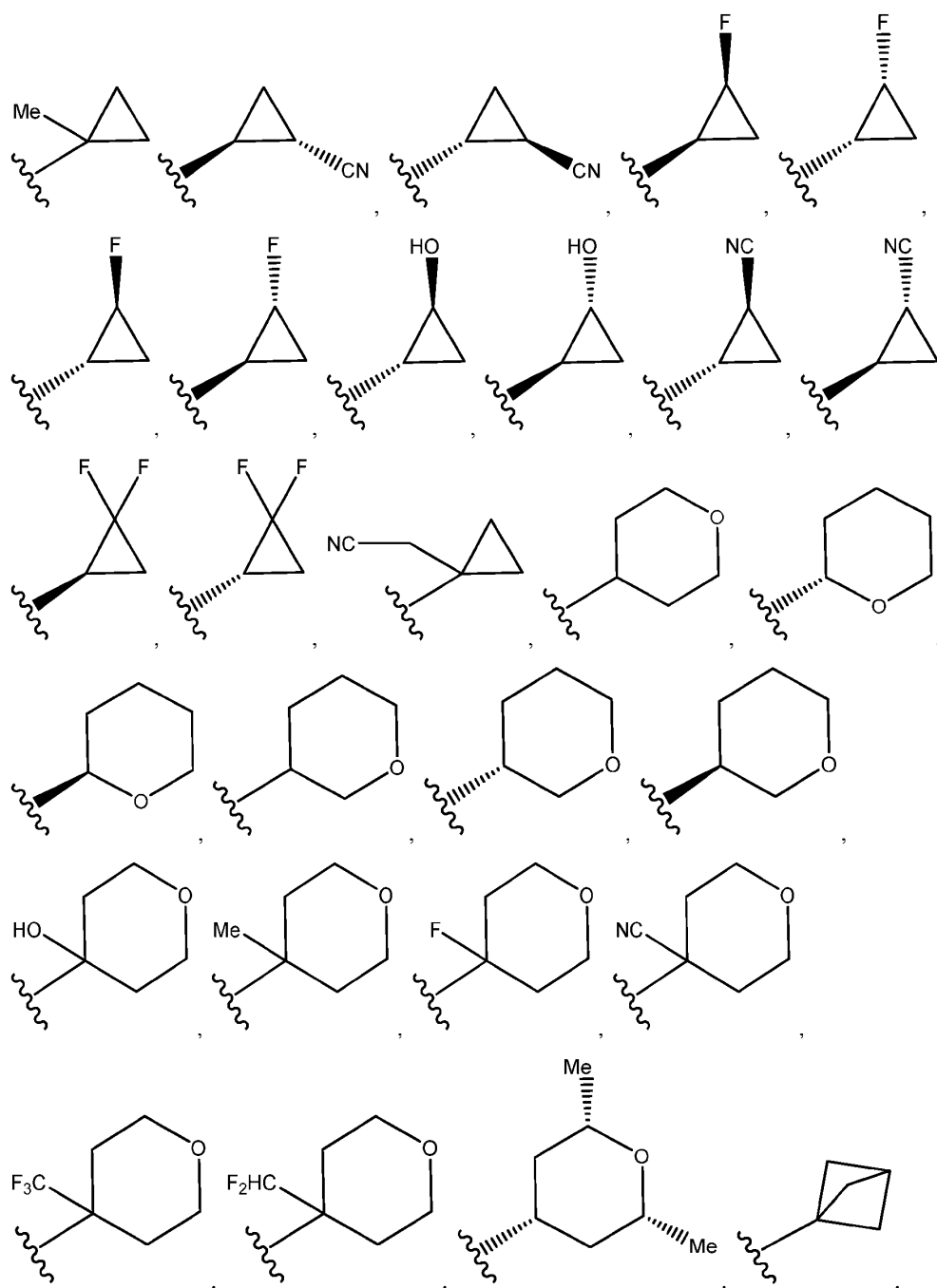
[0077] In some embodiments, Ring A is piperidinyl optionally substituted on its N atom with R^b and then optionally substituted on a ring carbon with 1 to 4 groups selected from the group consisting of fluoro, CN, methyl, ethyl, isopropyl, methoxy, and oxo. In some embodiments, Ring A is piperidinyl optionally substituted on its N atom with C₁-C₄alkyl. In some embodiments, Ring A is piperidinyl optionally substituted on its N atom with methyl. In certain embodiments, Ring A is piperidinyl substituted on its N atom with methyl.

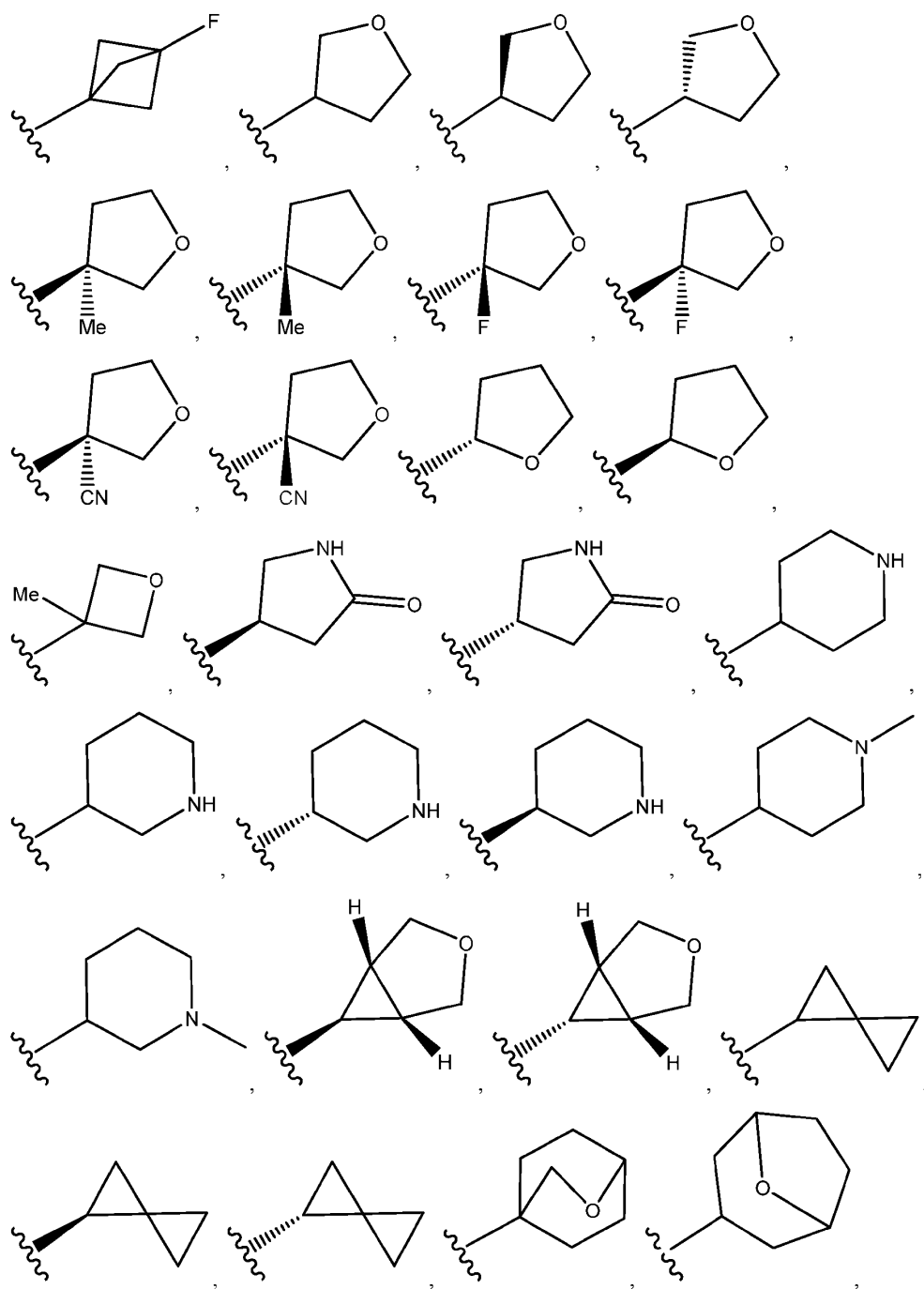


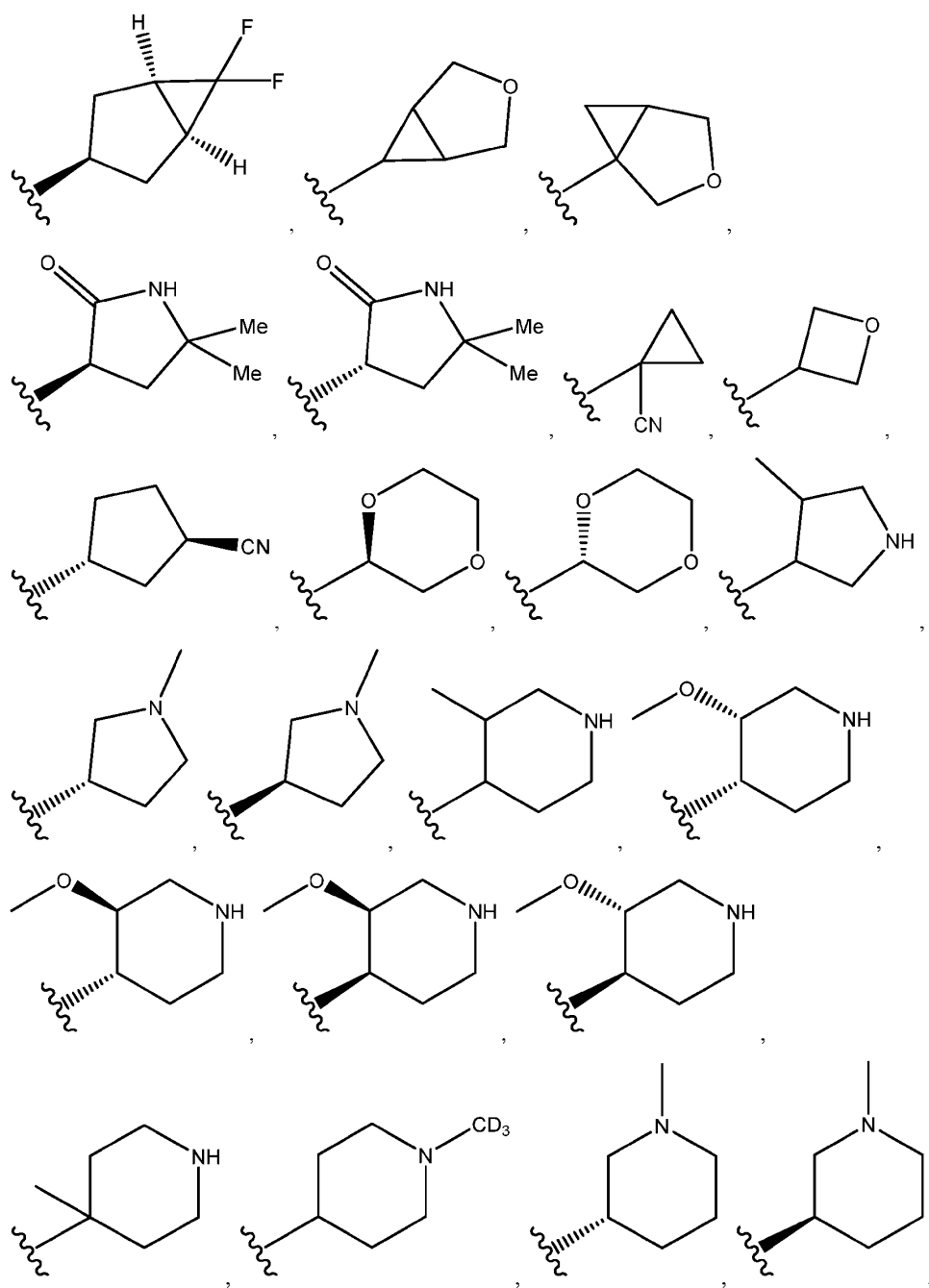
[0078] In some embodiments, Ring A is selected from the group consisting of

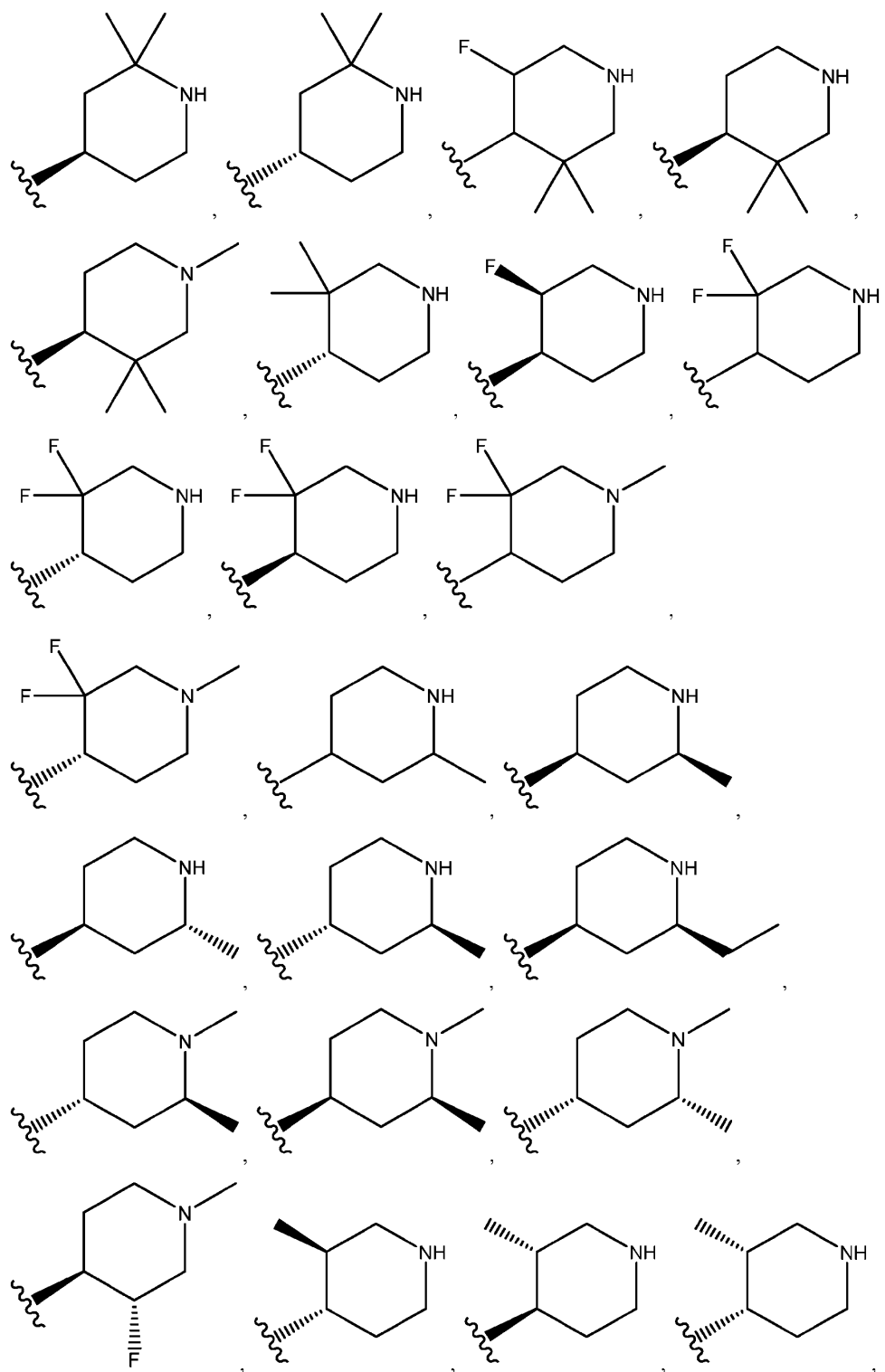


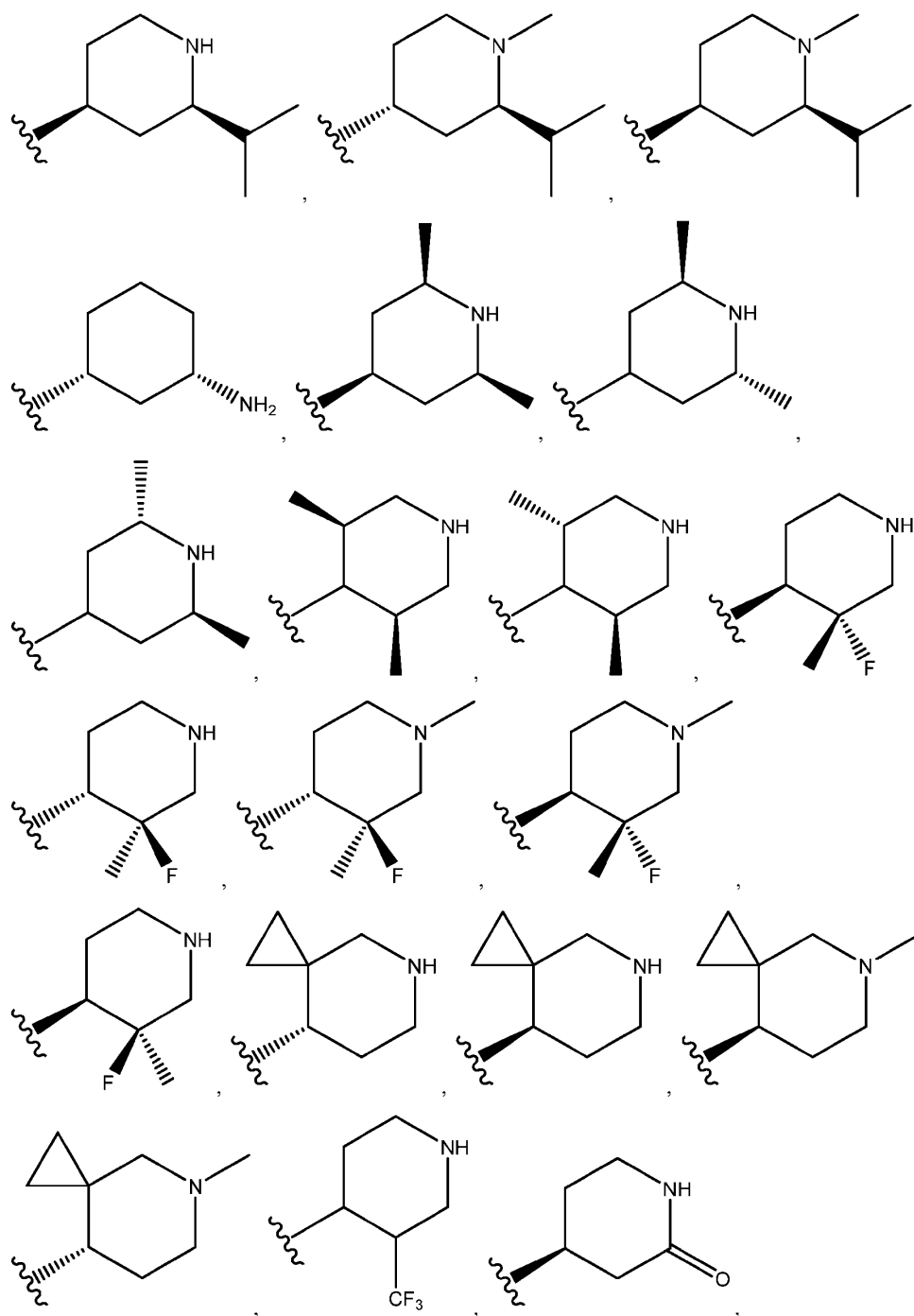


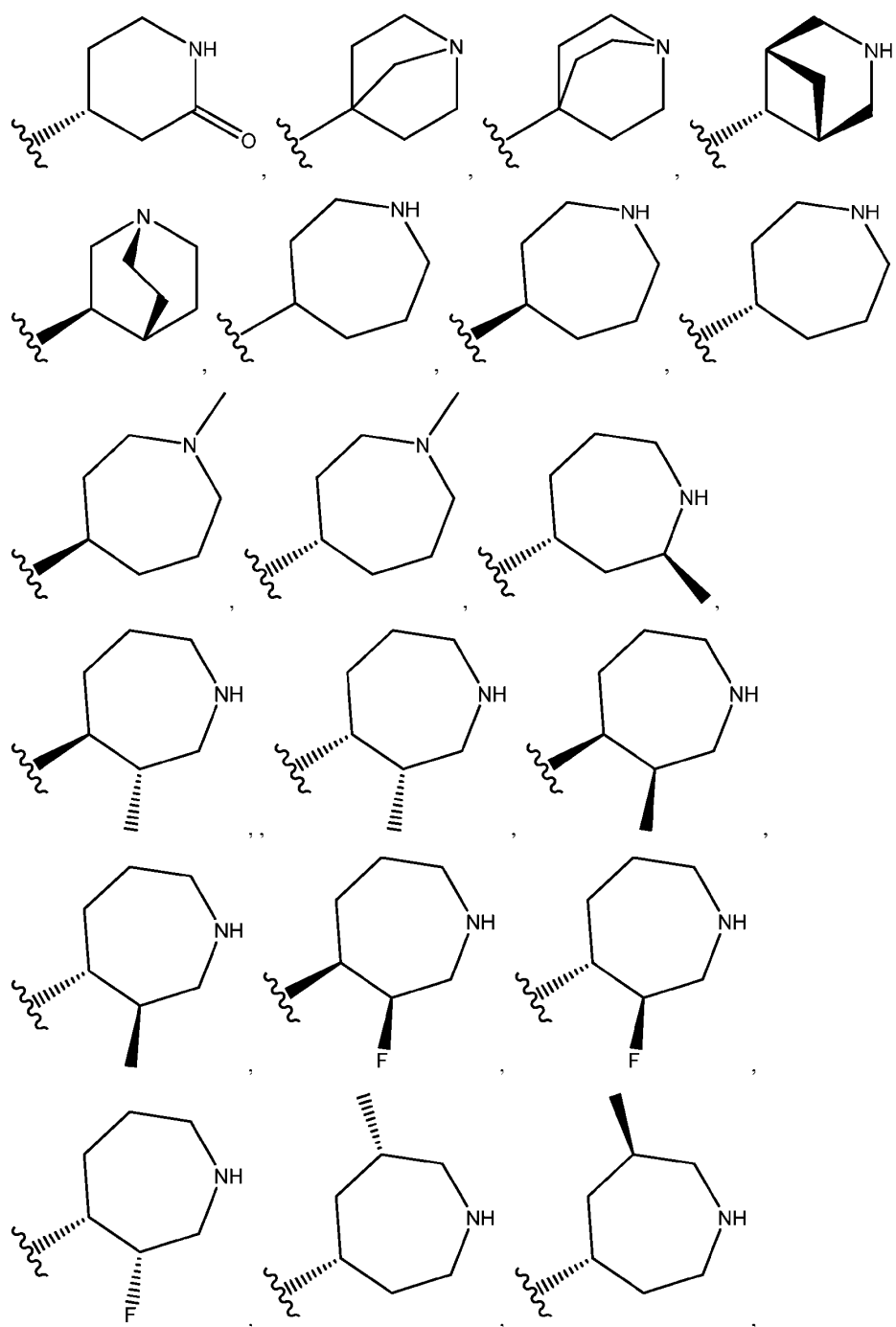


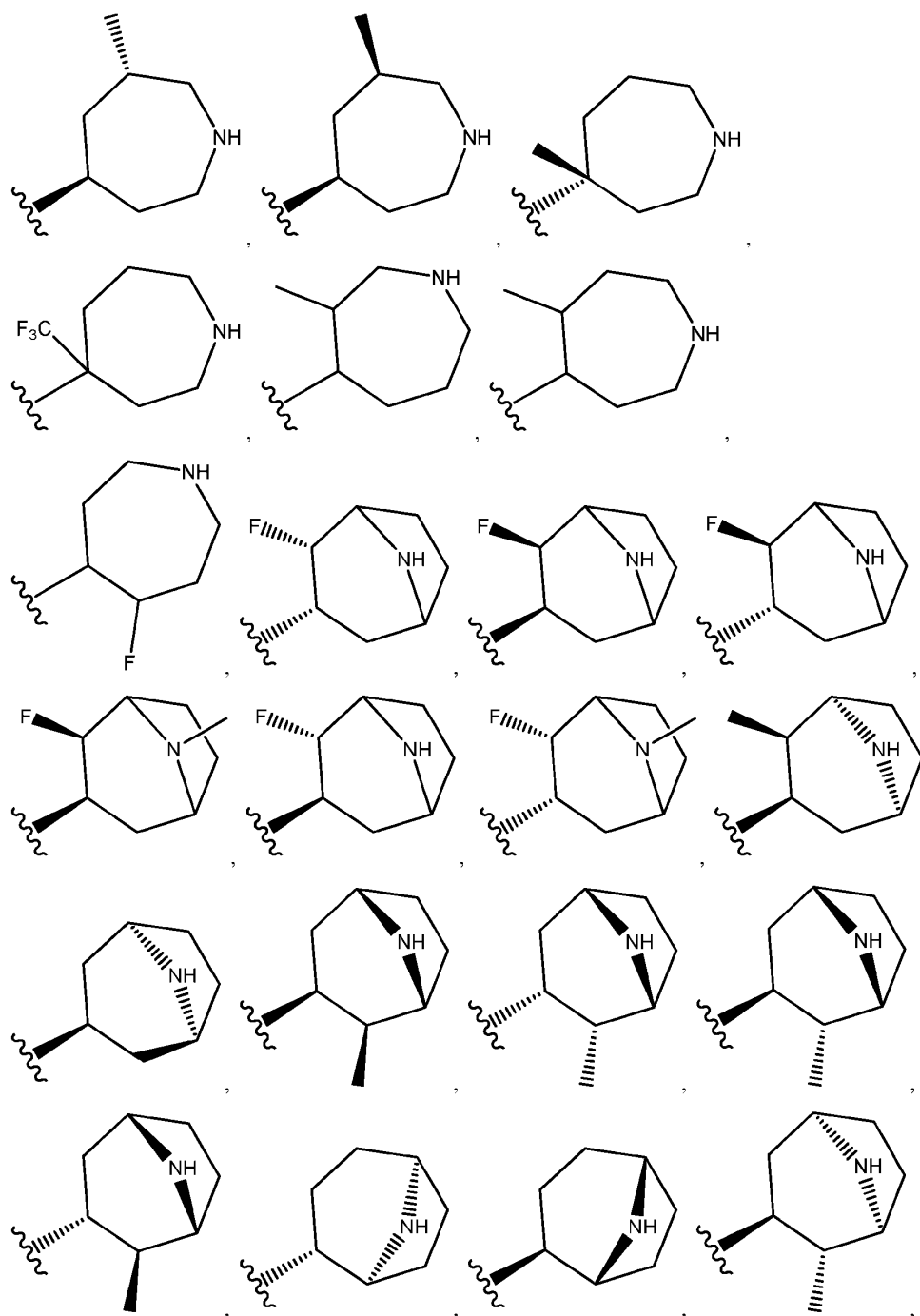


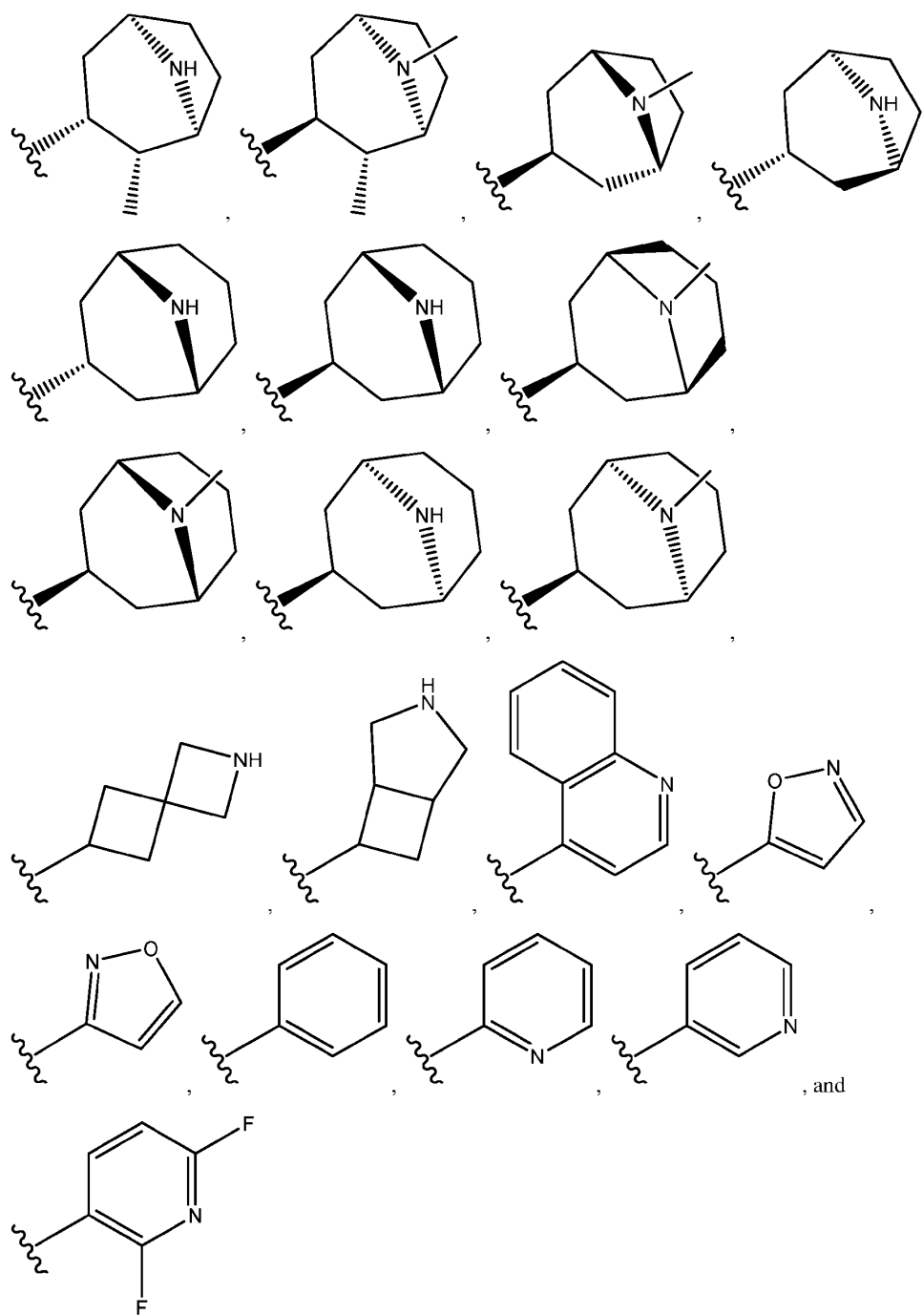


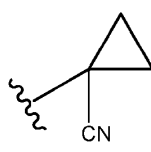


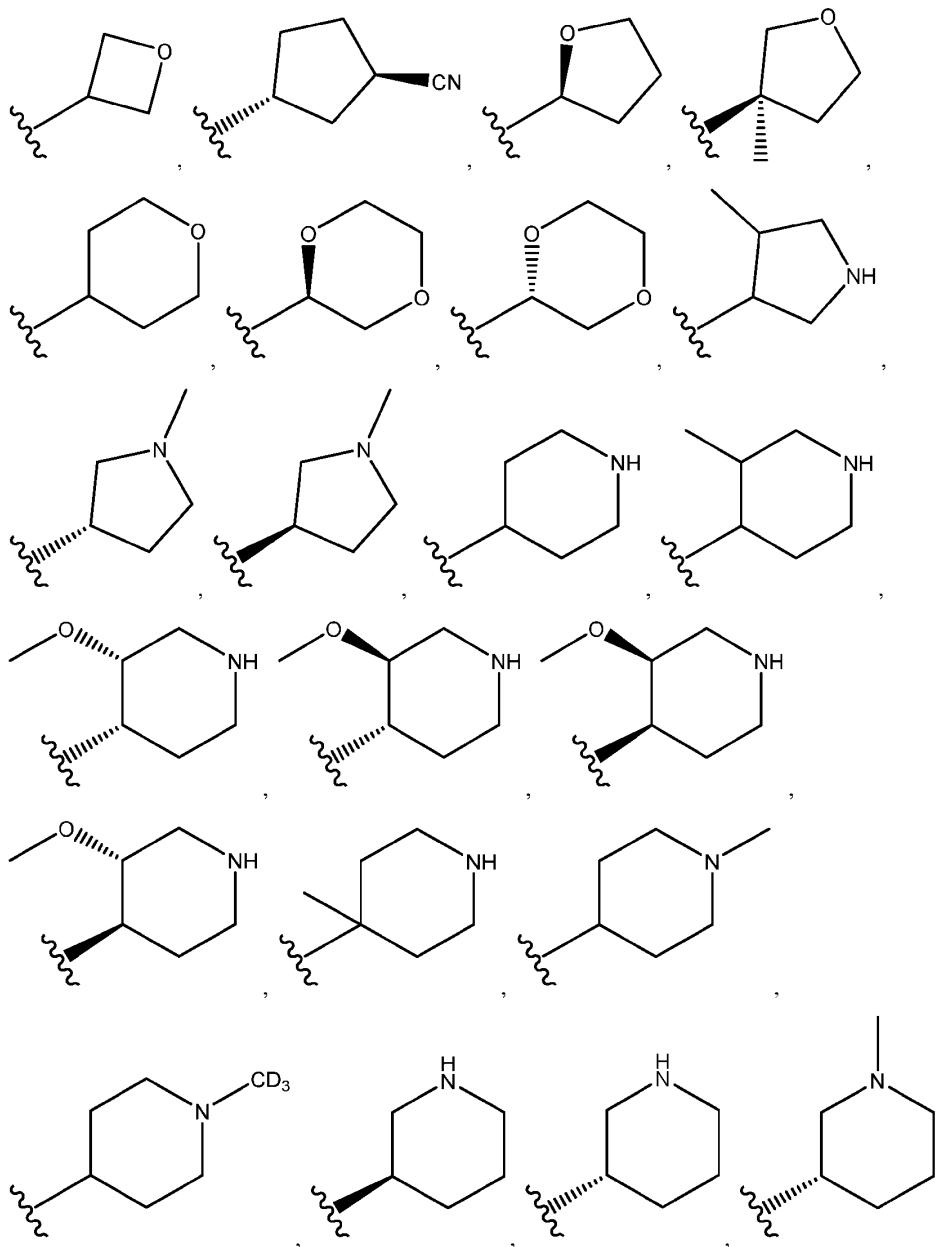


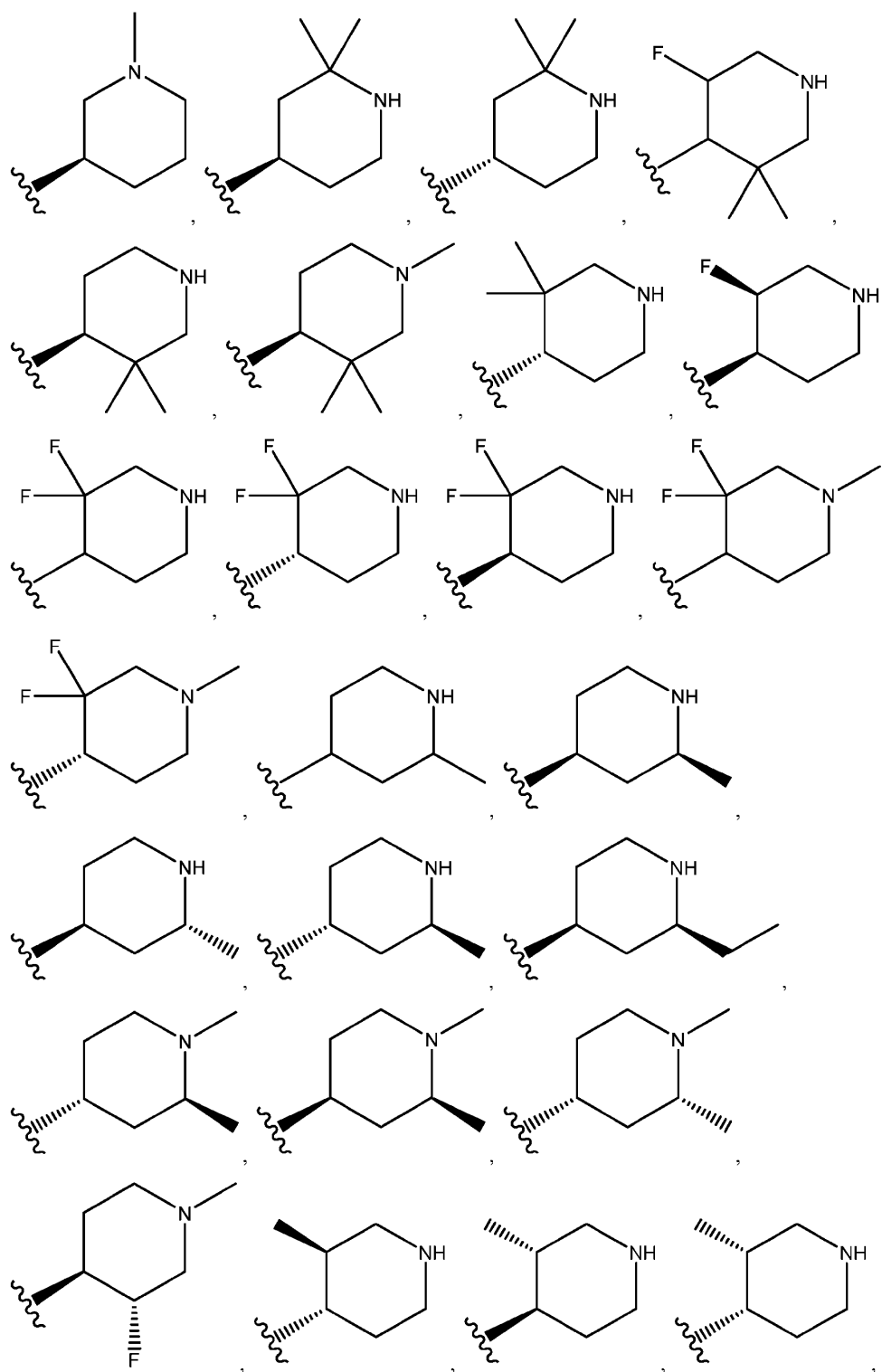


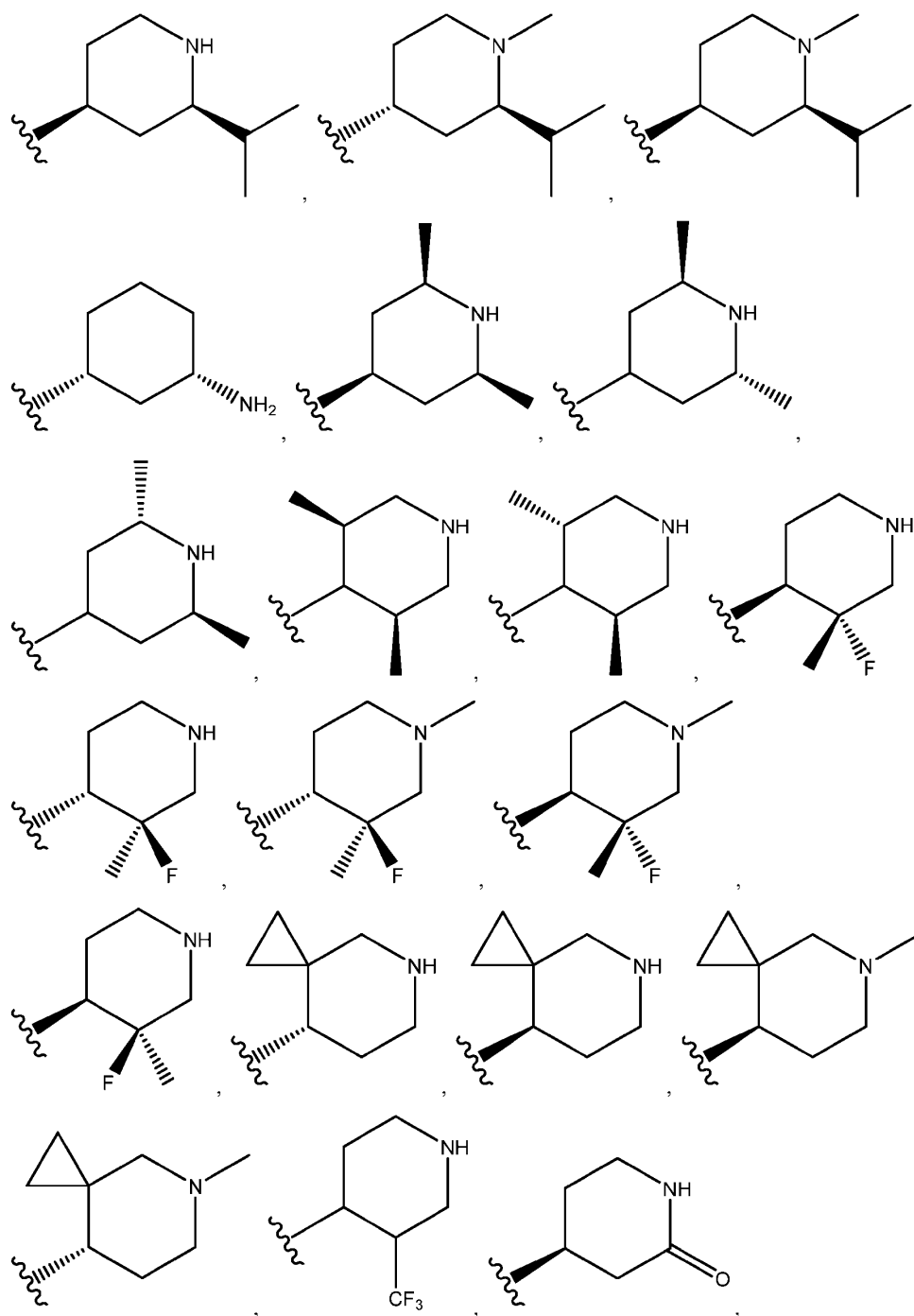


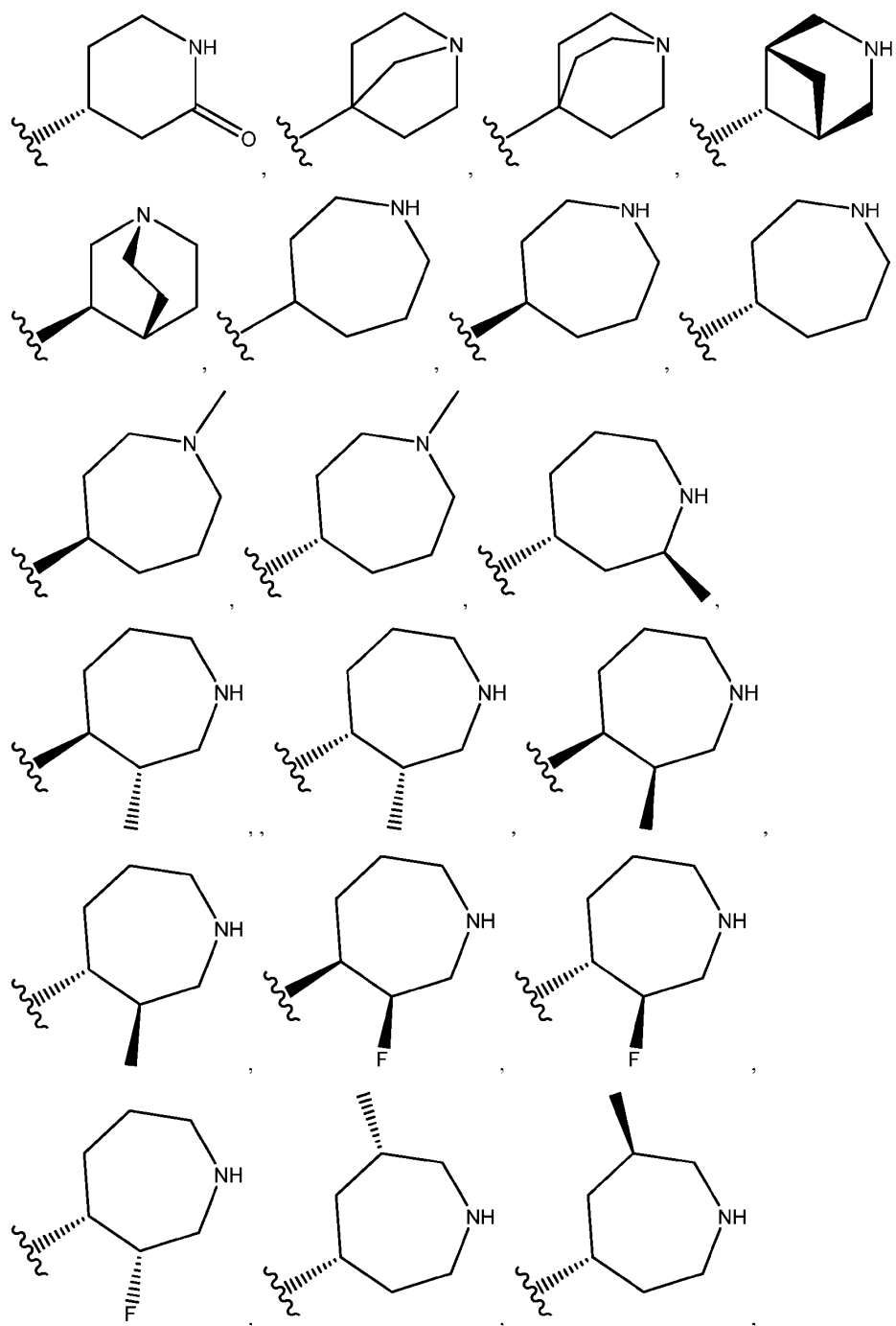


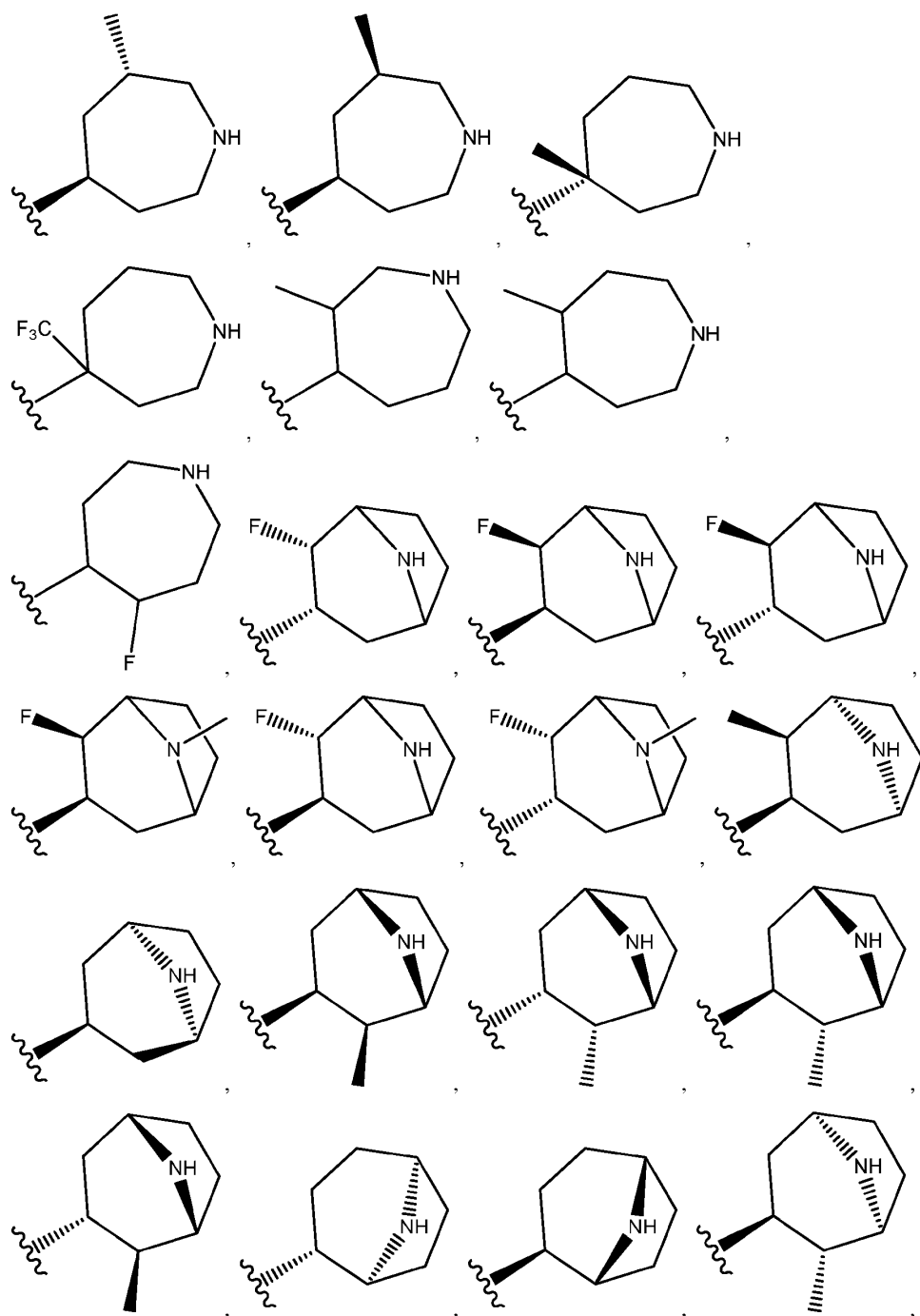
[0079] In some embodiments, Ring A is selected from the group consisting of ,

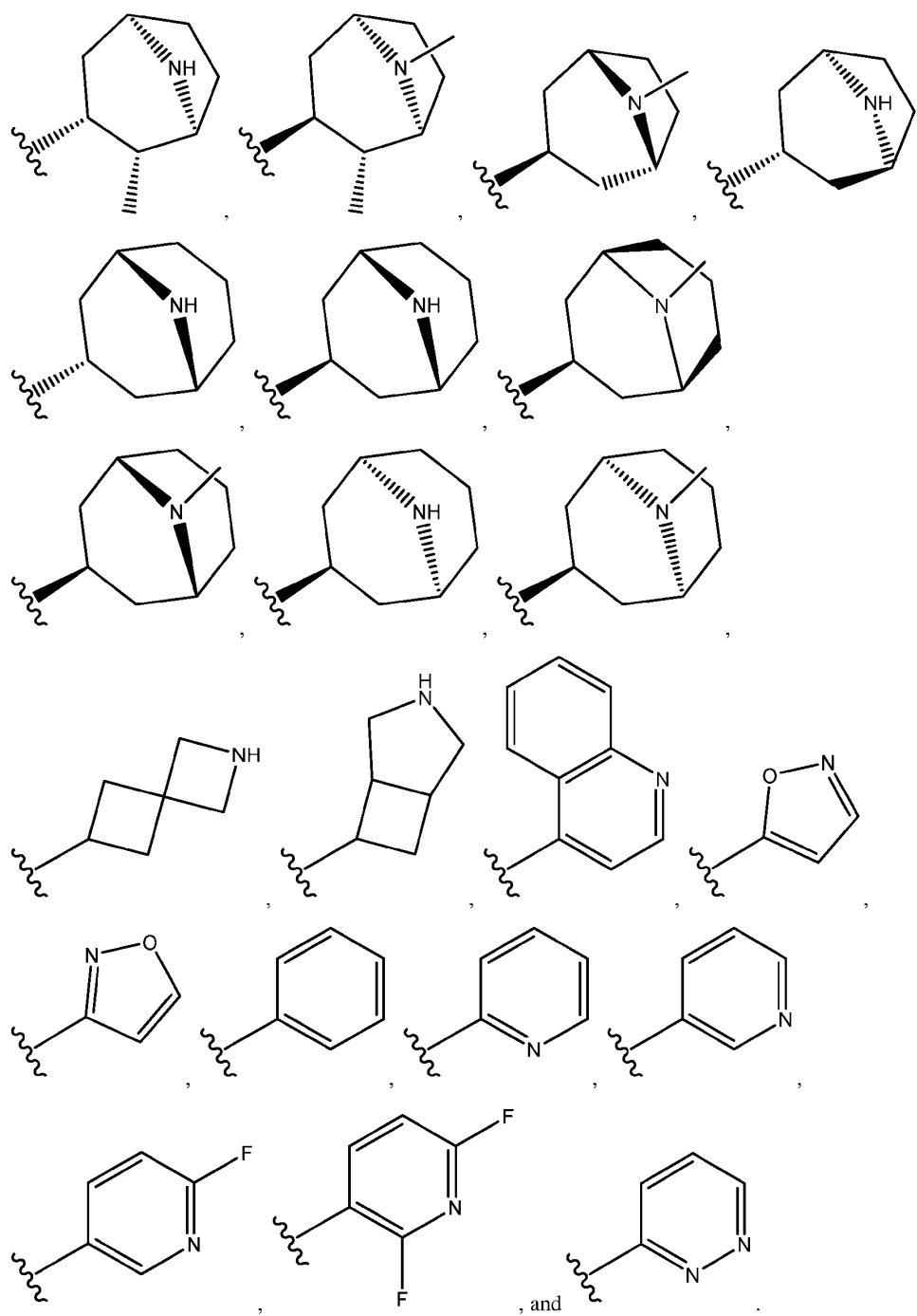


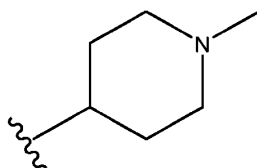












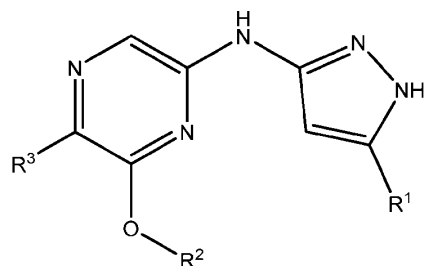
[0080] In certain embodiments, Ring A is

[0081] In some embodiments, R^a is selected from the group consisting of halo, OH, CN, $N(R^b)_2$, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy, or two R^a attached to the same atom, form a =O, wherein the C_1 - C_4 alkyl and C_1 - C_4 alkoxy are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of D, halo, OH, and CN. In some embodiments, R^a is selected from the group consisting of halo, OH, CN, $N(R^b)_2$, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy, or two R^a attached to the same atom, form a =O. In some embodiments, halo, OH, CN, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy, or two R^a , attached to the same atom, form a =O.

[0082] In some embodiments, R^a is selected from the group consisting of fluoro, chloro, OH, CN, methyl, ethyl, isopropyl, CD_3 , CD_2H , CDH_2 , CF_3 , CHF_2 , CH_2F , CH_2CN , methoxy, ethoxy, NH_2 , and two R^a , attached to the same atom, form a =O. In some embodiments, R^a is selected from the group consisting of fluoro, OH, cyano, methyl, CD_3 , CF_3 , isopropyl, methoxy, oxo, and NH_2 .

[0083] In some embodiments, n is 1.

[0084] In some embodiments, the compound is of Formula (Va),



(Va), or a pharmaceutically acceptable salt thereof,

wherein

R^1 is C_1 - C_4 alkyl or C_1 - C_4 alkoxy optionally substituted with 1 to 3 R^a , or 4 to 10-membered heterocyclyl having 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then optionally substituted on a ring carbon with 1 to 3 R^a ;

R^2 is Ring A selected from the group consisting of phenyl, 4 to 6-membered heterocyclyl, and 6-membered heteroaryl, wherein the phenyl is optionally substituted with 1 to 3 R^a , and 4 to 6-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a , wherein the 6-membered heteroaryl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, and N and then is optionally substituted on a ring carbon with 1 to 3 R^a ;

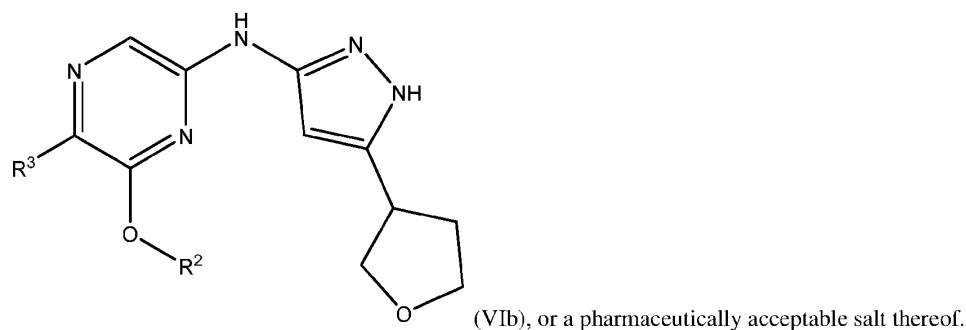
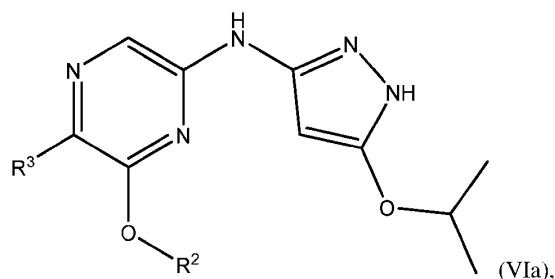
R^3 is H or C_1 - C_4 alkyl;

Each R^a is independently selected from the group consisting of halo, OH, CN, C_1 - C_4 alkyl, and C_1 -

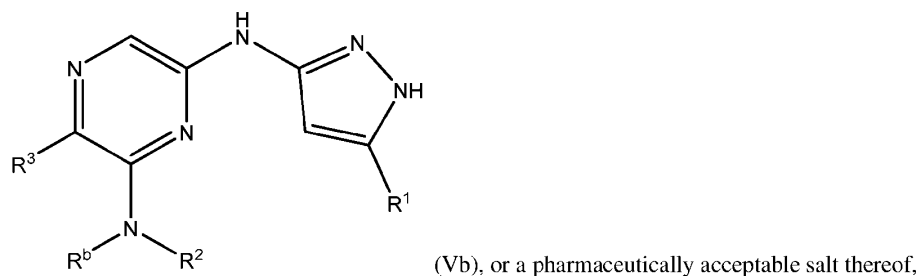
C_4 alkoxy, or two R^a , attached to the same atom, form a =O; and

Each R^b is independently H or C_1 - C_4 alkyl.

[0085] In some embodiments, the compound is of Formula (VIa) or (VIb),



[0086] In some embodiments, the compound is of Formula (Vb),



wherein

R^1 is C_1 - C_4 alkyl or C_1 - C_4 alkoxy optionally substituted with 1 to 3 R^a , or 4 to 10-membered heterocyclyl having 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N and NR^b and then optionally substituted on a ring carbon with 1 to 3 R^a ;

R^2 is Ring A selected from the group consisting of phenyl, 4 to 6-membered heterocyclyl, and 6-membered heteroaryl, wherein the phenyl is optionally substituted with 1 to 3 R^a , and 4 to 6-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a , wherein the 6-membered heteroaryl has 1 to 3 ring heteroatoms each independently selected

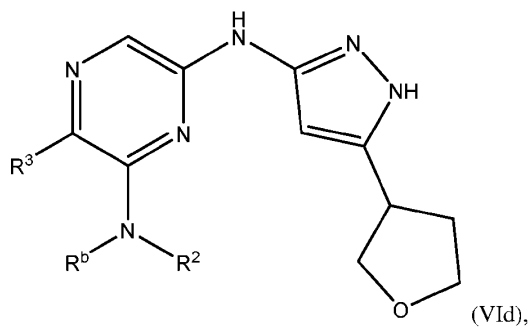
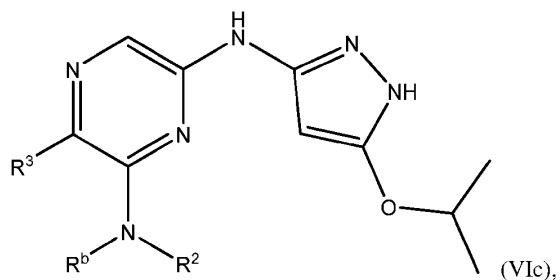
from the group consisting of O, S, and N and then is optionally substituted on a ring carbon with 1 to 3 R^a;

R³ is H or C₁-C₄alkyl;

Each R^a is independently selected from the group consisting of halo, OH, CN, C₁-C₄alkyl, and C₁-C₄alkoxy, or two R^a, attached to the same atom, form a =O; and

Each R^b is independently H or C₁-C₄alkyl.

[0087] In some embodiments, the compound is of Formula (VIc) or (VId),



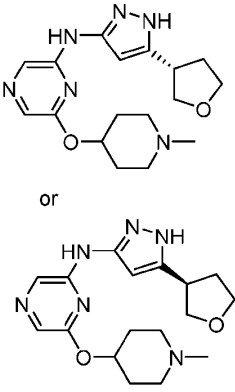
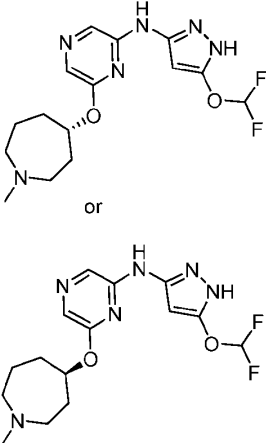
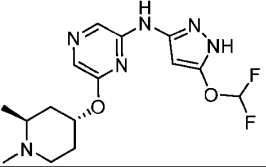
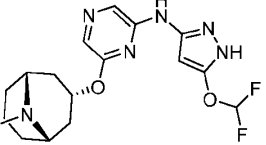
or a pharmaceutically acceptable salt thereof.

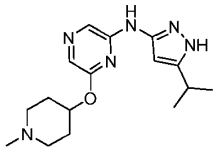
[0088] In some embodiments, R^b is selected from H and methyl.

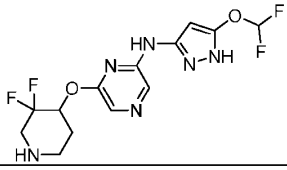
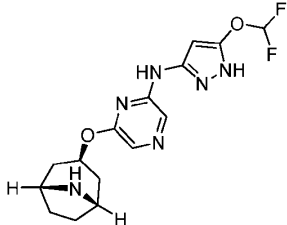
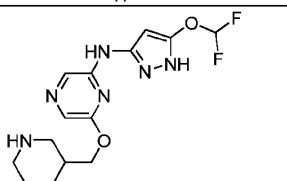
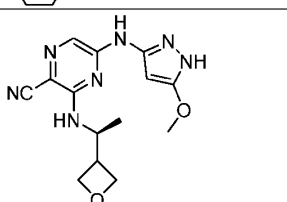
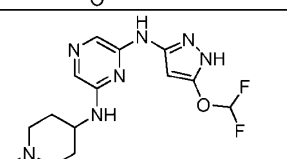
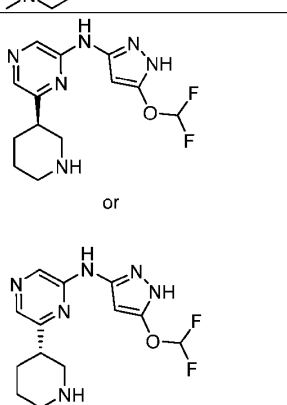
[0089] In one embodiment, the compound is a compound or a pharmaceutically acceptable salt thereof selected from the following two tables:

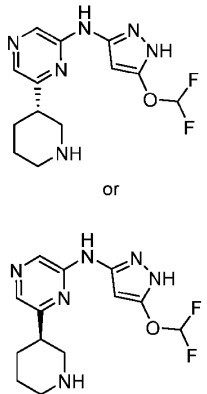
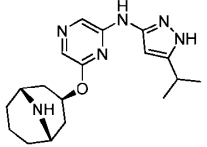
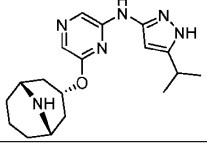
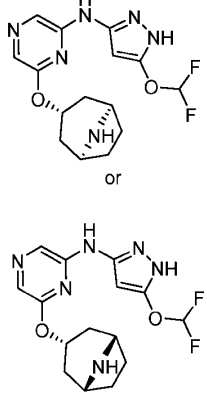
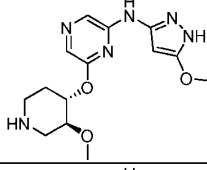
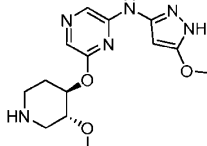
Example No.	Structure	Name	Scheme No.
1		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine	1
2		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((4-methylpiperidin-4-yl)oxy)pyrazin-2-amine	1

3		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine	1
4		6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine formate	1
5		6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine hydrochloride or 6-(((1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine hydrochloride	1
6		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-methoxypiperidin-4-yl)oxy)pyrazin-2-amine	1
7		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	1
8		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	2

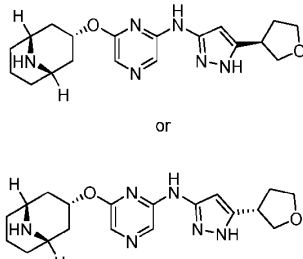
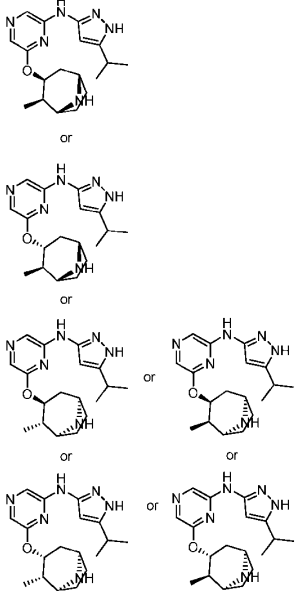
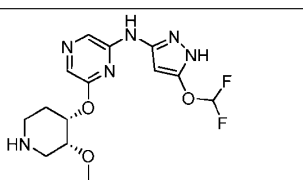
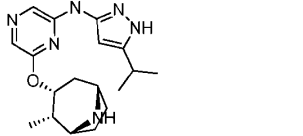
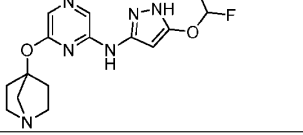
9		(S)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine formate or (R)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine formate	
10		(S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylazepan-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylazepan-4-yl)oxy)pyrazin-2-amine	2
11		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	6
12		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyrazin-2-amine	6

Ex. No.	Structure	Name	LCMS	Scheme No.
13		N-(5-isopropyl-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS: $m/z = 317$ $[M+H]^+$	2

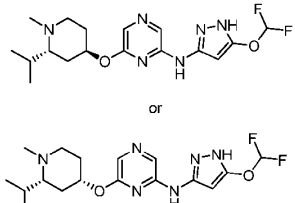
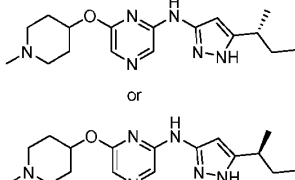
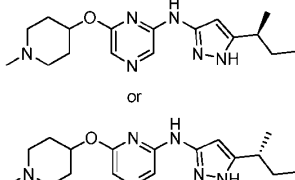
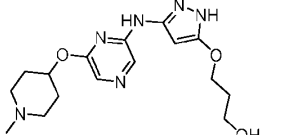
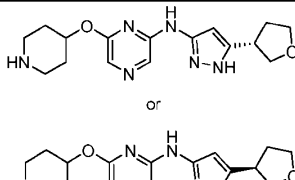
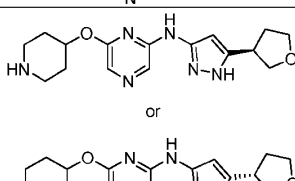
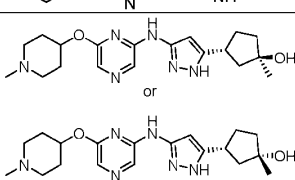
14		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-difluoropiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 363 [M+H] ⁺	1
15		Rac-6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 353 [M+H] ⁺	1
16		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-ylmethoxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
17		(S)-5-((5-methoxy-1H-pyrazol-3-yl)amino)-3-((1-(oxetan-3-yl)ethyl)amino)pyrazine-2-carbonitrile	LCMS m/z = 316 [M+H] ⁺	3
18		N2-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-N6-(1-methylpiperidin-4-yl)pyrazine-2,6-diamine	LCMS m/z = 340 [M+H] ⁺	1
19		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine	LCMS m/z = 411 [M+H] ⁺	4

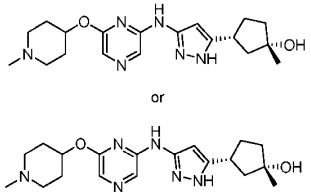
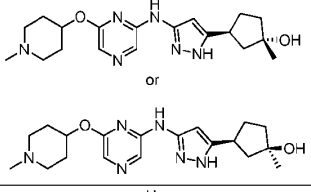
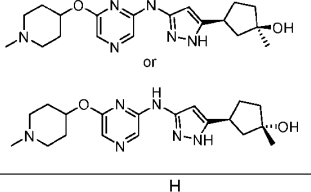
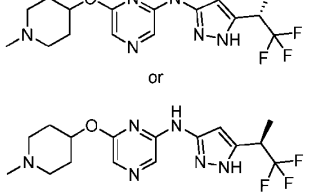
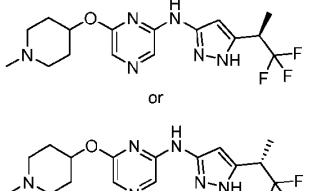
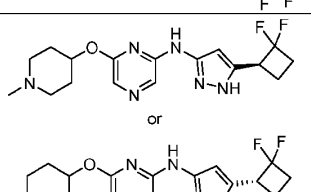
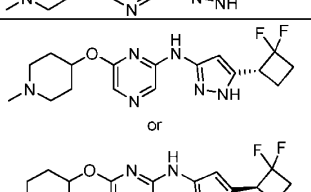
20		(S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine	LCMS m/z = 411 [M+H] ⁺	4
21		6-(((1R,3S,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 343 [M+H] ⁺	1
22		6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 343 [M+H] ⁺	1
23		6-(((1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 353 [M+H] ⁺	1
24		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methoxypiperidin-4-yl)oxy)pyrazin-2-amine	LCMS: m/z = 357 [M+H] ⁺	1
25		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methoxypiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 357 [M+H] ⁺	1

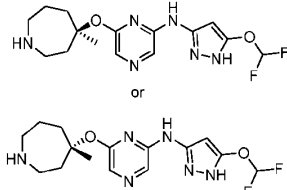
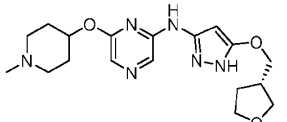
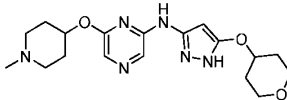
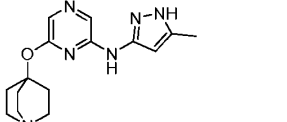
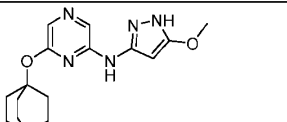
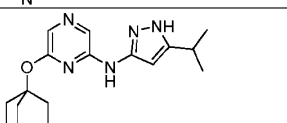
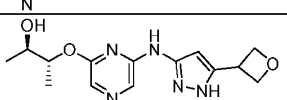
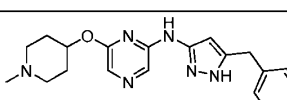
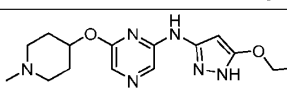
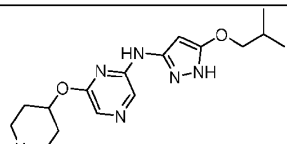
26		6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS: m/z = 367 [M+H] ⁺	1
27		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,3s,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyrazin-2-amine	LCMS: m/z = 381 [M+H] ⁺	6
28		(R)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or -(S)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS: m/z = 345 [M+H] ⁺	1
29		(S)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS: m/z = 345 [M+H] ⁺	1
30		6-(((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS: m/z = 385 [M+H] ⁺	6
31		6-(((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS: m/z = 385 [M+H] ⁺	6
32		6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS: m/z = 371 [M+H] ⁺	1

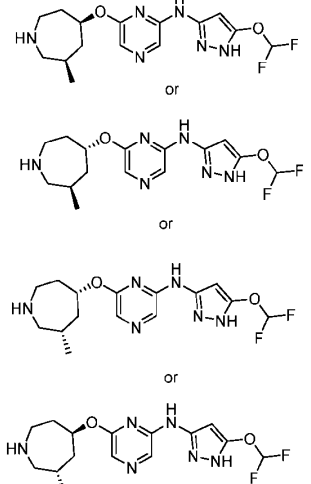
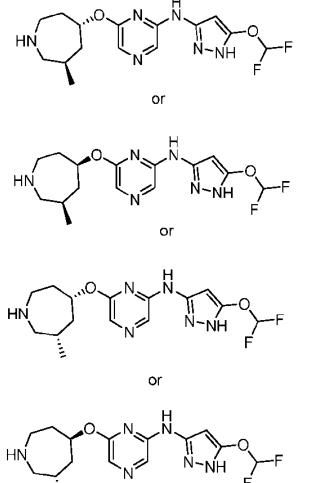
33		6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 371 [M+H] ⁺	1
34		N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 343 [M+H] ⁺	1
35		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methoxypiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 357 [M+H] ⁺	1
36		N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 343 [M+H] ⁺	1
37		6-((1-azabicyclo[2.2.1]heptan-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 339 [M+H] ⁺	2

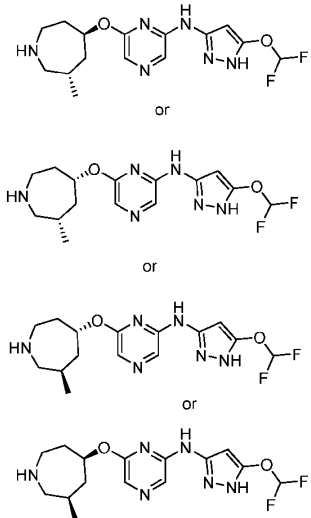
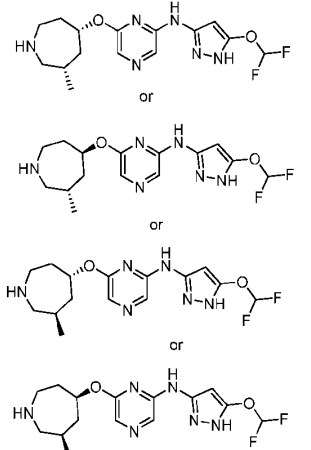
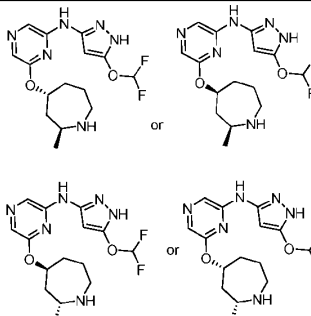
38		6-((2-azaspiro[3.3]heptan-6-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 339 [M+H] ⁺	1
39		6-((3-azabicyclo[3.2.0]heptan-6-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 339 [M+H] ⁺	1
40		N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 343 [M+H] ⁺	1
41		(S)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-((tetrahydrofuran-3-yl)methoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 375 [M+H] ⁺	5
42		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-isopropyl-1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-isopropyl-1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 383 [M+H] ⁺	6

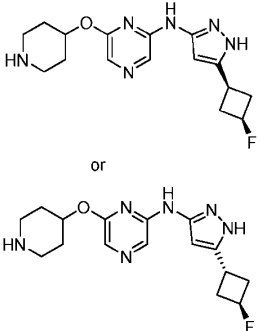
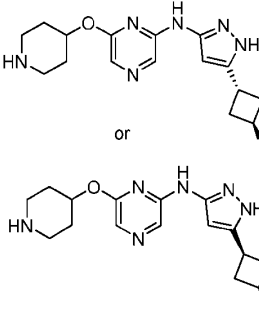
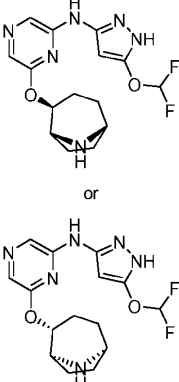
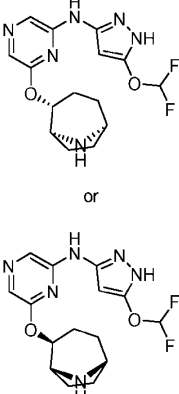
43		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-isopropyl-1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-isopropyl-1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 383 [M+H] ⁺	6
44		(R)-N-(5-(sec-butyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(sec-butyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 331 [M+H] ⁺	2
45		(S)-N-(5-(sec-butyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(sec-butyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 331 [M+H] ⁺	2
46		3-(((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)oxy)propan-1-ol	LCMS m/z = 349 [M+H] ⁺	5
47		(S)-6-(piperidin-4-yloxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-(piperidin-4-yloxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 331 [M+H] ⁺	1
48		(R)-6-(piperidin-4-yloxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-(piperidin-4-yloxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 331 [M+H] ⁺	1
49		(1R,3R)-1-methyl-3-(3-(((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-yl)cyclopentan-1-ol or (1S,3R)-1-methyl-3-(3-(((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-yl)cyclopentan-1-ol	LCMS m/z = 373 [M+H] ⁺	6

50		(1S,3R)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol or (1R,3R)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol	LCMS m/z = 373 [M+H] ⁺	6
51		(1S,3S)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol or (1R,3S)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol	LCMS m/z = 373 [M+H] ⁺	6
52		(1R,3S)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol or (1S,3S)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol	LCMS m/z = 373 [M+H] ⁺	6
53		(S)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 371 [M+H] ⁺	2
54		(R)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 371 [M+H] ⁺	2
55		(S)-N-(5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 365 [M+H] ⁺	2
56		(R)-N-(5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 365 [M+H] ⁺	2

57		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((4-methylazepan-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((4-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
58		(R)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-((tetrahydrofuran-3-yl)methoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 375 [M+H] ⁺	5
59		6-((1-methylpiperidin-4-yl)oxy)-N-(5-((tetrahydro-2H-pyran-4-yl)oxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 375 [M+H] ⁺	2A
60		N-(5-methyl-1H-pyrazol-3-yl)-6-(quinuclidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 301 [M+H] ⁺	2
61		N-(5-methoxy-1H-pyrazol-3-yl)-6-(quinuclidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 317 [M+H] ⁺	2
62		N-(5-isopropyl-1H-pyrazol-3-yl)-6-(quinuclidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 329 [M+H] ⁺	2
63		(2R,3R)-3-((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)butan-2-ol	LCMS m/z = 306 [M+H] ⁺	2
64		N-(5-benzyl-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 365 [M+H] ⁺	2
65		N-(5-ethoxy-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 319 [M+H] ⁺	2
66		N-(5-isobutoxy-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 347 [M+H] ⁺	2

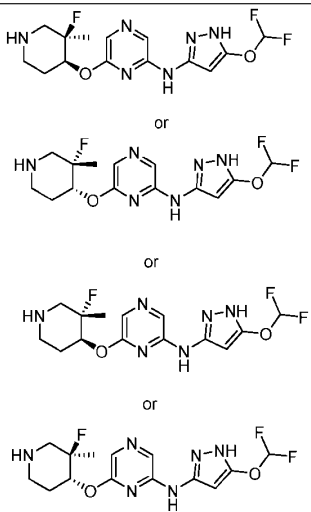
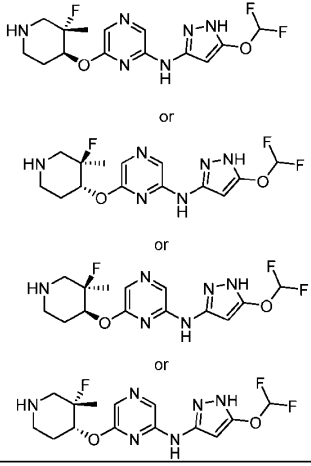
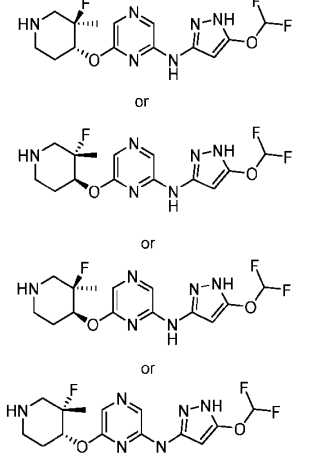
67		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
68		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1

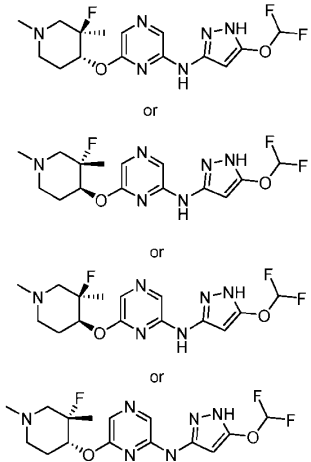
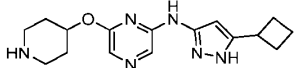
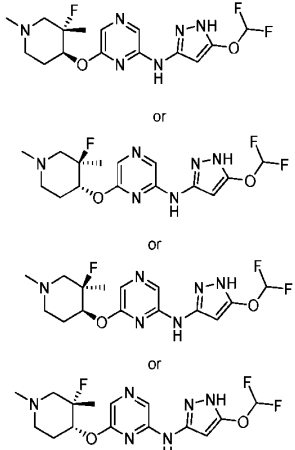
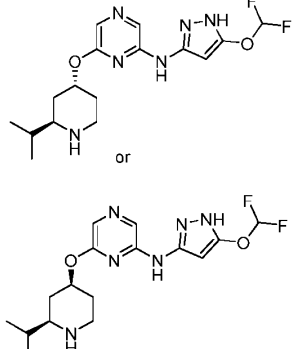
69		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
70		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
71		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-2-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-2-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS: m/z = 355 [M+H] ⁺	1

72	 or	N-(5-((1s,3s)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine or N-(5-((1r,3r)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 333 [M+H] ⁺	1
73	 or	N-(5-((1r,3r)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine or N-(5-((1s,3s)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 333 [M+H] ⁺	1
74	 or	6-(((1R,2S,5S)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1S,2R,5R)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 353 [M+H] ⁺	1
75	 or	6-(((1S,2R,5R)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1R,2S,5S)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 353 [M+H] ⁺	1

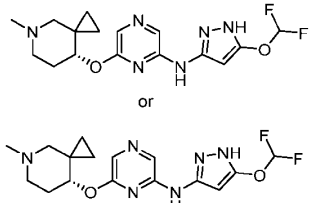
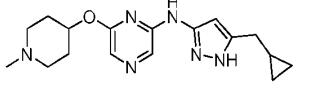
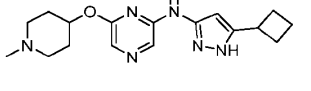
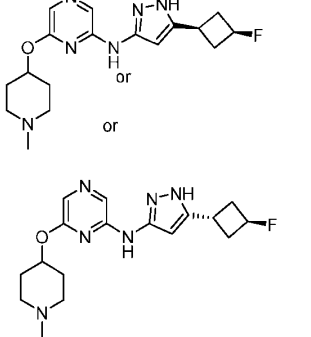
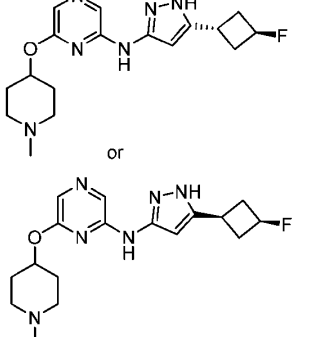
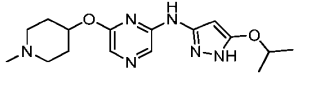
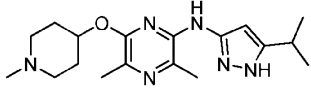
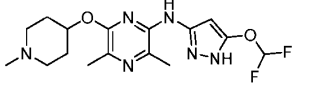
76		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(quinuclidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 353 [M+H] ⁺	2
77		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,3R,4S)-quinuclidin-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 353 [M+H] ⁺	2
78		(R)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclohexan-1-one or (S)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclohexan-1-one	LCMS m/z = 300 [M+H] ⁺	4
79		(S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
80		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
81		6-(((1R,3S)-3-aminocyclohexyl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
82		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-2-ethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-2-ethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1

83		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3-methyl-6-(piperidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
84		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-5-methyl-6-(piperidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
85		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,6R)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,6S)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
86		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,6S)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,6R)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
87		N-(5-(3,3-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 365 [M+H] ⁺	2
88		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3,5-dimethyl-6-(piperidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
89		N-(5-isopropyl-1H-pyrazol-3-yl)-3,5-dimethyl-6-(piperidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 331 [M+H] ⁺	1

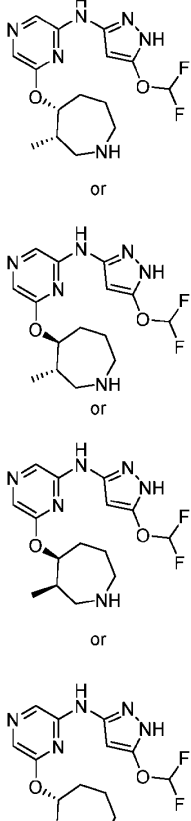
90		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 359 [M+H] ⁺	1
91		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 359 [M+H] ⁺	1
92		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 359 [M+H] ⁺	1

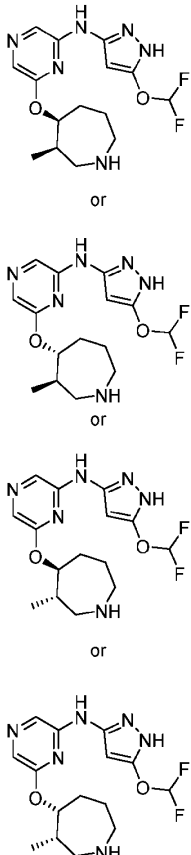
93		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 373 [M+H] ⁺	6
94		N-(5-(cyclobutyl)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 315 [M+H] ⁺	1
95		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 373 [M+H] ⁺	6
96		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-isopropylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-isopropylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 369 [M+H] ⁺	1

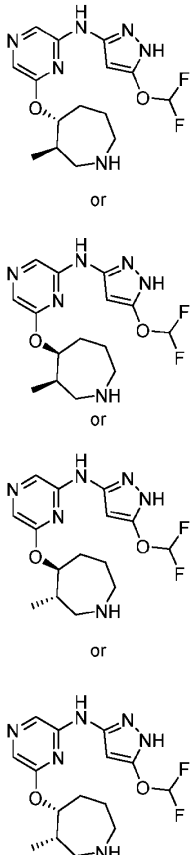
97		(R)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 345 [M+H] ⁺	2
98		N-(5-isobutyl-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 331 [M+H] ⁺	2
99		(S)-N-(5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 351 [M+H] ⁺	2
100		(R)-N-(5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 351 [M+H] ⁺	2
101		(S)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 353 [M+H] ⁺	1
102		(R)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 353 [M+H] ⁺	1
103		(S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-methyl-5-azaspiro[2.5]octan-8-yl)oxy)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-methyl-5-azaspiro[2.5]octan-8-yl)oxy)pyrazin-2-amine	LCMS m/z = 367 [M+H] ⁺	6

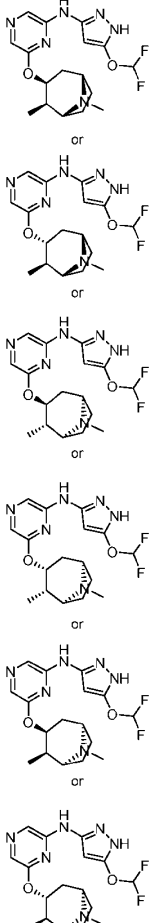
104		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-methyl-5-azaspiro[2.5]octan-8-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-methyl-5-azaspiro[2.5]octan-8-yl)oxy)pyrazin-2-amine	LCMS m/z = 367 [M+H] ⁺	6
105		N-(5-(cyclopropylmethyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 329 [M+H] ⁺	2
106		N-(5-(cyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 329 [M+H] ⁺	2
107		N-(5-((1s,3s)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-((1r,3r)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 347 [M+H] ⁺	2
108		N-(5-((1r,3r)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-((1s,3s)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 347 [M+H] ⁺	2
109		N-(5-isopropoxy-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 333 [M+H] ⁺	2
110		N-(5-isopropyl-1H-pyrazol-3-yl)-3,5-dimethyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 345 [M+H] ⁺	2
111		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3,5-dimethyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 369 [M+H] ⁺	2

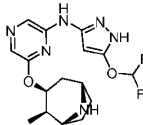
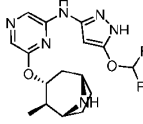
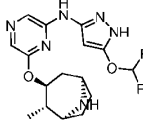
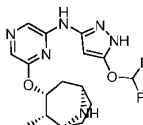
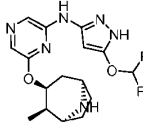
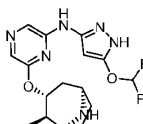
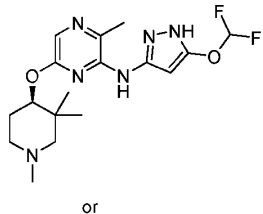
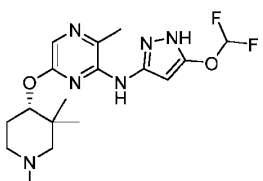
112		6-((1-methylpiperidin-4-yl)oxy)-N-(5-propyl-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 317 [M+H] ⁺	2
113		N-(5-ethyl-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 303 [M+H] ⁺	2
114		5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3-((1-methylpiperidin-4-yl)oxy)pyrazine-2-carbonitrile	LCMS m/z = 366 [M+H] ⁺	6
115	 or or or or	N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1

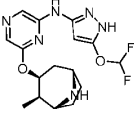
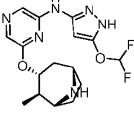
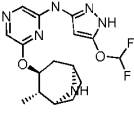
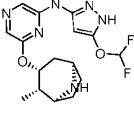
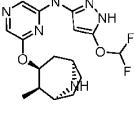
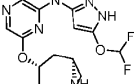
116		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H]⁺	1
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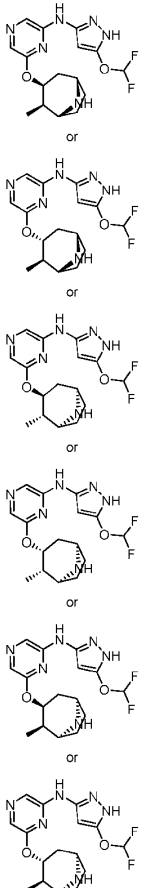
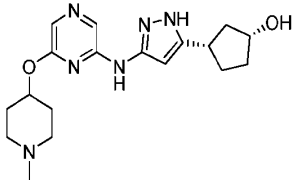
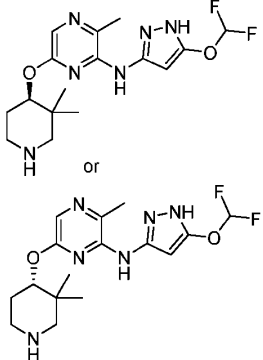
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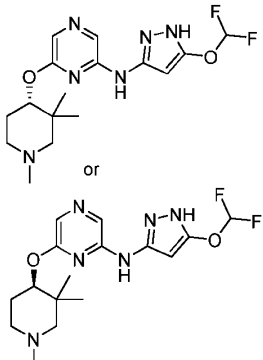
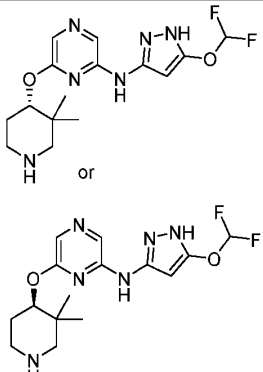
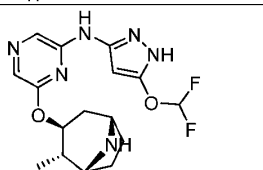
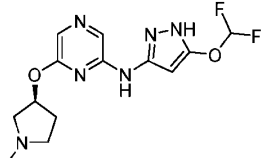
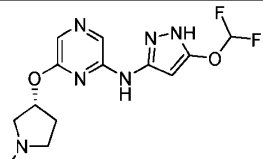
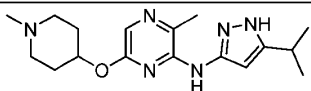
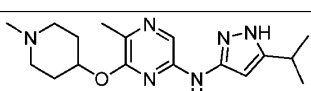
118	 or or or or	N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
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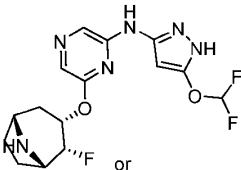
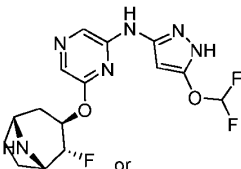
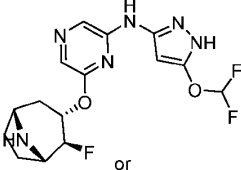
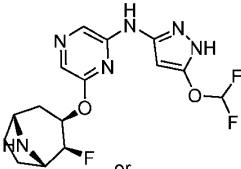
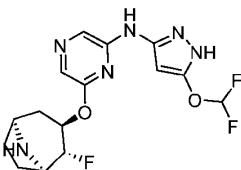
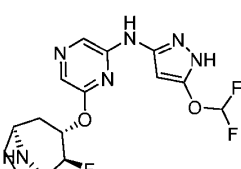
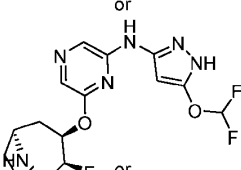
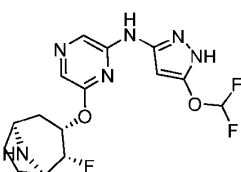
119		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 381 [M+H]⁺	6
120		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 367 [M+H]⁺	1

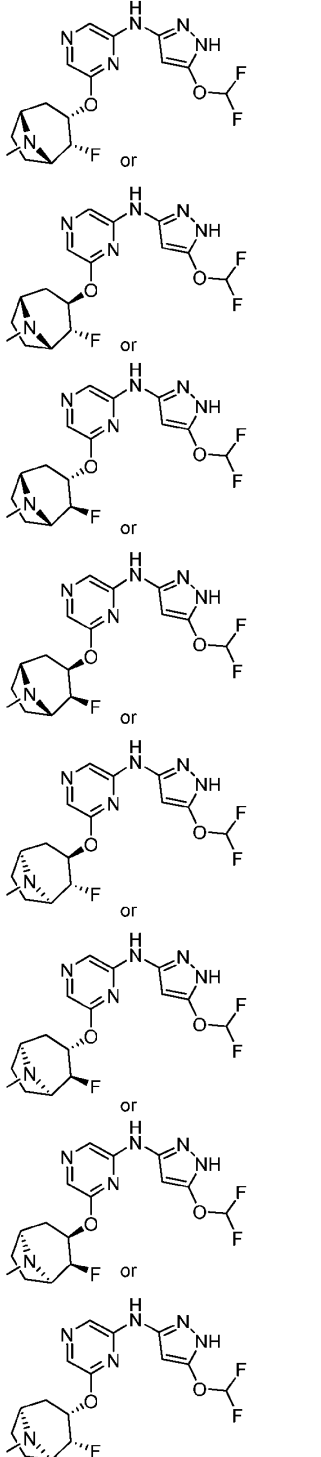
	 or  or  or  or  or 	6-(((1S,2R,3S,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine		
121	 or 	(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3-methyl-6-((1,3,3-trimethylpiperidin-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3-methyl-6-((1,3,3-trimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 383 [M+H] ⁺	6

122	 or  or  or  or  or 	N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 367 [M+H]⁺	1
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123		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 367 [M+H] ⁺	1
124		(1R,3S)-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol	LCMS m/z = 359 [M+H] ⁺	2A
125		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-dimethylpiperidin-4-yl)oxy)-3-methylpyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-dimethylpiperidin-4-yl)oxy)-3-methylpyrazin-2-amine	LCMS m/z = 369 [M+H] ⁺	1

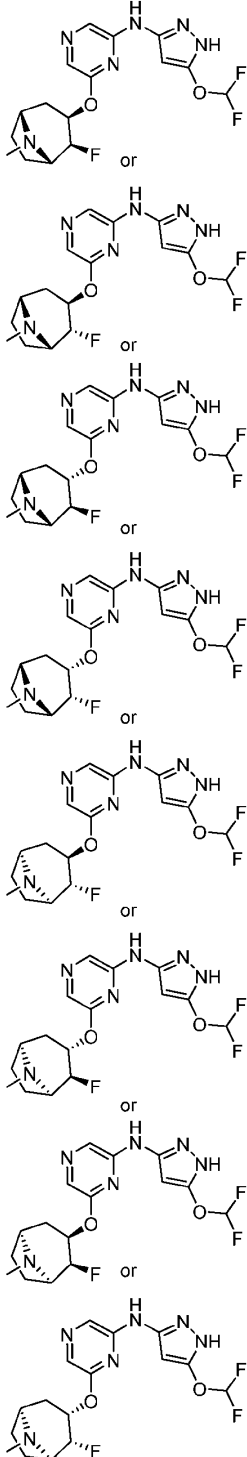
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127		(S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 359 [M+H] ⁺	1
128		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 367 [M+H] ⁺	1
129		(S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpyrrolidin-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 327 [M+H] ⁺	2
130		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpyrrolidin-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 327 [M+H] ⁺	2
131		N-(5-isopropyl-1H-pyrazol-3-yl)-3-methyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 331 [M+H] ⁺	2
132		N-(5-isopropyl-1H-pyrazol-3-yl)-5-methyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 331 [M+H] ⁺	2

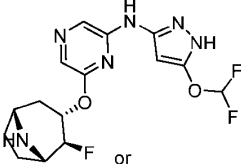
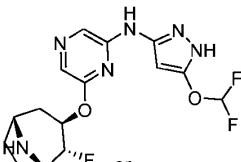
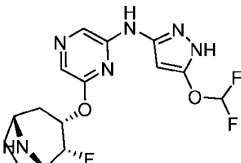
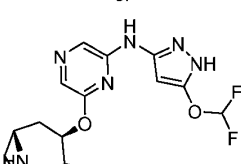
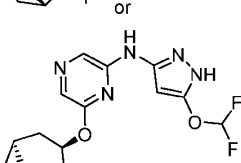
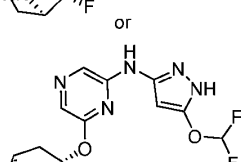
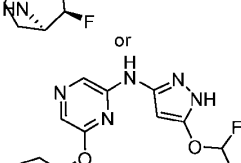
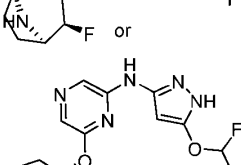
133	       	N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 371 [M+H]⁺	1
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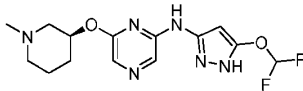
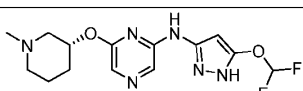
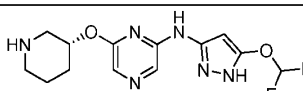
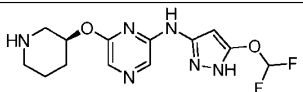
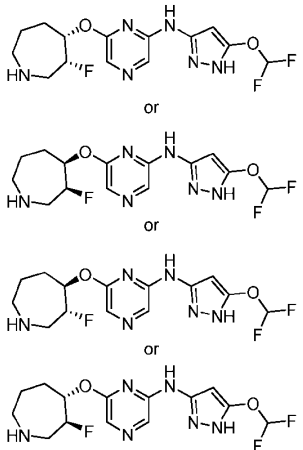
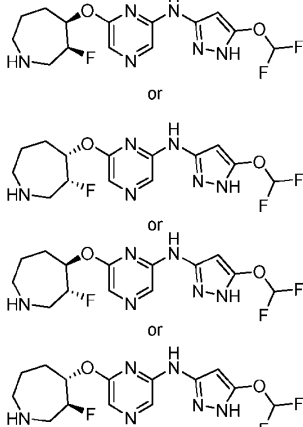
134		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 385 [M+H]⁺	6
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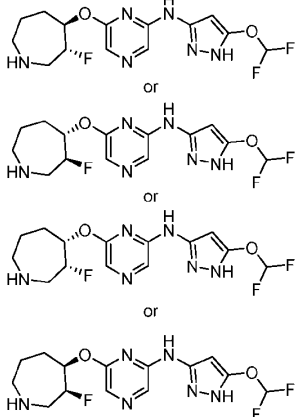
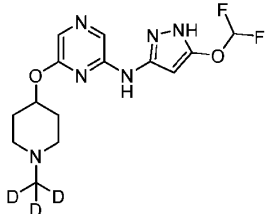
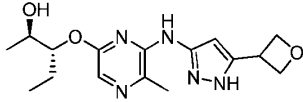
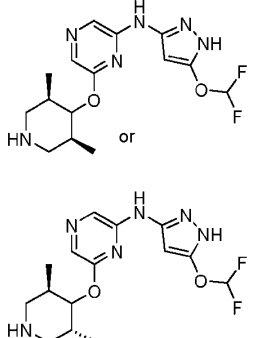
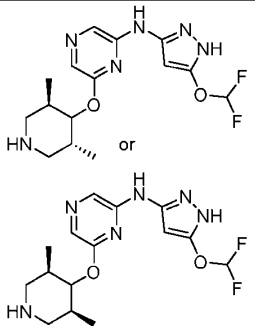
135		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 371 [M+H]⁺	1
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136		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 371[M+ H]⁺	1
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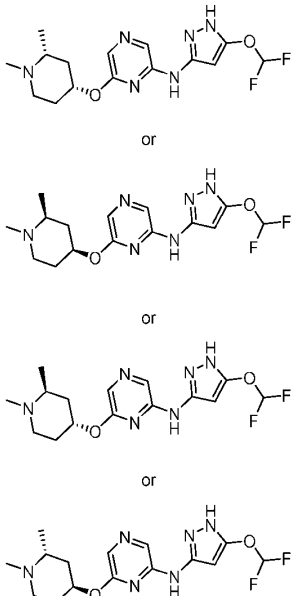
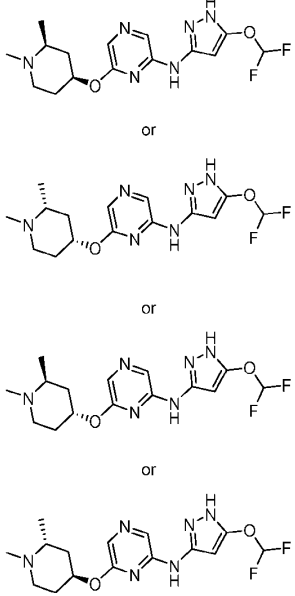
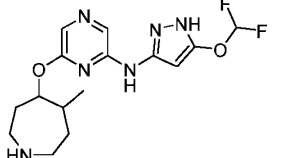
137		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 385 [M+H]⁺	6
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138	       	N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 371 [M+H]⁺	1
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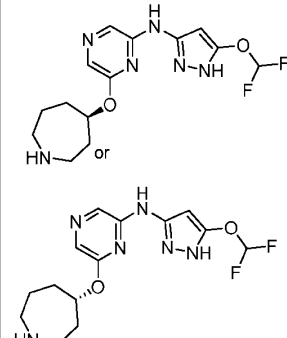
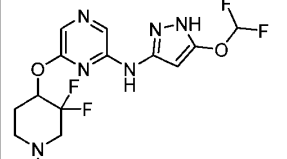
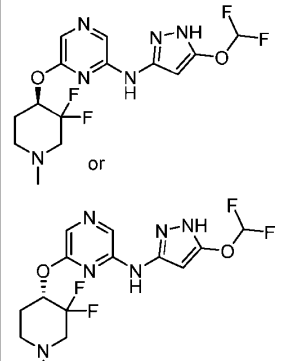
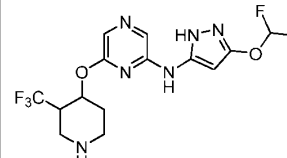
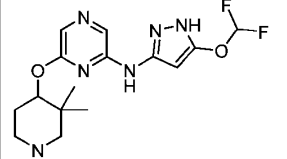
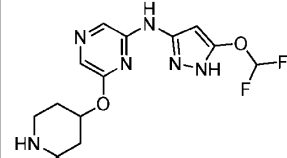
139		(S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	6
140		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	6
141		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yloxy)pyrazin-2-amine	LCMS m/z = 327 [M+H] ⁺	1
142		(S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yloxy)pyrazin-2-amine	LCMS m/z = 327 [M+H] ⁺	1
143		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 359 [M+H] ⁺	1
144		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 359 [M+H] ⁺	1

145		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 359 [M+H] ⁺	1
146		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-(methyl-d3)piperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 344 [M+H] ⁺	2
147		(2R,3R)-3-((5-methyl-6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol	LCMS m/z = 334 [M+H] ⁺	2
148		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = [M+H] ⁺	1
149		rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = [M+H] ⁺	1

150		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine	LCMS m/z = [M+H] ⁺	2
151		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylazepan-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	2
152		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((4-(trifluoromethyl)azepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 409 [M+H] ⁺	1
153		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
154		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-fluoroazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 359 [M+H] ⁺	1

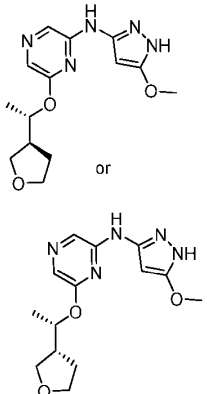
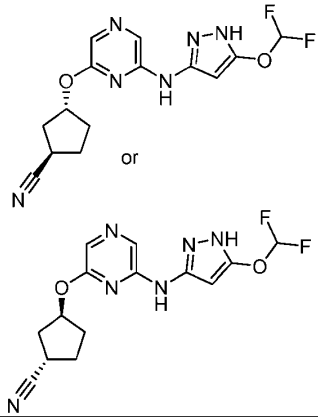
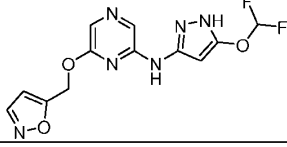
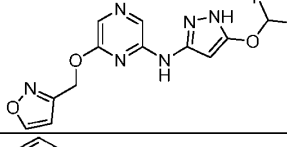
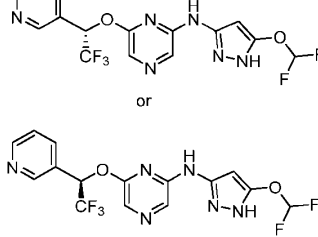
155		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	2
156		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	2
157		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-methylazepan-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1

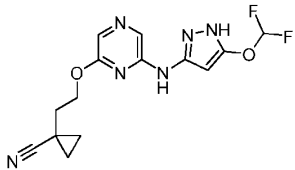
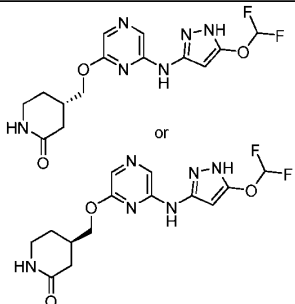
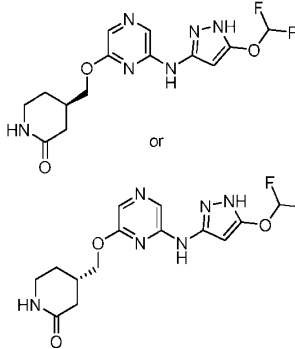
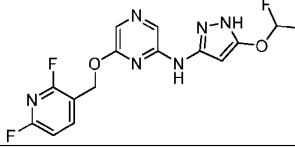
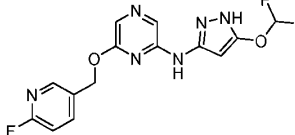
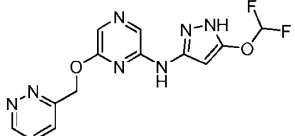
158		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
159		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
160		N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-(((3S,4S)-3-fluoro-1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 359 [M+H] ⁺	1
161		N-(5-(oxetan-3-yl)-1H-pyrazol-3-yl)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyrazin-2-amine	LCMS m/z = 332 [M+H] ⁺	2
162		(S)-6-(azepan-4-yloxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-(azepan-4-yloxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1

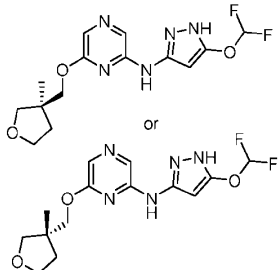
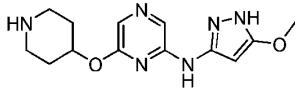
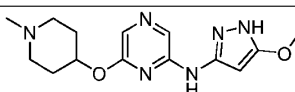
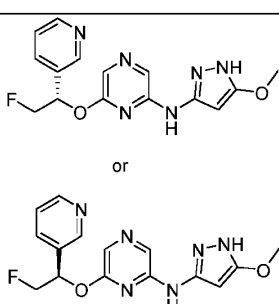
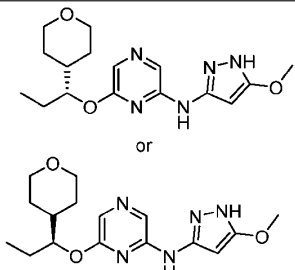
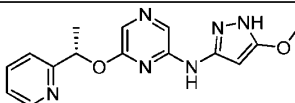
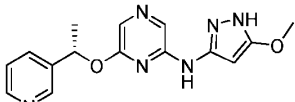
163		(R)-6-(azepan-4-yloxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-(azepan-4-yloxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
164		6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 377 [M+H] ⁺	2
165		(R)-6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 377 [M+H] ⁺	2
166		N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-((3-(trifluoromethyl)piperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 395 [M+H] ⁺	1
167		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
168		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1

169		(S)-N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-((3,3-difluoropiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 363 [M+H] ⁺	1
170		(R)-N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-((3,3-difluoropiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 363 [M+H] ⁺	1
171		rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine		1
172		rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine		1
173		rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,5S)-5-fluoro-3,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 373 [M+H] ⁺	1
174		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
175		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
176		(S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-ylmethoxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1

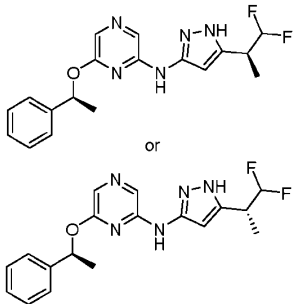
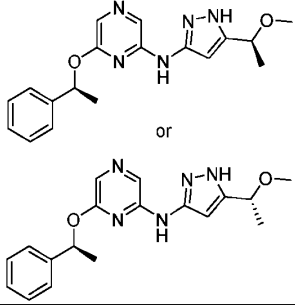
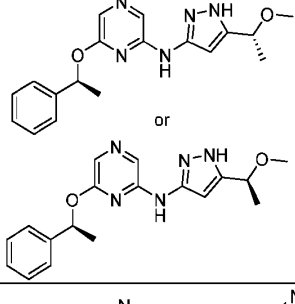
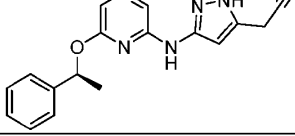
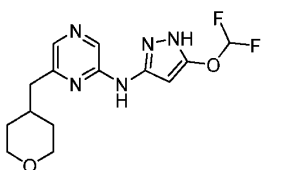
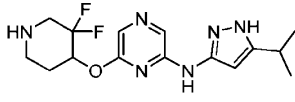
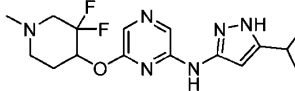
177		rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-4-methylpyrrolidin-3-yl)methoxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
178		6-(azepan-4-yloxy)-N-[5-(difluoromethoxy)-1H-pyrazol-3-yl]pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
179		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 341 [M+H] ⁺	1
180		N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-(((3S,4R)-3-fluoropiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 345 [M+H] ⁺	1
181		6-((3-azabicyclo[3.1.1]heptan-6-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 339 [M+H] ⁺	1
182		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-ylmethoxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
183		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4r,6R)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
184		Rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,6R)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 355 [M+H] ⁺	1
185		N-(5-methoxy-1H-pyrazol-3-yl)-6-(((S)-1-((S)-tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine or N-(5-	LCMS m/z =	

		methoxy-1H-pyrazol-3-yl)-6-((S)-1-((R)-tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine	306 [M+H] ⁺	
186		(1R,3R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)cyclopentane-1-carbonitrile or (1S,3S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)cyclopentane-1-carbonitrile	LCMS m/z = 337 [M+H] ⁺	2
187		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(isoxazol-5-ylmethoxy)pyrazin-2-amine	LCMS m/z = 325 [M+H] ⁺	2
188		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(isoxazol-3-ylmethoxy)pyrazin-2-amine	LCMS m/z = 325 [M+H] ⁺	2
189		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(2,2,2-trifluoro-1-(pyridin-3-yl)ethoxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(2,2,2-trifluoro-1-(pyridin-3-yl)ethoxy)pyrazin-2-amine	LCMS m/z = 403 [M+H] ⁺	2

190		1-(2-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)ethyl)cyclopropane-1-carbonitrile	LCMS m/z = 337 [M+H] ⁺	2
191		(S)-4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidin-2-one or (R)-4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidin-2-one	LCMS m/z = 355 [M+H] ⁺	2
192		(R)-4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidin-2-one or (S)-4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidin-2-one	LCMS m/z = 355 [M+H] ⁺	2
193		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,6-difluoropyridin-3-yl)methoxy)pyrazin-2-amine	LCMS m/z = 371 [M+H] ⁺	2
194		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((6-fluoropyridin-3-yl)methoxy)pyrazin-2-amine	LCMS m/z = 353 [M+H] ⁺	2
195		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(pyridazin-3-yl)methoxy)pyrazin-2-amine	LCMS m/z = 336 [M+H] ⁺	2

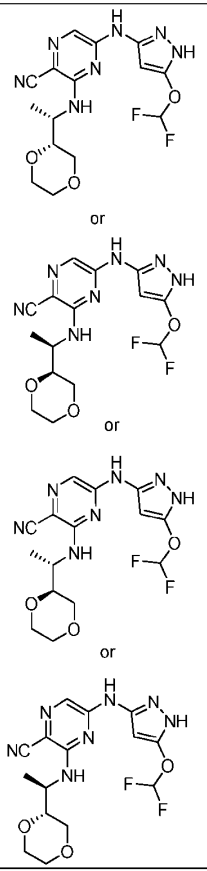
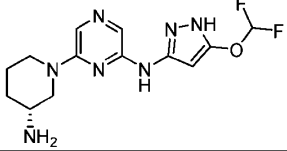
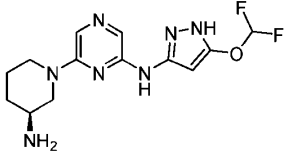
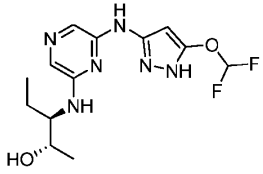
196		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3-methyltetrahydrofuran-3-yl)methoxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3-methyltetrahydrofuran-3-yl)methoxy)pyrazin-2-amine	LCMS m/z = 342 [M+H] ⁺	2
197		N-(5-methoxy-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 291 [M+H] ⁺	1
198		N-(5-methoxy-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 305 [M+H] ⁺	2
199		(S)-6-(2-fluoro-1-(pyridin-3-yl)ethoxy)-N-(5-methoxy-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-(2-fluoro-1-(pyridin-3-yl)ethoxy)-N-(5-methoxy-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 331 [M+H] ⁺	2
200		(R)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)propoxy)pyrazin-2-amine or (S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)propoxy)pyrazin-2-amine	LCMS m/z = 334 [M+H] ⁺	2
201		(S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridin-2-yl)ethoxy)pyrazin-2-amine	LCMS m/z = 313 [M+H] ⁺	2
202		(S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridin-3-yl)ethoxy)pyrazin-2-amine	LCMS m/z = 313 [M+H] ⁺	2

203		(S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridazin-3-yl)ethoxy)pyrazin-2-amine or (R)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridazin-3-yl)ethoxy)pyrazin-2-amine	LCMS m/z = 314 [M+H] ⁺	2
204		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((S)-1-((R)-tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((S)-1-((S)-tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine	LCMS m/z = 342 [M+H] ⁺	2
205		(2S,3S)-3-((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol or (2S,3R)-3-((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol	LCMS m/z = 320 [M+H] ⁺	2
206		N-(5-((R)-1,1-difluoropropan-2-yl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine or N-(5-((S)-1,1-difluoropropan-2-yl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine	LCMS m/z = 360 [M+H] ⁺	2

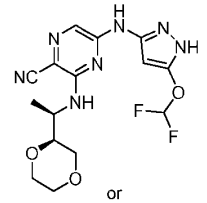
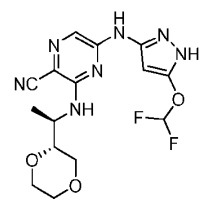
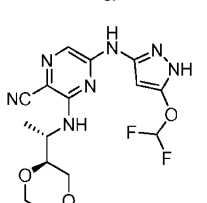
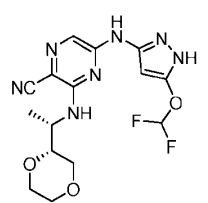
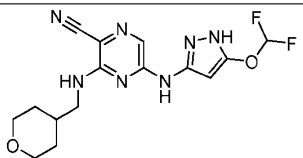
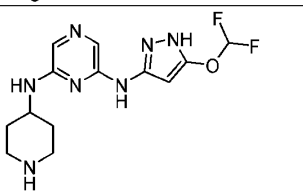
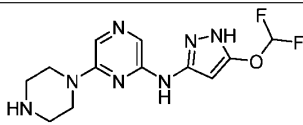
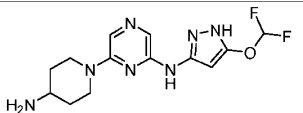
207		N-(5-((S)-1,1-difluoropropan-2-yl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine or N-(5-((R)-1,1-difluoropropan-2-yl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine	LCMS m/z = 360 [M+H] ⁺	2
208		N-(5-((S)-1-methoxyethyl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine or N-(5-((R)-1-methoxyethyl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine	LCMS m/z = 340 [M+H] ⁺	2
209		N-(5-((R)-1-methoxyethyl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine or N-(5-((S)-1-methoxyethyl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine	LCMS m/z = 340 [M+H] ⁺	2
210		(S)-2-(3-((6-(1-phenylethoxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)acetonitrile	LCMS m/z = 321 [M+H] ⁺	6
211		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((tetrahydro-2H-pyran-4-yl)methyl)pyrazin-2-amine	LCMS m/z = 326 [M+H] ⁺	4
212		6-((3,3-difluoropiperidin-4-yl)oxy)-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 339 [M+H] ⁺	1
213		6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z =	2

			353 [M+H] ⁺	
214		(R)-N-(5-isopropyl-1H-pyrazol-3-yl)-6-((1-methylpyrrolidin-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 303 [M+H] ⁺	2
215		(S)-N-(5-isopropyl-1H-pyrazol-3-yl)-6-((1-methylpyrrolidin-3-yl)oxy)pyrazin-2-amine	LCMS m/z = 303 [M+H] ⁺	2
216		Rac-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((2S,4S)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine or rac-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((2S,4R)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine	LCMS m/z = 317 [M+H] ⁺	1
217		N-(5-isopropyl-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine	LCMS m/z = 303 [M+H] ⁺	1
218		(2R,3R)-3-(((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol or (2R,3S)-3-(((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol	LCMS m/z = 320 [M+H] ⁺	2
219		(S)-6-(1-phenylethoxy)-N-(5-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 364 [M+H] ⁺	2
220		(S)-N-(5-(cyclopropylmethoxy)-1H-pyrazol-3-yl)-6-(1-phenylethoxy)pyrazin-2-amine	LCMS m/z = 352 [M+H] ⁺	2
221		(S)-3-(((6-(1-phenylethoxy)pyrazin-2-yl)amino)-1H-pyrazole-5-carbonitrile	LCMS m/z = 307 [M+H] ⁺	2

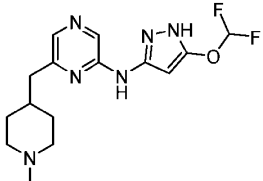
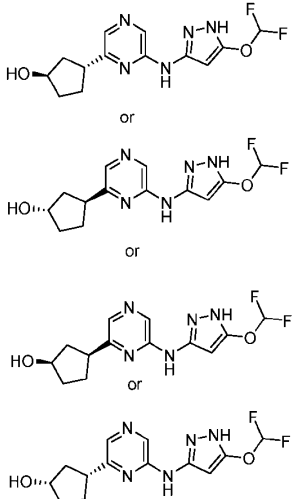
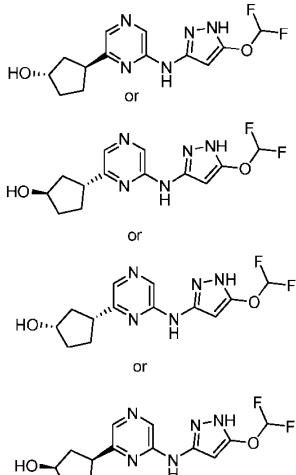
222		(S)-N-(5-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-6-(1-phenylethoxy)pyrazin-2-amine	LCMS m/z = 336 [M+H] ⁺	2
223		(S)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-6-(1-phenylethoxy)pyrazin-2-amine	LCMS m/z = 322 [M+H] ⁺	2
224		(S)-6-(1-phenylethoxy)-N-(5-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 366 [M+H] ⁺	2
225		3-cyclopropyl-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(pentan-3-yloxy)pyrazin-2-amine	LCMS m/z = 330 [M+H] ⁺	2
226		3-ethyl-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(pentan-3-yloxy)pyrazin-2-amine	LCMS m/z = 318 [M+H] ⁺	2
227		6-(benzyloxy)-5-ethyl-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 338 [M+H] ⁺	2

228		3-(((R)-1-((S)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((R)-1-((R)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((S)-1-((S)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((S)-1-((R)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile	LCMS m/z = 382 [M+H] ⁺	3
229		(R)-6-(3-aminopiperidin-1-yl)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 326 [M+H] ⁺	1
230		(S)-6-(3-aminopiperidin-1-yl)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 326 [M+H] ⁺	1
231		(2S,3R)-3-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)amino)pentan-2-ol	LCMS m/z = 329 [M+H] ⁺	2

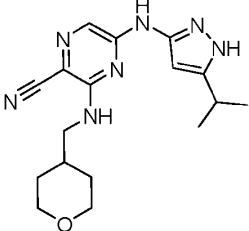
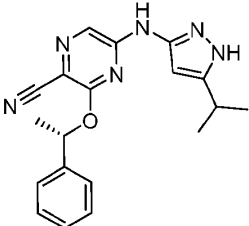
232		N2-benzyl-N6-(5-isopropyl-1H-pyrazol-3-yl)-3-(methylsulfonyl)pyrazine-2,6-diamine	LCMS m/z = 387 [M+H] ⁺	6
233		(3-(benzylamino)-5-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)(imino)(methyl)-16-sulfanone	LCMS m/z = 386 [M+H] ⁺	2
234		(R)-5-((5-ethyl-1H-pyrazol-3-yl)amino)-3-((1-(oxetan-3-yl)ethyl)amino)pyrazine-2-carbonitrile or (S)-5-((5-ethyl-1H-pyrazol-3-yl)amino)-3-((1-(oxetan-3-yl)ethyl)amino)pyrazine-2-carbonitrile	LCMS m/z = 314 [M+H] ⁺	3
235		(R)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3-((1-(pyridazin-3-yl)ethyl)amino)pyrazine-2-carbonitrile or (S)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3-((1-(pyridazin-3-yl)ethyl)amino)pyrazine-2-carbonitrile	LCMS m/z = 398 [M+H] ⁺	3
236		(R)-5-((5-methoxy-1H-pyrazol-3-yl)amino)-3-((1-(pyridazin-3-yl)ethyl)amino)pyrazine-2-carbonitrile or (S)-5-((5-methoxy-1H-pyrazol-3-yl)amino)-3-((1-(pyridazin-3-yl)ethyl)amino)pyrazine-2-carbonitrile	LCMS m/z = 338 [M+H] ⁺	3
237		(S)-3-(((1,4-dioxan-2-yl)methyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile	LCMS m/z = 368 [M+H] ⁺	3
238		3-(((R)-1-((S)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((R)-1-((R)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((S)-1-((S)-1,4-dioxan-2-	LCMS m/z = 382 [M+H] ⁺	3

	 or  or  or 	yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((S)-1-((R)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile		
239		5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3-(((tetrahydro-2H-pyran-4-yl)methyl)amino)pyrazine-2-carbonitrile	LCMS m/z = 366 [M+H] ⁺	3
240		N2-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-N6-(1-methylpiperidin-4-yl)pyrazine-2,6-diamine	LCMS m/z = 326 [M+H] ⁺	1
241		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperazin-1-yl)pyrazin-2-amine	LCMS m/z = 312 [M+H] ⁺	1
242		6-(4-aminopiperidin-1-yl)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 326 [M+H] ⁺	1

243		6-(1,4-diazepan-1-yl)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	LCMS m/z = 326 [M+H] ⁺	1
244		N2-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-N6-methyl-N6-(piperidin-4-yl)pyrazine-2,6-diamine	LCMS m/z = 340 [M+H] ⁺	1
245		N2-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-N6-methyl-N6-(1-methylpiperidin-4-yl)pyrazine-2,6-diamine	LCMS m/z = 354 [M+H] ⁺	2
246		(R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazin-2-amine	LCMS m/z = 340 [M+H] ⁺	2
247		(S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazin-2-amine	LCMS m/z = 340 [M+H] ⁺	4
248		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-4-ylmethyl)pyrazin-2-amine	LCMS m/z = 325 [M+H] ⁺	4

249		N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)methyl)pyrazin-2-amine	LCMS m/z = 339 [M+H] ⁺	4
250		(1S,3S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1R,3R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1S,3R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1R,3S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol	LCMS m/z = 312 [M+H] ⁺	4
251		(1S,3R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1R,3S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or 1S,3S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1R,3R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol	LCMS m/z = 312 [M+H] ⁺	6

252		(1R,3S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1S,3R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1R,3S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1R,3R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol	LCMS m/z = 312 [M+H] ⁺	6
253		N-(5-isopropyl-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine	LCMS m/z = 287 [M+H] ⁺	4
254		3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-one	LCMS m/z = 286 [M+H] ⁺	4
255		rac-(1R,3S)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or rac-(1R,3R)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol	LCMS m/z = 288 [M+H] ⁺	6
256		rac-(1R,3R)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or rac-(1R,3S)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol	LCMS m/z = 288 [M+H] ⁺	6
257		(S)-N-(5-Isopropyl-1H-pyrazol-3-yl)-6-(1-phenylethoxy)pyrazin-2-amine	LCMS m/z = 324 [M+H] ⁺	2

258		5-((5-Isopropyl-1H-pyrazol-3-yl)amino)-3-(((tetrahydro-2H-pyran-4-yl)methyl)amino)pyrazine-2-carbonitrile	342 [M+H] ⁺	3
259		(S)-5-((5-Isopropyl-1H-pyrazol-3-yl)amino)-3-(1-phenylethoxy)pyrazine-2-carbonitrile	LCMS m/z = 349 [M+H] ⁺	3

[0090] Previous Examples 78 and 211 have been intentionally excluded, and previous Examples 257 and 258 have been renumbered as Examples 78 and 211, respectively. New Examples 257, 258, and 259 have been added.

[0091] The term “pharmaceutically acceptable salt” refers to a pharmaceutical salt that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, and allergic response, and is commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.* describes pharmacologically acceptable salts in *J. Pharm. Sci.*, 1977, 66, 1–19.

[0092] Included in the present teachings are pharmaceutically acceptable salts of the compounds disclosed herein. Compounds having basic groups can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically acceptable acid addition salts of the compounds described herein include salts of inorganic acids (such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids) and of organic acids (such as acetic, benzenesulfonic, benzoic, ethanesulfonic, methanesulfonic, and succinic acids). Compounds of the present teachings with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

[0093] Compounds having one or more chiral centers can exist in various stereoisomeric forms, *i.e.*, each chiral center can have an *R* or *S* configuration, or can be a mixture of both. Stereoisomers are compounds that differ only in their spatial arrangement. Stereoisomers include all diastereomeric and enantiomeric forms of a compound. Enantiomers are stereoisomers that are mirror images of

each other. Diastereomers are stereoisomers having two or more chiral centers that are not identical and are not mirror images of each other.

[0094] When the stereochemical configuration at a chiral center in a compound having one or more chiral centers is depicted by its chemical name (*e.g.*, where the configuration is indicated in the chemical name by “*R*” or “*S*”) or structure (*e.g.*, the configuration is indicated by “wedge” bonds), the enrichment of the indicated configuration relative to the opposite configuration is greater than 50%, 60%, 70%, 80%, 90%, 99% or 99.9% (except when the designation “rac” or “racemate” accompanies the structure or name, as explained in the following two paragraphs). “Enrichment of the indicated configuration relative to the opposite configuration” is a mole percent and is determined by dividing the number of compounds with the indicated stereochemical configuration at the chiral center(s) by the total number of all of the compounds with the same or opposite stereochemical configuration in a mixture.

[0095] When the stereochemical configuration at a chiral center in a compound is depicted by chemical name (*e.g.*, where the configuration is indicated in the name by “*R*” or “*S*”) or structure (*e.g.*, the configuration is indicated by “wedge” bonds) and the designation “rac” or “racemate” accompanies the structure or is designated in the chemical name, a racemic mixture is intended.

[0096] When two stereoisomers are depicted by their chemical names or structures, and the names or structures are connected by an “or”, one or the other of the two stereoisomers is intended, but not both.

[0097] When a disclosed compound having a chiral center is depicted by a structure without showing a configuration at that chiral center, the structure is meant to encompass the compound with the *S* configuration at that chiral center, the compound with the *R* configuration at that chiral center, or the compound with a mixture of the *R* and *S* configuration at that chiral center. When a disclosed compound having a chiral center is depicted by its chemical name without indicating a configuration at that chiral center with “*S*” or “*R*”, the name is meant to encompass the compound with the *S* configuration at that chiral center, the compound with the *R* configuration at that chiral center or the compound with a mixture of the *R* and *S* configuration at that chiral center.

[0098] A racemic mixture means a mixture of 50% of one enantiomer and 50% of its corresponding enantiomer. The present teachings encompass all enantiomerically-pure, enantiomerically-enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures, and diastereomeric mixtures of the compounds disclosed herein.

[0099] Enantiomeric and diastereomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and diastereomers can also

be obtained from diastereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

[00100] “Peak 1” in the Experimental section refers to an intended reaction product compound obtained from a chromatography separation/purification that elutes earlier than a second intended reaction product compound from the same preceding reaction. The second intended product compound is referred to as “peak 2”.

[00101] When a disclosed compound is designated by a name or structure that indicates a single enantiomer, unless indicated otherwise, the compound is at least 60%, 70%, 80%, 90%, 99% or 99.9% optically pure (also referred to as “enantiomerically pure”). Optical purity is the weight in the mixture of the named or depicted enantiomer divided by the total weight in the mixture of both enantiomers.

[00102] When the stereochemistry of a disclosed compound is named or depicted by structure, and the named or depicted structure encompasses more than one stereoisomer (*e.g.*, as in a diastereomeric pair), it is to be understood that, unless otherwise indicated, one of the encompassed stereoisomers or any mixture of the encompassed stereoisomers are included. It is to be further understood that the stereoisomeric purity of the named or depicted stereoisomers is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight. The stereoisomeric purity in this case is determined by dividing the total weight in the mixture of the stereoisomers encompassed by the name or structure by the total weight in the mixture of all of the stereoisomers.

[00103] In the compounds of the disclosure, any position specifically designated as “D” or “deuterium” is understood to have deuterium enrichment at 50, 80, 90, 95, 98 or 99%. “Deuterium enrichment” is a mole percent and is determined by dividing the number of compounds with deuterium at the indicated position by the total number of all of the compounds. When a position is designated as “H” or “hydrogen”, the position has hydrogen at its natural abundance. When a position is silent as to whether hydrogen or deuterium is present, the position has hydrogen at its natural abundance. One specific alternative embodiment is directed to a compound of the disclosure having deuterium enrichment of at least 5, 10, 25, 50, 80, 90, 95, 98 or 99% at one or more positions not specifically designated as “D” or “deuterium”.

[00104] As used herein, many moieties (*e.g.*, alkyl, alkoxy, cycloalkyl or heterocyclyl) are referred to as being either “substituted” or “optionally substituted”. When a moiety is modified by one of these terms, unless otherwise noted, it denotes that any portion of the moiety that is known to one skilled in the art as being available for substitution can be substituted, which includes one or more substituents. Where if more than one substituent is present, then each substituent may be independently selected. Such means for substitution are well-known in the art and/or taught by the instant disclosure. The optional substituents can be any substituents that are suitable to attach to the moiety.

[00105] Compounds of the disclosure are CDK2 inhibitors. As used herein, the term “selective CDK2 inhibitor” means a compound which selectively inhibits CDK2 over other CDKs and the kinome. Said another way, a selective CDK2 inhibitor has no or low activity against other CDKs and the kinome. A selective CDK2 inhibitor’s inhibitory activity against CDK2 is more potent in terms of IC_{50} value (*i.e.*, the IC_{50} value is subnanomolar) when compared with its inhibitory activity against other CDKs and many other kinases. Potency can be measured using known biochemical assays.

[00106] In some embodiments, the compounds of the disclosure are selective against CDK2 versus CDK1. In some such embodiments, compounds show at least 10-fold selectivity for CDK2 versus CDK1. In other embodiments, compounds show at least 20-fold selectivity for CDK2 versus CDK1. In specific embodiments, compounds show at least 30-fold selectivity for CDK2 versus CDK1. In certain embodiments, compounds show at least 40-fold selectivity for CDK2 versus CDK1. In other embodiments, compounds show at least 50-fold selectivity for CDK2 versus CDK1. For example, compounds show at least 100-fold selectivity for CDK2 versus CDK1. In some embodiments, the compounds of the invention are selective against CDK2 versus CDK4 and/or CDK6. In some such embodiments, compounds show at least 10-fold selectivity for CDK2 versus CDK4 and/or CDK6. In other embodiments, compounds show at least 20-fold selectivity for CDK2 versus CDK4 and/or CDK6. In specific embodiments, compounds show at least 30-fold selectivity for CDK2 versus CDK4 and/or CDK6.

[00107] Some compounds of the disclosure have the advantage of good metabolic stability. One indicator of good metabolic stability is high microsomal stability. Hepatic metabolism is a predominant route of elimination for small molecule drugs. The clearance of compounds by hepatic metabolism can be assessed in vitro using human liver microsomes (HLMs) or human hepatocytes. Compounds are incubated with HLMs plus appropriate co-factors or human hepatocytes and compound depletion is measured to determine an in vitro intrinsic clearance (Cl_{int}). The Cl_{int} is scaled to total body clearance (CL), and a hepatic extraction ratio (ER) is determined by dividing CL to standard human hepatic blood flow. Compounds that have a low hepatic extraction ratio are considered to have good metabolic stability. In some embodiments, a compound of the disclosure has a calculated ER of <0.3, <0.4, <0.5, <0.6. In some embodiments, a compound of the disclosure may eliminate certain side effects, for example, drug-drug interactions.

Pharmaceutical Compositions

[00108] Pharmaceutical compositions of the disclosure (also referred to herein as the “disclosed pharmaceutical compositions”) comprise one or more pharmaceutically acceptable carrier(s) or diluent(s) and a compound of the disclosure (*e.g.*, a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId)), or a pharmaceutically acceptable salt thereof.

[00109] “Pharmaceutically acceptable carrier” and “pharmaceutically acceptable diluent” refer to a substance that aids the formulation and/or administration of an active agent to and/or absorption by a subject and can be included in the pharmaceutical compositions of the disclosure without causing a significant adverse toxicological effect on the subject. Non-limiting examples of pharmaceutically acceptable carriers and/or diluents include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer’s solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, hydroxymethylcellulose, fatty acid esters, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with or interfere with the activity of the compounds provided herein. One of ordinary skill in the art will recognize that other pharmaceutical excipients are suitable for use with disclosed compounds or pharmaceutically acceptable salts thereof.

[00110] The pharmaceutical compositions of the disclosure optionally include one or more pharmaceutically acceptable carriers and/or diluents therefor, such as lactose, starch, cellulose and dextrose. Other excipients, such as flavoring agents, sweeteners, and preservatives, such as methyl, ethyl, propyl and butyl parabens, can also be included. More complete listings of suitable excipients can be found in the Handbook of Pharmaceutical Excipients (5th Ed., Pharmaceutical Press (2005)). A person skilled in the art would know how to prepare formulations suitable for various types of administration routes. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington’s Pharmaceutical Sciences (2003 - 20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999. The carriers, diluents and/or excipients are “acceptable” in the sense of being compatible with the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

Methods of Treatment

[00111] The compounds disclosed herein inhibit CDK2 and therefore are useful for treating diseases for which CDK2 is dysregulated, such as cancer. The present disclosure provides a method of inhibiting CDK2 in a subject in need thereof, comprising administering to the subject an effective amount of a compound disclosed herein, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein.

[00112] In some embodiments, the disclosure provides a method of treating a disease or disorder associated with CDK2 in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I) or any of the formulas as described herein, or a

pharmaceutically acceptable salt thereof. In some embodiments, the disease or disorder associated with CDK2 is associated with an amplification of the cyclin E1 (CCNE1) gene and/or overexpression of CCNE1. In some embodiments, the disease or disorder is cancer.

[00113] Subjects “in need of inhibiting CDK2” are those having a disease for which a beneficial therapeutic effect can be achieved by inhibiting CDK2, *e.g.*, a slowing in disease progression, alleviation of one or more symptoms associated with the disease or increasing the longevity of the subject in view of the disease.

[00114] In some embodiments, the disclosure provides a method of treating a disease/condition/or cancer associated with or modulated by CDK2, wherein the inhibition of CDK2 is of therapeutic benefit, including but not limited to the treatment of cancer in a subject in need thereof. The method comprises administering to the subject an effective amount of a compound disclosed herein, a pharmaceutically acceptable salt thereof, or pharmaceutical composition disclosed herein.

[00115] In another embodiment, the disclosure provides a method of treating a subject with cancer, comprising administering to the subject an effective amount of a compound disclosed herein, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein. In another embodiment, the cancer is characterized by amplification and/or overexpression of CCNE1 or CCNE2.

[00116] Accordingly, in some embodiments of the methods, the subject or patient has been previously determined to have an amplification of the cyclin E1 (CCNE1) gene and/or an expression level of CCNE1 in a biological sample obtained from the subject or patient that is higher than a control expression level of CCNE1.

[00117] In another embodiment, the disclosure provides a method for inhibiting growth of tumor (*e.g.*, cancer) cells *in vitro*. The method includes contacting the tumor (*e.g.*, cancer) cells *in vitro* with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId) or a pharmaceutically acceptable salt thereof. In another embodiment, the present disclosure provides a method for inhibiting growth of tumor (*e.g.*, cancer) cells with CCNE1 amplification and/or overexpression in a subject or a patient. The method includes administering to the subject or patient in need thereof a therapeutically effective amount of a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof.

[00118] In another embodiment, the disclosure provides a method of treating a subject with cancer, comprising administering to the subject an effective amount of a compound disclosed herein, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein in conjunction with other agents or standard cancer treatments, as described below.

[00119] As used herein “cancer” refers to any malignant and/or invasive growth or tumor caused by abnormal cell growth. Cancer includes solid tumors named for the type of cells that form them, cancer of blood, bone marrow, or the lymphatic system. Examples of solid tumors include sarcomas

and carcinomas. Cancers of the blood include, but are not limited to, leukemia, lymphoma and myeloma. Cancer also includes primary cancer that originates at a specific site in the body, a metastatic cancer that has spread from the place in which it started to other parts of the body, a recurrence from the original primary cancer after remission, and a second primary cancer that is a new primary cancer in a person with a history of previous cancer of a different type from the latter one. In some such embodiments, the cancer is characterized by amplification and/or overexpression of CCNE1 and/or CCNE2.

[00120] Cancers to be treated according to the disclosed methods include breast cancer, ovarian cancer, bladder cancer, uterine cancer (e.g., uterine carcinosarcoma), prostate cancer (e.g., androgen receptor (AR)-dependent and AR-independent), lung cancer (including NSCLC, SCLC, squamous cell carcinoma (e.g., lung squamous cell carcinoma (LUSC), or adenocarcinoma (e.g., lung adenocarcinoma (LUAD)), esophageal cancer, head and neck cancer, colorectal cancer (e.g., colon cancer, colorectal adenocarcinoma (COADREAD)), kidney cancer (including RCC), liver cancer (including HCC), pancreatic cancer (including pancreatic adenocarcinoma (PAAD) and pancreatic ductal adenocarcinoma (PDAC)), stomach (i.e., gastric) cancer, urothelial cancer, brain cancers, mesothelioma (MESO), skin cancer (e.g., melanoma), sarcoma, or thyroid cancer, including metastasis (in particular brain metastasis) of all cancers listed. In one embodiment, the cancer is uterine cancer (including uterine carcinosarcoma (UCS), uterine corpus endometrial carcinoma (UCEC)), endometrial cancer (including serous endometrial cancer (SEC)), breast cancer (including breast invasive carcinoma (BRCA), TNBC (triple negative breast cancer), HR+ breast cancer (hormone receptor positive breast cancer), ER+ breast cancer (estrogen receptor positive breast cancer), HR+/HER2- breast cancer (hormone receptor positive, human epidermal growth factor 2 negative breast cancer), ER+/HER2- breast cancer (estrogen receptor positive, human epidermal growth factor 2 negative breast cancer), PR+/HER2- breast cancer (progesterone receptor positive, human epidermal growth factor 2 negative breast cancer), HER2- breast cancer (human epidermal growth factor 2 negative breast cancer), HER2-low breast cancer (human epidermal growth factor 2 low breast cancer), and HER2+ breast cancer (human epidermal growth factor 2 positive breast cancer), ovarian cancer (e.g. ovarian serous cystadenocarcinoma (OV) and high grade serous ovarian cancer (HGSOC)), stomach cancer (including stomach adenocarcinoma (STAD)), gastric cancer (including gastrointestinal stromal tumor), colorectal cancer, pancreatic cancer (including pancreatic adenocarcinoma (PAAD) and pancreatic ductal adenocarcinoma (PDAC)), kidney cancer, head and neck cancer, liver cancer, prostate cancer (including androgen receptor (AR)-dependent, AR-independent, and castration-resistant prostate cancer (CRPC)), skin cancer, leukemia (including AML (acute myeloid leukemia)), lymphoma (including B-cell lymphoma), myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), sarcoma (SARC), esophageal cancer (including esophageal carcinoma (ESCA)), bladder cancer (including bladder urothelial carcinoma), lung cancer (including lung squamous carcinoma, small cell lung cancer (SCLC) and non-small cell lung cancer

(NSCLC), e.g., EGFRm (epidermal growth factor receptor mutant)+ non-small cell lung cancer), cholangiocarcinoma, adrenocortical carcinoma (ACC), or mesothelioma. In some embodiments, the cancer is characterized by at overexpression and/or amplification of CCNE1 and/or CCNE2 described herein. In some embodiments of the methods provided herein, the subject is identified as having a cancer characterized by amplification and/or overexpression of CCNE1 and/or CCNE2.

[00121] In further embodiments of the methods provided herein, the cancer is breast cancer, ovarian cancer, bladder cancer, uterine cancer, prostate cancer, lung cancer, esophageal cancer, liver cancer, pancreatic cancer or stomach cancer. In some such embodiments, the cancer is characterized by amplification and/or overexpression of CCNE1 and/or CCNE2.

[00122] In further embodiments, of the methods provided herein, the cancer is selected from the group consisting of breast cancer (including ER+/HER2- breast cancer, HR+/HER2- breast cancer, PR+/HER2- breast cancer, and triple negative breast cancer), endometrial cancer, esophageal cancer, gastric cancer, ovarian cancer, pancreatic cancer (including PDAC), and prostate cancer (including androgen receptor positive (AR+) prostate cancer). In some embodiments of the methods provided herein, the cancer is selected from the group consisting of ovarian cancer, endometrial cancer, gastric cancer, esophageal cancer, triple negative breast cancer, and lung adenosarcoma. In some embodiments, the cancer is characterized by CCNE1 overexpression and/or amplification. In some embodiments, the cancer has progressed despite platinum treatment.

[00123] In some embodiments, the cancer is platinum-resistant and/or platinum-refractory. In some embodiments, the cancer has progressed despite platinum treatment.

[00124] In some embodiments, the cancer is an adenocarcinoma, carcinoma, or cystadenocarcinoma.

[00125] In other embodiments, the cancer is breast cancer, including, e.g., ER-positive/HR-positive, HER2-negative breast cancer; ER-positive/HR-positive, HER2-positive breast cancer; triple negative breast cancer (TNBC); or inflammatory breast cancer. In some embodiments, the breast cancer is chemotherapy or radiotherapy resistant breast cancer, endocrine resistant breast cancer, trastuzumab resistant breast cancer, or breast cancer demonstrating primary or acquired resistance to CDK4/CDK6 inhibition. In some embodiments, the breast cancer is advanced or metastatic breast cancer. In some embodiments of each of the foregoing, the breast cancer is characterized by amplification and/or overexpression of CCNE1 and/or CCNE2.

[00126] In some embodiments, the cancer is HR-positive breast cancer. In some embodiments, the breast cancer is ER-positive breast cancer. In some embodiments, the breast cancer is HR-positive, HER2-negative breast cancer. In some embodiments, the breast cancer is ER-positive, HER2-negative breast cancer. In some embodiments, the breast cancer is PR-positive, HER2-negative breast cancer. In some embodiments, the breast cancer is responsive to treatment with a CDK4/6 inhibitor. In some embodiments, the breast cancer is resistant to treatment with a CDK4/6 inhibitor. In some

embodiments, the breast cancer has progressed despite treatment with a CDK4/6 inhibitor. In some embodiments, the CDK4/6 inhibitor is palbociclib. In some embodiments, the CDK4/6 inhibitor is ribociclib. In some embodiments, the breast cancer has progressed despite first treatment with palbociclib, ribociclib, and/or fulvestrant and second treatment with abemaciclib and/or fulvestrant. In some embodiments, the method further comprises administering an effective amount of a CDK4/6 inhibitor. In some embodiments, the CDK4/6 inhibitor is selected from palbociclib and ribociclib, or a combination thereof. In some embodiments, the CDK4/6 inhibitor is ribociclib. In some embodiments, the breast cancer has CCNE amplification and/or overexpression.

[00127] In some embodiments, the breast cancer is triple negative breast cancer.

[00128] In some embodiments, the cancer is ovarian cancer. In some such embodiments, the cancer is ovarian cancer characterized by amplification and/or overexpression of CCNE1 and/or CCNE2. In some such embodiments, the cancer is (a) ovarian cancer; (b) characterized by amplification and/or overexpression of cyclin E1 (CCNE1) or cyclin E2 (CCNE2); or (c) both (a) and (b). In some embodiments, the ovarian cancer is high grade serous ovarian cancer (HGSOC).

[00129] In some embodiments, the cancer is endometrial cancer. In some such embodiments, the cancer is endometrial cancer characterized by amplification and/or overexpression of CCNE1 and/or CCNE2. In some such embodiments, the cancer is (a) endometrial cancer; (b) characterized by amplification and/or overexpression of cyclin E1 (CCNE1) or cyclin E2 (CCNE2); or (c) both (a) and (b). In some embodiments, the endometrial cancer is serous endometrial cancer (SEC). In some embodiments, the cancer is CCNE1-amplified ovarian cancer or CCNE1-amplified endometrial cancer.

[00130] In some embodiments, the cancer is lung cancer. In some such embodiments, the cancer is lung cancer characterized by amplification and/or overexpression of CCNE1 and/or CCNE2. In some such embodiments, the cancer is (a) lung cancer; (b) characterized by amplification and/or overexpression of cyclin E1 (CCNE1) or cyclin E2 (CCNE2); or (c) both (a) and (b). In some embodiments, the lung cancer is non-small cell lung cancer (NSCLC). In some embodiments, the lung cancer is small cell lung cancer (SCLC).

[00131] In some embodiments, the compound of the disclosure is administered as first line therapy. In other embodiments, the compound of the disclosure is administered as second (or later) line therapy. In some embodiments, the compound of the disclosure is administered as second (or later) line therapy following treatment with an endocrine therapeutic agent and/or a CDK4/CDK6 inhibitor. In some embodiments, the compound of the disclosure is administered as second (or later) line therapy following treatment with an endocrine therapeutic agent, e.g., an aromatase inhibitor, a SERM or a SERD. In some embodiments, the compound of the disclosure is administered as second (or later) line therapy following treatment with a CDK4/CDK6 inhibitor. In some embodiments, the compound of the disclosure is administered as second (or later) line therapy following treatment with

one or more chemotherapy regimens, e.g., including taxanes, platinum agents, pyrimidine antagonists, and/or gemcitabine. In some embodiments, the compound of the disclosure is administered as second (or later) line therapy following treatment with HER2 targeted agents, e.g., trastuzumab. In some embodiments, the compound of the disclosure is administered as second (or later) line therapy following treatment with an EGFR inhibitor, e.g., osimertinib. In some embodiments, the compound of the disclosure is administered as second (or later) line therapy following treatment with pyrimidine antagonists (e.g., 5-fluorouracil (5-FU)) and/or gemcitabine, and/or platinum agents (e.g., cisplatin).

[00132] In some embodiments, the cancer is N-myc amplified neuroblastoma cells (see Molenaar, et al., Proc Natl Acad Sci USA 106(31): 12968-12973) K-Ras mutant lung cancers (see Hu, S., et al., Mol Cancer Ther, 2015. 14(11): 2576-85, and cancers with FBW7 mutation and CCNE1 overexpression (see Takada, et al., Cancer Res, 2017.77(18): 4881-4893).

[00133] Examples of cancers that are treatable using the compounds of the present disclosure include, but are not limited to, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, endometrial cancer, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or urethra, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers. The compounds of the present disclosure are also useful for the treatment of metastatic cancers.

[00134] In some embodiments, cancers treatable with compounds of the present disclosure include, but are not limited to, melanoma (e.g., metastatic malignant melanoma, BRAF and HSP90 inhibition-resistant melanoma, skin cutaneous melanoma (SKCM), renal cancer (e.g., clear cell carcinoma), prostate cancer (e.g., hormone refractory prostate adenocarcinoma), breast cancer, colon cancer, lung cancer (e.g., non-small cell lung cancer and small cell lung cancer), squamous cell head and neck cancer (e.g., head and neck squamous cell carcinoma (NHSC), urothelial cancer (e.g., bladder) and cancers with high microsatellite instability (MSI^{high}). Additionally, the disclosure includes refractory or recurrent malignancies whose growth may be inhibited using the compounds of the disclosure.

[00135] In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to, solid tumors (e.g., prostate cancer, colon cancer, esophageal cancer, endometrial cancer, ovarian cancer, uterine cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, sarcoma, bladder cancer, etc.), hematological cancers (e.g., lymphoma, leukemia such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), DLBCL, mantle cell lymphoma, Non-Hodgkin lymphoma (including follicular lymphoma, including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma or multiple myeloma) and combinations of said cancers.

[00136] In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to, cholangiocarcinoma, bile duct cancer, triple negative breast cancer, rhabdomyosarcoma, small cell lung cancer, leiomyosarcoma, hepatocellular carcinoma (e.g., liver hepatocellular carcinoma (LIHC)), Ewing's sarcoma, brain cancer, brain tumor, astrocytoma, neuroblastoma, neurofibroma, basal cell carcinoma, chondrosarcoma, epithelioid sarcoma, eye cancer, Fallopian tube cancer, gastrointestinal cancer, gastrointestinal stromal tumors, hairy cell leukemia, intestinal cancer, islet cell cancer, oral cancer, mouth cancer, throat cancer, laryngeal cancer, lip cancer, mesothelioma, neck cancer, nasal cavity cancer, ocular cancer, ocular melanoma, pelvic cancer, rectal cancer, renal cell carcinoma, salivary gland cancer, sinus cancer, spinal cancer, tongue cancer, tubular carcinoma, urethral cancer, and ureteral cancer.

[00137] In some embodiments, cancers treatable with compounds of the present disclosure include Genomic Identification of Significant Targets in Cancer (GISTIC) and pheochromocytoma and paraganglioma (PCPG).

[00138] In some embodiments, cancers treatable with compounds of the present disclosure include advanced/relapsed tumors; platinum-resistant or platinum-refractory ovarian cancer; endometrial cancer (with prior platinum therapy) that has progressed following 2 or more lines of therapies; gastric cancer (with prior platinum therapy) that has progressed following 2 or more lines of therapies; and HR+/HER2- BC (including both ER+ HER2- BC and PR+/HER2- BC) that has progressed despite CDK4/6i. In some embodiments, cancers treatable with compounds of the present disclosure include platinum-resistant or platinum-refractory CCNE1 amplified ovarian cancer; CCNE1 amplified endometrial cancer that has failed 2 or more lines of therapies; CCNE1 amplified advanced/relapsed tumors that do not belong to the other groups; HR+/HER2- BC that has progressed despite CDK4/6i; and platinum-resistant or platinum-refractory CCNE1 amplified ovarian cancer. In one embodiment, the subject has CCNE1 amplified advanced/relapsed tumors. In one embodiment, the subject has CCNE1 amplified platinum-resistant or platinum-refractory ovarian cancer. In one embodiment, the subject has endometrial cancer (with prior platinum therapy, e.g., wherein the patient has been previously treated with a platinum therapy) that has progressed following 2 or more lines of therapies

(including the platinum therapy). In one embodiment, the subject has CCNE1 amplified endometrial cancer that has failed 2 or more lines of therapies (which may include a prior platinum therapy). In one embodiment, the subject has gastric cancer (with prior platinum therapy e.g., wherein the patient has been previously treated with a platinum therapy) that has progressed following 2 or more lines of therapies (including the platinum therapy). In one embodiment, the subject has HR+/HER- breast cancer that has progressed despite treatment with one or more CDK4/6 inhibitors. In one embodiment, the subject has TNBC that has progressed despite one or more lines of therapies. In one embodiment, the subject has AR+ prostate cancer that has progressed despite one or more lines of therapies. In one embodiment, the subject has pancreatic cancer that has progressed despite one or more lines of therapies. In one embodiment, the subject has PDAC that has progressed despite one or more lines of therapies. In one embodiment, the subject has CCNE1 amplified lung cancer. In one embodiment, the subject has NSCLC that has progressed despite treatment with one or more EGFR inhibitors (e.g., osimertinib). In one embodiment, the subject has CCNE1 amplified NSCLC that has progressed despite treatment with one or more EGFR inhibitors (e.g., osimertinib).

[00139] In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to hematological cancers, sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

[00140] Exemplary hematological cancers include lymphomas and leukemias such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Non-Hodgkin lymphoma (including relapsed or refractory NHL and recurrent follicular), Hodgkin lymphoma, myeloproliferative diseases (e.g., primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocytosis (ET)), myelodysplasia syndrome (MDS), T-cell acute lymphoblastic lymphoma (T-ALL) and multiple myeloma (MM).

[00141] Exemplary sarcomas include chondrosarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, angiosarcoma, fibrosarcoma, liposarcoma, myxoma, rhabdomyoma, rhabdosarcoma, fibroma, lipoma, hamatoma, and teratoma.

[00142] Exemplary lung cancers include non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), bronchogenic carcinoma, squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma, alveolar (bronchiolar) carcinoma, bronchial adenoma, chondromatous hamartoma, and mesothelioma. Exemplary gastrointestinal cancers include cancers of the esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors,

Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), and colorectal cancer.

[00143] Exemplary genitourinary tract cancers include cancers of the kidney (adenocarcinoma, Wilm's tumor [nephroblastoma]), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma (PRAD), sarcoma, AR+ or AR-dependent prostate cancer, AR-independent prostate cancer, and CRPC), and testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma).

[00144] Exemplary liver cancers include hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma.

[00145] Exemplary bone cancers include, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and giant cell tumors

[00146] Exemplary nervous system cancers include cancers of the skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, brain lower grade glioma (LGG), ependymoma, germinoma (pinealoma), glioblastoma, glioblastoma multiforme (GBM), oligodendroglioma, schwannoma, retinoblastoma, congenital tumors, and spinal cord (neurofibroma, meningioma, glioma, sarcoma), as well as neuroblastoma and Lhermitte-Duclos disease.

[00147] Exemplary gynecological cancers include cancers of the uterus (endometrial carcinoma), cervix (cervical carcinoma, cervical squamous cell carcinoma (CESC), pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and fallopian tubes (carcinoma).

[00148] Exemplary skin cancers include melanoma, basal cell carcinoma, Merkel cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, and keloids. In some embodiments, cancers that are treatable using the compounds of the present disclosure include, but are not limited to, triple-negative breast cancer (TNBC), myelodysplastic syndromes, testicular cancer, bile duct cancer, esophageal cancer, and urothelial carcinoma.

Combinations

[00149] Compounds of the disclosure may be administered as single agents or may be administered in combination with other anti-cancer therapeutic agents, in particular standard of care agents appropriate for the particular cancer.

[00150] The term “additional anticancer therapeutic agent” as used herein means any one or more therapeutic agent, other than a compound of the disclosure, that is or can be used in the treatment of cancer. In some embodiments, such additional anticancer therapeutic agents include compounds derived from the following classes: mitotic inhibitors, alkylating agents, antimetabolites, antitumor antibiotics, anti-angiogenesis agents, topoisomerase I and II inhibitors, plant alkaloids, hormonal agents and antagonists, growth factor inhibitors, radiation, signal transduction inhibitors, such as inhibitors of protein tyrosine kinases and/or serine/threonine kinases, cell cycle inhibitors, biological response modifiers, enzyme inhibitors, antisense oligonucleotides or oligonucleotide derivatives, cytotoxics, immuno-oncology agents, and the like.

[00151] In some embodiments, the additional anticancer agent is an endocrine agent, such as an aromatase inhibitor, a Selective Estrogen-Receptor Downregulator (SERD) or a Selective Estrogen Receptor Modulator (SERM). In some embodiments, the additional anticancer agent is a SERD. In some embodiments, the SERD is fulvestrant.

[00152] In some embodiments, the additional anticancer agent is a PIK3CA inhibitor including, but not limited to, alpelisib (PIQRAY), BEBT-908, BPI-21668, buparlisib, inavolisib, TQB-3525, RLY-2608, miransertib, MEN-1611, LOXO-783, HS-10352, HH-CYH33, gedatolisib, and fimepinostat. In some embodiments, the PIK3CA inhibitor is alpelisib.

[00153] In some embodiments, the additional anticancer agent is an antibody-drug conjugates including, but not limited to, Trastuzumab deruxtecan (Enhertu), Trastuzumab duocarmazine, Trastuzumab emtansine (Kadcyla), Upifitamab rilsodotin, mirvetuximab soravtansine, Tisotumab vedotin (Tivdak), Praluzatamab ravtansine, Sacituzumab govitecan or Sacituzumab Govitecan-hziy (Trodelvy), Datopotamab deruxtecan, Ladiratuzumab vedotin, Patritumab deruxtecan, STRO-002, MORab-202, DS-6000, Anetumab, avtansine, XMT-2056, Disitamab Vedotin (RC48-ADC, Aidexi).

[00154] In some embodiments, the additional anticancer agent is a PLK1 inhibitor including, but not limited to onvansertib, BI2536, BI6727, GSK461364A, TAK960, rigosertib.

[00155] In some embodiments, the additional anticancer agent is Estrogen PROTAC (ARV-471, H3B-5942).

[00156] In other embodiments, a compound of the disclosure may be administered in combination with a standard of care agent. In some embodiments, a compound of the disclosure may be administered in combination with endocrine therapy, e.g., agents such as letrozole, fulvestrant, tamoxifen, exemestane, or anastrozole. In some embodiments, a compound of the disclosure may be administered in combination with a chemotherapeutic agent, e.g., docetaxel, paclitaxel, cisplatin,

carboplatin, capecitabine, gemcitabine, vinorelbine, or liposomal doxorubicin. In other embodiments, a compound of the invention may be administered in combination with an anti-HER2 agent, e.g., trastuzumab or pertuzumab.

[00157] In some embodiments, a compound of the disclosure (for example, a compound of Formula (I) or a pharmaceutically acceptable salt thereof) may be administered in combination with an effective amount of 5-FU, alpelisib, carboplatin, cisplatin, enzalutamide, fulvestrant, gemcitabine, osimertinib, ribociclib, or a combination thereof. In some embodiments, a compound of the disclosure may be administered in combination with an effective amount of carboplatin, ribociclib, fulvestrant, or a combination thereof.

[00158] In some embodiments, the additional anticancer agent is an anti-angiogenesis agent, including for example VEGF inhibitors, VEGFR inhibitors, TIE-2 inhibitors, PDGFR inhibitors, angiopoietin inhibitors, PKC β inhibitors, COX-2 (cyclooxygenase II) inhibitors, integrins (alpha-v/beta-3), MMP-2 (matrix-metalloproteinase 2) inhibitors, and MMP-9 (matrix-metalloproteinase 9) inhibitors. Preferred anti-angiogenesis agents include sunitinib (SutentTM), bevacizumab (AvastinTM), axitinib (AG 13736), SU 14813 (Pfizer), and AG 13958 (Pfizer). Additional anti-angiogenesis agents include vatalanib (CGP 79787), Sorafenib (NexavarTM), pegaptanib octasodium (MacugenTM), vandetanib (ZactimaTM), PF-0337210 (Pfizer), SU 14843 (Pfizer), AZD 2171 (AstraZeneca), ranibizumab (LucentisTM), NeovastatTM (AE 941), tetrathiomolybdate (CoproxaTM), AMG 706 (Amgen), VEGF Trap (AVE 0005), CEP 7055 (Sanofi-Aventis), XL 880 (Exelixis), telatinib (BAY 57-9352), and CP-868,596 (Pfizer). Other anti-angiogenesis agents include enzastaurin (LY 317615), midostaurin (CGP 41251), perifosine (KRX 0401), teprenone (SelbexTM) and UCN 01 (Kyowa Hakko). Other examples of anti-angiogenesis agents include celecoxib (CelebrexTM), parecoxib (DynastatTM), deracoxib (SC 59046), lumiracoxib (PreigeTM), valdecoxib (BextraTM), rofecoxib (VioxxTM), iguratimod (CareramTM), IP 751 (Invedus), SC-58125 (Pharmacia) and etoricoxib (ArcoxiaTM). Yet further anti-angiogenesis agents include exisulind (AptosynTM), salsalate (AmigesicTM), diflunisal (DolobidTM), ibuprofen (MotrinTM), ketoprofen (OrudisTM), nabumetone (RelafenTM), piroxicam (FeldeneTM), naproxen (AleveTM, NaprosynTM), diclofenac (VoltarenTM), indomethacin (IndocinTM), sulindac (ClinorilTM), tolmetin (TolectinTM), etodolac (LodineTM), ketorolac (ToradolTM), and oxaprozin (DayproTM). Yet further anti-angiogenesis agents include ABT 510 (Abbott), apratastat (TMI 005), AZD 8955 (AstraZeneca), incyclinide (MetastatTM), and PCK 3145 (Procyon).

[00159] Yet further anti-angiogenesis agents (including VEGFR / PDGFR inhibitors) include, but are not limited to, ponatinib (Iclusig), BT1718, anlotinib, lenvatinib (Lenvima), tivozanib (Fotivda), dovitinib, brolucizumab (Beovu), aflibercept (Eylea), and faricimab.

[00160] Yet further anti-angiogenesis agents include acitretin (NeotigasonTM), plitidepsin (aplidineTM), cilengtide (EMD 121974), combretastatin A4 (CA4P), fenretinide (4 HPR),

halofuginone (TempostatTM), PanzemTM (2-methoxyestradiol), PF-03446962 (Pfizer), rebimastat (BMS 275291), catumaxomab (RemovabTM), lenalidomide (RevlimidTM), squalamine (EVIZONTM), thalidomide (ThalomidTM), UkrainTM (NSC 631570), VitaxinTM (MEDI 522), and zoledronic acid (ZometaTM).

[00161] In other embodiments, the additional anti-cancer agent is a so-called signal transduction inhibitor (e.g., inhibiting how regulatory molecules that govern the fundamental processes of cell growth, differentiation, and survival communicated within the cell). Signal transduction inhibitors include small molecules, antibodies, and antisense molecules. Signal transduction inhibitors include for example kinase inhibitors (e.g., tyrosine kinase inhibitors or serine/threonine kinase inhibitors) and cell cycle inhibitors. More specifically signal transduction inhibitors include, for example, farnesyl protein transferase inhibitors, EGF inhibitor, ErbB-1 (EGFR), ErbB-2, pan erb, IGF1R inhibitors, MEK, c-Kit inhibitors, FLT-3 inhibitors, K-Ras inhibitors, PI3 kinase inhibitors, JAK inhibitors, STAT inhibitors, Raf kinase inhibitors, Akt inhibitors, mTOR inhibitor, P70S6 kinase inhibitors, inhibitors of the WNT pathway and so called multi-targeted kinase inhibitors. Additional examples of signal transduction inhibitors which may be used in conjunction with a compound of the invention and pharmaceutical compositions described herein include BMS 214662 (Bristol-Myers Squibb), lonafarnib (SarasarTM), pelitrexol (AG 2037), matuzumab (EMD 7200), nimotuzumab (TheraCIM h-R3TM), panitumumab (VectibixTM), Vandetanib (ZactimaTM), pazopanib (SB 786034), ALT 110 (Alteris Therapeutics), BIBW 2992 (Boehringer Ingelheim), and CerveneTM (TP 38). Other examples of signal transduction inhibitors include gefitinib (IressaTM), cetuximab (ErbixTM), erlotinib (TarcevaTM), trastuzumab (HerceptinTM), sunitinib (SutentTM), imatinib (GleevecTM), crizotinib (Pfizer), lorlatinib (Pfizer), dacomitinib (Pfizer), bosutinib (Pfizer), gedatolisib (Pfizer), canertinib (CI 1033), pertuzumab (OmnitargTM), lapatinib (TycerbTM), pelitinib (EKB 569), miltefosine (MiltefosinTM), BMS 599626 (Bristol-Myers Squibb), Lapuleucel-T (NeuvengeTM), NeuVaxTM (E75 cancer vaccine), OsidemTM (IDM 1), mubritinib (TAK-165), CP-724,714 (Pfizer), panitumumab (VectibixTM), ARRY 142886 (Array Biopharm), everolimus (CerticanTM), zotarolimus (EndeavorTM), temsirolimus (ToriselTM), AP 23573 (ARIAD), and VX 680 (Vertex), XL 647 (Exelixis), sorafenib (NexavarTM), LE-AON (Georgetown University), and GI-4000 (Globelimmune). Other signal transduction inhibitors include ABT 751 (Abbott), alvocidib (flavopiridol), BMS 387032 (Bristol Myers), EM 1421 (Erimos), indisulam (E 7070), seliciclib (CYC 200), BIO 112 (Onc Bio), BMS 387032 (Bristol-Myers Squibb), palbociclib (Pfizer), and AG 024322 (Pfizer).

[00162] In other embodiments, the additional anti-cancer agent is a so called classical antineoplastic agent. Classical antineoplastic agents include but are not limited to hormonal modulators such as hormonal, anti-hormonal, androgen agonist, androgen antagonist and anti-estrogen therapeutic agents, histone deacetylase (HDAC) inhibitors, DNA methyltransferase inhibitors, silencing agents or gene activating agents, ribonucleases, proteosomics, Topoisomerase I inhibitors, Camptothecin derivatives, Topoisomerase II inhibitors, alkylating agents, antimetabolites, poly(ADP-

ribose) polymerase-1 (PARP-1) inhibitor (such as, e.g., talazoparib, olapariv, rucaparib, niraparib, iniparib, veliparib), microtubulin inhibitors, antibiotics, plant derived spindle inhibitors, platinum-coordinated compounds, gene therapeutic agents, antisense oligonucleotides, vascular targeting agents (VTAs), and statins. Examples of classical antineoplastic agents used in combination therapy with a compound of the invention, optionally with one or more other agents include, but are not limited to, glucocorticoids, such as dexamethasone, prednisone, prednisolone, methylprednisolone, hydrocortisone, and progestins such as medroxyprogesterone, megestrol acetate (Megace), mifepristone (RU-486), Selective Estrogen Receptor Modulators (SERMs; such as tamoxifen, raloxifene, lasofoxifene, afimoxifene, arzoxifene, bazedoxifene, fispemifene, ormeloxifene, ospemifene, toremifene, trilostane and CHF 4227 (Cheisi), Selective Estrogen-Receptor Downregulators (SERD's; such as fulvestrant, LSZ102, G1T48, RAD1901, elacestrant, GDC-9545, giredestrant, SAR439859, amcenestrant, AZD9833, camizestrant, LY3484356, Zn-c5, D-0502), exemestane (Aromasin), anastrozole (Arimidex), atamestane, fadrozole, letrozole (Femara), formestane; gonadotropin-releasing hormone (GnRH; also commonly referred to as luteinizing hormone-releasing hormone [LHRH]) agonists such as buserelin (Suprefact), goserelin (Zoladex), leuporelin (Lupron), and triptorelin (Trelstar), abarelix (Plenaxis), cyproterone, flutamide (Eulexin), megestrol, nilutamide (Nilandron), and osaterone, dutasteride, epristeride, finasteride, Serenoa repens, PHL 00801, abarelix, goserelin, leuporelin, triptorelin, bicalutamide; antiandrogen agents, such as enzalutamide, abiraterone acetate, bicalutamide (Casodex); and combinations thereof. Other examples of classical antineoplastic agents used in combination with a compound of the invention include but are not limited to suberolanilide hydroxamic acid (SAHA, Merck Inc./Aton Pharmaceuticals), depsipeptide (FR901228 or FK228), G2M-777, MS-275, pivaloyloxymethyl butyrate and PXD-101; Onconase (ranpirinase), PS-341 (MLN-341), Velcade (bortezomib), 9-aminocamptothecin, belotecan, BN-80915 (Roche), camptothecin, diflomotecan, edotecarin, exatecan (Daiichi), gimatecan, 10-hydroxycamptothecin, irinotecan HCl (Camptosar), lurtotecan, Orathecin (rubitecan, Supergen), SN-38, topotecan, camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, irinotecan, SN-38, edotecarin, topotecan, aclarubicin, adriamycin, amonafide, amrubicin, annamycin, daunorubicin, doxorubicin, elsamitrucin, epirubicin, etoposide, idarubicin, galarubicin, hydroxycarbamide, nemorubicin, novantrone (mitoxantrone), pirarubicin, pixantrone, procarbazine, rebeccamycin, sobuzoxane, tafluposide, valrubicin, Zinecard (dexrazoxane), nitrogen mustard N-oxide, cyclophosphamide, AMD-473, altretamine, AP-5280, apaziquone, brostallicin, bendamustine, busulfan, carboquone, carmustine, chlorambucil, dacarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine, mafosfamide, mechlorethamine, melphalan, mitobronitol, mitolactol, mitomycin C, mitoxatrone, nimustine, ranimustine, temozolomide, thiotepe, and platinum-coordinated alkylating compounds such as cisplatin, Paraplatin (carboplatin), eptaplatin, lobaplatin, nedaplatin, Eloxatin (oxaliplatin, Sanofi), streptozocin, satraplatin, and combinations thereof.

[00163] In still other embodiments, the additional anti-cancer agent is a so called dihydrofolate reductase inhibitors (such as methotrexate and NeuTrexin (trimetresate glucuronate)), purine antagonists (such as 6-mercaptopurine riboside, mercaptopurine, 6-thioguanine, cladribine, clofarabine (Clolar), fludarabine, nelarabine, and raltitrexed), pyrimidine antagonists (such as 5-fluorouracil (5-FU), Alimta (premetrexed disodium, LY231514, MTA), capecitabine (Xeloda™), cytosine arabinoside, Gemzar™ (gemcitabine, Eli Lilly), Tegafur (UFT Orzel or Uforal and including TS-1 combination of tegafur, gimestat and otostat), doxifluridine, carmofur, cytarabine (including ocfosfate, phosphate stearate, sustained release and liposomal forms), enocitabine, 5-azacitidine (Vidaza), decitabine, and ethynylcytidine) and other antimetabolites such as eflornithine, hydroxyurea, leucovorin, nolatrexed (Thymitaq), triapine, trimetrexate, N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid, AG-014699 (Pfizer Inc.), ABT-472 (Abbott Laboratories), INO-1001 (Inotek Pharmaceuticals), KU-0687 (KuDOS Pharmaceuticals) and GPI 18180 (Guilford Pharm Inc) and combinations thereof. In some embodiments, the additional anti-cancer agent is a pyrimidine antagonist. In some embodiments, the pyrimidine antagonist is 5-FU.

[00164] Other examples of classical antineoplastic cytotoxic agents include, but are not limited to, Abraxane (Abraxis BioScience, Inc.), Batabulin (Amgen), EPO 906 (Novartis), Vinflunine (Bristol-Myers Squibb Company), actinomycin D, bleomycin, mitomycin C, neocarzinostatin (Zinostatin), vinblastine, vincristine, vindesine, vinorelbine (Navelbine), docetaxel (Taxotere), Ortataxel, paclitaxel (including Taxoprexin a DHA/paclitaxel conjugate), cisplatin, carboplatin, Nedaplatin, oxaliplatin (Eloxatin), Satraplatin, Camptosar, capecitabine (Xeloda), oxaliplatin (Eloxatin), Taxotere alitretinoin, Canfosfamide (Telcyta™), DMXAA (Antisoma), ibandronic acid, L-asparaginase, pegaspargase (Oncaspar™), Efaproxiral (Efaproxyn™ - radiation therapy), bexarotene (Targretin™), Tesmilifene (DPPE— enhances efficacy of cytotoxics), Theratope™ (Biomira), Tretinoin (Vesanoid™), tirapazamine (Trizaone™), motexafin gadolinium (Xcytrin™) Cotara™ (mAb), and NBI-3001 (Protox Therapeutics), polyglutamate-paclitaxel (Xyotax™) and combinations thereof. Further examples of classical antineoplastic agents include, but are not limited to, as Advexin (ING 201), TNFerade (GeneVec, a compound which express TNFalpha in response to radiotherapy), RB94 (Baylor College of Medicine), Genasense (Oblimersen, Genta), Combretastatin A4P (CA4P), Oxi-4503, AVE-8062, ZD-6126, TZZT-1027, Atorvastatin (Lipitor, Pfizer Inc.), Pravastatin (Pravachol, Bristol-Myers Squibb), Lovastatin (Mevacor, Merck Inc.), Simvastatin (Zocor, Merck Inc.), Fluvastatin (Lescol, Novartis), Cerivastatin (Baycol, Bayer), Rosuvastatin (Crestor, AstraZeneca), Lovostatin, Niacin (Advicor, Kos Pharmaceuticals), Caduet, Lipitor, torcetrapib, and combinations thereof.

[00165] In other embodiments, the additional anti-cancer agent is an epigenetic modulator, for example an inhibitor or EZH2, SMARCA4, PBRM1, ARID1A, ARID2, ARID1B, DNMT3A, TET2,

MLL1/2/3, NSD1/2, SETD2, BRD4, DOT1L, HKMTsanti, PRMT1-9, LSD1, UTX, IDH1/2 or BCL6.

[00166] In further embodiments, the additional anti-cancer agent is an immunomodulatory agent, such as, but not limited to, an inhibitor of CTLA-4 (e.g., ipilimumab), PD-1 or PD-L1 (e.g., pembrolizumab, nivolumab, avelumab, atezolizumab, durvalumab, cemiplimab, or dostertolimab), LAG-3 (e.g., relatlimab, TIM-3, TIGIT, 4-1BB, OX40, GITR, CD40, or a CAR-T-cell therapy.

[00167] In some embodiments, the additional anticancer agent is an EGFR inhibitor such as afatinib, osimertinib, lapatinib, erlotinib, dacomitinib, poziotinib, neratinib or gefitinib or an EGFR antibody such as cetuximab, panitumumab, or necitumumab. In some embodiments, the EGFR inhibitor is osimertinib.

[00168] Alternatively, a compound of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein can be administered in combination with other anti-cancer agents that are not EGFR inhibitors e.g., in combination with MEK, including mutant MEK inhibitors (trametinib, cobimetinib, binimetinib, selumetinib, refametinib); c-MET, including mutant c-Met inhibitors (savolitinib, cabozantinib, foretinib) and MET antibodies (emibetuzumab); mitotic kinase inhibitors (CDK4/6 inhibitors such as palbociclib, ribociclib, abemaciclib, lerociclib, trilaciclib, dalpiciclib, BPI-16350); anti-angiogenic agents e.g., bevacizumab, nintedanib; apoptosis inducers such as Bcl-2 inhibitors e.g. venetoclax, obatoclax, navitoclax and Mcl-1 inhibitors e.g., AZD-5991, AMG-176, S-64315; and mTOR inhibitors e.g. rapamycin, temsirolimus, everolimus, ridofoleimus. In some embodiments, the CDK4/6 inhibitor is palbociclib. In some embodiments, the CDK4/6 inhibitor is ribociclib.

[00169] A compound of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein can be administered in combination with a CDK4/6 inhibitor. In some embodiments, the CDK4/6 inhibitor is selected from the group consisting of palbociclib, ribociclib, abemaciclib, lerociclib, trilaciclib, dalpiciclib, BPI-16350. In some embodiments, the CDK4/6 inhibitor is ribociclib.

[00170] A compound of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein can be administered in combination with a CDK4/6 inhibitor and a SERD. In some embodiments, a compound of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein can be administered in combination with ribociclib and fulvestrant. In some embodiments, a compound of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein can be administered in combination with a pyrimidine antagonist and gemcitabine. In some embodiments, a compound of the disclosure can be administered in combination with a pyrimidine antagonist, gemcitabine, and a CDK4/6 inhibitor. In some embodiments, the combination further comprises a platinum agent. In some embodiments, a compound of the disclosure can be administered in

combination with 5-FU, gemcitabine, ribociclib, and, optionally, cisplatin. In some embodiments, a compound of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein can be administered in combination with an EGFR inhibitor. In some embodiments, a compound of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein can be administered in combination with osimertinib. In some embodiments, a compound of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein can be administered in combination with a PARP-1 inhibitor. In some embodiments, a compound of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein can be administered in combination with olaparib.

[00171] A compound of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein can also be administered in combination with an effective amount of a second agent selected from the group consisting of palbociclib (e.g., ibrance®), ribociclib, abemaciclib, tamoxifen, letrozole, olaparib (e.g., lynparza®), niraparib, carboplatin, cisplatin, paclitaxel, gemcitabine, megestrol acetate, medroxyprogesterone acetate, capecitabine (e.g., xeloda®), regorafenib (e.g., stivarga®), afatinib (e.g., gilotrif®), osimertinib (e.g., tagrisso®), gefitinib (e.g., iressa®), erlotinib (e.g., tarceva®), ramucirumab (e.g., cyramza®), an EGFR inhibitor, pralsetinib, ABT-263 (navitoclax), MK-1775 (adavosertib), BAY-1895344, berzosertib, ceralasertib, SRA-737, LY2603618 (rabusertib), and trastuzumab (e.g., herceptin®), or combinations thereof. The EGFR inhibitor may be selected from afatinib, osimertinib, lapatinib, erlotinib, dacomitinib, poziotinib, neratinib, gefitinib JBJ-04-125-02, alflutinib (AST 2818), aumolertinib (formerly almonertinib) (HS10296), BBT-176, BI-4020, BPI-361175, BPI-D0316, CH7233163, gilitertinib, icotinib, JND-3229, lazertinib, nazartinib (EGF 816), avitinib, PCC-0208027, rezivertinib (BPI-7711), TQB3804, zorifertinib (AZ-3759), or DZD9008; an EGFR antibody such as cetuximab, panitumumab, necitumumab, HLX07, JMT101; or a bispecific EGFR and MET antibody (e.g., amivantamab ((JNJ-61186372, JNJ-372)).

Biomarkers and Pharmacodynamics Markers

[00172] The disclosure further provides predictive markers (e.g., biomarkers and pharmacodynamic markers, e.g., levels, gene copy number, gene sequence, expression levels, phosphorylation levels, or mutations) to identify those human subjects having, suspected of having, or at risk of developing a disease or disorder associated with CDK2 (e.g., a cancer) for whom administering a CDK2 inhibitor (“a CDK2 inhibitor” as used herein refers to a compound of the disclosure, or a pharmaceutically acceptable salt thereof) is likely to be effective.

CCNE1

[00173] In one embodiment, the biomarker is CCNE1. In some embodiments, CCNE1 is absent. In some embodiments, the loss of CCNE1 is a biomarker. In some embodiments, CCNE1 is mutated (e.g., a loss of function mutation). In some embodiments, CCNE1 or a mutated CCNE1 is functional. In some embodiments, CCNE1 is a biomarker for sensitivity to a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof. In some embodiments, treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, modulates the levels of CCNE1. In some embodiments, the levels of CCNE1 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%. In some embodiments, the levels of CCNE1 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of CCNE1 before and after treatment are changed by about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of CCNE1 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are increased. In some embodiments, the levels of CCNE1 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are reduced.

[00174] In some embodiments, an amplification of the cyclin E1 (CCNE1) gene and/or a higher or over expression level of CCNE1 in a biological sample would indicate that the patient or subject could benefit from administration of a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof.

[00175] CCNE1 is a cell cycle factor essential for the control of the cell cycle at the G1/S transition (Ohtsubo et al., 1995, Mol. Cell. Biol. 15:2612-2624). CCNE1 acts as a regulatory subunit of CDK2, interacting with CDK2 to form a serine/threonine kinase holoenzyme complex. The CCNE1 subunit of this holoenzyme complex provides the substrate specificity of the complex (Honda et al., 2005, EMBO 24:452- 463). CCNE1 is encoded by the cyclin E1 ("CCNE1") gene (GenBank Accession No. NM_001238). The amino acid sequence of human CCNE1 is found at GenBank Accession No. NP_001229 / UniProtKB Accession No. P24864).

[00176] In one aspect, the present disclosure provides a method of treating a subject having, or at risk of developing, a disease or disorder associated with CDK2 (e.g., a cancer), comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, wherein

the subject has an amplification of the CCNE1 gene (e.g., based on copy number) and/or has a level of CCNE1 higher than a control level of CCNE1. In some embodiments, the disease or disorder associated with CDK2 is cancer.

[00177] Also provided herein is a method of treating a patient having an amplified expression level of CCNE1 and suffering from, or at risk of developing, a solid tumor cancer, comprising administering to the patient a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein.

[00178] In some embodiments, an amplification of the CCNE1 gene and/or a level of CCNE1 that is higher than a control level of CCNE1 is indicative/predictive that a human subject having or at risk of developing a cancer will respond to a CDK2 inhibitor (e.g., a compound disclosed herein, or a pharmaceutically acceptable salt thereof). In some embodiments, the expression level of CCNE1 may be the level of CCNE1 mRNA. In other embodiments, the expression level of CCNE1 may be the level of CCNE1 protein. In some embodiments, the levels of CCNE1 are modulated in response to administration of a therapeutically effective amount of a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, to a subject.

Other biomarkers

[00179] In some embodiments, the contemplated biomarker is p16 (also known as cyclin-dependent kinase inhibitor 2A, cyclin-dependent kinase 4 inhibitor A, multiple tumor suppressor 1, and p16-INK4a), which acts as a negative regulator of the proliferation of normal cells by interacting with CDK4 and CDK6. In some embodiments, treatment with a therapeutically effective amount of a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, modulates the levels of p16. In some embodiments, p16 is absent. In some embodiments, the loss of p16 is a biomarker. In some embodiments, p16 has a mutation (e.g., a loss of function mutation). In some embodiments, p16 or a p16 mutant is functional. In some embodiments, p16 is a biomarker for sensitivity to a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof.

[00180] In some embodiments, a change in the levels of p16 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, is indicative/predictive that a subject having or at risk of developing a cancer has responded to treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof. In some embodiments, the levels of p16 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%. In some embodiments, the levels of p16 before and after treatment with a

compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of p16 before and after treatment are changed by about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of p16 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are increased. In some embodiments, the levels of p16 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are reduced.

[00181] In some embodiments, the contemplated biomarker is retinoblastoma protein (pRb or RB), which is encoded by the gene RB transcriptional corepressor 1 (RB1). In some embodiments, the contemplated biomarker is phosphorylation of Rb at any phosphorylation site. In some embodiments, the biomarker is phosphorylation at the serine corresponding to amino acid position 780 (Ser780 or S780) and/or the serine corresponding to amino acid position 795 (Ser795 or S795). In some embodiments, the contemplated biomarker is phosphorylation of Rb at the serine corresponding to amino acid position 807 (Ser807 or S807) and/or the serine corresponding to amino acid position 811 (Ser811 or S811). In some embodiments, the contemplated biomarker is phosphorylation of Rb at the threonine corresponding to amino acid position 821 (Thr821) and/or the threonine corresponding to amino acid position 826 (Thr826). Rb is a regulator of the cell cycle and acts as a tumor suppressor. Rb is activated upon phosphorylation by cyclin D-CDK4/6 at Ser780 and Ser795 and by cyclin E/CDK2 at Ser807 and Ser811. In some embodiments, treatment with a therapeutically effective amount of a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, modulates the levels of phosphorylated Rb. In some embodiments, phosphorylated Rb or RB is absent. In some embodiments, the loss of phosphorylated Rb or RB is a biomarker. In some embodiments, RB has a mutation (e.g., a loss of function mutation). In some embodiments, RB or an RB mutant is functional. In some embodiments, phosphorylated Rb or RB is a biomarker for sensitivity to a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof.

[00182] In some embodiments, a change in the levels of phosphorylated Rb or RB before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, is indicative/predictive that a subject having or at risk of developing a cancer has responded to treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof. In some embodiments, the levels of phosphorylated Rb at any phosphorylation site before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%. In some

embodiments, the levels of phosphorylated Rb at any phosphorylation site before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of phosphorylated Rb at any phosphorylation site before and after treatment are changed by about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of phosphorylated Rb at any phosphorylation site or RB before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are increased. In some embodiments, the levels of phosphorylated Rb at any phosphorylation site or RB before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are reduced.

[00183] In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of levels of phosphorylated Rb at Ser780 and/or Ser795 before and after treatment are changed by about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are increased.

[00184] In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are reduced. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 10%. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 20%. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 30%. In some

embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 40%. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 50%. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 60%. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 70%. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 80%. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 90%. In some embodiments, the levels of phosphorylated Rb at Ser780 and/or Ser795 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 100%.

[00185] In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of levels of phosphorylated Rb at Ser807 and/or Ser811 before and after treatment are changed by about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are increased.

[00186] In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are reduced. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 10%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or

Ser811 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 20%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 30%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 40%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 50%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 60%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 70%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 80%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 90%. In some embodiments, the levels of phosphorylated Rb at Ser807 and/or Ser811 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 100%.

[00187] In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of levels of phosphorylated Rb at Thr821 and/or Thr826 before and after treatment are changed by about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are increased.

[00188] In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are reduced. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after administration of a compound

disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 10%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 20%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 30%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 40%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 50%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 60%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 70%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 80%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 90%. In some embodiments, the levels of phosphorylated Rb at Thr821 and/or Thr826 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 100%.

[00189] In some embodiments, the contemplated biomarker is TK1 (thymidine kinase 1). TK1 is involved in cellular proliferation through the recovery of the nucleotide thymidine in the DNA salvage pathway. TK1 is important for cell repair following DNA damage because TK1 is necessary for the formation of nucleotides outside of the S phase. In some embodiments, treatment with a therapeutically effective amount of a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, modulates the levels of TK1. In some embodiments, TK1 is absent. In some embodiments, the loss of TK1 is a biomarker. In some embodiments, TK1 has a mutation (e.g., a loss of function mutation). In some embodiments, TK1 or a TK1 mutant is functional. In some embodiments, TK1 is serum TK1. In some embodiments, TK1 is a biomarker for sensitivity to a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof.

[00190] In some embodiments, a change in the levels of TK1 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, is indicative/predictive that a subject having or at risk of developing a cancer has responded to treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof. In some embodiments, the levels of TK1 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%. In some embodiments, the levels of TK1 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of TK1 before and after treatment are changed by about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of TK1 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are increased.

[00191] In some embodiments, the levels of TK1 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VId), or a pharmaceutically acceptable salt thereof, are reduced. In some embodiments, the levels of TK1 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of TK1 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 10%. In some embodiments, the levels of TK1 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 20%. In some embodiments, the levels of TK1 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 30%. In some embodiments, the levels of TK1 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 40%. In some embodiments, the levels of TK1 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 50%. In some embodiments, the levels of TK1 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 60%. In some embodiments, the levels of TK1 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 70%. In some embodiments, the levels of TK1 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 80%. In some embodiments, the levels of TK1 before and after administration of a compound

disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 90%. In some embodiments, the levels of TK1 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 100%.

[00192] In some embodiments, the contemplated biomarker is a marker of proliferation Ki-67 (Ki-67). In some embodiments, treatment with a therapeutically effective amount of a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, modulates the levels of Ki-67. In some embodiments, Ki-67 is absent. In some embodiments, the loss of Ki-67 is a biomarker. In some embodiments, Ki-67 has a mutation (e.g., a loss of function mutation). In some embodiments, Ki-67 or a Ki-67 mutant is functional. In some embodiments, Ki-67 is a biomarker for sensitivity to a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof.

[00193] In some embodiments, a change in the levels of Ki-67 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, is indicative/predictive that a subject having or at risk of developing a cancer has responded to treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof. In some embodiments, the levels of Ki-67 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%. In some embodiments, the levels of Ki-67 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of Ki-67 before and after treatment are changed by about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of Ki-67 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are increased. In some embodiments, the levels of Ki-67 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are reduced.

[00194] In some embodiments, the contemplated biomarker is the biomarker is cancer antigen 125 or (CA-125). In some embodiments, the cancer is ovarian cancer. In some embodiments, treatment with a therapeutically effective amount of a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, modulates the levels of CA-125. In some embodiments, CA-125 is absent. In some embodiments, the loss of CA-125 is a biomarker. In some embodiments, CA-125 has a mutation (e.g., a loss of function mutation). In some embodiments, CA-125 or a CA-125 mutant is functional. In some embodiments, CA-125 is a

biomarker for sensitivity to a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof.

[00195] In some embodiments, a change in the levels of CA-125 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, is indicative/predictive that a subject having or at risk of developing a cancer has responded to treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof. In some embodiments, the levels of CA-125 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%. In some embodiments, the levels of CA-125 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are changed by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of CA-125 before and after treatment are changed by about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of CA-125 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are increased.

[00196] In some embodiments, the levels of CA-125 before and after treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof, are reduced. In some embodiments, the levels of CA-125 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the levels of CA-125 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 10%. In some embodiments, the levels CA-125 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 20%. In some embodiments, the levels of CA-125 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 30%. In some embodiments, the levels of CA-125 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 40%. In some embodiments, the levels of CA-125 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 50%. In some embodiments, the levels of CA-125 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 60%. In some embodiments, the levels of CA-125 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 70%. In some embodiments, the

levels of CA-125 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 80%. In some embodiments, the levels of CA-125 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 90%. In some embodiments, the levels of CA-125 before and after administration of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, are reduced by at least 100%.

[00197] The contemplated biomarker may also be selected from the group consisting of RB1, RBL1, RBL2, CA-125, CDKN2A, CDKN1A, CDKN1B, FBXW7, CCNE1, CCNE2, CCNA1, CCNA2, CCND1, CCND2, CCND3, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK18, CDKN2A, CDKN1A, CDKN1B, CHK1, E2F1, E2F2, E2F3, Ki-67, MYC, MYCL, MYCN, p16, EZH2, ER, HER2, HER3, TK1, and EGFR. In some embodiments, the levels of any one of the biomarkers disclosed herein may be modulated in response to treatment with a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof.

[00198] In another aspect, provided herein is a method of determining a change in levels of one or more biomarkers after administering to a subject having or at risk of developing a cancer a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId), or a pharmaceutically acceptable salt thereof.

Biological Samples

[00199] Suitable biological samples for the methods described herein include any sample that contains blood or tumor cells obtained or derived from the human subject in need of treatment. For example, a biological sample can contain tumor cells from biopsy from a patient suffering from a solid tumor. A tumor biopsy can be obtained by a variety of means known in the art. Alternatively, a blood sample can be obtained from a patient suffering from a hematological cancer.

[00200] A biological sample can be obtained from a human subject having, suspected of having, or at risk of developing, a disease or disorder associated with CDK2. In some embodiments, the disease or disorder associated with CDK2 is a cancer (such as those described supra).

[00201] Methods for obtaining and/or storing samples that preserve the activity or integrity of molecules (e.g., nucleic acids or proteins) in the sample are well known to those skilled in the art. For example, a biological sample can be further contacted with one or more additional agents such as buffers and/or inhibitors, including one or more of nuclease, protease, and phosphatase inhibitors, which preserve or minimize changes in the molecules in the sample.

Methods of Administration and Dosage Forms

[00202] The precise amount of compound administered to provide an “effective amount” to the subject will depend on the mode of administration, the type, and severity of the cancer, and on the characteristics of the subject, such as general health, age, sex, body weight, and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. When administered in combination with other therapeutic agents, *e.g.*, when administered in combination with an anti-cancer agent, an “effective amount” of any additional therapeutic agent(s) will depend on the type of drug used. Suitable dosages are known for approved therapeutic agents and can be adjusted by the skilled artisan according to the condition of the subject, the type of condition(s) being treated and the amount of a compound of Formulas (I), (II), (III), (IVa), (IVb), (Va), (Vb), (VIa), (VIb), (VIc), or (VIId) being used by following, for example, dosages reported in the literature and recommended in the *Physician’s Desk Reference* (57th Ed., 2003).

[00203] “Treating” or “treatment” refers to obtaining a desired pharmacological and/or physiological effect. The effect can be therapeutic, which includes achieving, partially or substantially, one or more of the following results: partially or substantially reducing the extent of the disease, condition or cancer; ameliorating or improving a clinical symptom or indicator associated with the disease, condition or cancer; delaying, inhibiting or decreasing the likelihood of the progression of the disease, condition or cancer; or decreasing the likelihood of recurrence of the disease, condition or cancer.

[00204] The term “effective amount” means an amount when administered to the subject which results in beneficial or desired results, including clinical results, *e.g.*, inhibits, suppresses or reduces the symptoms of the condition being treated in the subject as compared to a control. For example, a therapeutically effective amount can be given in unit dosage form (*e.g.*, 0.1 mg to about 50 g per day, alternatively from 1 mg to about 5 grams per day; and in another alternative from 10 mg to 1 gram per day).

[00205] The terms “administer”, “administering”, “administration”, and the like, as used herein, refer to methods that may be used to enable delivery of compositions to the desired site of biological action. These methods include, but are not limited to, intraarticular (in the joints), intravenous, intramuscular, intratumoral, intradermal, intraperitoneal, subcutaneous, orally, topically, intrathecally, inhalationally, transdermally, rectally, and the like. Administration techniques that can be employed with the agents and methods described herein are found in *e.g.*, Goodman and Gilman, *The Pharmacological Basis of Therapeutics*, current ed.; Pergamon; and Remington’s, *Pharmaceutical Sciences* (current edition), Mack Publishing Co., Easton, Pa.

[00206] In addition, a compound of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the disclosure can be co-administered with other therapeutic agents. As used herein, the terms “co-administration”, “administered in combination with”, and their

grammatical equivalents, are meant to encompass administration of two or more therapeutic agents to a single subject, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different times. In some embodiments the one or more compounds of the disclosure, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the disclosure will be co-administered with other agents. These terms encompass administration of two or more agents to the subject so that both agents and/or their metabolites are present in the subject at the same time. They include simultaneous administration in separate compositions, administration at different times in separate compositions, and/or administration in a composition in which both agents are present. Thus, in some embodiments, the compounds described herein and the other agent(s) are administered in a single composition. In some embodiments, the compounds described herein and the other agent(s) are admixed in the composition.

[00207] The particular mode of administration and the dosage regimen will be selected by the attending clinician, taking into account the particulars of the case (*e.g.* the subject, the disease, the disease state involved, the particular treatment). Treatment can involve daily or multi-daily or less than daily (such as weekly or monthly etc.) doses over a period of a few days to months, or even years. However, a person of ordinary skill in the art would immediately recognize appropriate and/or equivalent doses looking at dosages of approved compositions for treating a disease using the disclosed CDK2 inhibitors for guidance.

[00208] The compounds of the disclosure or a pharmaceutically acceptable salt thereof can be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds of the present teachings may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal and topical modes of administration. Parenteral administration can be by continuous infusion over a selected period of time.

[00209] The pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. In an embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, intramuscular, oral, intranasal, or topical administration to human beings. In preferred embodiments, the pharmaceutical composition is formulated for intravenous administration.

[00210] Typically, for oral therapeutic administration, a compound of the disclosure or a pharmaceutically acceptable salt thereof may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

[00211] Typically for parenteral administration, solutions of a compound of the disclosure can generally or a pharmaceutically acceptable salt thereof be prepared in water suitably mixed with a

surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00212] Typically, for injectable use, sterile aqueous solutions or dispersion of, and sterile powders of, a compound of the disclosure for the extemporaneous preparation of sterile injectable solutions or dispersions are appropriate.

[00213] The following examples are intended to be illustrative and are not intended to be limiting in any way to the scope of the disclosure.

EXEMPLIFICATION

Preparation of Exemplary Compounds

[00214] Definitions

AcOH means acetic acid;

t-AmOH means tert-amyl alcohol;

Aq. means aqueous;

Bn means benzyl;

Boc means *tert*-butoxy carbonyl;

Boc₂O means di-*tert*-butyl dicarbonate;

(BPin)₂ means 4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi-1,3,2-dioxaborolane;

br means broad;

Brettphos means 2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl;

BrettPhos Pd G3 means [(2-Di-cyclohexylphosphino-3,6-dimethoxy-2',4',6'- triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1' -biphenyl)]palladium(II) methanesulfonate;

n-BuOH means butan-1-ol;

t-BuOH means tertiary butanol;

t-BuOK means potassium *tert*-butoxide;

t-BuXPhos Pd G3 means (2-Di-*tert*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl) palladium(II) methanesulfonate;

°C means degrees Celsius;

CDCl₃ means deuterio-chloroform;

Cs₂CO₃ means cesium carbonate;

CuCN means copper cyanide;

d means chemical shift;

d means doublet;

dd means doublet of doublets;

dq means doublet of quartets;
dt means doublet of triplets;
DAST means Diethylaminosulfur trifluoride;
DBU means 1,8-diazabicyclo[5.4.0]undec-7-ene;
DCM means dichloromethane;
DEA means diethylamine;
DEAD means diethyl azodicarboxylate;
DIAD means diisopropyl azodicarboxylate;
DIBAL-H means diisobutylaluminium hydride;
DIPEA means N-ethyl-diisopropylamine or N,N-diisopropylethylamine;
DMA means N,N-Dimethylacetamide;
DMF means N,N-dimethylformamide;
DMSO means Dimethylsulfoxide;
DMSO-d₆ means hexadeuterodimethyl sulfoxide;
EA means ethyl acetate;
Et means ethyl;
Et₂O means diethyl ether;
EtOAc means ethyl acetate;
EtOH means ethanol;
Eq. means equivalent;
g means gram;
HATU means 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate;
HBF₄ means tetrafluoroboric acid;
HCl means hydrochloric acid;
HCOH means formaldehyde;
HCO₂H means formic acid;
Hept means heptet;
¹H NMR means proton nuclear magnetic resonance;
H₂O means water;
H₂O₂ means hydrogen peroxide;
HPLC means high pressure liquid chromatography;
h means hour;
IPA means 2-propanol;
K₂CO₃ means potassium carbonate;
KI means potassium iodide;
KOH means potassium hydroxide;

K_3PO_4 means potassium phosphate tribasic;
L means litre;
LCMS means liquid chromatography mass spectrometry;
LDA means lithium diisopropylamide;
 $LiAlH_4$ means lithium aluminium hydride;
LiOH means lithium hydroxide;
m means multiplet;
M means molar;
Me means methyl;
MeCN means acetonitrile;
MeI means iodomethane;
MeLi means methyl lithium;
MeMgBr means methyl magnesium bromide;
MeNH₂ means methylamine;
MeOH means methanol;
MeOH-d₄ means deuterio-methanol;
mg means milligram;
MgSO₄ means magnesium sulfate;
MHz means mega Hertz;
mins means minutes;
mL means millilitres;
mmol means millimole;
MPLC means medium pressure liquid chromatography;
MS m/z means mass spectrum peak;
MTBE means methyl tert-butyl ether;
N₂ means nitrogen;
NaBH₄ means sodium borohydride;
Na₂CO₃ means sodium carbonate;
NaH means sodium hydride;
NaHCO₃ means sodium bicarbonate;
NaOH means sodium hydroxide;
Na₂SO₄ means sodium sulfate;
NCS means N-chlorosuccinimide;
NH₃ means ammonia;
NH₄Cl means ammonium chloride;
NH₄HCO₃ means ammonium carbonate;
NH₂OH means hydroxylamine;

NH₄OH is ammonium hydroxide;
NMP means N-methyl pyrrolidine;
PE means petroleum ether;
Pd(amphos)Cl₂ means Bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II);
Pd(t-Bu₃P)₂ means Bis(tri-tert-butylphosphine)palladium(0);
Pd(OAc) means palladium acetate;
Pd₂(dba)₃ means tris(dibenzylideneacetone)dipalladium (0);
Pd(dppf)Cl₂ means [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II);
Pd(PPh₃)₄ means tetrakis(triphenylphosphine)palladium(0);
Pd(PPh₃)Cl₂ means Palladium(II)bis(triphenylphosphine) dichloride;
Pd/C means palladium on charcoal;
Pd(OH)₂ means palladium hydroxide;
PPh₃ means triphenylphosphine;
q means quartet;
rt means room temperature;
RT means retention time;
RuPhos Pd G3 means (2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate;
s means singlet;
sat. means saturated;
SFC means supercritical fluid chromatography;
soln. means solution;
t means triplet;
TBAF means Tetrabutylammonium fluoride;
TBDMSCl means tert-Butyl(chloro)dimethylsilane;
TEA means triethylamine;
TFA means trifluoroacetic acid;
TfOH means trifluoroethanesulfonic acid;
THF means tetrahydrofuran;
TLC means thin layer chromatography;
TsOH means p-toluenesulfonic acid;
μL means micro litres;
μmol means micromole;
Xantphos means 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene;
Xantphos Pd G2 means Chloro[(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium(II);

Xantphos Pd G3 means [(4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate;

XPhos Pd G2 means Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II).

[00215] Methods for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

[00216] Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Wuts and Greene, *Protective Groups in Organic Synthesis*, 5th ed., John Wiley & Sons: New Jersey, (2014), which is incorporated herein by reference in its entirety.

[00217] Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance (NMR) spectroscopy (e.g., ¹H or ¹³C), infrared (IR) spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry (MS), or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC). Analytical instruments and methods for compound characterization:

[00218] LC-MS: The liquid chromatography-mass spectrometry (LC-MS) data were obtained with an Agilent Technologies 1200 Series LCMSD utilizing API-ESI ionization fitted with a reverse-phase column (Sunfire C18, 3.5 μm particle size, 4.6 x 50mm dimensions) at 50 degrees Celsius. The mobile phase consisted of a mixture of solvent 0.01% TFA in water and 0.01% TFA in acetonitrile. A constant gradient from 5% increase to 95% organic within 1.3 min, 95% organic for 1.7 min was utilized. The flow rate was constant at 2 mL/min. Alternatively, the liquid chromatography-mass spectrometry (LC-MS) data were obtained with a Agilent Technologies 1200 Series LCMSD utilizing API-ESI ionization utilizing ESI ionization fitted with a reverse-phase column (XBridge C18, 3.5 μm particle size, 4.6 x 50mm dimensions) at 45 degrees Celsius. The mobile phase consisted of a mixture of solvent 10 mM NH₄HCO₃ in water and acetonitrile. A constant gradient from 5% increase to 95% organic within 1.4 min, 95% organic for 1.6 min was utilized. The flow rate was constant at 1.8 mL/min.

[00219] Prep LC-MS: Preparative HPLC was performed on a Gilson 281 Preparative system fitted with a Welch Xtimate 10u C18 100A, AXIA packed, 250 x 21.2 mm reverse-phase column at

20 degrees Celsius. The mobile phase consisted of a mixture of solvent 0.1% formic acid in water and 0.1% formic acid in acetonitrile. A constant gradient from 70% aqueous/30% organic to 30% aqueous/70% organic mobile phase over the course of 15 minutes was utilized. The flow rate was constant at 30 mL/min. Alternatively, fitted with Column: Welch Xtimate 10u C18 21.2*250mm, 10 µm; The mobile phase consisted of a mixture of solvent Water (10 mmol/L $\text{NH}_4\text{HCO}_3 + 0.05\% \text{NH}_3 \cdot \text{H}_2\text{O}$) and acetonitrile. A constant gradient from 70% aqueous/30% organic to 30% aqueous/70% organic mobile phase over the course of 15 minutes was utilized. The flow rate was constant at 30 mL/min.

[00220] Silica gel chromatography: Silica gel chromatography was performed on a Biotage® Isolera One unit, or a Biotage® Isolera Prime unit.

[00221] Proton NMR: ^1H NMR spectra were obtained with a Bruker AVANCE III 400 MHz , 400 MHz NMR instrument (acquisition time = 3.16 seconds with a 1 second delay; 8 to 32 scans) or a Bruker AVANCE III 400MHz , 400 MHz NMR instrument (acquisition time = 3.98 seconds with a 1 second delay; 8 to 32 scans) or a Bruker AVANCE III 500MHz , 500 MHz NMR instrument (acquisition time = 3.17 seconds with a 1 second delay; 8 to 32 scans). Unless otherwise indicated, all protons were reported in DMSO- d_6 solvent as parts-per million (ppm) with respect to residual DMSO (2.50 ppm).

[00222] SFC: Waters Preparative system(SFC80, SFC150, SFC200 , SFC350).

[00223] Chiral-HPLC: Gilson 281(vendor: GILSON)

[00224] One of ordinary skill in the art will recognize that modifications of the gradient, column length, and flow rate are possible and that some conditions may be more suitable for compound characterization than others, depending on the chemical species being analyzed.

[00225] The following codes refer to the preparative HPLC conditions used as indicated in the Preferred Examples and Preparation sections. Individual gradients were optimized for each compound as appropriate.

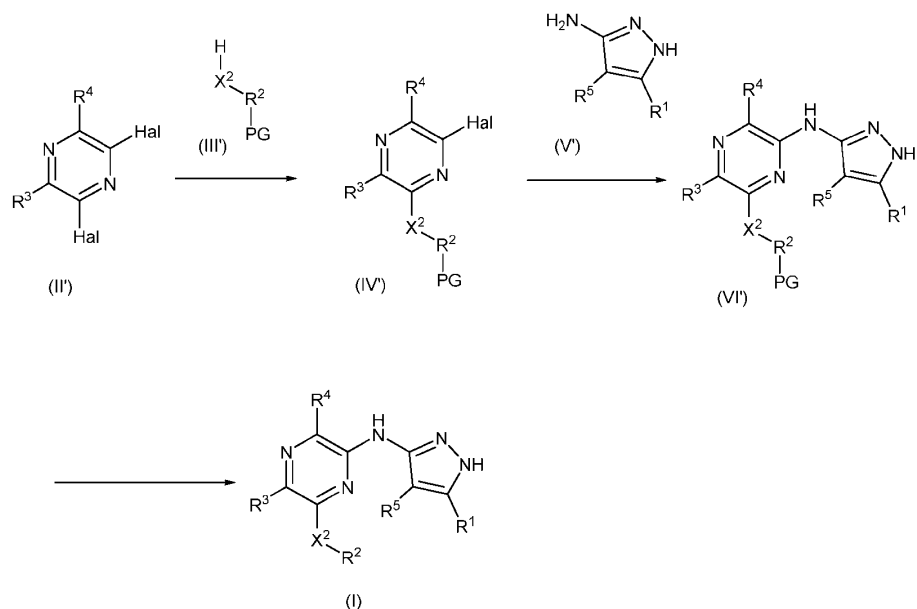
Prep-HPLC Code	Conditions
Method A	Prep-HPLC (Mobile phase: A = water (0.1% NH_4HCO_3), B = MeCN; Gradient: B = 15%-95% in 18 min; Column: Welch Xtimate 10µm 150A 21.2 × 250 mm)
Method B	Prep-HPLC (Mobile phase: A = water (0.1% FA), B= MeCN, Gradient: B = 15% - 35% over 8 min; Column: Welch Xtimate 10µm 150A 21.2 x 250 mm)
Method C	Prep-HPLC (Mobile phase: A = water (10 mM NH_4HCO_3 and $\text{NH}_3 \cdot \text{H}_2\text{O}$), B= MeCN; Gradient: B = 15%-80% in 18 min; Column: Welch Xtimate 10µm 150A 21.2 x 250 mm)

Method D	Prep-HPLC (Mobile phase: A = water (0.225% FA), B= MeCN; Column: Welch Xtimate 10µm 150A 25 mm x 5µm)
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[00226] SFC Conditions

- [00227] Method A:** Column: OD 20*250mm, 10 µm (Daicel), Column temperature: 35°C
Mobile phase: CO₂/MeOH [0.2%NH₃ (7M in MeOH)], Flow rate: 100 g/min, Back pressure: 100 bar, isocratic gradient optimised for each separation.
- [00228] Method B:** Column: IC 20*250mm, 10 µm (Daicel), Column temperature: 35 °C,
Mobile phase: CO₂/ MeOH (0.2%Methanol Ammonia), Flow rate: 100 g/min , Back pressure: 100 bar
- [00229] Method C:** Column: IG 20*250mm, 10 µm (Daicel), Column temperature: 35 °C,
Mobile phase:, CO₂/MeOH [0.2%NH₃(7M in MeOH)], Flow rate: 100 g/min , Back pressure: 100 bar
- [00230] Method D:** Column: IG 20*250mm, 10 µm (Daicel), Column temperature: 35 °C,
Mobile phase: CO₂/IPA[0.5%NH₃(7M in MeOH)], Flow rate: 100 g/min, Back pressure: 100 bar
- [00231] Method E:** Column: AD 20*250mm, 10 µm (Daicel), Column temperature: 35 °C,
Mobile phase: CO₂/MeOH [0.2%NH₃(7M in MeOH)], Flow rate: 100 g/min, back pressure 100 bar
- [00232] Method F:** Column: AD 20*250mm, 10 µm (Daicel), Column temperature: 35°C,
Mobile phase: CO₂/EtOH (0.5%Methanol Ammonia), Flow rate: 100 g/min, Back pressure: 100 bar
- [00233] Method G:** Column: OZ 20*250mm, 10 µm (Daicel), Column temperature: 35°C,
Mobile phase: CO₂/EtOH (0.5%NH₃ (7M in MeOH), Flow rate: 100 g/min , Back pressure: 100 bar
- [00234] Method H:** Column: OJ 20*250mm, 10 µm (Daicel), Column temperature: 35°C,
Mobile phase: CO₂/MeOH (0.2%MeOH/NH₃), Flow rate: 100 g/min
- [00235] Method I:** Column: OX 20*250mm, 10 µm (Daicel), Column temperature: 35°C,
Mobile phase: CO₂/EtOH [0.5%NH₃(7M in MeOH)], Flow rate: 100 g/min, Back pressure: 100 bar
- [00236] Method J:** Column: AS 20*250mm, 10 µm (Daicel), Column temperature: 35 °C,
Mobile phase: CO₂/MeOH [0.2%NH₃ (7M in MeOH)], Flow rate: 100 g/min , Back pressure: 100 bar

General Schemes



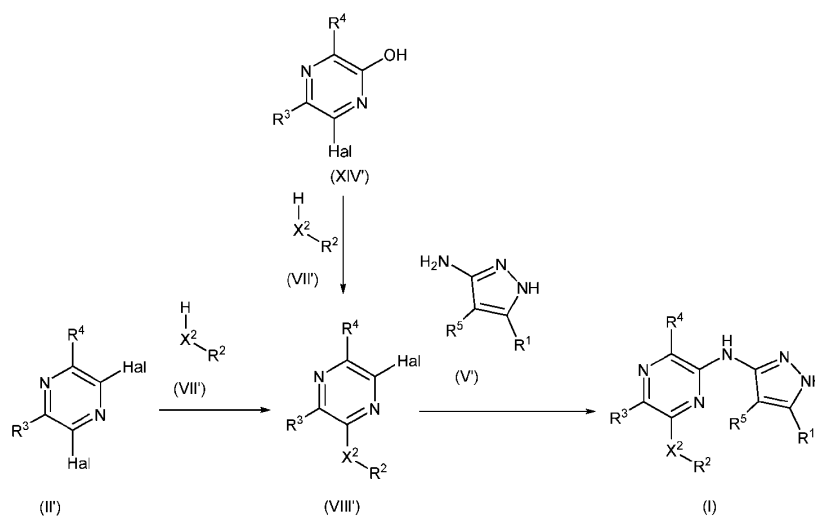
Scheme 1

[00237] In Scheme 1, X^2 is $-O-$, $-NR^b-$, $-NR^b-(C(R^c)_2)_m-$, $-O(C(R^c)_2)_m-$, and $-(C(R^d)_2)_n-O-$. Hal is a halide, preferably Br or Cl or F. PG is a suitable protecting group for a heteroatom, typically an N or O atom. Suitable protecting groups are THP or benzyl for a primary alcohol, or Boc for a primary or secondary amine.

[00238] The compound of formula (IV') may be obtained by the arylation of compound (III') with the aryl halide (II') in the presence of a suitable strong organic or inorganic base, optionally at elevated temperature and optionally under microwave irradiation.

[00239] The compound of Formula (VI') may be obtained from the halide (IV') and the amine (V') by a Buchwald type, palladium catalyzed, cross coupling reaction using a suitable palladium catalyst in the presence of suitable phosphine ligands, in the presence of a suitable inorganic base, in a solvent at elevated temperature.

[00240] Wherein, PG is Boc, the compound of Formula (I) may be obtained by treatment of the compound (VI') with an acid such as HCl or TFA.

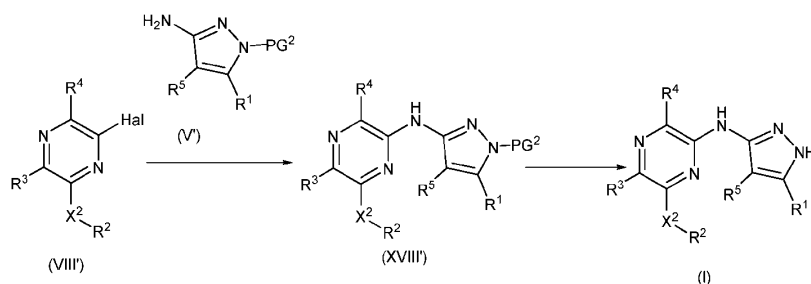


Scheme 2

[00241] In Scheme 2, wherein, X² is -O-, -NR^b-, -NR^b-(C(R^c)₂)_m-, -O(C(R^c)₂)_m-, and -(C(R^d)₂)_n-O-, the compound of Formula (VIII') may be obtained by the arylation of compound (VII') with the aryl halide (II') in the presence of a suitable strong organic or inorganic base, optionally at elevated temperature and under microwave irradiation.

[00242] Alternatively, wherein, X² is -O-, -NR^b-, -NR^b-(C(R^c)₂)_m-, -O(C(R^c)₂)_m-, and -(C(R^d)₂)_n-O-, the compound of Formula (VIII') may be obtained by reaction of the compound (XIV') with the compound (VII') under Mitsunobu conditions.

[00243] The compound of Formula (I) may be obtained from the halide (VIII') and the amine (V') by a Buchwald type, palladium catalyzed, cross coupling reaction as described in Scheme 1.

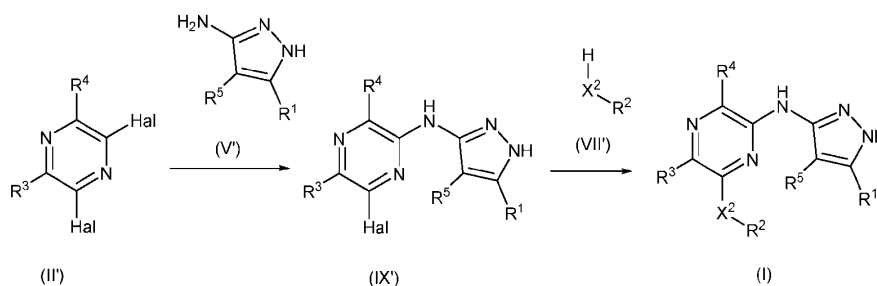


Scheme 2A

[00244] PG₂ is a suitable pyrazole N protecting group, typically a t-butyl or tosyl group.

[00245] Alternatively, it may be necessary to employ a pyrazole protecting group strategy, PG² as shown in Scheme 2A. The compound of Formula (XVIII') may be obtained by reaction of the halide of Formula (VIII') and the amine of Formula (XVIII') under Buchwald type reaction conditions as

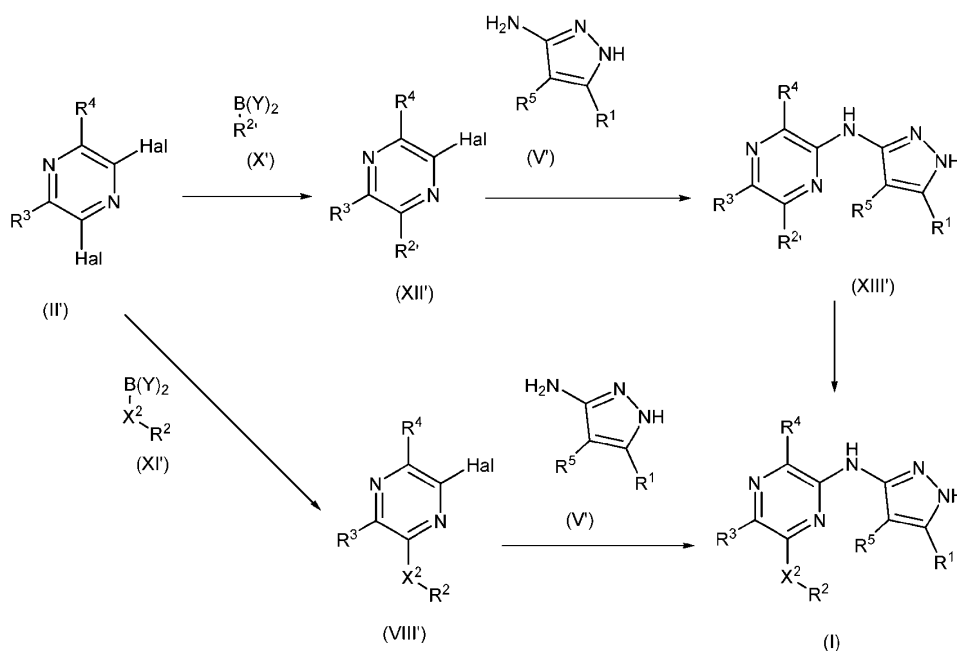
described in Scheme 1. The compound of Formula (I) may be obtained by the deprotection of the compound of Formula (XVIII').



Scheme 3

[00246] The compound of Formula (IX') may be obtained from the halide (II') by an amination reaction with amine (V') in the presence of an inorganic base and suitable solvent at ambient temperature.

[00247] Wherein X^2 is X^2 is $-O-$, $-NR^b$, $-NR^b-(C(R^c)_2)_m-$, $-O(C(R^c)_2)_m-$, or $-(C(R^d)_2)_n-O-$, the compound of Formula (I) may be obtained by the arylation of compound (VII') with the aryl halide (IX') in the presence of a suitable organic or inorganic base, optionally at elevated temperature and optionally under microwave irradiation.



Scheme 4

[00248] R^{2*} is the unsaturated pre-cursor of X^2-R^2 . $B(Y)_2$ is a suitable boronic acid or boronic ester, such as a pinacol ester.

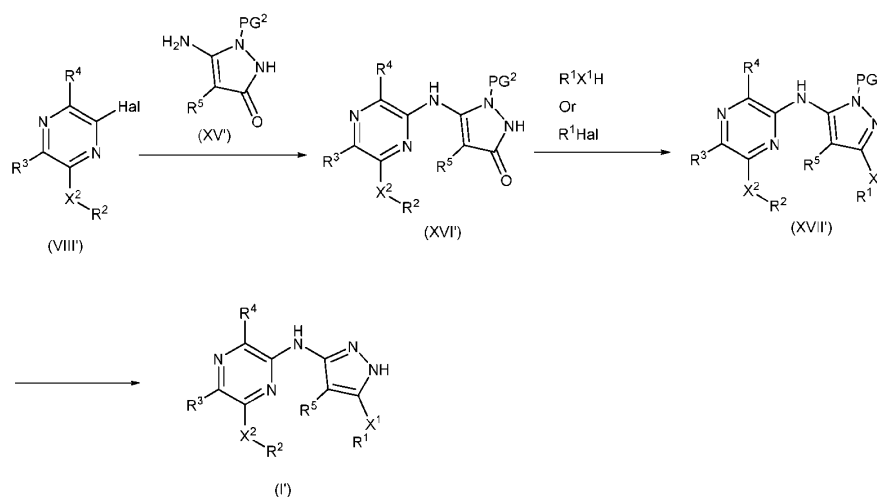
[00249] In Scheme 4, wherein X^2 is $-(C(R^d)_2)_n-$ and R^2 is C_1 - C_4 alkyl, or X^2 and R^2 together form Ring B bonded to the pyrazine, wherein Ring B is C_3 - C_{10} cycloalkyl or 4 to 12-membered heterocyclyl, the compound of Formula (XII') may be obtained from the halide of formula (II') and the boronate ester (X') by a Suzuki type, palladium catalyzed, cross coupling reaction using a suitable palladium catalyst in the presence of suitable phosphine ligands, in the presence of a suitable inorganic base, in a solvent at elevated temperature.

[00250] The compound of Formula (XIII') may be obtained from the halide of formula (XII') and the amine of formula (V') by a Buchwald type, palladium catalyzed, cross coupling reaction as described in Scheme 1.

[00251] The compound of Formula (I) may be obtained from the compound of Formula (XIII') by a hydrogenation reaction, with a suitable transition metal catalyst.

[00252] Alternatively, the compound of Formula (I), wherein X^2 and R^2 together form Ring B bonded to the pyrazine, wherein Ring B is 4 to 12-membered aryl, or 4 to 12-membered heteroaryl, may be obtained from the compounds of Formula (II'), (XI') and (V'), as described for the synthesis of compounds (XII') and (XIII').

[00253] Wherein X^1 is selected from the group consisting of O, $-O(C(R^e)_2)_m-$, the compounds of Formula (I') may be prepared according to Scheme 5.



Scheme 5

[00254] PG^2 is a suitable pyrazole N protecting group, typically a t-butyl or tosyl group.

[00255] The compound of Formula (XVI') may be obtained from the halide of Formula (VIII') and the amine of Formula (XV') by a Buchwald type, palladium catalyzed, cross coupling reaction as described in Scheme 1.

[00256] The compound of Formula (XVII') may be obtained by reaction of the alcohol R¹X¹H and the compound of Formula (XVI') under Mitsunobu reaction conditions. Alternatively, the compound of Formula (XVII') may be obtained by the alkylation of the compound of Formula (XVI') by R¹Hal in the presence of a suitable organic or inorganic base such as K₂CO₃.

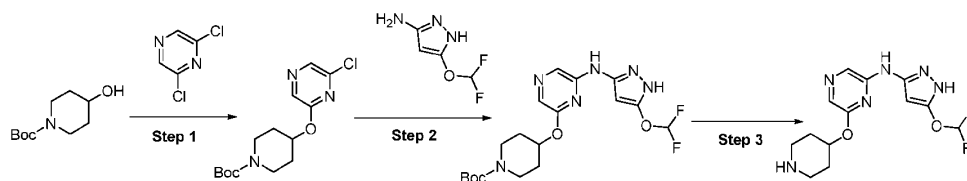
[00257] The compound of Formula (I') may be obtained from the compound of Formula (XVII') by the deprotection of the protecting group. Wherein PG² is t-Butyl, this may be achieved by treatment with formic acid.

[00258] Scheme 6 Compounds of Formula (I) may be converted to alternative compounds of Formula (I) by standard chemical transformations known to those skilled in the art. Examples of these transformations include, but are not limited to: reductive amination reaction with a C₁-C₃alkylaldehyde in the presence of a suitable reducing agent such as NaCN(BH); Grignard reaction of a carbonyl group to provide a secondary or tertiary alcohol; transformation of a primary alcohol to a nitrile group, via a tosylate; oxidation of a thioalkyl group to provide a sulfoxide group; and reduction of a carbonyl group to provide an alcohol. Compounds of Formula (IV'), (VIII'), (XVIII'), (XVI') and (XVII') may be converted to alternative compounds of Formula (IV'), (VIII'), (XVIII'), (XVI') and (XVII') by standard chemical transformations, including those described in Scheme 6.

[00259] Compounds that contain one or more stereocenters may be separated into their separate stereoisomers by typical methods such as chiral SFC or chiral HPLC techniques as indicated in the Examples below.

[00260] It will be appreciated by those skilled in the art that it may be necessary to utilize a suitable protecting group strategy for the preparation of compounds of Formula (I). Typical protecting groups may comprise, benzyl or carbamate and preferably Boc for the protection of primary or secondary aliphatic amines.

[00261] **Example 1, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine**



[00262] *Step 1: Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)piperidine-1-carboxylate*

[00263] To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (30.0 g, 149 mmol) in THF (500 mL) was added NaH (10.7 g, 267 mmol) at 0°C, and the solution stirred for 1 h. 2,6-

Dichloropyrazine (22.1 g, 149 mmol) was added and the reaction mixture stirred at rt for 16 h under N₂. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/1) to give the title product (40 g, 86%) as a yellow solid. LCMS *m/z* = 258 [M-56+H]⁺.

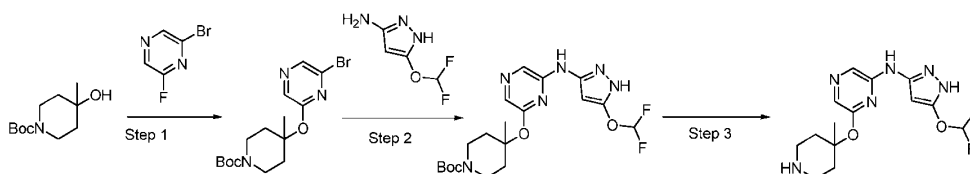
[00264] *Step 2: Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate*

A mixture of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)piperidine-1-carboxylate (28.0 g, 89.2 mmol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (13.2 g, 89.2 mmol), tBuXPhos Pd G3 (4.10 g, 4.46 mmol) and KOAc (26.2 g, 267 mmol) in dioxane (800 mL) was stirred at 100 °C for 16 h under N₂. The reaction was diluted with EtOAc, washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/1) to give the title product (23.6 g, 61%) as a yellow solid. LCMS *m/z* = 427 [M+H]⁺.

[00265] *Step 3: Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-4-yl)oxy)pyrazin-2-amine*

A mixture of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate (23.6 g, 55.3 mmol) and TFA (80 mL) in DCM (300 mL) was stirred at 50 °C for 3 h under N₂. The reaction mixture was concentrated and the residue was purified by Prep-HPLC (Method A) to afford the title product (5.8 g, 31%) as a white solid. LCMS *m/z* = 327 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 10.39 (br s, 1H), 7.78 (s, 1H), 7.58 (s, 1H), 7.25 (t, 1H), 5.99 (s, 1H), 5.10-4.99 (m, 1H), 3.90-3.80 (m, 1H), 3.05-2.97 (m, 2H), 2.69-2.61 (m, 2H), 2.02-1.98 (m, 2H), 1.65-1.53 (m, 2H).

[00266] **Example 2, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((4-methylpiperidin-4-yl)oxy)pyrazin-2-amine**



[00267] *Step 1: Synthesis of tert-butyl 4-((6-bromopyrazin-2-yl)oxy)-4-methylpiperidine-1-carboxylate*

A mixture of 2-bromo-6-fluoropyrazine (200 mg, 1.14 mmol), tert-butyl 4-hydroxy-4-methylpiperidine-1-carboxylate (366 mg, 1.70 mmol) and sodium tert-butoxide (109 mg, 1.14 mmol) in DMA (2 mL) was irradiated by microwave at 80°C for 40 mins. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was concentrated to afford the crude product (320 mg) as a brown oil which was used directly in the next step.

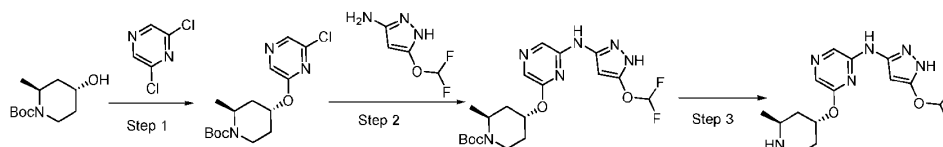
[00268] Step 2: Synthesis of *tert*-butyl 4-((6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-4-methylpiperidine-1-carboxylate

A mixture of *tert*-butyl 4-((6-bromopyrazin-2-yl)oxy)-4-methylpiperidine-1-carboxylate (320 mg, crude), 5-(difluoromethoxy)-1*H*-pyrazol-3-amine (30.1 mg, 0.20 mmol), BrettPhos Pd G4 (31.1 mg, 20 μ mol) and KOAc (117.6 mg, 1.20 mmol) in dioxane (3 mL) was stirred at 100 °C for 3 h under N₂. The reaction mixture was concentrated and the residue was purified by silica gel chromatography eluting with EtOAc/PE (1/4) to give the title product (20 mg, 11%) as a yellow solid. LCMS *m/z* = 441 [M+H]⁺.

[00269] Step 3: Synthesis of *N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-((4-methylpiperidin-4-yl)oxy)pyrazin-2-amine

To a solution of *tert*-butyl 4-((6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-4-methylpiperidine-1-carboxylate (20 mg, 45 μ mol) in DCM (1 mL) was added TFA (0.3 mL) at 0 °C and the reaction mixture stirred at rt for 15 min. The reaction mixture was concentrated and the residue was purified by Prep-HPLC (Method A) to afford the title product (1.5 mg, 9%) as a yellow solid. LCMS *m/z* = 341 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 12.13 (br s, 1H), 9.74 (br s, 1H), 7.78 (s, 1H), 7.57 (s, 1H), 7.22 (t, 1H), 5.95 (s, 1H), 2.80-2.68 (m, 4H), 2.33-2.32 (m, 1H), 2.21-2.17 (m, 2H), 1.69-1.63 (m, 2H), 1.54 (s, 3H).

[00270] Example 3, *N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-(((2*S*,4*R*)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00271] Step 1: Synthesis of *tert*-butyl (2*S*,4*R*)-4-((6-chloropyrazin-2-yl)oxy)-2-methylpiperidine-1-carboxylate

The title compound was obtained as a yellow solid, 1.1 g, 76%, from *tert*-butyl (2*S*,4*R*)-4-hydroxy-2-methylpiperidine-1-carboxylate and 2,6-dichloropyrazine, following the procedure described in Example 1, step 1. LCMS *m/z* = 228 [M-100+H]⁺.

[00272] Step 2: Synthesis of *tert*-butyl (2*S*,4*R*)-4-((6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methylpiperidine-1-carboxylate

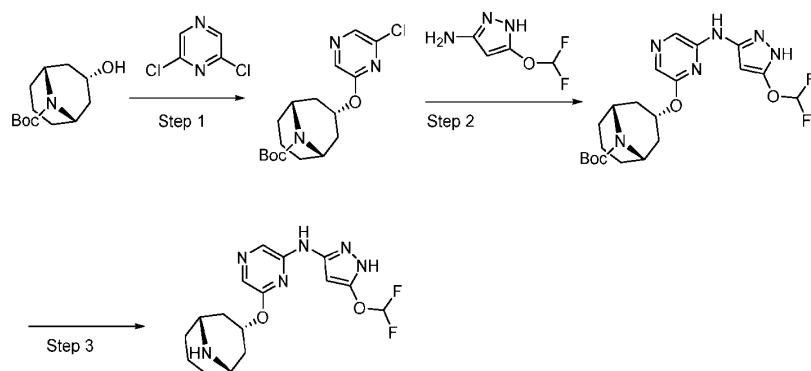
The title compound was obtained as a yellow solid, 750 mg, 51%, from *tert*-butyl (2*S*,4*R*)-4-((6-chloropyrazin-2-yl)oxy)-2-methylpiperidine-1-carboxylate and 5-(difluoromethoxy)-1*H*-pyrazol-3-amine following the procedure described in Example 2 step 2. LCMS *m/z* = 441 [M+H]⁺.

[00273] Step 3: Synthesis of *N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-(((2*S*,4*R*)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine

To a mixture of *tert*-butyl (2*S*,4*R*)-4-((6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-

yl)oxy)-2-methylpiperidine-1-carboxylate (470 mg, 1.06 mmol) in DCM (5 mL) was added 4M HCl in dioxane (5.3 mL) and the reaction mixture stirred at rt for 16 h. The mixture was concentrated and the residue was purified by Prep-HPLC (Method A) to give the title product (226 mg, 62%) as a white solid. LCMS m/z = 341 $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 12.11 (br s, 1H), 10.06 (br s, 1H), 7.76 (s, 1H), 7.60 (s, 1H), 7.24 (t, 1H), 5.95 (s, 1H), 5.30-5.25 (m, 1H), 2.94-2.67 (m, 4H), 1.87-1.78 (m, 2H), 1.68-1.62 (m, 1H), 1.39-1.32 (m, 1H), 0.96 (d, 3H).

[00274] Example 4, 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine formate



[00275] Step 1: Synthesis of tert-butyl (1R,3r,5S)-3-((6-chloropyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate

The title compound was obtained as a yellow oil, 500 mg, 86%, from *tert*-butyl (1R,3r,5S)-3-hydroxy-9-azabicyclo[3.3.1]nonane-9-carboxylate and 2,6-dichloropyrazine, following a similar procedure to that described in Example 1, step 1. LCMS m/z = 354 $[M+H]^+$.

[00276] Step 2: Synthesis of tert-butyl (1R,3r,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate

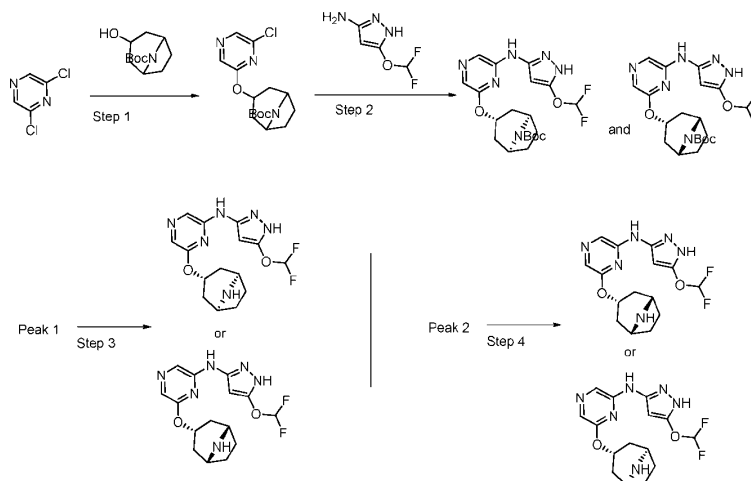
The title compound was obtained as a yellow solid, 300 mg, 91%, from *tert*-butyl (1R,3r,5S)-3-((6-chloropyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar procedure to that described in Example 2, step 2. LCMS m/z = 467 $[M+H]^+$.

[00277] Step 3: Synthesis of 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine formate

To a solution of *tert*-butyl (1R,3r,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate (200 mg, 0.43 mmol) in DCM (3 mL) was added a solution of HCl in dioxane (1 mL, 6M, 6.0 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated *in vacuo* and the residue was purified by Prep-HPLC (Method B) to afford the title product (125.6 mg, 70%) as a white solid. LCMS m/z = 367 $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 12.93 (br s, 1H), 11.26 (br s, 1H), 8.44 (s, 1H), 7.77 (s, 1H), 7.58 (s, 1H), 7.27 (t,

1H), 6.00 (s, 1H), 5.27 (quintet, 1H), 3.55 (s, 2H), 2.53-2.50 (m, 1H), 2.50-2.44 (m, 2H), 2.44-2.36 (m, 1H), 1.90-1.80 (m, 4H), 1.62-1.54 (m, 2H), 1.50-1.44 (m, 1H).

[00278] Example 5 and Example 23, 6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine hydrochloride and 6-(((1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine hydrochloride



[00279] Step 1: Synthesis of tert-butyl 3-((6-chloropyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate

[00280] tert-Butyl 3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (99.9 mg, 0.44 mmol) was dissolved in THF (4 mL), NaH (100 mg, 2.40 mmol, 60% w/mineral oil) was added and the mixture was shaken at 30 °C for 0.5 h. 2,6-Dichloropyrazine (59.6 mg, 0.40 mmol) was added and the reaction mixture was shaken at 30 °C for 2 h. The reaction mixture was diluted with water (3 mL) and extracted with EtOAc (10 mL x 3). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound.

[00281] Step 2: Synthesis of tert-butyl (1R,3r,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1R,3s,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate

[00282] A mixture of 5-(difluoromethoxy)-1H-pyrazol-3-amine (89.4 mg, 0.60 mmol), tert-butyl 3-((6-chloropyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (crude, 0.40 mmol), KOAc (117.6 mg, 1.20 mmol) and Brettphos Pd G3 (18.12 mg, 0.02 mmol) in t-AmOH (3 mL) was stirred at 100°C for 2 h under N₂. The cooled reaction mixture was diluted with EtOAc (5 mL) and washed with water (5 mL x 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to afford crude product. This was purified by Prep-HPLC (Method A) to afford tert-butyl

3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate. This product was then separated by Chiral SFC (Column: IC 20*250mm, 10 μ m (Daicel), Column temperature: 35 $^{\circ}$ C, Mobile phase: CO₂/ MeOH (0.2% MeOH/NH₃) = 75/25, at 100 g/min, to give Peak 1, tert-butyl (1R,3r,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1R,3s,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate and Peak 2, tert-butyl (1R,3s,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1R,3r,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate. LCMS m/z = 453 [M+H]⁺.

[00283] *Step 3: Synthesis of 6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine hydrochloride or 6-(((1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine hydrochloride*

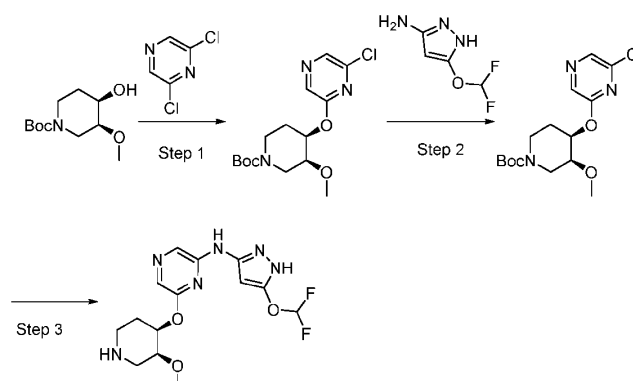
[00284] To a mixture of Peak 1, step 2 (7.0 mg, 15.5 μ mol) in DCM (2.0 mL) was added 4M HCl/dioxane (0.5 mL) at 0 $^{\circ}$ C under N₂ and the reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was evaporated under reduced pressure to afford the title product,

Example 23, (1.8 mg, 33%) as a yellow solid. LCMS m/z = 353 [M+H]⁺. ¹HNMR (400 MHz, DMSO-d₆) δ ppm 10.07 (s, 1H), 9.20 (s, 1H), 7.83 (s, 1H), 7.61 (s, 1H), 7.38 (s, 1H), 7.26 (t, 1H), 7.13 (s, 1H), 5.96 (s, 1H), 5.37-5.30 (m, 1H), 4.08-4.01 (m, 2H), 2.25-2.18 (m, 2H), 2.05-1.82 (m, 6H).

[00285] *Step 4: Synthesis of 6-(((1R,3r,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine hydrochloride or 6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine hydrochloride*

[00286] HCl/dioxane (0.5 mL) was added to a solution of Peak 2, step 2, (8.0 mg, 17.7 μ mol) in DCM (2 mL) and the reaction mixture stirred at 25 $^{\circ}$ C for 2 h. The mixture was concentrated to afford the title product, **Example 5**, (3.4 mg, 54%) as a yellow solid. LCMS m/z = 353 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-d₆) δ ppm 10.11 (br s, 1H), 9.02 (br s, 1H), 8.81 (br s, 1H), 7.84 (s, 1H), 7.66 (s, 1H), 7.28 (t, 1H), 5.92 (s, 1H), 5.35-5.30 (m, 1H), 5.30-5.25 (m, 1H), 4.01-3.96 (m, 2H), 2.35-1.97 (m, 8H).

[00287] **Example 6**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-methoxypiperidin-4-yl)oxy)pyrazin-2-amine



[00288] Step 1: *tert-butyl (3S,4R)-4-((6-chloropyrazin-2-yl)oxy)-3-methoxypiperidine-1-carboxylate*

[00289] To a solution of *tert-butyl (3S,4R)-4-hydroxy-3-methoxypiperidine-1-carboxylate* (0.50 g, 2.16 mmol) in THF (4.32 mL, 2.16 mmol) was added NaH (0.104 g, 4.32 mmol) in portions at 0°C. After stirring for 1 h, 2,6-dichloropyrazine (0.32 g, 2.16 mmol) was added and the reaction mixture stirred at rt for 5 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with EtOAc/Hexane (1/4) to afford the title compound (636 mg, 86 %) as a white solid.

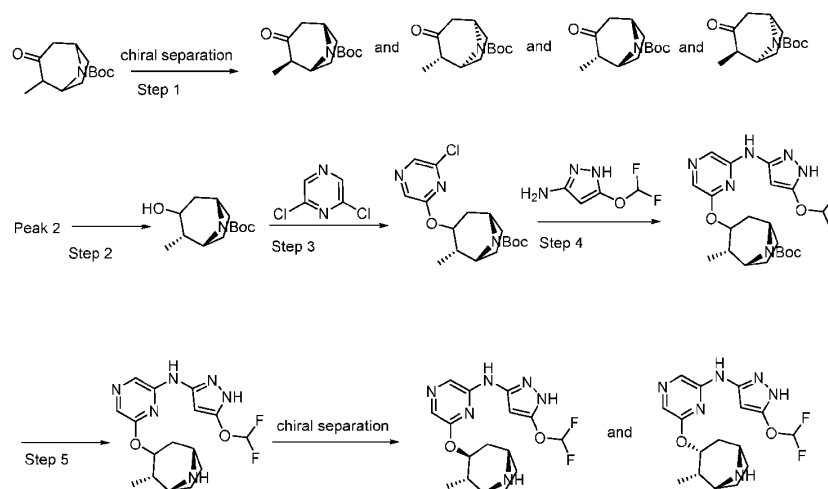
[00290] Step 2: *tert-butyl (3S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methoxypiperidine-1-carboxylate*

[00291] A mixture of the compound from step 1 (0.318 g, 0.925 mmol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (0.152 g, 1.02 mmol), Brettphos Pd G4 (21 mg, 0.023 mmol) and KOAc (0.182 g, 1.85 mmol) in dioxane (4.62 mL) was heated at 100°C overnight under N₂. The reaction mixture was cooled to rt and concentrated, and the residue was purified by column chromatography on silica gel eluting with EtOAc/hexane (5/1 to 1:5) to give the title compound (0.27 g, 64.0 %).

[00292] Step 3: *N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-methoxypiperidin-4-yl)oxy)pyrazin-2-amine*

[00293] The compound from step 2 (0.27 g, 0.592 mmol) was dissolved in DCM (2 mL) and TFA (0.5 mL) and the reaction mixture was stirred overnight at rt. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC (Method A) to give the title compound (0.112 g, 34.0 %). LCMS *m/z* = 357.1 [M+H]⁺. ¹H NMR (500 MHz, DMSO) δ ppm 10.20 (br s, 1H), 8.25 (s, 1H), 7.71 (s, 1H), 7.54 (d, *J* = 3.4 Hz, 1H), 7.18 (s, 1H), 5.87 (s, 1H), 5.27-5.17 (m, 1H), 3.41 (s, 3H), 2.95-2.77 (m, 2H), 2.69-2.61 (m, 2H), 1.84-1.79 (m, 2H), 1.66-1.61 (m, 2H).

[00294] **Example 7**, *N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine* and **Example 128**, *N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine*



[00295] Step 1: Synthesis of *tert*-butyl (1*R*,2*R*,5*S*)-2-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate, *tert*-butyl (1*S*,2*S*,5*R*)-2-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate, *tert*-butyl (1*R*,2*S*,5*S*)-2-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate and *tert*-butyl (1*S*,2*R*,5*R*)-2-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate

[00296] *Tert*-butyl 2-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (1.9 g) was separated by chiral Prep-SFC (Column: IG 20*250mm, 10 μ m (Daicel), Column temperature: 35 °C, Mobile phase: CO₂/ MeOH (0.2% MeOH/NH₃) = 60/40, at 100 g/min) to give Peak 1, as a mixture of 2 isomers, Peak 2 (600 mg) *tert*-butyl (1*R*,2*S*,5*S*)-2-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate and Peak 3. Peak 2 was further purified by Prep-HPLC (Method A) to afford the title product (210 mg) as a yellow solid.

[00297] Step 2: Synthesis of *tert*-butyl (1*R*,2*S*,5*S*)-3-hydroxy-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate

[00298] To a mixture of Peak 2, step 1 (210 mg, 0.88 mmol) in MeOH (5 mL) was added NaBH₄ (33 mg, 0.88 mmol) at 0° and the reaction mixture stirred at 0 °C to rt for 2 h. The reaction was quenched with water at 0 °C and concentrated in vacuo. The residue was partitioned between EtOAc and water, the layers separated, the aqueous layer extracted with EtOAc and the combined organic phases concentrated in vacuo. The residue was purified by silica gel chromatography eluting with EtOAc/PE (1/4) to give the title product (143 mg, 68%). LCMS *m/z* = 186 [M-56+H]⁺.

[00299] Step 3: Synthesis of *tert*-butyl (1*R*,2*S*,5*S*)-3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate

[00300] The title compound was obtained as a yellow solid, 195 mg, 93%, from the compound from step 2 and 2,6-dichloropyrazine, following a similar procedure to that described in Example 1, step 1. LCMS *m/z* = 298 [M-56+H]⁺.

[00301] *Step 4: Synthesis of tert-butyl (1R,2S,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate*

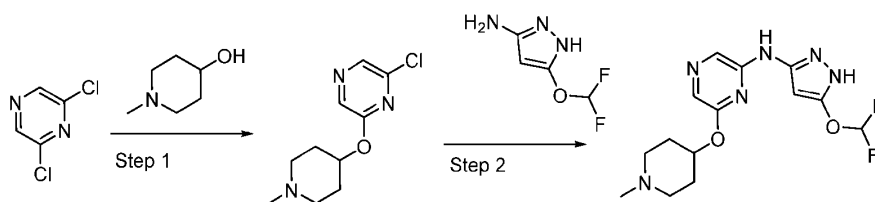
[00302] The title compound was obtained as a brown oil, 195 mg, 76%, from the compound from step 3 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 2, step 2. LCMS m/z = 467 $[M+H]^+$.

[00303] *Step 5: Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine and N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine*

[00304] At 0°C, to a mixture of the compound from step 4 (195 mg, 0.42 mmol) in DCM (5 mL) was added TFA (2.5 mL) and the reaction mixture allowed to warm to rt and stirred for 2 h. The solution was concentrated in vacuo and the residue was purified by Prep-HPLC (Method A). The product was further purified by chiral Prep-SFC (Column: AS 20*250mm, 10 μ m (Daicel), Column temperature: 35 °C, Mobile phase: CO₂/MeOH [0.2%NH₃(7M in MeOH)] = 75/25 at 100 g/min to give peak 1, Example 128, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine. ¹H NMR (500 MHz, DMSO-d₆): δ 12.15 (br s, 1H), 10.10 (br s, 1H), 7.75 (s, 1H), 7.56 (s, 1H), 7.24 (t, 1H), 5.98 (s, 1H), 4.85-4.78 (m, 1H), 3.56-3.52 (m, 1H), 2.10-2.04 (m, 1H), 1.98-1.90 (m, 1H), 1.84-1.70 (m, 2H), 1.66-1.56 (m, 2H), 1.48-1.40 (m, 1H), 0.87 (d, 3H).

[00305] and peak 2, Example 7 (15.7 mg, 10%) as an off-white solid. The structure of Example 7 was confirmed by X-ray crystallography. LCMS m/z = 367 $[M+H]^+$. ¹H NMR (500 MHz, DMSO-d₆) δ 12.12 (br s, 1H), 10.26 (br s, 1H), 7.75 (s, 1H), 7.57 (s, 1H), 7.25 (t, 1H), 5.94 (s, 1H), 5.14-5.12 (m, 1H), 3.19 - 3.15 (m, 1H), 2.25 - 2.18 (m, 1H), 2.17 - 2.11 (m, 1H), 1.96 - 1.90 (m, 1H), 1.85 - 1.75 (m, 2H), 1.71 - 1.62 (m, 1H), 1.61 - 1.52 (m, 1H), 0.89 (d, 3H)

[00306] **Example 8**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



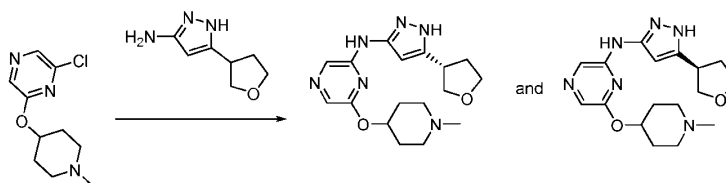
[00307] *Step 1: Synthesis of 2-chloro-6-((1-methylpiperidin-4-yl)oxy)pyrazine*

The title compound was obtained as a pale-yellow oil, 15 g, 64%, from 1-methylpiperidin-4-ol and 2,6-dichloropyrazine, following a similar procedure to that described in Example 1, step 1. LCMS m/z = 228 $[M+H]^+$.

[00308] *Step 2: Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

A mixture of 2-chloro-6-((1-methylpiperidin-4-yl)oxy)pyrazine (13.0 g, 57.0 mmol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (8.49 g, 57.0 mmol), KOAc (10.20 g, 104 mmol) and BrettPhos Pd G4 (1.5 g, 0.97 mmol) in dioxane (220 mL) was stirred at 100°C for 24 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with MeOH/DCM (1/5) to give crude product (5.2 g). This was further purified by Prep-HPLC (Method A) to give the title product (3.70 g, 19%). LCMS $m/z = 341$ $[M+H]^+$. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ ppm 11.93 (br s, 1H), 9.95 (br s, 1H), 7.77 (s, 1H), 7.59 (s, 1H), 7.24 (t, 1H), 5.97 (s, 1H), 4.93 (quintet, 1H), 2.70-2.55 (m, 2H), 2.24 (s, 3H), 2.26-2.12 (m, 2H), 2.00-1.93 (m, 2H), 1.75-1.63 (m, 2H).

[00309] Example 9 and Example 97, (S)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine formate or (R)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine formate and (R)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine formate or (S)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine formate

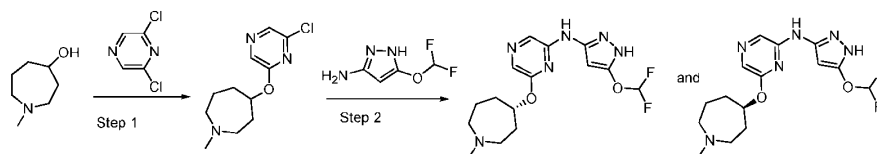


[00310] A mixture of Example 8, step 1 (200 mg, 878 μmol), 5-(oxolan-3-yl)-1H-pyrazol-3-amine (160 mg, 1.05 mmol), BrettPhos-Pd-G4 (20 mg, 0.02 mmol) and KOAc (171 mg, 1.75 mmol) in dioxane (20 mL) was stirred at 120 °C for 15 h under N_2 . The cooled reaction mixture was diluted with EtOAc, filtered and the filtrate was concentrated under reduced pressure. The crude was purified by Prep-HPLC (Method A) to afford the racemic product (80 mg) and then separated by chiral Prep-SFC (Column: OD 20*250mm, 10 μm (Daicel), Column temperature: 35 °C, Mobile phase: CO_2/EtOH [0.5% NH_3 (7M in MeOH)] = 65/35 at 100 g/min, Back pressure: 100 bar to give Example 9, Peak 1 (31.5 mg, 10%). $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ ppm 12.13 (br s, 1H), 9.69 (br s, 1H), 7.92 (s, 1H), 7.45 (s, 1H), 6.31 (s, 1H), 4.95-4.90 (m, 1H), 4.04-3.99 (m, 1H), 3.90-3.85 (m, 1H), 3.83-3.77 (m, 1H), 3.63-3.55 (m, 1H), 3.42-3.37 (m, 1H), 2.75-2.65 (m, 2H), 2.33-2.25 (m, 1H), 2.23 (s, 3H), 2.20-2.04 (m, 2H), 2.03-1.93 (m, 3H), 1.74-1.69 (m, 2H).

[00311] and Example 97, Peak 2, (24.1 mg, 8%). LCMS $m/z = 345$ $[M+H]^+$. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ ppm 11.93 (br s, 1H), 9.68 (br s, 1H), 7.93 (s, 1H), 7.46 (s, 1H), 6.31 (s, 1H), 4.95-4.90 (m, 1H), 4.04-3.99 (m, 1H), 3.90-3.85 (m, 1H), 3.83-3.77 (m, 1H), 3.63-3.55 (m, 1H), 3.42-3.37 (m, 1H), 2.75-2.65 (m, 2H), 2.33-2.25 (m, 1H), 2.23 (s, 3H), 2.20-2.04 (m, 2H), 2.03-1.93 (m, 3H), 1.74-1.69 (m, 2H).

[00312] **Example 10**, (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylazepan-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylazepan-4-yl)oxy)pyrazin-2-amine and

[00313] **Example 151**, (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylazepan-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylazepan-4-yl)oxy)pyrazin-2-amine



[00314] *Step 1: Synthesis of 4-((6-chloropyrazin-2-yl)oxy)-1-methylazepane*

To a solution of 1-methylazepan-4-ol (1.0 g, 7.75 mmol) and 2,6-dichloropyrazine (1.25 g, 8.36 mmol) in THF (10 mL) was added NaH (200 mg, 8.36 mmol) at 0 °C, and the reaction mixture stirred at rt for 1 h. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered and concentrated to afford the title compound (1.5 g, 79%) which was used directly in the next step. LCMS m/z = 242 [M+H]⁺.

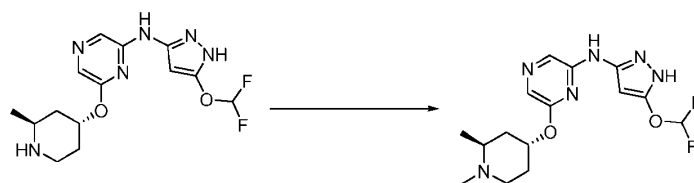
[00315] *Step 2: Synthesis of (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylazepan-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylazepan-4-yl)oxy)pyrazin-2-amine*

A mixture of 4-((6-chloropyrazin-2-yl)oxy)-1-methylazepane (500 mg, 2.07 mmol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (463 mg, 3.11 mmol), Brettphos-Pd-G4 (50 mg, 0.03 mmol) and KOAc (608 mg, 6.21 mmol) in dioxane (20 mL) was stirred at 90 °C overnight. The reaction mixture was cooled to rt and concentrated to give a residue which was purified by Prep-HPLC (Method A), to afford the racemic product. This was then separated by chiral Prep-SFC (Column: OZ 20*250mm, 10μm (Daicel), Column temperature: 35 °C Mobile phase: CO₂/ EtOH (0.5% NH₃ (7M in MeOH) = 70/30, at 100 g/min, to give

[00316] peak 1, Example 151, LCMS m/z = 355 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.01 (br s, 1H), 10.06 (br s, 1H), 7.77 (s, 1H), 7.57 (s, 1H), 7.25 (t, 1H), 5.98 (s, 1H), 5.24-5.19 (m, 1H), 2.81-2.75 (m, 2H), 2.73-2.69 (m, 2H), 2.41 (s, 3H), 2.27-2.10 (m, 2H), 2.01-1.93 (m, 2H), 1.89-1.76 (m, 2H).

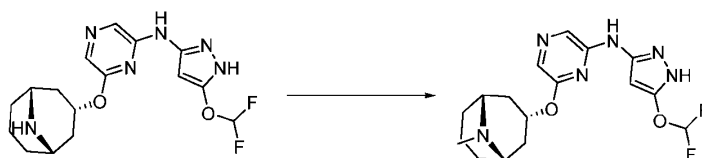
[00317] and peak 2, Example 10 (10.6 mg, 1%). LCMS m/z = 355 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.98 (br s, 1H), 10.05 (s, 1H), 7.77 (s, 1H), 7.58 (s, 1H), 7.26 (t, 1H), 5.97 (s, 1H), 5.26-5.20 (m, 1H), 3.00-2.89 (m, 2H), 2.79-2.67 (m, 2H), 2.45 (s, 3H), 2.15-2.09 (m, 2H), 1.96-1.91 (m, 2H), 1.87-1.77 (m, 2H)..

[00318] **Example 11**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine



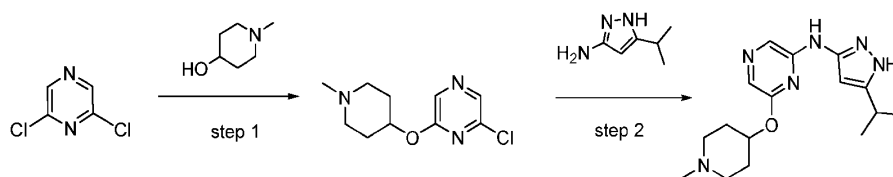
[00319] A mixture of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine (Example 3, 500 mg, 1.46 mmol), acetic acid (0.2 mL) and aq. HCHO (0.2 mL) in MeOH (10 mL) was stirred at rt for 1 h. NaBH₃CN (135.8 mg, 2.19 mmol) was added and the resulting mixture was stirred for 1 h. The reaction mixture was concentrated and the residue was purified by Prep-HPLC (Method A) to afford the title product (130.1 mg, 25%) as a white solid. LCMS *m/z* = 355 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.93 (br s, 1H), 9.98 (s, 1H), 7.77 (s, 1H), 7.59 (s, 1H), 7.24 (t, 1H), 5.95 (s, 1H), 5.23-5.17 (m, 1H), 2.60-2.54 (m, 1H), 2.38-2.27 (m, 2H), 2.19 (s, 3H), 1.89-1.80 (m, 3H), 1.60-1.50 (m, 1H), 0.98 (d, 3H).

[00320] **Example 12**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyrazin-2-amine



[00321] The title compound was obtained as a white solid, 43.7 mg, 28% from 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine (Example 4), following the procedure described in Example 11. LCMS *m/z* = 381 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.94 (br s, 1H), 9.96 (s, 1H), 7.77 (s, 1H), 7.57 (s, 1H), 7.23 (t, 1H), 6.02 (s, 1H), 5.31 (quintet, 1H), 2.98-2.92 (m, 2H), 2.50-2.40 (m, 2H), 2.39 (s, 3H), 2.24-2.16 (m, 1H), 1.95-1.85 (m, 2H), 1.54-1.40 (m, 3H), 1.25-1.11 (m, 2H).

[00322] **Example 13**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylazepan-4-yl)oxy)pyrazin-2-amine



[00323] *Step 1: Synthesis of 4-((6-chloropyrazin-2-yl)oxy)-1-methylazepane:*

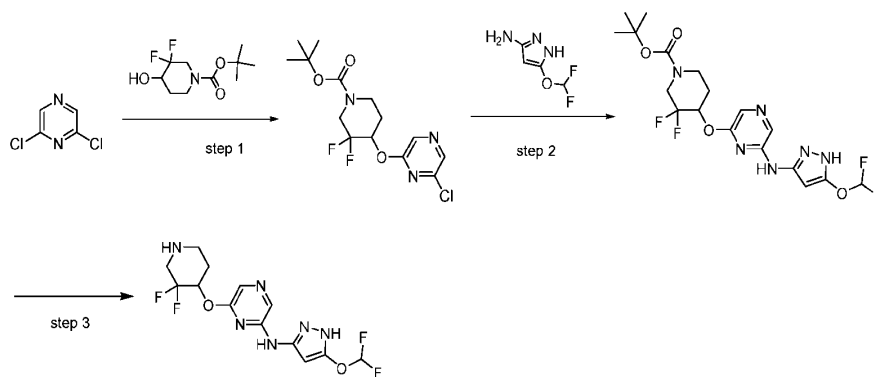
[00324] 1-Methylpiperidin-4-ol (92.65 mg, 0.81 mmol) was dissolved in THF (4 mL), NaH (193.2 mg, 4.83 mmol, 60% w/mineral oil) was added and the mixture was shaken at 30 °C for 0.5 h. 2,6-Dichloropyrazine (119.1 mg, 0.81 mmol) was added and the reaction mixture was shaken at 30 °C for 2 h. Water (3 mL) was added and the mixture extracted with EtOAc (10 mLx3). The combined

organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the title product which was used into the next step without further purification.

[00325] Step 2: *Synthesis of N-(5-isopropyl-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

[00326] 5-Isopropyl-1H-pyrazol-3-amine (111.2 mg, 0.89 mmol), 2-chloro-6-((1-methylpiperidin-4-yl)oxy)pyrazine (crude, 0.40 mmol), KOAc (157.8 mg, 1.61 mmol) and tBuXPhos Pd G3 (31.97 mg, 0.04 mmol) were combined in THF (4 mL) and the reaction mixture was stirred at 110 °C for 5 h under N_2 . The reaction mixture was diluted with EtOAc (5 mL) and washed with water (5 mL x 3). The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford crude product. This was purified by prep-HPLC (Method C) to afford the title product (91.42 mg, 35.9% yield). LCMS: $m/z = 317$ $[\text{M}+\text{H}]^+$.

[00327] **Example 14**, *N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-difluoropiperidin-4-yl)oxy)pyrazin-2-amine*



[00328] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-3,3-difluoropiperidine-1-carboxylate*

[00329] The title product was obtained from tert-butyl 3,3-difluoro-4-hydroxypiperidine-1-carboxylate and 2,6-dichloropyrazine, following the procedure described in Example 13, step 1.

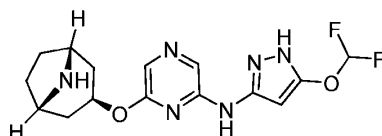
[00330] Step 2: *Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3,3-difluoropiperidine-1-carboxylate*

[00331] 5-(Difluoromethoxy)-1H-pyrazol-3-amine (89.4 mg, 0.60 mmol), tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-3,3-difluoropiperidine-1-carboxylate (crude, 0.40 mmol), KOAc (117.6 mg, 1.20 mmol) and BrettPhos Pd G3 (18.12 mg, 0.02 mmol) were combined in t-AmOH (3 mL) and the reaction mixture was stirred at 100 °C for 2 h under N_2 . The mixture was diluted with EtOAc (5 mL) and washed with water (5 mL x 3). The organic layer was dried over Na_2SO_4 , filtered and evaporated to afford the title product, which was used without further purification.

[00332] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-difluoropiperidin-4-yl)oxy)pyrazin-2-amine*

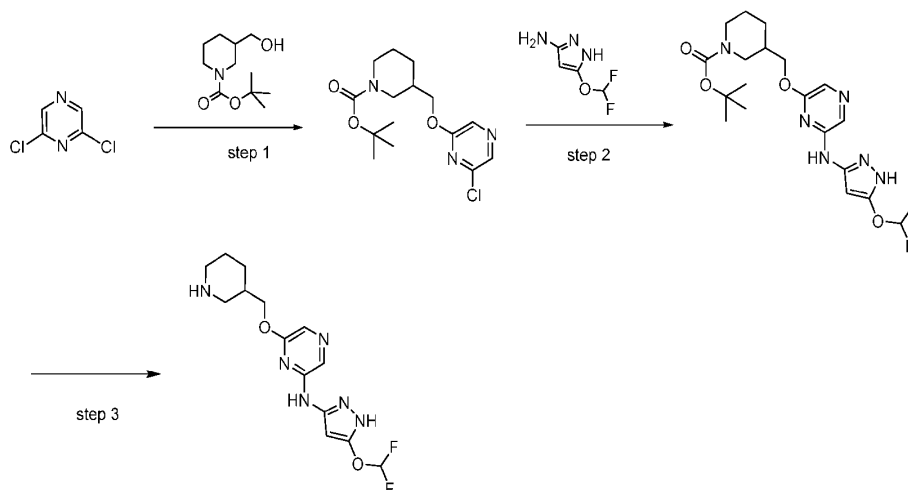
[00333] tert-Butyl 4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3,3-difluoropiperidine-1-carboxylate (crude, 0.40 mmol) was dissolved in DCM (3 mL), then TFA (1 mL) was added and the reaction mixture was stirred at 30 °C for 2 h. The mixture was concentrated under reduced pressure and the crude product was purified by prep-HPLC (Method C) to afford the title product (28.65 mg, 19.8% yield). LCMS m/z = 363 [M+H]⁺

[00334] **Example 15**, Rac-6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



[00335] The title compound was obtained from 2,6-dichloropyrazine, rac-tert-butyl (1R,3s,5S)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the 3-step procedure described in Example 14. LCMS m/z = 353 [M+H]⁺

[00336] **Examples 16**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-ylmethoxy)pyrazin-2-amine



[00337] **Step 1: Synthesis of tert-butyl 3-(((6-chloropyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate:**

[00338] The title compound was obtained, crude from tert-butyl 3-(hydroxymethyl)piperidine-1-carboxylate and 2,6-dichloropyrazine following the procedure described in Example 13, step 1.

[00339] **Step 2: Synthesis of tert-butyl 3-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate:**

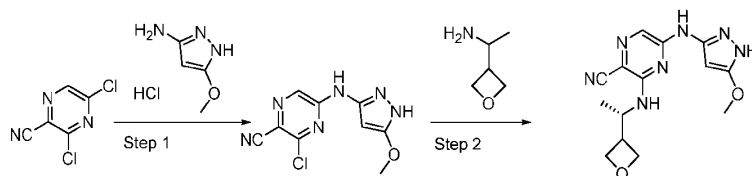
[00340] 5-(Difluoromethoxy)-1H-pyrazol-3-amine (89.4 mg, 0.60 mmol), tert-butyl 3-(((6-chloropyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate (crude, 0.40 mmol), Cs₂CO₃ (390.9 mg, 1.20

mmol) and BrettPhos Pd G3 (18.12 mg, 0.02 mmol) were combined in t-AmOH (3 mL) and the reaction mixture was stirred at 100 °C for 2 h under N₂. The reaction was diluted with EtOAc (5 mL) and washed with water (5 mL x 3). The organic layer was dried over Na₂SO₄, filtered and evaporated to afford the title product which was used into the next step without further purification.

[00341] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-ylmethoxy)pyrazin-2-amine*

The title compound was obtained, 29.9 mg, 22% from tert-butyl 3-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate, following the procedure described in Example 14, step 3. LCMS *m/z* = 341 [M+H]⁺.

[00342] **Example 17, (S)-5-((5-methoxy-1H-pyrazol-3-yl)amino)-3-((1-(oxetan-3-yl)ethyl)amino)pyrazine-2-carbonitrile**



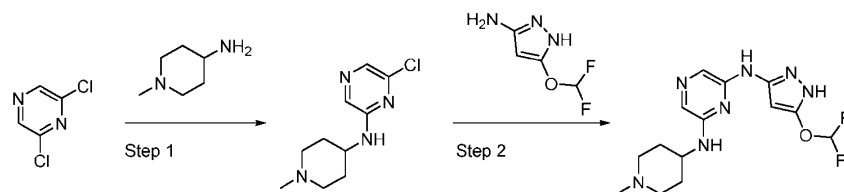
[00343] Step 1: *Synthesis of 3-chloro-5-((5-methoxy-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile*

[00344] A mixture of 3,5-dichloropyrazine-2-carbonitrile (600 mg, 3.44 mmol), 5-methoxy-1H-pyrazol-3-amine hydrochloride (466 mg, 4.12 mmol) and NaHCO₃ (1.15 g, 13.7 mmol) in DMA (20 mL) was stirred at rt for 4 h under N₂. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was purified by column chromatography on silica gel eluting with EtOAc/PE (1/1) to afford the title compound (130 mg, 15% yield) as a white solid. LCMS *m/z* = 251 [M+H]⁺

[00345] Step 2: *Synthesis (S)-5-((5-methoxy-1H-pyrazol-3-yl)amino)-3-((1-(oxetan-3-yl)ethyl)amino)pyrazine-2-carbonitrile*

[00346] A mixture of 3-chloro-5-((5-methoxy-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile (130 mg, 0.5 mmol), 1-(oxetan-3-yl)ethan-1-amine (62.7 mg, 0.6 mmol) and DIPEA (199 mg, 1.55 mmol) in NMP (8 mL) was stirred at 100°C for 16 h under N₂. The reaction mixture was purified by Prep-HPLC (Method A) to afford 5-((5-methoxy-1H-pyrazol-3-yl)amino)-3-((1-(oxetan-3-yl)ethyl)amino)pyrazine-2-carbonitrile (~90 mg). This was further separated by chiral Prep-HPLC Column: IC 20*250mm, 10 μm (Daicel), Column temperature: 35 °C, Mobile phase: CO₂/ MeOH (0.2% MeOH/NH₃) =65/35, Flow rate: 80 g/min to give peak 1, the title compound (35.6 mg, 21% yield) as a white solid. LCMS *m/z* = 316 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 12.05 (br s, 1H), 10.36 (br s, 1H), 7.52 (s, 1H), 7.06 (s, 1H), 5.99 (br s, 1H), 4.69-4.57 (m, 3H), 4.36-4.26 (m, 2H), 3.81 (s, 3H), 3.21-3.12 (m, 1H), 1.12 (d, 3H).

[00347] **Example 18,** N2-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-N6-(1-methylpiperidin-4-yl)pyrazine-2,6-diamine



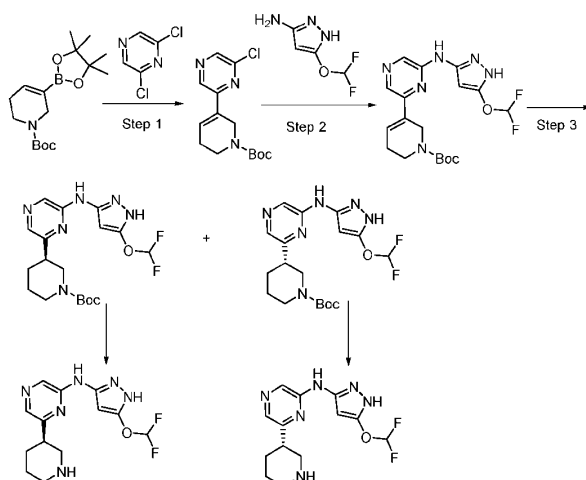
[00348] *Step 1: Synthesis of 6-chloro-N-(1-methylpiperidin-4-yl)pyrazin-2-amine*

[00349] A mixture of 2,6-dichloropyrazine (80.0 mg, 0.537 mmol), 1-methylpiperidin-4-amine (61.3 mg, 0.537 mmol) and DIPEA (207 mg, 1.65 mmol) in NMP (5 mL) was irradiated at 100 °C by microwave for 2 h. The reaction mixture was diluted with DCM and washed with water and brine. The organic layer was concentrated and the residue was purified by column chromatography on silica gel eluting with DCM/MeOH (10/1) to afford the title compound (50.0 mg, 41% yield) as a colorless oil. LCMS $m/z = 227$ $[M+H]^+$

[00350] *Step 2: Synthesis of N2-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-N6-(1-methylpiperidin-4-yl)pyrazine-2,6-diamine*

[00351] A mixture of 6-chloro-N-(1-methylpiperidin-4-yl)pyrazin-2-amine (50.0 mg, 0.22 mmol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (32.8 mg, 0.22 mmol), BrettPhos Pd G4 (20.2 mg, 22.0 μ mol) and KOAc (64.7 mg, 0.66 mmol) in dioxane (5 mL) was stirred at 100 °C for 16 h under N_2 . The reaction mixture was concentrated *in vacuo* and the residue was purified by Prep-HPLC (Method A) to afford the title compound (11.7 mg, 15% yield) as a yellow solid. LCMS $m/z = 340$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 11.99 (s, 1H), 9.82 (s, 1H), 7.31 (s, 1H), 7.30 (s, 1H), 7.24 (t, 1H), 6.90 (d, 1H), 5.66 (s, 1H), 3.48-3.45 (m, 1H), 2.77-2.74 (m, 2H), 2.20 (s, 3H), 2.10-2.05 (m, 2H), 1.93-1.88 (m, 2H), 1.50-1.42 (m, 2H).

[00352] **Example 19 and 20** (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine and (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine



[00353] Step 1: *Synthesis of tert-butyl 5-(6-chloropyrazin-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate*

[00354] A mixture of tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (500 mg, 1.61 mmol), 2,6-dichloropyrazine (479 mg, 3.22 mmol), Pd(dppf)Cl₂ (116 mg, 0.16 mmol) and KOAc (316 mg, 3.23 mmol) in dioxane (8 mL) and H₂O (2 mL) was stirred at 100 °C for 5 h. The reaction mixture was cooled to rt and concentrated to give a residue which was purified by column chromatography on silica gel (PE: EtOAc=1:4) to afford the title compound (380 mg, 80% yield) as a yellow solid. LCMS *m/z* = 296 [M-56+H]⁺.

[00355] Step 2: *Synthesis of tert-butyl 5-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate*

[00356] A mixture of tert-butyl 5-(6-chloropyrazin-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate (300 mg, 1.01 mmol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (195 mg, 1.31 mmol), BrettPhos Pd G4 (77.5 mg, 0.05 mmol) and KOAc (198 mg, 2.02 mmol) in dioxane (4 mL) was stirred at 100 °C for 15 h under N₂. The reaction mixture was cooled to rt and concentrated to give a residue which was purified by column chromatography on silica gel (PE: EtOAc=1:4) to afford the title compound (311 mg, 75% yield) as a yellow solid. LCMS *m/z* = 409 [M+H]⁺.

[00357] Step 3: *Synthesis of tert-butyl (R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate and tert-butyl (S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate*

[00358] A mixture of tert-butyl 5-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (300 mg, 734 μmol) and PtO₂ (49.9 mg, 220 μmol) in EtOAc (6 mL) was stirred under a balloon of H₂ at rt for 24 h. The reaction mixture was diluted with EtOAc and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by Prep-HPLC (Method A) to afford tert-butyl 3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-

yl)piperidine-1-carboxylate (~100 mg). This was separated by chiral Prep-HPLC Column: IG 20*250mm, 10 μ m (Daicel), Column temperature: 35 °C Mobile phase: CO₂/MeOH [0.2%NH₃(7M in MeOH)] = 80/20, Flow rate: 100 g/min to give peak 1, tert-butyl (R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate or tert-butyl (S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate (50 mg, 33% yield) and peak 2, tert-butyl (S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate or tert-butyl (R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate (40 mg, 26% yield). LCMS m/z = 411 [M+H]⁺

[00359] Step 4: *Synthesis of (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine*

[00360] To a solution of peak 1, tert-butyl (R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate or tert-butyl (S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate (50 mg, 0.12 mmol) in DCM (1 mL) was added TFA (1 mL) and the reaction mixture was stirred at rt for 0.5 h. The mixture was concentrated *in vacuo* and the residue was purified with Prep-HPLC (Method A) to give the desired product,

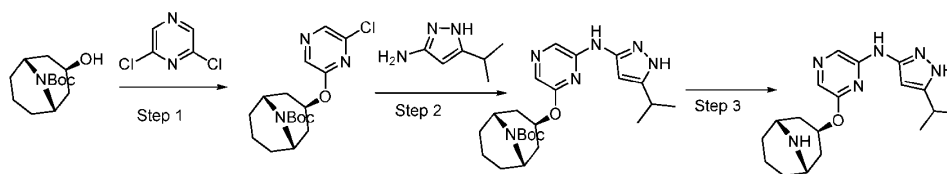
Example 20, (30.1 mg, 80% yield) as a white solid. LCMS m/z = 311 [M+H]⁺ ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 10.37 (br s, 1H), 8.05 (s, 1H), 7.92 (s, 1H), 7.26 (t, 1H), 5.91 (s, 1H), 3.17-3.04 (m, 2H), 2.98-2.87 (m, 1H), 2.87-2.75 (m, 2H), 2.75-2.65 (m, 1H), 2.02-1.81 (m, 1H), 1.75-1.57 (m, 2H), 1.54-1.38 (m, 1H).

[00361] Step 5: *Synthesis of (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine*

[00362] To a solution of peak 2, tert-butyl (S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate or tert-butyl (R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate (40 mg, 97.4 μ mol) in DCM (1 mL) was added TFA (1 mL) and the reaction mixture was stirred at rt for 0.5 h. The mixture was concentrated *in vacuo* and the residue was purified with Prep-HPLC (Method A) to obtain the desired product,

Example 19, (16.8 mg, 55% yield) as a white solid. LCMS m/z = 311 [M+H]⁺ ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 8.06 (s, 1H), 7.91 (s, 1H), 7.25 (t, 1H), 5.95 (s, 1H), 4.19-4.02 (m, 1H), 3.18-3.05 (m, 1H), 3.00-2.90 (m, 1H), 2.86-2.69 (m, 2H), 2.00-1.88 (m, 1H), 1.76-1.61 (m, 2H), 1.52-1.37 (m, 1H).

[00363] **Example 21**, 6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine



[00364] Step 1: *Synthesis of tert-butyl (1R,3s,5S)-3-((6-chloropyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate*

[00365] To a solution of tert-butyl (1R,3s,5S)-3-hydroxy-9-azabicyclo[3.3.1]nonane-9-carboxylate (300 mg, 1.24 mmol) and 2,6-dichloropyrazine (184 mg, 1.24 mmol) in THF (5 ml) was added 60% NaH (99.1 mg, 2.48 mmol) at 0 °C, then stirred at 0 °C for 2 hr. The LCMS showed the reaction was full conversion. The reaction mixture was quenched with water, diluted with EA. The separated organic layer was washed with water and brine, evaporated in vacuo. The residue was purified by silica gel chromatography (PE/EA=3/1) to give the title product (400 mg, yield 91%) as a colorless solid. LCMS m/z = 298 [M-56+H]⁺.

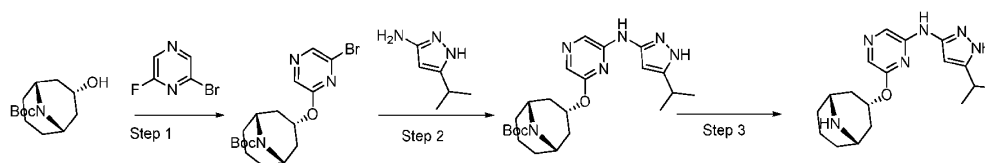
[00366] Step 2: *Synthesis of tert-butyl (1R,3s,5S)-3-((5-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate*

[00367] A mixture of tert-butyl (1R,3s,5S)-3-((6-chloropyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate (180 mg, 508 μmol), 5-(propan-2-yl)-1H-pyrazol-3-amine (63.5 mg, 508 μmol), BrettPhos Pd G4 (78.0 mg, 50.8 μmol) and KOAC (149 mg, 1.52 mmol) in dioxane (5ml) was stirred at 90 °C for 2hr. The LCMS showed the reaction was full conversion. The reaction mixture was concentrated, and the residue was purified by flash chromatography on silica gel (PE/EA=3/2) to give the title product (150 mg, yield 66%) as a colorless solid. LCMS m/z = 443 [M+H]⁺.

[00368] Step 3: *Synthesis of 6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine*

[00369] To a solution of tert-butyl (1R,3s,5S)-3-((6-([5-(propan-2-yl)-1H-pyrazol-3-yl]amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate (150 mg, 338 μmol) in DCM (2.0 mL) was added TFA (0.5 mL) at RT. The mixture was stirred at rt for 2hr. The LCMS showed the reaction was completed. The reaction mixture was concentrated, and the residue was purified by Prep-HPLC (Mobile phase: A = water (0.1% NH₄HCO₃), B = acetonitrile; Gradient: B = 15%-95% in 18 min; Column: Xtimate 10 μm 150A 21.2×250mm) to give the title product (25.7 mg, 22% yield) as a yellow solid. LCMS m/z = 343 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 12.01 (br. s., 1H), 9.58 (s, 1H), 7.88 (s, 1H), 7.38 (s, 1H), 6.24 (s, 1H), 5.84-5.75 (m, 1H), 3.27-3.25 (m, 2H), 2.91-2.86 (m, 1H), 2.19-2.14 (m, 2H), 1.82-1.68 (m, 6H), 1.63-1.60 (m, 3H), 1.21 (d, *J* = 7.2 Hz, 6H).

[00370] **Example 22**, 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine



[00371] Step 1: *Synthesis of tert-butyl (1R,3r,5S)-3-((6-bromopyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate*

To a mixture of tert-butyl (1R,3r,5S)-3-hydroxy-9-azabicyclo[3.3.1]nonane-9-carboxylate (750 mg, 3.10 mmol) and 2-bromo-6-fluoropyrazine (818 mg, 4.65 mmol) in dry THF (10 mL) was added NaH, 60% in mineral oil (186 mg, 4.65 mmol) at 0°C. The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/2) to obtain the title compound (659 mg, 53%). LCMS *m/z* = 399 [M+H]⁺.

[00372] Step 2: *Synthesis of tert-butyl (1R,3r,5S)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate*

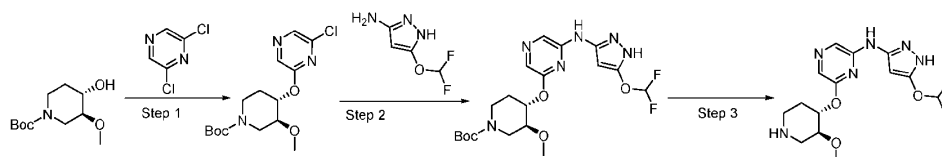
The title compound was obtained as a yellow solid, 150 mg, 45%, from the compound from step 1 and 5-(propan-2-yl)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS *m/z* = 443 [M+H]⁺.

[00373] Step 3: *Synthesis of 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine*

The title compound was obtained as a white solid, 38.6 mg, 38%, from the compound from step 2, following the procedure described in Example 3, step 3. LCMS *m/z* = 343 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.92 (br s, 1H), 9.57 (s, 1H), 7.94 (s, 1H), 7.42 (s, 1H), 6.28 (s, 1H), 5.39-5.31 (m, 1H), 3.27-3.22 (m, 2H), 2.92-2.88 (m, 1H), 2.41-2.37 (m, 2H), 2.14-2.08 (m, 1H), 1.59-1.56 (m, 2H), 1.48-1.35 (m, 6H), 1.22 (d, 6H).

[00374] Example 23 see Example 5.

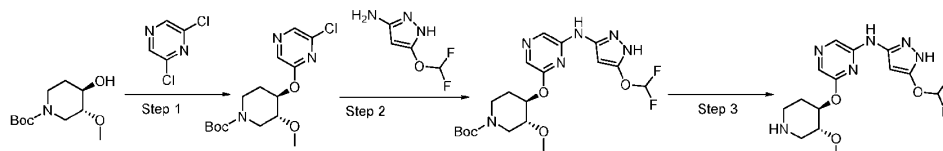
[00375] **Example 24**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methoxypiperidin-4-yl)oxy)pyrazin-2-amine



[00376] The title compound was obtained from tert-butyl (3S,4S)-4-hydroxy-3-methoxypiperidine-1-carboxylate, 2,6-dichloropyrazine and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the 3-step procedure described in Example 6. LCMS *m/z* = 357 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 12.02 (br s, 1H), 10.04 (s, 1H), 7.78 (s, 1H), 7.62 (s, 1H), 7.24 (t, 1H),

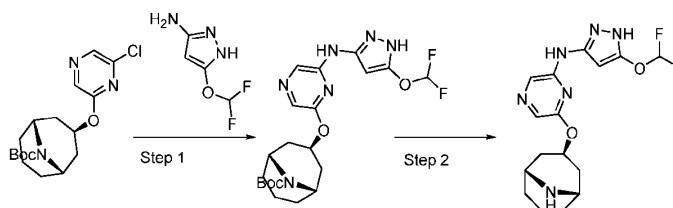
5.94 (s, 1H), 4.96-4.90 (s, 1H), 3.31 (s, 3H), 3.26-3.21 (m, 1H), 2.94-2.90 (m, 1H), 2.57-2.55 (m, 1H), 2.48-2.42 (m, 1H), 2.07-2.00 (m, 1H), 1.56-1.50 (m, 1H).

[00377] Example 25, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methoxypiperidin-4-yl)oxy)pyrazin-2-amine



[00378] The title compound was obtained from tert-butyl (3R,4R)-4-hydroxy-3-methoxypiperidine-1-carboxylate, 2,6-dichloropyrazine and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the 3-step procedure described in Example 6. LCMS $m/z = 357$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 13.06 (br s, 1H), 11.25 (s, 1H), 8.37 (s, 2H), 7.74 (s, 1H), 7.58 (s, 1H), 7.22 (t, 1H), 5.99 (s, 1H), 4.97-4.92 (m, 1H), 3.32 (s, 3H), 3.26-3.22 (m, 1H), 3.02-2.91 (m, 1H), 2.60-2.54 (m, 1H), 2.50-2.40 (m, 1H), 2.11-2.07 (m, 1H), 1.58-1.50 (m, 1H).

[00379] Example 26, 6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



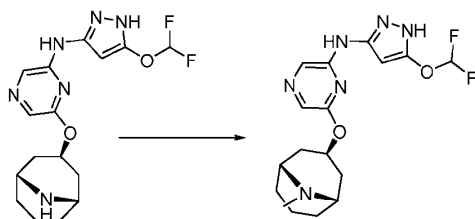
[00380] Step 1: *Synthesis of tert-butyl (1R,3s,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate*

The title compound was obtained as a yellow solid (563 mg, 77%), from Example 21, step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following the procedure described in Example 19 and 20, step 2. LCMS $m/z = 467$ $[M+H]^+$.

[00381] Step 2: *Synthesis of 6-(((1R,3s,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

The title compound was obtained as a white solid, 49.7 mg, 31%, from the compound from step 1, following the procedure described in Example 3, step 3. LCMS $m/z = 367$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 10.56 (br s, 1H), 7.75 (s, 1H), 7.54 (s, 1H), 7.23 (t, 1H), 6.05 (s, 1H), 5.93-5.74 (m, 1H), 4.45-4.35 (m, 1H), 3.38-3.30 (m, 2H), 3.20-3.13 (m, 1H), 2.24-2.06 (m, 2H), 1.88-1.73 (m, 4H), 1.73-1.63 (m, 4H).

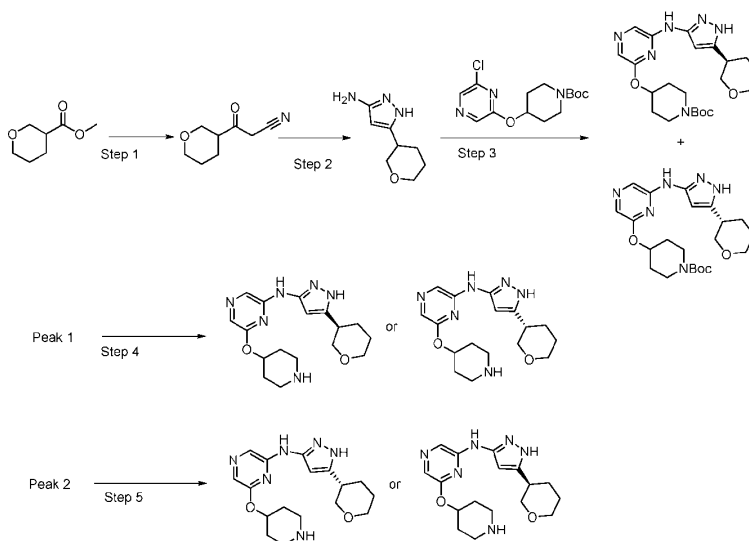
[00382] Example 27, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,3s,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyrazin-2-amine



[00383] The title compound was obtained as a white solid, 134.4 mg, 28%, from Example 26 and HCHO following the procedure described in Example 11. LCMS $m/z = 381$ $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 9.94 (br s, 1H), 7.75 (s, 1H), 7.54 (s, 1H), 7.21 (t, 1H), 6.03 (s, 1H), 5.74-5.65 (m, 1H), 3.50-3.40 (m, 2H), 2.98-2.87 (m, 2H), 2.41 (s, 3H), 1.96-1.82 (m, 5H), 1.75-1.62 (m, 2H), 1.51-1.45 (m, 2H).

[00384] **Example 28.** (R)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine and

[00385] **Example 29,** (S)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine



[00386] Step 1: *Synthesis of 3-oxo-3-(tetrahydro-2H-pyran-3-yl)propanenitrile*

A solution of LDA (10.0 mmol, n-hexane solution) in THF (15 mL) was cooled to -78°C under Ar and treated dropwise with MeCN (0.75 mL, 15.0 mmol) in THF (2 mL) and the solution stirred for 1 h at -78°C . A solution of methyl tetrahydro-2H-pyran-3-carboxylate (2.0 g, 13.0 mmol) in THF (10 mL) was added dropwise and the reaction mixture was stirred for 18 h from -78°C to 20°C . The reaction was quenched with water, then concentrated *in vacuo*. The residue was dissolved in water,

washed with Et₂O, the aqueous phase was acidified with 1N HCl to pH=3, then extracted with EtOAc. The organic phase was sequentially washed with water, brine, then dried over Na₂SO₄, filtered and evaporated. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/3) to give the title product (590 mg, 29%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.02-3.98 (m, 1H), 3.86-3.81 (m, 1H), 3.66-3.61 (m, 1H), 3.54 (s, 2H), 3.51-3.45 (m, 1H), 2.87-2.80 (m, 1H), 2.03-1.99 (m, 1H), 1.85-1.54 (m, 3H).

[00387] Step 2: *Synthesis of 5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-amine*

A solution of 3-oxo-3-(tetrahydro-2H-pyran-3-yl)propanenitrile (590 mg, 2.7 mmol), hydrazine hydrate (410 mg, 8.1 mmol) and conc. HCl (0.2 mL, 2.7 mmol) in IPA (5 mL) was stirred at 90°C for 18 h. The reaction mixture was diluted with MeOH and treated with solid Na₂CO₃, then filtered. The filtrate was concentrated and the residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/5 to 4/1) to give the title compound (600 mg, 90%) as a yellow oil. LCMS m/z = 168 [M+H]⁺.

[00388] Step 3: *Synthesis of tert-butyl (R)-4-((6-((5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate and tert-butyl (S)-4-((6-((5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate*

[00389] Peak 1, tert-butyl (R)-4-((6-((5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate or tert-butyl (S)-4-((6-((5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate (100 mg, 35%) and Peak 2, tert-butyl (S)-4-((6-((5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate or tert-butyl (R)-4-((6-((5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate (97 mg, 34%) were obtained from 5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-amine and Example 1, step 1 following the procedure described in Example 24 and 25, step 1. LCMS m/z = 445 [M+H]⁺.

[00390] Step 4: *Synthesis of (R)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine*

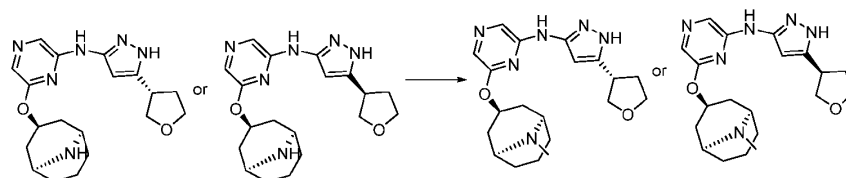
The title compound, **Example 28**, was obtained as a white solid, 41.5 mg, 53%, from Peak 1, step 3, following the method described in Example 2, step 3. LCMS m/z = 345 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.07 (br s, 1H), 9.64 (s, 1H), 7.94 (s, 1H), 7.46 (s, 1H), 6.26 (s, 1H), 5.06-5.03 (m, 1H), 3.94-3.91 (m, 1H), 3.84-3.80 (m, 1H), 3.40-3.31 (m, 2H), 3.13-3.11 (m, 2H), 2.90-2.76 (m, 3H), 2.11-1.96 (m, 3H), 1.74-1.53 (m, 6H).

[00391] Step 5: *Synthesis of (S)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-(piperidin-4-yloxy)-N-(5-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine*

The title compound, **Example 29**, was obtained as a white solid, 61 mg, 81%, from Peak 2, step 3,

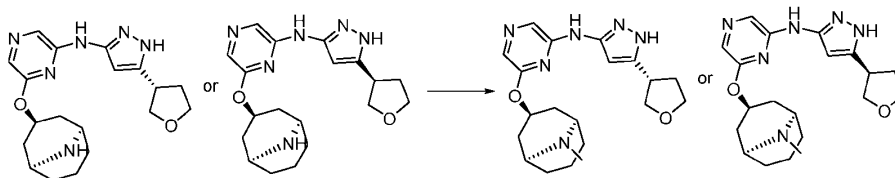
following the procedure described in Example 2, step 3. LCMS $m/z = 345$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.06 (br s, 1H), 9.64 (s, 1H), 7.94 (s, 1H), 7.46 (s, 1H), 6.26 (s, 1H), 5.04-5.05 (m, 1H), 3.94-3.91 (m, 1H), 3.84-3.80 (m, 1H), 3.40-3.31 (m, 2H), 3.13-3.11 (m, 2H), 2.90-2.76 (m, 3H), 2.11-1.96 (m, 3H), 1.74-1.53 (m, 6H).

[00392] Example 30, 6-(((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine



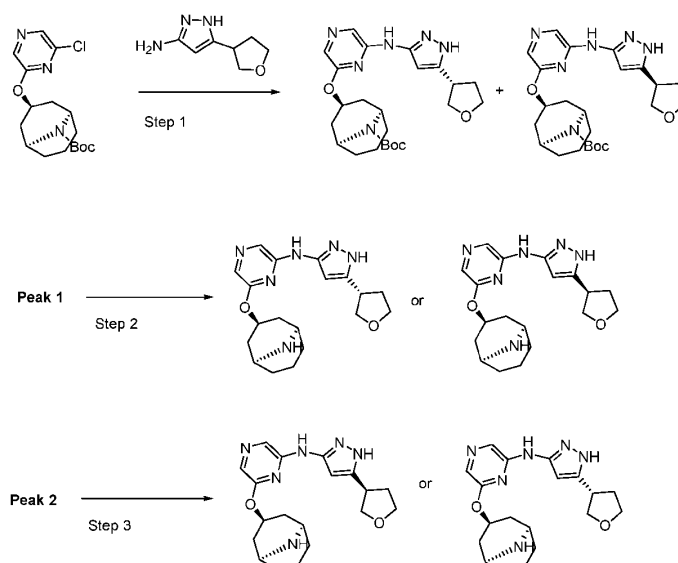
[00393] A mixture of Example 32 (80 mg, 215 μ mol), formaldehyde (50 mg, 645 μ mol) and NaCNBH₃ (40 mg, 645 μ mol) was stirred at rt for 16 h under N₂. The reaction mixture was purified by Prep-HPLC (Method A) to afford the title product (17.5 mg, 21%) as a yellow solid. LCMS $m/z = 385$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 12.09 (br s, 1H), 9.64 (s, 1H), 7.94 (s, 1H), 7.43 (s, 1H), 6.34 (s, 1H), 5.35-5.30 (m, 1H), 4.03-3.97 (m, 1H), 3.87-3.77 (m, 2H), 3.62-3.55 (m, 1H), 3.42-3.35 (m, 2H), 3.31-2.97 (m, 2H), 2.57-2.52 (m, 1H), 2.40 (s, 3H), 2.33-2.22 (m, 1H), 2.20-2.08 (m, 1H), 1.99-1.86 (m, 3H), 1.51-1.40 (m, 3H), 1.10-1.01 (m, 2H).

[00394] Example 31, 6-(((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine



[00395] The title compound was obtained as a yellow solid, 2.8 mg, 15%, from Example 33 and formaldehyde, following the procedure described in Example 30. LCMS $m/z = 385$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 12.09 (br s, 1H), 9.64 (s, 1H), 7.94 (s, 1H), 7.43 (s, 1H), 6.34 (s, 1H), 5.35-5.30 (m, 1H), 4.03-3.97 (m, 1H), 3.87-3.77 (m, 2H), 3.62-3.55 (m, 1H), 3.42-3.35 (m, 2H), 3.31-2.97 (m, 2H), 2.57-2.52 (m, 1H), 2.40 (s, 3H), 2.33-2.22 (m, 1H), 2.20-2.08 (m, 1H), 1.99-1.86 (m, 3H), 1.51-1.40 (m, 3H), 1.10-1.01 (m, 2H).

[00396] Example 32 and Example 33, 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine and 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine



[00397] Step 1: *Synthesis of tert-butyl (1R,3r,5S)-3-((6-((5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate and tert-butyl (1R,3r,5S)-3-((6-((5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate*

[00398] A mixture of Example 4, step 1 (400 mg, 1.13 mmol), 5-(oxolan-3-yl)-1H-pyrazol-3-amine (258 mg, 1.69 mmol), BrettPhos Pd G₄ (40 mg, 0.04 mmol) and KOAc (331 mg, 3.38 mmol) in dioxane (30 mL) was stirred at 100 °C for 16 h under N₂. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was purified by column chromatography on silica gel eluting with EtOAc/PE (10/1) to afford the racemic product compound (380 mg) as a yellow solid. This was separated by chiral -SFC (Column: IC 20*250mm, 10 μm (Daicel), Column temperature: 35 °C, Mobile phase: CO₂/ [MeOH/MeCN [0.2%NH₃(7M in MeOH)] 1:1]= 55/45, Flow rate: 120 g/min, Back pressure: 100 bar to give Peak 1, tert-butyl (1R,3r,5S)-3-((6-((5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate or tert-butyl (1R,3r,5S)-3-((6-((5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate (180 mg) and Peak 2, tert-butyl (1R,3r,5S)-3-((6-((5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate or tert-butyl (1R,3r,5S)-3-((6-((5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-9-azabicyclo[3.3.1]nonane-9-carboxylate (180 mg). LCMS m/z = 471 [M+H]⁺.

[00399] Step 2: *Synthesis of Example 32, 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine*

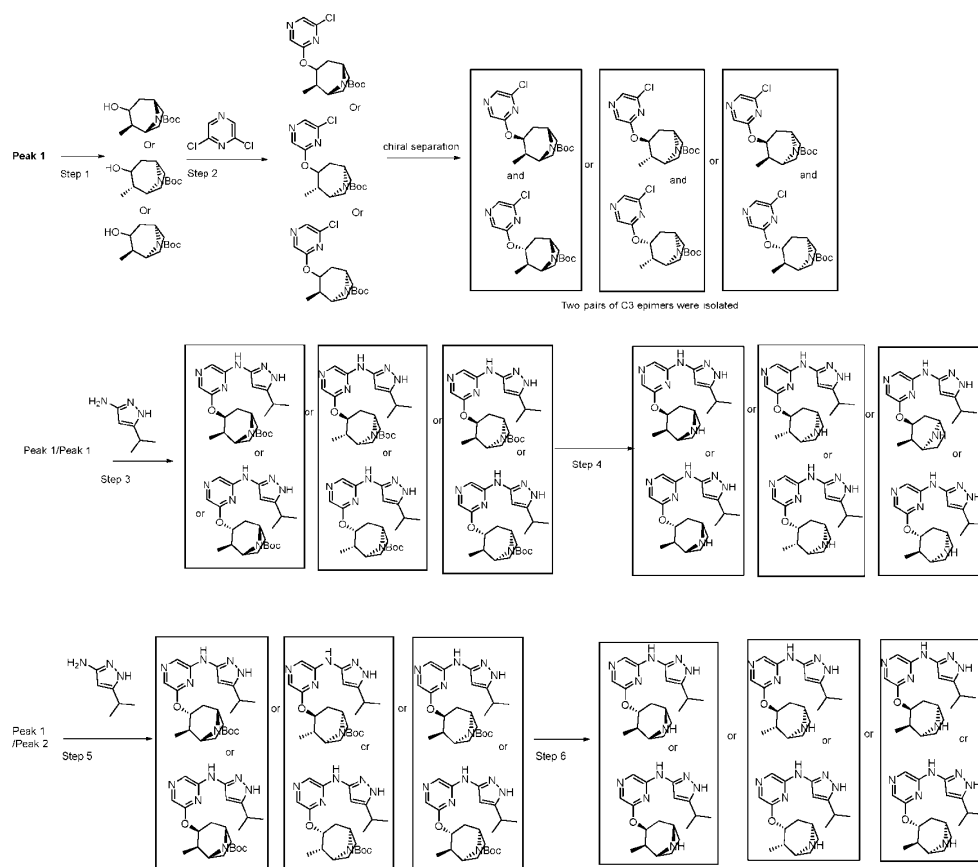
To a solution of Peak 1, step 1 (70 mg, 148 μ mol) in DCM (3 mL) was added TFA (1 mL) and the reaction mixture was stirred at rt for 16 h. The mixture was concentrated and the residue was purified by Prep-HPLC (Method B) to afford the title product (10.4 mg, 19%) as a white solid. LCMS m/z = 371 $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 11.94 (br s, 1H), 9.71 (s, 1H), 8.36 (s, 1H), 7.96 (s, 1H), 7.46 (s, 1H), 6.31 (s, 1H), 5.25-5.20 (m, 1H), 4.01-3.97 (m, 1H), 3.88-3.83 (m, 1H), 3.81-3.74 (m, 1H), 3.58-3.50 (m, 1H), 3.41-3.35 (m, 1H), 2.47-2.44 (m, 2H), 2.33-2.24 (m, 3H), 2.00-1.94 (m, 2H), 1.78-1.66 (m, 4H), 1.53-1.45 (m, 3H).

[00400] Step 3: *Synthesis of Example 33*, 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((S)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1R,3r,5S)-9-azabicyclo[3.3.1]nonan-3-yl)oxy)-N-(5-((R)-tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine

The title compound was obtained as a white solid, 9 mg, 16%, from Peak 2, step 1, following the procedure described in step 2. LCMS m/z = 371 $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 11.94 (br s, 1H), 9.71 (s, 1H), 8.36 (s, 1H), 7.96 (s, 1H), 7.46 (s, 1H), 6.31 (s, 1H), 5.25-5.20 (m, 1H), 4.01-3.97 (m, 1H), 3.88-3.83 (m, 1H), 3.81-3.74 (m, 1H), 3.58-3.50 (m, 1H), 3.41-3.35 (m, 1H), 2.47-2.44 (m, 2H), 2.33-2.24 (m, 3H), 2.00-1.94 (m, 2H), 1.78-1.66 (m, 4H), 1.53-1.45 (m, 3H).

[00401] **Example 34**, N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine and

[00402] **Example 40**, N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine



[00403] Step 1: Synthesis of *tert*-butyl (1*R*,2*R*,5*S*)-3-hydroxy-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or *tert*-butyl (1*S*,2*S*,5*R*)-3-hydroxy-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or *tert*-butyl (1*S*,2*R*,5*R*)-3-hydroxy-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate

[00404] To a solution of Peak 1, Step 1, Example 7 and 128 (1.0 g, 4.17 mmol) as a mixture of two enantiomers, in MeOH (10 mL) was added NaBH₄ (790 mg, 20.8 mmol) at 0 °C under N₂ and the reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to give a mixture of two of the title isomers. (950 mg, 95%) as a colorless oil. LCMS *m/z* = 186 [*M* -56+H]⁺.

[00405] Step 2: Synthesis of *tert*-butyl (1*R*,2*R*,3*S*,5*S*)-3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate, *tert*-butyl (1*R*,2*R*,3*R*,5*S*)-3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate, *tert*-butyl (1*S*,2*S*,3*S*,5*R*)-3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate, *tert*-butyl (1*S*,2*S*,3*R*,5*R*)-3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate, *tert*-butyl (1*S*,2*R*,3*R*,5*R*)-

3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2R,3S,5R)-3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate

[00406] To a solution of the compound mixture from Step 1 (0.95 g, 3.94 mmol) in THF (10 mL) was added 60% NaH (249 mg, 6.22 mmol) at 0 °C and the solution stirred for 30 min under N₂. 2,6-Dichloropyrazine (614 mg, 4.14 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The crude was purified by column chromatography on silica gel eluting with PE/EtOAc (4/1) to give the racemic products (800 mg, 56%). This was separated by chiral-SFC (Column: IG 20*250mm, 10 µm (Daicel), Column temperature: 35 °C, Mobile phase: CO₂/MeOH [0.5%NH₃(7M in MeOH)] = 85/15, Flow rate: 100 g/min, Back pressure: 100 bar to give Peak 1 (220 mg), Peak 2 (150 mg), Peak 3 (30 mg), Peak 4 (190 mg) as yellow solids.

[00407] Step 3: *Synthesis of tert-butyl (1R,2R,3S,5S)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1R,2R,3R,5S)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2S,3S,5R)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2S,3R,5R)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2R,3R,5R)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2R,3S,5R)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate*

[00408] To a solution of Peak 1, step 2 (130 mg, 368 µmol), 5-isopropyl-1H-pyrazol-3-amine (46 mg, 368 µmol) in dioxane (4.0 mL) was added KOAc (108 mg, 1.10 mmol) and BrettPhos Pd G₄ (33.2 mg) at rt under N₂ and the reaction mixture was allowed to warm to 90 °C and stirred for 18 h. The reaction mixture was cooled to rt, diluted with dioxane, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/1) to give the title compound (120 mg, 74%) as a yellow oil. LCMS m/z = 443 [M+H]⁺.

[00409] Step 4: *Synthesis of N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-*

azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine

[00410] To a solution of the compound from step 3 (120 mg, 271 μ mol) in DCM (3.0 mL) was added TFA (1.0 mL) at rt and the reaction mixture stirred for 1 h. The mixture was basified by 7N NH_3 in MeOH until pH=8. Then concentrated under reduced pressure. The crude was purified by Prep-HPLC (Method A) to afford **Example 34** (6.9 mg, 8%) as a white solid. LCMS m/z = 343 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.97 (br s, 1H), 9.55 (s, 1H), 7.88 (s, 1H), 7.40 (s, 1H), 6.22 (s, 1H), 4.89-4.85 (m, 1H), 3.47-3.40 (m, 1H), 3.27-3.23 (m, 1H), 2.95-2.90 (m, 1H), 2.06-2.01 (m, 1H), 1.89-1.84 (m, 2H), 1.76-1.70 (m, 2H), 1.63-1.40 (m, 2H), 1.23 (d, 6H), 0.85 (d, 3H).

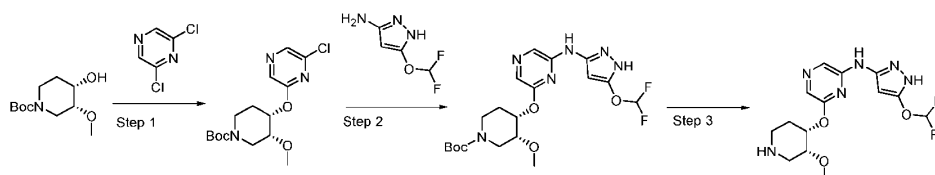
[00411] Step 5: *Synthesis of tert-butyl (1R,2R,3R,5S)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1R,2R,3S,5S)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2S,3S,5R)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2S,3R,5R)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2R,3S,5R)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2R,3R,5R)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate*

[00412] The title compound was obtained as a yellow oil, 120 mg, 74%, from Peak 2, step 2 and 5-isopropyl-1H-pyrazol-3-amine, following the procedure described in step 3. LCMS m/z = 443 $[\text{M}+\text{H}]^+$

[00413] Step 6: *Synthesis of N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine*

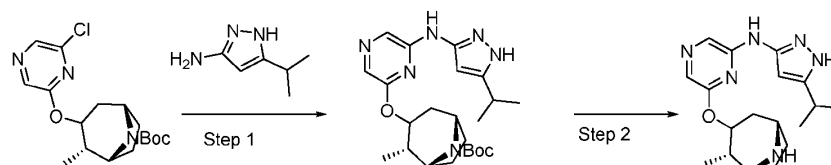
[00414] The title compound, **Example 40**, was obtained as a white solid, 20.4 mg, 22%, from the compound from step 5, following the procedure described in Step 4. LCMS m/z = 343 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.98 (br s, 1H), 9.53 (s, 1H), 7.89 (s, 1H), 7.40 (s, 1H), 6.23 (s, 1H), 5.28-5.20 (m, 1H), 3.50-3.40 (m, 1H), 3.30-3.20 (m, 1H), 2.97-2.87 (m, 1H), 2.18-2.12 (m, 1H), 1.78-1.58 (m, 6H), 1.26-1.20 (m, 6H), 0.92-0.84 (m, 3H).

[00415] Example 35, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methoxypiperidin-4-yl)oxy)pyrazin-2-amine



[00416] The title compound was obtained from tert-butyl (3R,4S)-4-hydroxy-3-methoxypiperidine-1-carboxylate, 2,6-dichloropyrazine and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the same 3 step procedure described in Example 6. LCMS $m/z = 357$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 12.08 (br s, 1H), 10.09 (br s, 1H), 7.78 (s, 1H), 7.61 (s, 1H), 7.25 (t, 1H), 5.94 (s, 1H), 5.28-5.23 (m, 1H), 3.50-3.45 (m, 1H), 3.25 (s, 3H), 3.00-2.95 (m, 1H), 2.90-2.85 (m, 1H), 2.73-2.65 (m, 1H), 2.58-2.53 (m, 1H), 1.90-1.85 (m, 1H), 1.70-1.62 (m, 1H).

[00417] Example 36, N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine



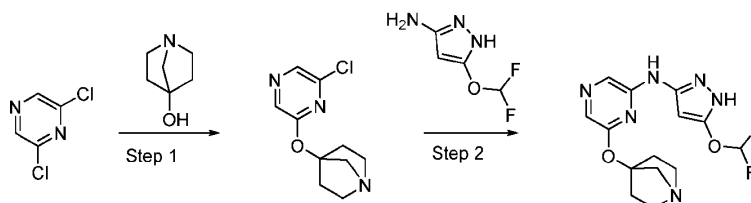
[00418] Step 1: *Synthesis of tert-butyl (1R,2S,5S)-3-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate*

[00419] The title compound was obtained as a yellow solid, 50 mg, 66%, from Example 7 and 128, step 3 and 5-isopropyl-1H-pyrazol-3-amine, following a similar procedure to that described in Example 37, step 2, except the crude was purified by column chromatography on silica gel (DCM/MeOH). LCMS $m/z = 443$ $[M+H]^+$.

[00420] Step 2: *Synthesis of N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((1R,2S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine*

[00421] The title compound was obtained as a white solid, 5.4 mg, 14%, from the compound from step 1, following the procedure described in Example 2 step 3. LCMS $m/z = 343$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.93 (br s, 1H), 9.53 (br s, 1H), 7.97 (s, 1H), 7.44 (s, 1H), 6.18 (s, 1H), 5.15 (s, 1H), 3.13-3.12 (m, 1H), 2.93-2.86 (m, 1H), 2.24-2.10 (m, 2H), 1.96-1.78 (m, 3H), 1.69-1.51 (m, 2H), 1.21 (d, 6H), 0.89 (d, 3H).

[00422] Example 37, 6-((1-azabicyclo[2.2.1]heptan-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



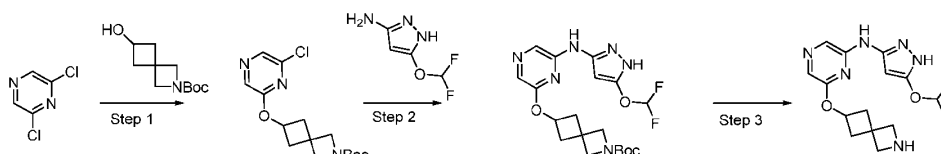
[00423] Step 1: *Synthesis of 4-((6-chloropyrazin-2-yl)oxy)-1-azabicyclo[2.2.1]heptane*

To a solution of bicyclo[2.2.1]heptan-1-ol (150 mg, 1.32 mmol) in dry DMSO (8.0 mL) was added NaH (60% in mineral oil, 196 mg, 5.11 mmol) at 0 °C under N₂. After stirring for 30 min, 2,6-dichloropyrazine (196 mg, 1.32 mmol) was added, and the reaction mixture was warmed to 60 °C and stirred overnight. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with MeOH (0.5% NH₃)/DCM (1/4) to afford the title compound (150 mg, 50%) as a white solid. LCMS *m/z* = 226 [M+H]⁺.

[00424] Step 2: *Synthesis of 6-((1-azabicyclo[2.2.1]heptan-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

[00425] A solution of 4-((6-chloropyrazin-2-yl)oxy)-1-azabicyclo[2.2.1]heptane (200 mg, 886 μmol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (132 mg, 886 μmol), KOAc (260 mg, 2.65 mmol), and BrettPhos Pd G4 (40.7 mg, 44.3 μmol) in dioxane (5 mL) was stirred at 100 °C for 18 h under N₂. The reaction mixture was cooled to rt and diluted with dioxane, filtered and the filtrate was concentrated under reduced pressure. The crude was purified by Prep-HPLC (Method A) to give the title compound (6.90 mg, 2.3%) as a yellow solid. LCMS *m/z* = 339 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ ppm 12.22 (br s, 1H), 9.62 (s, 1H), 7.79 (s, 1H), 7.62 (s, 1H), 7.24 (t, 1H), 5.94 (s, 1H), 3.02-2.95 (m, 2H), 2.74-2.64 (m, 4H), 1.93-1.81 (m, 4H).

[00426] **Example 38**, 6-((2-azaspiro[3.3]heptan-6-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



[00427] Step 1: *Synthesis of tert-butyl 6-((6-chloropyrazin-2-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate*

To a solution of tert-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (250 mg, 1.17 mmol) in dry THF (10 mL) was added NaH (60% in mineral oil, 373 mg, 9.36 mmol) at 0 °C. After stirring for 20 min, 2,6-dichloropyrazine (174 mg, 1.17 mmol) dissolved in dry THF (2 mL) was added via syringe. The reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction mixture was

quenched with saturated NH_4Cl solution and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with PE/EtOAc (1/1) to afford the title compound (300 mg, 78%) as a yellow oil. LCMS $m/z = 270$ $[\text{M}-56+\text{H}]^+$.

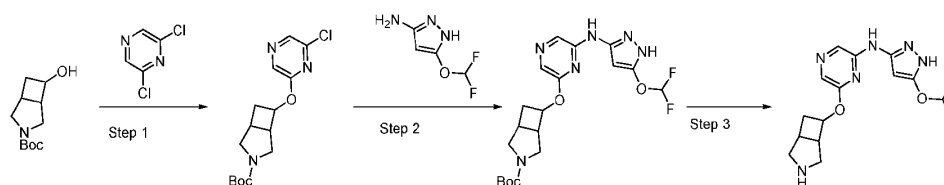
[00428] Step 2: *Synthesis of tert-butyl 6-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-azaspiro[3.3]heptane-2-carboxylate*

The title compound was obtained as a brown oil, 250 mg, 62%, from the compound from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS $m/z = 439$ $[\text{M}+\text{H}]^+$.

[00429] Step 3: *Synthesis of 6-((2-azaspiro[3.3]heptan-6-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

To a solution of the compound from step 2 (250 mg, 570 μmol) in DCM (5 mL) was added TFA (2 mL) at 0 °C under N_2 . After addition, the resulting mixture was allowed to warm to rt and stirred for 1.5 h. The reaction mixture was basified with NH_3 (7M in MeOH) to pH=10. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Method A) to afford the title compound (33.2 mg, 17%) as a brown solid. LCMS $m/z = 339$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.48 (br s, 1H), 8.44 (s, 1H), 7.75 (s, 1H), 7.53 (s, 1H), 7.26 (t, 1H), 6.05 (s, 1H), 5.09-5.04 (m, 1H), 3.94-3.89 (m, 4H), 2.76-2.71 (m, 2H), 2.33-2.29 (m, 2H).

[00430] **Example 39.** 6-((3-azabicyclo[3.2.0]heptan-6-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



[00431] Step 1: *Synthesis of tert-butyl 6-((6-chloropyrazin-2-yl)oxy)-3-azabicyclo[3.2.0]heptane-3-carboxylate*

To a mixture of tert-butyl 6-hydroxy-3-azabicyclo[3.2.0]heptane-3-carboxylate (213 mg, 1 mmol) and 2,6-dichloropyrazine (150 mg, 1.00 mmol) in THF (20 mL) was added NaH (60% in mineral oil, 43.8 mg, 1.10 mmol) at 0°C and the reaction mixture stirred at rt for 1 h under N_2 . The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na_2SO_4 , filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/5) to afford the title compound (300 mg, 92%) as a yellow oil. LCMS $m/z = 270$ $[\text{M}-56+\text{H}]^+$.

[00432] Step 2: *Synthesis of tert-butyl 6-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-azabicyclo[3.2.0]heptane-3-carboxylate*

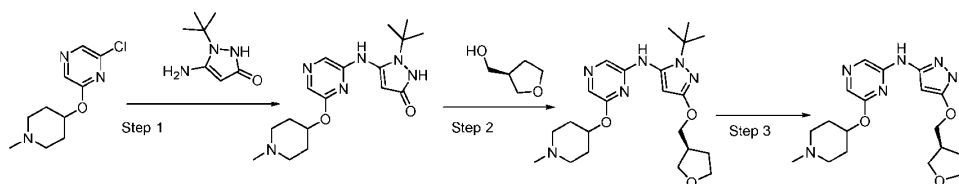
The title compound was obtained as a yellow solid, 200 mg, 74%, from the compound from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following the method described in Example 19 and 20, step 2. LCMS $m/z = 439$ $[M+H]^+$.

[00433] Step 3: *Synthesis of 6-((3-azabicyclo[3.2.0]heptan-6-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

To a solution of the compound from step 2 (150 mg, 342 μ mol) in DCM (5 mL) was added TFA (1.0 mL) at 0°C, and then stirred at 50°C for 5 h under N₂. The reaction mixture was concentrated *in vacuo* and the residue was purified by Prep-HPLC (Method C) to afford the title compound (39.6 mg, 34%) as a yellow solid. LCMS $m/z = 339$ $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.11 (br s, 1H), 10.20 (br s, 1H), 7.82 (s, 1H), 7.62 (s, 1H), 7.27 (t, 1H), 5.96 (s, 1H), 5.20-5.13 (m, 1H), 3.64-3.40 (m, 1H), 3.28-3.22 (m, 2H), 3.03-2.99 (m, 1H), 2.88-2.75 (m, 3H), 2.67-2.55 (m, 1H), 1.99-1.86 (m, 1H).

[00434] Example 40 see Example 34.

[00435] **Example 41**, (S)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-((tetrahydrofuran-3-yl)methoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



[00436] Step 1: *Synthesis of 1-(tert-butyl)-5-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1,2-dihydro-3H-pyrazol-3-one*

The title compound was obtained as a yellow solid, 1.23 g, 89%, from Example 8, step 1 and 5-amino-1-(tert-butyl)-1,2-dihydro-3H-pyrazol-3-one, following the procedure described in Example 19 and 20, step 2. LCMS $m/z = 348$ $[M+H]^+$.

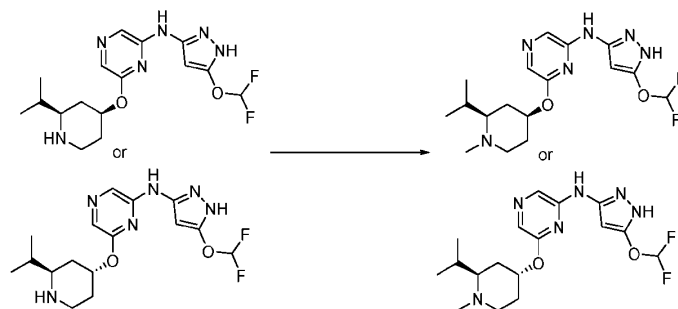
[00437] Step 2: *Synthesis of (S)-N-(1-(tert-butyl)-3-((tetrahydrofuran-3-yl)methoxy)-1H-pyrazol-5-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

To a mixture of the compound from step 1 (240 mg, 0.7 mmol), (*R*)-tetrahydrofuran-3-ylmethanol (70 mg, 0.7 mmol) and PPh₃ (263 mg, 1.0 mmol) in THF (10 mL) was added DIAD (202 mg, 1.0 mmol) at 0 °C and the reaction mixture was stirred overnight under N₂. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (0% to 100%) to afford the title compound (100 mg, 34%) as a yellow solid. LCMS $m/z = 431$ $[M+H]^+$.

[00438] Step 3: Synthesis of (S)-6-((1-methylpiperidin-4-yl)oxy)-N-((5-((tetrahydrofuran-3-yl)methoxy)-1H-pyrazol-3-yl)pyrazin-2-amine

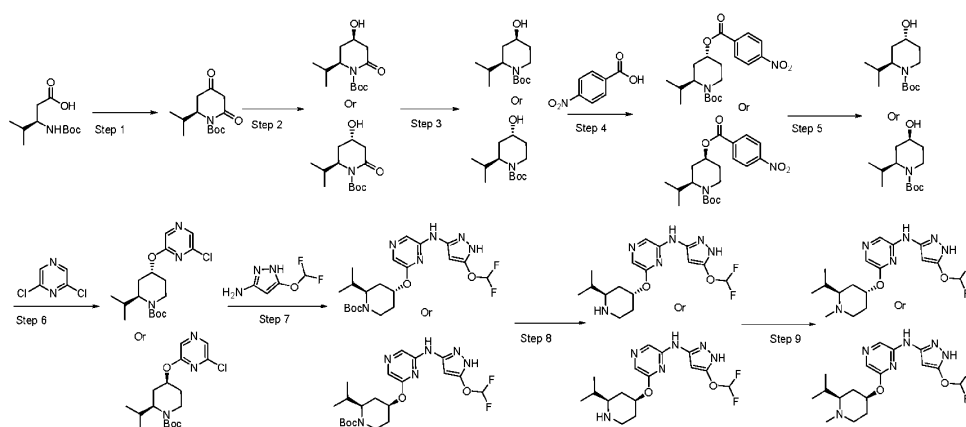
A solution of the compound from step 2 (100 mg, 0.23 mmol) in FA (3 mL) was stirred at 80 °C for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by Prep-HPLC (Method A) to obtain the title product (9.8 mg, 10%) as a yellow solid. LCMS $m/z = 375$ [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.85-11.26 (m, 1H), 9.73 (br s, 1H), 7.81 (br s, 1H), 7.49 (s, 1H), 5.75 (br s, 1H), 4.93-4.87 (m, 1H), 4.05-3.94 (m, 2H), 3.80-3.75 (m, 2H), 3.68-3.63 (m, 1H), 3.54-3.49 (m, 1H), 2.78-2.61 (m, 3H), 2.18 (s, 3H), 2.14-2.07 (m, 2H), 2.02-1.97 (m, 3H), 1.69-1.55 (m, 3H).

[00439] **Example 42**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-isopropylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-isopropylpiperidin-4-yl)oxy)pyrazin-2-amine



[00440] The title compound was obtained as a white solid, 10.1 mg, 20%, from the compound of Example 96 and HCHO, following the procedure described in Example 11. LCMS $m/z = 383$ [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.87 (br s, 1H), 9.99 (s, 1H), 7.77 (s, 1H), 7.57 (s, 1H), 7.25 (t, 1H), 5.97 (s, 1H), 4.91-4.81 (m, 1H), 2.89-2.83 (m, 1H), 2.76-2.72 (m, 1H), 2.68-2.52 (m, 2H), 2.14 (s, 3H), 2.05-1.95 (m, 2H), 1.83-1.78 (m, 1H), 1.63-1.53 (m, 1H), 1.25-1.13 (m, 1H), 0.83-0.77 (m, 6H).

[00441] **Example 43**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-isopropyl-1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-isopropyl-1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00442] Step 1: *Synthesis of tert-butyl (R)-2-isopropyl-4,6-dioxopiperidine-1-carboxylate*

To a solution of (R)-3-((tert-butoxycarbonyl)amino)-4-methylpentanoic acid (3 g, 12.9 mmol) in DCM (25 mL) was added 2,2-dimethyl-1,3-dioxane-4,6-dione (1.85 g, 12.9 mmol), EDCI (3.68 g, 19.3 mmol) and DMAP (2.35 g, 19.3 mmol) in an ice bath and the reaction mixture was stirred for 3 h at rt. The reaction was washed with 1N KHSO₄, dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was dissolved in EtOAc and heated under reflux for 4 h. The cooled reaction mixture was washed with 1N KHSO₄ and brine, dried over Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with PE/EtOAc (2:1) to obtain the title compound (2 g, 60%). LCMS *m/z* = 200 [M-tBu+H]⁺.

[00443] Step 2: *Synthesis of tert-butyl (2R,4R)-4-hydroxy-2-isopropyl-6-oxopiperidine-1-carboxylate or tert-butyl (2R,4S)-4-hydroxy-2-isopropyl-6-oxopiperidine-1-carboxylate*

To a solution of the compound from step 1 (2 g, 7.83 mmol) in DCM (20 mL) was added AcOH (1.5 mL) and NaBH₄ (865 mg, 23.4 mmol) in an ice bath and the reaction mixture was stirred for 72 h at rt. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with EtOAc/PE (2/1) to afford the title compound (500 mg, 24%) as a yellow oil. LCMS *m/z* = 202 [M-tBu+H]⁺.

[00444] Step 3: *Synthesis of tert-butyl (2R,4S)-4-hydroxy-2-isopropylpiperidine-1-carboxylate or tert-butyl (2R,4R)-4-hydroxy-2-isopropylpiperidine-1-carboxylate*

To a solution of the compound from step 2 (400 mg, 1.55 mmol) in THF (20 mL) in an ice bath under N₂ was added BH₃.SMe₂ (589 mg, 7.75 mmol) and the reaction mixture was stirred overnight at rt. The reaction was quenched with MeOH, then concentrated *in vacuo*. The residue was diluted with EtOAc, washed with water, sodium bicarbonate and 1 N KHSO₄, dried over Na₂SO₄, filtered and the residue was concentrated to afford the title compound (200 mg, 53%) as a colorless oil.

[00445] Step 4: *Synthesis of tert-butyl (2R,4R)-2-isopropyl-4-((4-nitrobenzoyl)oxy)piperidine-1-carboxylate or tert-butyl (2R,4S)-2-isopropyl-4-((4-nitrobenzoyl)oxy)piperidine-1-carboxylate*

To a solution of the compound from step 3 (300 mg, 1.23 mmol), 4-nitrobenzoic acid (307 mg, 1.84 mmol) and PPh_3 (482 mg, 1.84 mmol) in THF (15 mL) was added DIAD (743 mg, 3.68 mmol) in an ice bath under N_2 , then the reaction mixture was stirred for 1 h at rt. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/4) to afford the title compound (300 mg, 62%) as a yellow oil. LCMS m/z = 293 $[\text{M}-100+\text{H}]^+$.

[00446] Step 5: *Synthesis of tert-butyl (2R,4R)-4-hydroxy-2-isopropylpiperidine-1-carboxylate or tert-butyl (2R,4S)-4-hydroxy-2-isopropylpiperidine-1-carboxylate*

A mixture of the compound from step 4 (250 mg, 637 μmol) and LiOH (71.1 mg, 1.27 mmol) in MeOH (10 mL) and water (2 mL) was stirred at rt for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/1) to afford the title compound (120 mg, 77%) as a colorless oil. LCMS m/z = 188 $[\text{M}-\text{tBu}+\text{H}]^+$.

[00447] Step 6: *Synthesis of tert-butyl (2R,4R)-4-((6-chloropyrazin-2-yl)oxy)-2-isopropylpiperidine-1-carboxylate or tert-butyl (2R,4S)-4-((6-chloropyrazin-2-yl)oxy)-2-isopropylpiperidine-1-carboxylate*

The title compound was obtained as a yellow oil, 45 mg, 31%, from the compound from step 5 and 2,6-dichloropyrazine, following the procedure described in Example 39, step 1. LCMS m/z = 300 $[\text{M}-56+\text{H}]^+$.

[00448] Step 7: *Synthesis of tert-butyl (2R,4R)-4-(((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-isopropylpiperidine-1-carboxylate or tert-butyl (2R,4R)-4-(((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-isopropylpiperidine-1-carboxylate*

[00449] The title compound was obtained as a yellow solid, 40 mg, 67%, from the compound from step 6 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following the procedure described in Example 19 and 20, step 1. LCMS m/z = 469 $[\text{M}+\text{H}]^+$.

[00450] Step 8: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-isopropylpiperidin-4-yl)oxy)pyrazin-2-amine trifluoroacetate or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-isopropylpiperidin-4-yl)oxy)pyrazin-2-amine trifluoroacetate*

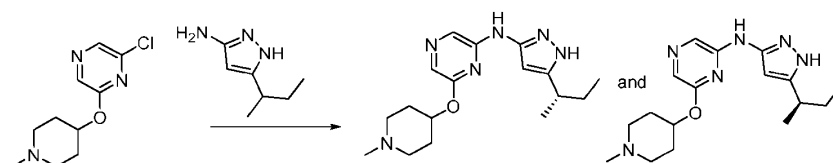
[00451] A mixture of the compound from step 7 (40 mg, 85.3 μmol) and TFA (1 mL) in DCM (3 mL) was stirred at rt for 1 h. The solvent was removed *in vacuo* to afford the title compound (30 mg, crude) as a yellow oil. LCMS m/z = 369 $[\text{M}+\text{H}]^+$.

[00452] Step 9: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-isopropyl-1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-isopropyl-1-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

The title compound was obtained as a white solid, 4.8 mg, 19%, from the compound from step 8 and HCHO, following a similar procedure to that described in Example 11, except HPLC (Method B) was used. LCMS m/z = 383 $[\text{M}+\text{H}]^+$. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.92 (br s, 1H), 10.01 (br s,

1H), 8.14 (s, 1H), 7.78 (s, 1H), 7.62 (s, 1H), 7.25 (t, 1H), 5.95 (s, 1H), 5.33-5.28 (m, 2H), 2.85-2.80 (m, 1H), 2.71-2.57 (m, 1H), 2.37 (s, 3H), 2.35-2.29 (m, 1H), 2.15-2.08 (m, 1H), 1.94-1.80 (m, 3H), 1.63-1.56 (m, 1H), 0.85-0.75 (m, 6H).

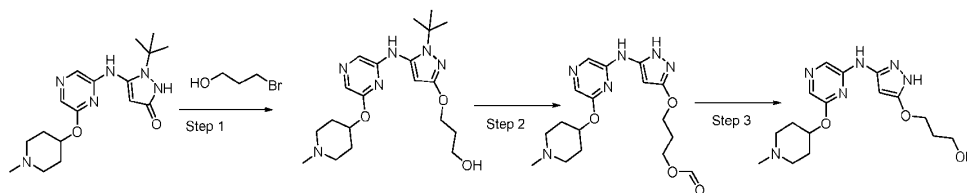
[00453] **Example 44**, (R)-N-(5-(sec-butyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(sec-butyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine and **Example 45**, (S)-N-(5-(sec-butyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine and (R)-N-(5-(sec-butyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00454] N-(5-(sec-Butyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine was obtained, 300 mg, from 5-(sec-butyl)-1H-pyrazol-3-amine and Example 8, step 1 following the procedure described in Example 37, step 2. This was separated by chiral SFC (Column: AD 20*250mm, 10 μ m (Daicel), Column temperature: 35 $^{\circ}$ C, Mobile phase: CO₂/[MeOH/MeCN[0.2%NH₃(7M in MeOH)] 1:1]= 60/40, Flow rate: 120 g/min, Back pressure: 100 bar to give **Example 45**, Peak 1, (86.8 mg, 29%) as a yellow solid. ¹HNMR (400 MHz, DMSO-*d*₆) δ ppm 11.95 (br s, 1H), 9.61 (s, 1H), 7.91 (s, 1H), 7.43 (s, 1H), 6.24 (s, 1H), 4.94-4.89 (m, 1H), 2.74-2.65 (m, 3H), 2.18 (s, 3H), 2.14-2.07 (m, 2H), 2.01-1.98 (m, 2H), 1.69-1.51 (m, 4H), 1.22 (d, 3H), 0.85 (t, 3H).

[00455] and **Example 44**, Peak 2, (94.5 mg, 31%) as a yellow solid. LCMS *m/z* = 331 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ ppm 11.96 (br s, 1H), 9.62 (s, 1H), 7.92 (s, 1H), 7.43 (s, 1H), 6.25 (s, 1H), 4.95-4.89 (m, 1H), 2.74-2.66 (m, 3H), 2.18 (s, 3H), 2.11-2.06 (m, 2H), 2.02-1.97 (m, 2H), 1.73-1.55 (m, 4H), 1.22 (d, 3H), 0.85 (t, 3H).

[00456] **Example 46**, 3-((3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)oxy)propan-1-ol



[00457] *Step 1: Synthesis of 3-((1-(tert-butyl)-5-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-3-yl)oxy)propan-1-ol*

To a stirred solution of Example 41, step 1 (150 mg, 432 μ mol) and 3-bromopropan-1-ol (60.0 mg, 432 μ mol) in DMF (3 mL) was added K₂CO₃ (178 mg, 1.29 mmol) at rt and the reaction mixture was

stirred for 12 h at 35°C under N₂. The resulting mixture was diluted with EtOAc, washed with brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (110 mg, crude) as yellow oil. LCMS *m/z* = 405 [M+H]⁺.

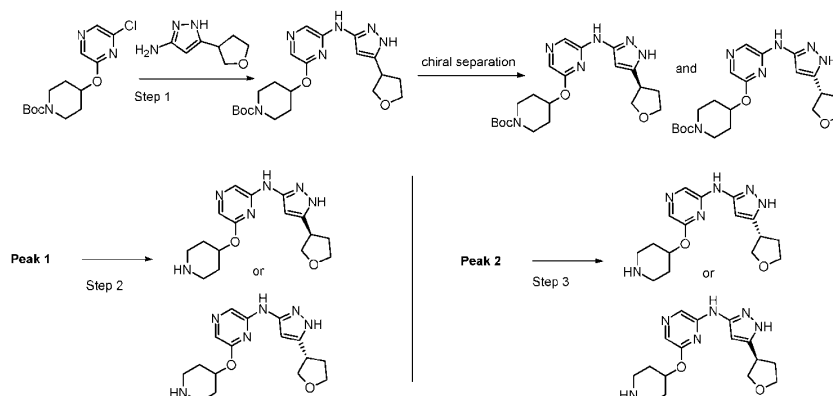
[00458] Step 2: *Synthesis of 3-((5-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-3-yl)oxy)propyl formate*

A mixture of the compound from step 1 (70 mg, 538 μmol) in FA (3 mL) was stirred for 1 h at 80°C under N₂. The reaction mixture was concentrated *in vacuo* to afford the title compound (70 mg, crude) as a yellow oil. LCMS *m/z* = 377 [M+H]⁺.

[00459] Step 3: *Synthesis of 3-((3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)oxy)propan-1-ol*

To a solution of the compound from step 2 (70 mg, 186 μmol) in MeOH (2 mL) and H₂O (2 mL) was added NaOH (22.1 mg, 555 μmol) at rt and the reaction mixture was stirred for 1 h at 50°C. The mixture was purified with Prep-HPLC (Method A) to obtain the title product (6.1 mg, 10%) as a yellow solid. LCMS *m/z* = 377 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.93 (br s, 1H), 9.77 (br s, 1H), 7.90 (s, 1H), 7.50 (s, 1H), 5.86 (s, 1H), 4.95-4.90 (m, 1H), 4.59-4.52 (m, 1H), 4.11 (t, 2H), 3.56-3.51 (m, 2H), 2.72-2.60 (m, 2H), 2.33 (s, 3H), 2.32-2.10 (m, 2H), 2.02-1.92 (m, 2H), 1.90-1.80 (m, 2H), 1.78-1.60 (m, 2H).

[00460] Example 47 and Example 48, (R)-6-(piperidin-4-yloxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine and (S)-6-(piperidin-4-yloxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine



[00461] Step 1: *Synthesis of tert-butyl (R)-4-((6-((5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate and tert-butyl (S)-4-((6-((5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate*

[00462] tert-Butyl 4-((6-((5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate was prepared from Example 1, step 1 and 5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. The racemic

product was separated by Chiral-SFC (Column: OZ 4.6*100mm 5 μ m, Column temperature: 40 °C , Mobile phase: CO₂/MeOH[0.2%NH₃(7M in MeOH)] = 50/50, Flow rate: 100 g/min, Back pressure: 100 bar) to give Peak 1, tert-butyl (R)-4-((6-((5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate or tert-butyl (S)-4-((6-((5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate (140 mg) and Peak 2, tert-butyl (S)-4-((6-((5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate or tert-butyl (R)-4-((6-((5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate (140 mg). LCMS m/z = 431 [M+H]⁺

[00463] Step 2: *Synthesis of Example 48, (R)-6-(piperidin-4-yloxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-(piperidin-4-yloxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine*

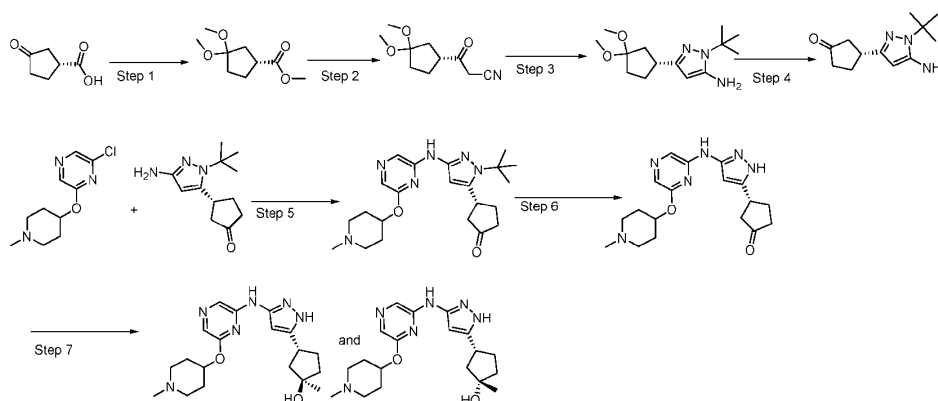
The title compound was obtained as a white solid, 52.7 mg, 48%, from Peak 1, step 1, following the procedure described in Example 3, step 3. LCMS m/z = 331 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 12.09 (br s, 1H), 9.68 (s, 1H), 7.92 (s, 1H), 7.45 (s, 1H), 6.30 (s, 1H), 5.01-4.95 (m, 1H), 4.03-3.98 (m, 1H), 3.92-3.77 (m, 2H), 3.60-3.53 (m, 1H), 3.45-3.35 (m, 2H), 3.02-2.99 (m, 2H), 2.62-2.56 (m, 2H), 2.33-2.25 (m, 1H), 2.02-1.91 (m, 3H), 1.55-1.48 (m, 2H).

[00464] Step 3: *Synthesis of Example 47, (S)-6-(piperidin-4-yloxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-(piperidin-4-yloxy)-N-(5-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine*

The title compound was obtained as a white solid, 60.2 mg, 56%, from Peak 2, step 1, following the procedure described in Example 3, step 3. LCMS m/z = 331 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 12.07 (br s, 1H), 9.67 (s, 1H), 7.92 (s, 1H), 7.44 (s, 1H), 6.30 (s, 1H), 4.99-4.94 (m, 1H), 4.01 (t, 1H), 3.90-3.76 (m, 2H), 3.59 (t, 1H), 3.45-3.35 (m, 2H), 3.01-2.98 (m, 2H), 2.61-2.56 (m, 2H), 2.33-2.25 (m, 1H), 2.00-1.91 (m, 3H), 1.54-1.47 (m, 2H).

[00465] **Example 49, (1R,3R)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol or (1S,3R)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol and**

[00466] **Example 50, (1S,3R)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol or (1R,3R)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol**



[00467] Step 1: *Synthesis of methyl (R)-3-(3,3-dimethoxycyclopentyl)-1-carboxylate*

To a solution of (R)-3-oxocyclopentane-1-carboxylic acid (3 g, 23.4 mmol) and trimethoxymethane (14.8 g, 140 mmol) in MeOH (15 mL) was added 4-methylbenzene-1-sulfonic acid hydrate (89.0 mg, 0.47 mmol) at rt under N₂ and the reaction mixture was stirred for 24 h. The reaction was quenched with sat. NaHCO₃ aq, then concentrated *in vacuo*. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to give the title product (3.5 g, crude) as a yellow oil.

[00468] Step 2: *Synthesis of (R)-3-(3,3-dimethoxycyclopentyl)-3-oxopropanenitrile*

To a solution of MeCN (1.51 g, 37.0 mmol) in THF (15 mL) was added BuLi (2.5 M, 14.8 mL, 37.0 mmol) at -78 °C under N₂. After stirring for 1 h, methyl (1R)-3-(3,3-dimethoxycyclopentyl)-3-oxopropanenitrile (3.5 g, 18.5 mmol) was added at -78 °C and the reaction mixture was stirred at 0 °C for 2 h. The reaction was neutralized with 1M HCl and extracted with EtOAc. The organic layer was washed with brine and concentrated to give the title product (3.5 g, crude) as a yellow oil.

[00469] Step 3: *Synthesis of (R)-1-(tert-butyl)-3-(3,3-dimethoxycyclopentyl)-1H-pyrazol-5-amine*

To a solution of tert-butylhydrazine hydrochloride (1.65 g, 13.3 mmol) in EtOH (10 mL) was added NaOH (531 mg, 13.3 mmol) at rt. After stirring for 1 h, methyl (R)-3-(3,3-dimethoxycyclopentyl)-3-oxopropanenitrile (2.2 g, 11.1 mmol) was added and the reaction mixture stirred at 75 °C for 18 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give crude product (2.5 g) as a red oil.

[00470] Step 4: *Synthesis of (R)-3-(5-amino-1-(tert-butyl)-1H-pyrazol-3-yl)cyclopentan-1-one*

To a solution of (R)-1-(tert-butyl)-3-(3,3-dimethoxycyclopentyl)-1H-pyrazol-5-amine (2.5 g, 9.35 mmol) in acetone (10 mL) and water (10 mL) was added 4-toluenesulfonic acid monohydrate (231 mg, 1.22 mmol) at rt and the reaction mixture was stirred for 3 h. The reaction was concentrated *in vacuo*, the residue was neutralized with sat. NaHCO₃ aq, then extracted with EtOAc. The combined

organic layers were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* to give the title product (2.2 g, crude) as a red oil. LCMS *m/z* = 222 [M+H]⁺.

[00471] *Step 5: Synthesis of (R)-3-(1-(tert-butyl)-3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-one*

The title compound was obtained as a yellow solid, 1.7 g, 60%, from (R)-3-(5-amino-1-(tert-butyl)-1H-pyrazol-3-yl)cyclopentan-1-one and Example 8, step 1, following the procedure described in Example 19 and 20, step 2. LCMS *m/z* = 413 [M+H]⁺.

[00472] *Step 6: Synthesis of (R)-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-one*

A mixture of (R)-3-(1-(tert-butyl)-3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-one (1.7 g, 4.12 mmol) in FA (10 mL) was heated to 80 °C for 1 h. The mixture was evaporated under reduced pressure. The residue was diluted with EtOAc, washed with saturated NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The crude was purified by column chromatography on silica gel eluting with PE/EtOAc (1/1) to afford the title compound (1.0 g, 68%) as a yellow solid. LCMS *m/z* = 357 [M+H]⁺.

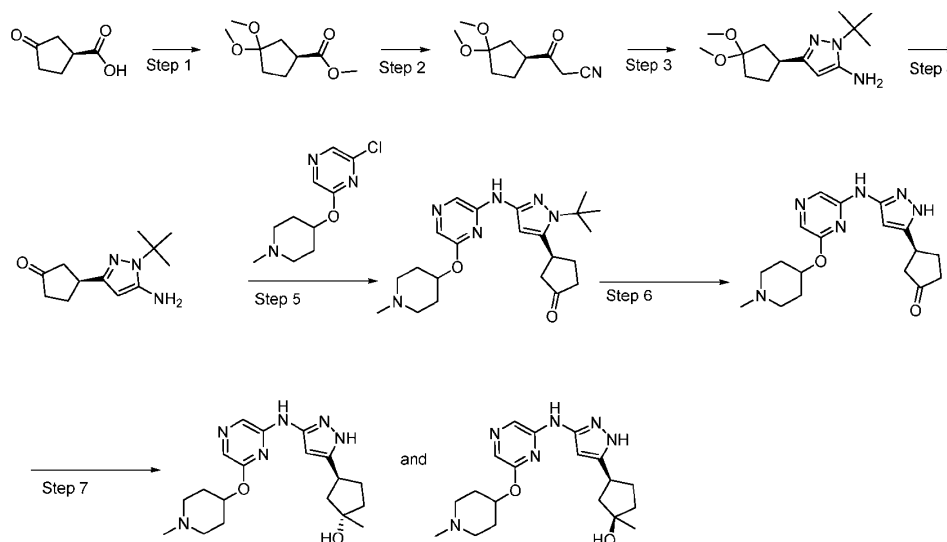
[00473] *Step 7: Synthesis of (1R,3R)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol and (1S,3R)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol*

A solution of (R)-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-one (1 g, 2.80 mmol) in THF (20 mL) was cooled to -78 °C. CH₃Li (1.6 M, 8.75 mL, 14 mmol) was added drop-wise and the reaction mixture stirred for 2 h. The reaction was quenched with sat. NH₄Cl solution and extracted with DCM. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The crude was purified by Prep-HPLC (Method A) to give the title product, **Example 49**, Peak 1 (121.9 mg, 12%) as a yellow solid, ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.87 (br s, 1H), 9.59 (s, 1H), 7.93 (s, 1H), 7.43 (s, 1H), 6.27 (s, 1H), 4.98-4.92 (m, 1H), 4.44 (s, 1H), 3.12-3.06 (m, 1H), 2.72-2.65 (m, 2H), 2.22-2.14 (m, 2H), 2.20 (s, 3H), 2.05-1.98 (m, 4H), 1.88-1.80 (m, 1H), 1.77-1.60 (m, 4H), 1.57-1.51 (m, 1H), 1.26 (s, 3H).

[00474] and **Example 50**, Peak 2, (15.7 mg, 1.5 %) as a yellow solid. LCMS *m/z* = 373 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.87 (br s, 1H), 9.58 (s, 1H), 7.93 (s, 1H), 7.43 (s, 1H), 6.29 (s, 1H), 4.99-4.92 (m, 1H), 4.44 (s, 1H), 3.09-3.07 (m, 1H), 2.70-2.67 (m, 2H), 2.18 (s, 3H), 2.17 - 2.14 (m, 2H), 2.02 - 1.98 (m, 4H), 1.88-1.86 (m, 1H), 1.77-1.68 (m, 4H), 1.67-1.65 (m, 1H), 1.26 (s, 3H).

[00475] Example 51, (1*S*,3*S*)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentan-1-ol or (1*R*,3*S*)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentan-1-ol and

[00476] Example 52, (1*R*,3*S*)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentan-1-ol or (1*S*,3*S*)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentan-1-ol



[00477] Steps 1 to 6: Synthesis of (S)-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentan-1-one

[00478] The title compound was obtained as a yellow solid, 120 mg, from (1*S*)-3-oxocyclopentane-1-carboxylic acid, following the same 6 step procedure described in Example 49 and 50, steps 1 to 6.

[00479] Step 7: Synthesis of (1*S*,3*S*)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentan-1-ol and (1*R*,3*S*)-1-methyl-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentan-1-ol

[00480] Example 51, Peak 1, (11.5 mg, 9.2%) and **Example 52, Peak 2,** (18.4 mg, 14.7 %) were obtained from (S)-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentan-1-one and CH₃Li, following the procedure described in Step 7, Example 49 and 50.

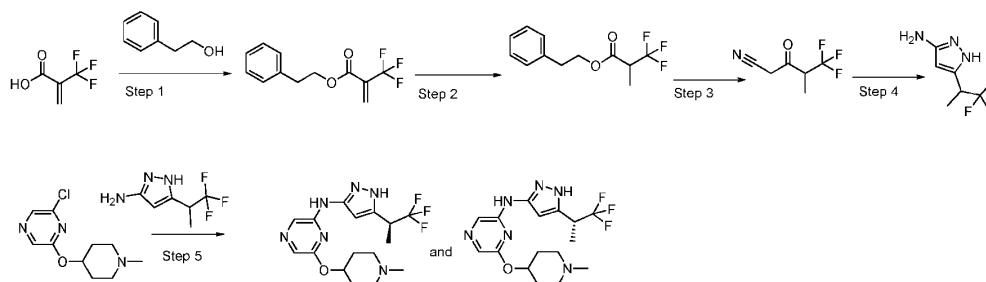
[00481] Peak 1: ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.95 (br s, 1H), 9.64 (s, 1H), 7.89 (s, 1H), 7.43 (s, 1H), 6.26 (s, 1H), 4.92-4.88 (m, 1H), 4.41 (s, 1H), 3.32-3.29 (m, 1H), 2.68-2.65 (m, 2H), 2.56 (s, 3H), 2.27 – 1.95 (m, 7H), 1.77 – 1.61 (m, 5H), 1.30 (s, 3H).

[00482] Peak 2. LCMS *m/z* = 373 [M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ ppm 11.89 (br s, 1H), 9.60 (s, 1H), 7.93 (s, 1H), 7.44 (s, 1H), 6.27 (s, 1H), 4.97-4.94 (m, 1H), 4.45 (s, 1H), 3.18-3.02

(m, 1H), 2.83- 2.70 (m, 2H), 2.28-2.22 (m, 5H), 2.08-1.94 (m, 4H), 1.90-1.83 (m, 1H), 1.81-1.64 (m, 4H), 1.61-1.45 (m, 1H), 1.27 (s, 3H).

[00483] **Example 53**, (S)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)pyrazin-2-amine and

[00484] **Example 54**, (R)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)pyrazin-2-amine



[00485] *Step 1: Synthesis of phenethyl 2-(trifluoromethyl)acrylate*

[00486] A mixture of 2-(trifluoromethyl)acrylic acid (30.0 g, 214 mmol), 2-phenylethanol (52.5 g, 430 mmol) and 4-methylbenzenesulfonic acid (74.0 g, 430 mmol) in toluene (800 mL) was stirred at 120 °C for 18 h under N₂. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1:10 to 1:5) to give the title product (29.0 g, 56%) as a colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ ppm 7.34-7.21 (m, 5H), 6.67 (q, 1H), 6.41 (q, 1H), 4.46 (t, 2H), 3.02 (t, 2H).

[00487] *Step 2: Synthesis of phenethyl 3,3,3-trifluoro-2-methylpropanoate*

A mixture of phenethyl 2-(trifluoromethyl)acrylate (29.0 g, 119 mmol) and Pd/C (wet, 6.0 g) in EtOAc (300 mL) was stirred at 20 °C for 18 h under H₂. The reaction mixture was filtered, the filtrate was concentrated, and the residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1:10 to 1:3) to give the title product (24.9 g, 85%) as a colorless oil. ¹H-NMR (400 MHz, CDCl₃) δ ppm 7.34-7.20 (m, 5H), 4.42-4.35 (m, 2H), 3.22-3.13 (m, 1H), 2.97 (t, 2H), 1.36 (d, 3H).

[00488] *Step 3: Synthesis of 5,5,5-trifluoro-4-methyl-3-oxopentanenitrile*

The title compound was obtained as a yellow oil, 100 mg, 9% from phenethyl 3,3,3-trifluoro-2-methylpropanoate and MeCN, following the procedure described in Example 28 and 29, step 1. ¹H-NMR (400 MHz, CDCl₃) δ ppm 3.74-3.61 (m, 2H), 3.54-3.47 (m, 1H), 1.42 (d, 3H).

[00489] *Step 4: Synthesis of 5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-amine*

The title compound was obtained as a yellow oil, 120 mg, 37% from 5,5,5-trifluoro-4-methyl-3-oxopentanenitrile and hydrazine hydrate, following the procedure described in Example 28 and 29, step 2. LCMS m/z = 180 [M+H]⁺.

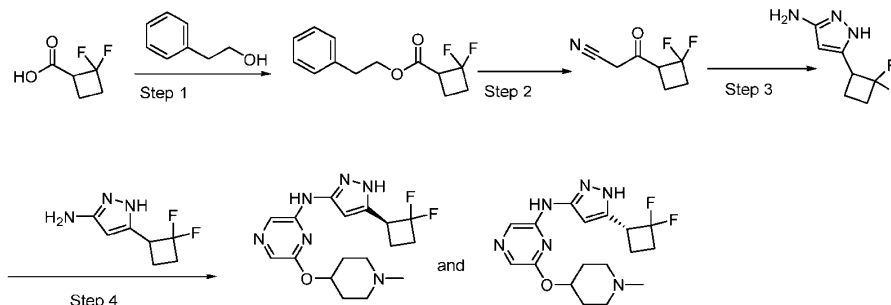
[00490] Step 5: *Synthesis of (S)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)pyrazin-2-amine and (R)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)pyrazin-2-amine*

6-((1-Methylpiperidin-4-yl)oxy)-N-(5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)pyrazin-2-amine was obtained as a yellow solid, 85 mg, 41% from Example 8, step 1 and 5-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. 85 mg of the racemic product was separated with prep-chiral SFC (Method E, 88/12) to give **Example 53**, Peak 1, (20.7 mg). ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 12.43 (br s, 1H), 9.76 (s, 1H), 7.91 (s, 1H), 7.47 (s, 1H), 6.55-6.25 (m, 1H), 4.95-4.88 (m, 1H), 3.90-3.85 (m, 1H), 2.72-2.65 (m, 2H), 2.17 (s, 3H), 2.15-2.07 (m, 2H), 1.99-1.95 (m, 2H), 1.73-1.63 (m, 2H), 1.46 (d, 3H).

[00491] and **Example 54**, Peak 2, (23.1 mg). ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 12.42 (br s, 1H), 9.76 (s, 1H), 7.90 (s, 1H), 7.47 (s, 1H), 6.55-6.25 (m, 1H), 4.95-4.88 (m, 1H), 3.90-3.85 (m, 1H), 2.72-2.65 (m, 2H), 2.17 (s, 3H), 2.15-2.07 (m, 2H), 1.99-1.95 (m, 2H), 1.73-1.63 (m, 2H), 1.45 (d, 3H).

[00492] **Example 55**, (S)-N-(5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine and

[00493] **Example 56**, (R)-N-(5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00494] Step 1: *Synthesis of phenethyl 2,2-difluorocyclobutane-1-carboxylate*

[00495] The title compound was obtained as a colorless oil, 1.0 g, 57%, from 2,2-difluorocyclobutane-1-carboxylic acid and 2-phenylethanol, following the procedure described in Example 53 and 54, step 1. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 7.34-7.21 (m, 5H), 4.32-4.28 (m, 2H), 3.92-3.85 (m, 1H), 2.92-2.88 (m, 2H), 2.55-2.43 (m, 2H), 1.97-1.92 (m, 2H).

[00496] Step 2: *Synthesis of 3-(2,2-difluorocyclobutyl)-3-oxopropanenitrile*

[00497] The title compound was obtained as a colorless oil, 180 mg, 57%, from MeCN and phenethyl 2,2-difluorocyclobutane-1-carboxylate, following the procedure described in Example 28

and 29, step 1. ¹H NMR (500 MHz, CDCl₃) δ ppm 3.98-3.88 (m, 1H), 3.63-3.53 (m, 2H), 2.65-2.49 (m, 2H), 2.37-2.30 (m, 1H), 1.98-1.92 (m, 1H).

[00498] Step 3: *Synthesis of 5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-amine*

The title compound was obtained as a yellow oil, 330 mg, 54%, from 3-(2,2-difluorocyclobutyl)-3-oxopropanenitrile and hydrazine hydrate, following the procedure described in Example 28 and 29, step 2. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.30 (br s, 1H), 5.29 (s, 1H), 4.95-4.33 (m, 2H), 3.85-3.76 (m, 1H), 2.59-2.50 (m, 1H), 2.50-2.40 (m, 1H), 2.15-2.01 (m, 1H), 1.97-1.84 (m, 1H).

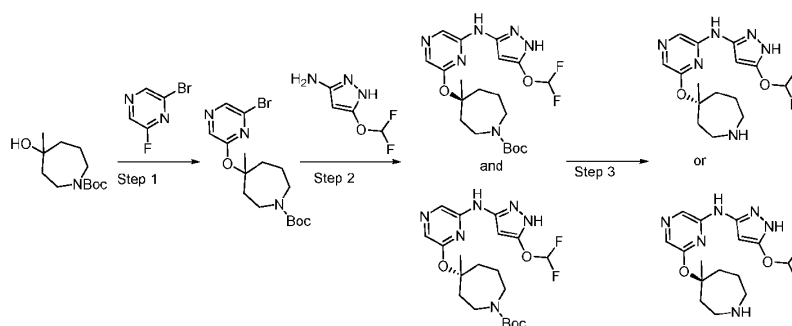
[00499] Step 4: *Synthesis of (S)-N-(5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine and (R)-N-(5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

[00500] The title compounds were obtained, **Example 55**, Peak 1, 70 mg, 24% and **Example 56**, Peak 2, 15.9 mg, 5%, from 5-(2,2-difluorocyclobutyl)-1H-pyrazol-3-amine and Example 8, step 1, following a similar procedure to that described in Example 28 and 29, step 3.

[00501] Peak 1: ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.28 (br s, 1H), 9.75 (s, 1H), 7.90 (s, 1H), 7.45 (s, 1H), 6.43 (s, 1H), 4.96-4.85 (m, 1H), 4.12-3.98 (m, 1H), 2.77-2.58 (m, 3H), 2.28-2.20 (m, 1H), 2.17 (s, 3H), 2.13-2.08 (m, 2H), 2.01-1.95 (m, 3H), 1.71-1.63 (m, 2H).

[00502] Peak 2: LCMS *m/z* = 365 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.30 (br s, 1H), 9.74 (s, 1H), 7.90 (s, 1H), 7.46 (s, 1H), 6.43 (s, 1H), 4.97-4.86 (m, 1H), 4.11-4.00 (m, 1H), 2.78-2.58 (m, 3H), 2.28-2.23 (m, 1H), 2.19 (s, 3H), 2.16-2.06 (m, 2H), 2.06-1.95 (m, 3H), 1.71-1.63 (m, 2H).

[00503] **Example 57**, (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((4-methylazepan-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((4-methylazepan-4-yl)oxy)pyrazin-2-amine



[00504] Step 1: *Synthesis of tert-butyl 4-((6-bromopyrazin-2-yl)oxy)-4-methylazepane-1-carboxylate*

[00505] To a solution of 2-bromo-6-fluoropyrazine (500 mg, 2.82 mmol) and tert-butyl 4-hydroxy-4-methylazepane-1-carboxylate (839 mg, 3.66 mmol) in DMA (5.0 mL) was added sodium tert-butoxide (271 mg, 2.82 mmol) and the reaction mixture was irradiated by MW at 80 °C for 40

min. After cooling to rt, the reaction was diluted with EtOAc and washed with water. The organic layer was evaporated under reduced pressure to give the title compound (1.0 g) as a brown oil.

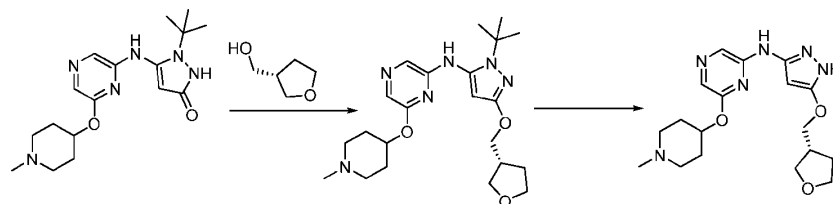
[00506] Step 2: *Synthesis of tert-butyl (R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-4-methylazepane-1-carboxylate and tert-butyl (S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-4-methylazepane-1-carboxylate*

[00507] The title compound was obtained as Peak 2, 18 mg, 6%, from tert-butyl 4-((6-bromopyrazin-2-yl)oxy)-4-methylazepane-1-carboxylate and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 24 and 25, step 1. LCMS $m/z = 455$ $[M+H]^+$.

[00508] Step 3: *Synthesis of (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((4-methylazepan-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((4-methylazepan-4-yl)oxy)pyrazin-2-amine*

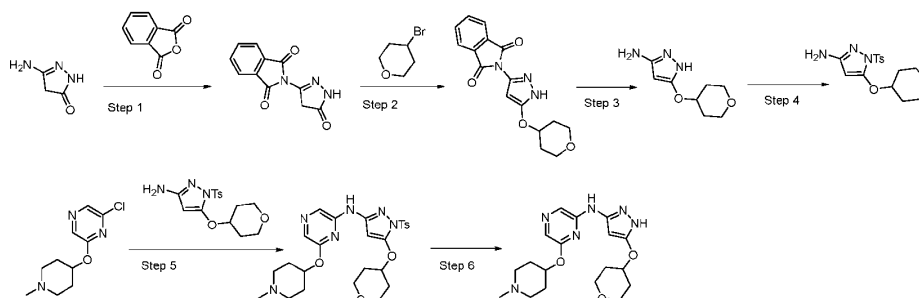
[00509] The title compound was obtained as a yellow solid, 11.3 mg, 81%, from Step 2, following the procedure described in Example 3, step 3. LCMS $m/z = 355$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 12.15 (br s, 1H), 9.70 (br s, 1H), 7.80 (s, 1H), 7.58 (s, 1H), 7.23 (t, 1H), 5.91 (s, 1H), 3.21-3.01 (m, 4H), 2.47-2.33 (m, 2H), 2.08-1.99 (m, 1H), 1.85-1.77 (m, 2H), 1.74-1.58 (m, 1H), 1.53 (s, 3H).

[00510] **Example 58**, (R)-6-((1-methylpiperidin-4-yl)oxy)-N-(5-((tetrahydrofuran-3-yl)methoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



[00511] The title compound was obtained from Example 41, step 1 and (S)-(tetrahydrofuran-3-yl)methanol, following the same 2 step procedure as described in Example 41, steps 2 and 3. LCMS $m/z = 375$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 11.87-11.26 (m, 1H), 9.73 (br s, 1H), 7.80 (br s, 1H), 7.50 (s, 1H), 5.78-5.73 (m, 1H), 4.93-4.87 (m, 1H), 4.05-3.94 (m, 2H), 3.80-3.75 (m, 2H), 3.68-3.63 (m, 1H), 3.54-3.49 (m, 1H), 2.78-2.61 (m, 3H), 2.18 (s, 3H), 2.14-2.07 (m, 2H), 2.02-1.97 (m, 3H), 1.69-1.55 (m, 3H).

[00512] **Example 59**, 6-((1-methylpiperidin-4-yl)oxy)-N-(5-((tetrahydro-2H-pyran-4-yl)oxy)-1H-pyrazol-3-yl)pyrazin-2-amine



[00513] *Step 1: Synthesis of 2-(5-oxo-4,5-dihydro-1H-pyrazol-3-yl)isoindoline-1,3-dione*

A mixture of 5-amino-2,4-dihydro-3H-pyrazol-3-one (11.0 g, 0.11 mol) and isobenzofuran-1,3-dione (17.0 g, 0.11 mol) in AcOH (200 mL) was stirred for 2 h at 120 °C. The reaction mixture was cooled to rt. The precipitate was collected by filtration to give the title compound (20.0 g, 80%) as a gray solid. LCMS $m/z = 230$ $[M+H]^+$.

[00514] *Step 2: Synthesis of 2-(5-((tetrahydro-2H-pyran-4-yl)oxy)-1H-pyrazol-3-yl)isoindoline-1,3-dione*

A mixture of the compound from Step 1 (6 g, 26.1 mmol), 4-bromooxane (8.61 g, 52.2 mmol) and K_2CO_3 (10.8 g, 78.3 mmol) in DMF (15 mL) was stirred at 35 °C for 16 h. The mixture was diluted with EtOAc and washed with water and brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with EtOAc/PE (3/2) to afford the title compound (320 mg, 4%) as yellow oil. LCMS $m/z = 314$ $[M+H]^+$.

[00515] *Step 3: Synthesis of 5-((tetrahydro-2H-pyran-4-yl)oxy)-1H-pyrazol-3-amine*

A mixture of the compound from step 2 (320 mg, 1.02 mmol) and $N_2H_4 \cdot H_2O$ (163 mg, 5.10 mmol) in EtOH (6 mL) was stirred at 70 °C for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with MeOH/DCM (1/3) to give the title product (160 mg, crude) as colorless oil. LCMS $m/z = 184$ $[M+H]^+$.

[00516] *Step 4: Synthesis of 5-((tetrahydro-2H-pyran-4-yl)oxy)-1-tosyl-1H-pyrazol-3-amine*

A mixture of the compound from step 3 (160 mg, crude), EtOAc (263 mg, 2.61 mmol), TsCl (165 mg, 873 μ mol) and DMAP (10.6 mg, 87.3 μ mol) in DCM (8 mL) was stirred at rt for 1 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with MeOH/DCM (1/8) to afford the title compound (130 mg, 44%) as a yellow oil.

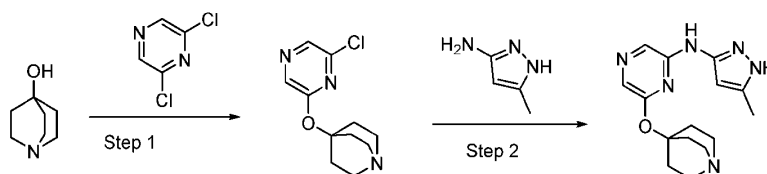
[00517] *Step 5: Synthesis of 6-((1-methylpiperidin-4-yl)oxy)-N-(5-((tetrahydro-2H-pyran-4-yl)oxy)-1-tosyl-1H-pyrazol-3-yl)pyrazin-2-amine*

The title compound was obtained as a yellow solid, 160 mg, 78%, from the compound from step 4 and Example 8, step 1, following the procedure described in Example 19 and 20, step 1. LCMS $m/z = 529$ $[M+H]^+$.

[00518] *Step 6: Synthesis of 6-((1-methylpiperidin-4-yl)oxy)-N-(5-((tetrahydro-2H-pyran-4-yl)oxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

A mixture of the compound from step 5 (130 mg, 245 μmol) and KOH (27.4 mg, 490 μmol) in EtOH (10 mL) was stirred at 65 °C for 1 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with MeOH/DCM (3/7) to afford the title compound (4.6 mg, 5%) as a yellow solid. LCMS $m/z = 375$ $[\text{M}+\text{H}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ ppm 7.74 (s, 1H), 7.68 (s, 1H), 6.86 (s, 1H), 5.37 (s, 1H), 4.95-4.90 (m, 1H), 4.67-4.61 (m, 1H), 3.99-3.90 (m, 2H), 3.59-3.53 (m, 2H), 2.73-2.67 (m, 2H), 2.46-2.40 (m, 2H), 2.34 (s, 3H), 2.10-2.05 (m, 4H), 1.97-1.87 (m, 2H), 1.84-1.74 (m, 2H).

[00519] Example 60, N-(5-methyl-1H-pyrazol-3-yl)-6-(quinuclidin-4-yloxy)pyrazin-2-amine



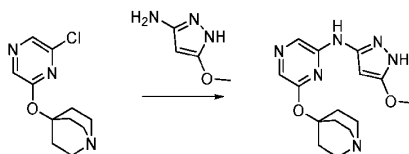
[00520] Step 1: Synthesis of 4-((6-chloropyrazin-2-yl)oxy)quinuclidine

The title compound was obtained as a white solid, 230 mg, 82%, from 1-azabicyclo[2.2.2]octan-4-ol and 2,6-dichloropyrazine, following the procedure described in Example 37, step 1. LCMS $m/z = 240$ $[\text{M}+\text{H}]^+$

[00521] Step 2: Synthesis of N-(5-methyl-1H-pyrazol-3-yl)-6-(quinuclidin-4-yloxy)pyrazin-2-amine

A mixture of 4-((6-chloropyrazin-2-yl)oxy)quinuclidine (70 mg, 292 μmol), 5-methyl-1H-pyrazol-3-amine (28.3 mg, 292 μmol), KOAc (85.9 mg, 876 μmol) and BrettPhos Pd G4 (26.8 mg, 29.2 μmol) in dioxane (5 mL) was stirred at 90 °C for 3 h under N_2 . The reaction mixture was diluted with dioxane, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with MeOH/DCM (1/4). The product was further purified by Prep-HPLC (Method A) to afford the title compound (10.1 mg, 10%) as a white solid. LCMS $m/z = 301$ $[\text{M}+\text{H}]^+$. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.88 (br s, 1H), 9.31 (s, 1H), 8.03 (s, 1H), 7.34 (s, 1H), 6.01 (s, 1H), 2.91-2.83 (m, 6H), 2.17 (s, 3H), 2.04-1.95 (m, 6H).

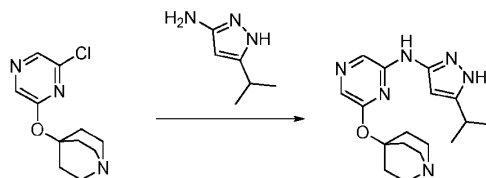
[00522] Example 61, N-(5-methoxy-1H-pyrazol-3-yl)-6-(quinuclidin-4-yloxy)pyrazin-2-amine



[00523] The title compound was obtained as a white solid, 12.5 mg, 14%, from Example 60, step 1 and 5-methoxy-1H-pyrazol-3-amine, following the procedure described in Example 60, step 2.

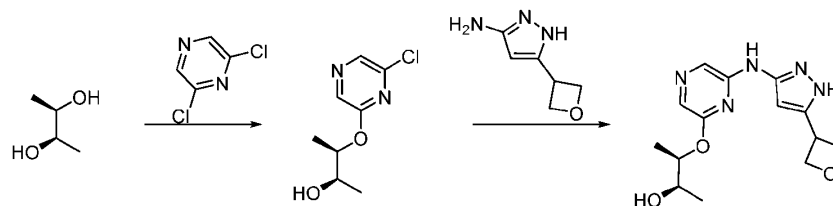
LCMS $m/z = 317$ $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.89-11.30 (m, 1H), 9.55-9.46 (m, 1H), 8.15-7.70 (m, 1H), 7.45 (s, 1H), 5.67 (s, 1H), 3.78 (s, 3H), 2.95-2.80 (m, 6H), 2.13-1.95 (m, 6H).

[00524] **Example 62**, N-(5-isopropyl-1H-pyrazol-3-yl)-6-(quinuclidin-4-yloxy)pyrazin-2-amine



[00525] The title compound was obtained as a yellow solid, 10.2 mg, 10%, from Example 60, step 1 and 5-isopropyl-1H-pyrazol-3-amine, following the procedure described in Example 60, step 2. LCMS $m/z = 329$ $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.94 (br s, 1H), 9.38 (s, 1H), 8.00 (s, 1H), 7.36 (s, 1H), 6.04 (s, 1H), 3.02-2.94 (m, 6H), 2.91-2.86 (m, 1H), 2.14-2.05 (m, 6H), 1.19 (d, 6H).

[00526] **Example 63**, (2R,3R)-3-(((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)butan-2-ol



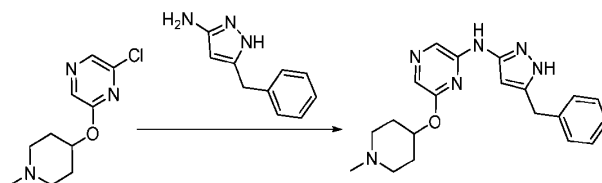
[00527] Step 1: *Synthesis of (2R,3R)-3-(((6-chloropyrazin-2-yl)oxy)butan-2-ol*

The title compound was obtained as a yellow solid, 219 mg, 50%, from (2R,3R)-butane-2,3-diol and 2,6-dichloropyrazine following the procedure described in Example 5, step 1. LCMS $m/z = 203$ $[M+H]^+$.

[00528] Step 2: *Synthesis of (2R,3R)-3-(((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)butan-2-ol*

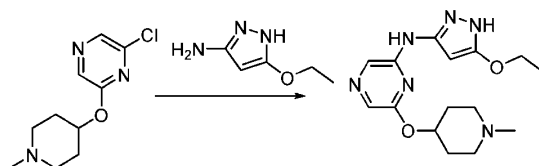
The title compound was obtained as a white solid, 110 mg, 35%, from (2R,3R)-3-(((6-chloropyrazin-2-yl)oxy)butan-2-ol and 5-(oxetan-3-yl)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS $m/z = 306$ $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.18 (br s, 1H), 9.60 (br s, 1H), 8.02 (s, 1H), 7.46 (s, 1H), 6.49 (s, 1H), 5.01-4.96 (m, 1H), 4.90-4.85 (m, 2H), 4.84-4.80 (m, 1H), 4.66-4.60 (m, 2H), 4.31-4.26 (m, 1H), 3.82-3.79 (m, 1H), 1.24 (d, 3H), 1.10 (d, 3H).

[00529] **Example 64**, N-(5-benzyl-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



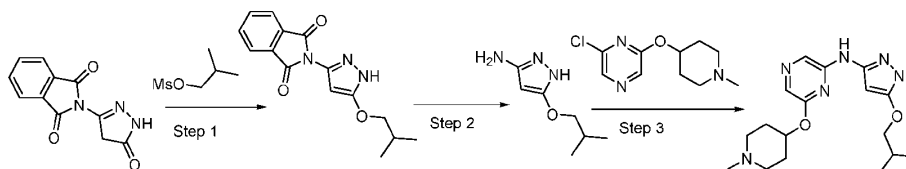
[00530] The title compound was obtained as a yellow solid, 44.5 mg, 46%, from Example 8, step 1 and 5-benzyl-1H-pyrazol-3-amine following the procedure described in Example 37, step 2. LCMS $m/z = 365$ $[M+H]^+$. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ ppm 12.15 (br s, 1H), 9.64 (s, 1H), 7.91 (s, 1H), 7.43 (s, 1H), 7.35-7.20 (m, 5H), 6.19 (s, 1H), 4.81-4.75 (m, 1H), 3.93 (s, 2H), 2.62-2.57 (m, 2H), 2.17 (s, 3H), 2.10-1.98 (m, 2H), 1.92-1.89 (m, 2H), 1.67-1.57 (m, 2H).

[00531] **Example 65**, N-(5-ethoxy-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00532] The title compound was obtained as a yellow solid, 54 mg, 43%, from Example 8, step 1 and 5-ethoxy-1H-pyrazol-3-amine, following a similar procedure to that described in Example 19 and 20, step 2. LCMS $m/z = 319$ $[M+H]^+$. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ ppm 11.58 (br s, 1H), 9.69 (br s, 1H), 7.88 (br s, 1H), 7.50 (s, 1H), 5.76-5.70 (m, 1H), 4.95-4.90 (m, 1H), 4.10 (q, 2H), 2.70-2.62 (m, 2H), 2.18 (s, 3H), 2.17-2.08 (m, 2H), 2.01-1.95 (m, 2H), 1.75-1.65 (m, 2H), 1.30 (t, 3H).

[00533] **Example 66**, N-(5-isobutoxy-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00534] *Step 1: Synthesis of 2-(5-isobutoxy-1H-pyrazol-3-yl)isoindoline-1,3-dione*

The title compound was obtained as a yellow oil, 120 mg, 9%, from Example 59, step 1 and 2-methylpropyl methanesulfonate, following the procedure in Example 59, step 2. LCMS $m/z = 286$ $[M+H]^+$.

[00535] *Step 2: Synthesis of 5-isobutoxy-1H-pyrazol-3-amine*

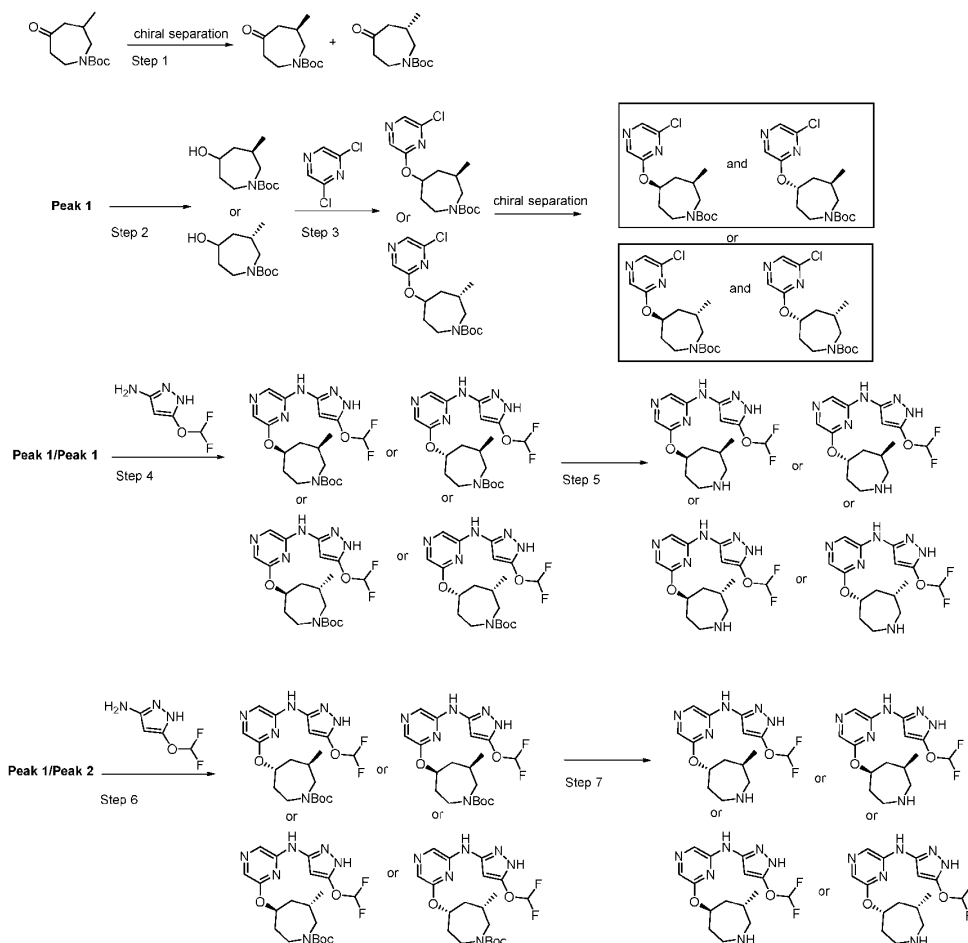
A mixture of 2-(5-isobutoxy-1H-pyrazol-3-yl)isoindoline-1,3-dione (120 mg, 420 μmol) and $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ (13.4 mg, 420 μmol) in EtOH (4 mL) was stirred at 75 °C for 2 h. The reaction mixture was purified by Prep-HPLC (Method A) to give the title product (60 mg, 92%) as a colorless oil. LCMS $m/z = 156$ $[M+H]^+$.

[00536] *Step 3: Synthesis of N-(5-isobutoxy-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

The title compound was obtained as a yellow solid, 4.5 mg, 4%, from 5-isobutoxy-1H-pyrazol-3-amine and Example 8, step 1 following the procedure described in Example 37, step 2. LCMS m/z = 347 [M+H]⁺. ¹H-NMR (400 MHz, CDCl₃) δ ppm 7.78 (s, 1H), 7.73 (br s, 1H), 7.66 (s, 1H), 5.49 (s, 1H), 4.99-4.90 (m, 1H), 3.89 (d, 2H), 2.81-2.64 (m, 2H), 2.45-2.30 (m, 2H), 2.33 (s, 3H), 2.14-2.02 (m, 3H), 1.95-1.83 (m, 2H), 1.01 (d, 6H).

[00537] **Example 67**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine and

[00538] **Example 68**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine



[00539] Step 1: *Synthesis of tert-butyl (R)-3-methyl-5-oxoazepane-1-carboxylate and tert-butyl (S)-3-methyl-5-oxoazepane-1-carboxylate*

[00540] tert-Butyl 3-methyl-5-oxoazepane-1-carboxylate (1 g) was separated by SFC (Method C, 75/25) to give Peak 1, tert-butyl (R)-3-methyl-5-oxoazepane-1-carboxylate or tert-butyl (S)-3-methyl-5-oxoazepane-1-carboxylate (360 mg) and Peak 2, tert-butyl (S)-3-methyl-5-oxoazepane-1-carboxylate or tert-butyl (R)-3-methyl-5-oxoazepane-1-carboxylate (410 mg).

[00541] Step 2: *Synthesis of tert-butyl (3R)-5-hydroxy-3-methylazepane-1-carboxylate or tert-butyl (3S)-5-hydroxy-3-methylazepane-1-carboxylate*

[00542] To a stirring solution of Peak 1, step 1 (360 mg, 1.58 mmol) in MeOH (5 ml) was added NaBH₄ (508 mg, 13.4 mmol) at rt under N₂ and the reaction mixture was stirred for 0.5 h. The mixture was diluted with EtOAc and washed with water and brine and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (350 mg) as light-yellow oil. LCMS m/z = 174 [M-56+H]⁺.

[00543] Step 3: *Synthesis of tert-butyl (3R,5S)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate, or tert-butyl (3R,5R)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate, or tert-butyl (3S,5S)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S,5R)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate*

[00544] tert-butyl (3R)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate, was obtained as a yellow oil, 360 mg, 75%, from the compound from Step 2 and 2,6-dichloropyrazine, following the procedure described in Example 5, step 1. The racemic product was separated by chiral-SFC (Method E, 75/25) to give Peak 1 (160 mg) and Peak 2 (180 mg). LCMS m/z = 286 [M-56+H]⁺.

[00545] Step 4: *Synthesis of tert-butyl (3R,5S)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate, or tert-butyl (3R,5R)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S,5S)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S,5R)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate*

[00546] The title compound was obtained as a light-yellow solid, 160 mg, 64%, from Peak 1, step 3 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS m/z = 455 [M+H]⁺.

[00547] Step 5: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine*

[00548] The title compound, **Example 67**, was obtained as a yellow solid, 11.3 mg, 14.5%, from the compound from step 4, following a similar procedure to that described in Example 3, step 3, except HPLC (Method B) was used. LCMS m/z = 355 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.96 (br s, 1H), 8.39 (s, 1H), 7.73 (s, 1H), 7.53 (s, 1H), 7.26 (t, 1H), 6.01 (s, 1H), 5.16-5.11 (m, 1H), 3.09-2.97 (m, 3H), 2.66-2.54 (m, 1H), 2.37-2.28 (m, 1H), 2.20-2.04 (m, 1H), 2.03-1.86 (m, 2H), 1.67-1.61 (m, 1H), 0.91 (d, 3H).

[00549] **Step 6:** *Synthesis of tert-butyl (3R,5R)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate, or tert-butyl (3R,5S)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S,5S)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S,5R)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate*

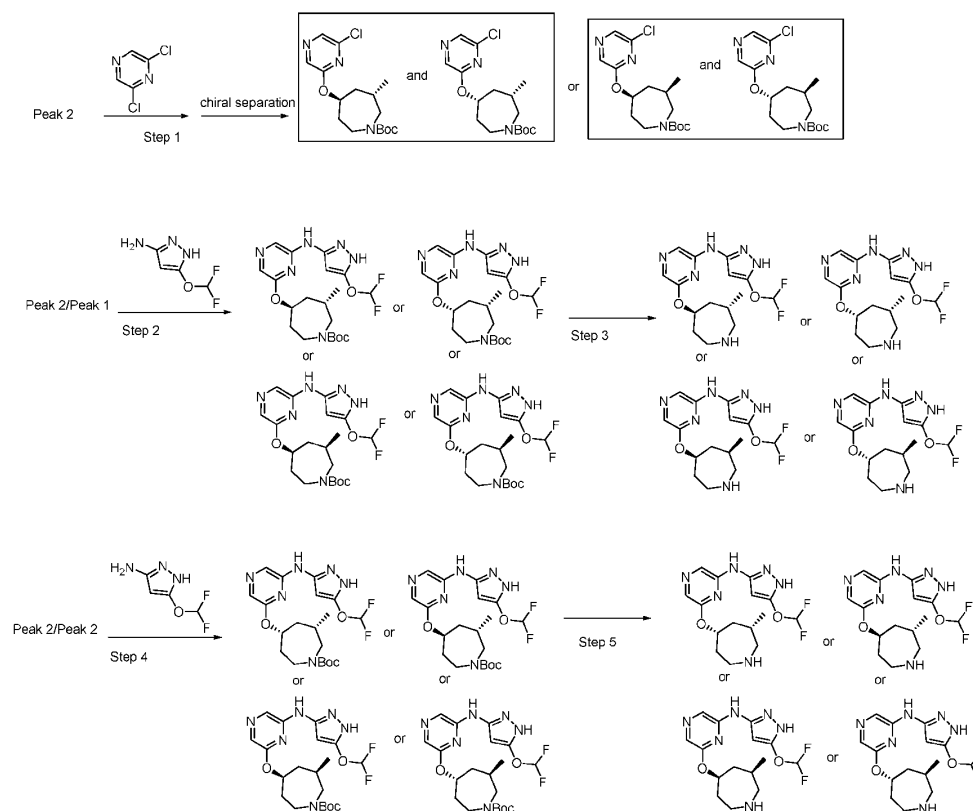
[00550] The title compound was obtained as a light-yellow oil, 110 mg, 57%, from Peak 2, step 3, and 5-(difluoromethoxy)-1H-pyrazol-3-amine following the procedure described in Example 19 and 20, step 2. LCMS m/z = 455 [M+H]⁺.

[00551] **Step 7:** *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine*

[00552] The title product, **Example 68**, was obtained (42.4 mg, 54%) as a yellow solid, from the product of step 6, following the procedure described in Step 5. LCMS m/z = 355 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 11.75 (br s, 1H), 8.69 (br s, 1H), 7.75 (s, 1H), 7.58 (s, 1H), 7.26 (t, 1H), 5.99 (s, 1H), 5.35-5.29 (m, 1H), 3.18-3.14 (m, 1H), 3.10-3.05 (m, 1H), -3.03-2.97 (m, 1H), 2.71-2.67 (m, 1H), 2.22-2.00 (m, 4H), 1.86-1.81 (m, 1H), 0.91 (d, 3H).

[00553] **Example 69**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine and

[00554] **Example 70**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine



[00555] Step 1: Synthesis of tert-butyl (3*S*,5*S*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate and tert-butyl (3*S*,5*R*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3*R*,5*S*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate and tert-butyl (3*R*,5*R*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate

[00556] tert-butyl (3*S*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3*R*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate was obtained as a yellow oil, 340 mg, 65%, from Example 67 and 68, step 1, Peak 2, following the procedure described in Example 39, step 1. This was further purified by chiral SFC (Column: OJ 20*250mm, 10 μ m (Daicel), Column temperature: 35 $^{\circ}$ C, Mobile phase: CO₂/IPA [0.5%NH₃(7M in MeOH)] = 95/5, Flow rate: 90 g/min, Back pressure: 100 bar to give Peak 1, tert-butyl (3*S*,5*S*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3*S*,5*R*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3*R*,5*S*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3*R*,5*R*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate (150 mg) and Peak 2, tert-butyl (3*S*,5*R*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3*S*,5*S*)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl

(3R,5S)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3R,5R)-5-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate (130 mg). LCMS m/z = 286 [M+H]⁺.

[00557] *Step 2: Synthesis of tert-butyl (3S,5S)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S,5R)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3R,5S)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3R,5R)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate*

[00558] The title compound was obtained as a light-yellow oil, 130 mg, 65%, from Peak 1, step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS m/z = 455 [M+H]⁺.

[00559] *Step 3: Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine*

[00560] The title compound, **Example 69**, was obtained as a yellow solid, 51.8 mg, 60%, from the compound from step 2, following the procedure described in Example 67 and 68, step 5. LCMS m/z = 355 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 13.15 (br s, 1H), 11.39 (br s, 1H), 8.40 (s, 1H), 7.75 (s, 1H), 7.58 (s, 1H), 7.25 (t, 1H), 5.98 (s, 1H), 5.35-5.30 (m, 1H), 3.20-3.10 (m, 1H), 3.10-3.04 (m, 1H), 3.01-2.95 (m, 1H), 2.73-2.58 (m, 1H), 2.22-2.09 (m, 3H), 2.06-1.97 (m, 1H), 1.84-1.79 (m, 1H), 0.91 (d, 3H).

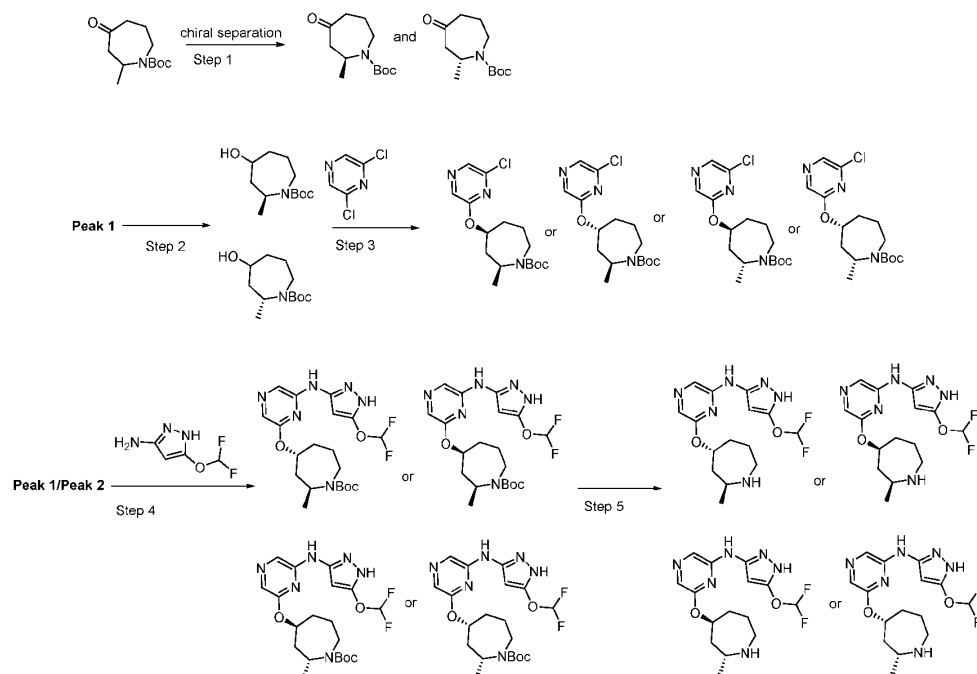
[00561] *Step 4: Synthesis of tert-butyl (3S,5R)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S,5S)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3R,5S)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3R,5R)-5-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate*

[00562] The title compound was obtained as a light-yellow oil, 120 mg, 69%, from Peak 2, step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS m/z = 455 [M+H]⁺.

[00563] *Step 5: Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6S)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4S,6R)-6-methylazepan-4-yl)oxy)pyrazin-2-amine*

[00564] The title compound, **Example 70**, was obtained as a yellow solid, 39.2 mg 50%, from the compound of step 4, following the procedure described in Example 67 and 68, step 5. LCMS m/z = 355 $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 12.75 (br s, 1H), 10.82 (br s, 1H), 8.35 (s, 1H), 7.75 (s, 1H), 7.54 (s, 1H), 7.25 (t, 1H), 5.99 (s, 1H), 5.20-5.12 (m, 1H), 3.10-3.02 (m, 3H), 2.67-2.50 (m, 1H), 2.31-2.20 (m, 1H), 2.17-2.09 (m, 1H), 2.00-1.87 (m, 2H), 1.71-1.59 (m, 1H), 0.91 (d, 3H).

[00565] **Example 71**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-2-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-2-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-methylazepan-4-yl)oxy)pyrazin-2-amine



[00566] Step 1: Synthesis of tert-butyl (S)-2-methyl-4-oxoazepane-1-carboxylate and tert-butyl (R)-2-methyl-4-oxoazepane-1-carboxylate

[00567] tert-butyl 3-methyl-5-oxoazepane-1-carboxylate (1.0 g) was separated by chiral SFC (Method C, 75/25) to give Peak 1, tert-butyl (S)-2-methyl-4-oxoazepane-1-carboxylate or tert-butyl (R)-2-methyl-4-oxoazepane-1-carboxylate (450 mg) and Peak 2, tert-butyl (R)-2-methyl-4-oxoazepane-1-carboxylate or tert-butyl (S)-2-methyl-4-oxoazepane-1-carboxylate (410 mg). LCMS m/z = 228 $[M+H]^+$.

[00568] Step 2: *Synthesis of tert-butyl (2S)-4-hydroxy-2-methylazepane-1-carboxylate and tert-butyl (2R)-4-hydroxy-2-methylazepane-1-carboxylate*

[00569] The title compound was obtained as a light-yellow oil, 430 mg, 95%, from Peak, step 1, following the procedure described in Example 67 and 68, step 2. LCMS m/z = 174 $[M-56+H]^+$.

[00570] Step 3: *Synthesis of tert-butyl (2S,4S)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2S,4R)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2R,4S)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2R,4R)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate*

[00571] tert-butyl (2S)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2R)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate was obtained, 510 mg, 79%, from the compound from step 2 and 2,6-dichloropyrazine, following the procedure described in Example 39, step 1. This racemic compound was further separated by chiral SFC (Method C, 85/15) to give Peak 1, tert-butyl (2S,4S)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2S,4R)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2R,4S)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2R,4R)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate (40 mg) and Peak 2, tert-butyl (2S,4R)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2S,4S)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2R,4S)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2R,4R)-4-((6-chloropyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate (440 mg). LCMS m/z = 286 $[M-56+H]^+$.

[00572] Step 4: *Synthesis of tert-butyl (2S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate or tert-butyl (2R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methylazepane-1-carboxylate*

[00573] The title compound was obtained as a light-yellow solid, 360 mg, 67%, from Peak 2, step 3 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS m/z = 455 $[M+H]^+$.

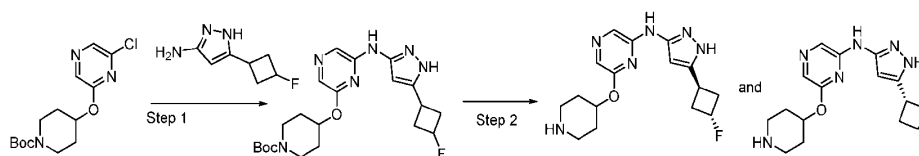
[00574] Step 5: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-2-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-2-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-methylazepan-4-yl)oxy)pyrazin-2-amine*

[00575] To a solution of the compound from step 4 (340 mg, 748 μ mol) in DCM (7 ml) was added 4M HCl/dioxane (4.0 mL) at 0 °C under N_2 and the reaction mixture was allowed to warm to rt

and stirred for 1 h. The mixture was basified by 7N NH₃ in MeOH until pH~8, then concentrated under reduced pressure. The crude was purified by Prep-HPLC (Method A) to obtain the title product (99.1 mg, 37%) as a white solid. LCMS m/z = 355[M+H]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ ppm 12.12 (br s, 1H), 10.09 (br s, 1H), 7.75 (s, 1H), 7.56 (s, 1H), 7.26 (t, 1H), 5.98 (s, 1H), 5.35-5.25 (m, 1H), 4.02-3.58 (m, 1H), 3.00-2.90 (m, 2H), 2.70-2.55 (m, 1H), 2.06-1.92 (m, 2H), 1.88-1.74 (m, 2H), 1.74-1.69 (m, 1H), 1.61-1.44 (m, 1H), 1.09-0.98 (m, 3H).

[00576] Example 72, N-(5-((1*s*,3*s*)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine or N-(5-((1*r*,3*r*)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine and

[00577] Example 73, N-(5-((1*r*,3*r*)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine or N-(5-((1*s*,3*s*)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine



[00578] Step 1: Synthesis of tert-butyl 4-((6-((5-(3-fluorocyclobutyl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate

[00579] The title compound was obtained as a brown oil, 300 mg, 87% from Example 1, step 1 and 5-(3-fluorocyclobutyl)-1H-pyrazol-3-amine following the procedure described in Example 60, step 2. LCMS m/z = 433 [M+H]⁺.

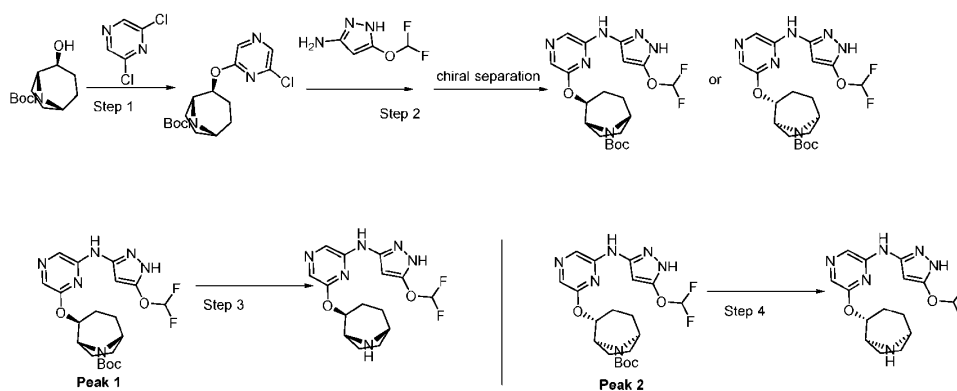
[00580] Step 2: Synthesis of N-(5-((1*r*,3*r*)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine and N-(5-((1*s*,3*s*)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine

[00581] To a solution of the compound from step 1 (170 mg, 393 μ mol) in DCM (5.0 mL) was added TFA (1.0 mL) at 0 °C under N₂. After addition, the reaction mixture was allowed to warm to rt and stirred for 5 h. The reaction mixture was basified with 7M NH₃ in MeOH to pH~10 and the resulting precipitate was filtered. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel eluting with DCM/MeOH (9/1) to afford the racemic product. This was further separated by Chiral-SFC (Column: IE 20*250mm, 10 μ m (Daicel), Column temperature: 35 °C, Mobile phase: CO₂/MeOH (0.2% MeOH/NH₃) = 50/50, Flow rate: 120 g/min, Back pressure: 100 bar to give Peak 1, **Example 73** (44.8 mg, 34.3%) ¹HNMR (400 MHz, DMSO-*d*₆) δ ppm: 12.07 (br s, 1H), 9.64 (s, 1H), 7.94 (s, 1H), 7.46 (s, 1H), 6.30 (s, 1H), 5.35-5.10 (m, 1H), 5.03-4.98 (m, 1H), 3.59-3.52 (m, 1H), 3.06-2.99 (m, 2H), 2.67-2.53 (m, 5H), 2.03-1.95 (m, 2H), 1.64-1.55 (m, 2H), 1.28-1.20 (m, 1H).

[00582] and Peak 2, **Example 72** (39.8 mg, 30.5%) as a white solid. LCMS m/z = 333 $[M+H]^+$. 1H -NMR (400 MHz, $DMSO-d_6$) δ ppm 12.17 (br s, 1H), 9.66 (s, 1H), 7.99 (s, 1H), 7.50 (s, 1H), 6.28 (s, 1H), 5.15-5.10 (m, 1H), 5.13-4.95 (m, 1H), 3.33-3.20 (m, 3H), 3.06-2.99 (m, 5H), 2.67-2.53 (m, 2H), 2.43-2.10 (m, 2H), 1.89-1.80 (m, 2H), 1.28-1.20 (m, 1H).

[00583] **Example 74**, 6-(((1R,2S,5S)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1S,2R,5R)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine and

[00584] **Example 75**, 6-(((1S,2R,5R)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1R,2S,5S)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



[00585] Step 1: *Synthesis of rac-tert-butyl (1R,2S,5S)-2-((6-chloropyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate*

[00586] The title compound was obtained as a light-yellow oil, 230 mg, 65%, from rac-tert-butyl (1R,2S,5S)-2-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate and 2,6-dichloropyrazine, following the procedure described in Example 39, step 1. LCMS m/z = 284 $[M-56+H]^+$.

[00587] Step 2: *Synthesis of tert-butyl (1R,2S,5S)-2-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1S,2R,5R)-2-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate*

[00588] The title compounds were obtained Peak 1 (50 mg) and Peak 2 (55 mg) from the compound from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 24 and 25, step 1. LCMS m/z = 453 $[M+H]^+$.

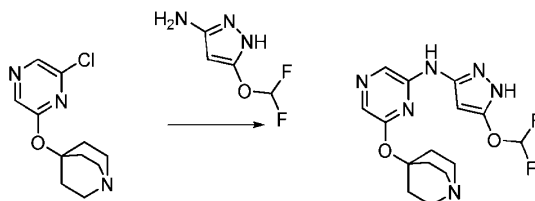
[00589] Step 3: *Synthesis of Example 74*, 6-(((1R,2S,5S)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or 6-(((1S,2R,5R)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine

[00590] The title compound was obtained as a white solid, 22.7 mg, 59%, from Peak 1, Step 2, following the procedure described in Example 3, step 3. LCMS $m/z = 353$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 11.98 (br, s, 1H), 10.02 (s, 1H), 7.78 (s, 1H), 7.65 (s, 1H), 7.25 (t, 1H), 5.93 (s, 1H), 4.81-4.78 (m, 1H), 3.60-3.53 (m, 1H), 3.44-3.38 (m, 1H), 1.98-1.60 (m, 8H), 1.35-1.32 (m, 1H).

[00591] Step 4: *Synthesis of Example 75*, 6-(((1*S*,2*R*,5*R*)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-*N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)pyrazin-2-amine or 6-(((1*R*,2*S*,5*S*)-8-azabicyclo[3.2.1]octan-2-yl)oxy)-*N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)pyrazin-2-amine

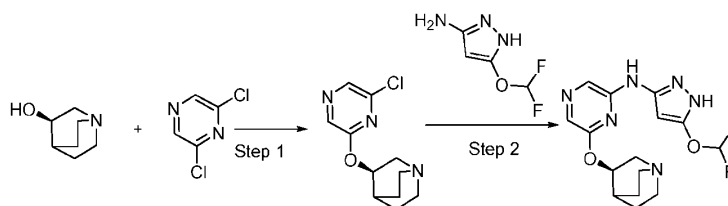
[00592] The title compound was obtained as a white solid, 26.7 mg, 63% from Peak 2, step 2, following the procedure described in Example 3, Step 3. LCMS $m/z = 353$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 12.19 (br, s, 1H), 10.04 (br, s, 1H), 7.77 (s, 1H), 7.64 (s, 1H), 7.24 (t, 1H), 5.94 (s, 1H), 4.78-4.75 (m, 1H), 3.54-3.50 (m, 1H), 3.37-3.33 (m, 1H), 2.02-1.67 (m, 8H), 1.33-1.32 (m, 1H).

[00593] **Example 76**, *N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-(quinuclidin-4-yloxy)pyrazin-2-amine



[00594] The title compound was obtained as a white solid, 79.8 mg, 23%, from Example 60, step 1 and 5-(difluoromethoxy)-1*H*-pyrazol-3-amine following the procedure described in Example 37, step 2. LCMS $m/z = 353$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.85 (br s, 1H), 9.70 (br s, 1H), 7.77 (s, 1H), 7.51 (s, 1H), 7.25 (t, 1H), 5.97 (s, 1H), 2.91-2.83 (m, 6H), 2.00-1.93 (m, 6H).

[00595] **Example 77**, *N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-(((1*S*,3*R*,4*S*)-quinuclidin-3-yl)oxy)pyrazin-2-amine



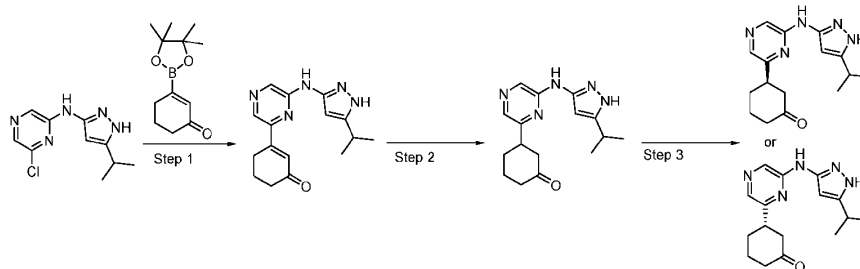
[00596] Step 1: *Synthesis of (R)-3-((6-chloropyrazin-2-yl)oxy)quinuclidine*

[00597] The title compound was obtained as a light-yellow oil, from (*R*)-quinuclidin-3-ol and 2,6-dichloropyrazine, following the procedure described in Example 39, step 1. LCMS $m/z = 240$ $[M+H]^+$.

[00598] Step 2: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,3R,4S)-quinuclidin-3-yl)oxy)pyrazin-2-amine*

[00599] The title compound was obtained as a white solid, 90 mg, 53%, from (R)-3-((6-chloropyrazin-2-yl)oxy)quinuclidine and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS $m/z = 353$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 12.00 (br s, 1H), 9.98 (s, 1H), 7.78 (s, 1H), 7.62 (s, 1H), 7.25 (t, 1H), 5.99 (s, 1H), 4.99-4.96 (m, 1H), 3.24-3.17 (m, 1H), 2.80-2.45 (m, 5H), 2.12-2.08 (m, 1H), 1.78-1.70 (m, 1H), 1.70-1.57 (m, 1H), 1.57-1.48 (m, 1H), 1.39-1.27 (m, 1H).

[00600] **Example 78**, (R)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclohexan-1-one or (S)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclohexan-1-one



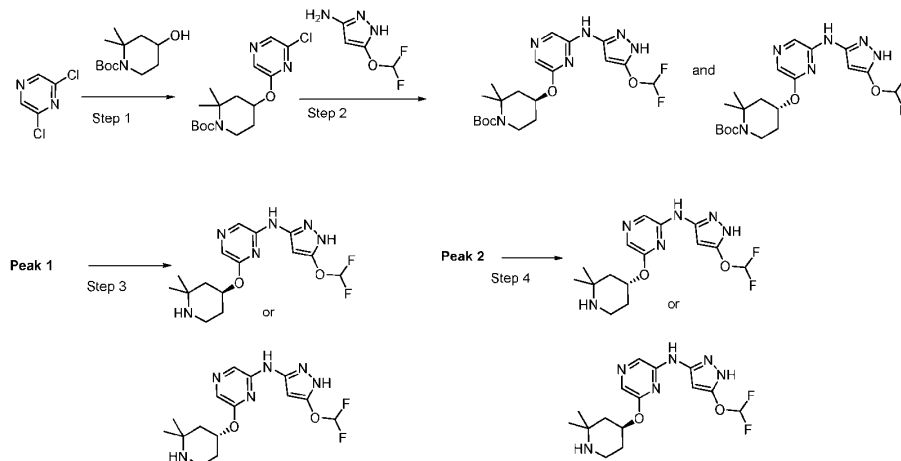
[00601] Step 1: *Synthesis of 3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclohexan-2-en-1-one*

[00602] The title compound was obtained as a yellow solid, 600 mg, 80%, from Example 254, Step 1 and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-cyclohexen-1-one, following the procedure described in Example 248, step 4 LCMS $m/z = 298$ $[M+H]^+$.

[00603] Step 2: *Synthesis of (R)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclohexan-1-one or (S)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclohexan-1-one*

[00604] To a solution of the compound from step 1 (250 mg, 841 μ mol) in EtOAc (15.0 mL) was added 10% Pd/C (wet, 125 mg) and TEA (8.5 mg, 84.1 μ mol) at rt. The reaction mixture was stirred for 16 h under H_2 , then diluted with EtOAc, filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC (Method A) to give the racemic product (50 mg, 20%), then separated by chiral Prep-SFC (Column: OJ 20*250mm, 10 μ m (Daicel), Column temperature: 35°C, Mobile phase: CO_2 /EtOH [0.5% NH_3 (7M in MeOH)] = 80/20, Flow rate: 100 g/min, Back pressure: 100 bar) to give peak 1, the title compound (21.1 mg, 8.4%) as a yellow solid. Note that this compound corresponds to previous Example 257. LCMS $m/z = 300$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.93 (br s, 1H), 9.56 (s, 1H), 8.38 (s, 1H), 7.82 (s, 1H), 6.24 (s, 1H), 3.17-3.11 (m, 1H), 2.96-2.87 (m, 1H), 2.77-2.66 (m, 1H), 2.50-2.36 (m, 2H), 2.33-2.24 (m, 1H), 2.10-1.96 (m, 2H), 1.95-1.83 (m, 1H), 1.78-1.66 (m, 1H), 1.23 (d, 6H).

[00605] Example 79 and Example 80, (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine and (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine



[00606] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-2,2-dimethylpiperidine-1-carboxylate*

[00607] The title compound was obtained as a light-yellow oil, 630 mg, 68%, from tert-butyl 4-hydroxy-2,2-dimethylpiperidine-1-carboxylate and 2,6-dichloropyrazine following the procedure described in Example 39, step 1. LCMS $m/z = 342$ $[M-100+H]^+$.

[00608] Step 2: *Synthesis of tert-butyl (S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2,2-dimethylpiperidine-1-carboxylate and tert-butyl (R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2,2-dimethylpiperidine-1-carboxylate*

[00609] tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2,2-dimethylpiperidine-1-carboxylate was obtained, 240 mg, 36%, from the compound from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. The racemic product was separated by chiral-SFC (Column: OX 20*250mm, 10 μ m (Daicel), Column temperature: 35 $^{\circ}$ C, Mobile phase: CO_2 / [MeOH/MeCN[0.2% NH_3 (7M in MeOH)] 1:1]= 65/35 at 100 g/min, Back pressure: 100 bar to obtain Peak 1, tert-butyl (S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2,2-dimethylpiperidine-1-carboxylate or tert-butyl (R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2,2-dimethylpiperidine-1-carboxylate (110 mg) and Peak 2, tert-butyl (R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2,2-dimethylpiperidine-1-carboxylate or tert-butyl (S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2,2-dimethylpiperidine-1-carboxylate (115 mg) as a yellow solid. LCMS $m/z = 455$ $[M+H]^+$.

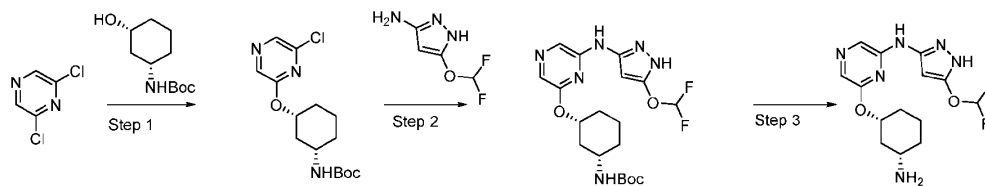
[00610] Step 3: *Synthesis of Example 79, (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine*

[00611] The title compound was obtained as a white solid, 44.7 mg, 57%, from Peak 1, step 2, following the procedure described in Example 3, step 3. LCMS $m/z = 355$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 10.51 (br s, 1H), 7.79 (s, 1H), 7.57 (s, 1H), 7.24 (t, 1H), 5.93 (s, 1H), 5.27-5.19 (m, 1H), 3.05-2.93 (m, 2H), 2.17-1.99 (m, 2H), 1.68-1.55 (m, 1H), 1.52-1.45 (m, 1H), 1.36 (s, 6H).

[00612] Step 4: *Synthesis of Example 80, (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine*

[00613] The title compound was obtained as a white solid, 51.9 mg, 60%, from Peak 2, step 2, following the procedure described in Example 3, Step 3. LCMS $m/z = 355$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ ppm 10.04 (br s, 1H), 7.75 (s, 1H), 7.54 (s, 1H), 7.22 (t, 1H), 5.99 (s, 1H), 5.18-5.14 (m, 1H), 2.86-2.76 (m, 2H), 1.98-1.90 (m, 2H), 1.42-1.35 (m, 1H), 1.30-1.23 (m, 1H), 1.13-1.01 (m, 6H).

[00614] **Example 81, 6-(((1R,3S)-3-aminocyclohexyl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine**



[00615] Step 1: *Synthesis of tert-butyl ((1S,3R)-3-((6-chloropyrazin-2-yl)oxy)cyclohexyl)carbamate*

[00616] The title compound was obtained as a colorless oil, 300 mg, 79% from tert-butyl N-((1S,3R)-3-hydroxycyclohexyl)carbamate and 2,6-dichloropyrazine, following the procedure described in Example 39, step 1. LCMS $m/z = 228$ $[M-100+H]^+$.

[00617] Step 2: *Synthesis of tert-butyl ((1S,3R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)cyclohexyl)carbamate*

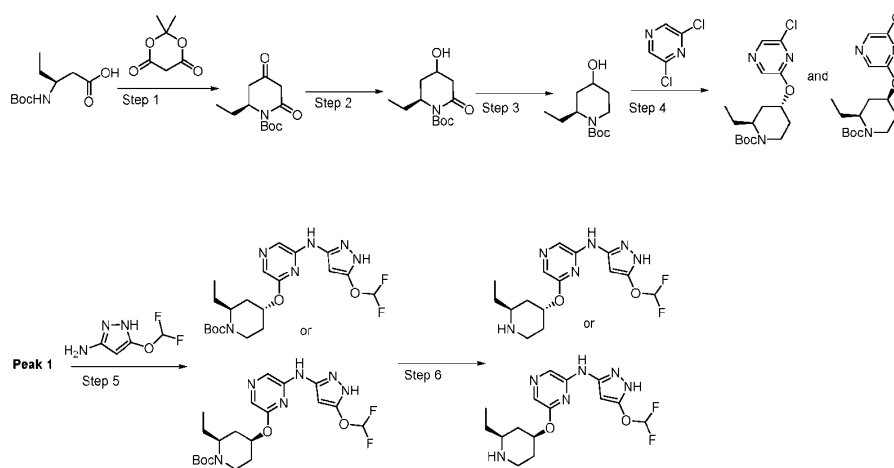
[00618] The title compound was obtained as a colorless oil, 180 mg, 45%, from the compound from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS $m/z = 441$ $[M+H]^+$.

[00619] Step 3: *Synthesis of 6-(((1R,3S)-3-aminocyclohexyl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

[00620] The title compound was obtained as a white solid, 32.9 mg, 24%, from the compound from step 2, following the procedure described in Example 71, step 5. LCMS $m/z = 341$ $[M+H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.99 (br s, 1H), 10.20 (br s, 1H), 7.75 (s, 1H), 7.55 (s, 1H), 7.22 (t, 1H), 5.98 (s, 1H), 4.90-4.85 (m, 1H), 2.74-2.67 (m, 1H), 2.22-2.17 (m, 1H), 2.07-2.02 (m, 1H), 1.79-1.71 (m, 2H), 1.34-1.14 (m, 3H), 1.05-0.97 (m, 1H).

[00621] **Example 82**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-2-ethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-2-ethylpiperidin-4-yl)oxy)pyrazin-2-amine



[00622] Step 1: *Synthesis of tert-butyl (S)-2-ethyl-4,6-dioxopiperidine-1-carboxylate*

[00623] The title compound was obtained (100 mg, 45%), from (S)-3-((tert-butoxycarbonyl)amino)pentanoic acid and 2,2-dimethyl-1,3-dioxane-4,6-dione, following the procedure described in Example 43, step 1. LCMS $m/z = 186$ $[M-56+H]^+$.

[00624] Step 2: *Synthesis of tert-butyl (2S)-2-ethyl-4-hydroxy-6-oxopiperidine-1-carboxylate*

[00625] The title compound was obtained as a yellow oil, 800 mg, 34%, from the compound from step 1, following a similar procedure to that described in Example 43, step 2. LCMS $m/z = 188$ $[M-56+H]^+$.

[00626] Step 3: *Synthesis of tert-butyl (2S)-2-ethyl-4-hydroxypiperidine-1-carboxylate*

[00627] The title compound was obtained as a yellow oil, 400 mg, 53%, from the compound from step 2, following the procedure described in Example 43, step 3. LCMS $m/z = 174$ $[M-56+H]^+$.

[00628] Step 4: *Synthesis of tert-butyl (2S,4R)-4-((6-chloropyrazin-2-yl)oxy)-2-ethylpiperidine-1-carboxylate or tert-butyl (2S,4S)-4-((6-chloropyrazin-2-yl)oxy)-2-ethylpiperidine-1-carboxylate*

[00629] tert-Butyl (2S)-4-((6-chloropyrazin-2-yl)oxy)-2-ethylpiperidine-1-carboxylate was obtained as a yellow solid, 300 mg, 50%, from tert-butyl (2S)-2-ethyl-4-hydroxypiperidine-1-

carboxylate and 2,6-dichloropyrazine, following the procedure described in Example 39, step 1. The racemic product was separated by chiral-SFC (Method C, 90/10) to give Peak 1, tert-butyl (2S,4R)-4-((6-chloropyrazin-2-yl)oxy)-2-ethylpiperidine-1-carboxylate or tert-butyl (2S,4S)-4-((6-chloropyrazin-2-yl)oxy)-2-ethylpiperidine-1-carboxylate (150 mg) and Peak 2, tert-butyl (2S,4S)-4-((6-chloropyrazin-2-yl)oxy)-2-ethylpiperidine-1-carboxylate or tert-butyl (2S,4R)-4-((6-chloropyrazin-2-yl)oxy)-2-ethylpiperidine-1-carboxylate (40 mg) as a yellow solid. LCMS m/z = 286 $[M-56+H]^+$.

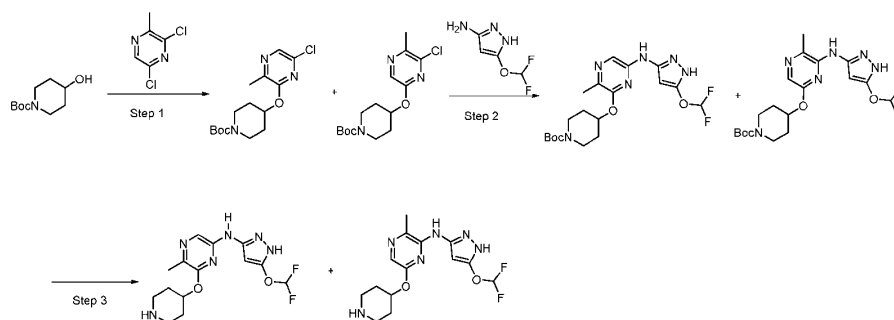
[00630] Step 5: Synthesis of *tert*-butyl (2S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-ethylpiperidine-1-carboxylate or *tert*-butyl (2S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-ethylpiperidine-1-carboxylate

[00631] The title compound was obtained as a yellow solid, 150 mg, 75%, from Peak 1, Step 4, and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS m/z = 455 $[M+H]^+$.

[00632] Step 6: Synthesis of *N*-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-2-ethylpiperidin-4-yl)oxy)pyrazin-2-amine or *N*-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-2-ethylpiperidin-4-yl)oxy)pyrazin-2-amine

[00633] The title compound was obtained as a yellow solid, 25.1 mg, 57%, from step 5, following a similar procedure to that described in Example 71, step 5, except HPLC (Method B) was used. LCMS m/z = 355 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 12.29 (br s, 1H), 10.42 (br s, 1H), 8.34 (s, 1H), 7.80 (s, 1H), 7.59 (s, 1H), 7.26 (t, 1H), 5.97 (s, 1H), 5.12-5.05 (m, 1H), 3.38-3.35 (m, 1H), 3.06-2.96 (m, 2H), 2.40-2.35 (m, 1H), 2.25-2.20 (m, 1H), 1.75-1.56 (m, 2H), 1.52-1.38 (m, 2H), 0.89 (t, 3H).

[00634] **Example 83**, *N*-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3-methyl-6-(piperidin-4-yloxy)pyrazin-2-amine and **Example 84**, *N*-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-5-methyl-6-(piperidin-4-yloxy)pyrazin-2-amine



[00635] Step 1: Synthesis of *tert*-butyl 4-((6-chloro-3-methylpyrazin-2-yl)oxy)piperidine-1-carboxylate and *tert*-butyl 4-((6-chloro-5-methylpyrazin-2-yl)oxy)piperidine-1-carboxylate

[00636] The title compounds were obtained as a mixture, 750 mg, 82%, from tert-butyl 4-hydroxypiperidine-1-carboxylate and 3,5-dichloro-2-methylpyrazine, following the procedure described in Example 5, step 1. LCMS m/z = 272 $[M-56+H]^+$.

[00637] Step 2: *Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3-methylpyrazin-2-yl)oxy)piperidine-1-carboxylate and tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-5-methylpyrazin-2-yl)oxy)piperidine-1-carboxylate*

[00638] The title compounds were obtained as a mixture, 310 mg, 66%, from the mixture from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS m/z = 441 $[M+H]^+$.

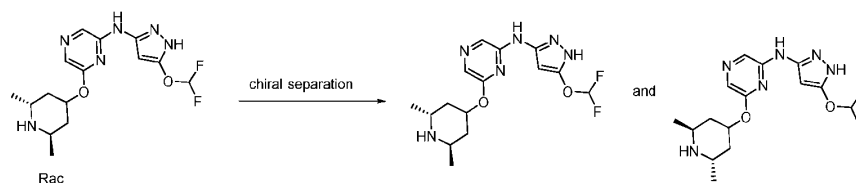
[00639] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-5-methyl-6-(piperidin-4-yloxy)pyrazin-2-amine and N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3-methyl-6-(piperidin-4-yloxy)pyrazin-2-amine*

[00640] To a solution of the mixture from step 2 (300 mg, 681.8 μ mol) in DCM (4.0 mL) was added 4M HCl/dioxane (2.0 mL) at 0 °C under N_2 and the reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction mixture was evaporated under reduced pressure and the residue purified by Prep-HPLC (Method A) to obtain a mixture of title products (110 mg, 47%). This was separated by chiral Prep-SFC (Method B, 60/40) to obtain **Example 84**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-5-methyl-6-(piperidin-4-yloxy)pyrazin-2-amine (61.4 mg). 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.43 (br s, 1H), 10.40 (br s, 1H), 8.38 (s, 1H), 7.66 (s, 1H), 7.42 (t, 1H), 5.96 (s, 1H), 5.14-5.11 (m, 1H), 3.22-3.13 (m, 2H), 2.84-2.71 (m, 2H), 2.67 (s, 3H), 2.11-1.99 (m, 2H), 1.71-1.65 (m, 2H).

[00641] and **Example 83**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3-methyl-6-(piperidin-4-yloxy)pyrazin-2-amine (6.4 mg, 6.7%) as a white solid. LCMS m/z = 341 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.80 (br s, 1H), 9.12 (br s, 1H), 7.53 (s, 1H), 7.52 (t, 1H), 6.05 (s, 1H), 4.98-4.92 (m, 1H), 3.32-3.16 (m, 2H), 2.74-2.67 (m, 2H), 2.65 (s, 3H), 2.00-1.98 (m, 2H), 1.64-1.55 (m, 2H).

[00642] **Example 85**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,6R)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine and N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,6S)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine and

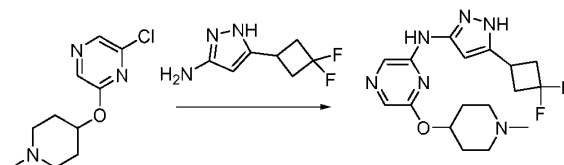
[00643] **Example 86**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,6S)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,6R)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine



[00644] Example 184, (55 mg) was separated by chiral-SFC (Column: OX 20*250mm, 10 μ m (Daicel) , Column temperature: 35 $^{\circ}$ C , Mobile phase: CO_2/MeOH [0.2% NH_3 (7M in MeOH)] = 60/40, Flow rate: 100 g/min , Back pressure: 100 bar to give Peak 1, **Example 86**, (17.5 mg, 32%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.14 (br s, 1H), 10.16 (s, 1H), 7.76 (s, 1H), 7.55 (s, 1H), 7.23 (t, 1H), 6.00 (s, 1H), 5.27-5.21 (m, 1H), 3.37-3.30 (m, 1H), 3.11-3.06 (m, 1H), 2.05-1.99 (m, 1H), 1.89-1.84 (m, 1H), 1.61-1.52 (m, 1H), 1.26-1.20 (m, 2H), 1.17 (d, 3H), 1.05 (d, 3H).

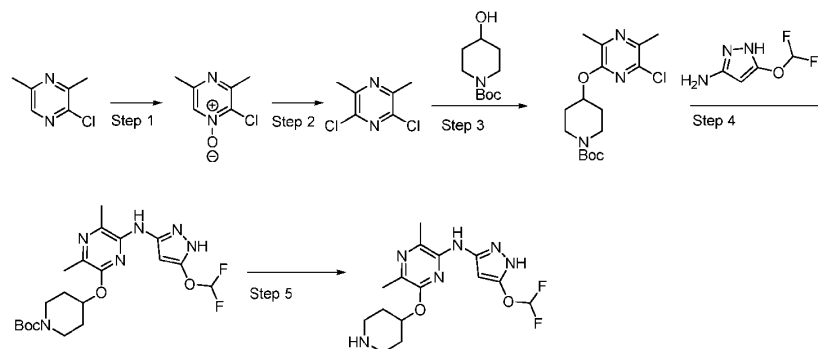
[00645] and Peak 2, **Example 85**, (15.7 mg, 28%) as a white solid. LCMS m/z = 355 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.20 (br s, 1H), 10.21 (br s, 1H), 7.76 (s, 1H), 7.55 (s, 1H), 7.23 (t, 1H), 6.00 (s, 1H), 5.27-5.21 (m, 1H), 3.37-3.30 (m, 1H), 3.11-3.06 (m, 1H), 2.05-1.99 (m, 1H), 1.89-1.84 (m, 1H), 1.61-1.52 (m, 1H), 1.26-1.20 (m, 2H), 1.17 (d, 3H), 1.05 (d, 3H).

[00646] **Example 87**, N-(5-(3,3-difluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00647] The title compound was obtained as a white solid, 69.7 mg, 33%, from 5-(3,3-difluorocyclobutyl)-1H-pyrazol-3-amine and Example 8, Step 1, following the procedure described in Example 37, step 2. LCMS m/z = 365 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.17 (br s, 1H), 9.69 (s, 1H), 7.91 (s, 1H), 7.46 (s, 1H), 6.38 (s, 1H), 4.96-4.91 (m, 1H), 3.41-3.33 (m, 1H), 3.05-2.97 (m, 2H), 2.75-2.69 (m, 1H), 2.70-2.60 (m, 4H), 2.19 (s, 3H), 2.19-2.06 (m, 2H), 2.03-1.95 (m, 2H), 1.70-1.60 (m, 2H).

[00648] **Example 88**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3,5-dimethyl-6-(piperidin-4-yloxy)pyrazin-2-amine



[00649] *Step 1: Synthesis of 2-chloro-3,5-dimethylpyridin-1-ium-1-olate*

[00650] To a solution of 2-chloro-3,5-dimethylpyrazine (2.0 g, 14 mmol) in conc. H_2SO_4 (15.0 mL) was added $\text{K}_2\text{S}_2\text{O}_8$ (4.0 g, 14.7 mmol) in portions at $<-10^\circ\text{C}$, and the resulting mixture was allowed to warm to rt and stirred for 24 h. The reaction mixture was quenched with cold water and extracted with CHCl_3 . The combined organic layers were washed with saturated NaHCO_3 solution and brine, dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude product was recrystallized from PE and EtOAc (v/v = 9/1) at 60°C to afford the title compound (2.0 g, 90%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.39 (s, 1H), 2.54 (s, 3H), 2.37 (s, 3H).

[00651] *Step 2: Synthesis of 2,6-dichloro-3,5-dimethylpyrazine*

[00652] A mixture of the compound from step 1 (2.5 g, 15.8 mmol) in POCl_3 (15 mL) was gently heated to 50°C and stirred until complete dissolution, then heated under reflux at 100°C for 3 h. The reaction mixture was concentrated under reduced pressure and the residual oil was poured into ice water. The resulting precipitate was filtered off and the filtrate neutralized with saturated Na_2CO_3 solution. The aqueous solution was washed with chloroform, and the combined organic layers were washed with brine, dried over sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with PE/EtOAc (85/15) to afford the title compound (500 mg, 18%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.54 (s, 6H).

[00653] *Step 3: Synthesis of tert-butyl 4-((6-chloro-3,5-dimethylpyrazin-2-yl)oxy)piperidine-1-carboxylate*

[00654] The title compound was obtained as a yellow solid, 126 mg, 78%, from the compound from step 2 and 2,6-dichloro-3,5-dimethylpyrazine, following the procedure described in Example 39, step 1. LCMS $m/z = 342$ $[\text{M}+\text{H}]^+$.

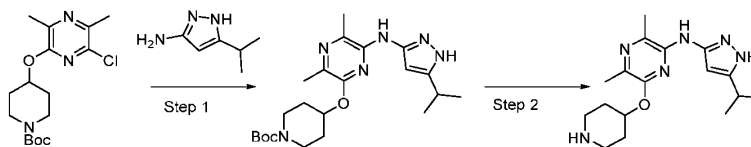
[00655] *Step 4: Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3,5-dimethylpyrazin-2-yl)oxy)piperidine-1-carboxylate*

[00656] The title compound was obtained as a yellow solid, (68.3 mg, 69%) from the compound from step 3 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS $m/z = 455$ $[M+H]^+$.

[00657] *Step 5: Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3,5-dimethyl-6-(piperidin-4-yloxy)pyrazin-2-amine*

[00658] To a solution of the compound from step 4 (68.3 mg, 150 μ mol) in DCM (2.0 mL) was added 4M HCl /dioxane (3.0 mL) at 0 °C under N_2 and the reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction mixture was evaporated under reduced pressure. The residue was purified by Prep-HPLC (Method B) to afford the title compound (6.0 mg, 11%) as a white solid. LCMS $m/z = [M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 12.47 (br s, 1H), 9.44 (s, 1H), 8.37 (s, 1H), 7.24 (t, 1H), 5.97 (s, 1H), 5.08-5.02 (m, 1H), 3.12-3.06 (m, 2H), 2.90-2.84 (m, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 2.05-2.00 (m, 2H), 1.75-1.70 (m, 2H).

[00659] **Example 89**, N-(5-isopropyl-1H-pyrazol-3-yl)-3,5-dimethyl-6-(piperidin-4-yloxy)pyrazin-2-amine



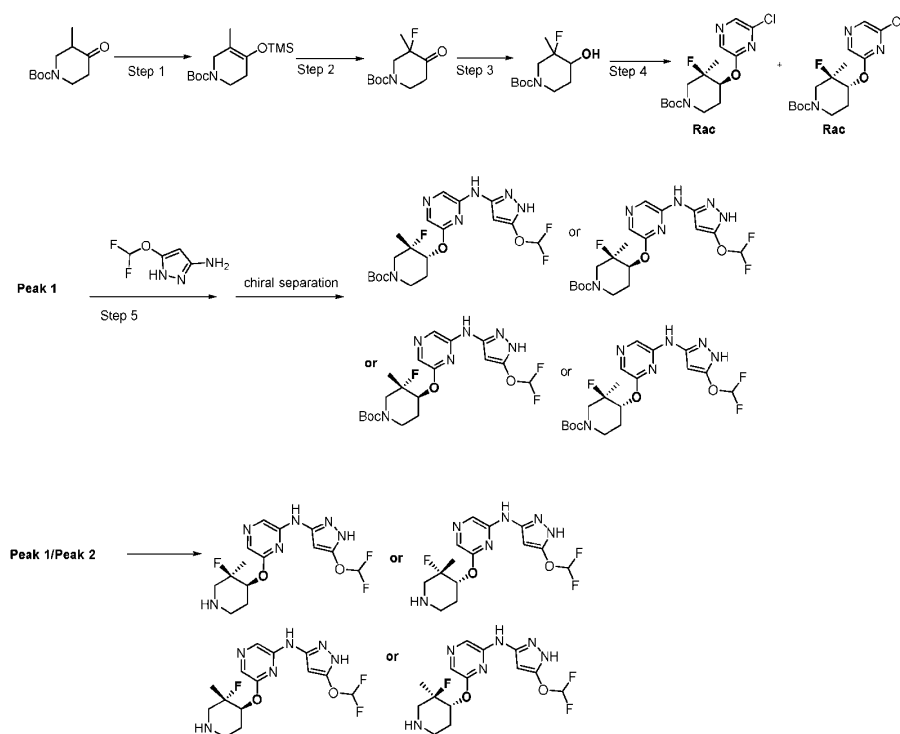
[00660] *Step 1: Synthesis of tert-butyl 4-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)-3,5-dimethylpyrazin-2-yl)oxy)piperidine-1-carboxylate*

[00661] The title compound was obtained as a yellow solid, 68.3 mg, 54%, from Example 88, step 3 and 5-(propan-2-yl)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS $m/z = 431$ $[M+H]^+$.

[00662] *Step 2: Synthesis of N-(5-isopropyl-1H-pyrazol-3-yl)-3,5-dimethyl-6-(piperidin-4-yloxy)pyrazin-2-amine*

[00663] The title compound was obtained as a white solid, 9.4 mg, 14%, from the compound from step 1 following the procedure described in Example 88, step 5. LCMS $m/z = 331$ $[M+H]^+$. 1H -NMR (400 MHz, $DMSO-d_6$) δ ppm 11.89 (br s, 1H), 8.31 (s, 1H), 6.28 (s, 1H), 4.99-4.92 (m, 1H), 3.04-2.98 (m, 2H), 2.94-2.89 (m, 1H), 2.68-2.55 (m, 2H), 2.33 (s, 3H), 2.22 (s, 3H), 2.01-1.95 (m, 2H), 1.61-1.53 (m, 2H), 1.23 (d, 6H).

[00664] **Example 90**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00665] *Step 1: Synthesis of tert-butyl 5-methyl-4-((trimethylsilyl)oxy)-3,6-dihydropyridine-1(2H)-carboxylate*

[00666] To a solution of tert-butyl 3-methyl-4-oxopiperidine-1-carboxylate (1.00 g, 4.68 mmol) and TEA (1.56 mL, 5.61 mmol) in DCM (50 mL) was added trimethylsilyl triflate (1.24 g, 5.61 mmol) at 0 °C under N₂ and the reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was quenched with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to give the crude product.

[00667] *Step 2: Synthesis of tert-butyl 3-fluoro-3-methyl-4-oxopiperidine-1-carboxylate*

[00668] The compound from step 1 was dissolved in MeCN (20 mL), then Selectfluor (1.83 g, 5.16 mmol) added at 0 °C under N₂. The resulting mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was diluted with MeCN, filtered and the filtrate was concentrated under reduced pressure. The crude was purified by column chromatography on silica gel eluting with EtOAc/PE (1/8) to give the title product (741 mg, 69%) as a colorless oil. LCMS m/z = 254 [M+Na]⁺.

[00669] *Step 3: Synthesis of tert-butyl 3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate*

[00670] To a solution of the compound from step 2 (741 mg, 3.20 mmol) in MeOH (10 mL) was added NaBH₄ (100 mg, 2.64 mmol) at 0 °C under N₂ and the reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction was quenched with water and the resulting mixture was

evaporated under reduced pressure. The crude was purified by column chromatography on silica gel eluting with EtOAc/PE (1/1) to give the title product (702 mg, 94%). LCMS m/z = 256 [M+Na]⁺.

[00671] Step 4: Synthesis of *rac-tert-butyl (3R,4S)-4-((6-chloropyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* and *rac-tert-butyl (3R,4R)-4-((6-chloropyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate*

[00672] The title compounds, Peak 1, (350 mg, 30%), *rac-tert-butyl (3R,4S)-4-((6-chloropyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* or *rac-tert-butyl (3R,4R)-4-((6-chloropyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* and Peak 2, *rac-tert-butyl (3R,4R)-4-((6-chloropyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* or *rac-tert-butyl (3R,4S)-4-((6-chloropyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* (83 mg, 8%) were obtained from the compound from step 3 and 2,6-dichloropyrazine, following the procedure described in Example 39, step 1. LCMS m/z = 368 [M+H]⁺.

[00673] Step 5: Synthesis of *tert-butyl (3S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* or *tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* or *tert-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* or *tert-butyl (3R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate*

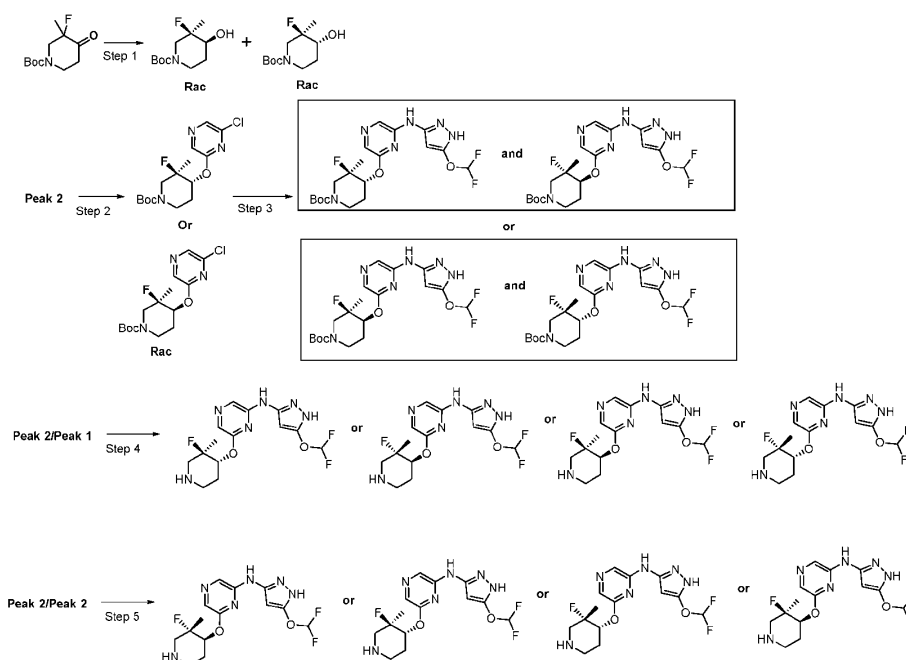
[00674] A mixture of Peak 1, step 4 (300 mg, 867 μ mol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (142 mg, 953 μ mol), BrettPhos Pd G4 (80 mg, 0.087 mmol) and KOAc (255 mg, 2.60 mmol) in dioxane (15.0 mL) was heated at 90 °C and stirred for 18 h. The reaction mixture was cooled to rt and diluted with dioxane, filtered and the filtrate was evaporated under reduced pressure. The crude was purified by column chromatography on silica gel eluting with EtOAc/PE (1/2 to 1/0) to give the racemic product (185 mg, 47%) and then separated by chiral-SFC (Method E, 80/20) to give Peak 1 (85 mg) and Peak 2, *tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* or *tert-butyl (3S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* or *tert-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* or *tert-butyl (3R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate* (81 mg) as a yellow solid. LCMS m/z = 459 [M+H]⁺.

[00675] Step 6: Synthesis of *N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine* or *N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine* or *N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine* or *N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

[00676] The title compound was obtained as a white solid, 21.1 mg, 37%, from Peak 2, step 5, following a similar procedure to that described in Example 38, step 3, except HPLC (Method B) was used. LCMS $m/z = 359$ $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.28 (br s, 1H), 10.12 (br s, 1H), 8.17 (s, 1H), 7.83 (s, 1H), 7.68 (s, 1H), 7.27 (t, 1H), 5.95 (s, 1H), 5.13-5.01 (m, 1H), 3.29-3.21 (m, 1H), 3.18-3.10 (m, 2H), 3.03-2.88 (m, 1H), 2.79-2.69 (m, 1H), 2.08-2.00 (m, 1H), 1.85-1.73 (m, 1H), 1.33 (d, 3H).

[00677] **Example 91**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine and

[00678] **Example 92**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00679] *Step 1: Synthesis of rac-tert-butyl (3R,4S)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate and rel-tert-butyl (3R,4R)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate*

[00680] At 0 °C, to a mixture of Example 90, step 2, (5.71 g, 24.6 mmol) in MeOH (100 mL) was added NaBH_4 (933 mg, 24.6 mmol) and the reaction mixture stirred at 0 °C to rt for 2 h. Water

was added at 0 °C and the resulting mixture extracted with EtOAc. The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with EtOAc/PE (1/1) to give Peak 1, rac-tert-butyl (3R,4S)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate or rac-tert-butyl (3R,4R)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate and Peak 2, rac-tert-butyl (3R,4R)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate or rac-tert-butyl (3R,4S)-3-fluoro-4-hydroxy-3-methylpiperidine-1-carboxylate (1.18 g, 21%). LCMS *m/z* = 256 [M+Na]⁺.

[00681] Step 2: *Synthesis of rac-tert-butyl (3R,4R)-4-((6-chloropyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate or tert-butyl (3R,4S)-4-((6-chloropyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate*

[00682] The title compound was obtained (1.91 g, 90%), from Peak 2, step 1 and 2,6-dichloropyrazine, following the procedure described in Example 39, step 1. LCMS *m/z* = 368 [M+Na]⁺.

[00683] Step 3: *Synthesis of tert-butyl (3R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate and tert-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate or tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate and tert-butyl (3S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate*

[00684] Rac-tert-butyl (3R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate or rac-tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate was obtained, 953 mg, 38%, from the compound of step 2 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. This was separated by chiral SFC (Column: IC 20*250mm, 10 µm (Daicel), Column temperature: 35 °C, Mobile phase: CO₂/MeOH [0.5%NH₃(7 M in MeOH)] = 70/30, Flow rate: 110 g/min, Back pressure: 100 bar to give Peak 1, tert-butyl (3R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate or tert-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate or tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate or tert-butyl (3S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate (428 mg) and Peak 2, tert-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate or tert-butyl (3R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate or tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-

carboxylate or tert-butyl (3S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoro-3-methylpiperidine-1-carboxylate (432 mg). LCMS m/z = 459 [M+H]⁺.

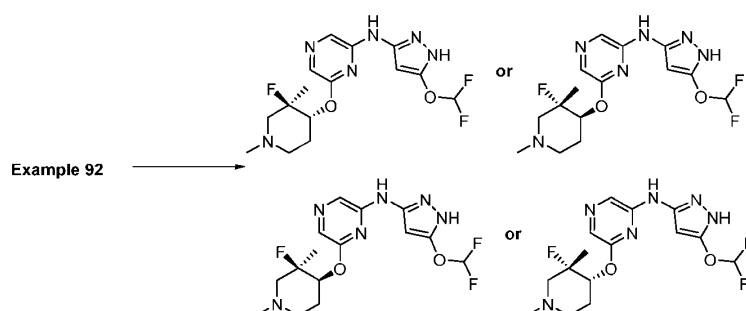
[00685] Step 4: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

[00686] The title compound, **Example 92**, was obtained as a white solid, 29.4 mg, 16%, from Peak 1, step 3, following a similar procedure to that described in Example 2, step 3, except HPLC (Method B) was used. LCMS m/z = 359 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.27 (br s, 1H), 10.37 (br s, 1H), 8.22 (s, 1H), 7.81 (s, 1H), 7.65 (s, 1H), 7.25 (t, 1H), 5.99 (s, 1H), 5.19 - 5.11 (m, 1H), 3.04 - 2.96 (m, 1H), 2.93 - 2.85 (m, 1H), 2.84 - 2.76 (m, 1H), 2.69 - 2.61 (m, 1H), 2.07 - 1.98 (m, 1H), 1.68 - 1.56 (m, 1H), 1.45 (d, 3H).

[00687] Step 5: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

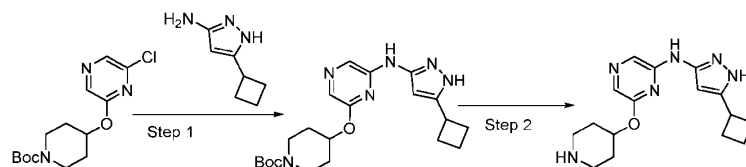
[00688] The title compound, **Example 91**, was obtained as a white solid, 146 mg, 68%, from Peak 2, step 3, following a similar procedure to that described in Example 2, step 3, except HPLC (Method B). LCMS = 359 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.16 (br s, 1H), 10.26 (br s, 1H), 8.19 (s, 1H), 7.84 (s, 1H), 7.67 (s, 1H), 7.26 (t, 1H), 5.97 (s, 1H), 5.22 - 5.15 (m, 1H), 3.18 - 3.11 (m, 1H), 3.10 - 3.04 (m, 1H), 2.98 - 2.90 (m, 1H), 2.86 - 2.78 (m, 1H), 2.12 - 2.02 (m, 1H), 1.86 - 1.76 (m, 1H), 1.45 (d, 3H).

[00689] **Example 93**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine



[00690] The title compound was obtained as a white solid, 77.5 mg, 45%, from Example 92, following the procedure described in Example 11. LCMS $m/z = 373$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.97 (br s, 1H), 10.05 (br s, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 7.26 (t, 1H), 5.97 (s, 1H), 5.11 - 5.03 (m, 1H), 2.78 - 2.62 (m, 2H), 2.30 - 2.20 (m, 1H), 2.22 (s, 3H), 2.16 - 2.02 (m, 2H), 1.70 - 1.58 (m, 1H), 1.49 (d, 3H).

[00691] **Example 94**, N-(5-cyclobutyl-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine



[00692] *Step 1: Synthesis of tert-butyl 4-((6-((5-cyclobutyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate*

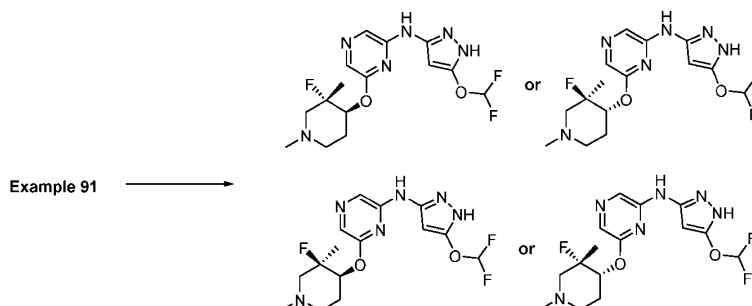
[00693] The title compound was obtained as a yellow solid, 160 mg, 80%, from Example 1, step 1 and 5-cyclobutyl-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS $m/z = 415$ $[M+H]^+$.

[00694] *Step 2: Synthesis of N-(5-cyclobutyl-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine*

[00695] The title compound was obtained as a white solid, 22.7 mg, 30%, from the compound from step 1, following a similar procedure to that described in Example 3, step 3, except HPLC (Method B) was used. LCMS $m/z = [M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 9.67 (br s, 1H), 8.42 (br s, 1H), 7.98 (s, 1H), 7.43 (s, 1H), 6.26 (s, 1H), 5.13-5.05 (m, 1H), 3.55-3.42 (m, 1H), 3.20-3.18 (m, 2H), 2.90-2.77 (m, 2H), 2.33-2.31 (m, 2H), 2.22-2.18 (m, 4H), 2.01-1.96 (m, 1H), 1.95-1.76 (m, 3H).

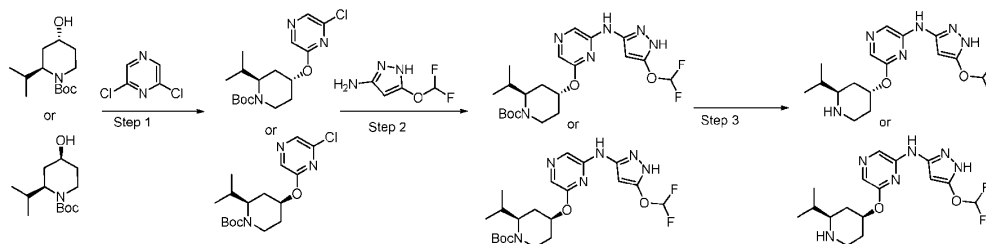
[00696] **Example 95**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-

(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoro-1,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine



[00697] The title compound was obtained as a white solid, 95.5 mg, 48%, from Example 91, following the procedure described in Example 11. LCMS $m/z = 373$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.96 (br s, 1H), 10.04 (br s, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 7.26 (t, 1H), 5.96 (s, 1H), 5.11 – 5.03 (m, 1H), 2.80 – 2.62 (m, 2H), 2.30 – 2.20 (m, 1H), 2.23 (s, 3H), 2.16 – 2.02 (m, 2H), 1.71 – 1.59 (m, 1H), 1.49 (d, 3H).

[00698] **Example 96**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-isopropylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-isopropylpiperidin-4-yl)oxy)pyrazin-2-amine



[00699] Step 1: *Synthesis of tert-butyl (2R,4R)-4-((6-chloropyrazin-2-yl)oxy)-2-isopropylpiperidine-1-carboxylate or tert-butyl (2R,4S)-4-((6-chloropyrazin-2-yl)oxy)-2-isopropylpiperidine-1-carboxylate*

[00700] The title compound was obtained (150 mg, 68%), from Example 43, step 3 and 2,6-dichloropyrazine following the procedure described in Example 39, step 1. This was separated by chiral-SFC (Column: R'R WHELK 20*250mm, 10 μ m (Daicel), Column temperature: 35 $^{\circ}$ C, Mobile phase: CO_2 /IPA [0.2% NH_3 (7M in MeOH)] = 90/10, Flow rate: 100 g/min, Back pressure: 100 bar to give Peak 1, the title compound (120 mg) as a yellow oil. LCMS $m/z = 256$ $[M-100+H]^+$.

[00701] Step 2: *Synthesis of tert-butyl (2R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-isopropylpiperidine-1-carboxylate or tert-butyl (2R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-isopropylpiperidine-1-carboxylate*

[00702] The title compound was obtained as a yellow oil, 90 mg, 57%, from the compound from step 4 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS m/z = 469 $[M+H]^+$.

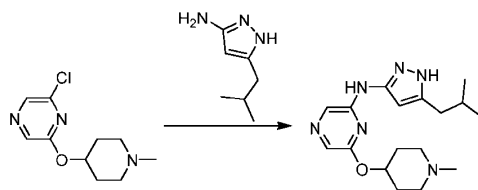
[00703] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-2-isopropylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-isopropylpiperidin-4-yl)oxy)pyrazin-2-amine*

[00704] The title compound was obtained as a yellow solid, 65 mg, 82%, from the compound from step 2, following the procedure described in Example 90, step 6. LCMS m/z = 369 $[M+H]^+$.

^1H NMR (400 MHz, DMSO- d_6) δ ppm 12.30 (br s, 1H), 10.44 (s, 1H), 8.27 (s, 1H), 7.79 (s, 1H), 7.58 (s, 1H), 7.27 (t, 1H), 5.98 (s, 1H), 5.08-4.99 (m, 1H), 3.27-3.24 (m, 2H), 2.89-2.83 (m, 1H), 2.76-2.72 (m, 1H), 2.28-2.24 (m, 1H), 2.20-2.13 (m, 1H), 1.79-1.70 (m, 1H), 1.63-1.53 (m, 1H), 1.35-1.23 (m, 1H), 0.92-0.87 (m, 6H).

[00705] **Example 97.** See Example 9.

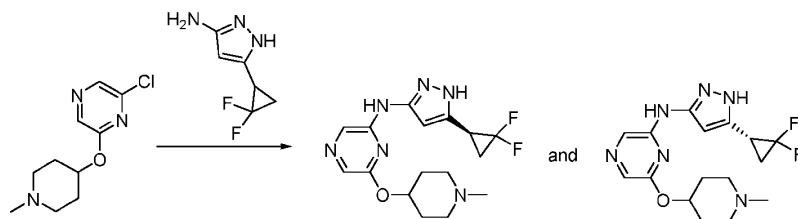
[00706] **Example 98,** N-(5-isobutyl-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00707] The title compound was obtained as a white solid, 12.6 mg, 17%, from Example 8, step 1 and 5-(2-methylpropyl)-1H-pyrazol-3-amine, following the procedure described in Example 37, step 2. LCMS m/z = 331 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.94 (br s, 1H), 9.60 (s, 1H), 7.91 (s, 1H), 7.42 (s, 1H), 6.24 (s, 1H), 4.93-4.86 (m, 1H), 2.72-2.65 (m, 2H), 2.46-2.40 (m, 2H), 2.17 (s, 3H), 2.11-2.06 (m, 2H), 2.00-1.97 (m, 2H), 1.92-1.85 (m, 1H), 1.71-1.63 (m, 2H), 0.90 (d, 6H).

[00708] **Example 99,** (S)-N-(5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine and

[00709] **Example 100,** (R)-N-(5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



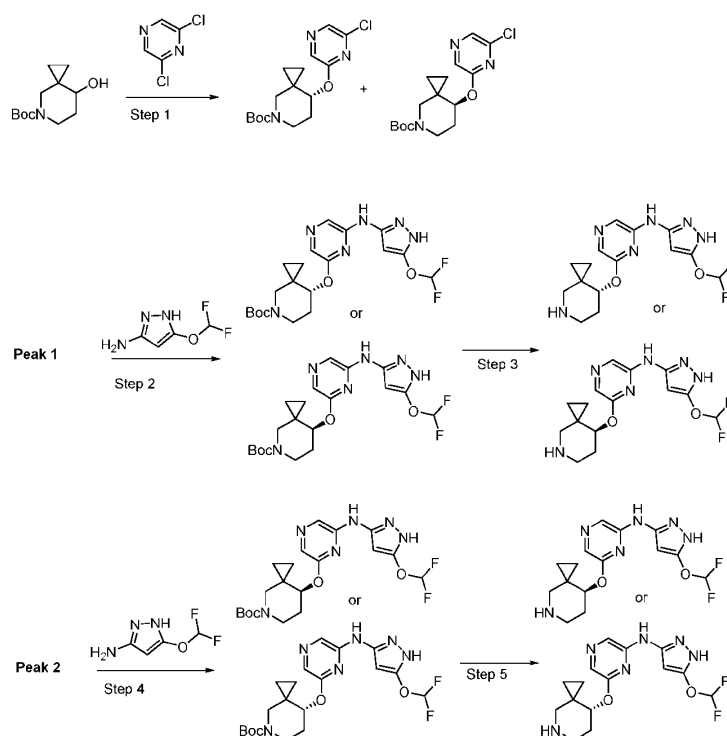
[00710] The title compounds were obtained, Peak 1, **Example 100**, (50.8 mg, 15%) and Peak 2, **Example 99** (20.1 mg, 6%, from 5-(2,2-difluorocyclopropyl)-1H-pyrazol-3-amine and Example 8, step 1, following a similar procedure to that described in Example 24 and 25, step 1.

[00711] Peak 1: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.27 (br s, 1H), 9.71 (s, 1H), 7.94 (s, 1H), 7.48 (s, 1H), 6.29 (s, 1H), 5.03-4.93 (m, 1H), 2.99-2.86 (m, 3H), 2.60-2.51 (m, 2H), 2.40 (s, 3H), 2.11-2.00 (m, 3H), 1.88-1.75 (m, 3H).

[00712] and Peak 2, LCMS $m/z = 351$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.45 (br s, 1H), 9.73 (s, 1H), 7.94 (s, 1H), 7.48 (s, 1H), 6.31 (s, 1H), 5.02-4.91 (m, 1H), 3.00-2.92 (m, 1H), 2.90-2.76 (m, 2H), 2.45-2.34 (m, 2H), 2.32 (s, 3H), 2.14-1.99 (m, 3H), 1.89-1.70 (m, 3H).

[00713] **Example 101**, (S)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine and

[00714] **Example 102**, (R)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



[00715] Step 1: *Synthesis of tert-butyl (R)-8-((6-chloropyrazin-2-yl)oxy)-5-azaspiro[2.5]octane-5-carboxylate and tert-butyl (S)-8-((6-chloropyrazin-2-yl)oxy)-5-azaspiro[2.5]octane-5-carboxylate*

[00716] tert-Butyl 8-((6-chloropyrazin-2-yl)oxy)-5-azaspiro[2.5]octane-5-carboxylate was obtained as a yellow oil, 1. g, 55%, from 2,6-dichloropyrazine and tert-butyl 8-hydroxy-5-azaspiro[2.5]octane-5-carboxylate, following the procedure described in Example 39, step 1. This was separated by chiral Prep-SFC (Method A, 85/15) to give Peak 1, tert-butyl (R)-8-((6-chloropyrazin-2-yl)oxy)-5-azaspiro[2.5]octane-5-carboxylate or tert-butyl (S)-8-((6-chloropyrazin-2-yl)oxy)-5-azaspiro[2.5]octane-5-carboxylate (423 mg) and Peak 2, tert-butyl (S)-8-((6-chloropyrazin-2-yl)oxy)-5-azaspiro[2.5]octane-5-carboxylate or tert-butyl (R)-8-((6-chloropyrazin-2-yl)oxy)-5-azaspiro[2.5]octane-5-carboxylate (450 mg). LCMS $m/z = 362$ $[M+Na]^+$.

[00717] Step 2: *Synthesis of tert-butyl (R)-8-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-5-azaspiro[2.5]octane-5-carboxylate or tert-butyl (S)-8-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-5-azaspiro[2.5]octane-5-carboxylate*

[00718] The title compound was obtained as a yellow solid, 230 mg, 86%, from Peak 1, step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS $m/z = 453$ $[M+H]^+$.

[00719] Step 3: *Synthesis of (R)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

[00720] The title compound, **Example 102**, was obtained, 25 mg, 14%, from the compound from step 2, following the procedure described in Example 2, step 3. LCMS $m/z = 353$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.47 (br s, 1H), 10.59 (s, 1H), 8.34 (s, 1H), 7.77 (s, 1H), 7.62 (s, 1H), 7.24 (t, 1H), 5.92 (s, 1H), 5.34-5.31 (m, 1H), 4.68 (s, 1H), 3.20-3.18 (m, 2H), 2.68-2.65 (m, 2H), 2.00-1.95 (m, 2H), 0.65-0.47 (m, 4H).

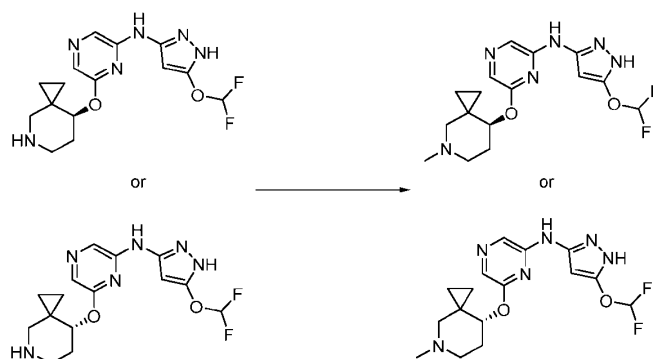
[00721] Step 4: *Synthesis of tert-butyl (S)-8-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-5-azaspiro[2.5]octane-5-carboxylate or tert-butyl (R)-8-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-5-azaspiro[2.5]octane-5-carboxylate*

[00722] The title compound was obtained as a yellow solid, 164 mg, 62%, from Peak 2, step 1, following the procedure described in Step 2. LCMS $m/z = 453$ $[M+H]^+$.

[00723] Step 5: *Synthesis of Example 101, (S)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-((5-azaspiro[2.5]octan-8-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

[00724] The title compound, **Example 101**, was obtained as a white solid, 16.8 mg, 55%, from step 4, following the procedure described in Example 2, Step 3. LCMS $m/z = 353$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.99 (br s, 1H), 11.32 (s, 1H), 8.40 (s, 1H), 7.76 (s, 1H), 7.61 (s, 1H), 7.24 (t, 1H), 5.93 (s, 1H), 4.68-4.65 (m, 1H), 3.29-3.26 (m, 1H), 3.11-3.09 (m, 2H), 2.61-2.58 (m, 1H), 2.07-2.05 (m, 2H), 0.69-0.51 (m, 4H).

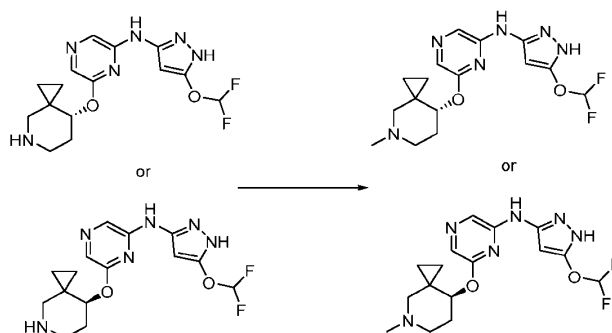
[00725] **Example 103**, (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-methyl-5-azaspiro[2.5]octan-8-yl)oxy)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-methyl-5-azaspiro[2.5]octan-8-yl)oxy)pyrazin-2-amine



[00726] The title compound was obtained as a white solid, 9 mg, 43%, from Example 102, and HCHO, following the procedure described in Example 11. LCMS $m/z = 367$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.31 (br s, 1H), 10.44 (s, 1H), 8.24 (s, 1H), 7.76 (s, 1H), 7.60 (s, 1H),

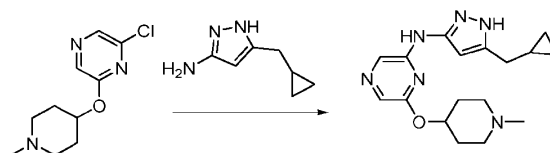
7.24 (t, 1H), 5.92 (s, 1H), 4.59 (s, 1H), 2.84-2.75 (m, 2H), 2.67-2.60 (m, 1H), 2.37 (s, 3H), 2.26-2.23 (m, 1H), 2.04-2.00 (m, 2H), 0.64-0.41 (m, 4H).

[00727] **Example 104**, (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-methyl-5-azaspiro[2.5]octan-8-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-methyl-5-azaspiro[2.5]octan-8-yl)oxy)pyrazin-2-amine



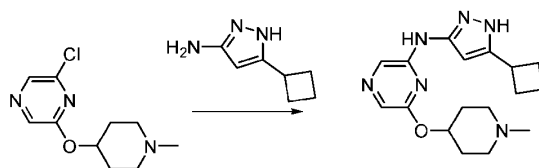
[00728] The title compound was obtained as a white solid, 3.8 mg, 18%, from Example 101, following the method described in Example 11. LCMS $m/z = 367 [M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.30 (br s, 1H), 10.45 (s, 1H), 8.25 (s, 1H), 7.76 (s, 1H), 7.58 (s, 1H), 7.24 (t, 1H), 5.92 (s, 1H), 4.62-4.57 (m, 1H), 2.67-2.60 (m, 3H), 2.25 (s, 3H), 2.11-2.08 (m, 1H), 2.05-1.89 (m, 2H), 0.64-0.58 (m, 1H), 0.52-0.49 (m, 2H), 0.40-0.35 (m, 1H).

[00729] **Example 105**, N-(5-(cyclopropylmethyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00730] The title compound was obtained as a yellow solid, 87.1 mg, 36%, from 5-(cyclopropylmethyl)-1H-pyrazol-3-amine and Example 8, step 1 following the procedure described in Example 37, step 2. LCMS $m/z = 329 [M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.93 (br s, 1H), 9.59 (s, 1H), 7.94 (s, 1H), 7.43 (s, 1H), 6.29 (s, 1H), 4.96-4.89 (m, 1H), 2.69-2.67 (m, 2H), 2.17 (s, 3H), 2.14-2.09 (m, 2H), 2.01-1.98 (m, 2H), 1.73-1.64 (m, 2H), 1.04-0.95 (m, 1H), 0.52-0.47 (m, 2H), 0.22-0.19 (m, 2H).

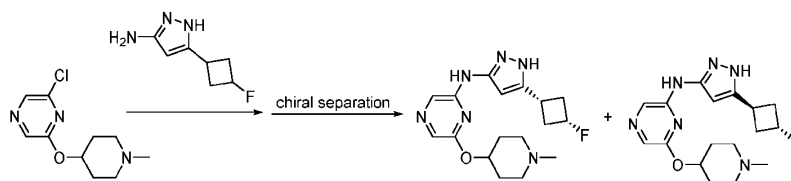
[00731] **Example 106**, N-(5-cyclobutyl-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00732] The title compound was obtained as a yellow solid, 11.5 mg, 10%, from Example 8, step 1 and 5-cyclobutyl-1H-pyrazol-3-amine, following the procedure described in Example 37, step 2. LCMS $m/z = 329$ $[M+H]^+$ ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.95 (br s, 1H), 9.62 (s, 1H), 7.90 (s, 1H), 7.43 (s, 1H), 6.33 (s, 1H), 4.94-4.92 (m, 1H), 3.48-3.49 (m, 1H), 2.79-2.76 (m, 2H), 2.31-2.29 (m, 2H), 2.15 (s, 3H), 2.13-2.11 (m, 2H), 2.10-2.03 (m, 4H), 1.94-1.83 (m, 1H), 1.72-1.69 (m, 2H).

[00733] **Example 107**, N-(5-((1*s*,3*s*)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine, or N-(5-((1*r*,3*r*)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine and

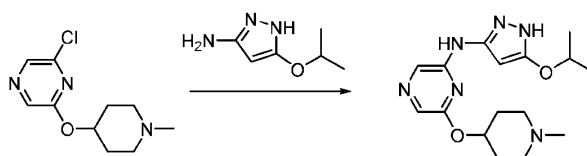
[00734] **Example 108**, N-(5-((1*r*,3*r*)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-((1*s*,3*s*)-3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00735] N-(5-((3-fluorocyclobutyl)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine was obtained, 60 mg, from Example 8, step 1 and 5-(3-fluorocyclobutyl)-1H-pyrazol-3-amine, following the procedure described in Example 37, step 2. The racemic product was separated by chiral SFC (Column: CHIRALPAK OD 20×250 mm, 10 μm (Daicel), Column temperature: 35 $^\circ\text{C}$, Mobile phase: CO_2/MeOH (0.1% DEtOAc) = 80/30, Flow rate: 80 g/min, Back pressure: 100 bar to give Peak 1, **Example 107** (21.3 mg, 35%) as a white solid. LCMS $m/z = 347$ $[M+H]^+$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.12 (br s, 1H), 9.66 (br s, 1H), 7.90 (s, 1H), 7.45 (s, 1H), 6.35 (s, 1H), 5.13-4.93 (m, 1H), 5.00-4.90 (m, 2H), 2.98-2.88 (m, 1H), 2.80-2.71 (m, 4H), 2.62-2.54 (m, 2H), 2.38-2.24 (m, 2H), 2.20 (s, 3H), 2.05-2.01 (m, 2H), 1.75-1.63 (m, 2H).

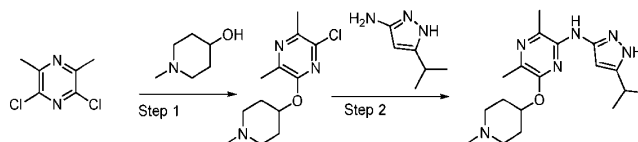
[00736] and Peak 2, **Example 108** (30.0 mg, 50%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) for δ ppm 12.06 (br s, 1H), 9.65 (br s, 1H), 7.92 (s, 1H), 7.46 (s, 1H), 6.32 (s, 1H), 5.37-5.17 (m, 1H), 5.00-4.90 (m, 1H), 3.58-3.52 (m, 1H), 2.80-2.71 (m, 2H), 2.68-2.54 (m, 4H), 2.38-2.24 (m, 2H), 2.21 (s, 3H), 2.05-1.98 (m, 2H), 1.75-1.63 (m, 2H).

[00737] **Example 109**, N-(5-isopropoxy-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00738] The title compound was obtained as a white solid, 23.7 mg, 16%, from Example 8, step 1 and 5-isopropoxy-1H-pyrazol-3-amine, following the procedure described on Example 37, step 2. LCMS $m/z = 333$ $[M+H]^+$. $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ ppm 7.83 (s, 1H), 7.48 (s, 1H), 5.94 (br s, 1H), 5.74 (s, 1H), 4.90-4.93 (m, 1H), 4.51-4.54 (m, 1H), 2.68-2.67 (m, 2H), 2.17 (s, 3H), 2.11-2.13 (m, 2H), 1.96-1.98 (m, 2H), 1.70-1.67 (m, 2H), 1.30 (d, 6H).

[00739] **Example 110**, N-(5-isopropyl-1H-pyrazol-3-yl)-3,5-dimethyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



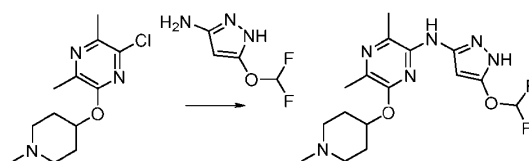
[00740] Step 1: *Synthesis of 2-chloro-3,5-dimethyl-6-((1-methylpiperidin-4-yl)oxy)pyrazine*

[00741] The title compound was obtained as a white solid, 100 mg, 28%, from Example 88, step 2, following a similar procedure to that described in Example 37, step 1. LCMS $m/z = 256$ $[M+H]^+$.

[00742] Step 2: *Synthesis of N-(5-isopropyl-1H-pyrazol-3-yl)-3,5-dimethyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

[00743] The title compound was obtained as a white solid, 37.4 mg, 19%, from the compound from step 1 and 5-(propan-2-yl)-1H-pyrazol-3-amine, following the procedure described in Example 37, step 2. LCMS $m/z = 345$ $[M+H]^+$. $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.92 (br s, 1H), 8.30 (s, 1H), 6.29 (s, 1H), 4.90-4.86 (m, 1H), 2.98-2.92 (m, 1H), 2.67-2.62 (m, 2H), 2.33 (s, 3H), 2.20 (s, 3H), 2.20-2.10 (m, 2H), 2.17 (s, 3H), 1.96-1.94 (m, 2H), 1.69-1.66 (m, 2H), 1.24 (d, 6H).

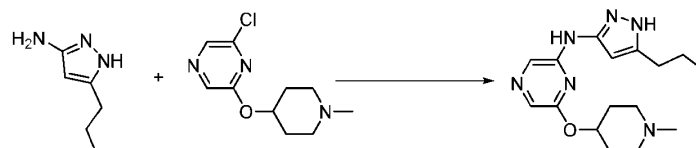
[00744] **Example 111**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3,5-dimethyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00745] The title compound was obtained as a white solid (31.1 mg, 22%) from the title compound of Example 110, Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar procedure to that described in Example 60, step 2. LCMS $m/z = 369$ $[M+H]^+$. $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.50 (br s, 1H), 8.83 (br s, 1H), 7.23 (t, 1H), 5.95 (s, 1H), 4.90-4.86 (m, 1H), 2.67-

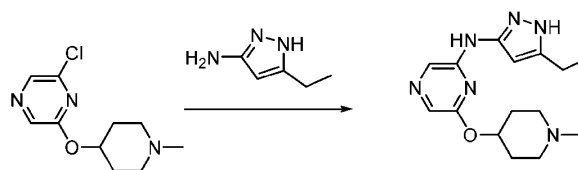
2.59 (m, 2H), 2.40 (s, 3H), 2.30-2.15 (m, 2H), 2.24 (s, 3H), 2.17 (s, 3H), 1.95-1.93 (m, 2H), 1.74-1.64 (m, 2H).

[00746] Example 112, 6-((1-methylpiperidin-4-yl)oxy)-N-(5-propyl-1H-pyrazol-3-yl)pyrazin-2-amine



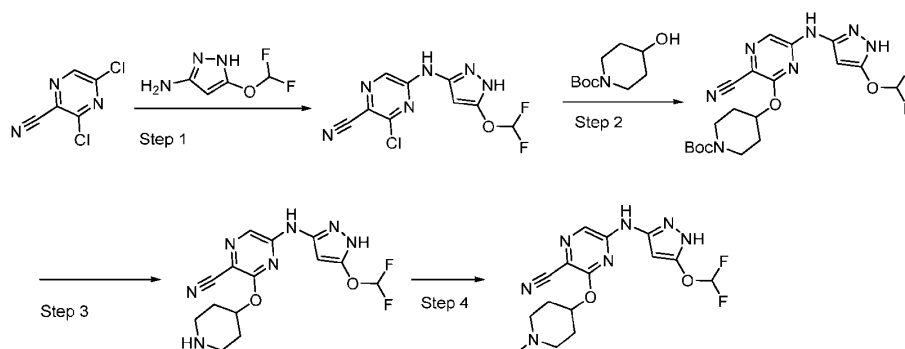
[00747] The title compound was obtained as a white solid (52.9 mg, 26%), from the title compound of Example 8, Step 1 and 5-propyl-1H-pyrazol-3-amine following a similar procedure to that described in Example 37, step 2. LCMS $m/z = 317$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 9.59 (s, 1H), 8.18 (s, 1H), 7.94 (s, 1H), 7.44 (s, 1H), 6.23 (s, 1H), 4.95-4.90 (m, 1H), 2.79-2.74 (m, 2H), 2.56-2.50 (m, 3H), 2.24 (s, 3H), 2.24-2.20 (m, 1H), 2.04-1.94 (m, 2H), 1.75-1.69 (m, 2H), 1.66-1.60 (m, 2H), 0.93 (t, 3H).

[00748] Example 113, N-(5-ethyl-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00749] The title compound was obtained as a yellow solid (40.2 mg, 30%) from the title compound of Example 8, step 1 and 5-ethyl-1H-pyrazol-3-amine following a similar procedure to that described in Example 60, step 2. LCMS $m/z = 303$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 9.58 (br s, 1H), 7.94 (s, 1H), 7.43 (s, 1H), 6.22 (s, 1H), 6.33 (s, 1H), 4.89-4.91 (m, 1H), 2.71-2.69 (m, 2H), 2.58 (q, 2H), 2.17 (s, 3H), 2.14-2.08 (m, 2H), 2.02-1.99 (m, 2H), 1.69-1.66 (m, 2H), 1.21 (t, 3H).

[00750] Example 114, 5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3-((1-methylpiperidin-4-yl)oxy)pyrazine-2-carbonitrile



[00751] Step 1: *Synthesis of 3-chloro-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile*

[00752] To a solution of 5-(difluoromethoxy)-1H-pyrazol-3-amine (2.8 g, 18.7 mmol) in NMP (30 mL) was added 3,5-dichloropyrazine-2-carbonitrile (3.25 g, 18.7 mmol) at 0°C. The mixture was stirred at rt for 6 d. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was concentrated to 10 mL. The precipitate was collected by filtration and dried *in vacuo* to give the title product (4.0 g, 74 %) as a yellow solid. LCMS $m/z = 287$ [M+H]⁺.

[00753] Step 2: *Synthesis of tert-butyl 4-((3-cyano-6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate*

[00754] To a mixture of the title compound of Step 1 (1.05 g, 3.67 mmol) and tert-butyl 4-hydroxypiperidine-1-carboxylate (1.11 g, 5.51 mmol) in NMP (10.0 mL) was added t-BuONa (704 mg, 7.34 mmol) at rt under N₂. The reaction mixture was allowed to warm to 100°C and stirred for 3 d, then cooled to rt and diluted with DCM and filtered. The filtrate was concentrated to dryness to give the crude which was purified by Prep-HPLC (Method A) to obtain the title product (28.0 mg, 2%) as a yellow solid. LCMS $m/z = 396$ [M-56+H]⁺.

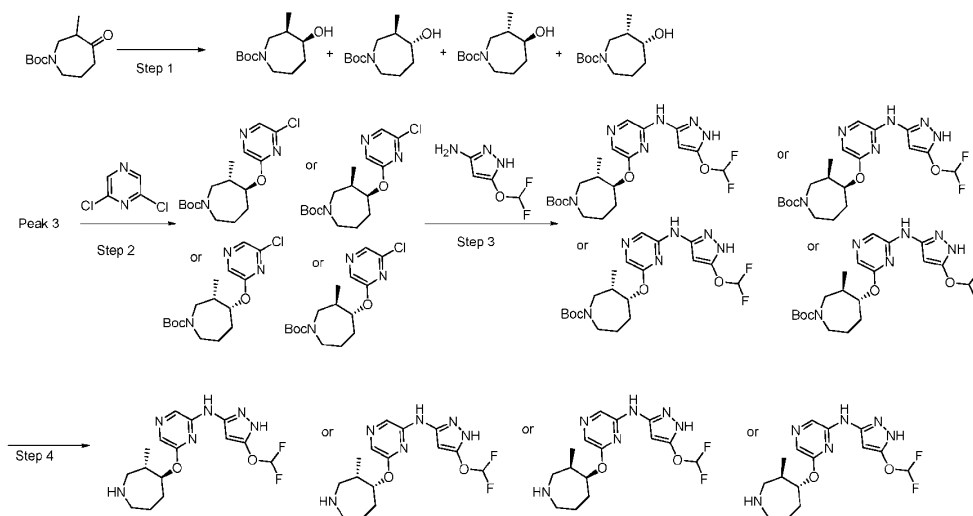
[00755] Step 3: *Synthesis of 5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3-(piperidin-4-yloxy)pyrazine-2-carbonitrile*

[00756] The title compound was obtained as a crude, 20 mg, from the title compound of Step 2 following a similar procedure to that described in Example 2, step 3 and was used in the next step without further purification. LCMS $m/z = 352$ [M+H]⁺.

[00757] Step 4: *Synthesis of 5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3-((1-methylpiperidin-4-yl)oxy)pyrazine-2-carbonitrile*

[00758] The title compound was obtained as a yellow solid, 11.0 mg, 53%, from the title compound of Step 4 and HCHO following a similar procedure to that described in Example 11. LCMS $m/z = 366$ [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.43 (br s, 1H), 11.06 (br s, 1H), 7.87 (s, 1H), 7.28 (t, 1H), 6.11 (s, 1H), 5.14-5.02 (m, 1H), 2.72-2.60 (m, 2H), 2.33-2.23 (m, 2H), 2.23 (s, 3H), 2.05-1.94 (m, 2H), 1.83-1.72 (m, 2H).

[00759] **Example 115**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine



[00760] Step 1: *Synthesis of tert-butyl (3R,4R)-4-hydroxy-3-methylazepane-1-carboxylate or tert-butyl (3S,4S)-4-hydroxy-3-methylazepane-1-carboxylate or tert-butyl (3R,4S)-4-hydroxy-3-methylazepane-1-carboxylate or tert-butyl (3S,4R)-4-hydroxy-3-methylazepane-1-carboxylate*

[00761] To a mixture of tert-butyl 3-methyl-4-oxoazepane-1-carboxylate (1.18 g, 5.18 mmol) in MeOH (10.0 mL) was added NaBH₄ (294 mg, 7.77 mmol) at 0°C under N₂. The reaction mixture was allowed to warm to rt and stirred for 4 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure. The crude was purified by Prep-HPLC (Method A) to afford the racemic product (1 g) and then separated by chiral Prep-SFC (Column: IG 20*250mm, 10 μm (Daicel), Column temperature: 35°C, Mobile phase: CO₂/MeOH (0.2% Methanol Ammonia) = 75/25, Flow rate: 80 g/min, Back pressure: 100 bar) to give peak 1 (238 mg, 33%), peak 2 (176 mg, 26% yield), peak 3 (25 mg, 4%) and peak 4 (134 mg, 19%). LCMS m/z = 174 [M-56+H]⁺.

[00762] Step 2: *Synthesis of tert-butyl (3R,4R)-4-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S,4S)-4-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3R,4S)-4-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S,4R)-4-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate*

[00763] The title compound was obtained as a yellow solid (53 mg, 78%) from Peak 3, Step 1 and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS m/z = 286 [M-56+H]⁺.

[00764] Step 3: *Synthesis of tert-butyl (3R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-*

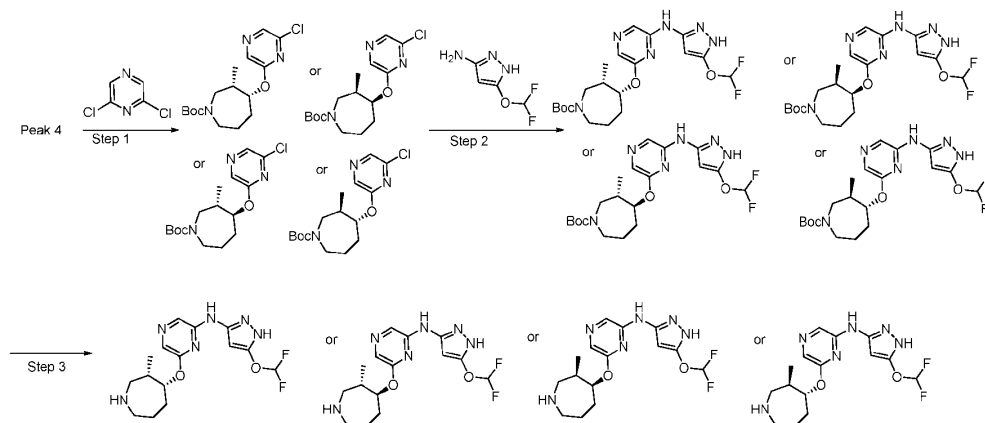
butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate or tert-butyl (3S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate

[00765] The title compound was obtained as a yellow solid (40 mg, 98%) from the compound of Step 2 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar procedure to that described in Example 19 and 20, step 2. LCMS $m/z = 455$ $[M+H]^+$.

[00766] Step 4: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine*

[00767] To a mixture of the compound of Step 3 (40 mg, 88 μ mol) in DCM (2.0 mL) was added 4M HCl/dioxane (3 mL) at rt. The mixture was stirred at rt for 30 min, then concentrated under reduced pressure. The crude was purified with Prep-HPLC (Method B) to obtain the title product (6.2 mg, 20%) as a white solid. LCMS $m/z = 355$ $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 12.70 (br s, 1H), 10.92 (br s, 1H), 8.33 (s, 1H), 7.75 (s, 1H), 7.58 (s, 1H), 7.25 (t, 1H), 5.99 (s, 1H), 4.78-4.74 (m, 1H), 3.04-2.99 (m, 2H), 2.99-2.85 (m, 2H), 2.77-2.69 (m, 1H), 2.19-2.12 (m, 1H), 2.10-2.01 (m, 1H), 1.90-1.78 (m, 2H), 1.68-1.60 (m, 1H), 0.97 (d, 3H).

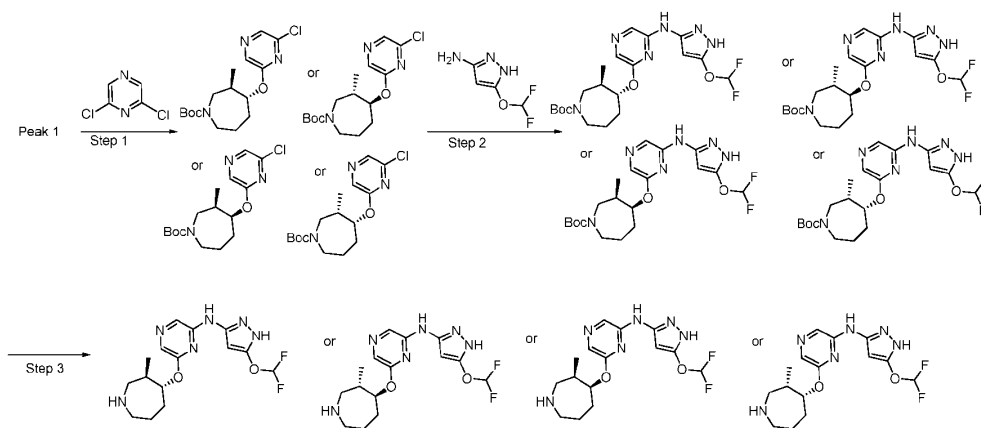
[00768] **Example 116**, *N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine*



[00769] The title compound was obtained from Peak 4, step 1, Example 115, 2,6-dichloropyrazine and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar 3 step procedure

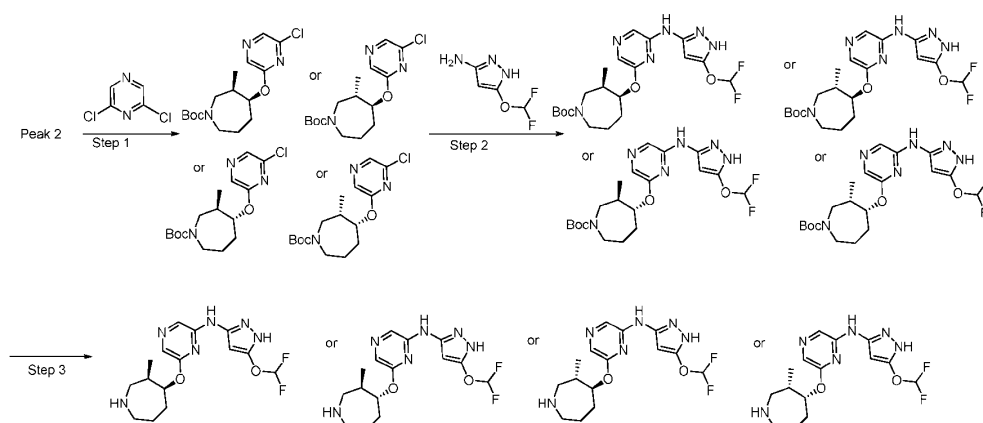
as described in Example 115, steps 2 to 4. LCMS $m/z = 355 [M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.05 (br s, 1H), 10.09 (br s, 1H), 7.76 (s, 1H), 7.59 (s, 1H), 7.26 (t, 1H), 6.00-5.95 (m, 1H), 4.75-4.70 (m, 1H), 3.60-3.50 (m, 1H), 2.88-2.79 (m, 2H), 2.67-2.58 (m, 2H), 1.99-1.90 (m, 2H), 1.88-1.85 (m, 1H), 1.74-1.68 (m, 1H), 1.65-1.50 (m, 1H), 0.94-0.88 (m, 3H).

[00770] Example 117, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine



[00771] The title compound was obtained from Peak 1, step 1, Example 115, 2,6-dichloropyrazine and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar 3 step procedure as described in Example 115, steps 2 to 4. LCMS $m/z = 355 [M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.90 (br s, 1H), 11.12 (br s, 1H), 8.41 (s, 1H), 7.75 (s, 1H), 7.62 (s, 1H), 7.26 (t, 1H), 5.99 (s, 1H), 5.23-5.17 (m, 1H), 3.51-3.22 (m, 1H), 3.05-3.03 (m, 2H), 3.02-2.96 (m, 2H), 2.14-2.09 (m, 1H), 1.85-1.75 (m, 1H), 1.68-1.65 (m, 2H), 0.96 (d, 3H).

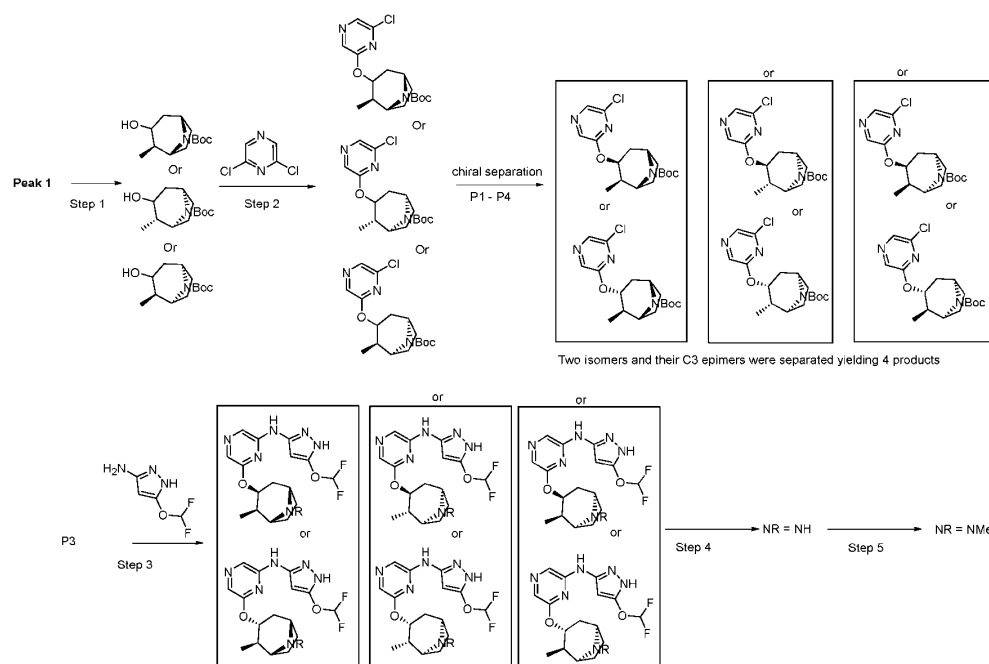
[00772] Example 118, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-methylazepan-4-yl)oxy)pyrazin-2-amine



[00773] The title compound was obtained from Peak 2, step 1, Example 115, 2,6-dichloropyrazine and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar 3 step procedure as described in Example 115, steps 2 to 4. LCMS $m/z = 355 [M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 13.07 (br s, 1H), 11.31 (br s, 1H), 8.43 (s, 1H), 7.75 (s, 1H), 7.62 (s, 1H), 7.26 (t, 1H), 5.99 (s, 1H), 5.23-5.18 (m, 1H), 4.50-3.50 (m, 3H), 3.10-3.03 (m, 2H), 3.02-2.94 (m, 1H), 2.41-2.31 (m, 1H), 2.17-2.07 (m, 1H), 1.91-1.73 (m, 1H), 1.73-1.64 (m, 1H), 0.98 (d, 3H).

[00774] **Example 119**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine and

[00775] **Example 120**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine



[00776] Step 2: Synthesis of *tert*-butyl (1*R*,2*R*,3*S*,5*S*)-3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate, *tert*-butyl (1*R*,2*R*,3*R*,5*S*)-3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate, *tert*-butyl (1*S*,2*S*,3*S*,5*R*)-3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate, *tert*-butyl (1*S*,2*S*,3*R*,5*R*)-3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or *tert*-butyl (1*S*,2*R*,3*S*,5*R*)-3-((6-chloropyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate

[00777] To a solution of the compound mixture of Peak 1 (mixture of two isomers of unknown stereochemistry and their C3 epimers) from Example 34 and 40, Step 1 (0.95 g, 3.94 mmol) in THF (10 mL) was added 60% NaH (249 mg, 6.22 mmol) at 0 °C and the solution stirred for 30 min under N₂. 2,6-Dichloropyrazine (614 mg, 4.14 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The crude was purified by column chromatography on silica gel eluting with PE/EtOAc (4/1) to give the racemic products (450 mg, 32%) and then separated by chiral-SFC (Method D, gradient: 85/15) to afford the title compounds Peak 1 (50 mg), Peak 2 (70 mg), Peak 3 (90 mg), Peak 4 (75 mg) as a yellow solid. LCMS *m/z* = 298 [M - 56 + H]⁺.

[00778] Step 3: Synthesis of *tert*-butyl (1*R*,2*R*,3*S*,5*S*)-3-((6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or *tert*-butyl *tert*-butyl (1*R*,2*R*,3*R*,5*S*)-3-((6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-

8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2S,3R,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2S,3S,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2R,3S,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2R,3R,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate

[00779] A mixture of Peak 3 of Step 2 (80 mg, 226 μ mol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (33.6 mg, 226 μ mol), BrettPhos Pd G₄ (20 mg, 21.7 μ mol) and KOAc (66.5 mg, 678 μ mol) in 1,4-dioxane (10.0 mL) was stirred at 100°C for 16 h under N₂. The reaction mixture was cooled to rt, diluted with dioxane, filtered and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with DCM/MeOH (10/1) to afford the title product (60 mg, 57%) as a yellow solid. LCMS m/z = 467 [M+H]⁺.

[00780] Step 4: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine*

[00781] A mixture of the title compound of Step 3 (20 mg, 48.2 μ mol) in DCM (2.0 mL) was added TFA (0.5 mL) at 0°C under N₂. The reaction mixture was allowed to warm to rt and stirred for 2 h. The mixture was basified by 7N NH₃ in MeOH until pH~8, then concentrated under reduced pressure to give the crude which was purified by Prep-HPLC (Method A) to afford the title product,

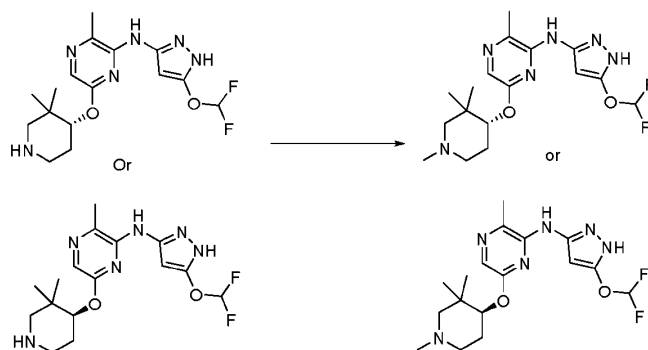
Example 120, (6.8 mg, 43%) as a white solid. LCMS m/z = 367 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.04 (br s, 1H), 10.03 (s, 1H), 7.75 (s, 1H), 7.56 (s, 1H), 7.25 (t, 1H), 5.93 (s, 1H), 4.82-4.77 (m, 1H), 3.18-3.14 (m, 1H), 2.05-1.95 (m, 4H), 1.82-1.64 (m, 5H), 1.07 (d, 3H).

[00782] Step 5: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-*

(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2,8-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine

[00783] A mixture a solution of the title compound of Step 4 (30 mg, 82.0 μ mol), AcOH (0.02 mL) and aq. HCHO (0.2 mL) in MeOH (3.0 mL) was stirred at rt for 1 h. NaBH₃CN (10.2 mg, 163 μ mol) was added. The reaction mixture was stirred for 1 h, then quenched with water and concentrated to dryness under reduced pressure. The residue was purified by Prep-HPLC (Method A) to afford the title product, **Example 119**, (5.6 mg, 18%) as a white solid. LCMS m/z = 381 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.99 (s, 1H), 9.95 (s, 1H), 7.75 (s, 1H), 7.56 (s, 1H), 7.24 (t, 1H), 5.93 (s, 1H), 4.76-4.71 (m, 1H), 3.03-3.00 (m, 1H), 2.81-2.75 (m, 1H), 2.12 (s, 3H), 2.12-1.67 (m, 7H), 1.06 (d, 3H).

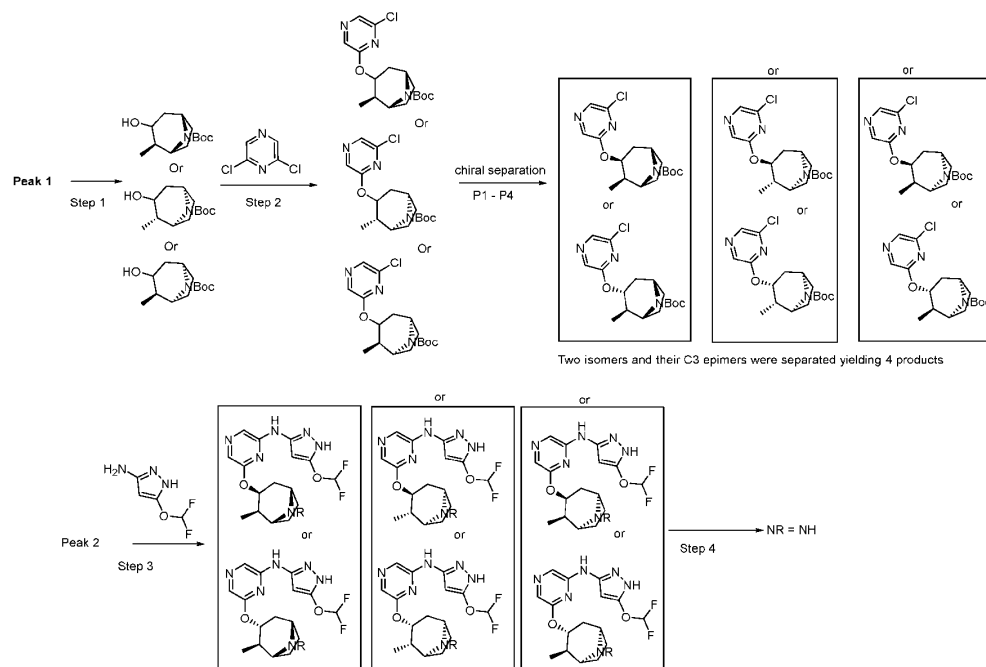
[00784] **Example 121**, (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3-methyl-6-((1,3,3-trimethylpiperidin-4-yl)oxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-3-methyl-6-((1,3,3-trimethylpiperidin-4-yl)oxy)pyrazin-2-amine



[00785] To a solution of the title compound of Example 125, Step 3 (30 mg, 0.081 mmol) in MeOH (3 mL) was added HCHO aq. (0.2 mL) and HOAc (0.2 mL). After stirring at rt for 0.5 h NaBH₃CN (10.0 mg, 0.162 mmol) was added. The reaction mixture stirred for 1 h, then concentrated *in vacuo* and the residue was purified by Prep-HPLC (Method B) to afford the title compound (6.6 mg, 21%) as a yellow solid. LCMS m/z = 383 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.36 (br s, 1H), 9.48 (s, 1H), 8.27 (s, 2H), 7.52 (s, 1H), 7.23 (t, 1H), 6.06 (s, 1H), 4.63-4.60 (m, 1H), 2.65-2.60 (m, 1H), 2.49-2.37 (m, 1H), 2.38 (s, 3H), 2.17 (s, 3H), 2.16-2.04 (m, 1H), 1.93-1.88 (m, 2H), 1.69-1.65 (m, 1H), 1.06 (s, 3H), 0.91 (s, 3H).

[00786] **Example 122**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-

(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine



[00787] Step 3: Synthesis of *tert*-butyl (1R,2R,3S,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or *tert*-butyl *tert*-butyl (1R,2R,3R,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or *tert*-butyl (1S,2S,3R,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or *tert*-butyl (1S,2S,3S,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or *tert*-butyl (1S,2R,3S,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or *tert*-butyl (1S,2R,3R,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate

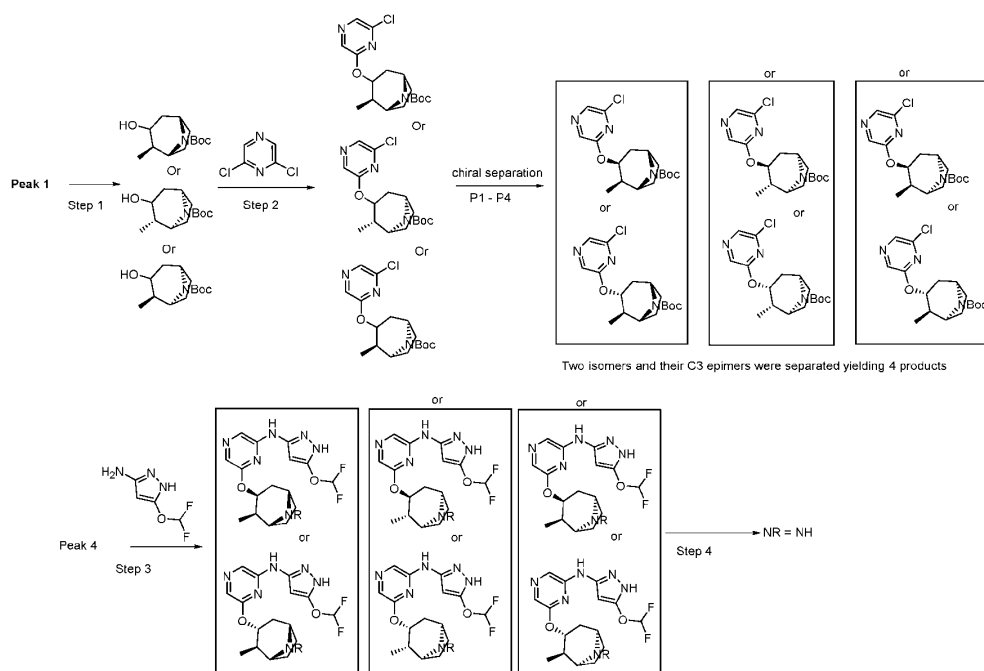
[00788] A mixture of Peak 2 of Example 119 and 120, Step 2 (70 mg, 0.20 mmol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (29.3 mg, 0.20 mmol), BrettPhos-G4-Pd (30.2 mg, 0.02 mmol) and KOAc (58.0 mg, 0.60 mmol) in dioxane (5 mL) was stirred at 100°C for 16 h under N₂. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (9/1) to afford the title compound (70 mg, 72% yield) as a yellow oil. LCMS *m/z* = 467 [M+H]⁺.

[00789] Step 4: Synthesis of *N*-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or *N*-(5-(difluoromethoxy)-1H-pyrazol-3-

yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine

[00790] A mixture of the title compound of Step 3 (30 mg, 64.3 μ mol) in DCM (2.0 mL) was added TFA (1 mL) at rt. The reaction mixture was stirred for 0.5 h, then concentrated under reduced pressure to give the crude which was purified by Prep-HPLC (Method B) to afford the title product (6.8 mg, 28%) as a white solid. LCMS m/z = 367 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.89 (br s, 1H), 10.94 (s, 1H), 8.37 (s, 1H), 7.75 (s, 1H), 7.56 (s, 1H), 7.24 (t, 1H), 6.01 (s, 1H), 5.36-5.29 (m, 1H), 3.85-3.75 (m, 1H), 3.70-3.60 (m, 1H), 2.39-2.32 (m, 1H), 2.00-1.79 (m, 6H), 0.97 (d, 3H).

[00791] **Example 123**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine



[00792] Step 3: *Synthesis of tert-butyl (1R,2R,3S,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl tert-butyl (1R,2R,3R,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2S,3R,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2S,3S,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2R,3S,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2R,3R,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate*

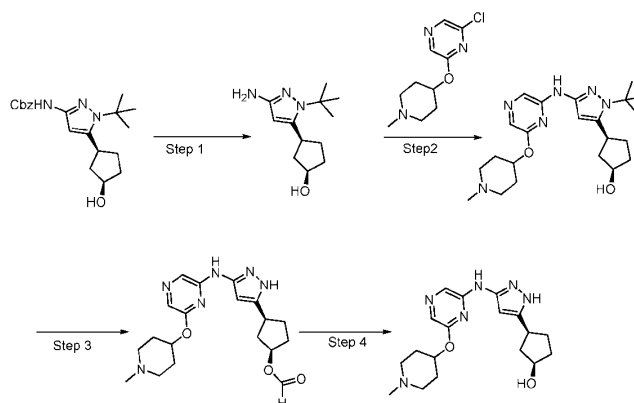
[00793] A mixture of peak 4 of Example 119 and 120, Step 2 (80 mg, 0.22 mmol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (33 mg, 0.22 mmol), BrettPhos Pd G₄ (20 mg, 0.2 mmol) and KOAc (64.6 mg, 0.66 mmol) in 1,4-dioxane (5.0 mL) was stirred at 90°C for 12 h under N₂. The reaction was cooled to rt and diluted with EtOAc, filtered and concentrated to dryness. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (2/1) to afford the title compound (50 mg, 49%) as a yellow oil. LCMS m/z = 467 [M+H]⁺.

[00794] Step 4: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-methyl-8-azabicyclo[3.2.1]octan-3-*

yl)oxy)pyrazin-2-amine or *N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-(((1*S*,2*S*,3*S*,5*R*)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or *N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-(((1*S*,2*R*,3*S*,5*R*)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or *N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-(((1*S*,2*R*,3*R*,5*R*)-2-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine

[00795] A mixture of the title compound of Step 3 (50 mg, 107 μ mol) in DCM (2.0 mL) was added 4 M HCl/dioxane (2.0 mL) at 0°C under N₂. The reaction mixture was stirred for 1 h at rt, then concentrated under reduced pressure to give the crude which was purified by Prep-HPLC (Method A) to afford the title product (6.2 mg, 15% yield) as a white solid. LCMS *m/z* = 367 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.73 (s, 1H), 7.53 (s, 1H), 7.23 (t, 1H), 6.01 (s, 1H), 5.26-5.21 (m, 1H), 4.38-4.14 (m, 1H), 3.19-3.17 (m, 1H), 2.15-2.10 (m, 1H), 1.78-1.66 (m, 6H), 0.91 (d, 3H).

[00796] **Example 124**, (1*R*,3*S*)-3-(3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1*H*-pyrazol-5-yl)cyclopentan-1-ol



[00797] Step 1: *Synthesis of (1R,3S)-3-(3-amino-1-(tert-butyl)-1H-pyrazol-5-yl)cyclopentan-1-ol*

[00798] A mixture of benzyl (1-(tert-butyl)-5-((1*S*,3*R*)-3-hydroxycyclopentyl)-1*H*-pyrazol-3-yl)carbamate (1.69 g, 3.71 mmol) and Pd/C (10%, 800 mg) in EtOAc (20 mL) was degassed and purged with H₂ (3x), then stirred at rt for 16 h under H₂. The reaction mixture was filtered through Celite® and the filtrate was evaporated under reduced pressure to afford the title compound (960 mg, 81%) as a red solid. LCMS *m/z* = 224 [M+H]⁺.

[00799] Step 2: *Synthesis of (1R,3S)-3-(1-(tert-butyl)-3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol*

[00800] The title compound was obtained as a yellow solid (30 mg, 27%) from the compound of Example 8, Step 1, following a similar procedure to that described in Example 19 and 20, Step 2. LCMS *m/z* = 415 [M+H]⁺.

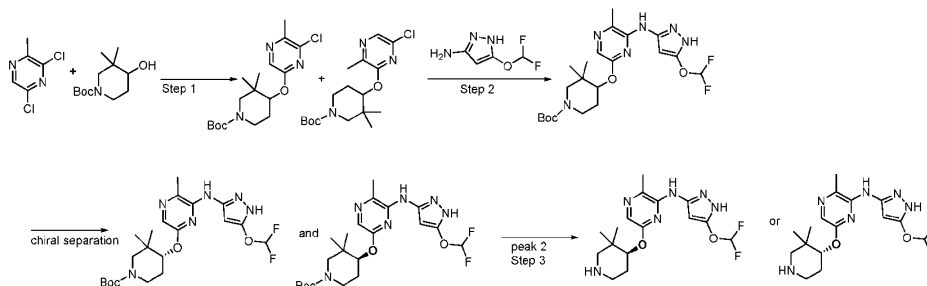
[00801] Step 3: Synthesis of *(1R,3S)*-3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentyl formate

[00802] A solution of the compound of Step 2 (30 mg, 72.3 μ mol) in HCOOH (3 mL) was stirred at 80°C for 1 h. The reaction mixture was cooled to rt and concentrated to give a residue which was purified by flash column chromatography on silica gel eluting with MeOH/EtOAc (1/5) to afford the title compound (25 mg, 89%) as a yellow solid. LCMS m/z = 387 [M+H]⁺.

[00803] Step 4: Synthesis of *(1R,3S)*-3-((6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)cyclopentan-1-ol

[00804] To a solution of the compound of Step 3 (25 mg, 64.6 μ mol) in THF (1.0 mL) and H₂O (2.0 mL) was added LiOH (4.6 mg, 193 μ mol). The reaction mixture was stirred for 1 h, then concentrated. The residue was purified by Prep-HPLC (Method A) to afford the title product (10.5 mg, 45%) as a yellow solid. LCMS m/z = 359 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.62 (s, 1H), 8.21 (s, 1H), 7.94 (s, 1H), 7.45 (s, 1H), 6.27 (s, 1H), 4.99-4.92 (m, 1H), 4.21-4.17 (m, 1H), 3.19-3.15 (m, 1H), 3.11-2.91 (m, 1H), 2.82-2.73 (m, 2H), 2.38-2.28 (m, 2H), 2.29 (s, 3H), 2.05-1.93 (m, 4H), 1.77-1.65 (m, 4H), 1.59-1.55 (m, 1H), 1.52-1.49 (m, 1H), 1.23-1.19 (m, 1H).

[00805] **Example 125**, (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-dimethylpiperidin-4-yl)oxy)-3-methylpyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-dimethylpiperidin-4-yl)oxy)-3-methylpyrazin-2-amine



[00806] Step 1: Synthesis of *tert*-butyl 4-((6-chloro-5-methylpyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate and *tert*-butyl 4-((6-chloro-3-methylpyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate

[00807] The title compounds were obtained as a mixture, 450 mg, from *tert*-butyl 4-hydroxy-3,3-dimethylpiperidine-1-carboxylate and 3,5-dichloro-2-methylpyrazine, following the procedure described in Example 39, step 1. LCMS m/z = 356 [M+H]⁺.

[00808] Step 2: Synthesis of *tert*-butyl (R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-5-methylpyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate or *tert*-butyl (S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-5-methylpyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate

[00809] A mixture of the compound of Step 1 (450 mg, 1.27 mmol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (284 mg, 1.90 mmol), KOAc (373 mg, 3.81 mmol) and Brettphos Pd G4 (43.1 mg, 28.1 μ mol) in dioxane (10 mL) was stirred at 100°C for 2 h under N₂. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/1). The product was further purified by chiral Prep-SFC (Method I, gradient: 80/20) to give racemic tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-5-methylpyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate (180 mg, 30%) as a yellow oil. LCMS *m/z* = 469 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.60 (br s, 1H), 9.00 (s, 1H), 7.56 (s, 1H), 7.26 (t, 1H), 6.00 (s, 1H), 4.73-4.70 (m, 1H), 3.70-3.67 (m, 1H), 3.45-3.44 (m, 1H), 3.08-3.06 (m, 1H), 2.92-2.89 (m, 1H), 2.37 (s, 3H), 1.87-1.84 (m, 1H), 1.57-1.54 (m, 1H), 1.40 (s, 9H), 0.97 (s, 3H), 0.91 (s, 3H). The racemate was separated into its enantiomers by chiral Prep-SFC (Method A, 85/15 gradient) to give Peak 1, tert-butyl (R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-5-methylpyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate or tert-butyl (S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-5-methylpyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate, 72 mg and Peak 2, tert-butyl (S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-5-methylpyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate or tert-butyl (R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-5-methylpyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate, 70 mg.

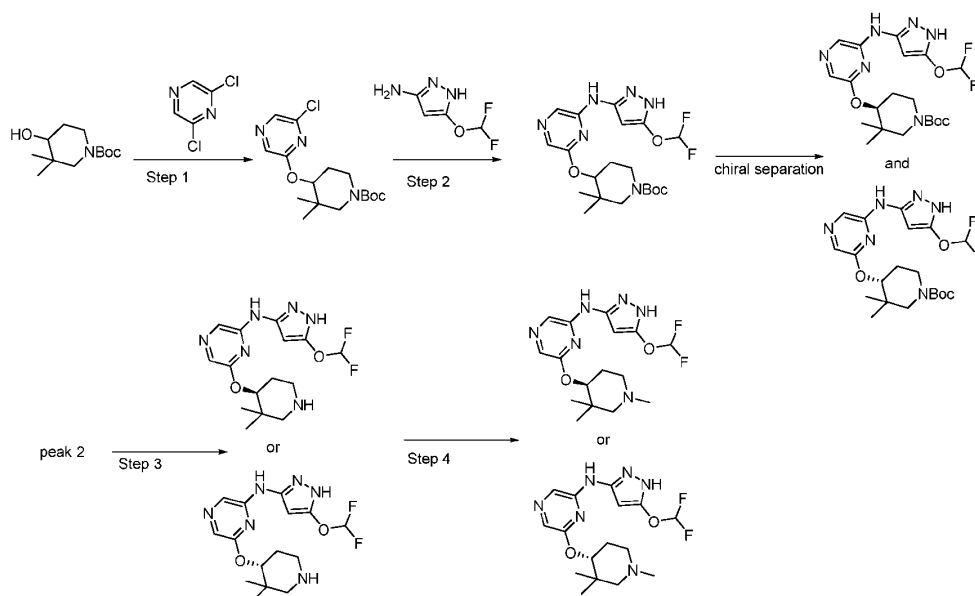
[00810] Step 3: *Synthesis of (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1,3,3-dimethylpiperidin-4-yl)oxy)-3-methylpyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1,3,3-dimethylpiperidin-4-yl)oxy)-3-methylpyrazin-2-amine*

[00811] A mixture of the compound of Step 2, Peak 2 (70 mg, 149 μ mol) and TFA (1 mL) in DCM (3 mL) was stirred at rt for 1 h. The solvent was removed *in vacuo* and the residue purified by Prep-HPLC (Method B) to afford the title compound (50 mg, 81%) as a white solid. LCMS *m/z* = 369 [M+H]⁺.

[00812] **Example 126**, (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1,3,3-trimethylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1,3,3-trimethylpiperidin-4-yl)oxy)pyrazin-2-amine and

[00813] **Example 127**, (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-

((3,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine



[00814] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate*

[00815] The title compound was obtained as yellow oil (600 mg, 99%) from tert-butyl 4-hydroxy-3,3-dimethylpiperidine-1-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.33 (s, 2H), 4.90-4.85 (m, 1H), 3.71-3.63 (m, 1H), 3.48-3.42 (m, 1H), 3.27-3.10 (m, 1H), 3.10-2.93 (m, 1H), 1.92-1.85 (m, 1H), 1.66-1.56 (m, 1H), 1.40 (s, 9H), 0.94 (s, 3H), 0.92 (s, 3H).

[00816] Step 2: *Synthesis of tert-butyl (S)-4-((5-((difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate or tert-butyl (R)-4-((5-((difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate*

[00817] tert-Butyl 4-((5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3,3-dimethylpiperidine-1-carboxylate was obtained, 340 mg, 44% from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 37, step 2. The racemic compound was then separated by chiral Prep-SFC (Method F, gradient: 85/15) to give peak 2, the title compound (174 mg, 22%) as a yellow solid. LCMS *m/z* = 455 [M+H]⁺.

[00818] Step 3: *Synthesis of (S)-N-(5-((difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-((difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine (Example 127)*

[00819] To a solution of the compound of Step 2 (174 mg, 0.38 mmol) in DCM (2.0 mL) was added 4M HCl/dioxane (4 mL) at 0°C under N₂. The reaction mixture was allowed to warm to rt and

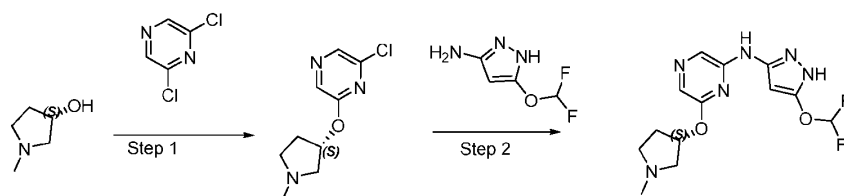
stirred for 1 h. The reaction mixture was directly concentrated under reduced pressure to give the crude product (70 mg). LCMS $m/z = 355$ $[M+H]^+$.

[00820] Step 4: *Synthesis of (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1,3,3-trimethylpiperidin-4-yl)oxy)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1,3,3-trimethylpiperidin-4-yl)oxy)pyrazin-2-amine (Example 126)*

[00821] The title compound was obtained as a yellow solid (19.2 mg, 26%) from the title compound of Step 3 and HCHO following a similar procedure to that described in Example 11. LCMS $m/z = 369$ $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 7.74 (s, 1H), 7.56 (s, 1H), 7.22 (t, 1H), 6.02 (s, 1H), 4.70-4.66 (m, 1H), 2.63-2.53 (m, 1H), 2.43-2.33 (m, 1H), 2.14 (s, 3H), 2.10-2.00 (m, 1H), 1.92-1.89 (m, 2H), 1.73-1.66 (m, 1H), 1.06 (s, 3H), 0.91 (s, 3H).

[00822] **Example 128.** See Example 7.

[00823] **Example 129,** (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpyrrolidin-3-yl)oxy)pyrazin-2-amine



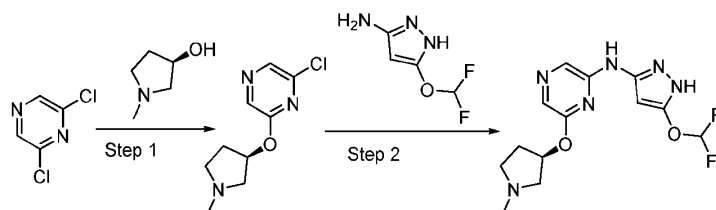
[00824] Step 1: *Synthesis of (S)-2-chloro-6-((1-methylpyrrolidin-3-yl)oxy)pyrazine*

[00825] The title compound was obtained as a white solid (200 mg, 95%) from (S)-1-methylpyrrolidin-3-ol and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS $m/z = 214$ $[M+H]^+$.

[00826] Step 2: *Synthesis of (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpyrrolidin-3-yl)oxy)pyrazin-2-amine*

[00827] The title compound was obtained as a white solid (28.5 mg, 20%) from the compound of Step 1 following a similar procedure to that described in Example 37, step 2. LCMS $m/z = 327$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.93 (br s, 1H), 9.97 (s, 1H), 7.77 (s, 1H), 7.59 (s, 1H), 7.25 (t, 1H), 5.95 (s, 1H), 5.35-5.33 (m, 1H), 3.33-3.29 (m, 1H), 2.73-2.69 (m, 3H), 2.32-2.30 (m, 2H), 2.26 (s, 3H), 1.86-1.84 (m, 1H).

[00828] **Example 130,** (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpyrrolidin-3-yl)oxy)pyrazin-2-amine



[00829] Step 1: *Synthesis of (R)-2-chloro-6-((1-methylpyrrolidin-3-yl)oxy)pyrazine*

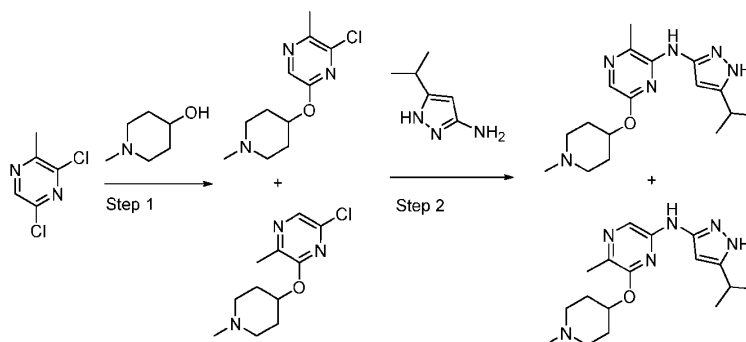
[00830] The title compound was obtained as a yellow oil, 100 mg, 47% from (3R)-1-methylpyrrolidin-3-ol (and 2,6-dichloropyrazine, following a similar procedure to that described in Example 39, step 1. LCMS $m/z = 214$ $[M+H]^+$.

[00831] Step 2: *Synthesis of (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpyrrolidin-3-yl)oxy)pyrazin-2-amine*

[00832] The title compound was obtained as a white solid, 75.3 mg, 49%, from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 37, step 2. LCMS $m/z = 327$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.32 (br s, 1H), 10.23 (s, 1H), 8.19 (s, 1H), 7.78 (s, 1H), 7.60 (s, 1H), 7.27 (t, 1H), 5.98 (s, 1H), 5.45-5.34 (m, 1H), 2.82-2.80 (m, 3H), 2.51-2.38 (m, 1H), 2.34 (s, 3H), 2.31-2.21 (m, 1H), 1.91-1.73 (m, 1H).

[00833] **Example 131**, N-(5-isopropyl-1H-pyrazol-3-yl)-3-methyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine and

[00834] **Example 132**, N-(5-isopropyl-1H-pyrazol-3-yl)-5-methyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00835] Step 1: *Synthesis of 3-chloro-2-methyl-5-((1-methylpiperidin-4-yl)oxy)pyrazine and 5-chloro-2-methyl-3-((1-methylpiperidin-4-yl)oxy)pyrazine*

[00836] The title compound was obtained as yellow oil, 300 mg, 67%, from 1-methylpiperidin-4-ol and 3,5-dichloro-2-methylpyrazine following a similar procedure to that described in Example 39, step 1. LCMS $m/z = 242$ $[M+H]^+$.

[00837] Step 2: *Synthesis of N-(5-isopropyl-1H-pyrazol-3-yl)-3-methyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine (Example 131) and N-(5-isopropyl-1H-pyrazol-3-yl)-5-methyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine (Example 132)*

[00838] A mixture of the compounds of Step 1 (124 mg, 0.99 mmol), 5-(propan-2-yl)-1H-pyrazol-3-amine (200 mg, 0.827 mmol), KOAc (243 mg, 2.48 mmol) and Brettphos Pd G4 (63.4 mg, 0.041 mmol) in dioxane (8 mL) was stirred at 100°C for 2 h under N₂. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with MeOH/DCM (1/4) and further purified by Prep-HPLC (Method B) to afford the two title compounds:

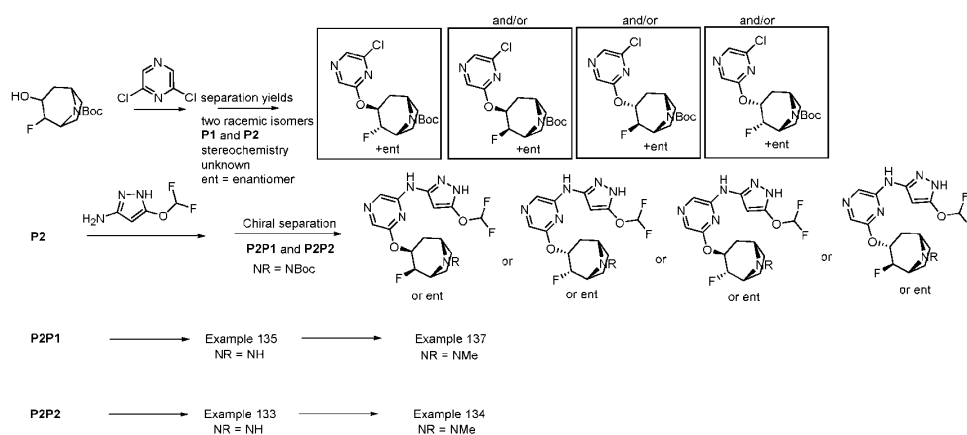
[00839] N-(5-isopropyl-1H-pyrazol-3-yl)-3-methyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine (**Example 131**, 22.0 mg, 8%) ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.59 (s, 1H), 8.22 (s, 1H), 7.38 (s, 1H), 6.62 (s, 1H), 4.91-4.89 (m, 1H), 2.94-2.82 (m, 3H), 2.36-2.29 (m, 8H), 2.02-1.99 (m, 2H), 1.74-1.71 (m, 2H), 1.25 (d, 6H)

[00840] N-(5-isopropyl-1H-pyrazol-3-yl)-5-methyl-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine (**Example 132**, 142 mg, 52%) as a white solid. LCMS *m/z* = 331 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.31 (s, 1H), 8.19 (s, 1H), 7.88 (s, 1H), 6.16 (s, 1H), 4.99-4.97 (m, 1H), 3.77-3.74 (m, 1H), 2.73-2.68 (m, 2H), 2.64-2.23 (m, 8H), 2.04-2.00 (m, 2H), 1.77-1.73 (m, 2H), 1.23 (d, 6H).

[00841] **Example 135 and Example 133**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine and

[00842] **Example 137 and Example 134**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine and

azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine



[00843] Step 1: *Synthesis of rac-tert-butyl (2R,3R)-3-((6-chloropyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate and/or rac-tert-butyl (2S,3R)-3-((6-chloropyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate*

[00844] The title compounds were obtained from tert-butyl 2-fluoro-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 37, Step 1. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (1/5) to give two fractions of racemic isomers, **P1** (634 mg, 44%) and **P2** (506 mg, 35%). LCMS $m/z = 302$ $[M-56+H]^+$.

[00845] Step 2: *Synthesis of tert-butyl (1R,2R,3S,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1S,2S,3R,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1R,2S,3R,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1S,2R,3S,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1R,2S,3S,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1S,2R,3R,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-*

8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2S,3S,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1R,2R,3S,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate

[00846] The title compounds were obtained from **P2** (500 mg, 1.4 mmol) and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar procedure to that described in Example 37, Step 2, to afford the racemic product (400 mg) and then separated by chiral Prep-SFC (Method C, gradient: 70/30) to give Peak 1, **P2P1** (141 mg, 21%) and Peak 2, **P2P2** (136 mg, 20%). LCMS m/z = 471 [M+H]⁺.

[00847] Step 3: Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine

[00848] To a solution of **P2P1** (36 mg, 76.5 μmol) in DCM (2.0 mL) was added TFA (0.5 mL) at 0°C under N₂. The reaction mixture was allowed to warm to 50°C and stirred for 3 h, then concentrated under reduced pressure. The residue was purified by Prep-HPLC (Method C) to afford the title compound (**Example 135**, 13.9 mg, 49%) as a yellow solid. LCMS m/z = 371 [M+H]⁺. ¹H NMR (500 MHz, DMSO-d₆) δ ppm 11.95 (br s, 1H), 10.09 (br s, 1H), 7.82 (s, 1H), 7.62 (s, 1H), 7.23 (t, 1H), 5.97 (s, 1H), 5.17-5.11 (m, 1H), 4.55-4.43 (m, 1H), 3.57-3.52 (m, 1H), 3.45-3.40 (m, 1H), 2.16-2.11 (m, 1H), 2.02-1.98 (m, 1H), 1.76-1.72 (m, 2H), 1.70-1.65 (m, 3H).

[00849] **Example 133** was obtained from **P2P2** using a similar method to that described for Example 135: 10.6 mg, 37% yellow solid. LCMS m/z = 371 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.93 (b. s, 1H), 10.07 (br s, 1H), 7.82 (s, 1H), 7.62 (s, 1H), 7.23 (t, 1H), 5.97 (s, 1H), 5.17-5.11 (m, 1H), 4.55-4.43 (m, 1H), 3.57-3.52 (m, 1H), 3.45-3.40 (m, 1H), 2.16-2.11 (m, 1H), 2.02-1.98 (m, 1H), 1.76-1.72 (m, 2H), 1.70-1.65 (m, 3H).

[00850] Step 4: Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-methyl-8-

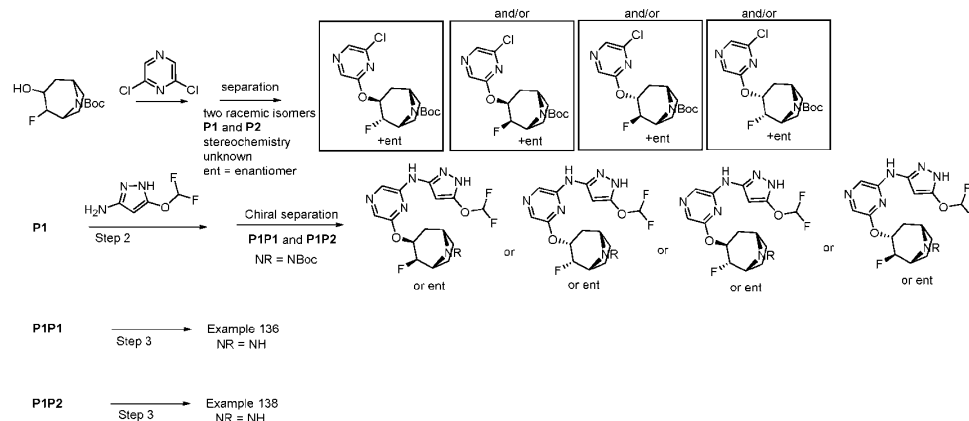
azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine

[00851] The title compound (**Example 137**) was obtained as a yellow solid (13.5 mg, 32%) from the product of Step 3, Example 135, following a similar procedure to that described in Example 11. LCMS $m/z = 385$ $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.86 (br s, 1H), 10.12 (br s, 1H), 7.83 (s, 1H), 7.61 (s, 1H), 7.21 (t, 1H), 5.97 (s, 1H), 5.11-5.05 (m, 1H), 4.60-4.47 (m, 1H), 3.25-3.11 (m, 1H), 2.27-2.20 (m, 1H), 2.23 (s, 3H), 2.04-1.95 (m, 2H), 1.79-1.67 (m, 3H).

[00852] **Example 134** was obtained from Example 133 following the same method as described for Example 137: 29.6 mg, 57%, yellow solid. LCMS $m/z = 385$ $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.86 (br s, 1H), 10.08 (br s, 1H), 7.81 (s, 1H), 7.61 (s, 1H), 7.21 (t, 1H), 5.97 (s, 1H), 5.10-5.03 (m, 1H), 4.60-4.47 (m, 1H), 3.25-3.11 (m, 2H), 2.24-2.18 (m, 1H), 2.21 (s, 3H), 2.04-1.95 (m, 2H), 1.79-1.67 (m, 3H).

[00853] **Example 136 and Example 138**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-

yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine



[00854] Step 2: Synthesis of tert-butyl (1R,2R,3S,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1S,2S,3R,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1R,2S,3R,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1S,2R,3S,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1R,2S,3S,5S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate and tert-butyl (1S,2R,3R,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate or tert-butyl (1S,2S,3S,5R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-fluoro-8-azabicyclo[3.2.1]octane-8-carboxylate

[00855] The title compounds were obtained from P1 (Example 135, Step 1, 634 mg, 1.77 mmol) and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar procedure to that described in Example 37, Step 2, to afford the racemic product (637mg) and then separated by chiral Prep-SFC (Method B, gradient: 65/35) to give peak 1, **P1P1** (175 mg) and peak 2, **P1P2** (131 mg). LCMS m/z = 471 [M+H]⁺.

[00856] Step 3: Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2R,3S,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2S,3R,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,2S,3R,5S)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1S,2R,3S,5R)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-

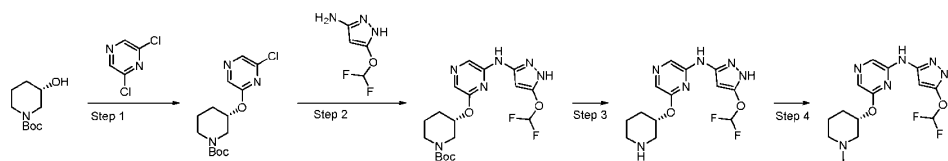
(((1*R*,2*S*,3*S*,5*S*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or *N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-(((1*S*,2*R*,3*R*,5*R*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or *N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-(((1*R*,2*R*,3*R*,5*S*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine or *N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-(((1*S*,2*S*,3*S*,5*R*)-2-fluoro-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine

[00857] To a solution of P1P1 (175 mg, 0.37 mmol) in DCM (2.0 mL) was added TFA (0.5 mL) at 0°C under N₂. The reaction mixture was allowed to warm to rt and stirred for 2 h under N₂, then concentrated under reduced pressure. The residue was purified by Prep-HPLC (Method B) to afford the title compound, **Example 136**, 33.4 mg, 24%) as a white solid. LCMS *m/z* = 371 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.35 (br s, 1H), 10.20 (s, 1H), 8.21 (s, 1H), 7.79 (s, 1H), 7.61 (s, 1H), 7.24 (t, 1H), 5.93 (s, 1H), 5.30-5.16 (m, 1H), 4.86-4.69 (m, 1H), 3.70-3.65 (m, 1H), 3.60-3.48 (m, 1H), 1.97-1.90 (m, 1H), 1.82-1.50 (m, 5H).

[00858] **Example 138** was obtained using a similar method to that described for Example 136: 29.2 mg, 25%, white solid. LCMS *m/z* = 371 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.17 (br s, 1H), 10.01 (s, 1H), 8.17 (s, 1H), 7.80 (s, 1H), 7.63 (s, 1H), 7.25 (t, 1H), 5.93 (s, 1H), 5.35-5.20 (m, 1H), 4.93-4.77 (m, 1H), 3.86-3.80 (m, 1H), 3.72-3.67 (m, 1H), 2.02-1.95 (m, 1H), 1.88-1.66 (m, 5H).

[00859] **Example 139**, (S)-*N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-((1-methylpiperidin-3-yl)oxy)pyrazin-2-amine and

[00860] **Example 142**, (S)-*N*-(5-(difluoromethoxy)-1*H*-pyrazol-3-yl)-6-(piperidin-3-yloxy)pyrazin-2-amine



[00861] Step 1: *Synthesis of tert-butyl (S)-3-((6-chloropyrazin-2-yl)oxy)piperidine-1-carboxylate*

[00862] The title compound was obtained as colourless oil (2.7 g, 87%) from tert-butyl (S)-3-hydroxypiperidine-1-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS *m/z* = 336 [M+Na]⁺.

[00863] Step 2: *Synthesis of tert-butyl (S)-3-((6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate*

[00864] The title compound was obtained as yellow paste (420 mg, 48%) from the compound of Step 1 and 5-(difluoromethoxy)-1*H*-pyrazol-3-amine following a similar procedure to that described in Example 19 and 20, step 2. LCMS *m/z* = 427 [M+H]⁺.

[00865] Step 3: *Synthesis of (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yloxy)pyrazin-2-amine (Example 142)*

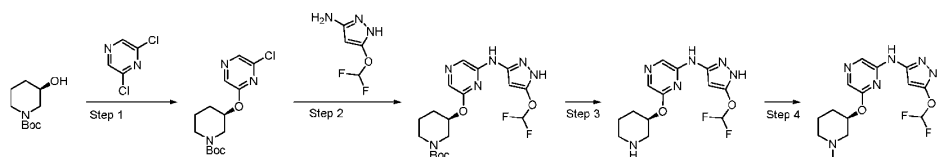
[00866] The title compound was obtained as white solid (62.9 mg, 59%) from the compound of Step 2 following a similar procedure to that described in Example 3, step 3. LCMS $m/z = 327$ $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 12.02 (br s, 1H), 10.06 (br s, 1H), 7.77 (s, 1H), 7.58 (s, 1H), 7.26 (t, 1H), 5.98 (s, 1H), 4.87-4.83 (m, 1H), 3.15-3.09 (m, 1H), 2.80-2.75 (m, 1H), 2.62-2.55 (m, 1H), 2.52-2.49 (m, 1H), 2.13-2.05 (m, 1H), 1.73-1.62 (m, 1H), 1.53-1.45 (m, 2H).

[00867] Step 4: *Synthesis of (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-3-yl)oxy)pyrazin-2-amine (Example 139)*

[00868] The title compound was obtained as white solid (20.5 mg, 8%) from the title compound of Step 3 following a similar procedure to that described in Example 11. LCMS $m/z = 341$ $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.89 (br s, 1H), 9.96 (br s, 1H), 7.77 (s, 1H), 7.58 (s, 1H), 7.24 (t, 1H), 5.96 (s, 1H), 5.00-4.95 (m, 1H), 3.33-3.30 (m, 1H), 2.90-2.85 (m, 1H), 2.55-2.51 (m, 1H), 2.19 (s, 3H), 2.20-2.16 (m, 1H), 2.10-2.06 (m, 1H), 1.97-1.93 (m, 1H), 1.75-1.71 (m, 1H), 1.55-1.49 (m, 1H), 1.45-1.40 (m, 1H).

[00869] **Example 140**, (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-3-yl)oxy)pyrazin-2-amine and

[00870] **Example 141**, (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yloxy)pyrazin-2-amine



[00871] Step 1: *Synthesis of tert-butyl (R)-3-((6-chloropyrazin-2-yl)oxy)piperidine-1-carboxylate*

[00872] The title compound was obtained as a yellow oil (1.2 mg, 77%) from tert-butyl (3R)-3-hydroxypiperidine-1-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS $m/z = 258$ $[M-56+H]^+$.

[00873] Step 2: *Synthesis of tert-butyl (R)-3-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate*

[00874] The title compound was obtained as a yellow solid (500 mg, 30%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 19 and 20, step 2. LCMS $m/z = 427$ $[M+H]^+$.

[00875] Step 3: *Synthesis of (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-yloxy)pyrazin-2-amine (Example 141)*

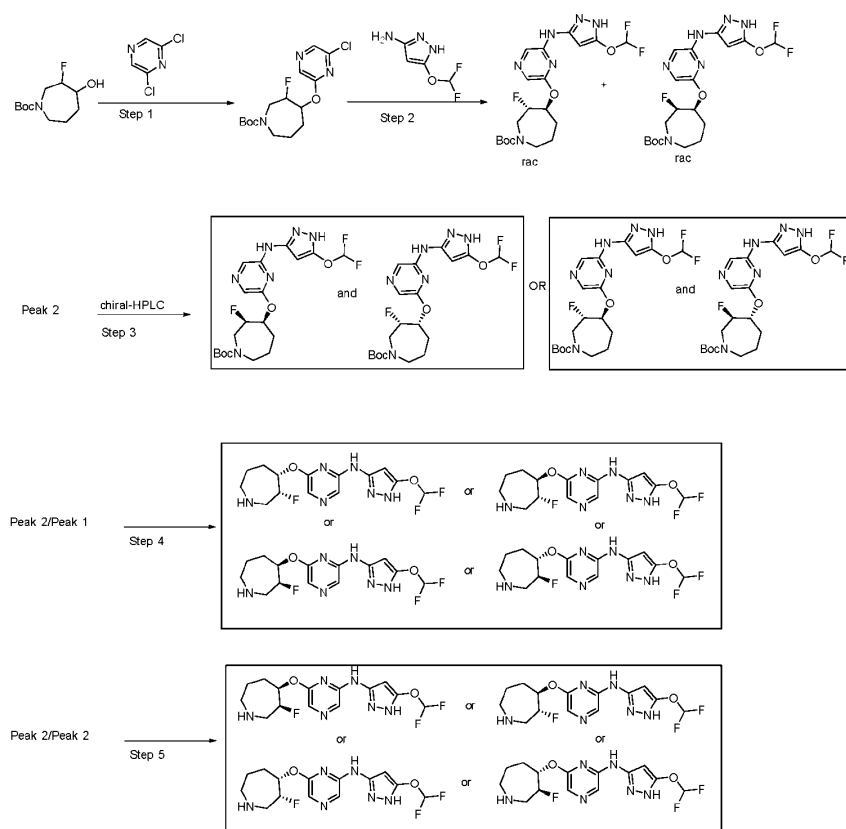
[00876] The title compound was obtained as a yellow oil (300 mg, 78% yield) from the compound of Step 2 following a similar procedure to that described in Example 2, step 3. LCMS m/z = 327 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 12.11 (br s, 1H), 10.16 (br s, 1H), 7.77 (s, 1H), 7.57 (s, 1H), 7.26 (t, 1H), 5.98 (s, 1H), 4.88-4.85 (m, 1H), 3.13-3.11 (m, 1H), 2.80-2.78 (m, 1H), 2.64-2.60 (m, 1H), 2.55-2.52 (m, 1H), 2.09-2.06 (m, 1H), 1.70-1.68 (m, 1H), 1.55-1.44 (m, 2H).

[00877] Step 4: *Synthesis of (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-3-yl)oxy)pyrazin-2-amine (Example 140)*

[00878] The title compound was obtained as a yellow solid (46.9 mg, 22%) from the compound of Step 3 following a similar procedure to that described in Example 11. LCMS m/z = 341 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.90 (br s, 1H), 9.96 (br s, 1H), 7.77 (s, 1H), 7.58 (s, 1H), 7.24 (t, 1H), 6.00 (s, 1H), 5.01-4.97 (m, 1H), 2.88 (d, 1H), 2.55-2.52 (m, 1H), 2.19 (s, 3H), 2.10-2.05 (m, 1H), 1.99-1.94 (m, 1H), 1.75-1.71 (m, 1H), 1.57-1.50 (m, 1H), 1.45-1.39 (m, 1H).

[00879] **Example 143**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine and

[00880] **Example 144**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine



[00881] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate*

[00882] The title compound was obtained as a yellow solid, 500 mg, 78%, from tert-butyl 3-fluoro-4-hydroxyazepane-1-carboxylate and 2,6-dichloropyrazine, following a similar procedure to that described in Example 125, step 1. LCMS $m/z = 368$ $[M+Na]^+$.

[00883] Step 2: *Synthesis of tert-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate and tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate*

[00884] To a solution of the compound of Step 1 (500 mg, 1.45 mmol) and 5-(difluoromethoxy)-1H-pyrazol-3-amine (283 mg, 1.90 mmol) in dioxane (25 mL) was added BrettPhos Pd G4 (174 mg, 0.19 mmol) and KOAc (558 mg, 5.70 mmol) at rt. The reaction mixture was stirred at 90°C for 14 h under N_2 . The mixture was evaporated and the residue was purified by Prep-HPLC (Method A) to give Peak 1, tert-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate and tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate (210 mg, 31%) as a white solid and Peak 2, tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-

yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate and tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate (200 mg, 30%) as a white solid. LCMS m/z = 459 [M+H]⁺.

[00885] Step 3: *Synthesis of tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate and tert-butyl (3S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate or tert-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate and tert-butyl (3R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate*

[00886] 200 mg of Peak 2 of Step 2 was separated by chiral Prep-SFC, (Method H, gradient: 75/25) to give Peak 2/Peak 1, tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate or tert-butyl (3S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate or tert-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate or tert-butyl (3R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate (80 mg) and Peak 2/Peak 2, tert-butyl (3S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate and tert-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate or tert-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate and tert-butyl (3R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate (80 mg).

[00887] Step 4: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine*

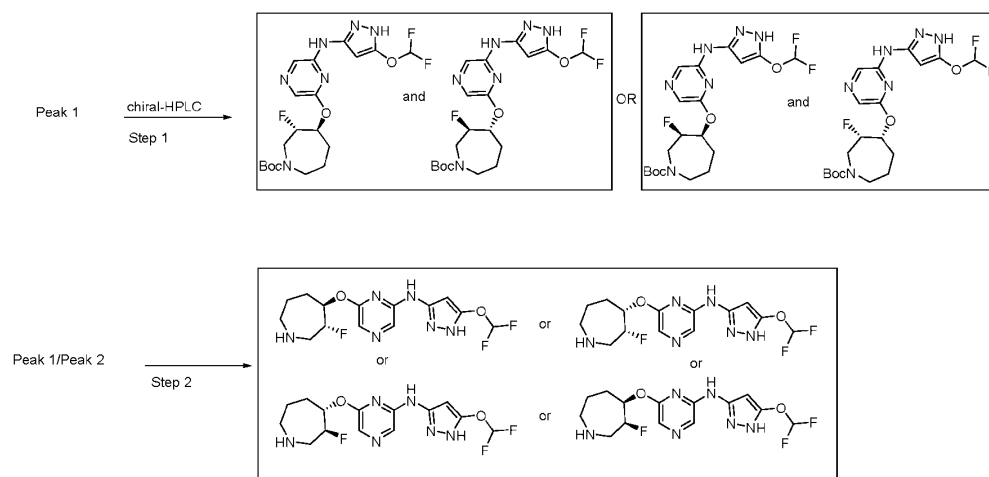
[00888] A mixture of Peak 2/Peak 1, Step 3 (80 mg, 0.174 mmol) in 7 M HCl/dioxane (2.0 mL) was stirred at rt for 4 h. The reaction mixture was concentrated and the residue was purified with Prep-HPLC (Method A) to obtain the title product, **Example 143** (56.7 mg, 90%) as a yellow solid. LCMS m/z = 359 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.01 (br s, 1H), 9.96 (s, 1H), 7.78 (s, 1H), 7.62 (s, 1H), 7.24 (t, 1H), 5.94 (s, 1H), 5.35-5.26 (m, 1H), 4.99-4.87 (m, 1H), 3.04-3.03 (m, 1H), 2.98-2.96 (m, 1H), 2.83-2.78 (m, 1H), 2.76-2.73 (m, 1H), 2.12-2.04 (m, 1H), 1.76-1.71 (m, 1H), 1.65-1.60 (m, 1H), 1.56-1.51 (m, 1H).

[00889] Step 5: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-*

fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine

[00890] The title compound, **Example 144**, was obtained as a yellow solid, 55.9 mg, 89%, from Peak 2/Peak 2, Step 3, following a similar procedure to that described in Step 4. LCMS m/z = 359 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.05 (br s, 1H), 10.01 (br s, 1H), 7.78 (s, 1H), 7.62 (s, 1H), 7.24 (t, 1H), 5.94 (s, 1H), 5.35-5.25 (m, 1H), 4.98-4.85 (m, 1H), 3.02-3.00 (m, 1H), 2.96-2.95 (m, 1H), 2.81-2.76 (m, 1H), 2.74-2.70 (m, 1H), 2.12-2.04 (m, 1H), 1.76-1.71 (m, 1H), 1.65-1.60 (m, 1H), 1.56-1.51 (m, 1H).

[00891] **Example 145**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine



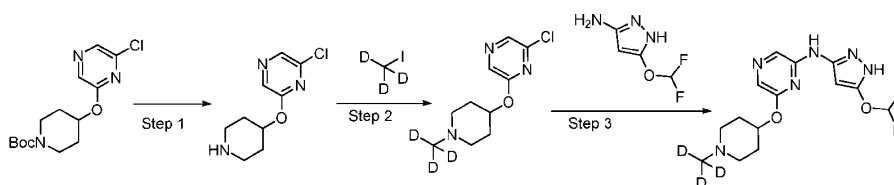
[00892] Step 1: *tert*-butyl (3R,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate and *tert*-butyl (3S,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate or *tert*-butyl (3R,4S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate and *tert*-butyl (3S,4R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-fluoroazepane-1-carboxylate

[00893] 210 mg of Example 143 and 144, Peak 1, Step 2 was separated by chiral Prep-SFC, Column: IC 20*250mm, 10 μ m (Daicel), Column temperature: 35 $^{\circ}$ C, Mobile phase: CO₂/MeOH (0.2% MeOH/NH₃) = 55/45, Flow rate: 80 g/min, Back pressure: 100 bar to give Peak 1/Peak 2 (100 mg).

[00894] Step 2: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4R)-3-fluoroazepan-4-yl)oxy)pyrazin-2-amine*

[00895] The title compound was obtained as a yellow solid, 42.2 mg, 53%, from Peak 1/Peak 2, Step 6, following a similar procedure to that described in Example 143 and 144, Step 4. LCMS m/z = 359 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.99 (br s, 1H), 9.93 (s, 1H), 7.79 (s, 1H), 7.61 (s, 1H), 7.24 (t, 1H), 5.97 (s, 1H), 5.27-5.24 (m, 1H), 4.80-4.66 (m, 1H), 3.29-3.14 (m, 2H), 3.03-3.02 (m, 1H), 2.95-2.91 (m, 1H), 1.82-1.65 (m, 4H).

[00896] **Example 146**, *N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-(methyl- d_3)piperidin-4-yl)oxy)pyrazin-2-amine*



[00897] Step 1: *Synthesis of 2-chloro-6-((piperidin-4-yloxy)pyrazine*

[00898] To a solution of the title compound of Example 1, Step 1 (500 mg, 1.59 mmol) in DCM (20 mL) was added TFA (2.0 mL), then the reaction mixture stirred at rt overnight. The reaction mixture was concentrated *in vacuo* to give the title product (crude, 450 mg). LCMS m/z = 214 $[M+H]^+$.

[00899] Step 2: *Synthesis of 2-chloro-6-((1-(methyl- d_3)piperidin-4-yl)oxy)pyrazine*

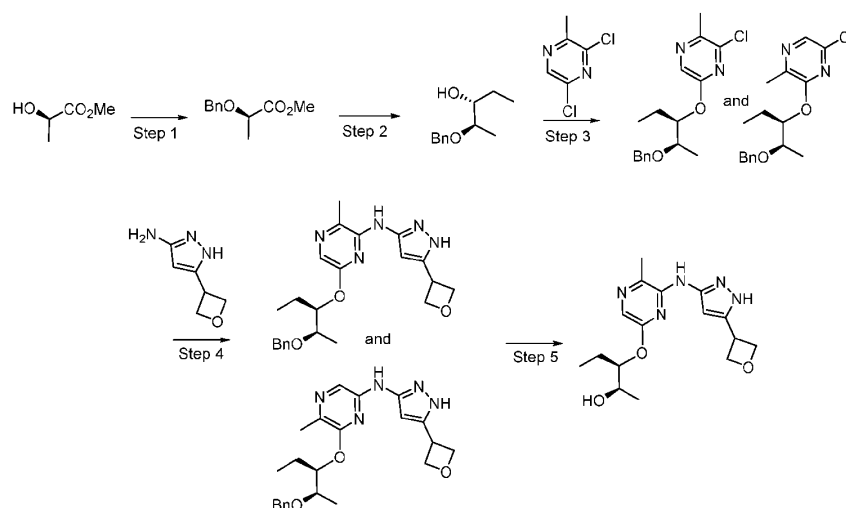
[00900] To a mixture of the compound of Step 1 (220 mg, 1.02 mmol) and iodo(D_3)methane (176 mg, 1.22 mmol) in THF (25.0 mL) was added NaH (60 %, 48.6 mg, 1.22 mmol) at 0°C under N_2 and the reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na_2SO_4 , filtered and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (1/1) to afford the title compound (200 mg, 85%) as a yellow solid. LCMS m/z = 231 $[M+H]^+$.

[00901] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-(methyl- d_3)piperidin-4-yl)oxy)pyrazin-2-amine*

[00902] A mixture of the compound of Step 2 (100 mg, 433 μ mol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (64.5 mg, 433 μ mol), BrettPhos Pd G₄ (10 mg, 0.01 mmol) and KOAc (126 mg, 1.29 mmol) in dioxane (20 mL) was stirred at 120°C for 18 h under N_2 . The reaction mixture was concentrated *in vacuo* and the residue was purified by Prep-HPLC (Method C) to afford the title

compound (16.4 mg, 11%) as a yellow solid. LCMS m/z = 344 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.95 (br s, 1H), 9.66 (s, 1H), 7.77 (s, 1H), 7.58 (s, 1H), 7.24 (t, 1H), 5.98 (s, 1H), 4.95-4.90 (m, 1H), 2.67-2.65 (m, 2H), 2.15 (t, 2H), 1.99-1.95 (m, 2H), 1.72-1.63 (m, 2H).

[00903] Example 147, (2R,3R)-3-((5-methyl-6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol



[00904] Step 1: Synthesis of methyl (2R)-2-(benzyloxy)propanoate

[00905] To a solution of methyl (2R)-2-hydroxypropanoate (2.0 g, 19.2 mmol) in dry THF (30 mL) was added NaH (60%, 760 mg, 19.2 mmol) at 0°C under N₂. After stirring for 30 min, (bromomethyl)benzene (3.60 g, 21.1 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction was quenched by sat. NH₄Cl and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel eluting with EtOAc/PE (1/1) to give the title product (1.22 g, 33%) as a colorless oil. LCMS m/z = 217 $[M+Na]^+$.

[00906] Step 2: Synthesis of (2R,3R)-2-(benzyloxy)pentan-3-ol

[00907] To a solution of the compound of Step 1 (1.13 g, 5.76 mmol) in THF (3.0 mL) was added DIBAL-H (1M, 6.9 mL, 6.9 mmol) at -78°C under N₂. After stirring at -78°C for 1 h, EtMgBr (3M, 5.8 mL, 17.4 mmol) was added. The resulting mixture was allowed to warm to rt and stirred for 4 h. The reaction was quenched by sat. NH₄Cl and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel eluting with EtOAc/PE (1/1) to give title product (889 mg, 80%). LCMS m/z = 217 $[M+Na]^+$.

[00908] Step 3: Synthesis of 5-(((2R,3R)-2-(benzyloxy)pentan-3-yl)oxy)-3-chloro-2-methylpyrazine and 3-(((2R,3R)-2-(benzyloxy)pentan-3-yl)oxy)-5-chloro-2-methylpyrazine

[00909] To a solution of the compound of Step 2 (870 mg, 4.47 mmol) in THF (10.0 mL) was added NaH (60%, 215 mg, 5.38 mmol) at 0 °C under N₂ and the solution stirred for 10 min. 3,5-Dichloro-2-methylpyrazine (873 mg, 5.36 mmol) was added and the reaction mixture was allowed to warm to 60 °C and stirred for 18 h. The reaction mixture was quenched by saturated NH₄Cl aqueous and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel eluting with EtOAc/PE (1/1) to give the title products (1.13 g) as a colorless oil. LCMS m/z = 321 [M+H]⁺.

[00910] Step 4: *Synthesis of 6-(((2R,3R)-2-(benzyloxy)pentan-3-yl)oxy)-3-methyl-N-(5-(oxetan-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine and 6-(((2R,3R)-2-(benzyloxy)pentan-3-yl)oxy)-5-methyl-N-(5-(oxetan-3-yl)-1H-pyrazol-3-yl)pyrazin-2-amine*

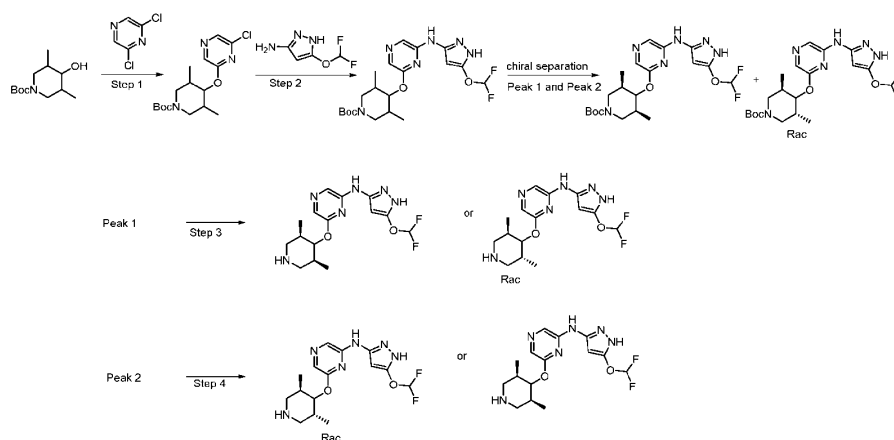
[00911] A mixture of the compounds of Step 3 (500 mg), 5-(oxetan-3-yl)-1H-pyrazol-3-amine (239 mg, 1.71 mmol), BrettPhos Pd G₄ (143 mg, 0.156 mmol) and KOAc (458 mg, 4.68 mmol) in dioxane (20.0 mL) was heated to 100°C and stirred for 18 h under N₂. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with MeOH/EtOAc (1/10) to give the title products (483 mg) as a brown oil. LCMS m/z = 424 [M+H]⁺.

[00912] Step 5: *Synthesis of (2R,3R)-3-((5-methyl-6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol*

[00913] A mixture of the compounds from Step 4 (466 mg), Pd/C (10%, 120 mg) and HCO₂H (2.0 mL) in EtOH (40.0 mL) was stirred at rt for 18 h under a balloon of H₂. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by Prep-HPLC (Method A) to give the title product (39.4 mg, 11%) as a yellow solid. LCMS m/z = 334 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.13 (br s, 1H), 8.68 (br s, 1H), 7.42 (s, 1H), 6.60 (br s, 1H), 4.92 – 4.80 (m, 3H), 4.75 – 4.63 (m, 3H), 4.32 – 4.22 (m, 1H), 3.88 – 3.78 (m, 1H), 2.37 (s, 3H), 1.79 – 1.69 (m, 1H), 1.63 – 1.53 (m, 1H), 1.07 (d, 3H), 0.88 (t, 3H).

[00914] **Example 148**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine and

[00915] **Example 149**, rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine



[00916] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-3,5-dimethylpiperidine-1-carboxylate*

[00917] The title compound was obtained as a brown oil (400 mg, 70%) from tert-butyl (3R)-3-hydroxypiperidine-1-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, Step 1. LCMS $m/z = 286$ $[M+56+H]^+$.

[00918] Step 2: *Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3,5-dimethylpiperidine-1-carboxylate*

[00919] The title compound was obtained as a brown oil (300 mg, 56%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar procedure to that described in Example 37, Step 2. The product was further separated by chiral Prep-SFC (Column: IC 20*250mm, 10 μ m (Daicel), Column temperature: 35 $^{\circ}$ C, Mobile phase: CO_2 /IPA(0.5% Methanol Ammonia) = 75/25, Flow rate: 100 g/min, Back pressure: 100 bar) to give peak 1 (100 mg, 18%) and peak 2 (70 mg, 13%) as white solids. LCMS $m/z = 455$ $[M+H]^+$.

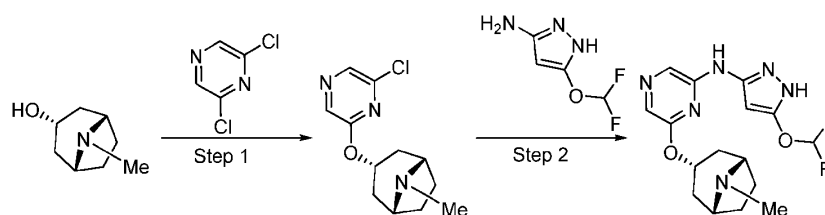
[00920] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine (Example 148)*

[00921] To a solution of the compound of Peak 1, Step 2 (100 mg, 220 μ mol) in DCM (5.0 mL) was added 4M HCl/dioxane (2.0 mL) at 0 $^{\circ}$ C under N_2 . The reaction mixture was allowed to warm to rt and stirred for 5 h, then adjusted to pH~10 with 7M NH_3 in MeOH. The resulting precipitate was filtered off and the filtrate and washings were concentrated under reduced pressure. The crude was purified by prep-HPLC (Method A) to afford the title compound (17.8 mg, 22%) as a yellow solid. LCMS $m/z = 355$ $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 12.11 (br s, 1H), 10.08 (br s, 1H), 7.77 (s, 1H), 7.63 (s, 1H), 7.24 (t, 1H), 6.08 (s, 1H), 4.66 (t, 1H), 3.00-2.94 (m, 2H), 2.28-2.22 (m, 2H), 1.74-1.64 (m, 2H), 0.76 (d, 6H).

[00922] Step 4: *Synthesis of rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,5R)-3,5-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine (Example 149)*

[00923] The title compound was obtained as a yellow solid (3.4 mg, 6%) from the compound of Peak 2 following a similar procedure to that described in Step 3. LCMS $m/z = 355$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.13 (br s, 1H), 10.11 (br s, 1H), 7.75 (s, 1H), 7.65 (s, 1H), 7.26 (t, 1H), 5.99 (s, 1H), 5.39-5.36 (m, 1H), 2.71-2.65 (m, 2H), 2.57-2.54 (m, 2H), 1.92-1.88 (m, 2H), 0.72 (d, 6H).

[00924] **Example 150**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine



[00925] Step 1: *Synthesis of (1R,3r,5S)-3-((6-chloropyrazin-2-yl)oxy)-8-methyl-8-azabicyclo[3.2.1]octane*

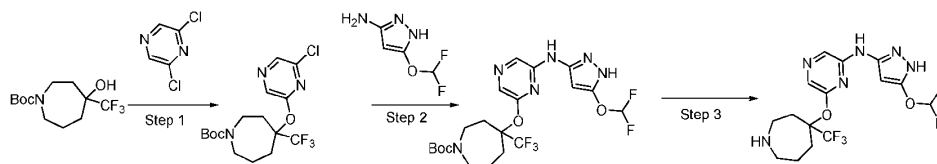
[00926] The title compound was obtained as a yellow oil (120 mg, 45%) from (1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS $m/z = 254$ $[M+H]^+$.

[00927] Step 2: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyrazin-2-amine*

[00928] The title compound was obtained as a white solid (35.6 mg, 20%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar procedure to that described in Example 19 and 20, step 2. LCMS $m/z = 367$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.88 (br s, 1H), 9.96 (br s, 1H), 7.76 (s, 1H), 7.57 (s, 1H), 7.24 (t, 1H), 5.93 (s, 1H), 5.17-5.12 (m, 1H), 3.15-3.11 (m, 2H), 2.32-2.24 (m, 3H), 2.12-2.08 (m, 2H), 1.96 (s, 3H), 1.83-1.80 (m, 2H).

[00929] **Example 151**. See Example 10.

[00930] **Example 152**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((4-(trifluoromethyl)azepan-4-yl)oxy)pyrazin-2-amine



[00931] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-4-(trifluoromethyl)azepane-1-carboxylate*

[00932] A mixture of tert-butyl 4-hydroxy-4-(trifluoromethyl)azepane-1-carboxylate (424 mg, 1.50 mmol), 2,6-dichloropyrazine (150 mg, 1.00 mmol) and t-BuOK (150 mg, 2.00 mmol) in NMP (10.0 mL) was stirred at 90°C for 15 h. The reaction mixture was cooled to rt and diluted with EtOAc, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel eluting with PE/EtOAc (1/4) to afford the title compound (183 mg, 31%) as a white solid. LCMS m/z = 340 $[M-56+H]^+$.

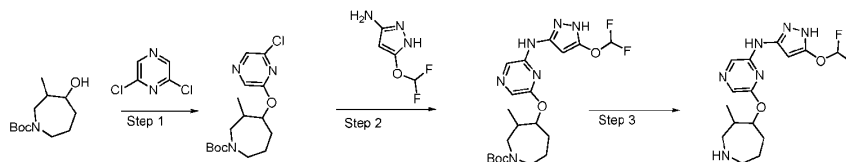
[00933] Step 2: *Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-4-(trifluoromethyl)azepane-1-carboxylate*

[00934] The title compound was obtained as a yellow solid (96 mg, 57%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 19 and 20, step 2. LCMS m/z = 509 $[M+H]^+$.

[00935] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((4-(trifluoromethyl)azepan-4-yl)oxy)pyrazin-2-amine*

[00936] The title compound was obtained as a white solid (4.2 mg, 8%) from the compound of Step 2 following a similar procedure to that described in Example 148 and 149, step 3. LCMS m/z = 409 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 12.26 (br s, 1H), 10.02 (br s, 1H), 8.03 (s, 1H), 7.71 (s, 1H), 7.25 (t, 1H), 5.93 (s, 1H), 3.28-3.27 (m, 2H), 3.17-3.11 (m, 2H), 2.61-2.57 (m, 2H), 2.38-2.33 (m, 2H), 2.18-2.10 (m, 1H), 1.92-1.79 (m, 2H).

[00937] **Example 153**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3-methylazepan-4-yl)oxy)pyrazin-2-amine



[00938] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate*

[00939] The title compound was obtained (crude, 320 mg, 77%) from tert-butyl 4-hydroxy-3-methylazepane-1-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 5, Step 1. LCMS m/z = 286 $[M-56+H]^+$.

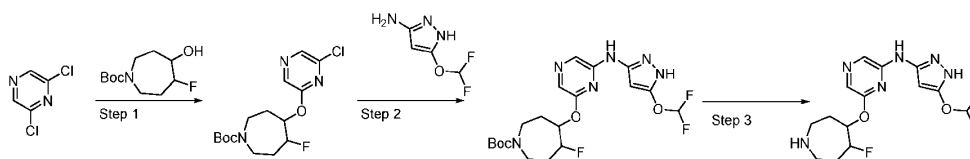
[00940] Step 2: *Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-3-methylazepane-1-carboxylate*

[00941] The title compound was obtained as a yellow solid (320 mg, 75%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar procedure to that described in Example 19 and 20, Step 2. LCMS m/z = 455 $[M+H]^+$.

[00942] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3-methylazepan-4-yl)oxy)pyrazin-2-amine*

[00943] The title compound was obtained as a white solid (49.7 mg, 32%) from the compound of Step 2 following a similar procedure to that described in Example 148 and 149, step 3. LCMS m/z = 355 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.94 (br s, 1H), 10.01 (s, 1H), 8.51 (br s, 1H), 7.80 (s, 1H), 7.66 (s, 1H), 7.26 (t, 1H), 5.94 (s, 1H), 5.23-2.19 (m, 1H), 3.15-3.05 (m, 3H), 3.02-2.98 (m, 1H), 2.40-2.33 (m, 1H), 2.16-2.07 (m, 1H), 1.91-1.76 (m, 2H), 1.73-1.65 (m, 1H), 0.98 (d, 3H).

[00944] **Example 154**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-fluoroazepan-4-yl)oxy)pyrazin-2-amine



[00945] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-5-fluoroazepan-1-carboxylate*

[00946] The title compound was obtained as a yellow oil (500 mg, 85%) from tert-butyl 4-fluoro-5-hydroxyazepan-1-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, Step 1. LCMS m/z = 290 $[M-56+H]^+$.

[00947] Step 2: *Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-5-fluoroazepan-1-carboxylate*

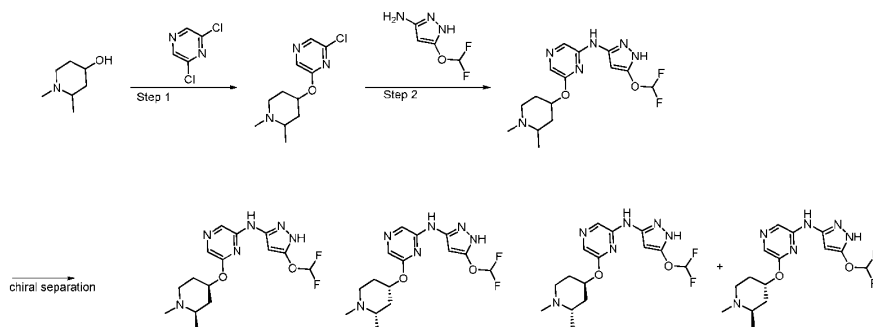
[00948] The title compound was obtained as a brown oil (400 mg, 61%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 19 and 20, step 2. LCMS m/z = 459 $[M+H]^+$.

[00949] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-fluoroazepan-4-yl)oxy)pyrazin-2-amine*

[00950] The title compound was obtained as a yellow solid (25.9 mg, 39%) from the compound of Step 2 following a similar procedure to that described in Example 148 and 149, Step 3. LCMS m/z = 359 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.06 (br s, 1H), 10.03 (br s, 1H), 7.81 (s, 1H), 7.65-7.61 (m, 1H), 7.25 (t, 1H), 5.99-5.93 (m, 1H), 5.36-5.29 (m, 1H), 5.02-4.85 (m, 1H), 2.94-2.85 (m, 4H), 2.17-2.04 (m, 3H), 1.98-1.80 (m, 2H).

[00951] **Example 155**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine and

[00952] Example 156, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine



[00953] Step 1: *Synthesis of 2-chloro-6-((1,2-dimethylpiperidin-4-yl)oxy)pyrazine*

[00954] The title compound was obtained as a yellow solid (200 mg, 26%) from 1,2-dimethylpiperidin-4-ol and 2,6-dichloropyrazine following a similar procedure to that described in Example 152, step 1. LCMS $m/z = 242$ $[M+H]^+$.

[00955] Step 2: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4R)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-1,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine*

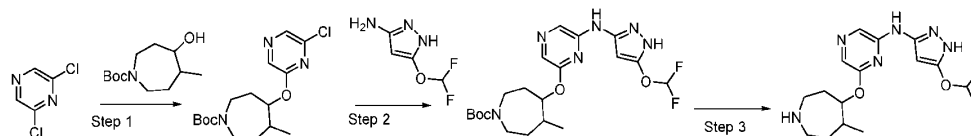
[00956] The racemates of the title compounds were obtained as a yellow solid (200 mg, 26%) from the title compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar procedure to that described in Example 37, Step 2.

[00957] Chiral Prep-SFC (Method A, gradient: 70/30) to give Peak 1 (39.5 mg, 13%) as a yellow solid and Peak 2 (38.2 mg, 13%) as a yellow solid.

[00958] Peak 1, **Example 155**: LCMS $m/z = 355$ $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.99 (br s, 1H), 10.00 (s, 1H), 7.78 (s, 1H), 7.57 (s, 1H), 7.24 (t, 1H), 5.99 (s, 1H), 4.92-4.85 (m, 1H), 2.92-2.86 (m, 1H), 2.21 (s, 3H), 2.21-2.04 (m, 2H), 2.08-2.04 (m, 2H), 1.64-1.57 (m, 1H), 1.37-1.31 (m, 1H), 1.05 (d, 3H).

[00959] Peak 2: **Example 156**: LCMS $m/z = 355$ $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.95 (br s, 1H), 10.00 (s, 1H), 7.78 (s, 1H), 7.57 (s, 1H), 7.24 (t, 1H), 5.98 (s, 1H), 4.92-4.85 (m, 1H), 2.92-2.86 (m, 1H), 2.22 (s, 3H), 2.22-2.04 (m, 2H), 2.08-2.04 (m, 2H), 1.64-1.57 (m, 1H), 1.37-1.31 (m, 1H), 1.06 (d, 3H).

[00960] **Example 157**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-methylazepan-4-yl)oxy)pyrazin-2-amine



[00961] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-5-methylazepan-1-carboxylate*

[00962] The title compound was obtained as a colourless oil (280 mg, 36%) from tert-butyl 4-hydroxy-5-methylazepan-1-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS m/z = 286 $[M-56+H]^+$.

[00963] Step 2: *Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-5-methylazepan-1-carboxylate*

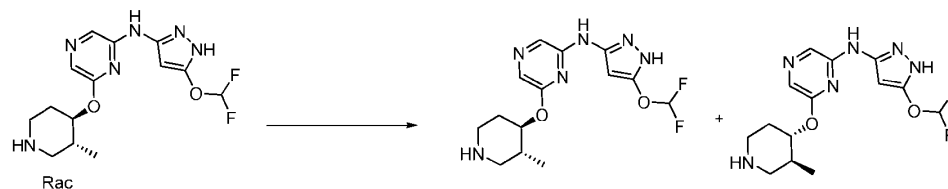
[00964] The title compound was obtained as a colourless oil (150 mg, 45%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 19 and 20, step 2. LCMS m/z = 455 $[M+H]^+$.

[00965] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((5-methylazepan-4-yl)oxy)pyrazin-2-amine*

[00966] The title compound was obtained as a brown solid (30 mg, 39%) from the compound of Step 2 following a similar procedure to that described in Example 148 and 149, step 3. LCMS m/z = 355 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 10.31 (br s, 1H), 7.76-7.74 (m, 1H), 7.60-7.57 (m, 1H), 7.25 (t, 1H), 5.98-5.94 (m, 1H), 5.21-4.83 (m, 1H), 3.38-3.31 (m, 3H), 2.92-2.80 (m, 1H), 2.80-2.73 (m, 2H), 2.23-2.15 (m, 1H), -2.15-1.95 (m, 1H), 1.95-1.78 (m, 1H), 1.77-1.63 (m, 1H), 1.60-1.52 (m, 1H), 0.99-0.95 (m, 3H).

[00967] **Example 158**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine and

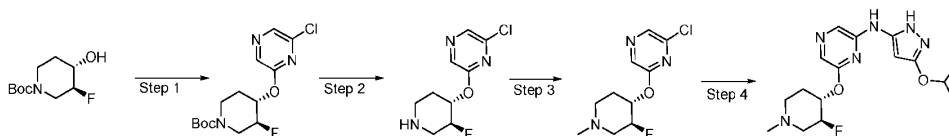
[00968] **Example 159**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3S,4S)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00969] The title compound of Example 172 (105.5 mg) was separated by chiral Prep-SFC (Method F, gradient: 80/20) to give Peak 1, **Example 158** (28.4 mg). LCMS $m/z = 341$ $[M+H]^+$ 1H NMR (500 MHz, DMSO- d_6) δ ppm 12.08 (br s, 1H), 10.18 (s, 1H), 7.80 (s, 1H), 7.61 (s, 1H), 7.25 (t, 1H), 5.97 (s, 1H), 4.76-4.73 (m, 1H), 3.24-3.15 (m, 2H), 2.82-2.77 (m, 1H), 2.65-2.61 (m, 1H), 2.49-2.23 (m, 1H), 2.24-2.22 (m, 1H), 2.01-1.97 (m, 1H), 1.64-1.57 (m, 1H), 0.94 (d, 3H)

[00970] and Peak 2, **Example 159** (34.0 mg) as a white solid. 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.97 (br s, 1H), 10.10 (s, 1H), 7.82 (s, 1H), 7.64 (s, 1H), 7.27 (t, 1H), 5.96 (s, 1H), 4.83-4.78 (m, 1H), 3.29-3.26 (m, 2H), 2.94-2.89 (m, 1H), 2.82-2.77 (m, 1H), 2.31-2.28 (m, 1H), 2.11-2.05 (m, 1H), 1.75-1.65 (m, 1H), 0.97 (d, 3H).

[00971] **Example 160**, N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-(((3S,4S)-3-fluoro-1-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[00972] Step 1: *Synthesis of tert-butyl (3S,4S)-4-((6-chloropyrazin-2-yl)oxy)-3-fluoropiperidine-1-carboxylate*

[00973] The title compound was obtained as a yellow oil (362 mg, 96%) from tert-butyl (3S,4S)-3-fluoro-4-hydroxypiperidine-1-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS $m/z = 276$ $[M-56+H]^+$.

[00974] Step 2: *Synthesis of 2-chloro-6-(((3S,4S)-3-fluoropiperidin-4-yl)oxy)pyrazine*

[00975] To mixture of the compound of Step 1 (362 mg, 1.09 mmol) in DCM (2.0 mL) was added 4M HCl/dioxane (2.0 mL) at 0°C under N_2 . After addition, the reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was concentrated under reduced pressure to give the crude product (324 mg) as a yellow solid. LCMS $m/z = 232$ $[M+H]^+$.

[00976] Step 3: *Synthesis of 2-chloro-6-(((3S,4S)-3-fluoro-1-methylpiperidin-4-yl)oxy)pyrazine*

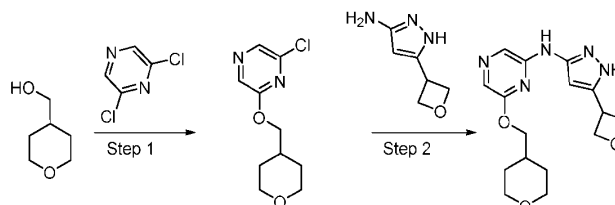
[00977] The title compound was obtained (170 mg, 51%) from the compound of Step 2 following a similar procedure to that described in Example 11. LCMS $m/z = 246$ $[M+H]^+$.

[00978] Step 4: *Synthesis of N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-(((3S,4S)-3-fluoro-1-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

[00979] The title compound was obtained as a white solid (86.8 mg, 35%) from the compound of Step 3 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 37, step 2. LCMS $m/z = 359$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 11.96 (br s, 1H), 10.03 (br s, 1H), 7.81 (s, 1H), 7.65 (s, 1H), 7.26 (t, 1H), 5.97 (s, 1H), 5.10-5.00 (m, 1H),

4.82-4.61 (m, 1H), 3.10-3.01 (m, 1H), 2.72-2.65 (m, 1H), 2.25 (s, 3H), 2.25-2.05 (m, 3H), 1.68-1.55 (m, 1H).

[00980] **Example 161**, N-(5-(oxetan-3-yl)-1H-pyrazol-3-yl)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyrazin-2-amine



[00981] Step 1: *Synthesis of 2-chloro-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyrazine*

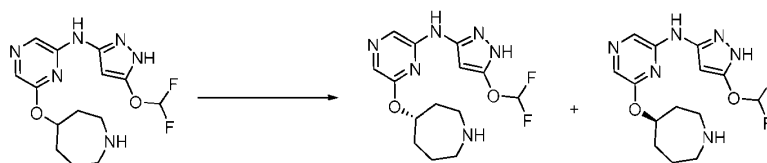
[00982] The title compound was obtained as a yellow solid (78 mg, 40%) from (tetrahydro-2H-pyran-4-yl)methanol and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS $m/z = 229$ $[M+H]^+$.

[00983] Step 2: *Synthesis of N-(5-(oxetan-3-yl)-1H-pyrazol-3-yl)-6-((tetrahydro-2H-pyran-4-yl)methoxy)pyrazin-2-amine*

[00984] The title compound was obtained as a white solid (56.1 mg, 35%) from the compound of Step 1 and 5-(oxetan-3-yl)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 19 and 20, Step 2. LCMS $m/z = 332$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.19 (br s, 1H), 9.67 (br s, 1H), 8.04 (s, 1H), 7.52 (s, 1H), 6.47 (s, 1H), 4.90-4.87 (m, 2H), 4.65-4.61 (m, 2H), 4.29-4.25 (m, 2H), 4.18-4.16 (m, 2H), 3.89-3.85 (m, 2H), 3.32-3.29 (m, 2H), 2.07-2.05 (m, 1H), 1.68-1.65 (m, 2H), 1.36-1.30 (m, 2H).

[00985] **Example 162**, (S)-6-(azepan-4-yloxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (R)-6-(azepan-4-yloxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine and

[00986] **Example 163**, (R)-6-(azepan-4-yloxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-(azepan-4-yloxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



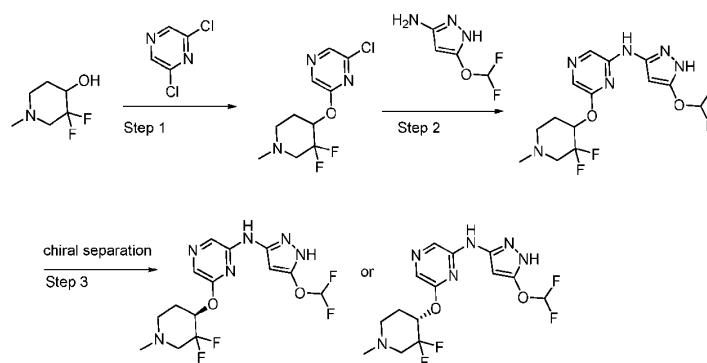
[00987] The compound of Example 178 (62.5 mg) was separated by chiral Prep-SFC (Column: AD 20*250mm, 10 μ m (Daicel), Column temperature: 35°C, Mobile phase: CO₂/EtOH (1.0%MeOH/NH₃) = 70/30, Flow rate: 100 g/min, Back pressure: 100 bar) to give peak 1, **Example 162**, 47.2 mg, white solid, LCMS $m/z = 341$ $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.95

(br s, 1H), 10.06 (s, 1H), 8.77 (br s, 1H), 7.80 (s, 1H), 7.60 (s, 1H), 7.27 (t, 1H), 5.93 (s, 1H), 5.24-5.23 (m, 1H), 3.22-3.18 (m, 1H), 3.13-3.08 (m, 3H), 2.24-2.19 (m, 1H), 2.12-2.04 (m, 2H), 1.93-1.87 (m, 2H), 1.74-1.70 (m, 1H);

[00988] and peak 2, **Example 163**, 33.9 mg, white solid, LCMS $m/z = 341$ $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 11.95 (br s, 1H), 10.06 (s, 1H), 8.77 (br s, 1H), 7.80 (s, 1H), 7.60 (s, 1H), 7.27 (t, 1H), 5.93 (s, 1H), 5.24-5.23 (m, 1H), 3.22-3.18 (m, 1H), 3.13-3.08 (m, 3H), 2.24-2.19 (m, 1H), 2.12-2.04 (m, 2H), 1.93-1.87 (m, 2H), 1.74-1.70 (m, 1H).

[00989] **Example 164**, 6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine

[00990] **Example 165**, (R)-6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



[00991] Step 1: *Synthesis of 2-chloro-6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)pyrazine*

[00992] The title compound was obtained as a yellow oil (200 mg, 76%) from 3,3-difluoro-1-methylpiperidin-4-ol and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS $m/z = 264$ $[M+H]^+$.

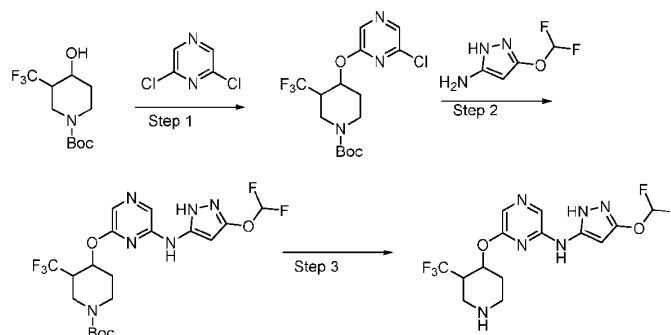
[00993] Step 2: *Synthesis of 6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

[00994] The title compound, **Example 164**, was obtained as a white solid (73.6 mg, 51%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 37, Step 2 except Prep-HPLC (Method C). LCMS $m/z = 377$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.05 (br s, 1H), 10.17 (br s, 1H), 7.87 (s, 1H), 7.70 (s, 1H), 7.27 (t, 1H), 5.94 (s, 1H), 5.37-5.29 (m, 1H), 3.01-2.92 (m, 1H), 2.66-2.53 (m, 2H), 2.35-2.25 (m, 1H), 2.26 (s, 3H), 2.11-2.06 (m, 1H), 1.88-1.81 (m, 1H).

[00995] Step 3: *Synthesis of (R)-6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

[00996] The compound from Step 2 was separated by Chiral Prep-SFC (Method B, gradient: 70/30) to give the title compound, Peak 2, **Example 165**, as a white solid. LCMS $m/z = 377$ $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ ppm 12.01 (br s, 1H), 10.14 (br s, 1H), 7.86 (s, 1H), 7.69 (s, 1H), 7.26 (t, 1H), 5.93 (s, 1H), 5.35-5.29 (m, 1H), 2.97-2.94 (m, 1H), 2.65-2.62 (m, 2H), 2.34-2.28 (m, 1H), 2.27 (s, 3H), 2.10-2.06 (m, 1H), 1.88-1.82 (m, 1H).

[00997] **Example 166**, N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-((3-(trifluoromethyl)piperidin-4-yl)oxy)pyrazin-2-amine



[00998] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-3-(trifluoromethyl)piperidine-1-carboxylate*

[00999] Tert-butyl 4-hydroxy-3-(trifluoromethyl)piperidine-1-carboxylate (0.44 mmol) was dissolved in THF (4 mL), NaH (100 mg, 2.40 mmol, 60% w/mineral oil) was added. The reaction mixture was shaken at 30°C for 0.5 h, then 2,6-dichloropyrazine (59.6 mg, 0.40 mmol) was added. The reaction mixture was shaken at 30°C for 2 h. Water was added (3 mL) and the mixture was extracted with EtOAc. The organic layer was collected and dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude product was used into the next step without further purification.

[001000] Step 2: *Synthesis of tert-butyl 4-((6-((3-(difluoromethoxy)-1H-pyrazol-5-yl)amino)pyrazin-2-yl)oxy)-3-(trifluoromethyl)piperidine-1-carboxylate*

[001001] The crude compound from Step 1 (0.40 mmol, 1.0 eq), 5-(difluoromethoxy)-1H-pyrazol-3-amine (89.4 mg, 0.60 mmol), KOAc (117.6 mg, 1.20 mmol) and BrettPhos Pd G3 (18.12 mg, 0.02 mmol) were combined in t-AmOH (3.0 mL) at rt under N_2 . The resulting mixture was stirred at 100°C for 2 h under N_2 . The reaction mixture was diluted with EtOAc (5 mL), washed with water (3 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 , filtered and evaporated to afford crude product.

[001002] Step 3: *N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-((3-(trifluoromethyl)piperidin-4-yl)oxy)pyrazin-2-amine (Example 166)*

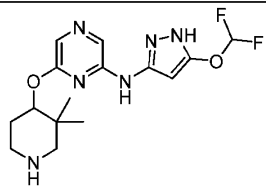
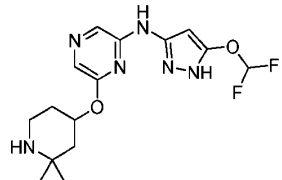
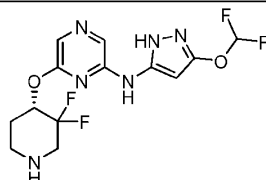
[001003] The crude compound from Step 2 (0.40 mmol) was dissolved in DCM (3.0 mL), then TFA (1.0 mL) was added at rt. The resulting mixture was stirred at 30°C for 2 h. The mixture was

concentrated under reduced pressure. The crude product was purified by prep-HPLC (Method D).

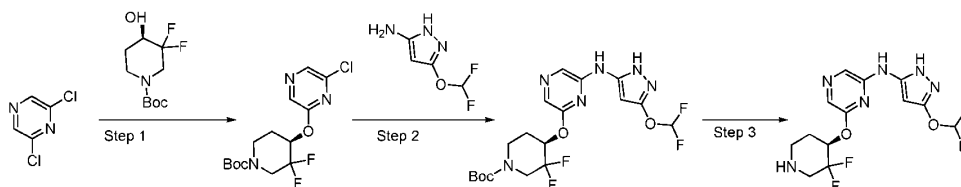
LCMS $m/z = 395$ $[M+H]^+$.

[001004] Examples 167 to 169

[001005] The compounds in the following table were prepared from the appropriate alcohol, following the 3 step procedure described in Example 166.

Example No.	Structure, Name	Starting Material (SM), Data
167	 N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	SM: tert-butyl 4-hydroxy-3,3-dimethylpiperidine-1-carboxylate; LCMS $m/z = 355$ $[M+H]^+$
168	 N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,2-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	SM: tert-butyl 4-hydroxy-2,2-dimethylpiperidine-1-carboxylate; LCMS $m/z = 355$ $[M+H]^+$
169	 (S)-N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-((3,3-difluoropiperidin-4-yl)oxy)pyrazin-2-amine	SM: tert-butyl (S)-4-hydroxy-3,3-difluoropiperidine-1-carboxylate; LCMS $m/z = 363$ $[M+H]^+$

[001006] **Example 170**, (R)-N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-((3,3-difluoropiperidin-4-yl)oxy)pyrazin-2-amine



[001007] Step 1: *Synthesis of tert-butyl (R)-4-((6-chloropyrazin-2-yl)oxy)-3,3-difluoropiperidine-1-carboxylate*

[001008] The title compound was obtained as a yellow oil (200 mg, 42%) from tert-butyl (4R)-3,3-difluoro-4-hydroxypiperidine-1-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, Step 1. LCMS $m/z = 294$ $[M+H]^+$.

[001009] Step 2: *Synthesis of tert-butyl (R)-4-((6-((3-(difluoromethoxy)-1H-pyrazol-5-yl)amino)pyrazin-2-yl)oxy)-3,3-difluoropiperidine-1-carboxylate*

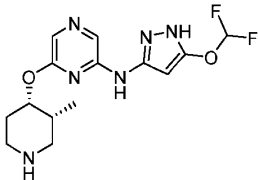
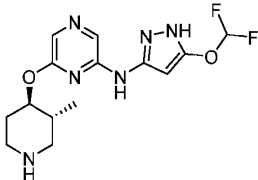
[001010] The title compound was obtained as a yellow oil (350 mg, 53%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 19 and 20, Step 2. LCMS $m/z = 463$ $[M+H]^+$.

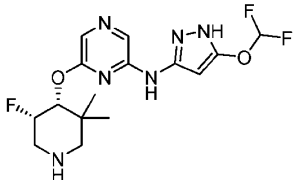
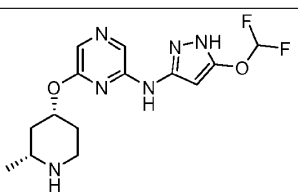
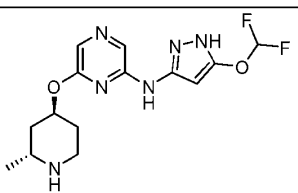
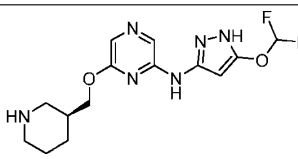
[001011] Step 3: *Synthesis of (R)-N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-((3,3-difluoropiperidin-4-yl)oxy)pyrazin-2-amine*

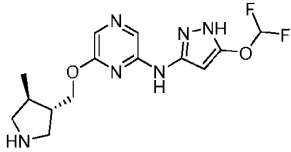
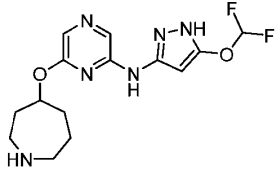
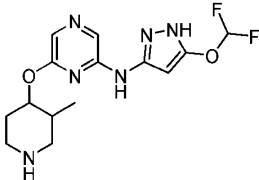
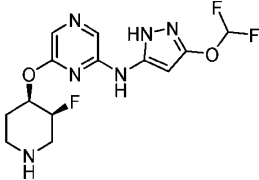
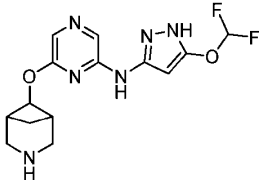
[001012] The title compound was obtained as a yellow solid (145 mg, 53%) from the compound of Step 2 following a similar procedure to that described in Example 2, Step 3 except Prep-HPLC (Method C). LCMS $m/z = 363$ $[M+H]^+$. 1H NMR (500 MHz, $CDCl_3$) δ ppm 12.00 (br s, 1H), 10.12 (br s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.27 (t, 1H), 5.94 (s, 1H), 5.46-5.41 (m, 1H), 3.32-3.25 (m, 2H), 3.10-2.96 (m, 2H), 2.77-2.71 (m, 1H), 2.13-2.11 (m, 1H), 1.82-1.79 (m, 1H).

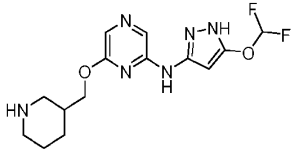
[001013] Examples 171 to 182

[001014] Examples 171 to 182 were prepared using 3 step procedure described for Example 166.

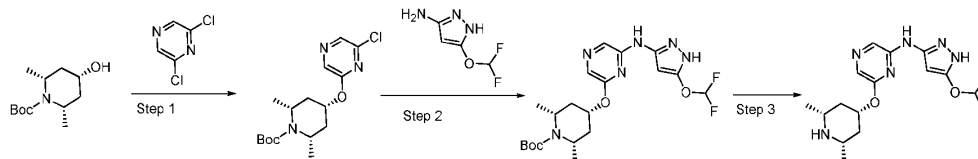
Example no	Structure, Name	Starting material (SM), Data
171	 rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4S)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine	SM: rac-tert-butyl (3R,4S)-4-hydroxy-3-methylpiperidine-1-carboxylate, LCMS $m/z = 395$ $[M+H]^+$
172	 rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine	SM: rac-tert-butyl (3R,4R)-4-hydroxy-3-methylpiperidine-1-carboxylate, LCMS $m/z = 395$ $[M+H]^+$

	rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-3-methylpiperidin-4-yl)oxy)pyrazin-2-amine	
173	 rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((4R,5S)-5-fluoro-3,3-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine	SM: rac-tert-butyl (4R,5S)-4-hydroxy-5-fluoro-3,3-dimethylpiperidine-1-carboxylate, LCMS m/z = 373 [M+H] ⁺
174	 N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4S)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine	SM: tert-butyl (2S,4S)-4-hydroxy-2-methylpiperidine-1-carboxylate, LCMS m/z = 341 [M+H] ⁺
175	 N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4S)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine	SM: tert-butyl (2R,4S)-4-hydroxy-2-methylpiperidine-1-carboxylate, LCMS m/z = 341 [M+H] ⁺
176	 (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-ylmethoxy)pyrazin-2-amine	SM: tert-butyl (S)-3-(hydroxymethyl)piperidine-1-carboxylate, LCMS m/z = 341 [M+H] ⁺

177	 rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((3R,4R)-4-methylpyrrolidin-3-yl)methoxy)pyrazin-2-amine	SM: rac-tert-butyl (3R,4R)-3-(hydroxymethyl)-4-methylpyrrolidine-1-carboxylate, LCMS m/z = 341 [M+H] ⁺
178	 6-(azepan-4-yloxy)-N-[5-(difluoromethoxy)-1H-pyrazol-3-yl]pyrazin-2-amine	SM: tert-butyl 4-hydroxyazepane-1-carboxylate, LCMS m/z = 341 [M+H] ⁺
179	 N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3-methylpiperidin-4-yl)oxy)pyrazin-2-amine	SM: tert-butyl 4-hydroxy-3-methylpiperidine-1-carboxylate; LCMS m/z = 341 [M+H] ⁺
180	 N-(3-(difluoromethoxy)-1H-pyrazol-5-yl)-6-(((3S,4R)-3-fluoropiperidin-4-yl)oxy)pyrazin-2-amine	SM: tert-butyl (3S,4R)-4-hydroxy-3-fluoropiperidine-1-carboxylate, LCMS m/z = 345 [M+H] ⁺
181	 6-((3-azabicyclo[3.1.1]heptan-6-yl)oxy)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine	SM: tert-butyl 6-hydroxy-3-azabicyclo[3.1.1]heptane-3-carboxylate, LCMS m/z = 339 [M+H] ⁺

182	 N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-3-ylmethoxy)pyrazin-2-amine	tert-butyl 3-(hydroxymethyl)piperidine-1-carboxylate, LCMS m/z = 355 [M+H] ⁺
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[001015] Example 183, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2S,4r,6R)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine



[001016] Step 1: *Synthesis of tert-butyl (2R,4r,6S)-4-((6-chloropyrazin-2-yl)oxy)-2,6-dimethylpiperidine-1-carboxylate*

[001017] The title compound was obtained as a yellow oil (150 mg, 32%) from tert-butyl (2R,4r,6S)-4-hydroxy-2,6-dimethylpiperidine-1-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS m/z = 286 [M-56+H]⁺.

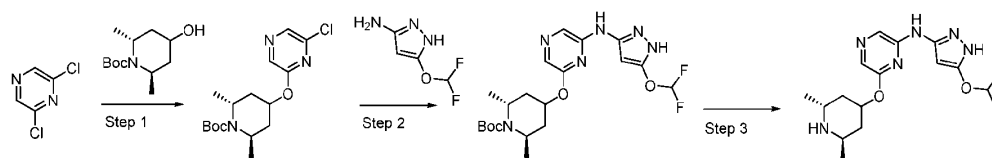
[001018] Step 2: *Synthesis of tert-butyl (2R,4r,6S)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2,6-dimethylpiperidine-1-carboxylate*

[001019] The title compound was obtained as a yellow solid (100 mg, 50%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 19 and 20, Step 2. LCMS m/z = 455 [M+H]⁺.

[001020] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,4r,6S)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine*

[001021] The title compound was obtained as a white solid (6.9 mg, 17%) from the compound of Step 2 following a similar procedure to that described in Example 2, Step 3 except Prep-HPLC (Method C). LCMS m/z = 355 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.01 (br s, 1H), 10.02 (br s, 1H), 7.77 (s, 1H), 7.56 (s, 1H), 7.23 (t, 1H), 5.99 (s, 1H), 4.96-4.90 (m, 1H), 2.76-2.70 (m, 2H), 2.08-2.01 (m, 2H), 1.11-1.03 (m, 2H), 1.03 (d, 6H).

[001022] Example 184, Rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(((2R,6R)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine



[001023] Step 1: *Synthesis of rac tert-butyl (2R,6R)-4-((6-chloropyrazin-2-yl)oxy)-2,6-dimethylpiperidine-1-carboxylate*

[001024] The title compound was obtained (crude, 250 mg) from rac tert-butyl (2R,6R)-4-hydroxy-2,6-dimethylpiperidine-1-carboxylate and 2,6-dichloropyrazine following a similar procedure to that described in Example 5, step 1. LCMS $m/z = 286$ $[M+56+H]^+$.

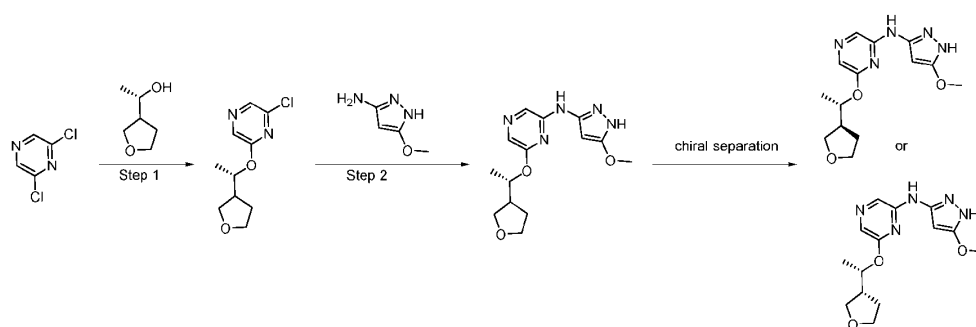
[001025] Step 2: *Synthesis of Rac tert-butyl (2R,6R)-4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2,6-dimethylpiperidine-1-carboxylate*

[001026] The title compound was obtained as a brown oil (160 mg, 45%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 19 and 20, Step 2. LCMS $m/z = 455$ $[M+H]^+$.

[001027] Step 3: *Synthesis of rac-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2R,6R)-2,6-dimethylpiperidin-4-yl)oxy)pyrazin-2-amine*

[001028] The title compound was obtained as a yellow solid (61.2 mg, 49%) from the compound of Step 2 following a similar procedure to that described in Example 2, Step 3. LCMS $m/z = 355$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.04 (br s, 1H), 10.03 (s, 1H), 7.76 (s, 1H), 7.55 (s, 1H), 7.22 (t, 1H), 5.99 (s, 1H), 5.28-5.18 (m, 1H), 3.30-3.20 (m, 2H), 3.06-3.00 (m, 1H), 2.04-1.95 (m, 1H), 1.87-1.82 (m, 1H), 1.61-1.52 (m, 1H), 1.18-1.10 (m, 1H), 1.15 (d, 3H), 1.02 (d, 3H).

[001029] **Example 185**, N-(5-methoxy-1H-pyrazol-3-yl)-6-((S)-1-((S)-tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine or N-(5-methoxy-1H-pyrazol-3-yl)-6-((S)-1-((R)-tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine



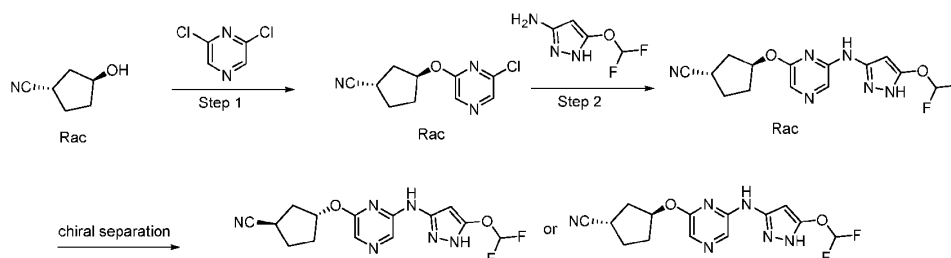
[001030] Step 1: *Synthesis of 2-chloro-6-((1S)-1-(tetrahydrofuran-3-yl)ethoxy)pyrazine*

[001031] The title compound was obtained as a yellow oil (130 mg, 85%) from (1S)-1-(tetrahydrofuran-3-yl)ethan-1-ol and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS $m/z = 229$ $[M+H]^+$.

[001032] Step 2: Synthesis of *N*-(5-methoxy-1H-pyrazol-3-yl)-6-((*S*)-1-((*S*)-tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine or *N*-(5-methoxy-1H-pyrazol-3-yl)-6-((*S*)-1-((*R*)-tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine

[001033] *N*-(5-methoxy-1H-pyrazol-3-yl)-6-((1S)-1-(tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine was obtained as a white solid (100 mg) from the compound of Step 1 and 5-methoxy-1H-pyrazol-3-amine, following a similar procedure to that described in Example 37, Step 2. Chiral Prep-SFC (Method F, gradient: 70/30) yielded peak 1, the title compound, as a white solid (26.5 mg, 15%). LCMS $m/z = 306$ $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 11.87-11.23 (m, 1H), 9.85-9.52 (m, 1H), 8.03-7.72 (m, 1H), 7.56-7.49 (m, 1H), 5.80-5.58 (m, 1H), 5.10-5.03 (m, 1H), 3.80-3.70 (m, 5H), 3.65-3.60 (m, 1H), 3.51-3.44 (m, 1H), 2.56-2.51 (m, 1H), 2.02-1.93 (m, 1H), 1.76-1.67 (m, 1H), 1.27 (d, 3H).

[001034] **Example 186**, (1R,3R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)cyclopentane-1-carbonitrile or (1S,3S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)cyclopentane-1-carbonitrile



[001035] Step 1: Synthesis of *rac*-(1S,3S)-3-((6-chloropyrazin-2-yl)oxy)cyclopentane-1-carbonitrile

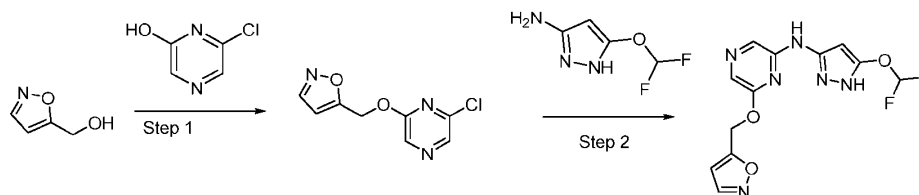
[001036] The title compound was obtained as a white solid (300 mg, 30%) from *trans*-3-hydroxycyclopentane-1-carbonitrile and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, Step 1. LCMS $m/z = 224$ $[M+H]^+$.

[001037] Step 2: Synthesis of (1R,3R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)cyclopentane-1-carbonitrile or (1S,3S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)cyclopentane-1-carbonitrile

[001038] *Rac*-(1S,3S)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)cyclopentane-1-carbonitrile was obtained as a white solid (120 mg) from the compound of step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 37, Step 2. The racemic product was separated by chiral Prep-SFC (Column: AD 20*250mm, 10 μm (Daicel), Column temperature: 35°C, Mobile phase: CO₂/MeOH (0.2% Methanol

Ammonia) = 75/25, Flow rate: 100 g/min, Back pressure: 100 bar) to afford peak 1, the title compound as a white solid (53.9 mg, 45%). LCMS $m/z = 337$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.91 (br s, 1H), 10.02 (br s, 1H), 7.78 (s, 1H), 7.57 (s, 1H), 7.27 (t, 1H), 5.96 (s, 1H), 5.46-5.42 (m, 1H), 3.24-3.17 (m, 1H), 2.30-2.12 (m, 4H), 1.90-1.80 (m, 2H).

[001039] Example 187, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(isoxazol-5-ylmethoxy)pyrazin-2-amine



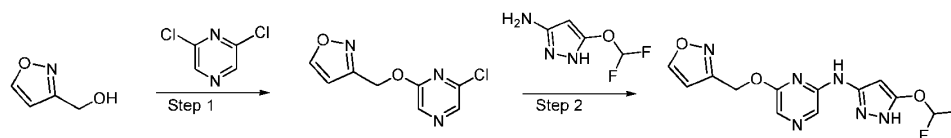
[001040] Step 1: *Synthesis of 5-(((6-chloropyrazin-2-yl)oxy)methyl)isoxazole*

[001041] The title compound was obtained as a yellow solid, 60 mg, 57%, from (1,2-oxazol-5-yl)methanol and 6-chloropyrazin-2-ol, following the procedure described in example 41, step 2. LCMS $m/z = 212$ $[M+H]^+$.

[001042] Step 2: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(isoxazol-5-ylmethoxy)pyrazin-2-amine*

[001043] To a mixture of the compound of Step 1 (60 mg, 0.28 mmol), 5-(difluoromethoxy)-1H-pyrazol-3-amine (50.6 mg, 340 μ mol) in dioxane (3.0 mL) was added KOAc (83.4 mg, 850 μ mol) and BrettPhos Pd G₄ (30 mg, 19.5 μ mol) at rt under N₂ and the reaction mixture was heated in a microwave at 100°C for 10 min. The reaction mixture was concentrated to dryness to give the crude which was purified by Prep-HPLC (Method A) to give the title product (7.0 mg, 8%) as a yellow solid. LCMS $m/z = 325$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 8.62-8.57 (m, 1H), 7.87-7.84 (m, 1H), 7.70 (s, 1H), 7.27 (t, 1H), 6.57 (s, 1H), 5.94 (s, 1H), 5.62-5.55 (m, 2H).

[001044] Example 188, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(isoxazol-3-ylmethoxy)pyrazin-2-amine



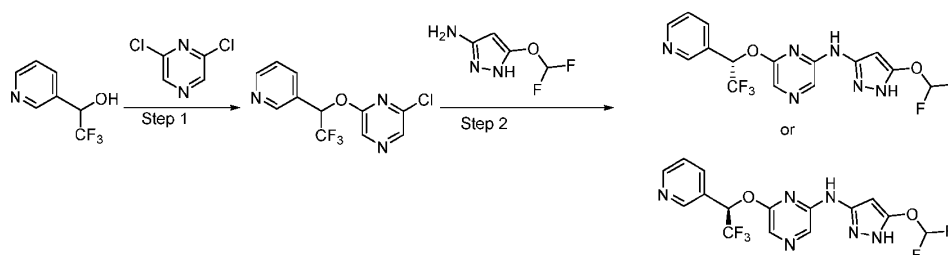
[001045] Step 1: *Synthesis of 3-(((6-chloropyrazin-2-yl)oxy)methyl)isoxazole*

[001046] The title compound was obtained as a white solid (420 mg, 65%) from isoxazol-3-ylmethanol and 2,6-dichloropyrazine following a similar procedure to that described in Example 37, Step 1. LCMS $m/z = 212$ $[M+H]^+$.

[001047] Step 2: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(isoxazol-3-ylmethoxy)pyrazin-2-amine*

[001048] The title compound was obtained as a yellow solid (37.1 mg, 5%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 37, Step 2. LCMS $m/z = 325$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 10.29 (br s, 1H), 8.95 (s, 1H), 7.84 (s, 1H), 7.70 (s, 1H), 7.28 (t, 1H), 6.68 (s, 1H), 5.91 (s, 1H), 5.52 (s, 2H).

[001049] **Example 189**, (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(2,2,2-trifluoro-1-(pyridin-3-yl)ethoxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(2,2,2-trifluoro-1-(pyridin-3-yl)ethoxy)pyrazin-2-amine



[001050] Step 1: *Synthesis of 2-chloro-6-(2,2,2-trifluoro-1-(pyridin-3-yl)ethoxy)pyrazine*

[001051] The title compound was obtained as a yellow oil (450 mg, 92%) from 2,2,2-trifluoro-1-(pyridin-3-yl)ethan-1-ol and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, Step 1. LCMS $m/z = 290$ $[M+H]^+$.

[001052] Step 2: *Synthesis of (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(2,2,2-trifluoro-1-(pyridin-3-yl)ethoxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(2,2,2-trifluoro-1-(pyridin-3-yl)ethoxy)pyrazin-2-amine*

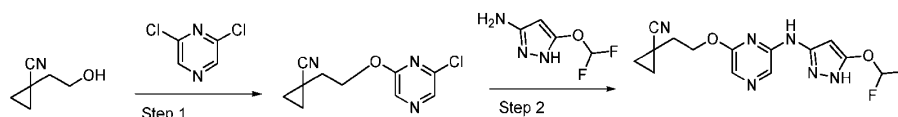
[001053] N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(2,2,2-trifluoro-1-(pyridin-3-yl)ethoxy)pyrazin-2-amine was obtained as a yellow oil (100 mg, 48%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 19 and 20, Step 2. The racemic product was separated by chiral-SFC

(Column: AD 20*250mm, 10 μ m (Daicel), Column temperature: 35°C, Mobile phase:

CO₂/MeOH(0.2% Methanol Ammonia) = 80/20, Flow rate: 80 g/min, Back pressure: 100 bar) to

afford peak 2, the title compound, 44.5 mg. LCMS $m/z = 403$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.03 (br s, 1H), 10.14 (s, 1H), 8.68 (s, 1H), 8.60 (d, 1H), 7.93-7.84 (m, 3H), 7.46-7.40 (m, 1H), 7.31 (t, 1H), 6.98-6.93 (m, 1H), 5.73 (s, 1H).

[001054] **Example 190**, 1-(2-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)ethyl)cyclopropane-1-carbonitrile



[001055] Step 1: *Synthesis of 1-(2-((6-chloropyrazin-2-yl)oxy)ethyl)cyclopropane-1-carbonitrile*

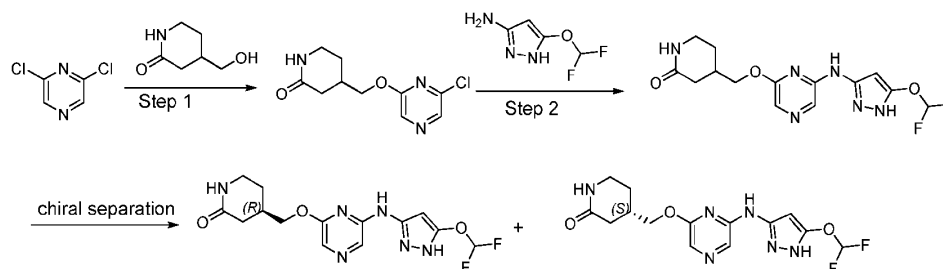
[001056] The title compound was obtained as a white solid (330 mg, 55%) from 1-(2-hydroxyethyl)cyclopropane-1-carbonitrile and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, Step 1. LCMS $m/z = 224$ $[M+H]^+$.

[001057] Step 2: *Synthesis of 1-(2-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)ethyl)cyclopropane-1-carbonitrile*

[001058] The title compound was obtained as a white solid (104 mg, 20%) from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 60, Step 2. LCMS $m/z = 337$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 8.54 (br s, 1H), 7.79 (s, 1H), 7.60 (s, 1H), 7.25 (t, 1H), 5.98 (s, 1H), 5.70 (br s, 1H), 4.46 (t, 2H), 1.95 (t, 2H), 1.25-1.19 (m, 2H), 1.02-0.96 (m, 2H).

[001059] **Example 191**, (S)-4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidin-2-one or (R)-4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidin-2-one and

[001060] **Example 192**, (R)-4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidin-2-one or (S)-4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidin-2-one



[001061] Step 1: *Synthesis of 4-(((6-chloropyrazin-2-yl)oxy)methyl)piperidin-2-one*

[001062] The title compound was obtained as a yellow oil (294 mg, 79%) from 4-(hydroxymethyl)piperidin-2-one and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, Step 1. LCMS $m/z = 242$ $[M+H]^+$.

[001063] Step 2: *Synthesis of (R)-4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidin-2-one and (S)-4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidin-2-one*

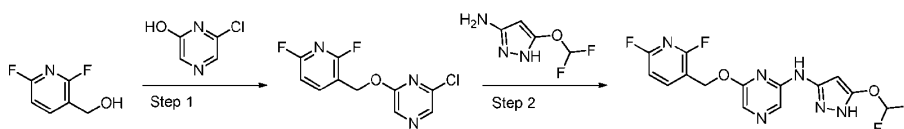
[001064] 4-(((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)methyl)piperidin-2-one was obtained, 120 mg, from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 37, Step

2. This was separated by chiral Prep-SFC (Method J, gradient: 60/40) to give two enantiomers, Peak 1 and Peak 2:

[001065] Peak 1, **Example 192**: 56.4 mg, 17%, white solid. LCMS $m/z = 355$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.91 (br s, 1H), 10.02 (s, 1H), 7.78 (s, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 7.26 (t, 1H), 5.94 (s, 1H), 4.25-4.16 (m, 2H), 3.24-3.12 (m, 2H), 2.33-2.25 (m, 2H), 2.03-1.97 (m, 1H), 1.87-1.84 (m, 1H), 1.51-1.45 (m, 1H); and

[001066] Peak 2, **Example 191**: 47.5 mg, 14%, white solid LCMS $m/z = 355$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.91 (br s, 1H), 10.02 (s, 1H), 7.78 (s, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 7.26 (t, 1H), 5.94 (s, 1H), 4.25-4.16 (m, 2H), 3.24-3.12 (m, 2H), 2.33-2.25 (m, 2H), 2.03-1.97 (m, 1H), 1.87-1.84 (m, 1H), 1.51-1.45 (m, 1H).

[001067] **Example 193**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,6-difluoropyridin-3-yl)methoxy)pyrazin-2-amine



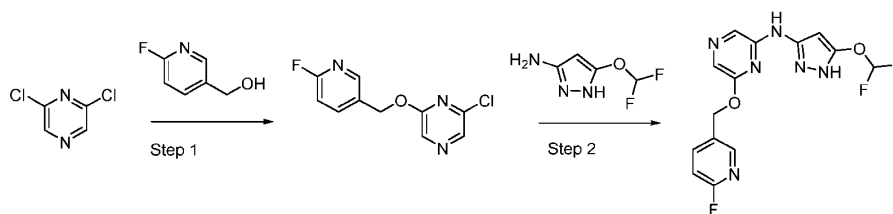
[001068] *Step 1: Synthesis of 2-chloro-6-((2,6-difluoropyridin-3-yl)methoxy)pyrazine*

[001069] The title compound was obtained as a yellow oil, 180 mg, 53%, from (2,6-difluoropyridin-3-yl)methanol and 6-chloropyrazin-2-ol, following the procedure described in Example 41, Step 2. LCMS $m/z = 258$ $[M+H]^+$.

[001070] *Step 2: Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((2,6-difluoropyridin-3-yl)methoxy)pyrazin-2-amine*

[001071] The title compound was obtained as a white solid, 105.5 mg, 48%, from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 37, step 2. LCMS $m/z = 371$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.00 (br s, 1H), 10.04 (br s, 1H), 8.31-8.23 (m, 1H), 7.85 (s, 1H), 7.71 (s, 1H), 7.28 (t, 1H), 7.22-7.20 (m, 1H), 5.94 (s, 1H), 5.44 (s, 2H).

[001072] **Example 194**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((6-fluoropyridin-3-yl)methoxy)pyrazin-2-amine



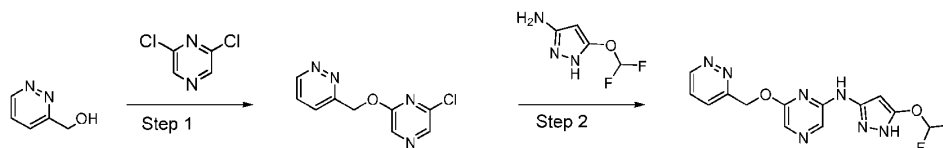
[001073] *Step 1: Synthesis of 2-chloro-6-((6-fluoropyridin-3-yl)methoxy)pyrazine*

[001074] The title compound was obtained as a yellow oil (300 mg, 31%) from (6-fluoropyridin-3-yl)methanol and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, Step 1. LCMS m/z = 240 $[M+H]^+$.

[001075] Step 2: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((6-fluoropyridin-3-yl)methoxy)pyrazin-2-amine*

[001076] The title compound was obtained as a white solid (76 mg, 40%) from the title compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, Step 2. LCMS m/z = 353 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 9.89 (br s, 1H), 8.34 (s, 1H), 8.10-8.05 (m, 1H), 7.83 (s, 1H), 7.69 (s, 1H), 7.27 (t, 1H), 7.23-7.20 (m, 1H), 5.95 (s, 1H), 5.42 (s, 2H).

[001077] **Example 195**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(pyridazin-3-ylmethoxy)pyrazin-2-amine



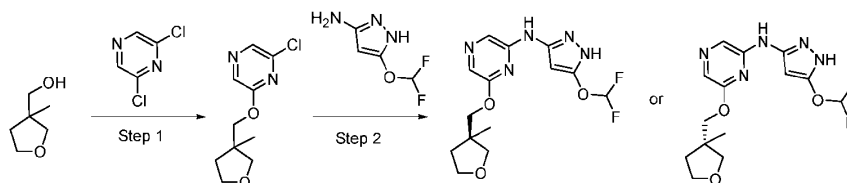
[001078] Step 1: *Synthesis of 3-(((6-chloropyrazin-2-yl)oxy)methyl)pyridazine*

[001079] The title compound was obtained as a colourless oil (200 mg, 49%) from pyridazin-3-ylmethanol and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, Step 1. LCMS m/z = 223 $[M+H]^+$.

[001080] Step 2: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(pyridazin-3-ylmethoxy)pyrazin-2-amine*

[001081] The title compound was obtained as a yellow solid (125 mg, 30%) from the compound from Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 37, Step 2. LCMS m/z = 336 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.12 (br s, 1H), 10.11 (br s, 1H), 9.22-9.19 (m, 1H), 7.83-7.80 (m, 2H), 7.76-7.74 (m, 2H), 7.28 (t, 1H), 5.81 (s, 1H), 5.69 (s, 2H).

[001082] **Example 196**, (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3-methyltetrahydrofuran-3-yl)methoxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3-methyltetrahydrofuran-3-yl)methoxy)pyrazin-2-amine



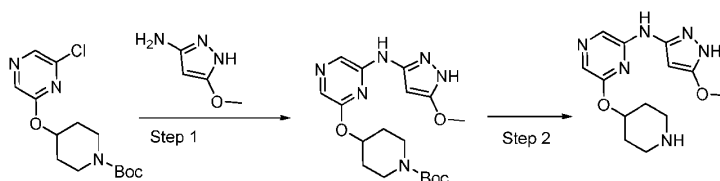
[001083] Step 1: *Synthesis of 2-chloro-6-((3-methyltetrahydrofuran-3-yl)methoxy)pyrazine*

[001084] The title compound was obtained as a colourless oil (500 mg, 72%) from (3-methyltetrahydrofuran-3-yl)methanol and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, Step 1. LCMS $m/z = 229$ $[M+H]^+$.

[001085] Step 2: *Synthesis of (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3-methyltetrahydrofuran-3-yl)methoxy)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3-methyltetrahydrofuran-3-yl)methoxy)pyrazin-2-amine*

[001086] N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((3-methyltetrahydrofuran-3-yl)methoxy)pyrazin-2-amine was obtained, 450 mg, from the compound of Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 37, Step 2. This was separated by chiral Prep-SFC (Column: AD 20*250mm, 10 μ m (Daicel), Column temperature: 35 °C, Mobile phase: CO₂ / MeOH (0.2% Methanol Ammonia) = 60/40, Flow rate: 80 g/min, Back pressure: 100 bar) to give peak 1, the title product as a yellow solid (95.0 mg, 19%). LCMS $m/z = 342$ $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.88 (s, 1H), 10.00 (s, 1H), 7.75 (s, 1H), 7.62 (s, 1H), 7.23 (t, 1H), 5.92 (s, 1H), 4.21-4.15 (m, 2H), 3.83-3.74 (m, 2H), 3.63-3.61 (m, 1H), 3.37-3.35 (m, 1H), 1.91-1.84 (m, 1H), 1.69-1.63 (m, 1H), 1.17 (s, 3H).

[001087] **Example 197**, N-(5-methoxy-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine



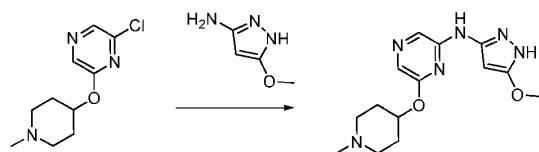
[001088] Step 1: *Synthesis of tert-butyl 4-((6-((5-methoxy-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate*

[001089] The title compound was obtained as a yellow solid (90 mg, 24%) from the compound of Example 1, Step 1 and 5-methoxy-1H-pyrazol-3-amine following a similar procedure to that described in Example 19 and 20, Step 2. LCMS $m/z = 391$ $[M+H]^+$.

[001090] Step 2: *Synthesis of N-(5-methoxy-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine*

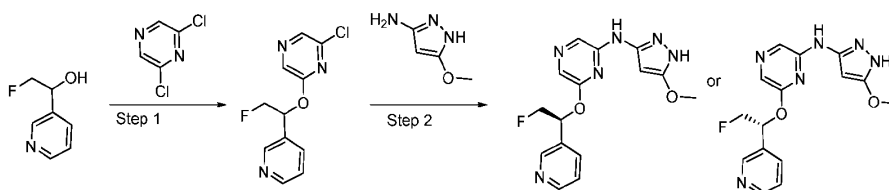
[001091] The title compound was obtained as a brown solid (24.2 mg, 35%) from the compound of Step 1 following a similar procedure to that described in Example 2, Step 3. LCMS $m/z = 291$ $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.90 (br s, 1H), 9.75 (br s, 1H), 7.85 (s, 1H), 7.52 (s, 1H), 5.71 (s, 1H), 5.02-4.97 (m, 1H), 3.79 (s, 3H), 3.03-2.99 (m, 2H), 2.67-2.56 (m, 2H), 2.03-1.95 (m, 2H), 1.58-1.50 (m, 2H).

[001092] **Example 198**, N-(5-methoxy-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)oxy)pyrazin-2-amine (CP107735)



[001093] The title compound was obtained as a white solid (52.9 mg, 26%), from the compound of Example 8, Step 1 and 5-methoxy-1H-pyrazol-3-amine following a similar procedure to that described in Example 37, Step 2. LCMS m/z = 305 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.26 (br s, 1H), 9.71 (br s, 1H), 7.83 (s, 1H), 7.52 (s, 1H), 5.73 (s, 1H), 4.96-4.86 (m, 1H), 3.79 (s, 3H), 2.69-2.64 (m, 2H), 2.19-2.10 (m, 2H), 2.18 (s, 3H), 2.02-1.96 (m, 2H), 1.75-1.62 (m, 2H).

[001094] **Example 199**, (R)-6-(2-fluoro-1-(pyridin-3-yl)ethoxy)-N-(5-methoxy-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-(2-fluoro-1-(pyridin-3-yl)ethoxy)-N-(5-methoxy-1H-pyrazol-3-yl)pyrazin-2-amine



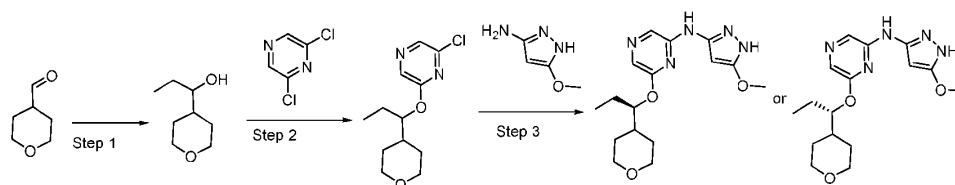
[001095] Step 1: *Synthesis of 2-chloro-6-(2-fluoro-1-(pyridin-3-yl)ethoxy)pyrazine*

[001096] The title compound was obtained as a yellow oil (150 mg, 42%) from 2-fluoro-1-(pyridin-3-yl)ethan-1-ol and 2,6-dichloropyrazine following a similar procedure to that described in Example 39, step 1. LCMS m/z = 254 $[M+H]^+$.

[001097] Step 2: *Synthesis of (R)-6-(2-fluoro-1-(pyridin-3-yl)ethoxy)-N-(5-methoxy-1H-pyrazol-3-yl)pyrazin-2-amine or (S)-6-(2-fluoro-1-(pyridin-3-yl)ethoxy)-N-(5-methoxy-1H-pyrazol-3-yl)pyrazin-2-amine*

[001098] 6-(2-fluoro-1-(pyridin-3-yl)ethoxy)-N-(5-methoxy-1H-pyrazol-3-yl)pyrazin-2-amine was obtained, 120 mg, 34%, from the compound of Step 1 and 5-methoxy-1H-pyrazol-3-amine, following the procedure described in Example 37, Step 2. The racemic product (120 mg) was separated by chiral-SFC (Column: AD 20*250mm, 10 μ m (Daicel), Column temperature: 35°C, Mobile phase: CO₂/(EtOH/ACN(0.2% Methanol Ammonia)=1:1) = 40/60, Flow rate: 100 g/min, Back pressure: 100 bar) to afford peak 1, and peak 2, the title compound (55.6 mg, 15%) as a yellow solid. LCMS m/z = 331 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.34 (br s, 1H), 9.71 (br s, 1H), 8.68 (s, 1H), 8.52 (d, 1H), 7.85-7.83 (m, 2H), 7.70 (s, 1H), 7.39 (d, 1H), 6.39-6.34 (m, 1H), 5.53 (s, 1H), 4.92 (d, 1H), 4.80 (d, 1H), 3.81 (s, 3H).

[001099] **Example 200**, (R)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)propoxy)pyrazin-2-amine or (S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)propoxy)pyrazin-2-amine



[001100] Step 1: *Synthesis of 1-(tetrahydro-2H-pyran-4-yl)propan-1-ol*

[001101] To a solution of tetrahydro-2H-pyran-4-carbaldehyde (1.0 g, 8.76 mmol) in THF (10 mL) was added dropwise EtMgBr (2 M in THF, 22 mL, 43.8 mmol) at 0°C under N₂, then stirred at rt for 2 h. The reaction was quenched with aq. sat. NH₄Cl and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na₂SO₄, filtered and concentrated to give the title product (900 mg, 99%) as a colorless oil.

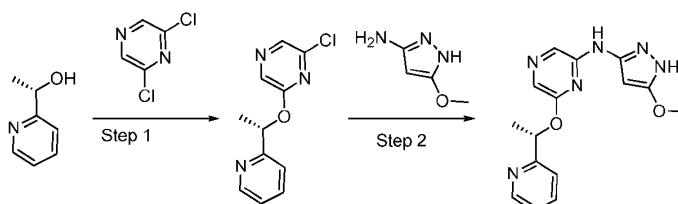
[001102] Step 2: *Synthesis of 2-chloro-6-(1-(tetrahydro-2H-pyran-4-yl)propoxy)pyrazine*

[001103] The title compound was obtained as a colorless oil, 600 mg, 33%, from the title compound of Step 1 and 2,6-dichloropyrazine, following the procedure described in Example 39, Step 1. LCMS $m/z = 257$ [M+H]⁺.

[001104] Step 3: *Synthesis of (R)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)propoxy)pyrazin-2-amine or (S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)propoxy)pyrazin-2-amine*

[001105] N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)propoxy)pyrazin-2-amine was obtained, 300 mg, from the compound of Step 2 and 5-methoxy-1H-pyrazol-3-amine following the procedure described in Example 37, Step 2. This was separated by chiral Prep-SFC (Method C, gradient: 70/30) to give peak 2, the title product (76.2 mg, 19%), as a white solid. LCMS $m/z = 334$ [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.31 (br s, 1H), 9.65 (br s, 1H), 7.83 (br s, 1H), 7.55 (s, 1H), 5.72 (s, 1H), 4.96-4.90 (m, 1H), 3.88-3.83 (m, 2H), 3.79 (s, 3H), 3.30-3.24 (m, 2H), 1.94-1.91 (m, 1H), 1.77-1.73 (m, 1H), 1.67-1.49 (m, 3H), 1.40-1.31 (m, 2H), 0.89 (t, 3H).

[001106] **Example 201**, (S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridin-2-yl)ethoxy)pyrazin-2-amine



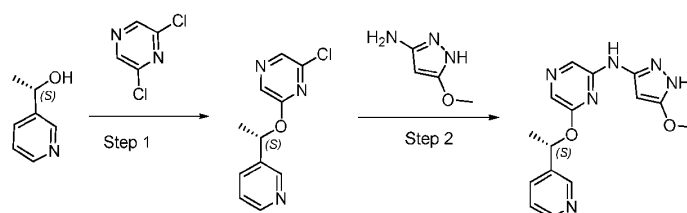
[001107] Step 1: *Synthesis of (S)-2-chloro-6-(1-(pyridin-2-yl)ethoxy)pyrazine*

[001108] The title compound was obtained as a colorless oil (600 mg, 78%) from (S)-1-(pyridin-2-yl)ethan-1-ol and 2,6-dichloropyrazine, following the procedure described in Example 39, Step 1. LCMS $m/z = 236$ [M+H]⁺.

[001109] Step 2: *Synthesis of (S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridin-2-yl)ethoxy)pyrazin-2-amine*

[001110] The title compound was obtained as a white solid (55.4 mg, 16%) from the compound of Step 1 and 5-methoxy-1H-pyrazol-3-amine, following the procedure described in Example 37, Step 2. LCMS $m/z = 313$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.52 (br s, 1H), 9.81 (br s, 1H), 8.56-8.53 (m, 1H), 7.81-7.77 (m, 2H), 7.64 (s, 1H), 7.50-7.44 (m, 1H), 7.32-7.28 (m, 1H), 6.08 (q, 1H), 5.53-5.46 (m, 1H), 3.81 (s, 3H), 1.64 (d, 3H).

[001111] **Example 202**, (S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridin-3-yl)ethoxy)pyrazin-2-amine



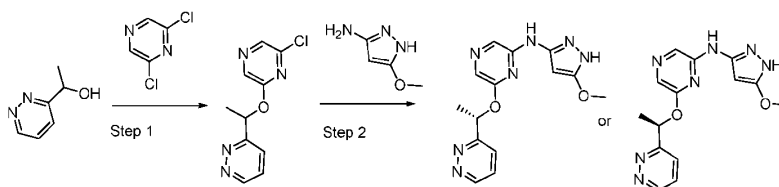
[001112] Step 1: *Synthesis of (S)-2-chloro-6-(1-(pyridin-3-yl)ethoxy)pyrazine*

[001113] The title compound was obtained as a colorless oil (300 mg, 78%) from (S)-1-(pyridin-3-yl)ethan-1-ol and 2,6-dichloropyrazine, following the procedure described in Example 39, Step 1. LCMS $m/z = 236$ $[M+H]^+$.

[001114] Step 2: *Synthesis of (S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridin-3-yl)ethoxy)pyrazin-2-amine*

[001115] A mixture of the compound of Step 1 (140 mg, 0.60 mmol), 5-methoxy-1H-pyrazol-3-amine (75 mg, 0.66 mmol), $Pd_2(dba)_3$ (55 mg, 0.06 mmol), tBuXPhos (95 mg, 0.12 mmol) and KOAc (147 mg, 1.50 mmol) in toluene (5 mL) was stirred at 90°C for 4 h under Ar. The reaction mixture was concentrated *in vacuo*. The residue was purified by Prep-HPLC (Method A) to afford the title product (28.7 mg, 15%) as a white solid. LCMS $m/z = 313$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.82 (br s, 1H), 9.75 (br s, 1H), 8.64 (s, 1H), 8.49-8.45 (m, 1H), 8.03-7.55 (m, 1H), 7.39-7.34 (m, 1H), 6.19-6.15 (m, 1H), 5.58 (s, 1H), 3.80 (s, 3H), 1.64 (d, 3H).

[001116] **Example 203**, (S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridazin-3-yl)ethoxy)pyrazin-2-amine or (R)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridazin-3-yl)ethoxy)pyrazin-2-amine



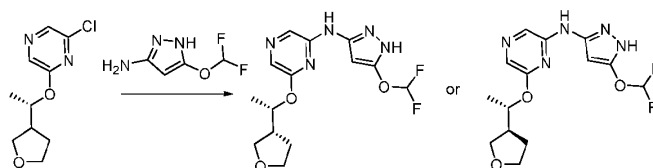
[001117] Step 1: *Synthesis of 3-(1-((6-chloropyrazin-2-yl)oxy)ethyl)pyridazine*

[001118] The title compound was obtained as a white solid (200 mg, 35%) from 1-(pyridazin-3-yl)ethan-1-ol and 2,6-dichloropyrazine, following a similar procedure to that described in Example 37, step 1. LCMS $m/z = 237$ $[M+H]^+$.

[001119] Step 2: *Synthesis of (S)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridazin-3-yl)ethoxy)pyrazin-2-amine or (R)-N-(5-methoxy-1H-pyrazol-3-yl)-6-(1-(pyridazin-3-yl)ethoxy)pyrazin-2-amine*

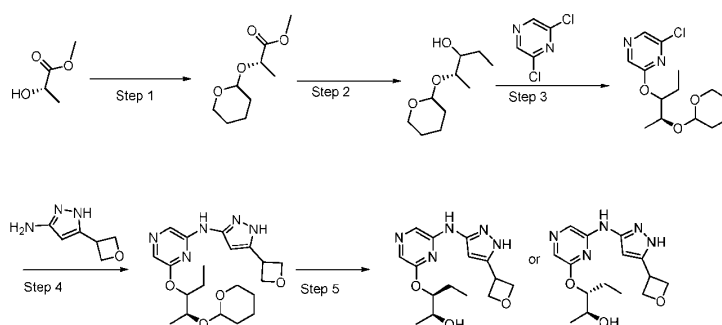
[001120] A mixture of the compound of Step 1 (200 mg, 0.84 mmol), 5-methoxy-1H-pyrazol-3-amine (95 mg, 0.84 mmol), KOAc (247 mg, 2.52 mmol) and BrettPhos Pd G4 (30 mg, 50 μ mol) in dioxane (3 mL) was stirred at 90°C under N_2 for 3 h. The reaction mixture was diluted with dioxane, filtered and evaporated under reduced pressure. The residue was purified by Prep-HPLC (Method A) to afford the racemic product (100 mg) and then separated by chiral Prep-SFC (Column: OX 20*250mm, 10 μ m (Daicel), Column temperature: 35°C, Mobile phase: CO_2 /(EtOH/MeCN(0.2% MeOH/Ammonia)=1:1) = 55/45, Flow rate: 100 g/min, Back pressure: 100 bar) to give Peak 1, the title product (38.7 mg, 38%), as a white solid. LCMS $m/z = 314$ $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 11.45 (br s, 1H), 9.75 (br s, 1H), 9.19-9.15 (m, 1H), 7.79-7.65 (m, 4H), 6.42-6.30 (m, 1H), 5.59-5.51 (m, 1H), 3.83 (s, 3H), 1.80-1.70 (m, 3H).

[001121] **Example 204**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((S)-1-((R)-tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine or N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((S)-1-((S)-tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine



[001122] Racemic N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1S)-1-(tetrahydrofuran-3-yl)ethoxy)pyrazin-2-amine was obtained as a yellow oil (200 mg, 89%) from the compound of Example 185, Step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following a similar procedure to that described in Example 19 and 20, Step 2. Chiral Prep-SFC (Method H, gradient: 80/20) yielded peak 2, the title product, (69.7 mg) as a yellow solid. LCMS $m/z = 342$ $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 11.90 (br s, 1H), 9.95 (s, 1H), 7.77 (s, 1H), 7.59 (s, 1H), 7.24 (t, 1H), 5.95 (s, 1H), 5.09-5.03 (m, 1H), 3.80-3.71 (m, 2H), 3.68-3.61 (m, 1H), 3.50-3.43 (m, 1H), 2.55-2.49 (m, 1H), 2.01-1.95 (m, 1H), 1.75-1.67 (m, 1H), 1.26 (d, 3H).

[001123] **Example 205**, (2S,3S)-3-((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol or (2S,3R)-3-((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol



[001124] *Step 1: Synthesis of methyl (2S)-2-((tetrahydro-2H-pyran-2-yl)oxy)propanoate*

[001125] A mixture of methyl (S)-2-hydroxypropanoate (10.0 g, 96.1 mmol), 3,4-dihydro-2H-pyran (8.08 g, 96.1 mmol) and TsOH (1.65 g, 9.61 mmol) in DCM (100 mL) was stirred for 3 h. The reaction mixture was washed with water and brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/30) to give the title product (9.70 g, 53%) as a yellow oil.

[001126] *Step 2: Synthesis of methyl (2S)-2-((tetrahydro-2H-pyran-2-yl)oxy)pentan-3-ol*

[001127] To a mixture of the compound of Step 1 (700 mg, 3.72 mmol) in toluene (30 mL) was added dropwise, DIBAL-H (1.5 M/toluene, 2.8 mL, 4.09 mmol) at -78 °C under N₂. The reaction was maintained at -70 °C for 30 min. Ethyl magnesium bromide (1.0 M to THF, 6.0 mL, 6.0 mmol) was then added at -70 °C, then stirred for 20 min and slowly warmed to rt. The reaction mixture was poured into ice-water, then aqueous HCl (10%) added until all precipitate was dissolved. The aqueous phase was extracted with THF/toluene, and the combined organic layers were washed with water, aqueous NaOH (1 M) and brine, dried over MgSO₄, filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/5) to give the title product (600 mg, 85%) as a yellow oil.

[001128] *Step 3: Synthesis of 2-chloro-6-(((2S)-2-((tetrahydro-2H-pyran-2-yl)oxy)pentan-3-yl)oxy)pyrazine*

[001129] The title compound was obtained as a white solid (300 mg, 37%) from the compound of Step 2 and 2,6-dichloropyrazine, following the procedure described in Example 39, Step 1.

[001130] *Step 4: Synthesis of N-(5-(oxetan-3-yl)-1H-pyrazol-3-yl)-6-(((2S)-2-((tetrahydro-2H-pyran-2-yl)oxy)pentan-3-yl)oxy)pyrazin-2-amine*

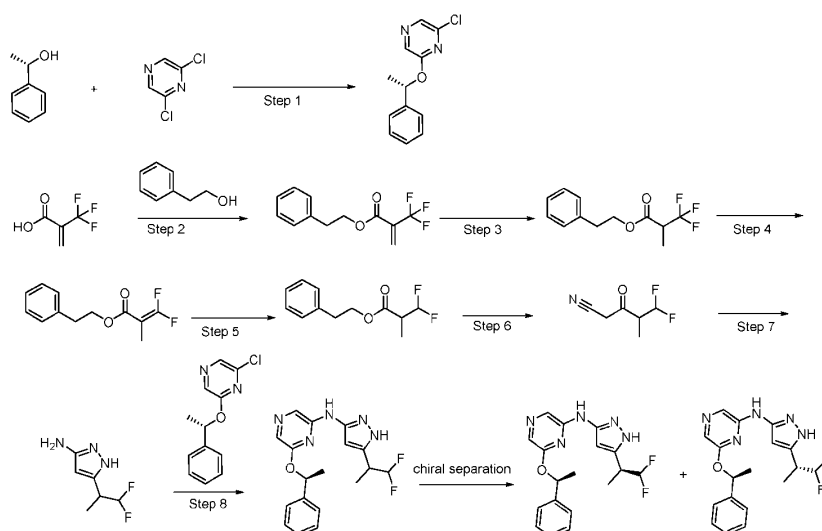
[001131] The title compound was obtained as a solid (130 mg, 48%) from the compound of Step 3 and 5-(oxetan-3-yl)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 202, Step 2. LCMS m/z = 404 [M+H]⁺.

[001132] *Step 5: Synthesis of (2S,3S)-3-((6-(((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-yl)oxy)pentan-2-ol or (2S,3R)-3-((6-(((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-yl)oxy)pentan-2-ol*

[001133] To a solution of the compound of Step 4 (130 mg, 0.32 mmol) in THF (5 mL) was added FA (0.5 mL) and the reaction mixture was stirred at rt for 2 h. The mixture was concentrated *in vacuo* and the residue was purified with Prep-HPLC (Method A) to give Peak 1, the title compound (10.8 mg, 10%) as a white solid. LCMS $m/z = 320$ $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.18 (br s, 1H), 9.61 (s, 1H), 8.00 (s, 1H), 7.49 (s, 1H), 6.53 (s, 1H), 4.96-4.90 (m, 1H), 4.89-4.84 (m, 2H), 4.79-4.74 (m, 1H), 4.69-4.60 (m, 2H), 4.31-4.23 (m, 1H), 3.90-3.81 (m, 1H), 1.82-1.69 (m, 1H), 1.67-1.58 (m, 1H), 1.08 (d, 3H), 0.90 (t, 3H).

[001134] **Example 206**, N-(5-((R)-1,1-difluoropropan-2-yl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine or N-(5-((S)-1,1-difluoropropan-2-yl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine and

[001135] **Example 207**, N-(5-((S)-1,1-difluoropropan-2-yl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine or N-(5-((R)-1,1-difluoropropan-2-yl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine



[001136] Step 1: *Synthesis of (S)-2-chloro-6-(1-phenylethoxy)pyrazine*

[001137] To a solution of (S)-1-phenylethanol (4.4 g, 36.0 mmol) in DMF (50 mL) was added NaH (4.0 g, 60%, 100.0 mmol) at 0°C and the solution stirred for 2 h. 2,6-Dichloropyrazine (4.44 g, 30.0 mmol) was added and the reaction mixture was stirred at rt for 5 h. The reaction was quenched by the addition of water and extracted with EtOAc. The organic layer was sequentially washed with water and brine and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1:8) to give the title product (6.7 g, 94%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ ppm 8.12 (s, 1H), 8.09 (s, 1H), 7.47-7.27 (m, 5H), 6.16 (q, 1H), 1.68 (d, 1H).

[001138] Step 2: *Synthesis of phenethyl 2-(trifluoromethyl)acrylate*

[001139] A mixture of 2-(trifluoromethyl)acrylic acid (30.0 g, 214 mmol), 2-phenylethanol (52.5 g, 430 mmol) and 4-methylbenzenesulfonic acid (74.0 g, 430 mmol) in toluene (800 mL) was stirred at 120°C for 18 h under N₂. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (1:10 to 1:5) to give the title compound (29.0 g, 56%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.34-7.21 (m, 5H), 6.67 (q, 1H), 6.41 (q, 1H), 4.46 (t, 2H), 3.02 (t, 2H).

[001140] Step 3: *Synthesis of phenethyl 3,3,3-trifluoro-2-methylpropanoate*

[001141] A mixture of phenethyl 2-(trifluoromethyl)acrylate (29.0 g, 119 mmol) and Pd/C (10%, wetted with ca. 55% water, 6.0 g) in EtOAc (300 mL) was stirred at 20°C for 18 h under H₂. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (1:10 to 1:3) to give the title compound (24.9 g, 85%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.34-7.20 (m, 5H), 4.42-4.35 (m, 2H), 3.22-3.13 (m, 1H), 2.97 (t, 2H), 1.36 (d, 3H).

[001142] Step 4: *Synthesis of phenethyl 3,3-difluoro-2-methylacrylate*

[001143] A solution of 3,3,3-trifluoro-2-methylpropanoate (3.7 g, 15.0 mmol) in THF (150 mL) under Ar was cooled to -78°C and treated dropwise with 1.0 M LiHMDS (18.0 mL, 18.0 mmol) in n-hexane. After stirring for 4 h the solution was quenched by the addition of sat. NH₄Cl aq, then extracted with EtOAc. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (1:8) to give the title compound (2.1 g, 62%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.34-7.19 (m, 5H), 4.38 (t, 2H), 2.98 (t, 2H), 1.77 (t, 3H).

[001144] Step 5: *Synthesis of phenethyl 3,3-difluoro-2-methylpropanoate*

[001145] A mixture of phenethyl 3,3-difluoro-2-methylacrylate (4.5 g, 18.4 mmol) and Pd/C (10%, wetted with ca. 55% H₂O, 1.15 g) in EtOAc (90 mL) was stirred at 20°C for 18 h under H₂. The reaction mixture was filtered, the residue was washed the solid cake with MeOH and the filtrate was concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel eluting with EtOAc/PE (1:10 to 1:4) to give the title compound (3.3 g, 73%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.34-7.20 (m, 5H), 5.97 (dt, 1H), 4.37 (t, 2H), 2.96 (t, 2H), 2.95-2.87 (m, 1H), 1.25 (d, 3H).

[001146] Step 6: *Synthesis of 5,5-difluoro-4-methyl-3-oxopentanenitrile*

[001147] A solution of LDA (10.0 mmol, in n-hexane) in THF (15 mL) was cooled to -78°C under Ar and treated dropwise with MeCN (0.75 mL, 15.0 mmol) in THF (2 mL). After stirring for 1 h the solution was kept at -78°C and treated dropwise with a solution of phenethyl 3,3-difluoro-2-methylpropanoate (1.6 g, 7.0 mmol) in THF (10 mL). The solution was stirred for 18 h from -78 to 20°C. The reaction was quenched by the addition of water, then concentrated under reduced pressure. The residue was dissolved in water and washed with ether. The aqueous phase was acidified with 1N

HCl to pH 3 and extracted with EtOAc. The organic phase was sequentially washed with water and brine, then dried over Na₂SO₄, filtered and evaporated. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/PE (1:3) to give the title compound (580 mg, 56%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.91 (dt, 1H), 3.63 (s, 2H), 3.28-3.19 (m, 1H), 1.32 (d, 3H).

[001148] Step 7: *Synthesis of 5-(1,1-difluoropropan-2-yl)-1H-pyrazol-3-amine*

[001149] A solution of 5,5-difluoro-4-methyl-3-oxopentanenitrile (400 mg, 2.7 mmol), hydrazine hydrate (410 mg, 8.1 mmol) and conc. HCl (0.2 mL, 2.7 mmol) in IPA (5 mL) was stirred at 90°C for 18 h. The reaction mixture was diluted with MeOH and treated with solid Na₂CO₃, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (0% ~100%) to give the title compound (150 mg, 34%) as a yellow oil. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.29 (br s, 1H), 6.04 (dt, 1H), 5.26 (s, 1H), 4.67 (s, 2H), 3.11-3.05 (m, 1H), 1.23 (d, 3H).

[001150] Step 8: *Synthesis of N-(5-((S)-1,1-difluoropropan-2-yl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine and N-(5-((R)-1,1-difluoropropan-2-yl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine*

[001151] A mixture of (S)-2-chloro-6-(1-phenylethoxy)pyrazine (350 mg, 1.5 mmol), 5-(1,1-difluoropropan-2-yl)-1H-pyrazol-3-amine (200 mg, 1.25 mmol), Pd₂(dba)₃ (230 mg, 0.25 mmol), tBuXPhos (210 mg, 0.5 mmol) and KOAc (340 mg, 3.5 mmol) in toluene (10 mL) was stirred at 100°C for 6 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (1:10 to 10:1) to give the racemic title compound (160 mg, 35%) as a yellow solid. LCMS *m/z* = 360 [M+H]⁺.

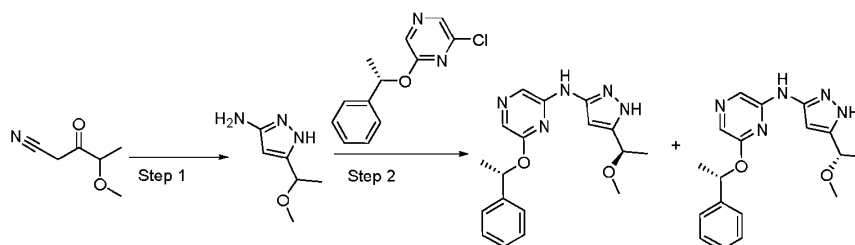
[001152] Chiral HPLC of 160 mg of the racemate (Column: IE 20*250mm, 10 μm (Daicel), Column temperature: 35°C, Mobile phase: CO₂/MeOH (0.2% Methanol Ammonia) = 70/30, Flow rate: 80 g/min, Back pressure: 100 bar) yielded two compounds, peak 1 (36.1 mg) and peak 2 (24.0 mg).

[001153] Peak 1, **Example 207**, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.19 (br s, 1H), 9.62 (s, 1H), 7.94 (s, 1H), 7.54 (s, 1H), 7.43-7.25 (m, 5H), 6.31-6.08 (m, 3H), 3.35-3.30 (m, 1H), 1.60 (d, 3H), 1.32 (d, 3H).

[001154] Peak 2, **Example 206**, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.19 (br s, 1H), 9.62 (s, 1H), 7.94 (s, 1H), 7.54 (s, 1H), 7.43-7.25 (m, 5H), 6.31-6.08 (m, 3H), 3.35-3.30 (m, 1H), 1.60 (d, 3H), 1.32 (d, 3H).

[001155] **Example 208**, N-(5-((S)-1-methoxyethyl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine or N-(5-((R)-1-methoxyethyl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine and

[001156] **Example 209**, N-(5-((R)-1-methoxyethyl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine or N-(5-((S)-1-methoxyethyl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine



[001157] Step 1: *Synthesis of 5-(1-methoxyethyl)-1H-pyrazol-3-amine*

[001158] The title compound was obtained as a yellow solid (420 mg, 73%) from 4-methoxy-3-oxopentanenitrile and hydrazine hydrate, following the procedure described in Example 28 and 29, step 2. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 11.26 (br s, 1H), 5.27 (s, 1H), 4.71-4.45 (m, 2H), 4.18 (s, 1H), 3.20 (s, 3H), 2.50-2.43 (m, 1H), 1.31 (d, 3H).

[001159] Step 2: *Synthesis of N-(5-((R)-1-methoxyethyl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine and N-(5-((S)-1-methoxyethyl)-1H-pyrazol-3-yl)-6-((S)-1-phenylethoxy)pyrazin-2-amine*

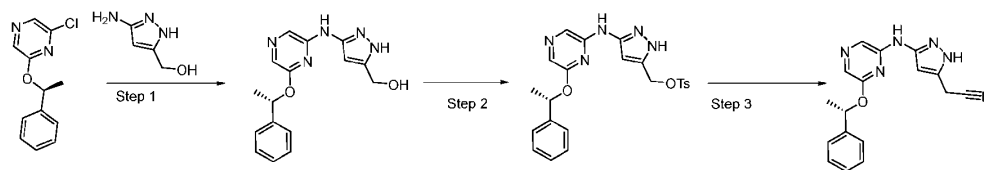
[001160] A mixture of the compound from Example 206 and 207, Step 1, (365 mg, 1.56 mmol), 5-(1-methoxyethyl)-1H-pyrazol-3-amine (220 mg, 1.56 mmol), Pd₂(dba)₃ (150 mg, 0.16 mmol), tBuXPhos (136 mg, 0.32 mmol) and KOAc (400 mg, 4.08 mmol) in toluene (15 mL) was stirred at 120 °C for 18 h. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1:10 to 10:1) and the product further purified by prep-HPLC to give the racemic product (200 mg, 38%). LCMS *m/z* = 340 [M+H]⁺.

[001161] This was separated by chiral SFC (Column: ID 20*250mm, 10 μm (Daicel), Column temperature: 35 °C, Mobile phase: CO₂/ MeOH (0.2% Methanol Ammonia) = 60/40, Flow rate: 80 g/min, Back pressure: 100 bar) to give two compounds:

[001162] Peak 1, **Example 209**, (83.5 mg), ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.21 (br s, 1H), 9.59 (s, 1H), 7.95 (s, 1H), 7.54 (s, 1H), 7.42-7.39 (m, 2H), 7.35-7.31 (m, 2H), 7.27-7.23 (m, 1H), 6.27-6.24 (m, 1H), 6.11-6.06 (m, 1H), 4.43-4.35 (m, 1H), 3.20 (s, 3H), 1.60 (d, 3H), 1.41 (d, 3H);

[001163] Peak 2, **Example 208**, (76.5 mg). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 12.21 (br s, 1H), 9.61 (s, 1H), 7.93 (s, 1H), 7.55 (s, 1H), 7.42-7.39 (m, 2H), 7.35-7.31 (m, 2H), 7.27-7.23 (m, 1H), 6.27-6.24 (m, 1H), 6.11-6.06 (m, 1H), 4.43-4.35 (m, 1H), 3.16 (s, 3H), 1.60 (d, 3H), 1.43 (d, 3H).

[001164] **Example 210**, (S)-2-(3-((6-(1-phenylethoxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)acetonitrile



[001165] Step 1: *Synthesis of (S)-3-((6-(1-phenylethoxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)methanol*

[001166] A mixture of Example 209, step 2, (200 mg, 0.85 mmol), (3-amino-1H-pyrazol-5-yl)methanol (96.4 mg, 0.85 mmol), KOAc (250 mg, 2.55 mmol), Pd₂(dba)₃ (156 mg, 0.1704 mmol) and t-BuXPhos (108 mg, 0.2556 mmol) in toluene (15 mL) was heated to 90°C for 15 h. The reaction mixture was diluted with DCM and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to dryness under reduced pressure to give the crude which was purified by flash chromatography on silica gel eluting with DCM/MeOH (10/1) to give the title product (150 mg, 57%) as a yellow solid. LCMS m/z = 312 [M+H]⁺.

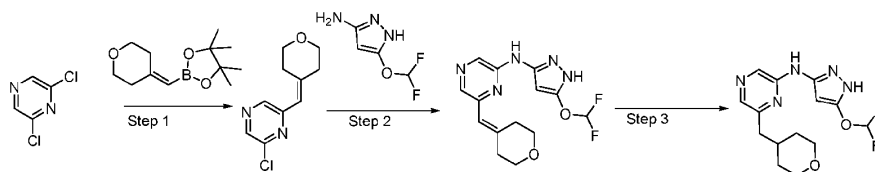
[001167] Step 2: *Synthesis of (S)-3-((6-(1-phenylethoxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)methyl 4-methylbenzenesulfonate*

[001168] A mixture of the compound from step 1 (150 mg, 0.48 mmol), TEA (145 mg, 1.44 mmol) in DCM (10 mL) was cooled to 0°C. 4-Methylbenzenesulfonyl chloride (274 mg, 1.44 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 2 h, then diluted with DCM and washed with saturated NaHCO₃ solution and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to give the title product (224 mg, crude) as a yellow solid. LCMS m/z = 466 [M+H]⁺.

[001169] Step 3: *Synthesis of (S)-2-3-((6-(1-phenylethoxy)pyrazin-2-yl)amino)-1H-pyrazol-5-yl)acetonitrile*

[001170] To a solution of the compound from step 2 (224 mg, 0.48 mmol) in DMSO (10 mL) was added KCN (93.7 mg, 1.44 mmol). The reaction mixture was allowed to warm to rt and stirred for 15 h. The reaction was diluted with EtOAc and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure, and the crude was purified by Prep-HPLC (Method A) to give the title product (20 mg, 13%) as a white solid. LCMS m/z = 321 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.35 (br s, 1H), 9.68 (br s, 1H), 7.93-7.91 (m, 2H), 7.57-7.23 (m, 5H), 6.40 (s, 1H), 6.10 (q, 2H), 4.09 (s, 2H), 1.60 (d, 3H).

[001171] **Example 211**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((tetrahydro-2H-pyran-4-yl)methyl)pyrazin-2-amine



[001172] Step 1: *Synthesis of 2-chloro-6-((tetrahydro-4H-pyran-4-ylidene)methyl)pyrazine*

[001173] To a solution of 4,4,5,5-tetramethyl-2-((tetrahydro-4H-pyran-4-ylidene)methyl)-1,3,2-dioxaborolane (200 mg, 892 μ mol) and 2,6-dichloropyrazine (397 mg, 2.67 mmol) in dioxane (5.0 mL) and H₂O (1.0 mL) was added K₃PO₄ (501 mg, 2.23 mmol) and Pd(dppf)Cl₂ (77 mg, 0.11 mmol) at rt under N₂. The reaction mixture was heated to 100°C and was stirred for 2 h. After cooling to rt the reaction mixture was evaporated and the residue was purified by flash chromatography on silica gel eluting with PE/EtOAc (1/1) to obtain the title product (110 mg, 58%) as a yellow solid. LCMS m/z = 211 [M+H]⁺.

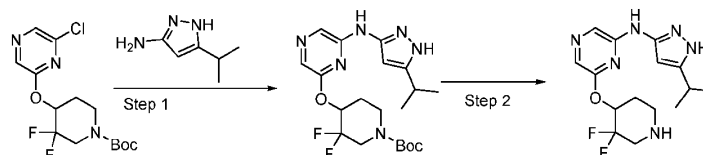
[001174] Step 2: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((tetrahydro-4H-pyran-4-ylidene)methyl)pyrazin-2-amine*

[001175] The title compound was obtained as a yellow solid, 90 mg, 53%, from the compound from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS m/z = 324 [M+H]⁺.

[001176] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((tetrahydro-2H-pyran-4-yl)methyl)pyrazin-2-amine*

[001177] To a solution of the compound from step 2 (90 mg, 278 μ mol) in MeOH (5.0 mL) was added PtO₂ (31.7 mg, 139 μ mol) at rt. The reaction mixture was stirred at rt for 24 h under H₂. The mixture was diluted with MeOH, filtered and the filtrate was concentrated under reduced pressure. The residue was purified Prep-HPLC (Method A) to obtain the title product (9.2 mg, 10%) as a white solid. LCMS m/z = 326 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.33 (br s, 1H), 10.52 (br s, 1H), 8.04 (s, 1H), 7.87 (s, 1H), 7.25 (t, 1H), 5.81 (s, 1H), 3.91-3.79 (m, 2H), 3.26-3.21 (m, 2H), 2.79-2.63 (m, 2H), 1.99-1.96 (m, 1H), 1.49-1.47 (m, 2H), 1.33-1.27 (m, 2H).

[001178] **Example 212**, 6-((3,3-difluoropiperidin-4-yl)oxy)-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine



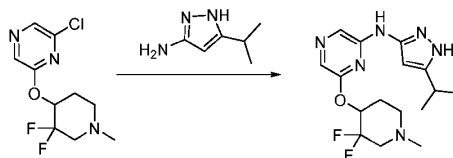
[001179] Step 1: *Synthesis of tert-butyl 3,3-difluoro-4-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate*

[001180] The title compound was obtained as a brown solid (210 mg, crude) from Example 14, step 1 and 5-isopropyl-1*H*-pyrazol-3-amine, following the procedure described in Example 210, step 1. LCMS m/z = 439 $[M+H]^+$.

[001181] *Step 2: Synthesis of 6-((3,3-difluoropiperidin-4-yl)oxy)-N-(5-isopropyl-1*H*-pyrazol-3-yl)pyrazin-2-amine*

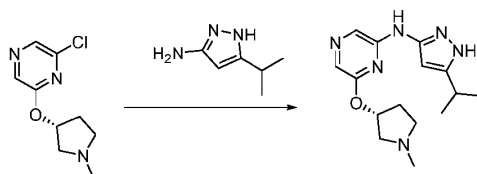
[001182] The title compound was obtained as a white solid (50 mg, 26%) from the compound from step 1, following the procedure described in Example 2, step 3. LCMS m/z = 339 $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.99 (br s, 1H), 9.69 (s, 1H), 8.05 (s, 1H), 7.55 (s, 1H), 6.19 (s, 1H), 5.42-5.33 (m, 1H), 3.22-3.11 (m, 1H), 2.97-2.90 (m, 2H), 2.87-2.82 (m, 1H), 2.68-2.50 (m, 2H), 2.12-2.07 (m, 1H), 1.82-1.75 (m, 1H), 1.24 (d, 6H).

[001183] **Example 213**, 6-((3,3-difluoro-1-methylpiperidin-4-yl)oxy)-*N*-(5-isopropyl-1*H*-pyrazol-3-yl)pyrazin-2-amine



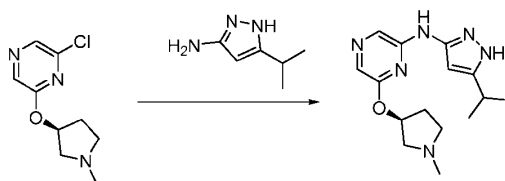
[001184] The title compound was obtained as a white solid (30.9 mg, 23%) from Example 164, step 1 and 5-isopropyl-1*H*-pyrazol-3-amine, following the procedure described in Example 202, step 2. LCMS m/z = 353 $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.99 (br s, 1H), 9.69 (s, 1H), 8.05 (s, 1H), 7.55 (s, 1H), 6.18 (s, 1H), 5.33-5.27 (m, 1H), 2.95-2.90 (m, 2H), 2.68-2.50 (m, 2H), 2.31-2.26 (m, 1H), 2.28 (s, 3H), 2.19-2.10 (m, 1H), 1.92-1.85 (m, 1H), 1.25 (d, 6H).

[001185] **Example 214**, (R)-*N*-(5-isopropyl-1*H*-pyrazol-3-yl)-6-((1-methylpyrrolidin-3-yl)oxy)pyrazin-2-amine



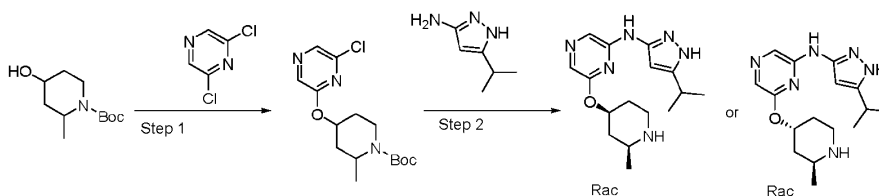
[001186] The title compound was obtained as a white solid (102.6 mg, 36%) from Example 130, step 1 and 5-isopropyl-1*H*-pyrazol-3-amine following the procedure described in Example 202, step 2. LCMS m/z = 303 $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.94 (br s, 1H), 9.55 (s, 1H), 7.98 (s, 1H), 7.45 (s, 1H), 6.25 (s, 1H), 5.34-5.28 (m, 1H), 2.95-2.89 (m, 1H), 2.85-2.78 (m, 1H), 2.71-2.61 (m, 2H), 2.38-2.30 (m, 2H), 2.28 (s, 3H), 1.87-1.79 (m, 1H), 1.23 (d, 6H).

[001187] **Example 215**, (S)-*N*-(5-isopropyl-1*H*-pyrazol-3-yl)-6-((1-methylpyrrolidin-3-yl)oxy)pyrazin-2-amine



[001188] The title compound was obtained as a white solid (211.6 mg, 75%) from Example 129, step 1 and 5-isopropyl-1H-pyrazol-3-amine following the procedure described in Example 202, step 2. LCMS m/z = 303 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.94 (br s, 1H), 9.55 (s, 1H), 7.98 (s, 1H), 7.45 (s, 1H), 6.25 (s, 1H), 5.34-5.28 (m, 1H), 2.95-2.89 (m, 1H), 2.85-2.78 (m, 1H), 2.71-2.61 (m, 2H), 2.38-2.30 (m, 2H), 2.28 (s, 3H), 1.87-1.79 (m, 1H), 1.23 (d, 6H).

[001189] **Example 216**, Rac-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((2S,4S)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine or rac-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((2S,4R)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine



[001190] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-2-methylpiperidine-1-carboxylate*

[001191] The title compound was obtained as a yellow solid (410 mg, 90%) from tert-butyl 4-hydroxy-2-methylpiperidine-1-carboxylate and 2,6-dichloropyrazine, following the procedure described in Example 39, step 1. LCMS m/z = 272 $[M-56+H]^+$.

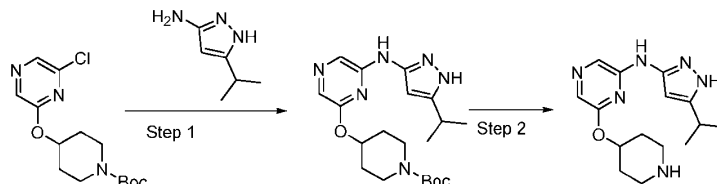
[001192] Step 2: *Synthesis of tert-butyl 4-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)-2-methylpiperidine-1-carboxylate*

[001193] The title compound was obtained as a solid (420 mg, 80%) from tert-butyl 4-((6-chloropyrazin-2-yl)oxy)-2-methylpiperidine-1-carboxylate and 5-(propan-2-yl)-1H-pyrazol-3-amine, following the procedure described in Example 210, step 1. LCMS m/z = 417 $[M+H]^+$.

[001194] Step 3: *Synthesis of rac-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((2S,4S)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine or rac-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(((2S,4R)-2-methylpiperidin-4-yl)oxy)pyrazin-2-amine*

[001195] The title compound, peak 1, was obtained as a yellow solid (4.1 mg, 1.3%) from the compound from step 2, following the procedure described in Example 2, step 3. LCMS m/z = 317 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 11.93 (br s, 1H), 9.54 (s, 1H), 7.97 (s, 1H), 7.47 (s, 1H), 6.20 (s, 1H), 5.29-5.25 (m, 1H), 3.04-2.96 (m, 1H), 2.94-2.80 (m, 3H), 1.96-1.90 (m, 2H), 1.76-1.65 (m, 1H), 1.47-1.37 (m, 1H), 1.22 (d, 6H), 1.00 (d, 3H).

[001196] **Example 217**, N-(5-isopropyl-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine



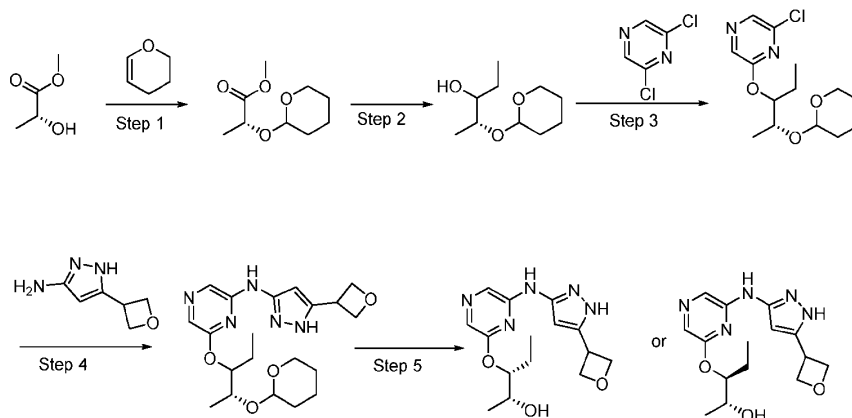
[001197] Step 1: *Synthesis of tert-butyl 4-((6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)piperidine-1-carboxylate*

[001198] The title compound was obtained as a yellow oil (550 mg, 86%) from Example 1, step 1 and 5-(propan-2-yl)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 210, step 1. LCMS $m/z = 403$ $[M+H]^+$.

[001199] Step 2: *Synthesis of N-(5-isopropyl-1H-pyrazol-3-yl)-6-(piperidin-4-yloxy)pyrazin-2-amine*

[001200] The title compound was obtained as a white solid (500 mg, 84%) from the compound from step 1, following a similar procedure to that described in Example 3, step 3, except Prep-HPLC (Method C) was used. LCMS $m/z = 303$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.97 (br s, 1H), 9.60 (s, 1H), 7.92 (s, 1H), 7.43 (s, 1H), 6.24 (s, 1H), 5.04-4.94 (m, 1H), 3.85-3.72 (m, 1H), 3.01-2.88 (m, 3H), 2.63-2.52 (m, 2H), 2.01-1.97 (m, 2H), 1.55-1.46 (m, 2H), 1.23 (d, 6H).

[001201] **Example 218**, (2R,3R)-3-((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol or (2R,3S)-3-((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol



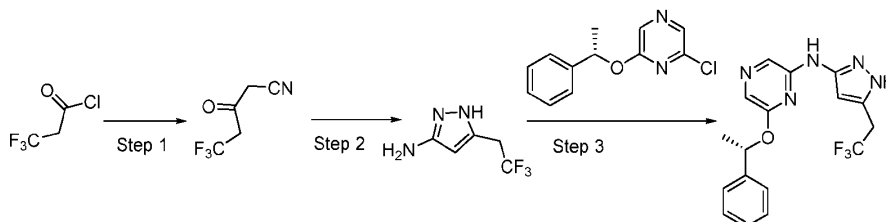
[001202] Steps 1 – 4: *Synthesis of N-(5-(oxetan-3-yl)-1H-pyrazol-3-yl)-6-(((2R)-2-((tetrahydro-2H-pyran-2-yl)oxy)pentan-3-yl)oxy)pyrazin-2-amine*

[001203] The title compound was obtained as a yellow oil, from methyl (R)-2-hydroxypropanoate, following the same 4 step procedure described in Example 205, steps 1 to 4. LCMS $m/z = 404$ $[M+H]^+$.

[001204] Step 5: *Synthesis of (2R,3R)-3-((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol or (2R,3S)-3-((6-((5-(oxetan-3-yl)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)oxy)pentan-2-ol*

[001205] To a solution of N-(5-(oxetan-3-yl)-1H-pyrazol-3-yl)-6-(((2R)-2-((tetrahydro-2H-pyran-2-yl)oxy)pentan-3-yl)oxy)pyrazin-2-amine (845 mg, 2.09 mmol) in dry DCM (6 mL) was added HCOOH (2.0 mL) at 0 °C under N₂ and the reaction mixture was allowed to warm to rt and stirred overnight. The reaction was basified with NH₃ in MeOH (7 M) to pH~8. The solid precipitate was filtered off and the filtrate was concentrated under reduced pressure. The crude was purified by Prep-HPLC (Method A) to afford the racemic compound (500 mg, 74%). This was separated by chiral-SFC (Column: OZ 20*250mm, 10 μ m (Daicel), Column temperature: 35 °C, Mobile phase: CO₂/MeOH [0.2%NH₃(7M in MeOH)] =55/45, Flow rate: 100 g/min, Back pressure: 100 bar) to give Peak 1, the title compound (219.5 mg, 32.8%) as a yellow solid. LCMS $m/z = 320$ $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.16 (br s, 1H), 9.59 (s, 1H), 7.98 (s, 1H), 7.49 (s, 1H), 6.49 (s, 1H), 4.96-4.84 (m, 3H), 4.75-4.70 (m, 1H), 4.69-4.63 (m, 2H), 4.34-4.22 (m, 1H), 3.90-3.81 (m, 1H), 1.80-1.74 (m, 1H), 1.67-1.55 (m, 1H), 1.08 (d, 3H), 0.90 (t, 3H).

[001206] **Example 219**, (S)-6-(1-phenylethoxy)-N-(5-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)pyrazin-2-amine



[001207] Step 1: *Synthesis of 5,5,5-trifluoro-3-oxopentanenitrile*

[001208] A solution of n-BuLi (16.0 mmol, n-hexane solution) was added dropwise to a solution of 2-cyanoacetic acid (1.15 g, 13.6 mmol) and 2,2'-bipyridyl (10 mg) in THF (60 mL) cooled to -78 °C under argon, and treated dropwise with 3,3,3-trifluoropropanoyl chloride (2.0 g, 13.6 mmol) in THF (8 mL). After stirring at this temperature for 3 h, the reaction was quenched by the addition of water. The mixture was concentrated *in vacuo*, the residue was dissolved in water and washed with ether. The aqueous phase was acidified with 1N HCl to pH=3 and extracted with EtOAc. The organic phase was sequentially washed with water and brine, then dried over Na₂SO₄, filtered and evaporated. The crude product was purified by column chromatography on silica gel eluting with EtOAc/PE (1:3)

to give the title product (800 mg, 39%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 3.63 (s, 2H), 3.46 (q, 2H).

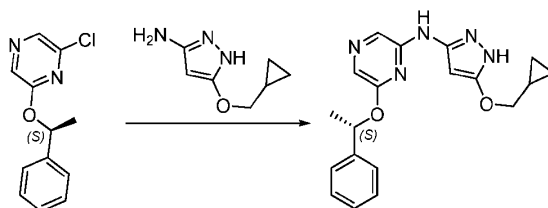
[001209] Step 2: *Synthesis of 5-(2,2,2-trifluoroethyl)-1H-pyrazol-3-amine*

[001210] A solution of 5,5,5-trifluoro-3-oxopentanenitrile (800 mg, 5.3 mmol), hydrazinehydrate (800 mg, 16.0 mmol) and conc. HCl aq. (0.6 mL, 8.0 mmol) in EtOH (10 mL) was stirred at 100 °C for 18 h. The reaction mixture was diluted with MeOH and treated with Na_2CO_3 solid, filtered, the filtrate was evaporated and concentrated. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (0% to 100%) to give the title product (80 mg, 9%) as a yellow oil. LCMS m/z = 166 $[\text{M}+\text{H}]^+$.

[001211] Step 3: *Synthesis of (S)-6-(1-phenylethoxy)-N-(5-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)pyrazin-2-amine*

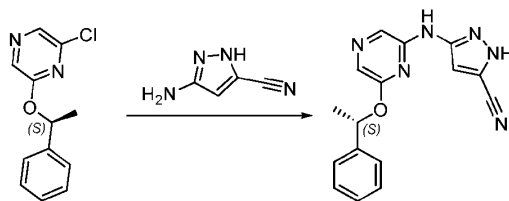
[001212] The title compound was obtained as a white solid (11 mg, 6%) from Example 209, step 2 and 5-(2,2,2-trifluoroethyl)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 202, step 2. LCMS m/z = 364 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.35 (br s, 1H), 9.68 (s, 1H), 7.94 (s, 1H), 7.56 (s, 1H), 7.43-7.39 (m, 2H), 7.36-7.31 (m, 2H), 7.29-7.24 (m, 1H), 6.40 (s, 1H), 6.13-6.07 (m, 1H), 3.80-3.70 (m, 2H), 1.59 (d, 3H).

[001213] **Example 220**, (S)-N-(5-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-6-(1-phenylethoxy)pyrazin-2-amine



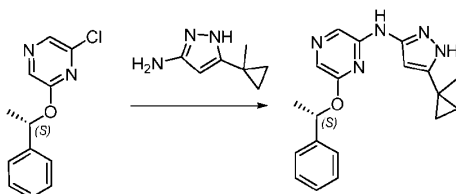
[001214] The title compound was obtained as a white solid (66.2 mg, 44%) from Example 209, step 2 and 5-(cyclopropylmethoxy)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 202, step 2. LCMS m/z = 352 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.71-11.12 (m, 1H), 9.73-9.46 (m, 1H), 7.99-7.55 (m, 2H), 7.40-7.24 (m, 5H), 6.11 (q, 1H), 5.65-5.51 (m, 1H), 3.88 (d, 2H), 1.60 (d, 3H), 1.30-1.14 (m, 1H), 0.60-0.52 (m, 2H), 0.44-0.25 (m, 2H).

[001215] **Example 221**, (S)-3-(((6-(1-phenylethoxy)pyrazin-2-yl)amino)-1H-pyrazole-5-carbonitrile



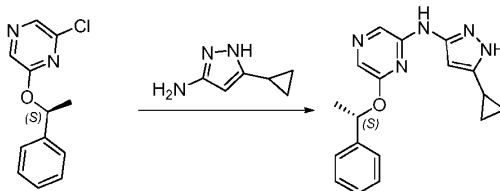
[001216] The title compound was obtained as a yellow solid (32.5 mg, 12.5%) from Example 209, step 2 and 3-amino-1H-pyrazole-5-carbonitrile, following a similar procedure to that described in Example 202, step 2. LCMS $m/z = 307$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 13.49 (br s, 1H), 10.07 (br s, 1H), 7.79 (s, 1H), 7.70 (s, 1H), 7.39-7.30 (m, 4H), 7.28-7.20 (m, 1H), 6.54 (s, 1H), 6.03 (q, 1H), 1.59 (d, 3H).

[001217] **Example 222**, (S)-N-(5-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-6-(1-phenylethoxy)pyrazin-2-amine



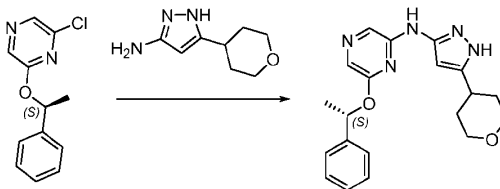
[001218] The title compound was obtained, 40 mg, 11% as a white solid, from Example 209, step 2, and 5-(1-methylcyclopropyl)-1H-pyrazol-3-amine following the procedure described in Example 207, step 8. LCMS $m/z = 336$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.86 (br s, 1H), 9.51 (s, 1H), 7.96 (s, 1H), 7.52 (s, 1H), 7.42-7.39 (m, 2H), 7.37-7.31 (m, 2H), 7.29-7.24 (m, 1H), 6.15-6.08 (m, 2H), 1.60 (d, 3H), 1.39 (s, 3H), 0.93-0.85 (m, 2H), 0.82-0.74 (m, 2H).

[001219] **Example 223**, (S)-N-(5-cyclopropyl-1H-pyrazol-3-yl)-6-(1-phenylethoxy)pyrazin-2-amine



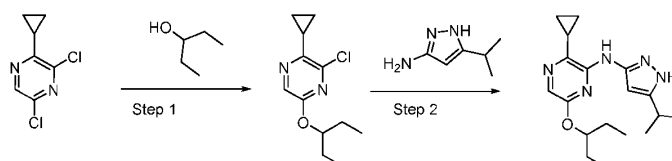
[001220] The title compound was obtained as a yellow solid (77.8 mg, 28.4%) from Example 209, step 2 and 5-cyclopropyl-1H-pyrazol-3-amine, following the procedure described in Example 202, step 2. LCMS $m/z = 322$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.93 (s, 1H), 9.49 (s, 1H), 7.95 (s, 1H), 7.53 (s, 1H), 7.41 (d, 2H), 7.35 (t, 2H), 7.26 (t, 1H), 6.08 (q, 1H), 5.96 (s, 1H), 2.00-1.75 (m, 1H), 1.60 (d, 3H), 0.97-0.91 (m, 2H), 0.79-0.54 (m, 2H).

[001221] **Example 224**, (S)-6-(1-phenylethoxy)-N-(5-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-3-yl)pyrazin-2-amine



[001222] The title compound was obtained as a white solid (39.6 mg, 26%) from Example 209, step 2 and 5-(oxan-4-yl)-1H-pyrazol-3-amine, following the procedure described in Example 202, step 2. LCMS $m/z = 366$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.01 (s, 1H), 9.54 (s, 1H), 7.96 (s, 1H), 7.54 (s, 1H), 7.41-7.40 (m, 2H), 7.36-7.30 (m, 2H), 7.27-7.24 (m, 1H), 6.12-6.07 (m, 1H), 6.10 (s, 1H), 3.95-3.88 (m, 2H), 2.89-2.82 (m, 1H), 1.82-1.79 (m, 2H), 1.68-1.64 (m, 2H), 1.60 (d, 3H).

[001223] **Example 225**, 3-cyclopropyl-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(pentan-3-yloxy)pyrazin-2-amine



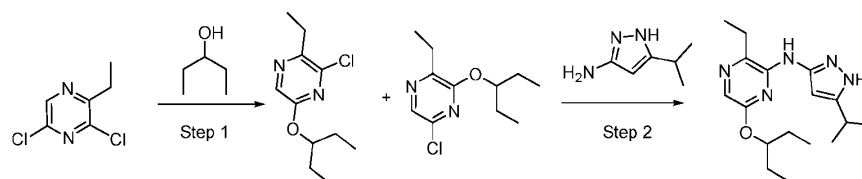
[001224] Step 1: *Synthesis of 3-chloro-2-cyclopropyl-5-(pentan-3-yloxy)pyrazine*

[001225] The title compound was obtained as yellow oil (250 mg, 70%) from pentan-3-ol and 3,5-dichloro-2-cyclopropylpyrazine, following the procedure described in Example 39, step 1. LCMS $m/z = 241$ $[M+H]^+$.

[001226] Step 2: *Synthesis of 3-cyclopropyl-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(pentan-3-yloxy)pyrazin-2-amine*

[001227] The title compound was obtained as a yellow solid (12.2 mg, 4%) from the compound from step 1 and 5-(propan-2-yl)-1H-pyrazol-3-amine, following the procedure described in Example 37, step 2. LCMS $m/z = 330$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 12.00 (br s, 1H), 8.71 (s, 1H), 7.35 (s, 1H), 6.36 (s, 1H), 4.89-4.82 (m, 1H), 2.96-2.90 (m, 1H), 2.40-2.31 (m, 1H), 1.70-1.57 (m, 4H), 1.23 (d, 6H), 0.93-0.77 (m, 10H).

[001228] **Example 226**, 3-ethyl-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(pentan-3-yloxy)pyrazin-2-amine



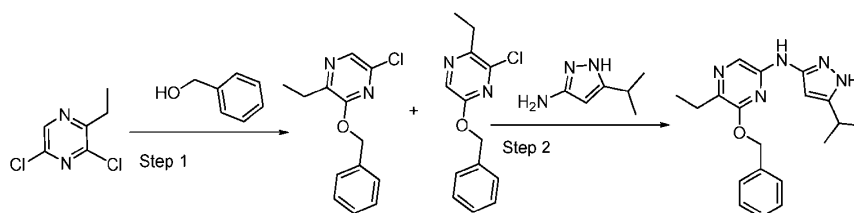
[001229] Step 1: *Synthesis of 3-chloro-2-ethyl-5-(pentan-3-yloxy)pyrazine and 5-chloro-2-ethyl-2-(pentan-3-yloxy)pyrazine*

[001230] The title compound was obtained as a yellow oil (150 mg, 58%) from 3,5-dichloro-2-ethylpyrazine and pentan-3-ol, following the procedure described in Example 39, step 1. LCMS $m/z = 229$ $[M+H]^+$.

[001231] Step 2: *Synthesis of 3-ethyl-N-(5-isopropyl-1H-pyrazol-3-yl)-6-(pentan-3-yloxy)pyrazin-2-amine*

[001232] The title compound was obtained, 11.2 mg, 6%, from 3-chloro-2-ethyl-5-(pentan-3-yloxy)pyrazine and 5-chloro-2-ethyl-3-(pentan-3-yloxy)pyrazine, following a similar procedure to that described in Example 24 and 25, step 1, except chiral Prep-SFC (Method C, gradient: 80/20) was used. LCMS $m/z = 330$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.98 (br s, 1H), 8.54 (s, 1H), 7.43 (s, 1H), 6.34 (s, 1H), 4.89-4.83 (m, 1H), 2.95-2.88 (m, 1H), 2.73 (q, 2H), 1.70-1.57 (m, 4H), 1.22 (d, 6H), 1.16 (t, 3H), 0.87 (t, 6H).

[001233] **Example 227**, 6-(benzyloxy)-5-ethyl-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine



[001234] Step 1: *Synthesis of 3-(benzyloxy)-5-chloro-2-ethylpyrazine and 5-(benzyloxy)-3-chloro-2-ethylpyrazine*

[001235] The title compound was obtained as a mixture of the title compounds (200 mg, 47%) from benzyl alcohol and 3,5-dichloro-2-ethylpyrazine, following a similar procedure to that described in Example 39, step 1. LCMS $m/z = 249$ $[M+H]^+$.

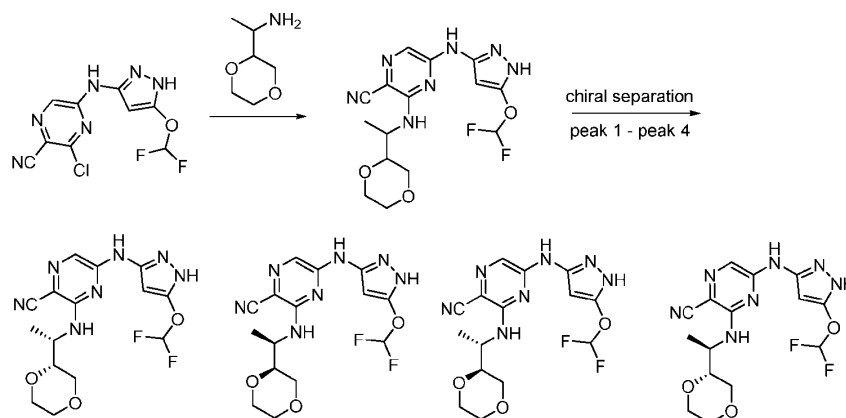
[001236] Step 2: *Synthesis of 6-(benzyloxy)-5-ethyl-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine*

[001237] The title compound was obtained, 27.2 mg, 40%, from the compounds from step 1 and 5-(propan-2-yl)-1H-pyrazol-3-amine, following a similar procedure to that described in Example 24 and 25, step 1. LCMS $m/z = 338$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.87 (s, 1H), 9.29 (s, 1H), 8.04 (s, 1H), 7.45-7.31 (m, 5H), 6.11 (s, 1H), 5.42 (s, 2H), 2.92-2.85 (m, 1H), 2.65 (q, 2H), 1.19 (d, 6H), 1.14 (t, 3H).

[001238] **Example 228**, 3-(((R)-1-((S)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((R)-1-((R)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((S)-1-((S)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((S)-1-((R)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile and

[001239] **Example 238**, 3-(((R)-1-((S)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((R)-1-((R)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((S)-1-((S)-1,4-dioxan-2-

yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile or 3-(((S)-1-((R)-1,4-dioxan-2-yl)ethyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile

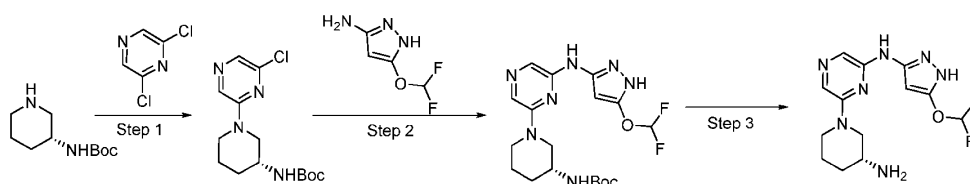


[001240] A mixture of Example 114, step 1, (300 mg, 1.04 mmol), 1-(1,4-dioxan-2-yl)ethan-1-amine (HCl salt, 162 mg, 1.24 mmol) and DIPEA (402 mg, 3.12 mmol) in NMP (8.0 mL) was stirred at 90°C for 4 h under N₂. The reaction mixture was concentrated under reduced pressure. The crude was purified by column chromatography on silica gel eluting with PE/EtOAc (1/4) to afford the racemic compound (108 mg, 27%) and then separated by chiral Prep-SFC (Column: AD 20*250mm, 10 μm (Daicel), Column temperature: 35°C, Mobile phase: CO₂/(MeOH/EtOH(0.2% MeOH/NH₃)=1:9) = 85/15, Flow rate: 120 g/min, Back pressure: 100 bar) to give 4.6 mg of Peak 3 (Example 238), 7.4 mg of Peak 4 and 40 mg of mixture containing Peak 1 and Peak 2. Peak 1 and Peak 2 were separated by chiral Prep-SFC (Column: OZ 20*250mm, 10 μm (Daicel), Column temperature: 35°C, Mobile phase: CO₂/MeOH (0.2% MeOH/NH₃) = 80/20, Flow rate: 100 g/min, Back pressure: 100 bar) to give 17.2 mg of Peak 1 (Example 228), and 19.9 mg of Peak 2.

[001241] Peak 1, **Example 228**: LCMS *m/z* = 382 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.16 (br s, 1H), 10.59 (br s, 1H), 7.51 (s, 1H), 7.25 (t, 1H), 7.07 (s, 1H), 5.98 (s, 1H), 4.18-4.09 (m, 1H), 3.61-3.58 (m, 2H), 3.55-3.47 (m, 2H), 3.46-3.43 (m, 1H), 3.38-3.29 (m, 1H), 3.28-3.27 (m, 1H), 1.23-1.19 (m, 3H).

[001242] Peak 3, **Example 238**: LCMS *m/z* = 382 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.15 (br s, 1H), 10.60 (br s, 1H), 7.48 (s, 1H), 7.25 (t, 1H), 7.01 (s, 1H), 5.99 (s, 1H), 4.18-4.09 (m, 1H), 3.61-3.58 (m, 2H), 3.55-3.47 (m, 2H), 3.46-3.43 (m, 1H), 3.38-3.29 (m, 1H), 3.28-3.27 (m, 1H), 1.15 (m, 3H).

[001243] **Example 229**, (R)-6-(3-aminopiperidin-1-yl)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazine-2-amine



[001244] Step 1: *Synthesis of tert-butyl (R)-(1-(6-chloropyrazin-2-yl)piperidin-3-yl)carbamate*

[001245] To a mixture of tert-butyl (R)-piperidin-3-ylcarbamate (190 mg, 948 μmol) and 2,6-dichloropyrazine (141 mg, 948 μmol) in MeCN (10 mL) was added TEA (287 mg, 2.84 mmol) at rt. The mixture was stirred for 1 h. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel eluting with PE/EtOAc (4/1) to give the title product (260 mg, 87%) as a colorless gum. LCMS m/z = 313 $[\text{M}+\text{H}]^+$.

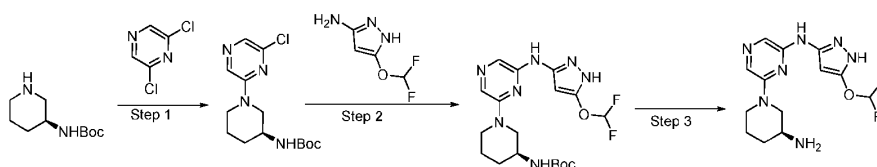
[001246] Step 2: *Synthesis of tert-butyl (R)-(1-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidin-3-yl)carbamate*

[001247] The title compound was obtained as a yellow solid, 200 mg, 56%, from the compound from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS m/z = 426 $[\text{M}+\text{H}]^+$.

[001248] Step 3: *Synthesis of (R)-6-(3-aminopiperidin-1-yl)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

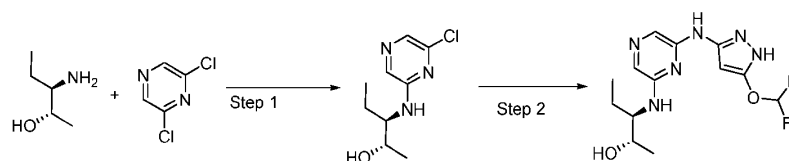
[001249] The title compound was obtained as a white solid, 41.2 mg, 27%, from the compound from step 2, following the procedure described in Example 3, step 3. LCMS m/z = 326 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.00 (br s, 1H), 9.77 (s, 1H), 7.64 (s, 1H), 7.43 (s, 1H), 7.24 (t, 1H), 5.86 (s, 1H), 4.04-3.97 (m, 3H), 2.94-2.87 (m, 2H), 2.74-2.67 (m, 2H), 1.88-1.85 (m, 1H), 1.74-1.70 (m, 1H), 1.46-1.43 (m, 1H), 1.28-1.25 (m, 1H).

[001250] **Example 230**, (S)-6-(3-aminopiperidin-1-yl)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



[001251] The title product was obtained using a similar method 3 step procedure to that described for Example 229 Steps 1 to 3. LCMS m/z = 326 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 12.52 (br s, 1H), 10.51 (s, 1H), 8.35 (s, 1H), 7.65 (s, 1H), 7.45 (s, 1H), 7.25 (t, 1H), 5.90 (s, 1H), 4.11-4.03 (m, 2H), 3.91-3.85 (m, 2H), 3.11-3.01 (m, 3H), 1.98-1.88 (m, 1H), 1.81-1.70 (m, 1H), 1.60-1.48 (m, 2H).

[001252] **Example 231**, (2S,3R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)amino)pentan-2-ol



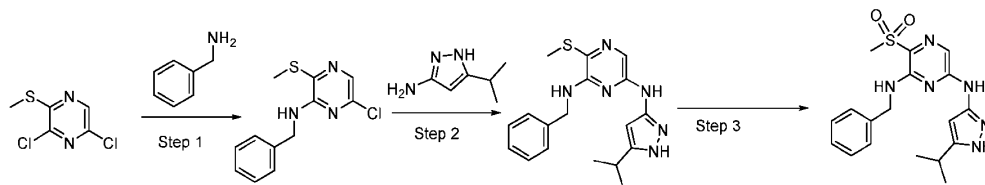
[001253] Step 1: *Synthesis of (2S,3R)-3-((6-chloropyrazin-2-yl)amino)pentan-2-ol*

[001254] A mixture of (2S, 3R)-3-aminopentan-2-ol (250 mg, 2.42 mmol), 2,6-dichloropyrazine (432 mg, 2.90 mmol) and TEA (732 mg, 7.25 mmol) in NMP (5 mL) was stirred at 100°C for 2 h under N₂. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel eluting with EtOAc/PE (9/1) to afford the title compound (300 mg, 57%) as yellow oil. LCMS *m/z* = 216 [M+H]⁺.

[001255] Step 2: *Synthesis of (2S,3R)-3-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)amino)pentan-2-ol*

[001256] The title compound was obtained as a yellow oil, 40 mg, 13%, from the compound from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following the procedure described in Example 37, step 2. LCMS *m/z* = 329 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆) δ ppm 12.14 (br s, 1H), 9.82 (s, 1H), 7.38 (s, 1H), 7.24 (t, 1H), 7.25 (s, 1H), 6.74 (d, 1H), 5.53 (s, 1H), 4.75-4.74 (m, 1H), 3.70-3.66 (m, 1H), 3.50-3.34 (m, 1H), 1.70-1.63 (m, 1H), 1.42-1.34 (m, 1H), 1.09-1.07 (m, 3H), 0.90-0.81 (m, 3H).

[001257] **Example 232**, N2-benzyl-N6-(5-isopropyl-1H-pyrazol-3-yl)-3-(methylsulfonyl)pyrazine-2,6-diamine



[001258] Step 1: *Synthesis of N-benzyl-6-chloro-3-(methylthio)pyrazin-2-amine*

[001259] To a solution of 3,5-dichloro-2-(methylsulfanyl)pyrazine (200 mg, 1.02 mmol) and benzylamine (130 mg, 1.22 mmol) in NMP (2.0 mL) was added KF (118 mg, 2.04 mmol) and the reaction mixture was stirred at 160°C for 1 h. The reaction mixture was diluted with EtOAc, washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/2) to give the title product (145 mg, 53%) as a white solid. LCMS *m/z* = 266 [M+H]⁺.

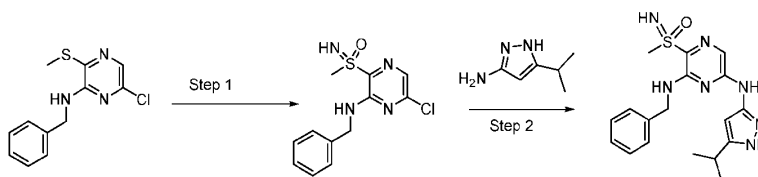
[001260] Step 2: *Synthesis of N2-benzyl-N6-(5-isopropyl-1H-pyrazol-3-yl)-3-(methylthio)pyrazine-2,6-diamine*

[001261] To a solution of the compound from step 1 (150 mg, 0.56 mmol) and 5-(propan-2-yl)-1H-pyrazol-3-amine (84.6 mg, 0.68 mmol) in toluene (3.0 mL) was added Pd₂(dba)₃ (102 mg, 0.112 mmol), tBuXPhos (95.5 mg, 0.225 mmol) and KOAc (165 mg, 1.69 mmol) and the reaction mixture was stirred at 80°C overnight. The reaction mixture was diluted with EtOAc, washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/PE (1/2) to give the title product (136 mg, 68%) as a yellow solid. LCMS m/z = 355 [M+H]⁺.

[001262] Step 3: *Synthesis of N2-benzyl-N6-(5-isopropyl-1H-pyrazol-3-yl)-3-(methylsulfonyl)pyrazine-2,6-diamine*

[001263] A solution of the compound from step 2 (70 mg, 0.197 mmol) and m-CPBA (101 mg, 0.591 mmol) in DCM (5.0 mL) was stirred at rt for 4 h. The mixture was diluted with DCM, quenched with aq. Na₂S₂O₃ and washed with aqueous NaHCO₃. The organic layer was concentrated and the residue was purified with Prep-HPLC (Method A) to give the title product (12.4 mg, 16%) as a yellow solid. LCMS m/z = 387 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.07 (br s, 1H), 10.22 (s, 1H), 7.57-7.49 (m, 2H), 7.35-7.30 (m, 4H), 7.24-7.21 (m, 1H), 6.18 (s, 1H), 4.70 (d, 2H), 3.18 (s, 3H), 2.85-2.80 (m, 1H), 1.11 (d, 6H).

[001264] **Example 233**, (3-(benzylamino)-5-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)(imino)(methyl)-λ⁶-sulfanone



[001265] Step 1: *Synthesis of (3-(benzylamino)-5-chloropyrazin-2-yl)(imino)(methyl)-λ⁶-sulfanone*

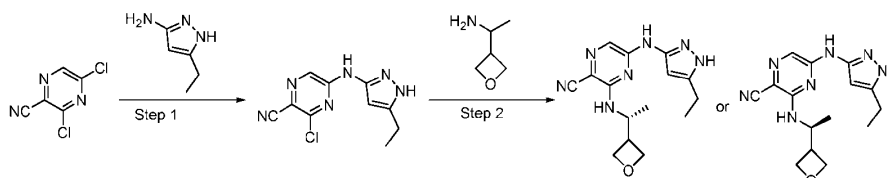
[001266] To a solution of Example 232, step 1 (120 mg, 0.45 mmol) in NH₃-MeOH (6 M, 10 mL) was added (diacetoxyiodo)benzene (434 mg, 1.35 mmol) at 25°C. The reaction mixture was stirred for 2 h, then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with EtOAc/PE (1/2) to give the title product (80 mg, 60%) as a yellow solid. LCMS m/z = 297 [M+H]⁺.

[001267] Step 3: *Synthesis of (3-(benzylamino)-5-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)(imino)(methyl)-λ⁶-sulfanone*

[001268] The title compound was obtained as a white solid, 10.7 mg, 16%, from the compound from step 1 and 5-(propan-2-yl)-1H-pyrazol-3-amine, following the procedure described in Example 202, step 2. LCMS m/z = 386 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.01 (br s, 1H), 10.02

(br s, 1H), 8.84-8.78 (m, 1H), 7.57 (s, 1H), 7.35-7.27 (m, 4H), 7.26-7.21 (m, 1H), 6.20 (s, 1H), 4.68 (d, 2H), 4.59 (s, 1H), 3.11 (s, 3H), 2.83 (m, 1H), 1.12 (d, 6H).

[001269] **Example 234**, (R)-5-((5-ethyl-1H-pyrazol-3-yl)amino)-3-((1-(oxetan-3-yl)ethyl)amino)pyrazine-2-carbonitrile or (S)-5-((5-ethyl-1H-pyrazol-3-yl)amino)-3-((1-(oxetan-3-yl)ethyl)amino)pyrazine-2-carbonitrile



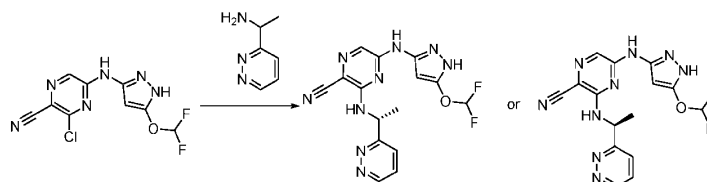
[001270] Step 1: *Synthesis of 3-chloro-5-((5-ethyl-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile*

[001271] A mixture of 3,5-dichloropyrazine-2-carbonitrile (1g, 5.74 mmol), 5-ethyl-1H-pyrazol-3-amine (764 mg, 6.88 mmol) and DIPEA (2.2 g, 17.2 mmol) in dioxane (30.0 mL) was stirred at rt for 4 h under N₂. The reaction mixture was diluted with EtOAc, washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated to dryness under reduced pressure to the title product (900 mg, 63%) as a white solid. LCMS m/z = 249 [M+H]⁺.

[001272] Step 2: *Synthesis of (R)-5-((5-ethyl-1H-pyrazol-3-yl)amino)-3-((1-(oxetan-3-yl)ethyl)amino)pyrazine-2-carbonitrile or (S)-5-((5-ethyl-1H-pyrazol-3-yl)amino)-3-((1-(oxetan-3-yl)ethyl)amino)pyrazine-2-carbonitrile*

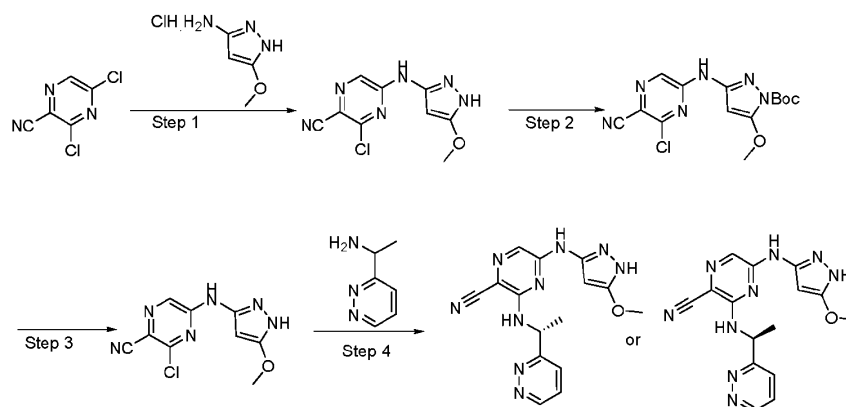
[001273] A mixture of the compound from step 1 (150 mg, 0.6 mmol), 1-(oxetan-3-yl)ethan-1-amine (73.1 mg, 0.7 mmol) and DIPEA (232 mg, 1.80 mmol) in NMP (8.0 mL) was stirred at 100 °C for 16 h under N₂. The reaction mixture was directly purified by Prep-HPLC (Method A) to afford the racemic product (120 mg) and then separated by chiral Prep-SFC (Method E, 60/40) to give peak 1, the title compound (39.5 mg, 21%) as a white solid. LCMS m/z = 314 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.13 (br s, 1H), 10.27 (br s, 1H), 7.58 (s, 1H), 6.94 (d, 1H), 6.45 (s, 1H), 4.69-4.65 (m, 1H), 4.63-4.57 (m, 2H), 4.37-4.27 (m, 2H), 3.24-3.14 (m, 1H), 2.60 (q, 2H), 1.21 (t, 3H), 1.12 (d, 3H).

[001274] **Example 235**, (R)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3-((1-(pyridazin-3-yl)ethyl)amino)pyrazine-2-carbonitrile or (S)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3-((1-(pyridazin-3-yl)ethyl)amino)pyrazine-2-carbonitrile



[001275] A mixture of Example 114, step 1, (250 mg, 0.9 mmol), 1-(pyridazin-3-yl)ethan-1-amine (107 mg, 0.9 mmol) and DIPEA (337 mg, 2.61 mmol) in NMP (2.0 mL) was stirred at 100°C for 16 h under N₂. The reaction mixture was directly purified by Prep-HPLC (Method A) to afford the racemic product (170 mg) and then separated by chiral Prep-SFC (Column: WHELK 20*250mm, 10 µm (Daicel), Column temperature: 35°C, Mobile phase: CO₂/MeOH (0.2% MeOH/NH₃) = 60/40, Flow rate: 100 g/min, Back pressure: 100 bar) to give the title compound (65.7 mg, 20%) as a yellow solid. LCMS *m/z* = 374 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.46 (br s, 1H), 10.74 (br s, 1H), 9.12 (d, 1H), 7.96 (d, 1H), 7.85 (d, 1H), 7.71 (dd, 1H), 7.48 (s, 1H), 7.37 (t, 1H), 5.85 (s, 1H), 5.50-5.43 (m, 1H), 1.65 (d, 3H).

[001276] **Example 236**, (R)-5-((5-methoxy-1H-pyrazol-3-yl)amino)-3-((1-(pyridazin-3-yl)ethyl)amino)pyrazine-2-carbonitrile or (S)-5-((5-methoxy-1H-pyrazol-3-yl)amino)-3-((1-(pyridazin-3-yl)ethyl)amino)pyrazine-2-carbonitrile



[001277] Step 1: *Synthesis of 3-chloro-5-((5-methoxy-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile*

[001278] A mixture of 3,5-dichloropyrazine-2-carbonitrile (4.0 g, 22.9 mmol), 5-methoxy-1H-pyrazol-3-amine hydrochloride (3.42 g, 22.9 mmol) and NaHCO₃ (9.57 g, 114 mmol) in DMA (35 mL) was stirred at rt for 14 h. The reaction mixture diluted with EtOAc and washed with water and brine. The organic layer was concentrated *in vacuo* to obtain the title product (1.8 g, crude) as a yellow solid. LCMS *m/z* = 251 [M+H]⁺.

[001279] Step 2: *Synthesis of tert-butyl 3-((6-chloro-5-cyanopyrazin-2-yl)amino)-5-methoxy-1H-pyrazole-1-carboxylate*

[001280] A mixture of the compound from step 1 (1.1 g, 4.38 mmol), Boc₂O (1.9 g, 8.76 mmol) and DIPEA (2.83 g, 21.9 mmol) in dioxane (10 mL) was stirred at 70°C for 14 h. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was concentrated *in vacuo* to give a residue which was purified by column chromatography on silica gel

eluting with PE/EtOAc (1/2) to afford the title compound (558 mg, 36%) as a yellow solid. LCMS $m/z = 373$ $[M+Na]^+$.

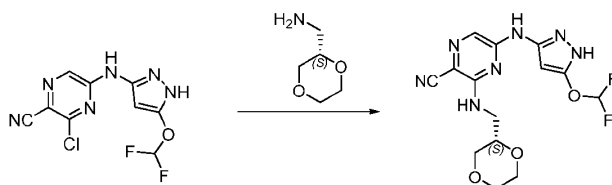
[001281] Step 3: *Synthesis of 3-chloro-5-((5-methoxy-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile*

[001282] A mixture of the compound from step 2 (558 mg, 1.59 mmol) in HCl/dioxane (7 M, 10 mL) was stirred at rt for 14 h. The reaction mixture was concentrated *in vacuo* to afford the title compound (370 mg, 92%) as a white solid. LCMS $m/z = 251$ $[M+H]^+$.

[001283] Step 4: *Synthesis of (R)-5-((5-methoxy-1H-pyrazol-3-yl)amino)-3-((1-(pyridazin-3-yl)ethyl)amino)pyrazine-2-carbonitrile or (S)-5-((5-methoxy-1H-pyrazol-3-yl)amino)-3-((1-(pyridazin-3-yl)ethyl)amino)pyrazine-2-carbonitrile*

[001284] A mixture of the compound from step 3 (250 mg, 997 μ mol), 1-(pyridazin-3-yl)ethan-1-amine (122 mg, 997 μ mol) and DIPEA (386 mg, 2.99 mmol) in NMP (10 mL) was stirred at 100 °C for 14 h. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was concentrated *in vacuo* and the residue was purified by Prep-HPLC (Method A). This product was separated by chiral Prep-SFC (Column: WHELK 20*250mm, 10 μ m (Daicel), Column temperature: 35°C, Mobile phase: CO₂/MeOH (0.5% Methanol Ammonia) = 50/50, Flow rate: 80 g/min, Back pressure: 100 bar) to give peak 2, the title compound (11 mg, 3%) as a white solid. LCMS $m/z = 338$ $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.85 (br s, 1H), 10.40 (br s, 1H), 9.13-9.08 (m, 1H), 7.82-7.77 (m, 2H), 7.70-7.67 (m, 1H), 7.50-7.46 (m, 1H), 5.54-5.46 (m, 1H), 3.90-3.84 (m, 3H), 3.42-3.39 (m, 1H), 1.63 (d, 3H).

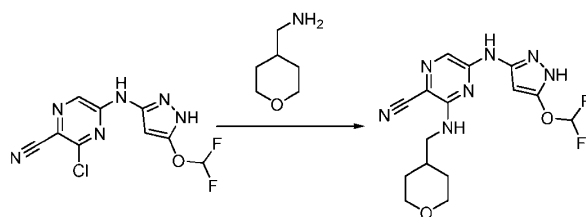
[001285] **Example 237**, (S)-3-(((1,4-dioxan-2-yl)methyl)amino)-5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile



[001286] A mixture of Example 114, step 1, (200 mg, 697 μ mol), (S)-((1,4-dioxan-2-yl)methanamine hydrochloride (159 mg, 1.04 mmol) and TEA (270 mg, 2.09 mmol) in NMP (2.0 mL) was stirred at 150°C for 18 h under N₂. The reaction mixture was purified by Prep-HPLC (Method C) to afford the title compound (44.5 mg, 17%) as a white solid. LCMS $m/z = 368$ $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.20 (br s, 1H), 10.67 (br s, 1H), 7.48 (s, 2H), 7.25 (t, 1H), 5.95-5.90 (m, 1H), 3.76-3.69 (m, 3H), 3.64-3.36 (m, 5H), 3.28-3.20 (m, 1H).

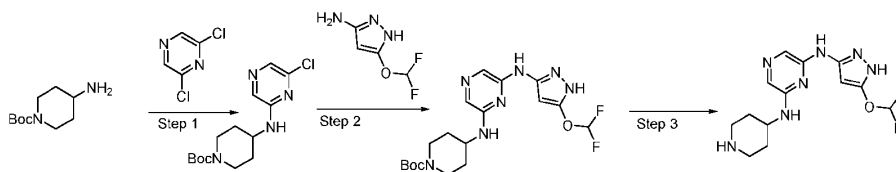
[001287] **Example 238**. See Example 228.

[001288] **Example 239**, 5-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)-3-(((tetrahydro-2H-pyran-4-yl)methyl)amino)pyrazine-2-carbonitrile



[001289] A mixture of Example 114, step 1, (100 mg, 0.35 mmol) and (tetrahydro-2H-pyran-4-yl)methanamine (120 mg, 1.05 mmol) in NMP (2.0 mL) was stirred at 100°C for 16 h under N₂. The reaction mixture was directly purified by Prep-HPLC (Method A) to give the title product (49.7 mg, 39%) as a yellow solid. LCMS m/z = 366 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.14 (br s, 1H), 10.61 (br s, 1H), 7.51 (s, 1H), 7.46 (s, 1H), 7.23 (t, 1H), 6.06 (s, 1H), 3.84-3.81 (m, 2H), 3.29-3.19 (m, 4H), 1.92-1.83 (m, 1H), 1.61-1.52 (m, 2H), 1.22-1.12 (m, 2H).

[001290] **Example 240**, N²-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-N⁶-(piperidin-4-yl)pyrazine-2,6-diamine



[001291] Step 1: *Synthesis of tert-butyl 4-((6-chloropyrazin-2-yl)amino)piperidine-1-carboxylate*

[001292] A mixture of 2,6-dichloropyrazine (300 mg, 1.84 mmol), DIPEA (784 mg, 5.52 mmol) and tert-butyl 4-aminopiperidine-1-carboxylate (405 mg, 1.84 mmol) in DMF (6.0 mL) was stirred at 90°C for 3 h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with PE/EtOAc (1/1) to obtain the crude product (210 mg, 33%) as a yellow oil. LCMS m/z = 257 [M+H]⁺.

[001293] Step 2: *Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)amino)piperidine-1-carboxylate*

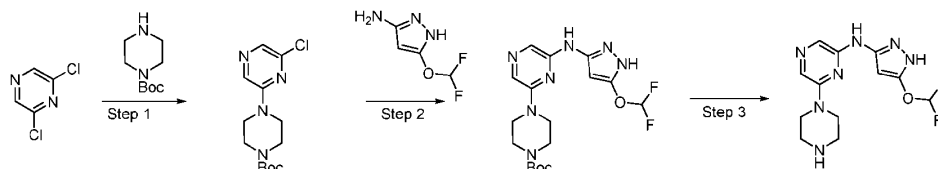
[001294] The title compound was obtained, 120 mg, 46%, from the compound from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine following the procedure described in Example 19 and 20, step 2. LCMS m/z = 426 [M+H]⁺.

[001295] Step 3: *Synthesis of N²-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-N⁶-(piperidin-4-yl)pyrazine-2,6-diamine*

[001296] The title compound was obtained as a white solid, 54.7 mg, 71%, from the compound from step 2, following the procedure described in Example 3, step 3. LCMS m/z = 326 [M+H]⁺. ¹H

NMR (400 MHz, DMSO- d_6) δ ppm 12.15 (br s, 1H), 9.94 (s, 1H), 7.31 (s, 1H), 7.30 (s, 1H), 7.24 (t, 1H), 6.92 (d, 1H), 5.67 (s, 1H), 3.92-3.90 (m, 1H), 3.73-3.67 (m, 1H), 3.07-2.95 (m, 2H), 2.68-2.58 (m, 2H), 1.98-1.91 (m, 2H), 1.43-1.27 (m, 2H)

[001297] **Example 241**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperazin-1-yl)pyrazin-2-amine



[001298] Step 1: *Synthesis of tert-butyl 4-(6-chloropyrazin-2-yl)piperazine-1-carboxylate*

[001299] A solution of 2,6-dichloropyrazine (478 mg, 3.21 mmol), tert-butyl piperazine-1-carboxylate (500 mg, 2.68 mmol) and TEA (813 mg, 8.04 mmol) in NMP (15 mL) was stirred at 90°C for 2 h. The reaction mixture was cooled to rt, diluted with EtOAc and washed with water and brine. The organic layer was dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with PE/EtOAc (95/5) to afford the title compound (650 mg, 81%) as a white solid. LCMS m/z = 299 [M+H]⁺.

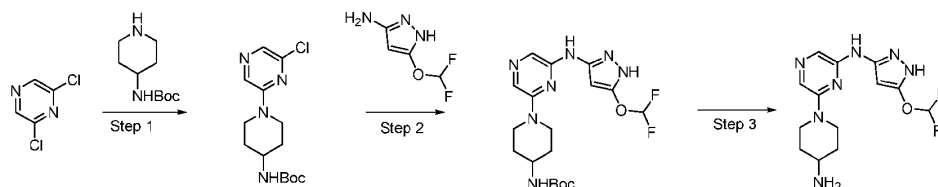
[001300] Step 2: *Synthesis of tert-butyl 4-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperazine-1-carboxylate*

[001301] The title compound was obtained as a brown oil, 250 mg, 61%, from the compound from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following the procedure described in Example 19 and 20, step 2. LCMS m/z = 412 [M+H]⁺.

[001302] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperazin-1-yl)pyrazin-2-amine*

[001303] The title compound was obtained as a white solid, 35.4 mg, 18.8%, from the compound from step 2, following the procedure described in Example 3 step 3. LCMS m/z = 312 [M+H]⁺. ¹H NMR (400 MHz, DMSO- d_6) δ ppm 11.88 (br s, 1H), 9.81 (br s, 1H), 7.63 (s, 1H), 7.46 (s, 1H), 7.25 (t, 1H), 5.84 (s, 1H), 3.45-3.30 (m, 4H), 2.90-2.75 (m, 4H).

[001304] **Example 242**, 6-(4-aminopiperidin-1-yl)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



[001305] Step 1: *Synthesis of tert-butyl (1-(6-chloropyrazin-2-yl)piperidin-4-yl)carbamate*

[001306] The title compound was obtained as a yellow oil (650 mg, 83%) from 2,6-dichloropyrazine and tert-butyl N-(piperidin-4-yl)carbamate using a similar method as described for Example 241, Step 1. LCMS $m/z = 313$ $[M+H]^+$.

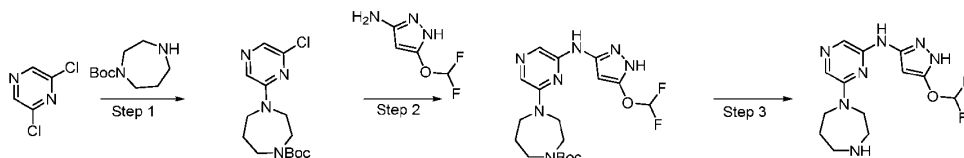
[001307] Step 2: *Synthesis of tert-butyl (1-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidin-4-yl)carbamate*

[001308] The title compound was obtained as a brown oil (200 mg, 59%) from the compound from step 1 and 5-(difluoromethoxy)-1H-pyrazol-3-amine using a similar method as described for Example 241, Step 2. LCMS $m/z = 426$ $[M+H]^+$.

[001309] Step 3: *Synthesis of 6-(4-aminopiperidin-1-yl)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine*

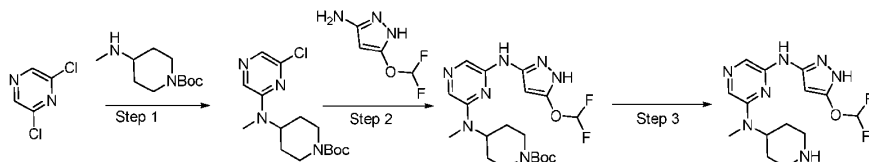
[001310] To a solution of the compound from step 2 (200 mg, 470 μ mol) in DCM (10.0 mL) was added 4 M HCl/dioxane (1.0 mL) at rt and stirred for 1 h. The reaction mixture was basified with NH_3 (7M in MeOH) to pH ~10. The solid suspension was filtered off and the filtrate and washings were concentrated under reduced pressure. The residue was purified by Prep-HPLC (Method A) to afford the title compound (20.7 mg, 14%) as a white solid. LCMS $m/z = 326$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 9.95 (br s, 1H), 7.67-7.64 (m, 1H), 7.43 (s, 1H), 7.24 (t, 1H), 5.88-5.84 (m, 1H), 4.17-4.09 (m, 2H), 3.57-3.50 (m, 1H), 3.02-2.90 (m, 2H), 1.83-1.74 (m, 2H), 1.39-1.22 (m, 2H).

[001311] **Example 243**, 6-(1,4-diazepan-1-yl)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)pyrazin-2-amine



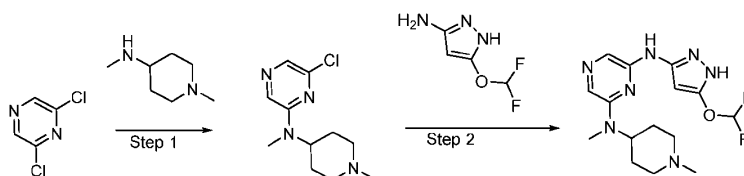
[001312] The title compound was obtained from 2,6-dichloropyrazine and tert-butyl N-(piperidin-4-yl)carbamate and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar 3 step procedure to that described in Example 242, steps 1 to 3. LCMS $m/z = 326$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.76 (br s, 1H), 9.66 (br s, 1H), 7.45 (s, 1H), 7.38 (s, 1H), 7.22 (t, 1H), 5.89 (s, 1H), 3.67-3.60 (m, 4H), 2.89-2.83 (m, 2H), 2.68-2.64 (s, 2H), 1.78-1.75 (m, 2H).

[001313] **Example 244**, N2-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-N6-methyl-N6-(piperidin-4-yl)pyrazine-2,6-diamine



[001314] The title compound was obtained from 2,6-dichloropyrazine and tert-butyl 4-(methylamino)piperidine-1-carboxylate and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar 3 step procedure to that described in Example 241, step 1 to 3. LCMS $m/z = 340$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 10.02 (br s, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.23 (t, 1H), 5.94 (s, 1H), 4.48-4.27 (m, 1H), 4.25-4.17 (m, 1H), 3.20-3.00 (m, 2H), 2.86 (s, 3H), 2.80-2.70 (m, 1H), 2.67-2.51 (m, 2H), 1.76-1.49 (m, 4H).

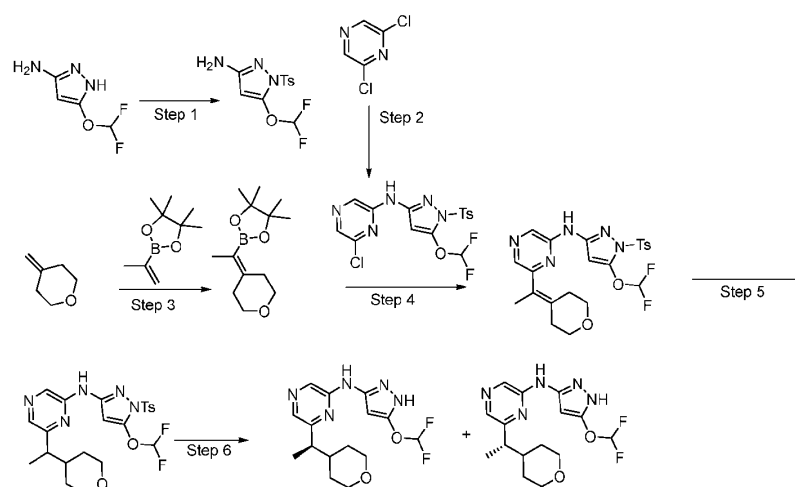
[001315] **Example 245**, N2-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-N6-methyl-N6-(1-methylpiperidin-4-yl)pyrazine-2,6-diamine



[001316] The title compound was obtained from 2,6-dichloropyrazine and N,1-dimethylpiperidin-4-amine and 5-(difluoromethoxy)-1H-pyrazol-3-amine, following a similar 2 step procedure to that described in Example 241, steps 1 to 2. LCMS $m/z = 354$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ ppm 11.93 (br s, 1H), 9.64 (s, 1H), 7.48 (s, 1H), 7.41 (s, 1H), 7.23 (t, 1H), 5.95 (s, 1H), 4.29-4.19 (m, 1H), 2.86 (s, 3H), 2.86-2.80 (m, 2H), 2.17 (s, 3H), 2.03-1.97 (m, 2H), 1.78-1.72 (m, 2H), 1.56-1.53 (m, 2H).

[001317] **Example 246**, (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazin-2-amine or (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazin-2-amine and

[001318] **Example 247**, (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazin-2-amine or (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazin-2-amine



[001319] Step 1: *Synthesis of 5-(difluoromethoxy)-1-tosyl-1H-pyrazol-3-amine*

[001320] To a solution of 5-(difluoromethoxy)-1H-pyrazol-3-amine (5 g, 33.5 mmol) in DCM (100 mL) was added TEA (16.8 g, 167 mmol), DMAP (409 mg, 3.35 mmol) and TsCl (7.01 g, 36.8 mmol) at 0°C and the reaction mixture was stirred at rt for 1 h. The reaction was diluted with DCM, then washed with water and brine. The organic layer was concentrated *in vacuo* and the residue purified by flash chromatography on silica gel eluting with PE/EtOAc (1/1) to afford the title compound (5 g, 49%) as a yellow solid. LCMS $m/z = 304$ $[M+H]^+$.

[001321] Step 2: *Synthesis of 6-chloro-N-(5-(difluoromethoxy)-1-tosyl-1H-pyrazol-3-yl)pyrazin-2-amine*

[001322] To a mixture of the compound from step 1 (5 g, 16.4 mmol) and 2,6-dichloropyrazine (2.44 g, 16.4 mmol) in dry DMF (100 mL) was added NaH (1.96 g, 49.1 mmol) at 0°C. The mixture was stirred at 0°C for 14 h, then quenched with water and extracted with EtOAc. The organic layer was washed with water and brine, then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with PE/EtOAc (1/1) to afford the title compound (3.0 g, 44%) as a yellow solid. LCMS $m/z = 416$ $[M+H]^+$.

[001323] Step 3: *Synthesis of 4,4,5,5-tetramethyl-2-(1-(tetrahydro-4H-pyran-4-ylidene)ethyl)-1,3,2-dioxaborolane*

[001324] A mixture of 4-methylenetetrahydro-2H-pyran (1.00 g, 10.2 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (5.1 g, 30.6 mmol) and Grubbs 2nd catalyst (172 mg, 0.24 mmol) in toluene (20 mL) was stirred at rt for 18 h under N₂. The reaction mixture was diluted with EtOAc, washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel eluting with PE/EtOAc (5/1) to afford the title compound (240 mg, 10%) as a white solid. LCMS $m/z = 239$ $[M+H]^+$.

[001325] Step 4: *Synthesis of N-(5-(difluoromethoxy)-1-tosyl-1H-pyrazol-3-yl)-6-(1-(tetrahydro-4H-pyran-4-ylidene)ethyl)pyrazin-2-amine*

[001326] To a solution of the compound from step 3 (240 mg, 1.01 mmol) and the compound from step 2 (300 mg, 0.71 mmol) in dioxane (5 mL) and H₂O (1 mL) was added Na₂CO₃ (318 mg, 3.03 mmol) and Pd(dppf)Cl₂ (73 mg, 0.11 mmol) at rt under N₂. The reaction mixture was allowed to warm to 100°C and stirred for 2 h under N₂. After cooling to rt, the reaction mixture was diluted with dioxane, filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with PE/EtOAc (1/1) to obtain the title product (200 mg, 40%) as a yellow solid. LCMS m/z = 492 [M+H]⁺.

[001327] Step 5: *Synthesis of N-(5-(difluoromethoxy)-1-tosyl-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazin-2-amine*

[001328] To a solution of the compound from step 4 (200 mg, 407 μmol) in MeOH (5.0 mL) was added PtO₂ (40 mg, 377 μmol) at rt. The reaction mixture was stirred at rt for 24 h under H₂, then diluted with MeOH and filtered through a pad of Celite®. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel eluting with PE/EtOAc (1/1) to obtain the title product (160 mg, 80%) as a yellow solid. LCMS m/z = 494 [M+H]⁺.

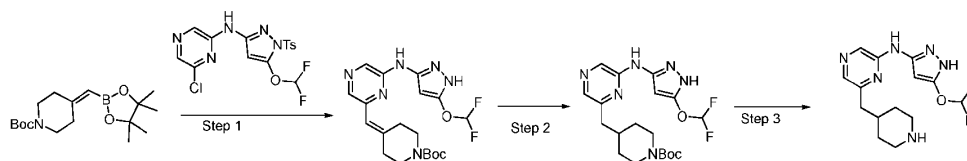
[001329] Step 6: *Synthesis of (R)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazin-2-amine and (S)-N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(1-(tetrahydro-2H-pyran-4-yl)ethyl)pyrazin-2-amine*

[001330] To a solution of the compound from step 5 (160 mg, 407 μmol) in EtOH (5.0 mL) was added KOH (40 mg, 377 μmol) at rt under N₂. The reaction mixture was allowed to warm to 90°C and stirred for 2 h under N₂. The reaction mixture was evaporated under reduced pressure. The residue was purified by Prep-HPLC (Method A) to afford the racemic product (34 mg) and then separated by chiral Prep-SFC (Column: OD 20*250mm, 10 μm (Daicel), Column temperature: 35 °C, Mobile phase: CO₂/MeOH (0.1% DEA) = 70/30, Flow rate: 80 g/min, Back pressure: 100 bar) to give peak 1 (10.8 mg) as a white solid and peak 2 (12.1 mg, 35%) as a white solid.

[001331] Peak 1, **Example 247**, LCMS m/z = 340 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.96 (br s, 1H), 10.25 (br s, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.26 (t, 1H), 5.95 (s, 1H), 3.91-3.85 (m, 1H), 3.77-3.72 (m, 1H), 3.33-3.24 (m, 1H), 3.17-3.12 (m, 1H), 2.68-2.63 (m, 1H), 1.85-1.80 (m, 1H), 1.77-1.73 (m, 1H), 1.25-1.22 (m, 1H), 1.22 (d, 3H), 1.18-1.11 (m, 2H).

[001332] Peak 2, **Example 246**, LCMS m/z = 340 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.96 (br s, 1H), 10.25 (br s, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.26 (t, 1H), 5.95 (s, 1H), 3.91-3.85 (m, 1H), 3.77-3.72 (m, 1H), 3.33-3.24 (m, 1H), 3.17-3.12 (m, 1H), 2.68-2.63 (m, 1H), 1.85-1.80 (m, 1H), 1.77-1.73 (m, 1H), 1.25-1.22 (m, 1H), 1.22 (d, 3H), 1.18-1.11 (m, 2H).

[001333] **Example 248**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-4-ylmethyl)pyrazin-2-amine



[001334] Step 1: *Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)methylene)piperidine-1-carboxylate*

[001335] A solution of Example 246, step 2 (250 mg, 601 μmol), tert-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidine-1-carboxylate (194 mg, 601 μmol), Pd(dppf)Cl₂ (43.6 mg, 60.1 μmol) and Cs₂CO₃ (586 mg, 1.80 mmol) in dioxane/water (4/1) (8 mL) was stirred at 90°C for 12 h under N₂. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with PE/EtOAc (1/2) to afford the title compound (200 mg, 79%) as a yellow oil. LCMS m/z = 423 [M+H]⁺.

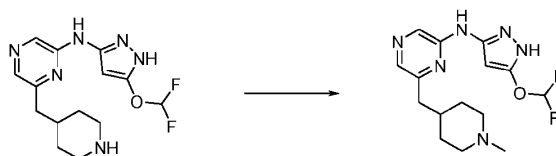
[001336] Step 2: *Synthesis of tert-butyl 4-((6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)methyl)piperidine-1-carboxylate*

[001337] A mixture of the compound from step 1 (200 mg, 473 μmol) and Pt₂O (21.4 mg, 94.6 μmol) in MeOH (8 mL) was stirred at rt for 7 h under H₂. The resulting mixture was filtered through Celite® and washed with MeOH. The filtrate and washings were concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with PE/EtOAc (1/1) to afford the title compound (120 mg, 44%) as a brown oil. LCMS m/z = 425 [M+H]⁺.

[001338] Step 3: *Synthesis of N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-(piperidin-4-ylmethyl)pyrazin-2-amine*

[001339] To a solution of the compound from step 2 (50 mg, 118 μmol) in DCM (5 mL) was added TFA (1 mL) and the resulting mixture was stirred at rt for 1.5 h. The reaction mixture was basified with NH₃ (7M in MeOH) to pH~10. The precipitate was filtered off and the filtrate and washings were concentrated *in vacuo*. The residue was purified by Prep-HPLC (Method D) to afford the title compound (4.6 mg, 12%) as a white solid. LCMS m/z = 325 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.13 (br s, 1H), 8.42 (s, 1H), 8.04 (s, 1H), 7.87 (s, 1H), 7.26 (t, 1H), 5.92 (s, 1H), 3.19-3.12 (m, 2H), 2.75-2.63 (m, 5H), 2.02-1.95 (m, 1H), 1.72-1.62 (m, 2H), 1.40-1.27 (m, 2H).

[001340] **Example 249**, N-(5-(difluoromethoxy)-1H-pyrazol-3-yl)-6-((1-methylpiperidin-4-yl)methyl)pyrazin-2-amine



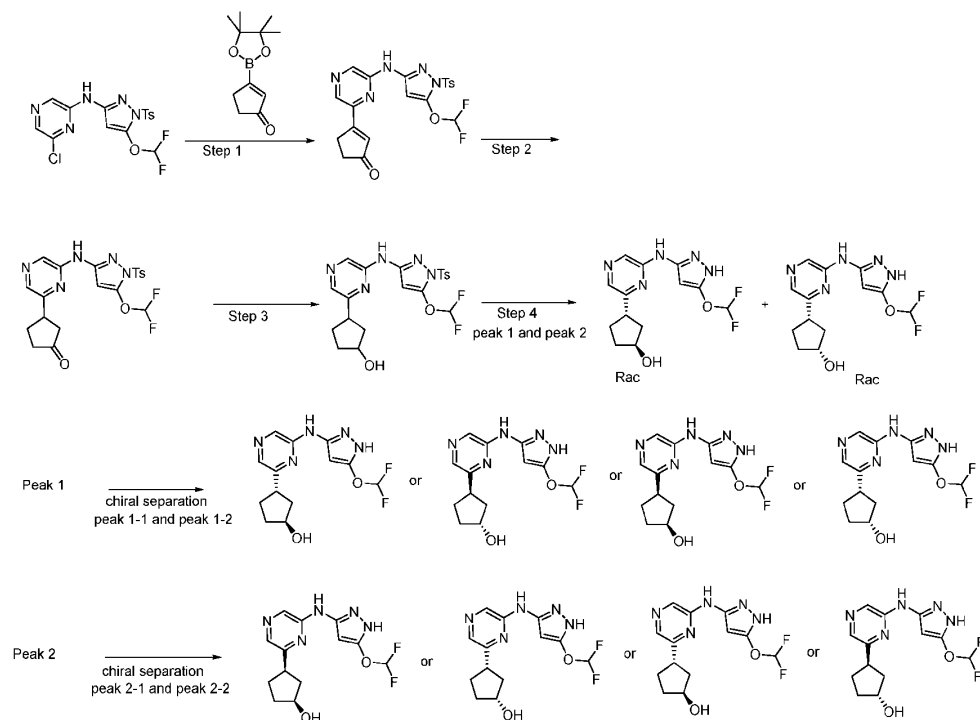
[001341] The title compound was obtained as a white solid, 6 mg, 15%, from the compound from Example 248, step 3, following the procedure described in Example 11. LCMS m/z = 339

[M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.19 (br s, 1H), 8.05 (s, 1H), 7.86 (s, 1H), 7.26 (t, 1H), 5.83 (s, 1H), 2.75-2.65 (m, 3H), 2.65-2.55 (m, 2H), 2.11 (s, 3H), 1.80-1.72 (m, 2H), 1.70-1.60 (m, 1H), 1.55-1.48 (m, 2H), 1.28-1.20 (m, 2H).

[001342] Example 250, (1*S*,3*S*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1*R*,3*R*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1*S*,3*R*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1*R*,3*S*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol and

[001343] Example 251, (1*R*,3*S*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1*S*,3*R*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1*S*,3*S*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1*R*,3*R*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol and and

[001344] Example 252, (1*S*,3*R*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol, (1*R*,3*S*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol, (1*S*,3*S*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or (1*R*,3*R*)-3-(6-((5-(difluoromethoxy)-1*H*-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol



[001345] Step 1: *Synthesis of 3-(6-((5-(difluoromethoxy)-1-tosyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopent-2-en-1-one*

[001346] To a solution of Example 246, Step 2 (1.25 g, 3.02 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-one (630 mg, 3.02 mmol) in dioxane (30 mL) and H₂O (3 mL) was added Pd(t-Bu₃P)₂ (154 mg, 0.3 mmol) and K₂CO₃ (834 mg, 6.04 mmol) at rt under N₂. The reaction mixture was allowed to warm to 80°C and was stirred for 14 h, then diluted with dioxane, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/PE (9/1) to afford the title compound (800 mg, 58%) as a yellow solid. LCMS m/z = 462 [M+H]⁺.

[001347] Step 2: *Synthesis of 3-(6-((5-(difluoromethoxy)-1-tosyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-one*

[001348] To a solution of the compound from step 1 (2.4 g, 5.20 mmol) in EtOAc (550 mL) was added Pt₂O (1.05 g, 2.60 mmol) at rt. The reaction mixture was stirred for 2 h under H₂, then diluted with EtOAc, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/PE (1/3) to afford the title compound (945 mg, 39%) as a white solid. LCMS m/z = 464 [M+H]⁺.

[001349] Step 3: *Synthesis of 3-(6-((5-(difluoromethoxy)-1-tosyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol*

[001350] To a solution of the compound from step 2 (980 mg, 2.11 mmol) in MeOH (20.0 mL) was added NaBH₄ (79.8 mg, 2.11 mmol) at 0°C under N₂. The reaction mixture was allowed to warm to rt and was stirred for 1 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The crude which was purified by flash chromatography on silica gel eluting with DCM/MeOH (9/1) to afford the title compound (600 mg, 61%) as a yellow solid. LCMS m/z = 466 [M+H]⁺.

[001351] Step 4: *Synthesis of (1R,3R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol, (1S,3S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol, (1R,3S)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol and/or (1S,3R)-3-(6-((5-(difluoromethoxy)-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol*

[001352] To a solution of the compound from step 3 (330 mg, 0.7 mmol) in EtOH (10.0 mL) was added KOH (198 mg, 3.53 mmol) at rt. The reaction mixture was allowed to warm to 60°C and was stirred for 1 h. The reaction was diluted with EtOAc, washed with water and brine, dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with DCM/MeOH (9/1) to afford peak 1 (160 mg, 73%) and peak 2 (40 mg, 18%) as a white solid.

[001353] 160 mg of peak 1 was separated by chiral Prep-SCF (Column: IC 20*250mm, 10 μ m (Daicel), Column temperature: 35°C, Mobile phase: CO₂/MeOH [0.5%NH₃(7M in MeOH)] = 85/15, Flow rate: 120 g/min, Back pressure: 100 bar) to afford peak 1-1 (36.5 mg) and peak 1-2, (48.7 mg) as white solid.

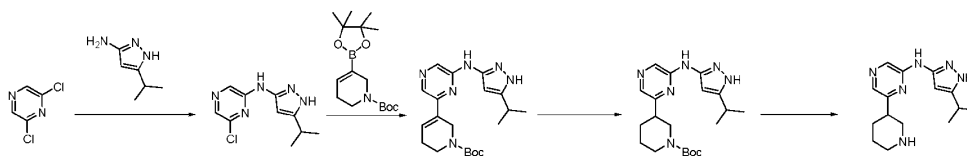
[001354] Peak 1-1, **Example 250**, LCMS m/z = 312 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) for δ ppm 12.44 (br s, 1H), 10.37 (br s, 1H), 8.02 (s, 1H), 7.92 (s, 1H), 7.23 (t, 1H), 5.65 (s, 1H), 5.14 (s, 1H), 4.34-4.26 (m, 1H), 3.30-3.21 (m, 1H), 2.23-2.15 (m, 1H), 20.7-1.95 (m, 1H), 1.93-1.80 (m, 1H), 1.80-1.63 (m, 3H).

[001355] 40 mg of peak 2 was separated by chiral Prep-SCF (Column: AD 20*250mm, 10 μ m (Daicel), Column temperature: 35°C, Mobile phase: CO₂/MeOH [0.5%NH₃(7M in MeOH)] = 75/25, Flow rate: 100 g/min, Back pressure: 100 bar) to afford peak 2-1 (11.5 mg) and peak 2-2 (7.6 mg) as a yellow solid.

[001356] Peak 2-1, **Example 251**, LCMS m/z = 312 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.90 (br s, 1H), 10.13 (br s, 1H), 8.04 (s, 1H), 7.83 (s, 1H), 7.24 (t, 1H), 5.94 (s, 1H), 4.61 (d, 1H), 4.35-4.28 (m, 1H), 3.46-3.40 (m, 1H), 2.15-2.06 (m, 1H), 2.03-1.93 (m, 1H), 1.93-1.82 (m, 2H), 1.74-1.66 (m, 1H), 1.65-1.56 (m, 1H). LCMS m/z = 312 [M+H]⁺.

[001357] Peak 2-2, **Example 252**, LCMS m/z = 312 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.88 (br s, 1H), 10.11 (br s, 1H), 8.05 (s, 1H), 7.93 (s, 1H), 7.25 (t, 1H), 5.94 (s, 1H), 4.56 (br. s., 1H), 4.34-4.30 (m, 1H), 3.45-3.39 (m, 1H), 2.15-2.06 (m, 1H), 2.03-1.93 (m, 1H), 1.93-1.82 (m, 2H), 1.74-1.65 (m, 1H), 1.65-1.56 (m, 1H). LCMS m/z = 312 [M+H]⁺.

[001358] **Example 253**, N-(5-isopropyl-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine



[001359] Step 1: *Synthesis of 6-chloro-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine*

[001360] The title compound was obtained as a white solid, 2.5 g, 31%, from 2,6-dichloropyrazine and 5-isopropyl-1H-pyrazol-3-amine, following the procedure described in Example 232, step 2. LCMS m/z = 238 [M+H]⁺.

[001361] Step 2: *Synthesis of tert-butyl 5-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate*

[001362] To a solution of the compound from step 1 (250 mg, 1.05 mmol) and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (390 mg, 1.26 mmol) in 1,4-dioxane (5.0 mL) and water (0.5 mL) was added Pd(dppf)Cl₂ (76 mg, 0.11 mmol) and Na₂CO₃ (335 mg, 3.16 mmol) at rt under N₂. The reaction mixture was allowed to warm to 110 °C and was stirred for 16 h, then diluted with dioxane, filtered and concentrated under reduced pressure.

The crude product was purified by flash chromatography on silica gel eluting with EA/PE (1/1) to afford the title compound (380 mg, 94%) as a yellow solid. LCMS $m/z = 385$ $[M+H]^+$.

[001363] Step 3: *Synthesis of tert-butyl 3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)piperidine-1-carboxylate*

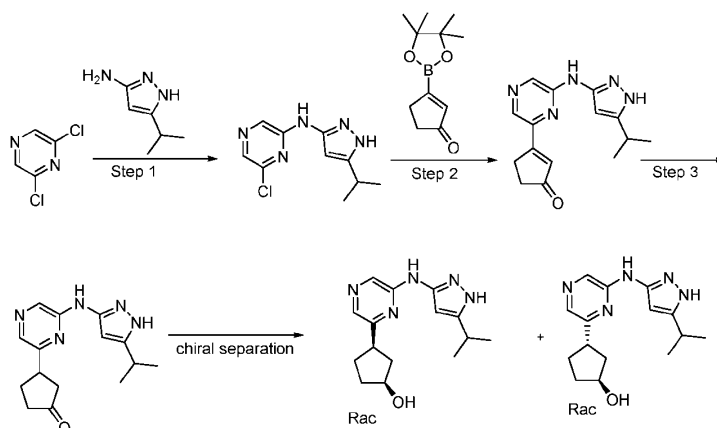
[001364] To a solution of the compound from step 2 (380 mg, 988 μmol) in EA (20 mL) was added 10% Pd/C (wet, 200 mg) at rt and stirred for 16 h under H_2 . The reaction mixture was filtered and evaporated under reduced pressure to give the title compound (293 mg, 76%) as a yellow solid. LCMS $m/z = 387$ $[M+H]^+$.

[001365] Step 4: *Synthesis of N-(5-isopropyl-1H-pyrazol-3-yl)-6-(piperidin-3-yl)pyrazin-2-amine*

[001366] To a solution of the compound from step 3 (193 mg, 0.5 mmol) in DCM (6.0 mL) was added TFA (2.0 mL) at 0 °C then stirred for 1 h at rt then concentrated under reduced pressure. The residue was purified by Prep-HPLC (Method A) to afford the title compound (40.9 mg, 28% yield) as a yellow solid. LCMS $m/z = 287$ $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.98 (br. s., 1H), 9.53 (s, 1H), 8.33 (s, 1H), 7.79 (s, 1H), 6.26 (s, 1H), 3.55-3.45 (m, 1H), 3.08-3.03 (m, 1H), 2.97-2.85 (m, 2H), 2.72-2.65 (m, 2H), 1.97-1.87 (m, 1H), 1.76-1.63 (m, 2H), 1.54-1.41 (m, 1H), 1.23 (d, $J = 6.8$ Hz, 6H).

[001367] **Example 254**, 3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-one and

[001368] **Example 255**, rac-(1R,3S)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or rac-(1R,3R)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol and **Example 256**, rac-(1R,3R)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol or rac-(1R,3S)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol



[001369] Step 1: *Synthesis of 6-chloro-N-(5-isopropyl-1H-pyrazol-3-yl)pyrazin-2-amine*

[001370] The title compound was obtained as a white solid, 2.5 g, 31%, from 2,6-dichloropyrazine and 5-isopropyl-1H-pyrazol-3-amine, following the procedure described in Example 232, step 2. LCMS m/z = 238 $[M+H]^+$.

[001371] Step 2: *Synthesis of 3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopent-2-en-1-one*

[001372] The title compound was obtained as a yellow solid, 680 mg, 71%, from the compound from step 1 and tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopent-2-en-1-one, following the procedure described in Example 253, Step 2. LCMS m/z = 284 $[M+H]^+$.

[001373] Step 3: *Synthesis of 3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-one*

[001374] To a solution of the compound from step 2 (680 mg, 2.4 mmol) in EtOH (10 mL) and THF (10 mL) was added 10% Pd/C (wet, 300 mg) at rt. The reaction mixture was allowed to warm to 55°C and stirred for 16 h under H₂. The reaction mixture was filtered and evaporated under reduced pressure. The crude was purified by Prep-HPLC (Method A) to give the title compound (40 mg, 4%) as a yellow solid. LCMS m/z = 286 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.93 (br s, 1H), 9.60 (s, 1H), 8.33 (s, 1H), 7.85 (s, 1H), 6.20 (s, 1H), 3.57-3.51 (m, 1H), 2.96-2.84 (m, 1H), 2.60-2.42 (m, 2H), 2.42-2.22 (m, 3H), 2.03-1.95 (m, 1H), 1.22 (d, 6H).

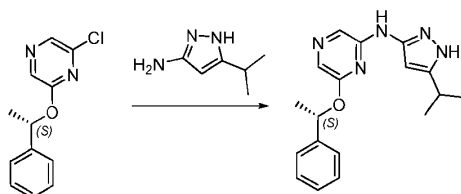
[001375] Step 4: *Synthesis of rac-(1R,3S)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol and rac-(1R,3R)-3-(6-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazin-2-yl)cyclopentan-1-ol*

[001376] To a solution of the compound from step 3 (35 mg, 122 μ mol) in MeOH (5.0 mL) was added NaBH₄ (23 mg, 613 μ mol) at 0°C under N₂. The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was quenched with ice water and evaporated under reduced pressure. The crude was purified by Prep-HPLC (Method A) to give Peak 1 (Example 255, 5.2 mg, 14%) as a white solid and Peak 2 (Example 256, 5.5 mg, 15%) as a white solid. LCMS m/z = 288 $[M+H]^+$.

[001377] **Example 255**, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.87 (br s, 1H), 9.52 (s, 1H), 8.27 (s, 1H), 7.77 (s, 1H), 6.28 (s, 1H), 4.57-4.52 (m, 1H), 4.35-4.30 (m, 1H), 3.41-3.33 (m, 1H), 2.92-2.85 (m, 1H), 2.13-2.05 (m, 1H), 2.03-1.94 (m, 1H), 1.91-1.85 (m, 2H), 1.77-1.67 (m, 1H), 1.66-1.56 (m, 1H), 1.21 (d, 6H).

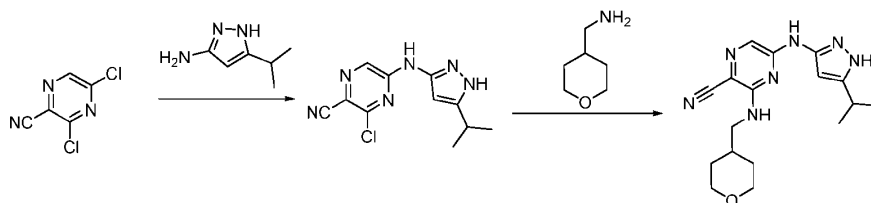
[001378] **Example 256**, ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.88 (br s, 1H), 9.51 (s, 1H), 8.31 (s, 1H), 7.77 (s, 1H), 6.35 (s, 1H), 4.65-4.60 (m, 1H), 4.25-4.16 (m, 1H), 3.10-2.99 (m, 1H), 2.93-2.85 (m, 1H), 2.26-2.17 (m, 1H), 1.97-1.85 (m, 2H), 1.85-1.76 (m, 1H), 1.74-1.61 (m, 2H), 1.22 (d, 6H).

[001379] **Example 257**, (*S*)-*N*-(5-Isopropyl-1H-pyrazol-3-yl)-6-(1-phenylethoxy)pyrazin-2-amine



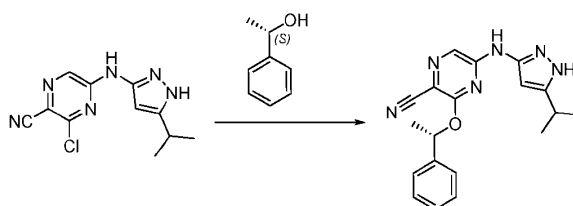
[001380] The title compound was obtained as a white solid, 43 mg, from (S)-2-chloro-6-(1-phenylethoxy)pyrazine, and 5-isopropyl-1H-pyrazol-3-amine following the procedure described in Example 207, step 8. LCMS $m/z = 324$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ 11.95 (s, 1H), 9.55 (s, 1H), 7.96 (s, 1H), 7.53 (s, 1H), 7.43-7.40 (m, 2H), 7.36-7.32 (m, 2H), 7.28-7.24 (m, 1H), 6.14-6.08 (m, 2H), 2.96-2.88 (m, 1H), 1.60 (d, $J = 6.8$ Hz, 3H), 1.23 (d, $J = 6.8$ Hz, 6H).

[001381] **Example 258**, 5-((5-Isopropyl-1H-pyrazol-3-yl)amino)-3-(((tetrahydro-2H-pyran-4-yl)methyl)amino)pyrazine-2-carbonitrile



[001382] The title compound was obtained as a gray solid, 47 mg, from, 3,5-dichloropyrazine-2-carbonitrile, 5-isopropyl-1H-pyrazol-3-amine, and (tetrahydro-2H-pyran-4-yl)methanamine following the two-step procedure described in Example 17, steps 1 and 2. LCMS $m/z = 342$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6) δ 12.16 (s, 1H), 10.27 (br. s., 1H), 7.51 (br. s., 1H), 7.29-7.26 (m, 1H), 6.43 (s, 1H), 3.86-3.82 (m, 2H), 3.34-3.20 (m, 4H), 2.94-2.90 (m, 1H), 1.93-1.88 (m, 1H), 1.61-1.58 (m, 2H), 1.25-1.18 (m, 8H).

[001383] **Example 259**, (S)-5-((5-Isopropyl-1H-pyrazol-3-yl)amino)-3-(1-phenylethoxy)pyrazine-2-carbonitrile



[001384] The title compound was obtained as a white solid, 54 mg, from, 3-chloro-5-((5-isopropyl-1H-pyrazol-3-yl)amino)pyrazine-2-carbonitrile and (S)-1-phenylethan-1-ol following the procedure described in Example 114, step 2. LCMS $m/z = 349$ $[M+H]^+$. 1H -NMR (500 MHz, DMSO- d_6) δ 12.26 (s, 1H), 10.72 (br. s., 1H), 7.87 (br. s., 1H), 7.43-7.35 (m, 4H), 7.31-7.28 (m, 1H), 6.24-6.20 (m, 2H), 2.98-2.94 (m, 4H), 1.66 (d, $J = 6.5$ Hz, 3H), 1.25 (d, $J = 7.0$ Hz, 6H).

Biological Example 1. *In vitro* Enzymatic Activity Assay

[001385] Inhibitory effects of the compounds of the disclosure were measured in biochemical assays that measure the enzymatic phosphorylation activity of CDK enzyme in complex of Cyclin proteins phosphorylates 7.5 micromolar fluorescently labelled peptide substrate, 5-FAM-QSPKKG-CONH₂, (FL-Peptide 18, Perkin Elmer, 760362) in the presence of adenosine-5'-triphosphate (ATP) and varying concentrations of the test compound in 100 mM 2-[4-(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid (HEPES), pH 7.5, 10 mM MgCl₂, 0.015% Brij-35, 1 mM dithiothreitol (DTT), 1.0% dimethylsulfoxide (DMSO). Assays were performed at 1.0 mM ATP or at ATP K_m of the CDK enzymes in complex with Cyclin proteins. Reactions proceeded until between 10% to 20% total peptides were phosphorylated at room temperature (25 °C) and were terminated with 35 mM 2,2',2'',2'''-(ethane-1,2-diyl)dinitrilo)tetraacetic acid (EDTA). Product was detected using the Caliper mobility shift detection method where the phosphorylated peptide (product) and substrate were electrophoretically separated and measured. Percent activity was plotted against log concentration of compound and points to generate an apparent IC₅₀. The following CDK enzymes in complex with different cyclin proteins were used in these assays:

CDK1/Cyclin B1, GST-tag (BPS, 40454), 1.5 nM used in the assay

CDK2/Cyclin E (Eurofins, 14-475), 1.25 nM used in the assays

Biological Example 2. *In vitro* Cellular Activity Assay

[001386] Cellular target engagement, or cellular binding of the testing compounds were measured in NanoBRET assays, which is based on binding competition between the testing compounds and a bioluminescent tracer in human embryonic kidney cells (HEK-293 cell line). In the assay, HEK-293 cells were cultured to appropriate confluence before being transiently transfected with a mix of CDK2-NanoLuc(R) Fusion Vector (Promega, NV2781) and CCNE1 expression vector (Promega, NV2641) for CDK2 NanoBRET assays, or CDK1-NanoLuc(R) Fusion Vector (Promega, NV2701) and CCNB1 expression vector (Promega, NV2601) for CDK1 NanoBRET assay, by using lipid:DNA complexes formed with FuGENE HD transfection agent (Promega, E2311). The transfected cells were cultured overnight in 1% FBS Opti-MEM media to allow the expression to fully occur. Once the expression fully occurred, varying concentrations of the test compounds were added to the cells, before a cell-permeable, fluorescent tracer (tracer K10 from Promega, N2840) was added to achieve final tracer concentration of 0.5 µM. After the addition of Nano-Glo substrate (part of a kit, Promega, N2840) and Extracellular NanoLuc inhibitor (part of a kit, Promega, N2840) 2 hrs after tracer addition, the cellular engagement of the tracer and the competition with testing compounds to the target protein was assessed based on the resulting bioluminescence resonance energy transfer (BRET) signal. BRET ratio was generated by dividing the acceptor emission signal (610 nm) by the donor emission signal (450 nm) for each sample. The raw BRET ratio was converted to millibRET ratio by

multiplying each raw value by 1000. The milliBRET ratio was then used directly for non-linear IC₅₀ fitting with n=1 at each concentration of the test compounds. All IC₅₀ curves were calculated using a 4 parameter logistic nonlinear regression model.

[001387] Biological assay data of the test compounds are provided in Table 1 below.

Table 1. Assay data with exemplary compounds.

Example	Enzyme CDK2/cyclin E IC50 (nM)	Enzyme CDK1/cyclin B1 IC50 (nM)	NanoBRET CDK2/Cyclin E1 IC50 (nM)	NanoBRET CDK1/Cyclin B IC50 (nM)
1	2.4	358.6	18.6	1292.3
2			9.3	35.9
3	1.8	332.5	21.0	123.9
4			15.6	642.8
5	84.8	8854.7	332.5	10000.0
6			4.5	123.8
7	14.0	1853.8	28.8	941.4
8	19.7	3165.5	20.2	842.7
9	40.1	3201.0	22.5	1036.5
10	63.0	9131.9	12.9	1060.9
11	22.2	3164.4	15.0	1265.6
12			18.0	1948.0
13	14.4	3130.4	9.0	622.4
14	3.2	349.7		
15	38.2	2944.4		
16	44.7	3811.0		
17	4.2	655.0		
18	14.4	2273.8	59.1	1882.1
19			46.8	887.1
20			153.0	4193.3
21			1.8	137.4
22			8.0	281.2
23	37.1	2657.8	33.8	4745.2
24			61.3	1697.9
25			1.2	643.8
26			26.6	400.2
27			17.7	803.8
28			372.6	4220.3
29			326.2	3020.9
30			23.4	751.4
31			19.9	657.9
32			53.5	783.3
33			64.4	1513.0
34			10.5	497.2

Example	Enzyme CDK2/cyclin E IC50 (nM)	Enzyme CDK1/cyclin B1 IC50 (nM)	NanoBRET CDK2/Cyclin E1 IC50 (nM)	NanoBRET CDK1/Cyclin B IC50 (nM)
35			273.0	10000.0
36			26.5	320.7
37			103.0	1625.0
38	148.1	4142.7	431.9	4460.6
39	32.3	1680.0		
40			8.0	37.9
41			77.8	667.2
42			72.9	10000.0
43			1.8	890.0
44			23.9	1167.0
45			22.7	2182.7
46			146.3	1095.9
47			243.5	1672.7
48			460.7	1489.9
49			64.5	954.4
50			36.1	1043.3
51			116.5	3704.8
52			67.6	5235.3
53			23.4	5394.7
54			24.9	2734.3
55	21.4	1298.5	10.3	395.9
56	6.9	382.8	6.1	111.7
57			13.2	194.6
58			31.3	549.0
59			70.4	2412.2
60			39.8	5126.6
61			73.4	1612.0
62			5.1	192.2
63			61.4	3191.9
64			5.1	200.2
65	49.5	2417.2	27.3	861.4
66			68.9	778.9
67	9.6	1451.8	30.8	1596.5
68	2.6	456.4	24.6	568.1
69			26.7	740.6
70	2.1	195.0	16.4	291.8
71			10.9	60.3
72	1.1	260.0	57.4	259.6
73	11.1	517.1	56.1	1044.1
74	130.1	6420.8	172.5	5520.3
75	9.0	393.5	41.2	454.8
76	4.5	556.4	19.6	280.0

Example	Enzyme CDK2/cyclin E IC50 (nM)	Enzyme CDK1/cyclin B1 IC50 (nM)	NanoBRET CDK2/Cyclin E1 IC50 (nM)	NanoBRET CDK1/Cyclin B IC50 (nM)
77			99.2	4376.6
78	20.3	1111.4		
79			21.8	538.7
80	116.2	8089.3	87.0	2554.1
81	104.2	5204.5	87.8	1759.7
82			78.6	3262.5
83	27.5	1786.2	58.3	815.9
84	10.6	936.1	17.1	833.8
85	2.1	568.6	22.2	456.8
86	5.0	909.4	11.6	290.7
87	34.2	2456.1	18.1	916.5
88			39.1	4084.0
89	12.6	1583.5	13.0	1616.5
90	38.9	2244.1	19.8	726.3
91	36.1	2201.0	21.6	3073.8
92	0.6	15.5	2.2	100.6
93			4.8	404.2
94	1.7	93.8	7.3	150.1
95			14.0	1501.3
96	22.9	1076.0	19.0	2624.5
97			39.0	4634.5
98	65.6	2744.3	21.5	1280.4
99	47.5	2907.0	23.2	3109.7
100	51.7	1772.1	16.7	2953.4
101	2.4	440.1	37.6	115.9
102	60.3	4859.7		
103	29.0	2221.7	16.1	1764.4
104			27.3	4696.0
105	24.4	1168.6	8.5	557.5
106	8.4	497.2	3.9	131.8
107	29.3	2167.8	11.5	1473.7
108	7.0	626.1	5.3	193.2
109	47.7	1633.3		
110	18.4	4433.8	12.9	1670.7
111	3.8	1377.3	15.4	1109.9
112	63.9	3401.0	4761.3	6193.7
113	95.2	6394.3	31.4	1731.1
114	99.5	9416.7		
115			24.8	622.5
116			11.1	301.1
117			23.9	344.6
118			14.9	286.5

Example	Enzyme CDK2/cyclin E IC50 (nM)	Enzyme CDK1/cyclin B1 IC50 (nM)	NanoBRET CDK2/Cyclin E1 IC50 (nM)	NanoBRET CDK1/Cyclin B IC50 (nM)
119			17.2	2371.7
120			25.4	448.3
121	22.7	2174.9	384.9	1354.9
122			7.2	89.1
123			95.4	1377.0
124	4.7	213.1	40.0	153.0
125	5.3	745.1	7.0	273.2
126	3.6	1059.1	16.7	1296.6
127	0.4	62.3	4.6	89.2
128	13.3	752.3	18.7	280.8
129	91.4	5880.0		
130	66.3	5359.5		
131	39.3	6483.7	19.4	7052.9
132	45.9	3514.7		
133	29.3	2264.2		
134			25.3	2893.9
135	42.2	2204.3		
136	25.9	2223.9	58.3	3228.1
137	72.7	8567.5		
138	35.4	3117.1		
139	32.3	4175.2		
140	32.1	717.1		
141	52.0	5849.2		
142	21.4	1477.8		
143	3.4	525.2		
144	34.2	2957.4		
145	5.5	698.1		
146	24.3	2993.8	16.9	2891.2
147	45.7	4776.2		
148	25.8	671.1		
149	9.2	1230.7		
150	46.4	5419.5		
151	25.6	6170.7	6.3	332.4
152	56.9	3446.0		
153	3.6	870.1		
154	1.8	168.0		
155	24.6	4032.5		
156	69.0	7553.8		
157	1.5	13.7		
158	65.8	4533.5		
159	12.4	1375.3		
160	6.6	926.3		

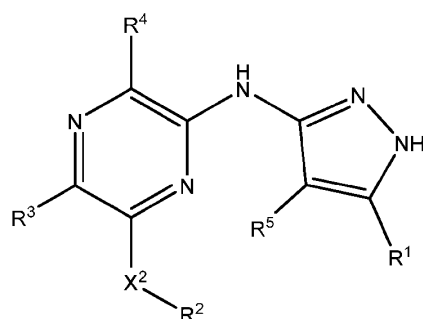
Example	Enzyme CDK2/cyclin E IC50 (nM)	Enzyme CDK1/cyclin B1 IC50 (nM)	NanoBRET CDK2/Cyclin E1 IC50 (nM)	NanoBRET CDK1/Cyclin B IC50 (nM)
161	50.0	1802.2	23.6	1272.8
162	90.7	6752.1		
163	5.8	977.9		
164	13.3	1063.6		
165	60.8	3408.3		
166	2.2	25.9		
167	2.1	303.4		
168	38.9	4850.4		
169	55.6	3208.6		
170	1.0	162.8		
171	2.3	37.3		
172	14.4	1224.0		
173	21.8	2067.9		
174	11.1	1615.6	33.7	2995.5
175	5.8	873.3		
176	34.0	3516.8		
177	49.6	3881.5		
178	3.6	633.8		
179	14.7	1101.1		
180	20.7	1610.7	12.4	282.1
181	7.3	946.4		
182	16.0	2943.1		
183	25.8	2281.5	21.3	1762.3
184	4.4	911.8		
185	4.2	467.4		
186	2.4	139.1		
187	11.5	401.7		
188	18.9	594.9		
189	12.6	2240.2		
190	18.9	876.9		
191	5.4	731.5		
192	7.8	1034.0		
193	7.0	493.4		
194	20.9	1330.9		
195	2.4	340.6		
196	4.2	1075.3		
197	26.8	1337.0		
198	115.8	6852.0		
199	1.8	272.8		
200	5.5	502.0		
201	3.7	614.2		
202	3.9	576.7		

Example	Enzyme CDK2/cyclin E IC50 (nM)	Enzyme CDK1/cyclin B1 IC50 (nM)	NanoBRET CDK2/Cyclin E1 IC50 (nM)	NanoBRET CDK1/Cyclin B IC50 (nM)
203	0.5	149.3		
204	1.2	274.4		
205	8.6	2135.7		
206	5.3	1939.2		
207	6.8	2240.2		
208	65.0	8939.0		
209	77.0	10000.0		
210	28.4	2632.0		
211			24.9	840.1
212	1.6	265.7	5.4	371.7
213	4.4	695.9		
214	129.0	10000.0		
215	51.0	8786.0		
216	3.4	650.3		
217	5.5	573.9	2.7	56.9
218	15.2	1540.5		
219	96.0	10000.0		
220	39.0	1278.0		
221	20.0	2175.0		
222	89.0	9724.0		
223	0.5	90.9		
224	86.0	3322.0		
225	52.0	7965.0		
226	11.7	1886.0		
227	59.9	2832.2		
228	34.0	4979.6		
229			51.7	710.9
230			81.0	2604.9
231			28.5	896.0
232	12.2	750.4		
233	2.8	227.9		
234	1.4	317.4		
235	0.7	144.5		
236	0.9	160.7		
237	14.2	2731.1		
238	33.7	5522.1		
239	0.8	152.6		
240			99.7	616.7
241			129.2	2356.1
242			32.5	259.5
243			65.3	1363.3
244			17.2	335.5

Example	Enzyme CDK2/cyclin E IC50 (nM)	Enzyme CDK1/cyclin B1 IC50 (nM)	NanoBRET CDK2/Cyclin E1 IC50 (nM)	NanoBRET CDK1/Cyclin B IC50 (nM)
245			22.0	1361.2
246			15.6	544.9
247			44.1	1727.6
248			203.3	631.4
249			90.0	2636.7
250			62.2	1309.7
251			98.6	1837.1
252			29.9	1666.7
253	23.1	678.0		
254	8.8	634.0		
255	6.4	478.0		
256	10.1	770.0		
257	1.3	342	7.8	187.4
258	0.1	46.1		
259	3.9	1121.7		

CLAIMS

1. A compound of Formula (I),



(I), or a pharmaceutically acceptable salt thereof,

wherein

R¹ is selected from the group consisting of CN, C₁-C₄alkyl, C₁-C₄alkoxy, -(C(R^d)₂)_p-C₃-C₁₀cycloalkyl, O(C(R^d)₂)_p-C₃-C₁₀cycloalkyl, -(C(R^d)₂)_p-4 to 12-membered heterocyclyl, -O(C(R^d)₂)_p-4 to 12-membered heterocyclyl, -(C(R^d)₂)_p-6 to 12-membered aryl, and -(C(R^d)₂)_p-4 to 12-membered heteroaryl, wherein the C₁-C₄alkyl, C₁-C₄alkoxy, C₃-C₁₀cycloalkyl, C₃-C₁₀cycloalkoxy, and 6 to 12-membered aryl are each optionally substituted with 1 to 4 R^a, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then are optionally substituted on a ring carbon with 1 to 4 R^a;

X² is selected from the group consisting of -O-, -(C(R^d)₂)_n-, -NR^b-, -NR^b-(C(R^c)₂)_m-, -O(C(R^c)₂)_m-, and -(C(R^d)₂)_n-O-;

R² is selected from C₁-C₄alkyl and Ring A, wherein the C₁-C₄alkyl is optionally substituted with 1 to 4 groups each independently selected from the group consisting of D, halo, CN, and OH and/or 1 group of 5 to 6 membered heteroaryl having 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b; or

X² and R² together form Ring B bonded to the pyrazine, wherein Ring B is C₃-C₁₀cycloalkyl or 4 to 12-membered heterocyclyl, wherein the C₃-C₁₀cycloalkyl is optionally substituted with 1 to 4 R^a, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b, and then is optionally substituted on a ring carbon with 1 to 4 R^a;

Ring A is selected from the group consisting of C₃-C₁₀cycloalkyl, 4 to 12-membered heterocyclyl, 6 to 12-membered aryl, and 4 to 12-membered heteroaryl, wherein the C₃-C₁₀cycloalkyl and 6 to 12-membered aryl are each optionally substituted with 1 to 4 R^a, wherein the 4 to 12-membered heterocyclyl and 4 to 12-membered heteroaryl have 1 to 4 ring heteroatoms each

independently selected from the group consisting of O, S, N, and NR^b and then are optionally substituted on a ring carbon with 1 to 4 R^a;

R³ is selected from the group consisting of H, D, halo, OH, CN, C₁-C₄ alkyl, -SO₂C₁-C₄alkyl, and -S(O)NR^b-C₁-C₄alkyl;

R⁴ is selected from the group consisting of H, D, C₁-C₄ alkyl, and C₃-C₁₀cycloalkyl;

R⁵ is selected from the group consisting of H, D, and C₁-C₄ alkyl;

Each R^a is independently selected from the group consisting of D, halo, OH, CN, N(R^b)₂, C₁-C₄alkyl, and C₁-C₄alkoxy, or two R^a attached to the same atom, form a =O, wherein the C₁-C₄alkyl and C₁-C₄alkoxy are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of D, halo, OH, and CN;

Each R^b is independently selected from the group consisting of H, D, and C₁-C₄alkyl, wherein the C₁-C₄alkyl is optionally substituted with 1 to 4 D;

Each R^c is independently selected from the group consisting of H, D, C₁-C₄alkyl, C₁-C₄alkoxy, C₃-C₁₀cycloalkyl, and 4 to 12-membered heterocyclyl, wherein the C₁-C₄alkyl, C₁-C₄alkoxy, and C₃-C₁₀cycloalkyl are each optionally substituted with 1 to 4 groups each independently selected from the group consisting of halo, OH, and CN, wherein the 4 to 12-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon with 1 to 4 groups each independently selected from the group consisting of halo, OH, and CN;

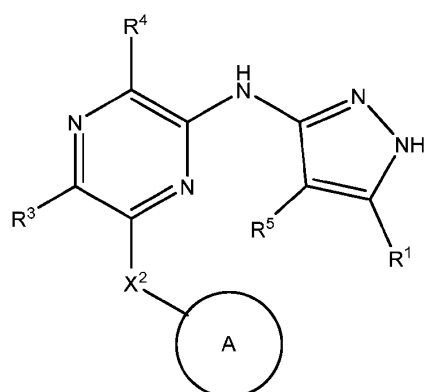
Each R^d is independently selected from the group consisting of H, D, and C₁-C₄alkyl;

m is 1 to 4;

n is 1 to 4; and

p is 0 to 3.

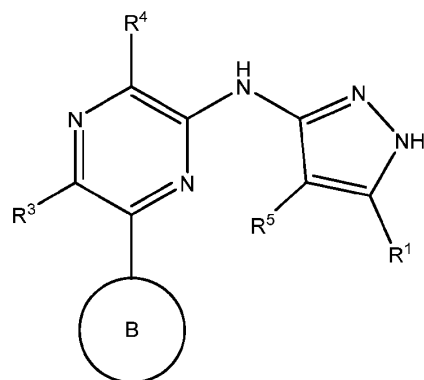
2. The compound of claim 1, wherein the compound is of Formula (II):



(II), or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 or 2, wherein X₂ is selected from the group consisting of -O-, -(CHR^d)_n-, -NR^b-, -NR^b-(CHR^c)_m-, and -O-(CHR^c)_m-.

4. The compound of claim 1, wherein the compound is of Formula (III):



(III), or a pharmaceutically acceptable salt thereof.

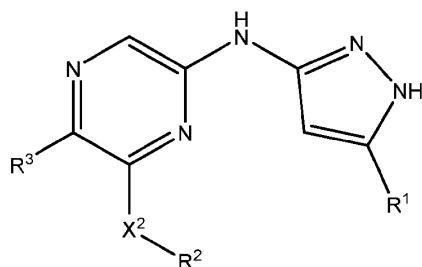
5. The compound of any one of claims 1, 3, and 4, wherein Ring B is C₄-C₆cycloalkyl or 4 to 8-membered heterocyclyl, wherein the C₄-C₆cycloalkyl is optionally substituted with 1 to 4 R^a, wherein the 4 to 8-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon by 1 to 4 R^a.

6. The compound of any one of claims 1 to 5, wherein R³ is selected from the group consisting of H, C₁-C₄alkyl, CN, -SO₂C₁-C₄alkyl, and -S(O)NH-C₁-C₄alkyl.

7. The compound of any one of claims 1 to 6, wherein R⁴ is selected from the group consisting of H, C₁-C₄ alkyl, and C₃-C₆cycloalkyl.

8. The compound of any one of claims 1 to 7, wherein R^5 is H.

9. The compound of claim 1, wherein the compound is of Formula (IVa):



(IVa), or a pharmaceutically acceptable salt thereof,

wherein

R^1 is selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_3 - C_8 cycloalkyl, and 4 to 10-membered heterocyclyl, wherein the C_1 - C_4 alkyl, C_1 - C_4 alkoxy, and C_3 - C_8 cycloalkyl are each optionally substituted with 1 to 3 R^a , wherein the 4 to 10-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a ;

X^2 is selected from the group consisting of -O-, $-O(C(R^c)_2)_m-$, and $-(C(R^d)_2)_n-O-$;

R^2 is selected from C_1 - C_4 alkyl and Ring A, wherein the C_1 - C_4 alkyl is optionally substituted with 1 to 3 groups each independently selected from the group consisting of halo, CN, and OH;

Ring A is selected from the group consisting of C_3 - C_8 cycloalkyl, 4 to 10-membered heterocyclyl, 6 to 10-membered aryl, and 4 to 10-membered heteroaryl, wherein the C_3 - C_8 cycloalkyl and 6 to 10-membered aryl are each optionally substituted with 1 to 3 R^a , wherein the 4 to 10-membered heterocyclyl and 4 to 10-membered heteroaryl have 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then are optionally substituted on a ring carbon with 1 to 3 R^a ;

R^3 is H or C_1 - C_4 alkyl;

Each R^a is independently selected from the group consisting of halo, OH, CN, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy, or two R^a , attached to the same atom, form a $=O$, wherein the C_1 - C_4 alkyl and C_1 - C_4 alkoxy are each optionally substituted with 1 to 3 groups each independently selected from the group consisting of halo, OH and CN;

Each R^b is independently H or C_1 - C_4 alkyl, wherein the C_1 - C_4 alkyl is optionally substituted with 1 to 4 D;

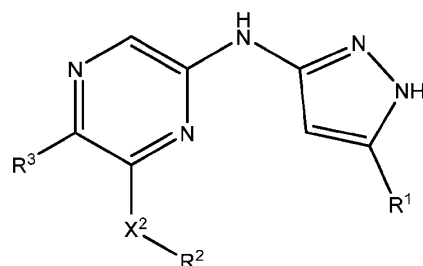
Each R^c is independently H or C_1 - C_4 alkyl;

Each R^d is independently H or C_1 - C_4 alkyl;

m is 1 or 2; and

n is 1 or 2.

10. The compound of claim 1, wherein the compound is of Formula (IVb):



(IVb), or a pharmaceutically acceptable salt thereof,

wherein

R^1 is selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_3 - C_8 cycloalkyl, and 4 to 10-membered heterocyclyl, wherein the C_1 - C_4 alkyl, C_1 - C_4 alkoxy, and C_3 - C_8 cycloalkyl are each optionally substituted with 1 to 3 R^a , wherein the 4 to 10-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a ;

X^2 is $-NR^b$ or $-NR^b-(C(R^c)_2)_m$;

R^2 is selected from C_1 - C_4 alkyl and Ring A, wherein the C_1 - C_4 alkyl is optionally substituted with 1 to 3 groups each independently selected from the group consisting of halo, CN, and OH;

Ring A is selected from the group consisting of C_3 - C_8 cycloalkyl, 4 to 10-membered heterocyclyl, 6 to 10-membered aryl, and 4 to 10-membered heteroaryl, wherein the C_3 - C_8 cycloalkyl and 6 to 10-membered aryl are each optionally substituted with 1 to 3 R^a , wherein the 4 to 10-membered heterocyclyl and 4 to 10-membered heteroaryl have 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then are optionally substituted on a ring carbon with 1 to 3 R^a ;

R^3 is H or C_1 - C_4 alkyl;

Each R^a is independently selected from the group consisting of halo, OH, CN, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy, or two R^a , attached to the same atom, form a $=O$, wherein the C_1 - C_4 alkyl and C_1 - C_4 alkoxy are each optionally substituted with 1 to 3 groups each independently selected from the group consisting of halo, OH and CN;

Each R^b is independently H or C_1 - C_4 alkyl, wherein the C_1 - C_4 alkyl is optionally substituted with 1 to 4 D;

Each R^c is independently H or C_1 - C_4 alkyl;

m is 1 or 2; and

n is 1 or 2.

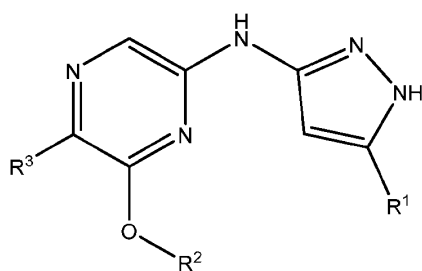
11. The compound of any one of claims 1 to 10, wherein R^1 is selected from the group consisting of CN, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, $-C_3$ - C_6 cycloalkyl, $-(CH_2)$ - C_3 - C_6 cycloalkyl, $-O(CH_2)$ - C_3 - C_6 cycloalkyl, 4 to 6-membered heterocyclyl, $-O$ -(4 to 6-membered heterocyclyl), $-O(CH_2)$ -(4 to 6-membered heterocyclyl), and $-(CH_2)$ -phenyl, wherein the C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_3 - C_6 cycloalkyl, and phenyl are each optionally substituted with 1 to 3 R^a , wherein the 4 to 6-membered heterocyclyl has 1 to 4 ring heteroatoms each independently selected from the group consisting of O, S, N and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a .

12. The compound of any one of claims 1 and 9 to 11, wherein R^2 is C_1 - C_4 alkyl optionally substituted with 1 to 4 OH.

13. The compound of any one of claims 1 to 3 and 9 to 12, wherein Ring A is 4 to 10-membered heterocyclyl having 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N and NR^b and then is optionally substituted on a ring carbon with 1 to 3 R^a .

14. The compound of any one of claims 1 to 13, wherein R^a is selected from the group consisting of halo, OH, CN, $N(R^b)_2$, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy, or two R^a , attached to the same atom, form a $=O$.

15. The compound of any one of claims 1, 2 and 9, wherein the compound is of Formula (Va),



(Va), or a pharmaceutically acceptable salt thereof,

wherein

R^1 is C_1 - C_4 alkyl or C_1 - C_4 alkoxy optionally substituted with 1 to 3 R^a , or 4 to 10-membered heterocyclyl having 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then optionally substituted on a ring carbon with 1 to 3 R^a ;

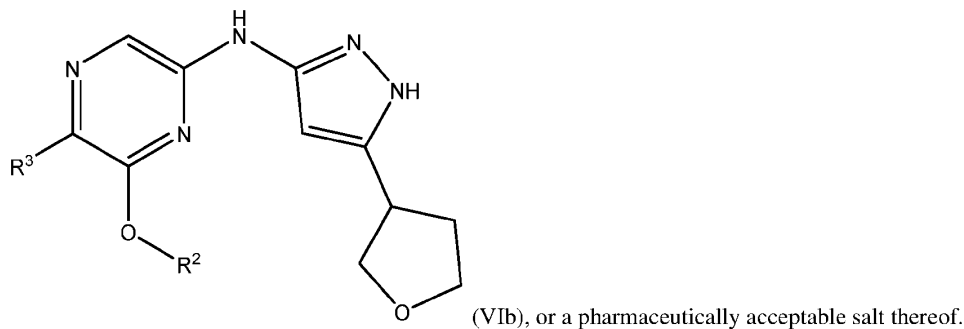
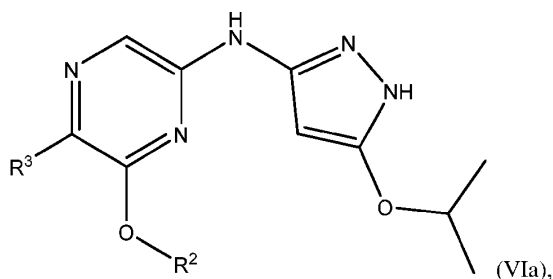
R^2 is Ring A selected from the group consisting of phenyl, 4 to 6-membered heterocyclyl, and 6-membered heteroaryl, wherein the phenyl is optionally substituted with 1 to 3 R^a , and 4 to 6-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring atom with 1 to 4 R^a , wherein the 6-membered heteroaryl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, and N and then is optionally substituted on a ring carbon with 1 to 3 R^a ;

R^3 is H or C_1 - C_4 alkyl;

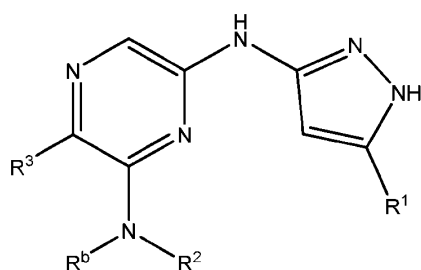
Each R^a is independently selected from the group consisting of halo, OH, CN, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy, or two R^a , attached to the same atom, form a =O; and

Each R^b is independently H or C_1 - C_4 alkyl.

16. The compound of any one of claims 1, 2, 9, and 15, wherein the compound is of Formula (VIa) or (VIb),



17. The compound of any one of claims 1, 2 and 10, wherein the compound is of Formula (Vb),



(Vb), or a pharmaceutically acceptable salt thereof,

wherein

R^1 is C_1 - C_4 alkyl or C_1 - C_4 alkoxy optionally substituted with 1 to 3 R^a , or 4 to 10-membered heterocyclyl having 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then optionally substituted on a ring carbon with 1 to 3 R^a ;

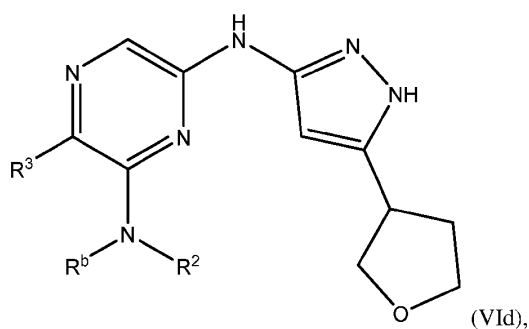
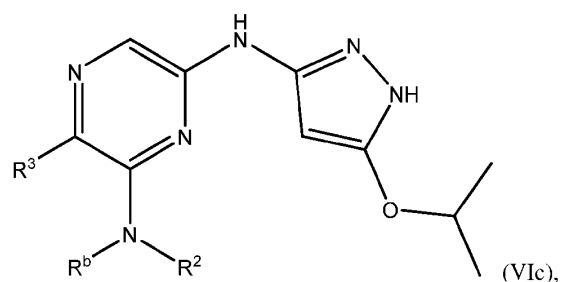
R^2 is Ring A selected from the group consisting of phenyl, 4 to 6-membered heterocyclyl, and 6-membered heteroaryl, wherein the phenyl is optionally substituted with 1 to 3 R^a , and 4 to 6-membered heterocyclyl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S, N, and NR^b and then is optionally substituted on a ring carbon with 1 to 4 R^a , wherein the 6-membered heteroaryl has 1 to 3 ring heteroatoms each independently selected from the group consisting of O, S and N and then is optionally substituted on a ring carbon with 1 to 3 R^a ;

R^3 is H or C_1 - C_4 alkyl;

Each R^a is independently selected from the group consisting of halo, OH, CN, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy, or two R^a , attached to the same atom, form a =O; and

Each R^b is independently H or C_1 - C_4 alkyl.

18. The compound of any one of claims 1, 2, 10, and 17, wherein the compound is of Formula (VIc) or (VIId),



or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof.
20. A method of treating a cancer, comprising administering to a subject in need thereof an effective amount of a compound of any of claims 1 to 18, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 19.
21. The method of claim 20, wherein the cancer is breast cancer.
22. The method of claim 21, wherein the breast cancer has progressed despite treatment with a CDK4/6 inhibitor.
23. The method of claim 21 or 22, wherein the method further comprises administering an effective amount of a CDK4/6 inhibitor.
24. The method of claim 20, wherein the cancer is selected from the group consisting of ovarian cancer, endometrial cancer, gastric cancer, esophageal cancer, breast cancer, pancreatic cancer, and prostate cancer.
25. The method of claim 24, wherein the cancer has CCNE1 overexpression and/or amplification.

26. The method of claim 24 or 25, wherein the cancer has progressed despite platinum treatment.
27. The method of any one of claims 20 to 22 and 24 to 26, wherein the method further comprises administering to the subject an effective amount of carboplatin, ribociclib, fulvestrant, or a combination thereof.
28. The method of any one of claims 20 to 22 and 24 to 26, wherein the compound of any of claims 1 to 18, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 19 is administered to the subject in combination with an effective amount of carboplatin, ribociclib, fulvestrant, or a combination thereof.
29. A method of treating a patient having an amplified expression level of CCNE1 and suffering from, or at risk of developing, a solid tumor cancer, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 19.
30. The method of claim 29, wherein the solid tumor cancer is at least one of: uterine cancer (including uterine carcinosarcoma, uterine corpus endometrial carcinoma), endometrial cancer, breast cancer (including breast invasive carcinoma, TNBC (triple negative breast cancer), ER (estrogen receptor)+HER2 (human epidermal growth factor 2)- breast cancer, and HER2+ breast cancer), ovarian cancer (e.g. ovarian serous cystadenocarcinoma), stomach cancer (including stomach adenocarcinoma), gastric cancer (including gastrointestinal stromal tumor), colorectal cancer, pancreatic cancer, kidney cancer, head and neck cancer, liver cancer, prostate cancer, skin cancer, lymphoma (including B-cell lymphoma), sarcoma, esophageal cancer (including esophageal carcinoma), bladder cancer (including bladder urothelial carcinoma), lung cancer (including lung squamous carcinoma and non-small cell lung cancer, e.g., EGFRm (epidermal growth factor receptor mutant)+ non-small cell lung cancer), cholangiocarcinoma, adrenocortical carcinoma, or mesothelioma.