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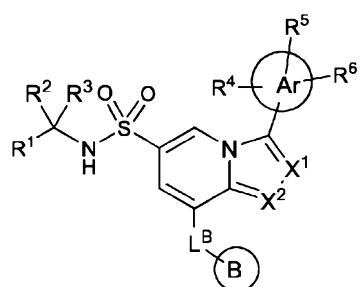
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(54) Title: HETEROARYL-SUBSTITUTED IMIDAZOPYRIDINE COMPOUNDS



(i)

(57) Abstract: Provided herein are compounds having the formula (I) or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, R⁴, R⁵, R⁶, Ar, X¹, X², L^B and ring B have the meanings as provided herein. The provided compounds are useful Poly ADP-ribose glycohydrolase (PARG) inhibitors.

HETEROARYL-SUBSTITUTED IMIDAZOPYRIDINE COMPOUNDS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C § 119(e) to U.S. Provisional Application Serial No. 63/484,906 filed February 14, 2023 and U.S. Provisional Application Serial No. 63/585,892 filed September 27, 2023, the disclosure of each is incorporated herein by reference in their entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

10 **REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK**

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] Cancer is caused by uncontrolled and unregulated cellular proliferation. The consequence of this often-rapid proliferation is a high level of oxidative stress within the tumor which damages DNA and leads to a much-increased mutation rate. Tumor cells therefore engage and rely heavily upon DNA damage repair mechanisms.

15 [0005] Single-strand breaks (SSBs) are the most common type of lesion arising in cells and PARG (Poly ADP-ribose glycohydrolase) together with PARP is involved along with a number 20 of other proteins in single strand break repair (SSBR) and another repair mechanism called base excision repair (BER).

25 [0006] One of the earliest events during single strand DNA repair is the binding of PARP (poly ADP-ribose polymerase) to the break and the rapid synthesis of poly ADP-ribose (PAR) on PARP itself. This molecular structure serves as a signal to recruit other DNA repair proteins, initially XRCC1, which will then repair the break (Mortusewicz, Fouquerel et al. 2011). The

signal initiated by these PAR chains is short-lived as they are rapidly degraded by the enzyme PAR glycohydrolase (PARG). When PARP is bound to PAR, its catalytic activity is reduced and therefore PARG activity helps to restore PARP to its catalytically active form (Curtin and Szabo 2013).

5 [0007] PARG exists as a single gene with isoforms that reside in the nucleus, mitochondria and cytosol. The only other known protein with glycohydrolase activity is ARH3 which is localized to the mitochondria (Mashimo, Kato et al. 2014). Although, known primarily for its direct role in DNA repair, PARG impacts PAR signaling in splicing, transcriptional and epigenetic pathways (Ji and Tulin 2009) (Le May, Iltis et al. 2012) (Dahl, Maturi et al. 2014) 10 (Guastafierro, Catizone et al. 2013) (Caiafa, Guastafierro et al. 2009).

[0008] Cancer cells may become addicted to a specific DNA repair pathway when other mechanisms of DNA repair are non-functional. Tumors carrying mutations in proteins involved in double strand break repair are often more sensitive to PARP inhibitors of SSBR. There is already some evidence that PARG depletion inhibits SSBR and reduces survival of BRCA2-deficient cells (Fathers, Drayton et al. 2012). However, other tumor mutations may give rise to deficiencies in double strand DNA repair mechanisms (so-called “BRCA-ness”) thereby 15 sensitizing tumour cells to PARG inhibition.

[0009] PARG depletion has been studied in a number of murine and human model systems. Murine cells that are null or depleted for PARG display an increased sensitivity to experimental 20 and clinical DNA damaging agents. However, as deficiency in PARG doesn't sensitize to all agents (e.g. gemcitabine, camptothecin) this suggests a specificity for PARG function with certain pathways of DNA damage repair and chemo- and radiotherapies (Fujihara, Ogino et al. 2009) (Shirai, Fujimori et al. 2013) (Zhou, Feng et al. 2010) (Zhou, Feng et al. 2011).

[0010] In humans PARG depletion sensitizes lung, cervical and pancreatic cancer cells to γ -irradiation or experimental DNA damaging agents (e.g. hydrogen peroxide, Methylmethanesulfonate) (Ame, Fouquerel et al. 2009) (Nakadate, Kodera et al. 2013) (Shirai, Poetsch et al. 2013).

[0011] PARP inhibitors are currently undergoing a raft of clinical trials where the concept of synthetic lethality or chemo-sensitization is being explored. Clinical resistance to PARP

inhibitors has already been described (Drost and Jonkers 2014) (Barber, Sandhu et al. 2013) and therefore there is a requirement that alternative inhibitors targeting the DNA damage repair machinery are found. As PARG depletion leads to reduced rates of SSBR to the same extent as depletion of PARP1, PARG inhibition may provide a therapeutic advantage in PARP inhibitor 5 resistant cells (Fisher, Hochegger et al. 2007). Furthermore, depletion of PARG has been reported to lead to a markedly different gene expression pattern to that of PARP depletion in breast cancer cells (Frizzell, Gamble et al. 2009).

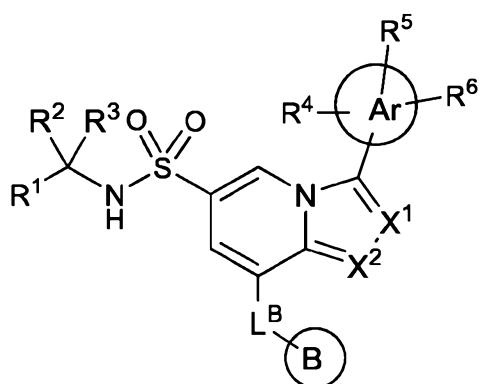
[0012] Although current models show that PARG depletion leads to PARP-dependent effects on DNA repair, recent research has shown a mechanistic differentiation from PARP inhibition. 10 Following a genotoxic stimulus depletion of PARG, in contrast to PARP depletion, leads to a drop in NAD levels. This leads to lung cancer cell death that may be as a result of energy failure (Erdelyi, Bai et al. 2009).

[0013] Cell permeable PARG inhibitors have been limited to compounds such as Tannic acid or Gallotannin which have questionable specificity for PARG and limited bioavailability (Sun, 15 Zhang et al. 2012) (Fathers, Drayton et al. 2012) (Blenn, Wyrscz et al. 2011).

[0014] An object of this invention is to provide cell permeable inhibitors of PARG.

SUMMARY

[0015] In one aspect, provided herein are compounds of Formula (I'):



20

(I')

wherein:

X¹ is selected from CR⁷ and N, X² is selected from CR⁷ and N;

R¹ is hydrogen, cyano, formyl, -CONH₂, -CH₂OH, -CH₂OC₁₋₂ alkyl, C₁₋₂ alkyl, C₁₋₂ deuteroalkyl, or C₁₋₂ haloalkyl;

R² and R³ are independently C₁₋₂ alkyl; or

R² and R³ together with the carbon atom to which they are attached form C₃₋₄ cycloalkyl, or 3- or 5- membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S, wherein the cycloalkyl or heterocyclyl is unsubstituted or substituted with 1 to 6 R^{2a}, each R^{2a} is independently deuterium, C₁₋₄ alkyl, halo, or C₁₋₄ haloalkyl;

Ar is a 5- or 6-membered heteroaryl having 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S;

10 R⁴ is C₁₋₃ alkyl, C₁₋₃ haloalkyl, hydroxyC₁₋₃alkyl, -C(O)H, or cyano;

R⁵ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R⁶ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

15 each R⁷ is independently hydrogen, deuterium, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, NR^{7a}R^{7b}, or hydroxy;

each R^{7a} and R^{7b} is independently H or C₁₋₄ alkyl;

L^B is a bond, C₁₋₂ alkylene, -O-, -NR^{LB}-, or -S-;

R^{LB} is hydrogen or C₁₋₄ alkyl;

20 ring B is a 3- to 6- membered heterocyclyl, a 5- to 12-membered spiro heterocyclyl, or a 5- to 7- membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein ring B is unsubstituted or substituted with R^a, R^b, and R^c, wherein

R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, 5- or 6- membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, or 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected

from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, or 3- or 6-membered heterocyclyl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocyclyl, or 5- to 12-membered spiro heterocyclyl, each heterocyclyl having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), or -S(O)₂NR^hRⁱ (where R^h and Rⁱ are independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, or hydroxyC₁₋₆ alkyl; or R^h and Rⁱ together with the nitrogen atom to which they are attached form a 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S);

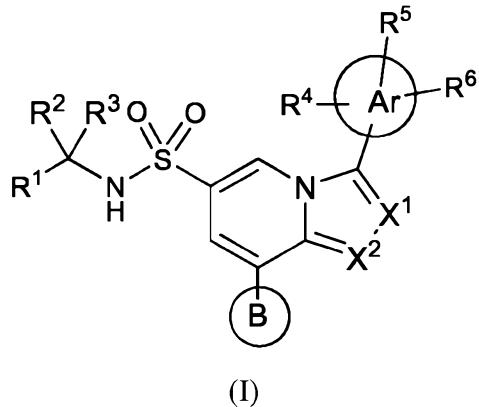
5 R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; R^c is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; or R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocyclyl combine to form

10 a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and

15 further wherein the heteroaryl and heterocyclyl of R^a, the phenyl, heteroaryl, and heterocyclyl of R^d, the heterocyclyl or spiro heterocyclyl formed by R^f and R^g combining with the nitrogen to which they are attached, and the heterocyclyl formed by R^h and Rⁱ combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents selected from C₁₋₆ alkyl, hydroxy, hydroxyC₁₋₆ alkyl, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl; or

20 a pharmaceutically acceptable salt thereof.

[0016] In one aspect, provided herein are compounds of Formula (I):



wherein:

X^1 is selected from CR⁷ and N, X^2 is selected from CR⁷ and N, and at least one of X^1 and

5 X^2 is N;

R¹ is hydrogen, cyano, formyl, -CONH₂, -CH₂OH, -CH₂OC₁₋₂ alkyl, C₁₋₂ alkyl, or
C₁₋₂ haloalkyl;

R² and R³ are independently C₁₋₂ alkyl; or

R² and R³ together with the carbon atom to which they are attached form C₃₋₄ cycloalkyl, or 3- or
10 4- membered heterocycll having 1 heteroatom ring vertex, selected from N, O, and S;

Ar is a 5- or 6-membered heteroaryl having 1to 3 heteroatom ring vertices, each independently
selected from N, O, and S;

R⁴ is C₁₋₃ alkyl, C₁₋₃ haloalkyl, hydroxyC₁₋₃alkyl, -C(O)H, or cyano;

R⁵ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆
15 haloalkoxy;

R⁶ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆
haloalkoxy;

each R⁷ is independently hydrogen, deuterium, halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;

ring B is a 3- to 6- membered heterocycll, a 5- to 12-membered spiro heterocycll, or a 5- to 7-
20 membered bridged heterocycll, each heterocycll having from 1 to 3 heteroatom ring
vertices, each independently selected from N, O, and S, wherein ring B is unsubstituted
or substituted with R^a, R^b, and R^c, wherein

R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxyC₁₋₆
alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, 5- or 6- membered
25 heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O,

and S, 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, or 3- to 6- membered

5 heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, or 3- or 6-membered heterocycll having 1 to 2 heteroatom ring

10 vertices, each independently selected from N, O, and S; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocycll, or 5- to 12-membered spiro heterocycll, each heterocycll having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), or -S(O)₂NR^hRⁱ (where R^h and Rⁱ are independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, or hydroxyC₁₋₆ alkyl; or R^h and Rⁱ together with the nitrogen atom to which they are attached

15 form a 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S);

R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R^c is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; or

20 R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocycll combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and

25 further wherein the heteroaryl and heterocycll of R^a, the phenyl, heteroaryl, and heterocycll of R^d, the heterocycll or spiro heterocycll formed by R^f and R^g combining with the nitrogen to which they are attached, and the heterocycll formed by R^h and Rⁱ combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents selected from C₁₋₆ alkyl, hydroxy, hydroxyC₁₋₆ alkyl, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl; or

a pharmaceutically acceptable salt thereof.

[0017] In another aspect, provided herein is a pharmaceutical composition comprising a compound of **Formula (I)** or **Formula (I')** (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

5 [0018] In another aspect, provided herein is a compound of **Formula (I)** or **Formula (I')** (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in therapy.

10 [0019] In another aspect, provided herein is a compound of **Formula (I)** or **Formula (I')** (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the treatment of cancer. In one embodiment, the cancer is a human cancer.

[0020] In another aspect, provided herein is a compound of **Formula (I)** or **Formula (I')** (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein, for use in the production of a PARG inhibitory effect.

15 [0021] In another aspect, provided herein is the use of a compound of **Formula (I)** or **Formula (I')** (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer. Suitably, the medicament is for use in the treatment of human cancers.

20 [0022] In another aspect, provided herein is the use of a compound of **Formula (I)** or **Formula (I')** (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the production of a PARG inhibitory effect.

[0023] In another aspect, provided herein is a method of inhibiting PARG *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound of **Formula (I)** or **Formula (I')** (or any embodiments thereof), or a pharmaceutically acceptable salt thereof.

25 [0024] In another aspect, provided herein is a method of inhibiting cell proliferation *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound of **Formula (I)** or **Formula (I')** (or any embodiments thereof), or a pharmaceutically acceptable salt thereof.

[0025] In another aspect, provided herein is a method of treating cancer in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of **Formula (I)** or **Formula (I')** (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as defined herein.

5 [0026] In another aspect, provided herein is a method of identifying PARG activity in a test compound of PARG inhibitory activity, said method comprising (i) contacting the test compound with isolated PARG enzyme, a biotinylated-PARYlated PARP substrate to form a PARG reaction pre-mixture; (ii) contacting the PARG reaction pre-mixture with a detection antibody and streptavidin-europium to form a PARG reaction mixture; and (iii) measuring fluorescence
10 intensity of the PARG reaction mixture, wherein said method further comprises performing steps (i)-(iii) with a positive control sample represented by **Formula (I)** or **Formula (I')** (or any embodiments thereof).

15 [0027] In another aspect, provided are methods of synthesizing a compound of **Formula (I)** or **Formula (I')** (or any embodiments thereof), or a pharmaceutically acceptable salt thereof, as defined herein.

[0028] In another aspect, provided herein is a compound as defined herein, or a pharmaceutically acceptable salt, obtainable by, or obtained by, or directly obtained by a method of synthesis as defined herein.

20 [0029] In another aspect, provided herein are novel intermediates as defined herein which are suitable for use in any one of the synthetic methods as set out herein.

[0030] Preferred, suitable, and optional features of any one particular aspect of the present invention are also preferred, suitable, and optional features of any other aspect.

BRIEF DESCRIPTION OF THE DRAWINGS

[0031] NOT APPLICABLE

25

DETAILED DESCRIPTION OF THE INVENTION

[0032] Before the present invention is further described, it is to be understood that the invention is not limited to the particular embodiments set forth herein, and it is also to be

understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0033] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the 5 upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in 10 the invention. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0034] As used herein, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to 15 exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology such as “solely,” “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

[0035] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Further, the dates of publication provided may be different 20 from the actual publication dates, which may need to be independently confirmed.

General

[0036] Provided herein, for example, are compounds and compositions for inhibition of PARG, and pharmaceutical compositions comprising the same. Also provided herein are, for example, methods of treating or preventing a disease, disorder or condition, or a symptom 25 thereof, mediated by inhibition of PARG.

Definitions

[0037] Unless otherwise indicated, the following terms are intended to have the meaning set forth below. Other terms are defined elsewhere throughout the specification.

[0038] The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a saturated straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (*i.e.* C₁₋₈ means one to eight carbons). Alkyl can include any number of carbons, such as C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅, C₁₋₆, C₁₋₇, C₁₋₈, C₁₋₉, C₁₋₁₀, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₃₋₄, C₃₋₅, C₃₋₆, C₄₋₅, C₄₋₆ and C₅₋₆. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[0039] The term "alkylene" refers to a straight or branched, saturated hydrocarbon radical having the number of carbon atoms indicated, and linking at least two other groups, *i.e.*, a divalent hydrocarbon radical. The two moieties linked to the alkylene can be linked to the same atom or different atoms of the alkylene group. Representative alkylene groups include, but are not limited to, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene and hexylene.

[0040] "Bridged heterocyclyl" means a saturated 5- to 7-membered monocyclic heterocycle having two non-adjacent ring atoms linked by a (X)_n group where n is 1 to 3, each X is CRR', NR, S(O)_{n1}, or O, wherein no more than one X is NR, S(O)_{n1} or O, and R and R' are independently H or methyl (also may be referred to herein as "bridging" group). The 5- to 7-membered heterocycle further having from one to three heteroatoms independently selected from N, O, and S(O)_{n1}, the remaining ring atoms being carbon, where n1 is an integer from 0 to 2. Examples include, but are not limited to, 2-azabicyclo[2.2.2]octane, quinuclidine, 7-oxabicyclo[2.2.1]heptane, and the like. Additional examples include 3,8-diazabicyclo[3.2.1]octane, and the like.

[0041] The term "cycloalkyl" refers to a saturated hydrocarbon ring having the indicated number of ring atoms (*e.g.*, C₃₋₆ cycloalkyl). Cycloalkyl is optionally substituted with one, two, or three substituents independently selected from C₁₋₆ alkyl, halo, hydroxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, or cyano, unless stated otherwise. Representative examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and the like.

[0042] The term "deuteroalkyl," means alkyl, as defined above, that is substituted with one or more deuterium atoms and includes monodeuteroalkyl and polydeuteroalkyl.

[0043] The term "halo" or "halogen," by itself or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

5 [0044] The term "haloalkyl," means alkyl, as defined above, that is substituted with one to five halo atoms and includes monohaloalkyl and polyhaloalkyl. For example, the term "C₁₋₄ haloalkyl" includes trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

10 [0045] The terms "alkoxy," and "haloalkoxy" refer to alkyl and haloalkyl groups respectively, each as defined herein, that is attached to the remainder of the molecule via an oxygen atom.

15 [0046] The term "alkoxyalkyl" refers to alkyl group connected to an oxygen atom that is further connected to a second alkyl group, the second alkyl group being the point of attachment to the remainder of the molecule: alkyl-O-alkyl. The alkyl portion can have any suitable number of carbon atoms, such as C₂₋₆, and can be straight or branched. Alkoxyalkyl groups include, for example, methoxymethyl (-CH₂OCH₃, a C₂ group), ethoxymethyl (-CH₂OCH₂CH₃, a C₃ group), methoxyethyl (-CH₂CH₂OCH₃, a C₃ group), ethoxyethyl (-CH₂CH₂OCH₂CH₃, a C₄ group), and the like.

[0047] The term "haloalkoxyalkyl" refers to an alkoxyalkyl group, as defined here, that is substituted with one to five halo atoms and includes monohaloalkyl and polyhaloalkyl.

20 [0048] The term "aryl" means, unless otherwise stated, an aromatic, hydrocarbon group which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. Non-limiting examples of aryl groups include phenyl, naphthyl, and biphenyl.

25 [0049] The term "heteroaryl" refers to a 5- to 10-membered aromatic ring that contains from one to five heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of heteroaryl groups include pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, benzotriazinyl, purinyl, benzimidazolyl,

benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiaxolyl, benzofuranyl, benzothienyl, indolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl, thienyl and the like.

5 [0050] The term "heterocycloalkyl" or "heterocyclyl" refers to a saturated or partially unsaturated 3- to 10-membered monocyclic or bicyclic ring having from one to four heteroatoms independently selected from N, O, and S and the remaining ring atoms being carbon. Non limiting examples of heterocycloalkyl groups include 3- to 6-membered heterocycloalkyl having 10 one, two, or three heteroatoms independently selected from N, O, and S and the remaining ring atoms being carbon. The bicyclic ring may be fused wherein the two atoms and the bond between them are shared among 2 rings of the bicyclic ring. No ring in the heterocycloalkyl group is aromatic or fully unsaturated. Partially unsaturated heterocycloalkyl groups have one or more double or triple bonds in the ring, but heterocycloalkyl group are not aromatic. Non 15 limiting examples of heterocycloalkyl groups include pyrrolidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-oxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrahydrothiophene, and the like. A heterocycloalkyl group can be attached to the remainder of the molecule through a ring 20 carbon or a heteroatom. Non limiting examples of heterocycloalkyl groups include pyridine-2(H)-one.

25 [0051] The term "spiro heterocyclyl" as used herein, means a saturated or partially unsaturated bicyclic ring of 5 to 12 ring atoms wherein one to three ring atoms are heteroatoms independently selected from N, N(oxide), O, S, SO and SO₂ and the remaining ring atoms being carbon and further wherein the 2 rings are linked together by one common atom. Non limiting examples of the spiro heterocyclyl include 6-azaspiro[3.4]octane, 2-oxa-6-azaspiro[3.4]octan-6-yl, 4-oxaspiro[2.4]heptanyl, spiro[3.5]non-6-ene, and 2,7-diazaspiro[4.4]nonanyl.

30 [0052] The term "hydroxyalkyl," means alkyl, as defined above, that is substituted with one or two hydroxy. For example, the term "hydroxyC₁₋₄ alkyl" is meant to include hydroxymethyl, 1-, or 2-hydroxyethyl, 1,2-dihydroxyethyl, hydroxypropyl, and the like.

[0053] As used herein, a wavy line, "~~~", that intersects a single, double or triple bond in any chemical structure depicted herein, represent the point attachment of the single, double, or triple bond to the remainder of the molecule. Additionally, a bond extending to the center of a ring (e.g., a phenyl ring) is meant to indicate attachment at any of the available ring vertices. One of
5 skill in the art will understand that multiple substituents shown as being attached to a ring will occupy ring vertices that provide stable compounds and are otherwise sterically compatible.

[0054] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0055] The term "pharmaceutically acceptable salts" is meant to include salts of the
10 compounds of **Formula (I)** or **Formula (I')** (or any embodiments thereof) which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of **Formula (I)** or **Formula (I')** contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent.
15 Examples of salts derived from pharmaceutically acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine,
20 choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine,
triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of
25 **Formula (I)** or **Formula (I')** contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the
30

like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0056] The neutral forms of the compounds of **Formula (I)** or **Formula (I')** (or any embodiments thereof) may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention. In addition to salt forms, provided herein are compounds of **Formula (I)** or **Formula (I')** which are in a prodrug form. Prodrugs of the compounds of **Formula (I)** or **Formula (I')** are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of **Formula (I)** or **Formula (I')**. Additionally, prodrugs can be converted to the compounds of **Formula (I)** or **Formula (I')** by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of **Formula (I)** or **Formula (I')** when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are described in more detail elsewhere herein.

[0057] Certain compounds of **Formula (I)** or **Formula (I')** (or any embodiments thereof) can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of **Formula (I)** or **Formula (I')** (or any embodiments thereof) may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0058] Certain compounds of **Formula (I)** or **Formula (I')** (or any embodiments thereof) possess asymmetric carbon atoms (optical centers) or double bonds; the racemates,

diastereomers, geometric isomers, regioisomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. When a stereochemical depiction is shown, it is meant to refer the compound in which one of the isomers is present and substantially free of the other isomer. ‘Substantially free of’ another isomer indicates at least an 80/20 ratio of the two isomers, more preferably 90/10, or 95/5 or more. In some embodiments, one of the isomers will be present in an amount of at least 99%.

[0059] The compounds of Formula (I) or Formula (I') (or any embodiments thereof) may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. Unnatural proportions of an isotope may be defined as ranging from the amount found in nature to an amount consisting of 100% of the atom in question. For example, the compounds may incorporate radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C), or non-radioactive isotopes, such as deuterium (²H) or carbon-13 (¹³C). Such isotopic variations can provide additional utilities to those described elsewhere within this application. For instance, isotopic variants of the compounds of the invention may find additional utility, including but not limited to, as diagnostic and/or imaging reagents, or as cytotoxic/radiotoxic therapeutic agents. Additionally, isotopic variants of the compounds of Formula (I) or Formula (I') can have altered pharmacokinetic and pharmacodynamic characteristics which can contribute to enhanced safety, tolerability or efficacy during treatment. All isotopic variations of the compounds of Formula (I) or Formula (I'), whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0060] The terms “patient” or “subject” are used interchangeably to refer to a human or a non-human animal (e.g., a mammal). In one embodiment, the patient or subject is a human.

[0061] The terms “administration”, “administer” and the like, as they apply to, for example, a subject, cell, tissue, organ, or biological fluid, refer to contact of, for example, an inhibitor of PARG, a pharmaceutical composition comprising same, or a diagnostic agent to the subject, cell, tissue, organ, or biological fluid. In the context of a cell, administration includes contact (e.g., in vitro or ex vivo) of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell.

[0062] The terms “treat”, “treating”, treatment” and the like refer to a course of action (such as administering an inhibitor of PARG or a pharmaceutical composition comprising same) initiated after a disease, disorder or condition, or a symptom thereof, has been diagnosed, observed, and the like so as to eliminate, reduce, suppress, mitigate, or ameliorate, either temporarily or

5 permanently, at least one of the underlying causes of a disease, disorder, or condition afflicting a subject, or at least one of the symptoms associated with a disease, disorder, condition afflicting a subject. Thus, treatment includes inhibiting (e.g., arresting the development or further development of the disease, disorder or condition or clinical symptoms association therewith) an active disease.

10 [0063] The term “in need of treatment” as used herein refers to a judgment made by a physician or other caregiver that a subject requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of the physician’s or caregiver’s expertise.

15 [0064] The terms “prevent”, “preventing”, “prevention” and the like refer to a course of action (such as administering a PARG inhibitor or a pharmaceutical composition comprising same) initiated in a manner (e.g., prior to the onset of a disease, disorder, condition or symptom thereof) so as to prevent, suppress, inhibit or reduce, either temporarily or permanently, a subject’s risk of developing a disease, disorder, condition or the like (as determined by, for example, the absence of clinical symptoms) or delaying the onset thereof, generally in the
20 context of a subject predisposed to having a particular disease, disorder or condition. In certain instances, the terms also refer to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

25 [0065] The term “in need of prevention” as used herein refers to a judgment made by a physician or other caregiver that a subject requires or will benefit from preventative care. This judgment is made based on a variety of factors that are in the realm of a physician’s or caregiver’s expertise.

[0066] The terms “inhibiting” and “reducing,” or any variation of these terms in relation of PARG, includes any measurable decrease or complete inhibition to achieve a desired result. For example, there may be a decrease of about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%,

50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, reduction of PARG activity compared to normal. About as used herein means within \pm 10%, preferably \pm 5% of a given value.

[0067] The phrase “therapeutically effective amount” refers to the administration of an agent 5 to a subject, either alone or as part of a pharmaceutical composition and either in a single dose or as part of a series of doses, in an amount capable of having any detectable, positive effect on any symptom, aspect, or characteristic of a disease, disorder or condition when administered to the subject. The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and 10 diagnostic analysis of the subject’s condition, and the like. By way of example, measurement of the serum level of a PARG inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been used.

[0068] The term “substantially pure” indicates that a component makes up greater than about 15 50% of the total content of the composition, and typically greater than about 60% of the total content. More typically, “substantially pure” refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest.

[0069] As used herein, “Poly ADP Ribose Polymerase (PARP) inhibitor” refers to an agent 20 that inhibits PARP activity, including PARP1 and PARP2. Examples of PARP inhibitors include, but are not limited to, niraparib, rucaparib, olaparib, talazoparib, and veliparib.

[0070] As used herein, “PARP inhibitor-resistant cancer” or “cancer resistant to one or more 25 PARP inhibitors” refers to cancers that do not respond to treatment with a PARP inhibitor. Nonresponsivness can be assessed by the continued growth of a tumor when administered the agent, a tumor that does not shrink in size when administered the agent, or other known means in the art. Nonresponsivness of a cancer can be determined through clinical observation, diagnosed as such by a medical professional, experimentally tested with isolated cells in a laboratory setting, or by another technical means.

[0071] As used herein, “platin-resistant cancer” or “cancer resistant to one or more platins” refers to cancers that do not respond to treatment with a platin. Nonresponsivness can be assessed by the continued growth of a tumor when administered the agent, a tumor that does not

shrink in size when administered the agent, or other known means in the art. Nonresponsiveness of a cancer can be determined through clinical observation, diagnosed as such by a medical professional, experimentally tested with isolated cells in a laboratory setting, or by another technical means.

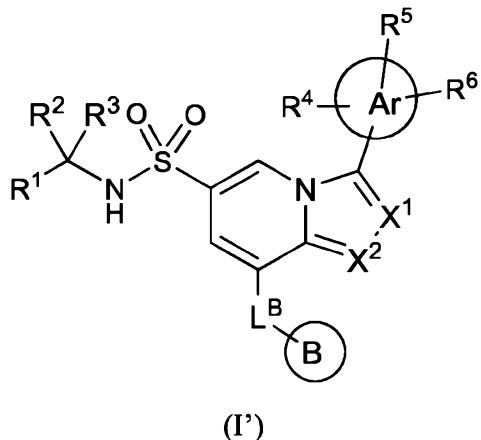
5 [0072] The phrase “platins” or “platinum based-chemotherapeutics” refers to a platinum containing class of chemotherapeutic drug used for treating cancer. Exemplary platins are cisplatin, carboplatin, satraplatin, heptaplatin, picoplatin, nedaplatin, triplatin, lipoplatin, and oxaliplatin.

10 [0073] As used herein “homologous recombination” refers to the cellular process of genetic recombination in which nucleotide sequences are exchanged between two similar or identical DNA sequences.

15 [0074] As used herein “homologous recombination deficient (HRD) cancer” refers to a cancer that is characterized by a reduction or absence of a functional HR repair pathway. HR deficiency may arise from absence or reduction of one or more HR-associated genes or presence of one or more mutations in one or more HR-associated genes. Examples of HR-associated genes include BRCA1, BRCA2, RAD54, RAD51B, ATM, BARD1, CHECK1, CHECK2, CDK12, RAD51B, RAD54L, RAD51D, PPP22A, BRIP1, CtIP (CtBP-interacting protein), PALB2 (Partner and Localizer of BRCA2), XRCC2 (X-ray repair complementing defective repair in Chinese hamster cells 2), RECQL4 (RecQ Protein-Like 4), BLM (Bloom syndrome, RecQ helicase-like), WRN (Werner syndrome , one or more HR-associated genes) Nbs 1 (Nibrin), and genes encoding Fanconi anemia (FA) proteins or FA-like genes e.g, FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANJ (BRIP1), FANCL, FANCM, FANCN (RALB2), FANCP (SLX4), FANCS (BRCA1), RAD51C, and XPF.

Compounds

25 [0075] In some aspects, provided herein are compounds of Formula (I'):



wherein:

X¹ is selected from CR⁷ and N, X² is selected from CR⁷ and N;

5 R¹ is hydrogen, cyano, formyl, -CONH₂, -CH₂OH, -CH₂OC₁₋₂ alkyl, C₁₋₂ alkyl, C₁₋₂ deutoalkyl, or C₁₋₂ haloalkyl;

R² and R³ are independently C₁₋₂ alkyl; or

R² and R³ together with the carbon atom to which they are attached form C₃₋₄ cycloalkyl, or 3- or 10 4- membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S,

wherein the cycloalkyl or heterocyclyl is unsubstituted or substituted with 1 to 6 R^{2a},

each R^{2a} is independently deuterium, C₁₋₄ alkyl, halo, or C₁₋₄ haloalkyl;

Ar is a 5- or 6-membered heteroaryl having 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S;

R⁴ is C₁₋₃ alkyl, C₁₋₃ haloalkyl, hydroxyC₁₋₃alkyl, -C(O)H, or cyano;

15 R⁵ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R⁶ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

each R⁷ is independently hydrogen, deuterium, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, NR^{7a}R^{7b}, or 20 hydroxy;

each R^{7a} and R^{7b} is independently H or C₁₋₄ alkyl;

L^B is a bond, C₁₋₂ alkylene, -O-, -NR^{LB}-, or -S-;

R^{LB} is hydrogen or C₁₋₄ alkyl;

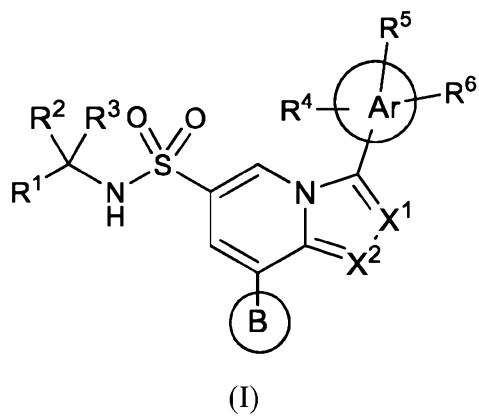
ring B is a 3- to 6- membered heterocyclyl, a 5- to 12-membered spiro heterocyclyl, or a 5- to 7- membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein ring B is unsubstituted or substituted with R^a, R^b, and R^c, wherein

- 5 R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, 5- or 6- membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, or 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, or 3- or 6-membered heterocyclyl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocyclyl, or 5- to 12-membered spiro heterocyclyl, each heterocyclyl having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), or -S(O)₂NR^hRⁱ (where R^h and Rⁱ are independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, or hydroxyC₁₋₆ alkyl; or R^h and Rⁱ together with the nitrogen atom to which they are attached form a 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S);
- 10 R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;
- 15 R^c is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; or R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocyclyl combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and
- 20 R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;
- 25 R^c is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; or R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocyclyl combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and
- 30 R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

further wherein the heteroaryl and heterocycll of R^a, the phenyl, heteroaryl, and heterocycll of R^d, the heterocycll or spiro heterocycll formed by R^f and R^g combining with the nitrogen to which they are attached, and the heterocycll formed by R^h and Rⁱ combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents selected from C₁₋₆ alkyl, hydroxy, hydroxyC₁₋₆ alkyl, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl; or

5 a pharmaceutically acceptable salt thereof.

[0076] In some aspects, provided herein are compounds of Formula (I):



wherein:

X¹ is selected from CR⁷ and N, X² is selected from CR⁷ and N, and at least one of X¹ and X² is N;

15 R¹ is hydrogen, cyano, formyl, -CONH₂, -CH₂OH, -CH₂OC₁₋₂ alkyl, C₁₋₂ alkyl, or C₁₋₂ haloalkyl;

R² and R³ are independently C₁₋₂ alkyl; or

R² and R³ together with the carbon atom to which they are attached form C₃₋₄ cycloalkyl, or 3- or 4- membered heterocycll having 1 heteroatom ring vertex, selected from N, O, and S;

20 Ar is a 5- or 6-membered heteroaryl having 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S;

R⁴ is C₁₋₃ alkyl, C₁₋₃ haloalkyl, hydroxyC₁₋₃alkyl, -C(O)H, or cyano;

R⁵ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R⁶ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

each R⁷ is independently hydrogen, deuterium, halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;

ring B is a 3- to 6- membered heterocyclyl, a 5- to 12-membered spiro heterocyclyl, or a 5- to 7-

5 membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein ring B is unsubstituted or substituted with R^a, R^b, and R^c, wherein

R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, 5- or 6- membered

10 heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, or 3- to 6- membered

15 heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, or 3- or 6-membered heterocyclyl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S; or R^f and R^g together with the

20 nitrogen atom to which they are attached form a 4- to 6- membered heterocyclyl, or 5- to 12-membered spiro heterocyclyl, each heterocyclyl having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), or -S(O)₂NR^hRⁱ (where R^h and Rⁱ are independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, or hydroxyC₁₋₆ alkyl; or R^h and Rⁱ together with the nitrogen atom to which they are attached

25 form a 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S);

R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R^c is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; or

R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocyclyl combine to form

30 a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S,

wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and

further wherein the heteroaryl and heterocycll of R^a, the phenyl, heteroaryl, and heterocycll of R^d, the heterocycll or spiro heterocycll formed by R^f and R^g combining with the nitrogen to which they are attached, and the heterocycll formed by R^h and Rⁱ combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents selected from C₁₋₆ alkyl, hydroxy, hydroxyC₁₋₆ alkyl, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl; or

10 a pharmaceutically acceptable salt thereof.

[0077] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R² and R³ together with the carbon atom to which they are attached form 3- or 4- membered heterocycll

15 having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocycll is unsubstituted or substituted with 1 to 6 R^{2a}. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R² and R³ together with the carbon atom to which they are attached form 3- or 4- membered heterocycll having 1 heteroatom ring vertex, selected from N,

20 O, and S, wherein the heterocycll is unsubstituted. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R² and R³ together with the carbon atom to which they are attached form 3- membered heterocycll having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocycll is unsubstituted or substituted with 1 to 6 R^{2a}. In some

25 embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R² and R³ together with the carbon atom to which they are attached form 4- membered heterocycll having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocycll is unsubstituted or substituted with 1 to 6 R^{2a}. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R² and R³

together with the carbon atom to which they are attached form 3- membered heterocycll having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocycll is unsubstituted. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R² and R³ together with the carbon atom to which they are attached form 4- membered heterocycll having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocycll is unsubstituted.

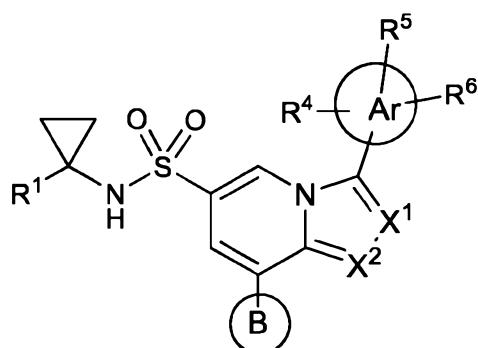
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[0078] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein L^B is a bond, C₁₋₂ alkylene, or –O–; In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein L^B is a bond. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein L^B is C₁₋₂ alkylene. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein L^B is –O–. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein L^B is NR^{LB}– or –S–.

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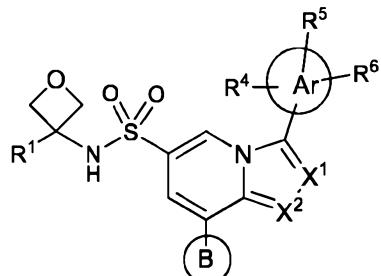
[0079] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is a compound having the formula (Ia)



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(Ia).

[0080] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is a compound having the formula (Ib)



(Ib).

[0081] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein at least one of 5 X^1 and X^2 is N. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein X^1 and X^2 are both N. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein X^1 is N and X^2 is CR⁷. In some embodiments, the compound or the pharmaceutically acceptable 10 salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein X^1 is CR⁷ and X^2 is N.

[0082] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R⁷ is hydrogen, fluoro, methyl, ethyl, difluoromethyl, or trifluoromethyl. In some embodiments, the 15 compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R⁷ is hydrogen.

[0083] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R¹ is hydrogen, cyano, methyl, or ethyl. In some embodiments, the compound or the 20 pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R¹ is hydrogen. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R¹ is cyano. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a 25 subembodiment thereof, wherein R¹ is methyl.

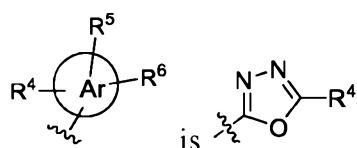
[0084] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R² and R³ are independently C₁₋₂ alkyl.

[0085] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is

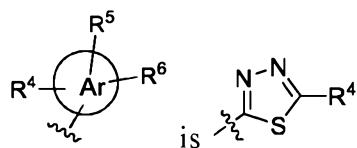
5 the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein Ar is pyridyl, pyridazinyl, pyrdimidinyl, pyrazinyl, or 1, 3, 5-triazinyl. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein Ar is imidazolyl, isoxazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, or 1,3,4-thiadiazolyl.

10 In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein Ar is pyridazin-3-yl. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein Ar is 1,3,4-oxadiazol-2-yl or 1,3,4-thiadiazol-2-yl.

15 **[0086]** In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein the group



[0087] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein the group



[0088] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R⁴ is methyl, ethyl, difluoromethyl, trifluoromethyl, cyano, or C(O)H. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R⁴ is difluoromethyl, methyl, trifluoromethyl, cyano, or

25

C(O)H. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R⁴ is methyl. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R⁴ is difluoromethyl.

[0089] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R⁵ and R⁶ are independently hydrogen or absent. In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R⁵ and R⁶ are each absent.

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[0090] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein ring B is a 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, unsubstituted or substituted with R^a, R^b, and R^c. In some 15 embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein ring B is morpholinyl, 1,1-dioxothiomorpholinyl, azetinyl, pyrrolidinyl, piperidinyl, 6-oxo-1,6-dihydropyridinyl, or piperazinyl, each ring is independently unsubstituted or substituted with R^a, R^b, and R^c.

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[0091] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein

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R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, or C₁₋₆ haloalkyl; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocycll, or 5- to 12-membered spiro heterocycll, each heterocycll having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), and

R^b is absent or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy;

R^c is absent or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy;

and further wherein

the heterocyclyl of R^d, and the heterocyclyl or spiro heterocyclyl formed by R^f and R^g

5 combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents independently selected from C₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl.

[0092] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein

10 R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, or C₁₋₆ haloalkyl; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocyclyl, or 5- to 12-membered spiro heterocyclyl, each heterocyclyl having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), and

20 further wherein the heterocyclyl of R^d, and the heterocyclyl or spiro heterocyclyl formed by R^f and R^g combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents independently selected from C₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl.

[0093] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein

25 R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocyclyl and combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is

substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

[0094] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein

5 R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycll and combine to form a 4- to 6-membered saturated or partially unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated or partially unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl, or oxo.

10 **[0095]** In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycll and combine to form a 4- to 6-membered saturated ring comprising 1 additional heteroatom ring vertex, selected from N, O, and S, wherein the 4- to 6-membered saturated ring is substituted 15 with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

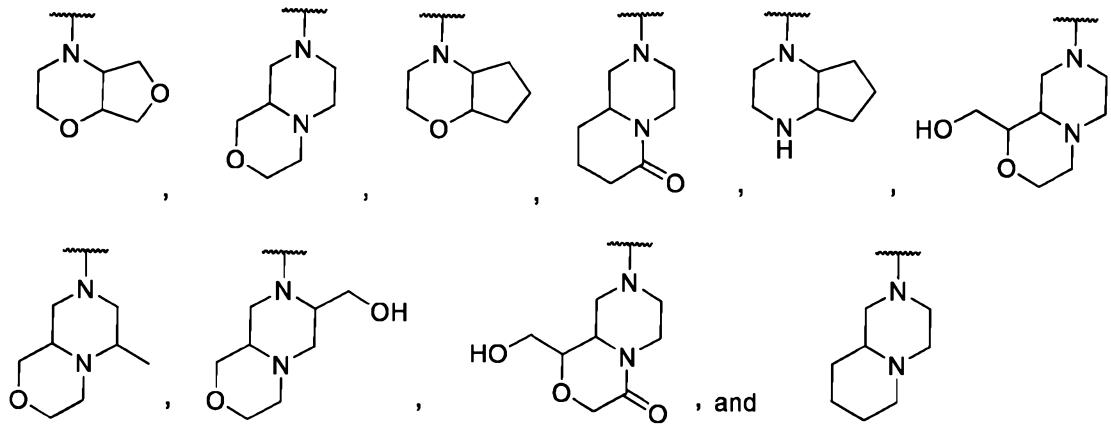
[0096] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein

20 R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycll and combine to form a 4- to 6-membered saturated ring comprising 0 additional heteroatom ring vertices, wherein the 4- to 6-membered saturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

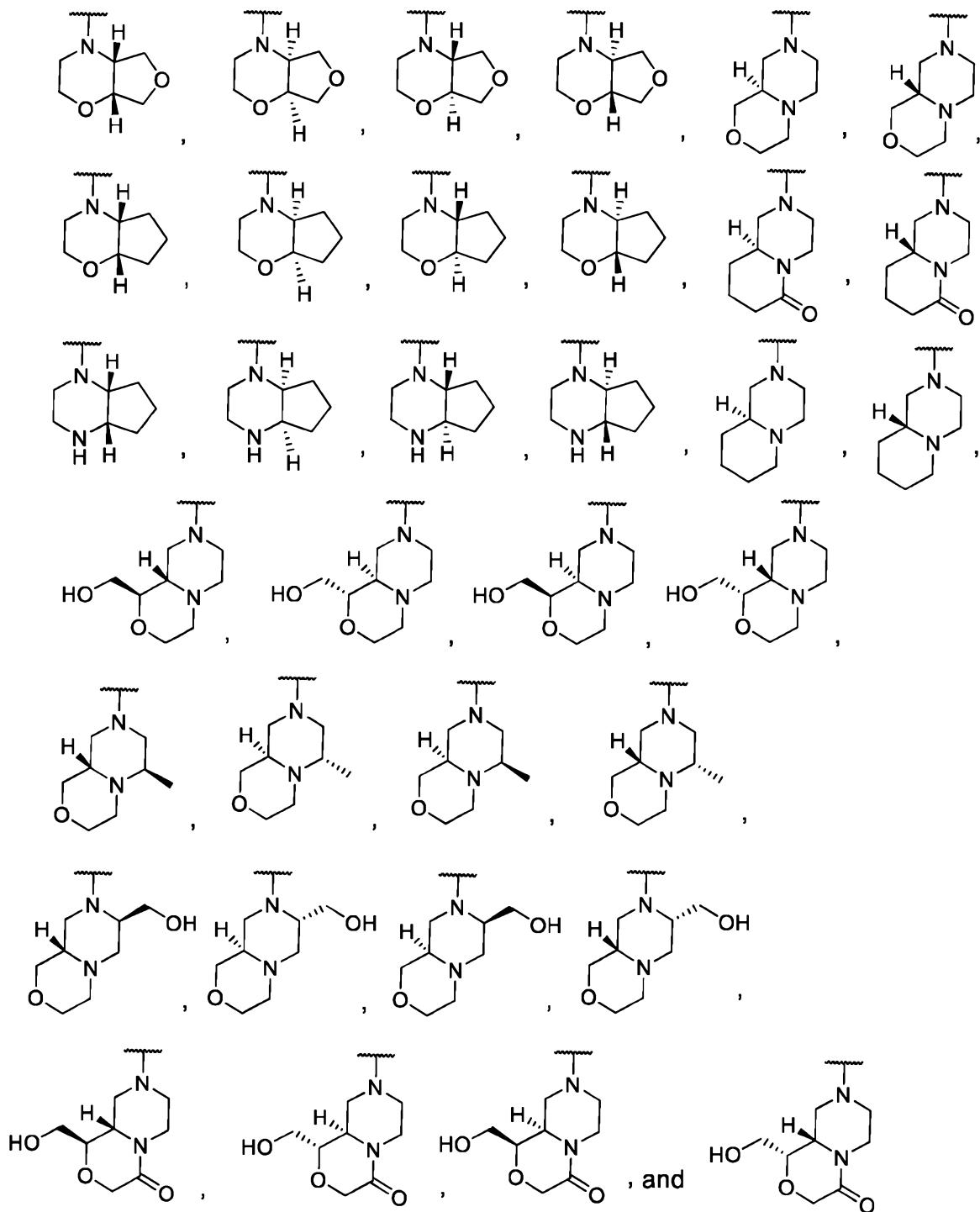
[0097] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein ring B is 25 octahydropyrazino[2,1-c][1,4]oxazinyl, octahydro-2H-pyrido[1,2-a]pyrazinyl, 6-methyloctahydropyrazino[2,1-c][1,4]oxazinyl, octahydro-6H-pyrido[1,2-a]pyrazin-6-only, or octahydropyrazino[2,1-c][1,4]oxazinyl substituted with a hydroxymethyl.

[0098] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein ring B is octahydro-1H-cyclopenta[b]pyrazinyl.

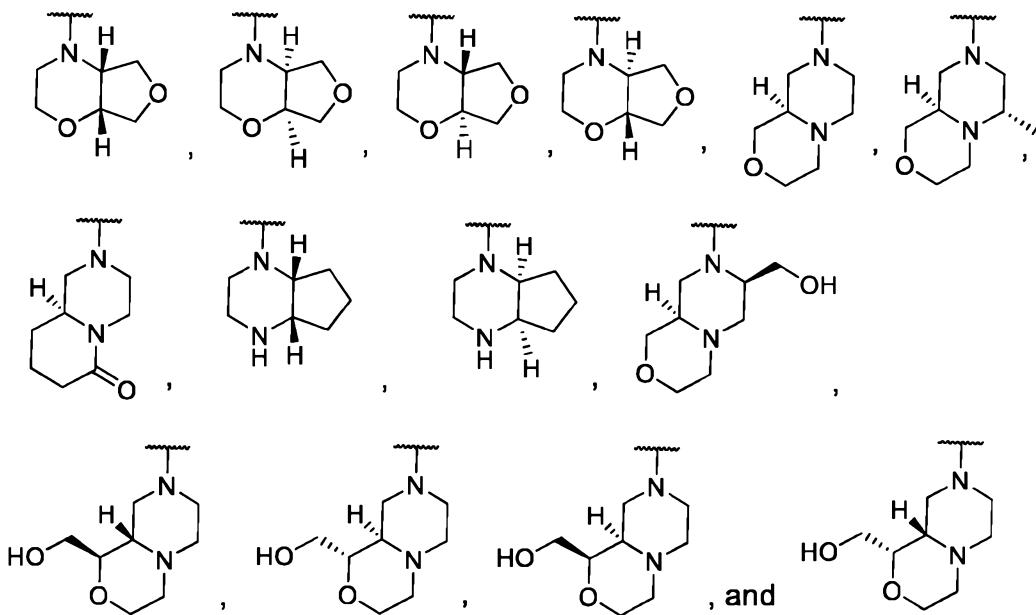
[0099] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is 5 the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



[0100] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is 10 the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



[0101] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



[0102] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein ring B is 5- to 12-membered spiro heterocyclyl, or 5- to 7- membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S,

5 wherein each ring is substituted or unsubstituted with R^a, R^b, and R^c.

[0103] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein ring B is 2-oxaspiro[3.5]non-6-en-7-yl, 2-oxaspiro[3.5]non-7-yl, 2-oxa-8-azaspiro[4.5]dec-8-yl, 9-oxa-3-

10 azaspiro[5.5]undec-3-yl, 2-oxa-6-azaspiro[3.4]oct-6-yl, 1-oxa-7-azaspiro[3.5]non-7-yl, 1-oxa-8-azaspiro[4.5]dec-8-yl, 6-oxa-2-azaspiro[3.3]hept-2-yl, 2,8-diazaspiro[4.5]dec-8-yl, 2-oxa-6-azaspiro[3.5]non-6-yl, , 3,6-diazabicyclo[3.1.1]hept-3-yl, 2,7-diazaspiro[3.5]non-7-yl, each ring optionally substituted with R^a where R^a is hydrogen or alkyl.

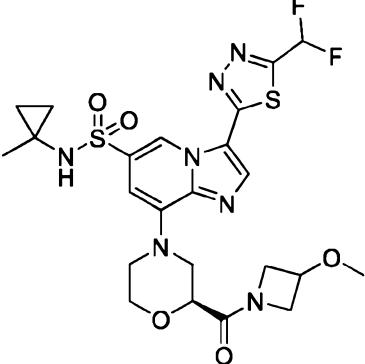
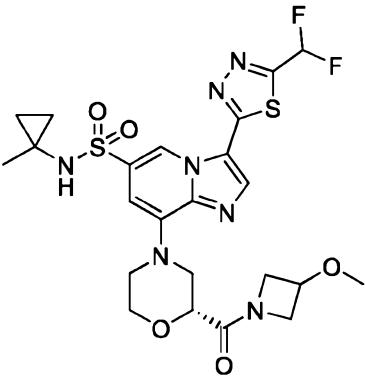
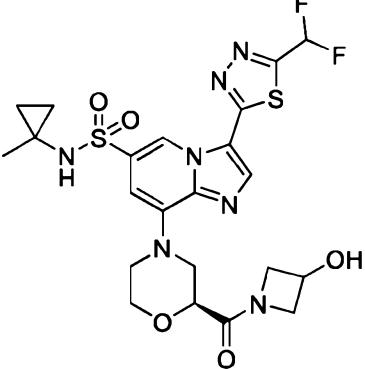
[0104] In some embodiments, the compound or the pharmaceutically acceptable salt thereof, is

15 the compound of Formula (I), Formula (I'), or a subembodiment thereof, wherein said compound is selected from the group in Table 1, Table 3, or Table 4.

Table 1

Example	Structure	Name
1		3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
2		8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-3-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
3		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-5-ethyl-2-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide
4		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((S)-2-((S)-2-(hydroxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

Example	Structure	Name
5		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((R)-2-((S)-2-(hydroxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
6		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((S)-2-((R)-2-(hydroxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
7		(S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-ethylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide
8		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((R)-2-((R)-2-(hydroxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

Example	Structure	Name
9		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-methoxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
10		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-methoxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
11		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-hydroxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

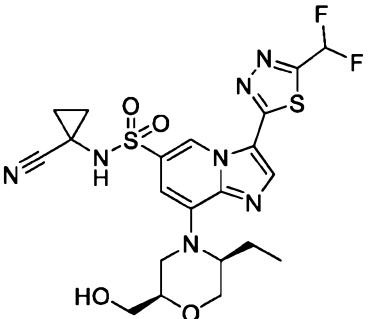
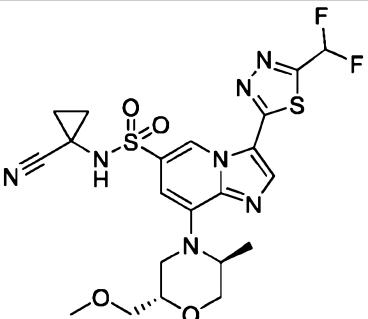
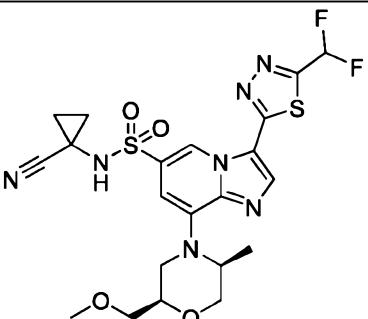
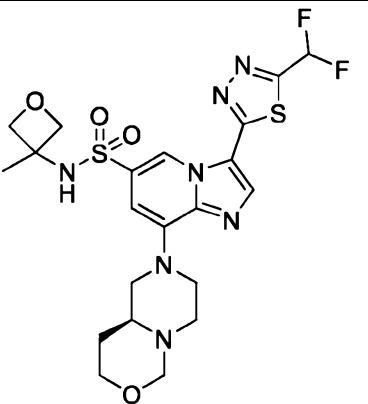
Example	Structure	Name
12		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-hydroxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
13		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(2-(morpholine-4-carbonyl)morpholino)imidazo[1,2-a]pyridine-6-sulfonamide
14		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(2-(morpholine-4-carbonyl)morpholino)imidazo[1,2-a]pyridine-6-sulfonamide

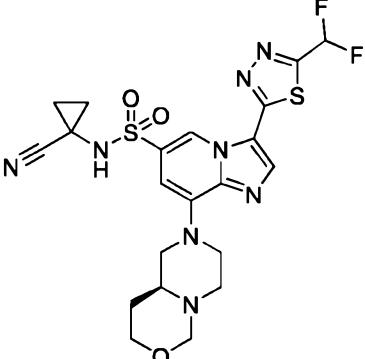
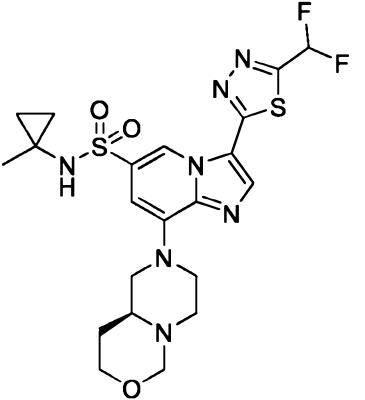
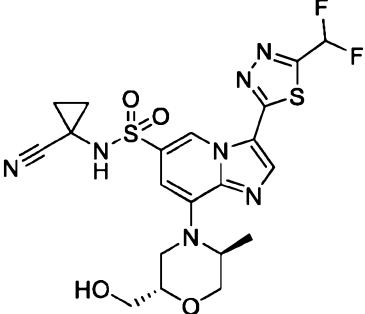
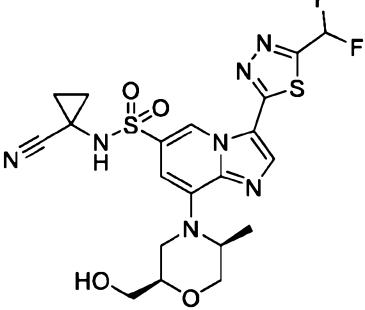
Example	Structure	Name
15		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aS,7aR)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
16		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aR,7aS)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
17		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aR,7aR)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
18		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aS,7aS)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)

Example	Structure	Name
19		3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
20		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(2,5-dioxa-8-azaspiro[3.5]nonan-8-yl)imidazo[1,2-a]pyridine-6-sulfonamide
21		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2,5-dimethylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide
22		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(methoxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

Example	Structure	Name
23		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(methoxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide
24		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(methoxymethyl)morpholino)imidazo[1,2-a]pyridine-6-sulfonamide
25		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide
26		rel-(R)-N-(1-cyanocyclopropyl)-8-(3-cyclopropylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide (stereochemistry arbitrary assigned)

Example	Structure	Name
27		rel-(S)-N-(1-cyanocyclopropyl)-8-(3-cyclopropylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide (stereochemistry arbitrary assigned)
28		(R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-ethylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide
29		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2-(methoxymethyl)-5-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide
30		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

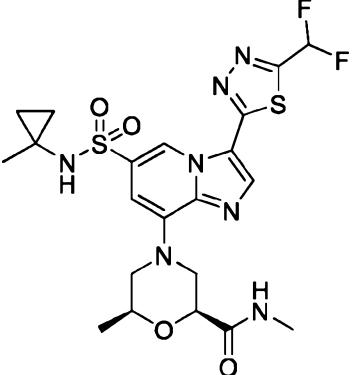
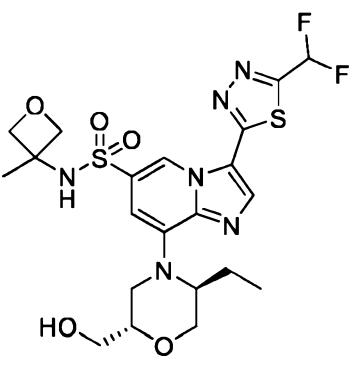
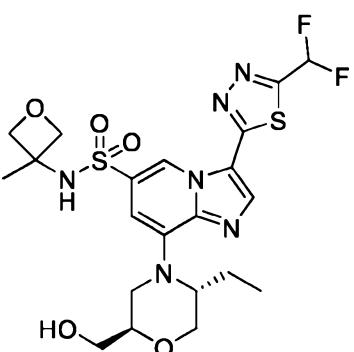
Example	Structure	Name
31		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)imidazo[1,2-a]pyridine-6-sulfonamide
32		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2-(methoxymethyl)-5-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide
33		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide
34		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

Example	Structure	Name
35		(R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide
36		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
37		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2-(hydroxymethyl)-5-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide
38		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide

Example	Structure	Name
39		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8((2S,5R)-5-ethyl-2-(hydroxymethyl)morpholino)imidazo[1,2-a]pyridine-6-sulfonamide
40		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8((4aR,7aS)-octahydro-1H-cyclopenta[b]pyrazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
41		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8((4aS,7aR)-octahydro-1H-cyclopenta[b]pyrazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
42		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-morpholinoimidazo[1,2-a]pyridine-6-sulfonamide

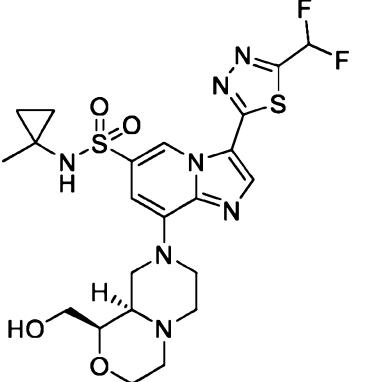
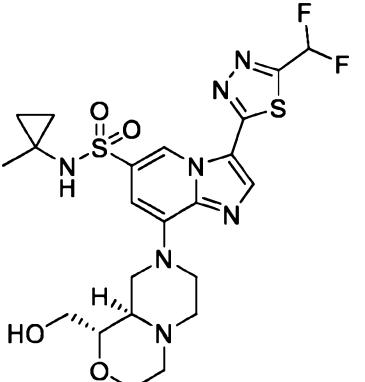
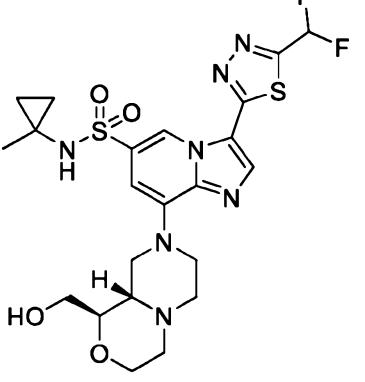
Example	Structure	Name
43		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide
44		(S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide
45		(R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide

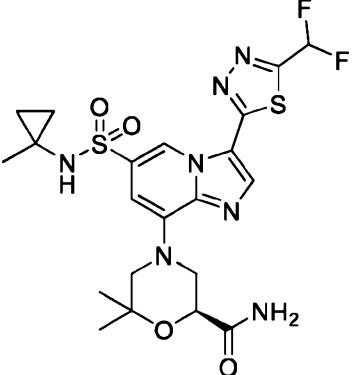
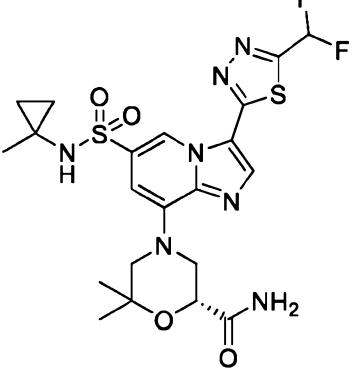
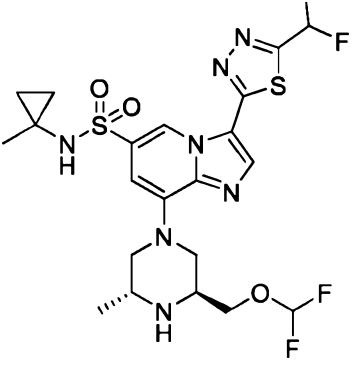
Example	Structure	Name
46		(S)-8-(2-(azetidine-1-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
47		(R)-8-(2-(azetidine-1-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
48		rel-(2R,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide (cis relative and enantiochemistry arbitrary assigned)

Example	Structure	Name
49		<p>rel-(2S,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide</p> <p>(cis relative and enantiochemistry arbitrary assigned)</p>
50		<p>rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>
51		<p>rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>

Example	Structure	Name
52		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
53		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
54		rel-N-(1-cyanocyclopropyl)-8-((3S,5R)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
55		rel-N-(1-cyanocyclopropyl)-8-((3R,5S)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

Example	Structure	Name
		(trans relative and enantiochemistry arbitrary assigned)
56		rel-8-((3S,5R)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
57		rel-8-((3R,5S)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
58		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1S,9aS)-1-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (stereochemistry arbitrarily assigned)

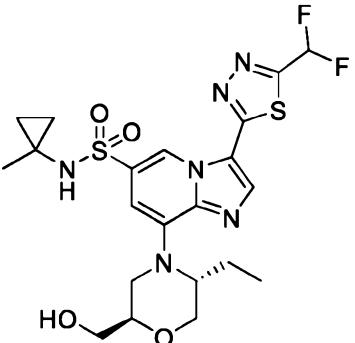
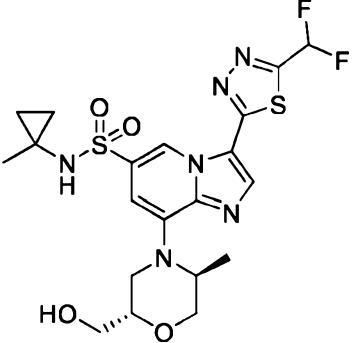
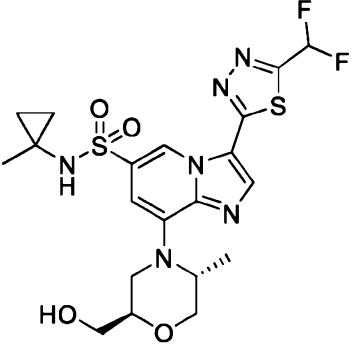
Example	Structure	Name
59	 <p>Chemical structure of compound 59: A complex heterocyclic molecule featuring a thiadiazole ring fused to a hexahdropyrazinopyrimidine system. The molecule includes a cyclopropylsulfonamide group at position 1, a hydroxymethyl group at position 8, and a difluoromethyl group at position 3.</p>	<p>rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1R,9aR)-1-(hydroxymethyl)hexahdropyrazin[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (stereochemistry arbitrarily assigned)</p>
60	 <p>Chemical structure of compound 60: Similar to compound 59, but with a different stereochemistry at the 1-position of the cyclopropylsulfonamide group.</p>	<p>rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1S,9aR)-1-(hydroxymethyl)hexahdropyrazin[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (stereochemistry arbitrarily assigned)</p>
61	 <p>Chemical structure of compound 61: Similar to compound 59, but with a different stereochemistry at the 9a-position of the hexahdropyrazinopyrimidine ring.</p>	<p>rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1R,9aS)-1-(hydroxymethyl)hexahdropyrazin[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (stereochemistry arbitrarily assigned)</p>

Example	Structure	Name
62		(S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6,6-dimethylmorpholine-2-carboxamide
63		(R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6,6-dimethylmorpholine-2-carboxamide
64		rel-8-((3S,5R)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)

Example	Structure	Name
65		<p>rel-8-((3R,5S)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>
66		<p>rel-8-((2S,6R)-2-((difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>
67		<p>rel-8-((2R,6S)-2-((difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>

Example	Structure	Name
68		rel-8-((2R,6R)-2-((difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
69		rel-8-((2S,6S)-2-((difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
70		rel-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)

Example	Structure	Name
71		rel-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-(hydroxymethyl)-6-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
72		(S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(6-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide
73		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(6-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide
74		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

Example	Structure	Name
		(trans relative and enantiochemistry arbitrary assigned)
75		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
76		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
77		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)

Example	Structure	Name
78		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
79		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
80		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

Example	Structure	Name
81		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide
82		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(6-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide
83		(R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

Example	Structure	Name
84		rel-(2S,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide (trans relative and enantiochemistry arbitrary assigned)
85		rel-(2R,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide (trans relative and enantiochemistry arbitrary assigned)
86		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide
87		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

Example	Structure	Name
88		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
89		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
90		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide
91		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

Example	Structure	Name
92		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-hydroxymethyl)-5-methylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
93		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide
94		rel-(S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-2-methylmorpholine-2-carboxamide (enantiochemistry arbitrary assigned)
95		rel-(R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-2-methylmorpholine-2-carboxamide (enantiochemistry arbitrary assigned)

Example	Structure	Name
96		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-hydroxymethyl)-6-methylmorpholino-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide
97		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-hydroxymethyl)-6-methylmorpholino-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide
98		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide
99		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-hydroxymethyl)-6-methylmorpholino-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)

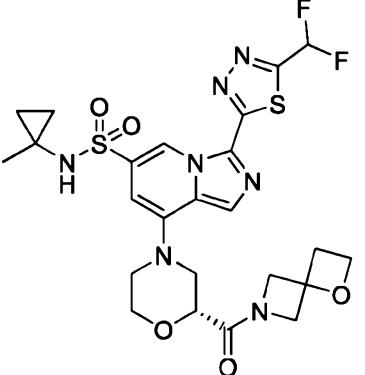
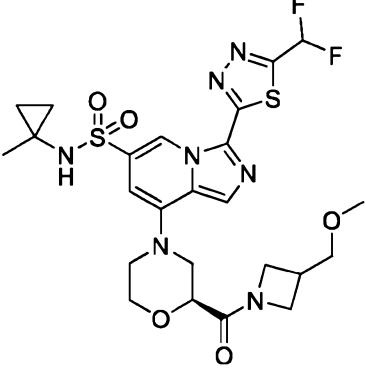
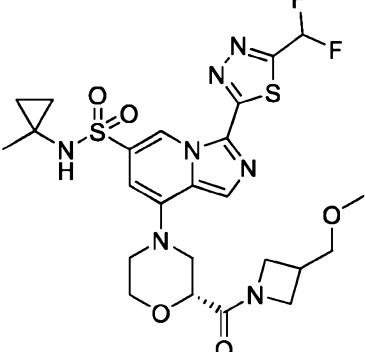
Example	Structure	Name
100		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-(hydroxymethyl)-6-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
101		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,2-a]pyridine-6-sulfonamide
102		rel-(2R,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide (cis relative and enantiochemistry arbitrary assigned)
103		rel-(2S,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide (cis relative and enantiochemistry arbitrary assigned)

Example	Structure	Name
104		3-(6-cyanopyridazin-3-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
105		(R)-3-(6-cyanopyridazin-3-yl)-8-(4-isobutryl-3-methylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
106		3-(6-cyanopyridazin-3-yl)-N-(1-methylcyclopropyl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,2-a]pyridine-6-sulfonamide

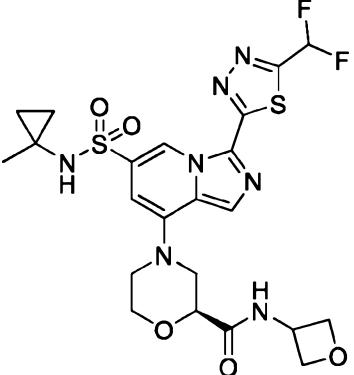
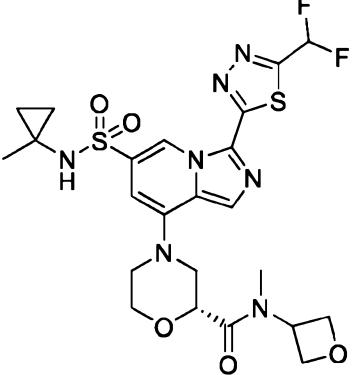
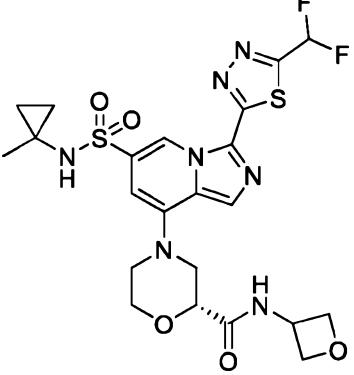
Example	Structure	Name
107		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
108		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1R,9aS)-1-hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative / enantioselectivity arbitrary assigned)
109		(S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(3-methyloxetan-3-yl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide

Example	Structure	Name
110		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide
111		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,2-a]pyridine-6-sulfonamide
112		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

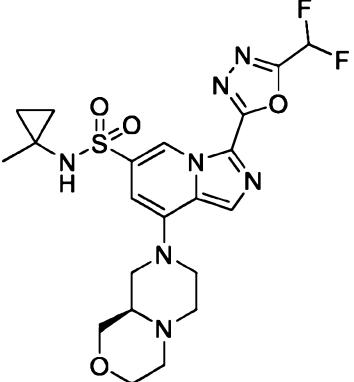
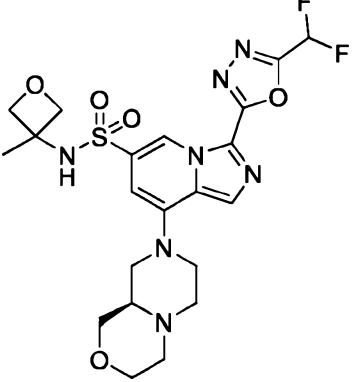
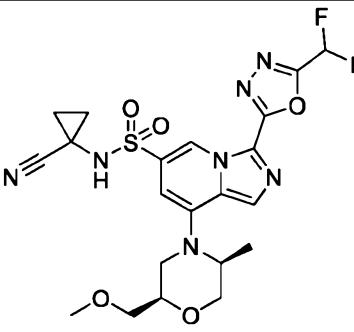
Example	Structure	Name
113		8-((3R,5R)-3,5-dimethylpiperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide
114		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide
115		(S)-8-(2-(1-oxa-6-azaspiro[3.3]heptane-6-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

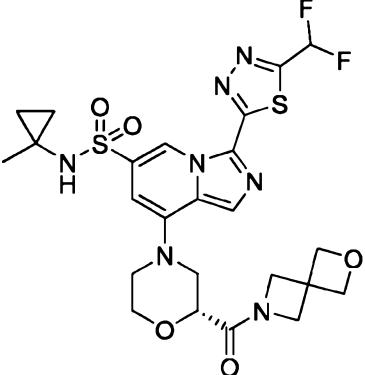
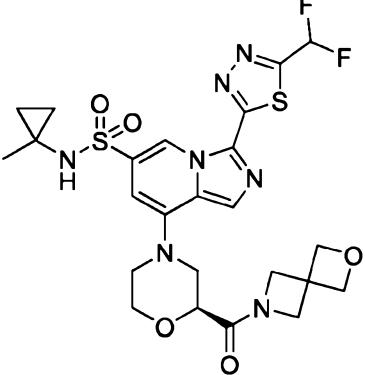
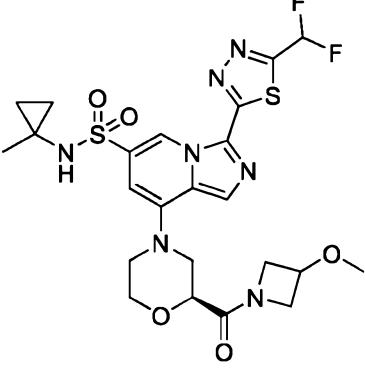
Example	Structure	Name
116		(R)-8-(2-(1-oxa-6-azaspiro[3.3]heptane-6-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
117		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-(methoxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
118		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-(methoxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

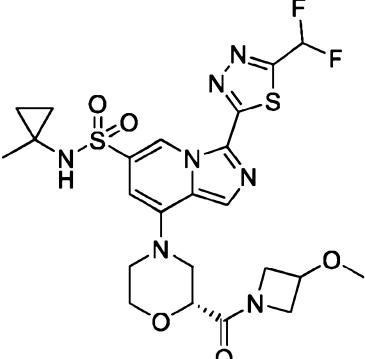
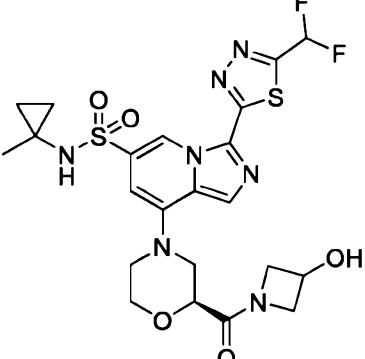
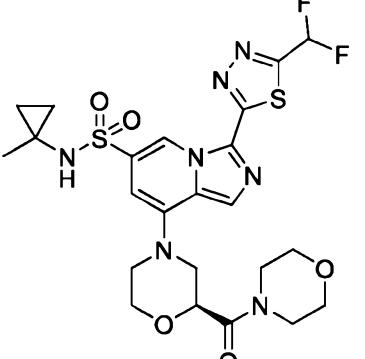
Example	Structure	Name
119		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-hydroxymethyl)azetidine-1-carbonyl)morpholino-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
120		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-hydroxymethyl)azetidine-1-carbonyl)morpholino-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
121		(S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methyl-N-(oxetan-3-yl)morpholine-2-carboxamide

Example	Structure	Name
122		(S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-(oxetan-3-yl)morpholine-2-carboxamide
123		(R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methyl-N-(oxetan-3-yl)morpholine-2-carboxamide
124		(R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-(oxetan-3-yl)morpholine-2-carboxamide

Example	Structure	Name
125		N-(1-cyanocyclopropyl)-8-((2R,5S)-2-(difluoromethoxy)methyl)-5-methylmorpholino-3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide
126		3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide
127		8-((2R,5S)-2-(difluoromethoxy)methyl)-5-methylmorpholino-3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Example	Structure	Name
128		(R)-3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
129		(R)-3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide
130		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide

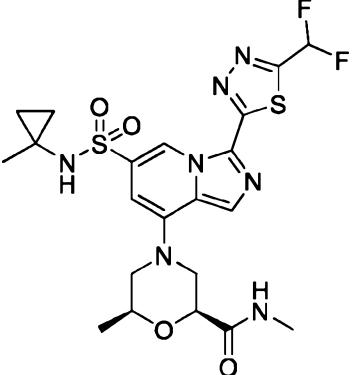
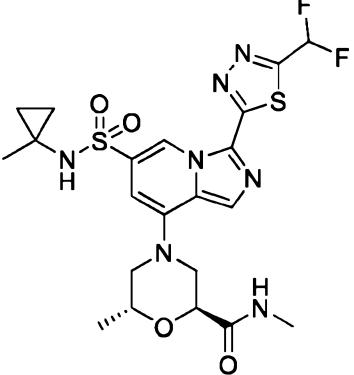
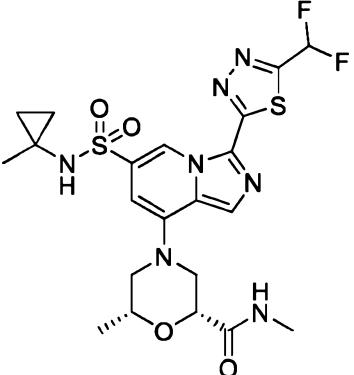
Example	Structure	Name
131		(R)-8-(2-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
132		(S)-8-(2-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
133		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-methoxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

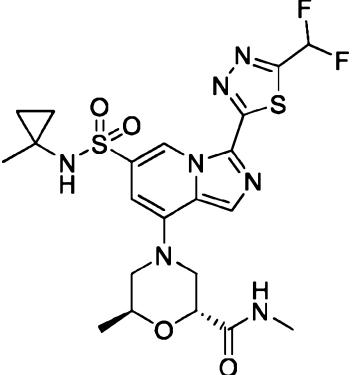
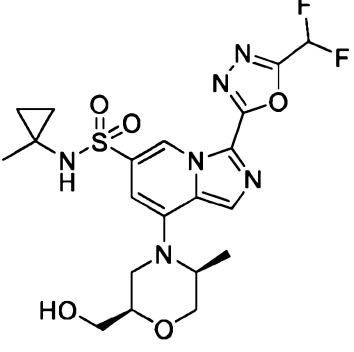
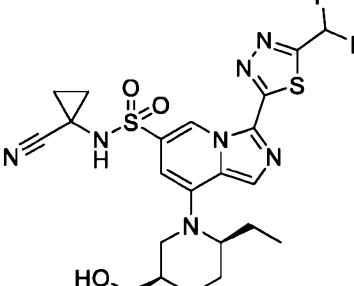
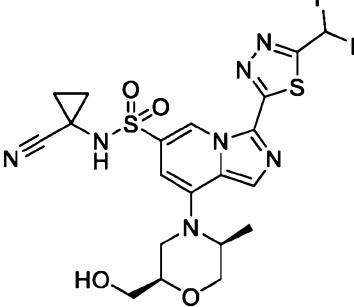
Example	Structure	Name
134		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-methoxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
135		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-hydroxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
136		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(2-(morpholine-4-carbonyl)morpholino)imidazo[1,5-a]pyridine-6-sulfonamide

Example	Structure	Name
137		3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
138		3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,6S)-2-(methoxymethyl)-6-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
139		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(2,5-dioxa-8-azaspiro[3.5]nonan-8-yl)imidazo[1,5-a]pyridine-6-sulfonamide
140		(2R,5S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,5-dimethylmorpholine-2-carboxamide

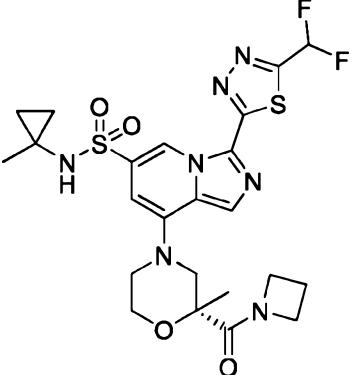
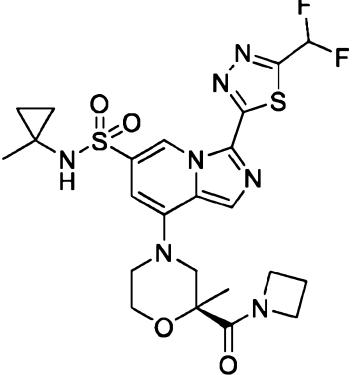
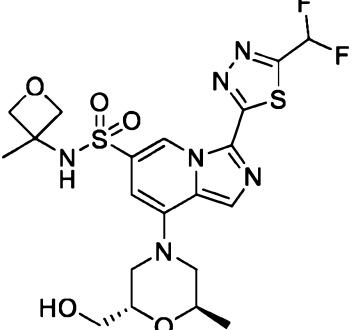
Example	Structure	Name
141		(2S,5S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,5-dimethylmorpholine-2-carboxamide
142		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide
143		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(methoxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide
144		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide

Example	Structure	Name
145		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aR,7aS)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
146		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aS,7aR)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
147		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aR,7aR)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
148		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aS,7aS)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)

Example	Structure	Name
149		<p>(2S,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide</p>
150		<p>rel-(2S,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide (trans relative and enantiochemistry arbitrary assigned)</p>
151		<p>(2R,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide</p>

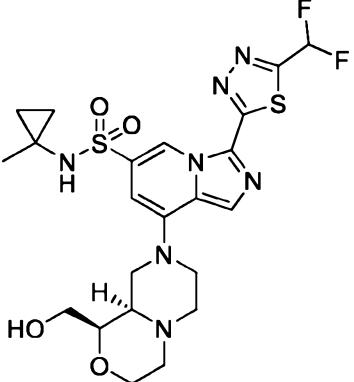
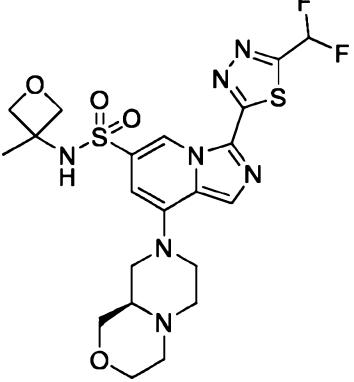
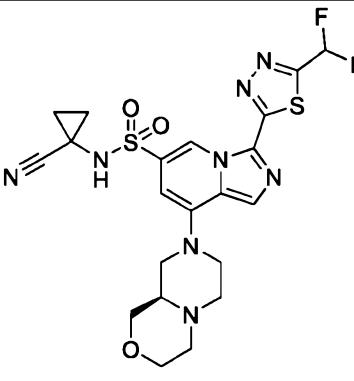
Example	Structure	Name
152		<p>rel-(2R,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>
153		<p>3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide</p>
154		<p>N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)imidazo[1,5-a]pyridine-6-sulfonamide</p>
155		<p>N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide</p>

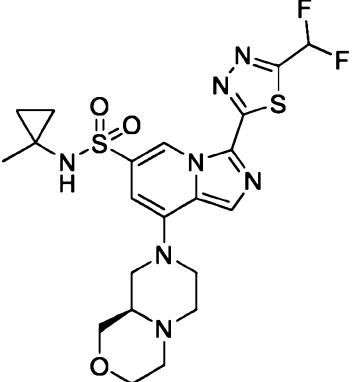
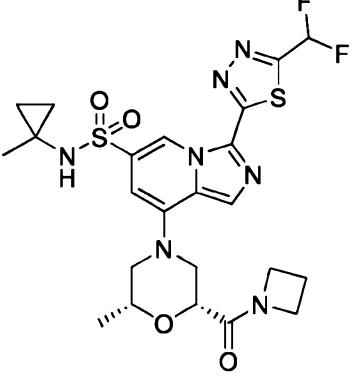
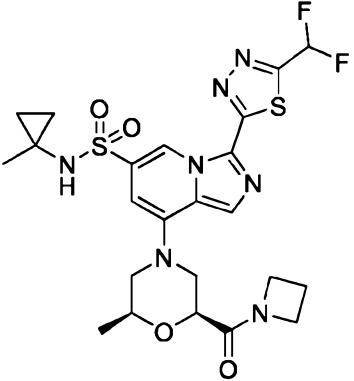
Example	Structure	Name
156		rel-(S)-N-(1-cyanocyclopropyl)-8-(3-cyclopropylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (enantiochemistry arbitrary assigned)
157		rel-(R)-N-(1-cyanocyclopropyl)-8-(3-cyclopropylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (enantiochemistry arbitrary assigned)
158		(S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-ethylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide
159		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Example	Structure	Name
160		<p>rel- (R)-8-(2-(azetidine-1-carbonyl)-2-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (enantiochemistry arbitrary assigned)</p>
161		<p>rel- (S)-8-(2-(azetidine-1-carbonyl)-2-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (enantiochemistry arbitrary assigned)</p>
162		<p>rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-(hydroxymethyl)-6-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)</p>

Example	Structure	Name
163		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
164		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-(hydroxymethyl)-6-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
165		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
166		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-((4aS,7aR)-octahydro-1H-cyclopenta[b]pyrazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)

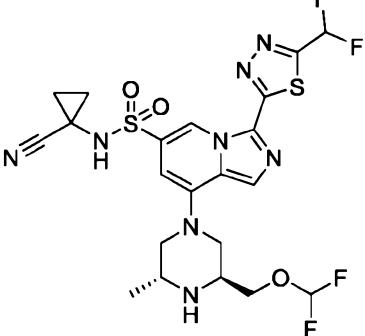
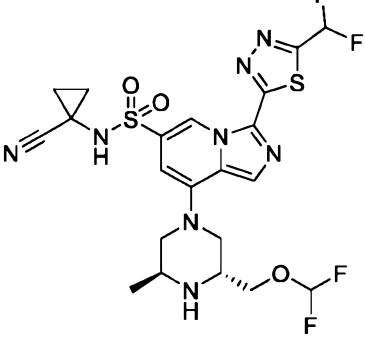
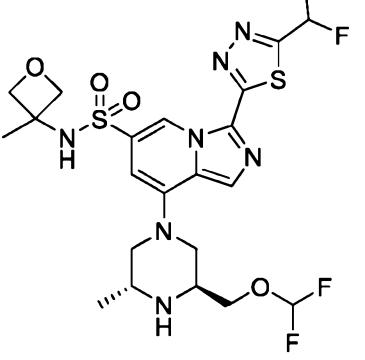
Example	Structure	Name
167		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-((4aR,7aS)-octahydro-1H-cyclopenta[b]pyrazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
168		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1S,9aS)-1-(hydroxymethyl)hexahydronaphthalen-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative / enantioselectivity arbitrary assigned)
169		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-morpholinoimidazo[1,5-a]pyridine-6-sulfonamide

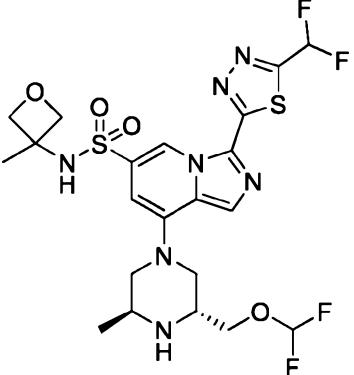
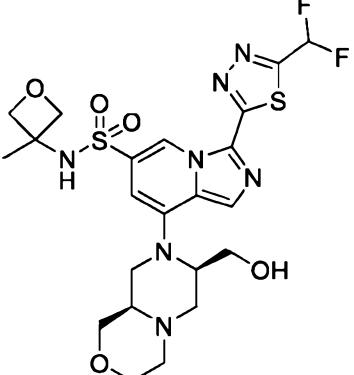
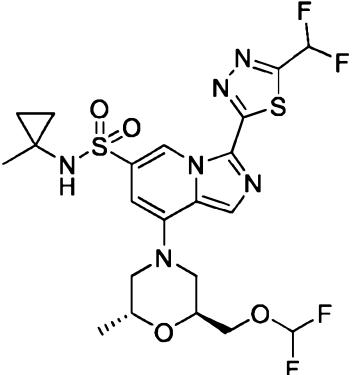
Example	Structure	Name
170		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1 <i>R</i> ,9 <i>aR</i>)-1-(hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1 <i>H</i>)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative / enantioselectivity arbitrary assigned)
171		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1 <i>H</i>)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide
172		(R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1 <i>H</i>)-yl)imidazo[1,5-a]pyridine-6-sulfonamide

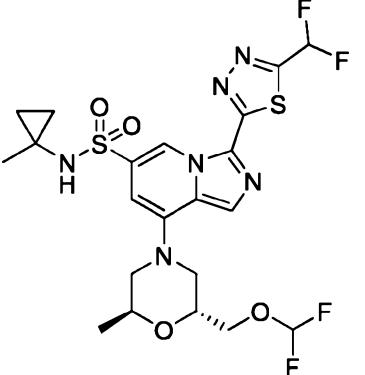
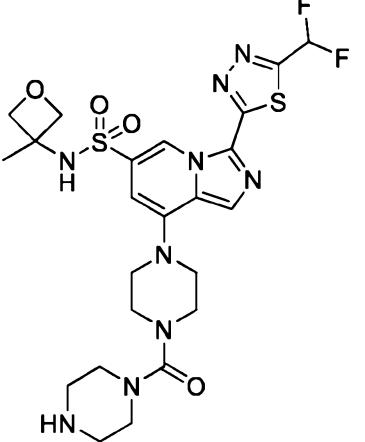
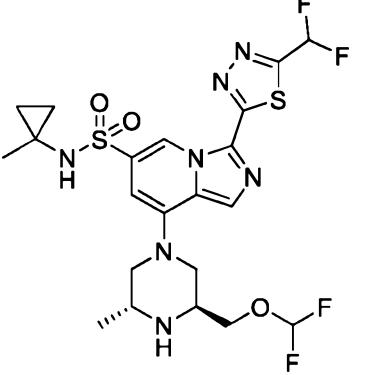
Example	Structure	Name
173		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
174		rel-8-((2R,6R)-2-(azetidine-1-carbonyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
175		rel-8-((2S,6S)-2-(azetidine-1-carbonyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)

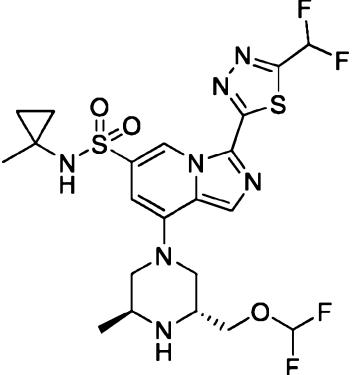
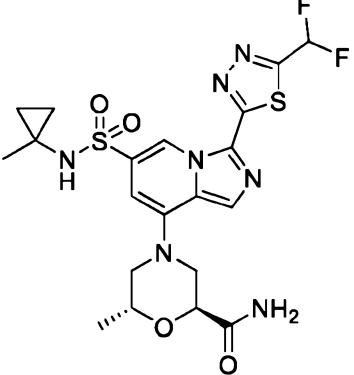
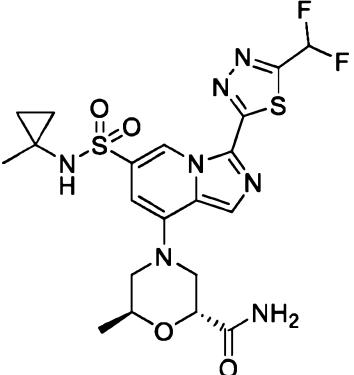
Example	Structure	Name
176		rel-(S)-8-(2-(azetidine-1-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (enantiochemistry arbitrary assigned)
177		rel-(R)-8-(2-(azetidine-1-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (enantiochemistry arbitrary assigned)
178		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)

Example	Structure	Name
179		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
180		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
181		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Example	Structure	Name
182		<p>rel-N-(1-cyanocyclopropyl)-8-((3S,5R)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>
183		<p>rel-N-(1-cyanocyclopropyl)-8-((3R,5S)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>
184		<p>rel-8-((3S,5R)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>

Example	Structure	Name
185		<p>rel-8-((3R,5S)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>
186		<p>3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((7R,9aR)-7-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide</p>
187		<p>rel-8-((2S,6R)-2-((difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>

Example	Structure	Name
188		<p>rel-8-((2R,6S)-2-(difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>
189		<p>3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide</p>
190		<p>rel-8-((3S,5R)-3-(difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>

Example	Structure	Name
191		<p>rel-8-((3R,5S)-3-(difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>
192		<p>rel-(2S,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>
193		<p>rel-(2R,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide</p> <p>(trans relative and enantiochemistry arbitrary assigned)</p>

Example	Structure	Name
194		rel-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-(hydroxymethyl)-6-methylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
195		rel-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
196		rel- 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)
197		rel- 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (trans relative and enantiochemistry arbitrary assigned)

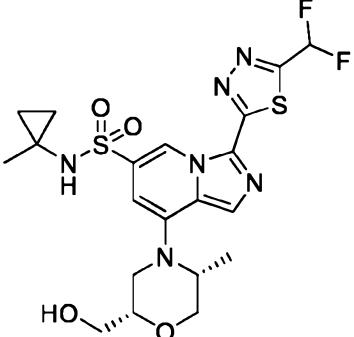
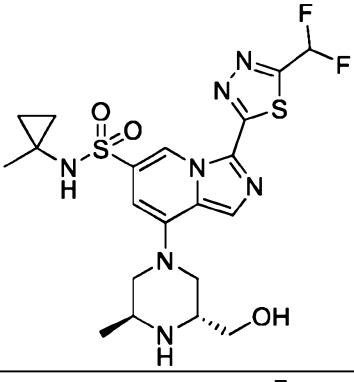
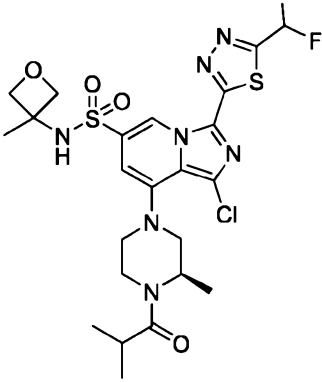
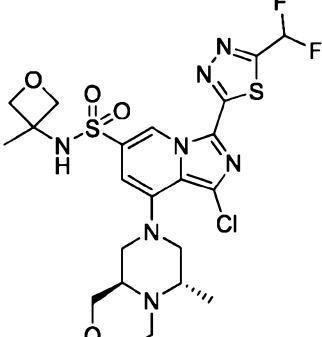
Example	Structure	Name
198		rel- 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
199		rel- 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative and enantiochemistry arbitrary assigned)
200		(R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6,6-dimethylmorpholine-2-carboxamide
201		(S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6,6-dimethylmorpholine-2-carboxamide

Example	Structure	Name
202		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((7R,9aR)-7-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide
203		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide
204		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide
205		(S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(6-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Example	Structure	Name
206		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(6-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide
207		(R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide
208		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Example	Structure	Name
209		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((7R,9aR)-7-hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
210		rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1S,9aR)-1-hydroxymethyl)hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (cis relative / enantioselectivity arbitrary assigned)
211		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide
212		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Example	Structure	Name
213		rel-(2S,6S)-4-(1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide (cis relative and enantiochemistry arbitrary assigned)
214		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
215		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
216		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

Example	Structure	Name
217		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2 <i>S</i> ,5 <i>R</i>)-2-hydroxymethyl)-5-methylmorpholino-N-(1-methylcyclopropyl)imidazo[1,5- <i>a</i>]pyridine-6-sulfonamide
218		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3 <i>R</i> ,5 <i>S</i>)-3-hydroxymethyl)-5-methylpiperazin-1-yl-N-(1-methylcyclopropyl)imidazo[1,5- <i>a</i>]pyridine-6-sulfonamide
219		(<i>R</i>)-1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5- <i>a</i>]pyridine-6-sulfonamide
220		1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6 <i>S</i> ,9 <i>aR</i>)-6-methylhexahdropyrazino[2,1- <i>c</i>][1,4]oxazin-8(1 <i>H</i>)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5- <i>a</i>]pyridine-6-sulfonamide

Example	Structure	Name
221		(R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide
222		rel-(2R,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide (cis relative and enantiochemistry arbitrary assigned)
223		rel-(2S,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide (cis relative and enantiochemistry arbitrary assigned)
224		1-chloro-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6S,9aR)-6-methylhexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide

Example	Structure	Name
225		(S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(6-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide
226		(R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-2-methylmorpholine-2-carboxamide
227		(S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-2-methylmorpholine-2-carboxamide

Example	Structure	Name
228		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide
229		N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide
230		1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide
231		(S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide

Example	Structure	Name
232		(R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide
233		3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide
234		(2S,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide
235		8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)-3-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(1-cyanocyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

Biological Activity

[0105] The PARG enzyme and cell assays described in accompanying Example section may be used to measure the pharmacological effects of the compounds of the present invention.

[0106] Although the pharmacological properties of the compounds of Formula (I) or Formula (I') (or any embodiments thereof) vary with structural change, as expected, the compounds of the 5 invention were found to be active in these PARG assays.

[0107] In general, the compounds of the invention demonstrate an EC₅₀ of 10 µM or less in the PARG enzyme assay described herein, with preferred compounds of the invention demonstrating an EC₅₀ of 1000nM or less, or 500 nM or less, and the most preferred compounds of the invention demonstrating an EC₅₀ of 200 nM or less.

10 [0108] In general, the compounds of the invention demonstrate an EC₅₀ of 1 µM or less in the PARG cell assay described herein, with preferred compounds of the invention demonstrating an EC₅₀ of 500 nM or less and the most preferred compounds of the invention demonstrating an EC₅₀ of 200 nM or less.

PHARMACEUTICAL COMPOSITIONS

15 [0109] Also provided are pharmaceutical compositions which comprises a compound of Formula (I) or Formula (I'), a subembodiment thereof, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

20 [0110] The compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a 25 suppository for rectal dosing).

[0111] The compositions may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

[0112] An effective amount of a compound of **Formula (I)**, **Formula (I')**, a subembodiment thereof, or a pharmaceutically salt thereof for use in therapy is an amount sufficient to treat or prevent a proliferative condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

5 [0113] The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the individual treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of **Formula (I)**, **Formula (I')**, a subembodiment thereof, or a pharmaceutically salt thereof (more suitably from 0.5 to 100 mg, 10 for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

15 [0114] The size of the dose for therapeutic or prophylactic purposes of a compound of the **Formula (I)** or **Formula (I')** (or any embodiments thereof) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

20 [0115] In using a compound of **Formula (I)**, **Formula (I')**, a subembodiment thereof, or a pharmaceutically salt thereof for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general, lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous or intraperitoneal administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration may also be suitable, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

THERAPEUTIC USES AND APPLICATIONS

[0116] Provided herein are compounds that function as inhibitors of PARG.

[0117] The present invention therefore provides a method of inhibiting PARG enzyme activity *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof.

[0118] The present invention also provides a method of selectively inhibiting PARG enzyme 5 activity over PARP1 or ARH3 enzyme activity *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof.

[0119] The present invention also provides a method of treating a disease or disorder in which 10 PARG activity is implicated in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein.

[0120] Provided herein is a method of inhibiting cell proliferation, *in vitro* or *in vivo*, said 15 method comprising contacting a cell with an effective amount of a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof.

[0121] Provided herein is a method of treating a proliferative disorder in a patient in need of such treatment, said method comprising administering to said patient a therapeutically effective amount of a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein.

[0122] Provided herein is a method of treating cancer in a patient in need of such treatment, 20 said method comprising administering to said patient a therapeutically effective amount of a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein.

[0123] Provided herein is a compound of Formula (I), Formula (I'), a subembodiment thereof, 25 or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein for use in therapy.

[0124] Provided herein is a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of a proliferative condition.

[0125] Provided herein is a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, or a pharmaceutical composition as defined herein for use in the treatment of cancer. In a particular embodiment, the cancer is human cancer. In some embodiments, the cancer is ovarian, gastric, or breast cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is breast cancer.

10 [0126] Provided herein is a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, as defined herein for use in the inhibition of PARG enzyme activity.

15 [0127] Provided herein is a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, as defined herein for use in the treatment of a disease or disorder in which PARG activity is implicated.

[0128] Provided herein is a use of a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, as defined herein in the manufacture of a medicament for the treatment of a proliferative condition.

20 [0129] Provided herein is a use of a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, as defined herein in the manufacture of a medicament for the treatment of cancer. Suitably, the medicament is for use in the treatment of human cancers. In some embodiments, the cancer is ovarian, gastric, or breast cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is breast cancer.

25 [0130] Provided herein is a use of a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof in the manufacture of a medicament for the inhibition of PARG enzyme activity.

[0131] Provided herein is a use of a compound of **Formula (I)**, **Formula (I')**, a subembodiment thereof, or a pharmaceutically salt thereof in the manufacture of a medicament for the selective inhibition of PARG enzyme activity over PARP1 or ARH3 enzyme activity.

5 [0132] Provided herein is a use of a compound of **Formula (I)**, **Formula (I')**, a subembodiment thereof, or a pharmaceutically salt thereof in the manufacture of a medicament for the treatment of a disease or disorder in which PARG activity is implicated.

10 [0133] The terms “proliferative disorder” and “proliferative condition” are used interchangeably herein and pertain to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth, whether in vitro or in vivo. Examples of proliferative conditions include, but are not limited to, pre-malignant and malignant cellular proliferation, including but not limited to, malignant neoplasms and tumors, cancers, leukemias, psoriasis, bone diseases, fibroproliferative disorders (e.g., of connective tissues), and atherosclerosis. Any type of cell may be treated, including but not limited to, lung, colon, breast, ovarian, prostate, liver, pancreas, brain, and skin.

15 [0134] The anti-proliferative effects of the compounds of **Formula (I)**, **Formula (I')**, a subembodiment thereof, or a pharmaceutically salt thereof have particular application in the treatment of human cancers (by virtue of their inhibition of PARG enzyme activity).

20 [0135] The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the regulation of cell proliferation, the inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumor from its origin), the inhibition of invasion (the spread of tumor cells into neighboring normal structures), or the promotion of apoptosis (programmed cell death).

25 [0136] In a particular embodiment of the invention, the proliferative condition to be treated is cancer. In some embodiments, the cancer is ovarian, gastric, or breast cancer. In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is gastric cancer. In some embodiments, the cancer is breast cancer.

[0137] In some embodiments, subjects treated for cancer are refractory to one or more agents. In some embodiments, subjects treated for cancer are refractory to one or more platins (e.g.,

carboplatin, cisplatin, etc.). In some embodiments, subjects treated for cancer are refractory to one or more PARP inhibitors (e.g., niraparib, olaparib, rucaparib, etc.).

ROUTES OF ADMINISTRATION

[0138] The compounds of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, or pharmaceutical compositions comprising these compounds may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or topically (i.e., at the site of desired action).

[0139] Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eye drops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

COMBINATION THERAPIES

[0140] The antiproliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumor agents: other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumor antibiotics (for example anthracyclines like bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine,

vinorelbine; taxol and taxotere and polo kinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin); cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride; anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (BMS-354825; *J. Med. Chem.*, 2004, **47**, 6658-6661) and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase]; inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [HerceptinTM], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* (*Critical reviews in oncology/haematology*, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777) and lonafarnib (SCH66336)), inhibitors of MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, PI3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors

(for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors; antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab 5 (AvastinTM) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 10 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin α v β 3 function and angiostatin)]; vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213; an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan; antisense therapies, for 15 example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense; gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or 20 radiotherapy such as multi-drug resistance gene therapy; and immunotherapy approaches, including for example *ex-vivo* and *in-vivo* approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, 25 approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

[0141] In a particular embodiment, the antiproliferative treatment defined hereinbefore may involve, in addition to the compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, conventional surgery or radiotherapy or chemotherapy.

[0142] Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically active agent within its approved dosage range.

5 [0143] According to this aspect of the invention there is provided a combination for use in the treatment of a cancer (for example a cancer involving a solid tumour) comprising a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, and another anti-tumour agent.

10 [0144] According to this aspect of the invention there is provided a combination for use in the treatment of a proliferative condition, such as cancer (for example a cancer involving a solid tumour), comprising a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, and any one of the anti-tumour agents listed herein above.

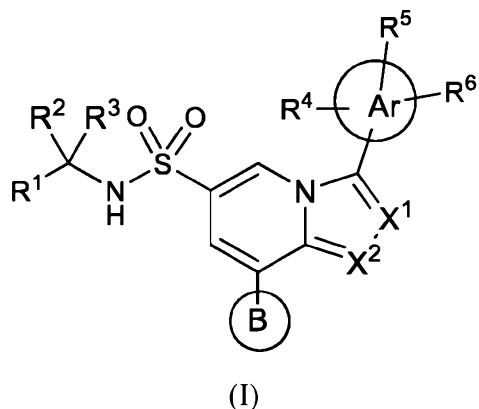
15 [0145] In a further aspect of the invention there is provided a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, for use in the treatment of cancer in combination with another anti-tumour agent, optionally selected from one listed herein above.

20 [0146] Herein, where the term “combination” is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention “combination” refers to simultaneous administration. In another aspect of the invention “combination” refers to separate administration. In a further aspect of the invention “combination” refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

25 [0147] According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I), Formula (I'), a subembodiment thereof, or a pharmaceutically salt thereof, in combination with an anti-tumour agent (optionally selected from one listed herein above), in association with a pharmaceutically acceptable diluent or carrier.

NON-LIMITING EXEMPLARY EMBODIMENTS

[0148] Embodiment 1. A compound of Formula (I):



wherein:

- 5 X^1 is selected from CR⁷ and N, X^2 is selected from CR⁷ and N, and at least one of X^1 and X^2 is N;
- R¹ is hydrogen, cyano, formyl, -CONH₂, -CH₂OH, -CH₂OC₁₋₂ alkyl, C₁₋₂ alkyl, or C₁₋₂ haloalkyl;
- R² and R³ are independently C₁₋₂ alkyl; or
- 10 R² and R³ together with the carbon atom to which they are attached form C₃₋₄ cycloalkyl, or 3- or 4- membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S;
- Ar is a 5- or 6-membered heteroaryl having 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S;
- R⁴ is C₁₋₃ alkyl, C₁₋₃ haloalkyl, hydroxyC₁₋₃alkyl, -C(O)H, or cyano;
- 15 R⁵ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;
- R⁶ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;
- R⁷ is hydrogen, deuterium, halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;
- 20 ring B is a 3- to 6- membered heterocyclyl, a 5- to 12-membered spiro heterocyclyl, or a 5- to 7- membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein ring B is unsubstituted or substituted with R^a, R^b, and R^c, wherein

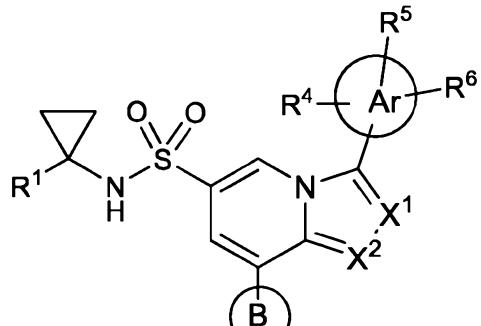
R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, 5- or 6-membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, 3- to 6-membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, or 3- to 6-membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, or 3- or 6-membered heterocyclyl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocyclyl, or 5- to 12-membered spiro heterocyclyl, each heterocyclyl having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), or -S(O)₂NR^hRⁱ (where R^h and Rⁱ are independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, or hydroxyC₁₋₆ alkyl; or R^h and Rⁱ together with the nitrogen atom to which they are attached form a 3- to 6-membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S);

20 R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; R^c is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; or R^b and R^c when on adjacent ring vertices of the 3- to 6-membered heterocyclyl combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and further wherein the heteroaryl and heterocyclyl of R^a, the phenyl, heteroaryl, and heterocyclyl of R^d, the heterocyclyl or spiro heterocyclyl formed by R^f and R^g combining with the nitrogen to which they are attached, and the heterocyclyl formed by R^h and Rⁱ combining with the nitrogen to which they are attached are each independently unsubstituted or

substituted with one, two, or three substituents selected from C₁₋₆ alkyl, hydroxy, hydroxyC₁₋₆ alkyl, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl; or

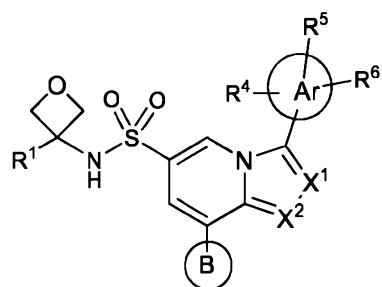
a pharmaceutically acceptable salt thereof.

- 5 [0149] Embodiment 2. The compound of embodiment 1, having the formula (Ia)



(Ia).

- [0150] Embodiment 3. The compound of embodiment 1, having the formula (Ib)



10

(Ib).

- [0151] Embodiment 4. The compound of any one of embodiments 1 to 3, or a pharmaceutically acceptable salt thereof, wherein X¹ and X² are both N.

- [0152] Embodiment 5. The compound of any one of embodiments 1 to 3, or a pharmaceutically acceptable salt thereof, wherein X¹ is N and X² is CR⁷.

- 15 [0153] Embodiment 6. The compound of any one of embodiments 1 to 3, or a pharmaceutically acceptable salt thereof, wherein X¹ is CR⁷ and X² is N.

[0154] Embodiment 7. The compound of any one of embodiments **1** to **6**, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, fluoro, methyl, ethyl, difluoromethyl, or trifluoromethyl.

5 [0155] Embodiment 8. The compound of any one of embodiments **1** to **6**, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen.

[0156] Embodiment 9. The compound of any one of embodiments **1** to **8**, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen, cyano, methyl, or ethyl.

[0157] Embodiment 10. The compound embodiment **9**, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen.

10 [0158] Embodiment 11. The compound embodiment **9**, or a pharmaceutically acceptable salt thereof, wherein R¹ is cyano.

[0159] Embodiment 12. The compound embodiment **9**, or a pharmaceutically acceptable salt thereof, wherein R¹ is methyl.

15 [0160] Embodiment 13. The compound of embodiment **1** or any one of embodiments **4** to **12**, or a pharmaceutically acceptable salt thereof, wherein R² and R³ are independently C₁₋₂ alkyl.

[0161] Embodiment 14. The compound of any one of embodiments **1** to **13**, or a pharmaceutically acceptable salt thereof, wherein Ar is pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, or 1, 3, 5-triazinyl.

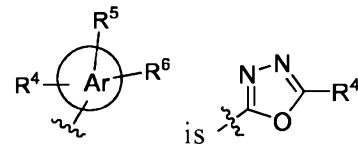
20 [0162] Embodiment 15. The compound of any one of embodiments **1** to **13**, or a pharmaceutically acceptable salt thereof, wherein Ar is imidazolyl, isoxazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, or 1,3,4-thiadiazolyl.

[0163] Embodiment 16. The compound of any one of embodiments **1** to **13**, or a pharmaceutically acceptable salt thereof, wherein Ar is pyridazin-3-yl.

25 [0164] Embodiment 17. The compound of any one of embodiments **1** to **13**, or a pharmaceutically acceptable salt thereof, wherein Ar is 1,3,4-oxadiazol-2-yl or 1,3,4-thiadiazol-2-yl.

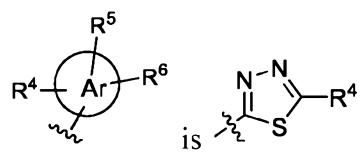
[0165] Embodiment 18. The compound of any one of embodiments 1 to 13, or a

pharmaceutically acceptable salt thereof, wherein the group



[0166] Embodiment 19. The compound of any one of embodiments 1 to 13, or a

pharmaceutically acceptable salt thereof, wherein the group



5 [0167] Embodiment 20. The compound of any one of embodiments 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R⁴ is methyl, ethyl, difluoromethyl, trifluoromethyl, cyano, or C(O)H.

10 [0168] Embodiment 21. The compound of any one of embodiments 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R⁴ is difluoromethyl, methyl, trifluoromethyl, cyano, or C(O)H.

[0169] Embodiment 22. The compound of any one of embodiments 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R⁴ is methyl.

[0170] Embodiment 23. The compound of any one of embodiments 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R⁴ is difluoromethyl.

15 [0171] Embodiment 24. The compound of any one of embodiments 1 to 23, or a pharmaceutically acceptable salt thereof, wherein R⁵ and R⁶ are independently hydrogen or absent.

[0172] Embodiment 25. The compound of any one of embodiments 1 to 23, or a pharmaceutically acceptable salt thereof, wherein R⁵ and R⁶ are each absent.

20 [0173] Embodiment 26. The compound of any one of embodiments 1 to 25, or a pharmaceutically acceptable salt thereof, wherein ring B is a 3- to 6- membered heterocycl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, unsubstituted or substituted with R^a, R^b, and R^c.

[0174] Embodiment 27. The compound of embodiment 26, or a pharmaceutically acceptable salt thereof, wherein ring B is morpholinyl, 1,1-dioxothiomorpholinyl, azetinyl, pyrrolidinyl, piperidinyl, 6-oxo-1,6-dihdropyridinyl, or piperazinyl, each ring is independently unsubstituted or substituted with R^a, R^b, and R^c.

5 [0175] Embodiment 28. The compound of any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, wherein

R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or 3- to 6- membered heterocycll having from 1 to 2 10 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, or C₁₋₆ haloalkyl; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocycll, or 5- to 12-membered spiro heterocycll, each heterocycll having 0 to 2 additional heteroatom ring vertices, each independently selected from 15 N, O, and S), and

R^b is absent or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy;

R^c is absent or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy; and further wherein

the heterocycll of R^d, and the heterocycll or spiro heterocycll formed by R^f and R^g

20 combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents independently selected from C₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl.

[0176] Embodiment 29. The compound of any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, wherein

25 R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆

alkyl, or C₁₋₆ haloalkyl; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocyclyl, or 5- to 12-membered spiro heterocyclyl, each heterocyclyl having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), and

5 further wherein the heterocyclyl of R^d, and the heterocyclyl or spiro heterocyclyl formed by R^f and R^g combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents independently selected from C₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl.

[0177] Embodiment 30. The compound of any one of embodiments 1 to 27 and 29, or a
10 pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocyclyl and combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is
15 substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

[0178] Embodiment 31. The compound of any one of embodiments 1 to 27 and 29, or a pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocyclyl and combine to form a 4- to 6-membered saturated or partially unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated or partially unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl, or oxo.

[0179] Embodiment 32. The compound of any one of embodiments 1 to 27 and 29, or a
25 pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocyclyl and combine to form a 4- to 6-membered saturated ring comprising 1 additional heteroatom ring vertex, selected from N, O, and S, wherein the 4- to 6-membered saturated ring is substituted

with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

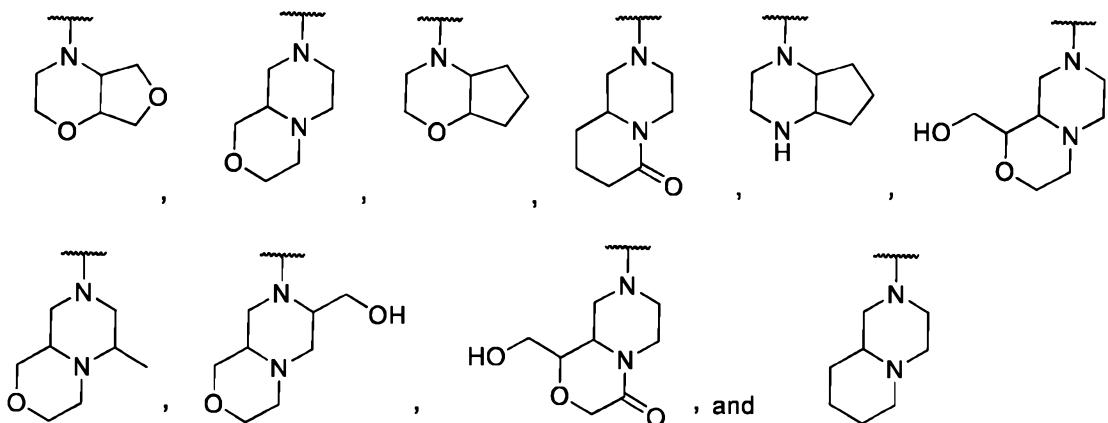
[0180] Embodiment 33. The compound of any one of embodiments 1 to 27 and 29, or a pharmaceutically acceptable salt thereof, wherein

5 R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycll and combine to form a 4- to 6-membered saturated ring comprising 0 additional heteroatom ring vertices, wherein the 4- to 6-membered saturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

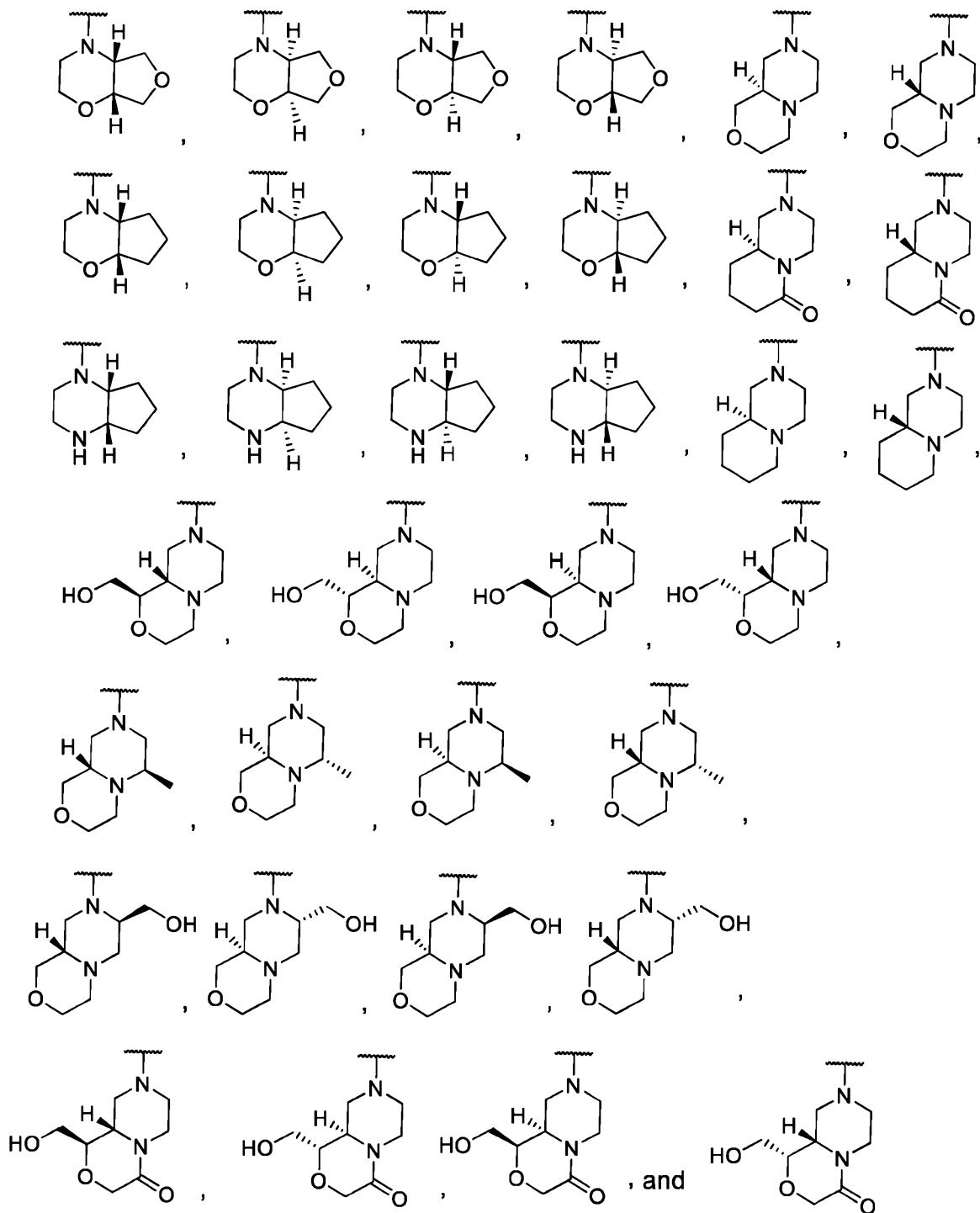
[0181] Embodiment 34. The compound of any one of embodiments 1 to 25 and 29, or a pharmaceutically acceptable salt thereof, wherein ring B is octahydropyrazino[2,1-c][1,4]oxazinyl, octahydro-2H-pyrido[1,2-a]pyrazinyl, 6-methyloctahydropyrazino[2,1-c][1,4]oxazinyl, octahydro-6H-pyrido[1,2-a]pyrazin-6-only, or octahydropyrazino[2,1-c][1,4]oxazinyl substituted with a hydroxymethyl.

[0182] Embodiment 35. The compound of any one of embodiments 1 to 25 and 29, or a pharmaceutically acceptable salt thereof, wherein ring B is octahydro-1H-cyclopenta[b]pyrazinyl.

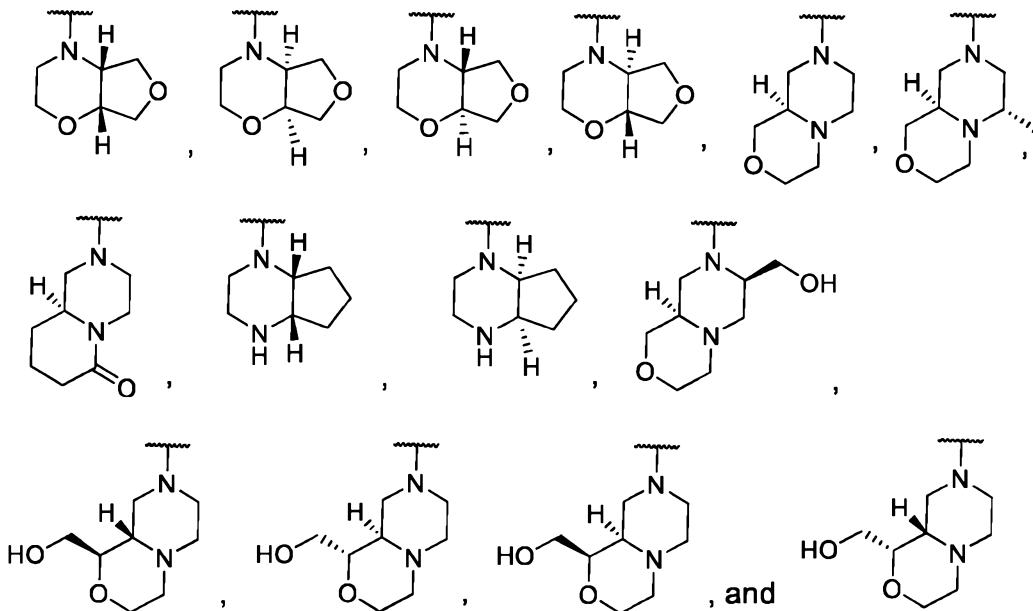
[0183] Embodiment 36. The compound of embodiment 26, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



[0184] Embodiment 37. The compound of embodiment 26, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



[0185] Embodiment 38. The compound of embodiment 26, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



- 5 **[0186]** Embodiment 39. The compound of any one of embodiments 1 to 25, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- to 12-membered spiro heterocyclyl, or 5- to 7- membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein each ring is substituted or unsubstituted with R^a, R^b, and R^c.
- 10 **[0187]** Embodiment 40. The compound of embodiment 39, or a pharmaceutically acceptable salt thereof, wherein ring B is 2-oxaspiro[3.5]non-6-en-7-yl, 2-oxaspiro[3.5]non-7-yl, 2-oxa-8-azaspiro[4.5]dec-8-yl, 9-oxa-3-azaspiro[5.5]undec-3-yl, 2-oxa-6-azaspiro[3.4]oct-6-yl, 1-oxa-7-azaspiro[3.5]non-7-yl, 1-oxa-8-azaspiro[4.5]dec-8-yl, 6-oxa-2-azaspiro[3.3]hept-2-yl, 2,8-diazaspiro[4.5]dec-8-yl, 2-oxa-6-azaspiro[3.5]non-6-yl, , 3,6-diazabicyclo[3.1.1]hept-3-yl, 2,7-diazaspiro[3.5]non-7-yl, each ring optionally substituted with R^a where R^a is hydrogen or alkyl.

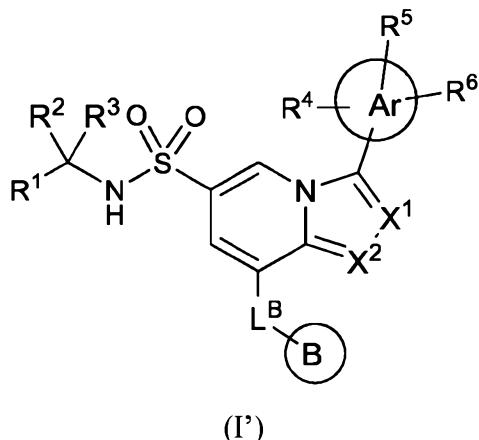
[0188] Embodiment 41. A compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group in Table 1.

[0189] Embodiment 42. A compound or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group of compounds in Table 3.

[0190] Embodiment 43. A compound or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group of compounds in Table 4.

5 ADDITIONAL NON-LIMITING EXEMPLARY EMBODIMENTS

[0191] Embodiment 1. A compound of Formula (I'):



wherein:

- 10 X^1 is selected from CR⁷ and N, X^2 is selected from CR⁷ and N;
 R¹ is hydrogen, cyano, formyl, -CONH₂, -CH₂OH, -CH₂OC₁₋₂ alkyl, C₁₋₂ alkyl, C₁₋₂ deuteroalkyl, or C₁₋₂ haloalkyl;
 R² and R³ are independently C₁₋₂ alkyl; or
 R² and R³ together with the carbon atom to which they are attached form C₃₋₄ cycloalkyl, or 3- or
 15 4-membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S,
 wherein the cycloalkyl or heterocyclyl is unsubstituted or substituted with 1 to 6 R^{2a};
 each R^{2a} is independently deuterium, C₁₋₄ alkyl, halo, or C₁₋₄ haloalkyl;
 Ar is a 5- or 6-membered heteroaryl having 1 to 3 heteroatom ring vertices, each independently
 selected from N, O, and S;
 20 R⁴ is C₁₋₃ alkyl, C₁₋₃ haloalkyl, hydroxyC₁₋₃alkyl, -C(O)H, or cyano;
 R⁵ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R⁶ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R⁷ is hydrogen, deuterium, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, NR^{7a}R^{7b}, or hydroxy; each R^{7a} and R^{7b} is independently H or C₁₋₄ alkyl;

5 L^B is a bond, C₁₋₂ alkylene, -O-, -NR^{LB}-, or -S-;

R^{LB} is hydrogen or C₁₋₄ alkyl;

ring B is a 3- to 6- membered heterocyclyl, a 5- to 12-membered spiro heterocyclyl, or a 5- to 7-membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein ring B is unsubstituted or substituted with R^a, R^b, and R^c, wherein

10 R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, 5- or 6- membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each

15 independently selected from N, O, and S, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, or 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where

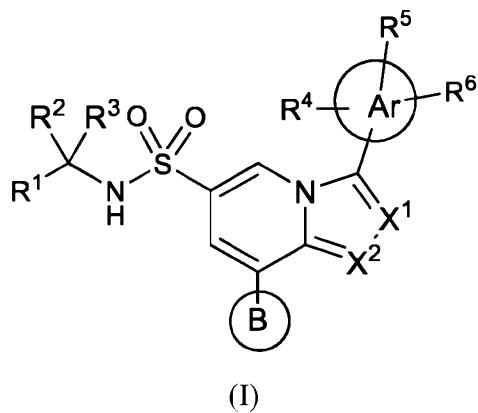
20 R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, or 3- or 6-membered heterocyclyl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocyclyl, or 5- to 12-membered spiro heterocyclyl, each heterocyclyl having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), or -S(O)₂NR^hRⁱ (where R^h and Rⁱ are independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, or hydroxyC₁₋₆ alkyl; or R^h and Rⁱ together with the nitrogen atom to which they are attached form a 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S);

25 30 R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R^c is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; or

R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocyclyl combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C_{1-6} alkyl, C_{1-6} haloalkyl, halo, hydroxy, C_{1-6} alkoxy, hydroxy C_{1-6} alkyl, or oxo; and further wherein the heteroaryl and heterocyclyl of R^a , the phenyl, heteroaryl, and heterocyclyl of R^d , the heterocyclyl or spiro heterocyclyl formed by R^f and R^g combining with the nitrogen to which they are attached, and the heterocyclyl formed by R^h and R^i combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents selected from C_{1-6} alkyl, hydroxy, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-8} alkoxyalkyl, and C_{2-8} haloalkoxyalkyl; or a pharmaceutically acceptable salt thereof.

15 [0192] Embodiment 2. A compound of Formula (I):



wherein:

X^1 is selected from CR⁷ and N, X^2 is selected from CR⁷ and N, and at least one of X^1 and 20 X^2 is N;
 R^1 is hydrogen, cyano, formyl, -CONH₂, -CH₂OH, -CH₂OC₁₋₂ alkyl, C₁₋₂ alkyl, or C₁₋₂ haloalkyl;
 R^2 and R^3 are independently C₁₋₂ alkyl; or

R² and R³ together with the carbon atom to which they are attached form C₃₋₄ cycloalkyl, or 3- or 4- membered heterocycll having 1 heteroatom ring vertex, selected from N, O, and S; Ar is a 5- or 6-membered heteroaryl having 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S;

- 5 R⁴ is C₁₋₃ alkyl, C₁₋₃ haloalkyl, hydroxyC₁₋₃alkyl, -C(O)H, or cyano;
R⁵ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;
R⁶ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;
- 10 R⁷ is hydrogen, deuterium, halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;
ring B is a 3- to 6- membered heterocycll, a 5- to 12-membered spiro heterocycll, or a 5- to 7- membered bridged heterocycll, each heterocycll having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein ring B is unsubstituted or substituted with R^a, R^b, and R^c, wherein
- 15 R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, 5- or 6- membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, or 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, or 3- or 6-membered heterocycll having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocycll, or 5- to 12-membered spiro heterocycll, each heterocycll having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), or -S(O)₂NR^hRⁱ (where R^h and Rⁱ are independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, or hydroxyC₁₋₆ alkyl; or R^h and Rⁱ together with the nitrogen atom to which they are attached

form a 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S);

R^b is absent, or C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy;

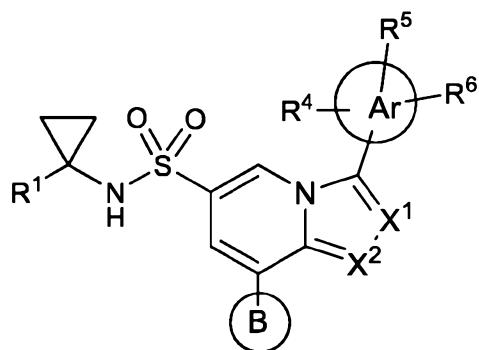
R^c is absent, or C_{1-6} alkyl, hydroxy, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, or C_{1-6} haloalkoxy; or

5 R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocyclyl combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C_{1-6} alkyl, C_{1-6} haloalkyl, halo, hydroxy, C_{1-6} alkoxy, hydroxy C_{1-6} alkyl, or oxo; and

10 further wherein the heteroaryl and heterocyclyl of R^a , the phenyl, heteroaryl, and heterocyclyl of R^d , the heterocyclyl or spiro heterocyclyl formed by R^f and R^g combining with the nitrogen to which they are attached, and the heterocyclyl formed by R^h and R^i combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents selected from C_{1-6} alkyl, hydroxy, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy, halo, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-8} alkoxyalkyl, and C_{2-8} haloalkoxyalkyl; or

15 a pharmaceutically acceptable salt thereof.

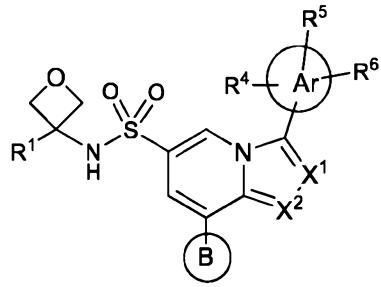
[0193] Embodiment 3. The compound of embodiment 2, having the formula (Ia)



20

(Ia).

[0194] Embodiment 4. The compound of embodiment 2, having the formula (Ib)



(Ib).

[0195] Embodiment 5. The compound of embodiment **1**, or a pharmaceutically acceptable salt thereof, wherein at least one of X¹ and X² is N.

5 **[0196] Embodiment 6.** The compound of any one of embodiments 1 to **4**, or a pharmaceutically acceptable salt thereof, wherein X¹ and X² are both N.

[0197] Embodiment 7. The compound of any one of embodiments 1 to **4**, or a pharmaceutically acceptable salt thereof, wherein X¹ is N and X² is CR⁷.

10 **[0198] Embodiment 8.** The compound of any one of embodiments 1 to **4**, or a pharmaceutically acceptable salt thereof, wherein X¹ is CR⁷ and X² is N.

[0199] Embodiment 9. The compound of any one of embodiments **1** to **8**, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, fluoro, methyl, ethyl, difluoromethyl, or trifluoromethyl.

15 **[0200] Embodiment 10.** The compound of any one of embodiments **1** to **8**, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen.

[0201] Embodiment 11. The compound of any one of embodiments **1** to **10**, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen, cyano, methyl, or ethyl.

[0202] Embodiment 12. The compound of embodiment **11**, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen.

20 **[0203] Embodiment 13.** The compound of embodiment **11**, or a pharmaceutically acceptable salt thereof, wherein R¹ is cyano.

[0204] Embodiment 14. The compound of embodiment **11**, or a pharmaceutically acceptable salt thereof, wherein R¹ is methyl.

[0205] Embodiment 15. The compound of embodiment 1, 2 or any one of embodiments 6 to 14, or a pharmaceutically acceptable salt thereof, wherein R² and R³ are independently C₁₋₂ alkyl.

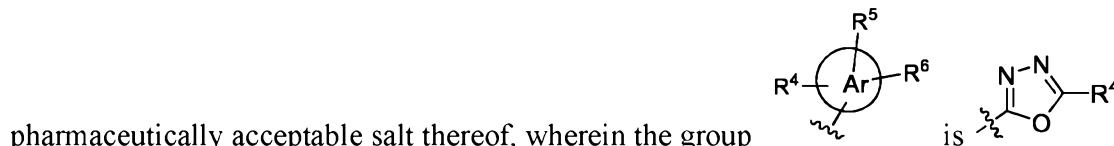
[0206] Embodiment 16. The compound of any one of embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein Ar is pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, or 1, 3, 5-triazinyl.

[0207] Embodiment 17. The compound of any one of embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein Ar is imidazolyl, isoxazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, or 10 1,3,4-thiadiazolyl.

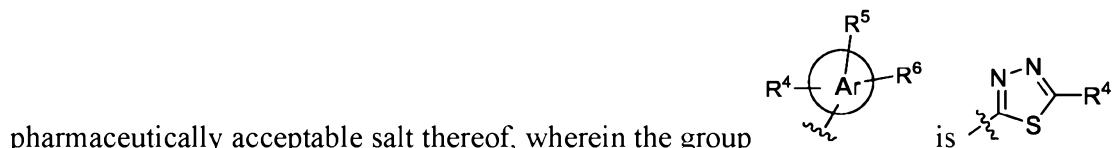
[0208] Embodiment 18. The compound of any one of embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein Ar is pyridazin-3-yl.

[0209] Embodiment 19. The compound of any one of embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein Ar is 1,3,4-oxadiazol-2-yl or 1,3,4-thiadiazol-15 2-yl.

[0210] Embodiment 20. The compound of any one of embodiments 1 to 15, or a



[0211] Embodiment 21. The compound of any one of embodiments 1 to 15, or a



[0212] Embodiment 22. The compound of any one of embodiments 1 to 21, or a pharmaceutically acceptable salt thereof, wherein R⁴ is methyl, ethyl, difluoromethyl, trifluoromethyl, cyano, or C(O)H.

[0213] Embodiment 23. The compound of any one of embodiments 1 to 21, or a pharmaceutically acceptable salt thereof, wherein R⁴ is difluoromethyl, methyl, trifluoromethyl, cyano, or C(O)H.

5 [0214] Embodiment 24. The compound of any one of embodiments 1 to 21, or a pharmaceutically acceptable salt thereof, wherein R⁴ is methyl.

[0215] Embodiment 25. The compound of any one of embodiments 1 to 21, or a pharmaceutically acceptable salt thereof, wherein R⁴ is difluoromethyl.

10 [0216] Embodiment 26. The compound of any one of embodiments 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R⁵ and R⁶ are independently hydrogen or absent.

[0217] Embodiment 27. The compound of any one of embodiments 1 to 25, or a pharmaceutically acceptable salt thereof, wherein R⁵ and R⁶ are each absent.

15 [0218] Embodiment 28. The compound of any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, wherein ring B is a 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, unsubstituted or substituted with R^a, R^b, and R^c.

20 [0219] Embodiment 29. The compound of embodiment 28, or a pharmaceutically acceptable salt thereof, wherein ring B is morpholinyl, 1,1-dioxothiomorpholinyl, azetinyl, pyrrolidinyl, piperidinyl, 6-oxo-1,6-dihydropyridinyl, or piperazinyl, each ring is independently unsubstituted or substituted with R^a, R^b, and R^c.

[0220] Embodiment 30. The compound of any one of embodiments 1 to 29, or a pharmaceutically acceptable salt thereof, wherein

25 R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, or C₁₋₆ haloalkyl; or R^f and R^g together with the nitrogen atom to which they are attached

form a 4- to 6- membered heterocycll, or 5- to 12-membered spiro heterocycll, each heterocycll having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), and

R^b is absent or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy;

5 R^c is absent or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy; and further wherein

the heterocycll of R^d, and the heterocycll or spiro heterocycll formed by R^f and R^g combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents independently selected from C₁₋₆ alkyl, 10 hydroxyC₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl.

[0221] Embodiment 31. The compound of any one of embodiments 1 to 29, or a pharmaceutically acceptable salt thereof, wherein

R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, -C(O)R^d (where R^d is hydrogen, C₁₋₆ 15 alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, or C₁₋₆ haloalkyl; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocycll, or 5- to 12-membered spiro heterocycll, each 20 heterocycll having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), and

further wherein the heterocycll of R^d, and the heterocycll or spiro heterocycll formed by R^f and R^g combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents independently selected from C₁₋₆ 25 alkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl.

[0222] Embodiment 32. The compound of any one of embodiments 1 to 29 or 31, or a pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycll and combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring

comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

- 5 [0223] Embodiment 33. The compound of any one of embodiments 1 to 29 or 31, or a pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycl and combine to form a 4- to 6-membered saturated or partially unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 10 4- to 6-membered saturated or partially unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl, or oxo.

- [0224] Embodiment 34. The compound of any one of embodiments 1 to 29 or 31, or a pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycl and combine to form a 4- to 6-membered saturated ring comprising 1 additional heteroatom ring vertex, selected from N, O, and S, wherein the 4- to 6-membered saturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

- 15 [0225] Embodiment 35. The compound of any one of embodiments 1 to 29 or 31, or a pharmaceutically acceptable salt thereof. wherein

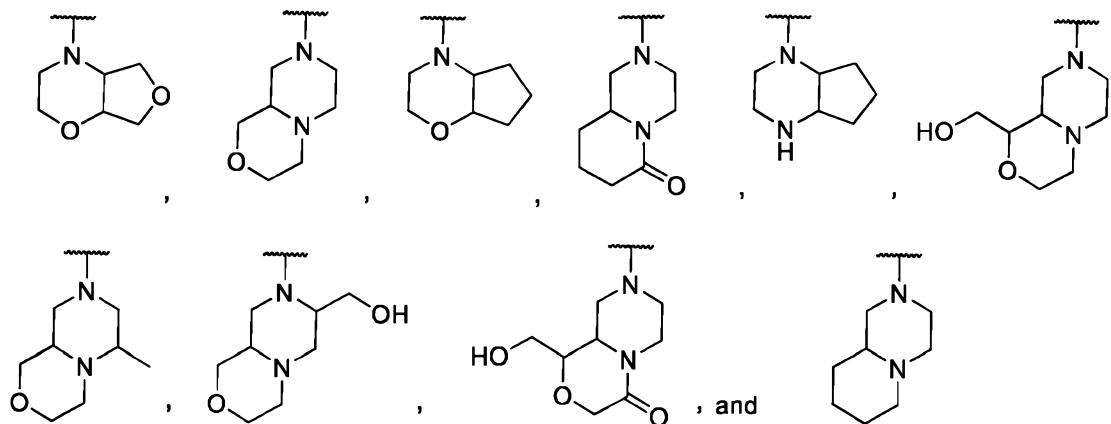
R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycl and combine to form a 4- to 6-membered saturated ring comprising 0 additional heteroatom ring vertices, wherein the 4- to 6-membered saturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

- 20 [0226] Embodiment 36. The compound of any one of embodiments 1 to 27 or 31, or a pharmaceutically acceptable salt thereof, wherein ring B is octahydropyrazino[2,1-c][1,4]oxazinyl, octahydro-2H-pyrido[1,2-a]pyrazinyl, 6-methyloctahydropyrazino[2,1-

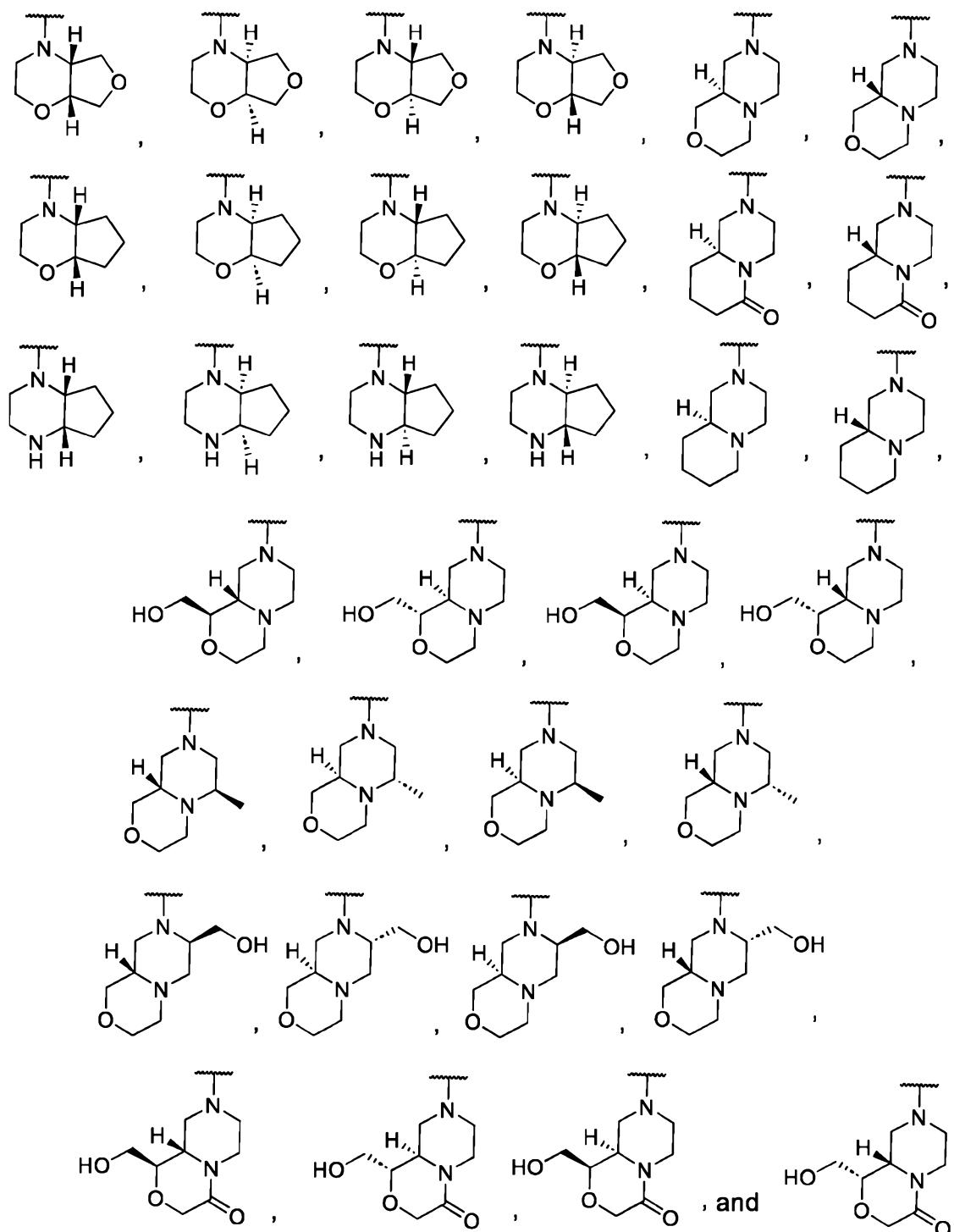
c][1,4]oxazinyl, octahydro-6H-pyrido[1,2-a]pyrazin-6-only, or octahdropyrazino[2,1-c][1,4]oxazinyl substituted with a hydroxymethyl.

[0227] Embodiment 37. The compound of any one of embodiments 1 to 27 or 31, or a pharmaceutically acceptable salt thereof, wherein ring B is octahydro-1H-
5 cyclopenta[b]pyrazinyl.

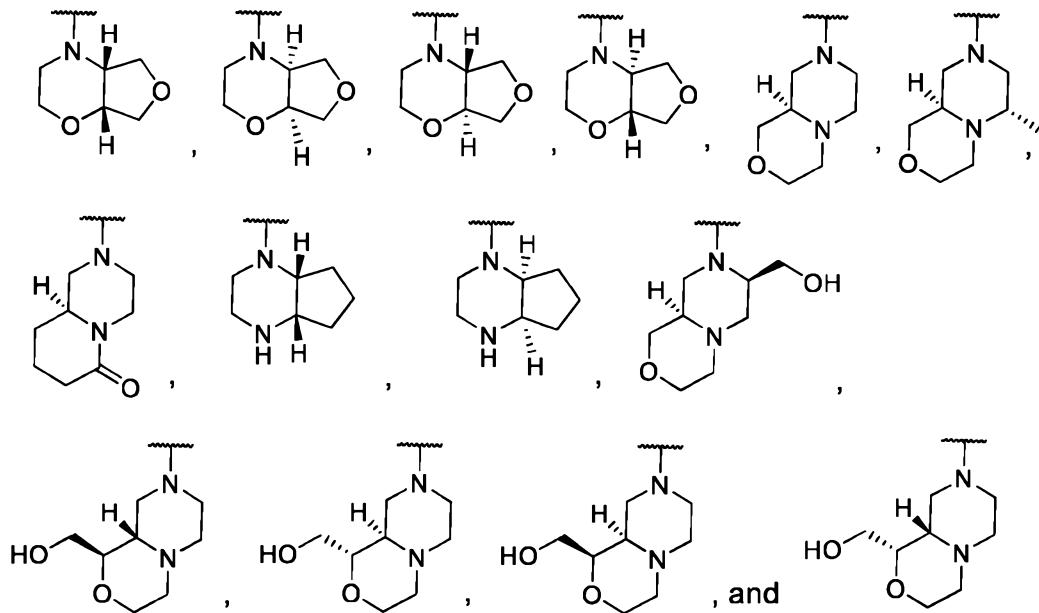
[0228] **Embodiment 38.** The compound of embodiment 28, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



[0229] Embodiment 39. The compound of embodiment 28, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



[0230] Embodiment 40. The compound of embodiment 28, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c combined with ring B form the moiety selected from 5 the group consisting of:



[0231] Embodiment 41. The compound of any one of embodiments 1 to 27, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- to 12-membered spiro heterocyclyl, or 5- to 7- membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein each ring is substituted or unsubstituted with R^a, R^b, and R^c.

[0232] Embodiment 42. The compound of embodiment 41, or a pharmaceutically acceptable salt thereof, wherein ring B is 2-oxaspiro[3.5]non-6-en-7-yl, 2-oxaspiro[3.5]non-7-yl, 2-oxa-8-azaspiro[4.5]dec-8-yl, 9-oxa-3-azaspiro[5.5]undec-3-yl, 2-oxa-6-azaspiro[3.4]oct-6-yl, 1-oxa-7-azaspiro[3.5]non-7-yl, 1-oxa-8-azaspiro[4.5]dec-8-yl, 6-oxa-2-azaspiro[3.3]hept-2-yl, 2,8-diazaspiro[4.5]dec-8-yl, 2-oxa-6-azaspiro[3.5]non-6-yl, , 3,6-diazabicyclo[3.1.1]hept-3-yl, 2,7-diazaspiro[3.5]non-7-yl, each ring optionally substituted with R^a where R^a is hydrogen or alkyl.

[0233] Embodiment 43. A compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group in Table 1, Table 3, or Table 4.

[0234] Embodiment 44. A pharmaceutical composition comprising a compound of any one of embodiments 1 to 43, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[0235] Embodiment 45. A method of treating a disease or disorder in which PARG activity is implicated in a patient, said method comprising administering to said patient an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 43, or a pharmaceutical composition of embodiment 44.

5 [0236] Embodiment 46. A method of treating cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 43, or a pharmaceutical composition of embodiment 44.

10 [0237] Embodiment 47. The method of embodiment 46, wherein said cancer is ovarian, gastric, or breast cancer.

[0238] Embodiment 48. A compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 43, or a pharmaceutical composition of embodiment 44, for use in therapy.

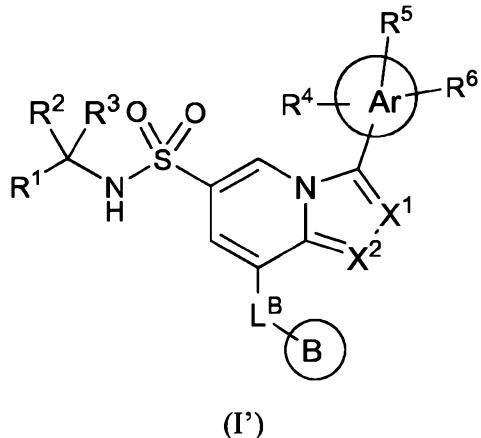
15 [0239] Embodiment 49. The compound or pharmaceutically acceptable salt thereof or composition according to embodiments 48, wherein said therapy is the treatment of a cancer.

[0240] Embodiment 50. The compound or pharmaceutically acceptable salt thereof, or composition according to embodiments 49, wherein said cancer is ovarian, gastric, or breast cancer.

20 [0241] Embodiment 51. The use of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 43, or a pharmaceutical composition of embodiment 44 in the manufacture of a medicament for use in therapy.

FURTHER NON-LIMITING EXEMPLARY EMBODIMENTS

[0242] Embodiment 1. A compound of Formula (I'):



wherein:

X¹ is selected from CR⁷ and N, X² is selected from CR⁷ and N;

5 R¹ is hydrogen, cyano, formyl, -CONH₂, -CH₂OH, -CH₂OC₁₋₂ alkyl, C₁₋₂ alkyl, C₁₋₂ deutoalkyl, or C₁₋₂ haloalkyl;

R² and R³ are independently C₁₋₂ alkyl; or

R² and R³ together with the carbon atom to which they are attached form C₃₋₄ cycloalkyl, or 3- or 10 4- membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S,

wherein the cycloalkyl or heterocyclyl is unsubstituted or substituted with 1 to 6 R^{2a},

each R^{2a} is independently deuterium, C₁₋₄ alkyl, halo, or C₁₋₄ haloalkyl;

Ar is a 5- or 6-membered heteroaryl having 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S;

R⁴ is C₁₋₃ alkyl, C₁₋₃ haloalkyl, hydroxyC₁₋₃alkyl, -C(O)H, or cyano;

15 R⁵ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R⁶ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

each R⁷ is independently hydrogen, deuterium, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, NR^{7a}R^{7b}, or 20 hydroxy;

each R^{7a} and R^{7b} is independently H or C₁₋₄ alkyl;

L^B is a bond, C₁₋₂ alkylene, -O-, -NR^{LB}-, or -S-;

R^{LB} is hydrogen or C₁₋₄ alkyl;

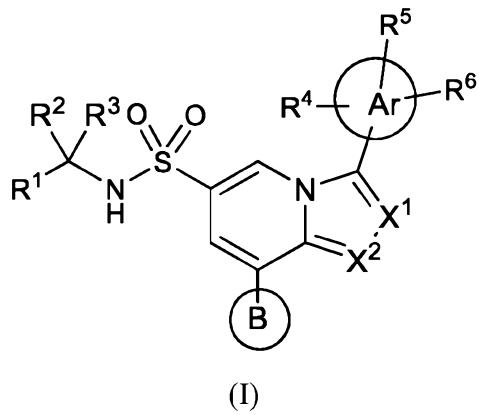
ring B is a 3- to 6- membered heterocycll, a 5- to 12-membered spiro heterocycll, or a 5- to 7- membered bridged heterocycll, each heterocycll having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein ring B is unsubstituted or substituted with R^a, R^b, and R^c, wherein

- 5 R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, 5- or 6- membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, or 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, or 3- or 6-membered heterocycll having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocycll, or 5- to 12-membered spiro heterocycll, each heterocycll having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), or -S(O)₂NR^hRⁱ (where R^h and Rⁱ are independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, or hydroxyC₁₋₆ alkyl; or R^h and Rⁱ together with the nitrogen atom to which they are attached form a 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S);
- 10 R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;
- 15 R^c is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; or R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocycll combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and
- 20 R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocycll combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and
- 25 R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocycll combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and
- 30 R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocycll combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and

further wherein the heteroaryl and heterocycll of R^a, the phenyl, heteroaryl, and heterocycll of R^d, the heterocycll or spiro heterocycll formed by R^f and R^g combining with the nitrogen to which they are attached, and the heterocycll formed by R^h and Rⁱ combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents selected from C₁₋₆ alkyl, hydroxy, hydroxyC₁₋₆ alkyl, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl; or

5 a pharmaceutically acceptable salt thereof.

[0243] Embodiment 2. A compound of Formula (I):



10 wherein:

X¹ is selected from CR⁷ and N, X² is selected from CR⁷ and N, and at least one of X¹ and X² is N;

15 R¹ is hydrogen, cyano, formyl, -CONH₂, -CH₂OH, -CH₂OC₁₋₂ alkyl, C₁₋₂ alkyl, or C₁₋₂ haloalkyl;

R² and R³ are independently C₁₋₂ alkyl; or

R² and R³ together with the carbon atom to which they are attached form C₃₋₄ cycloalkyl, or 3- or 4- membered heterocycll having 1 heteroatom ring vertex, selected from N, O, and S;

20 Ar is a 5- or 6-membered heteroaryl having 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S;

R⁴ is C₁₋₃ alkyl, C₁₋₃ haloalkyl, hydroxyC₁₋₃alkyl, -C(O)H, or cyano;

R⁵ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R⁶ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

each R⁷ is independently hydrogen, deuterium, halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;

ring B is a 3- to 6- membered heterocyclyl, a 5- to 12-membered spiro heterocyclyl, or a 5- to 7-

5 membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein ring B is unsubstituted or substituted with R^a, R^b, and R^c, wherein

R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, 5- or 6- membered

10 heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, or 3- to 6- membered

15 heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, or 3- or 6-membered heterocyclyl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S; or R^f and R^g together with the

20 nitrogen atom to which they are attached form a 4- to 6- membered heterocyclyl, or 5- to 12-membered spiro heterocyclyl, each heterocyclyl having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), or -S(O)₂NR^hRⁱ (where R^h and Rⁱ are independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, or hydroxyC₁₋₆ alkyl; or R^h and Rⁱ together with the nitrogen atom to which they are attached

25 form a 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S);

R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R^c is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; or

R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocyclyl combine to form

30 a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S,

wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and

further wherein the heteroaryl and heterocyclyl of R^a, the phenyl, heteroaryl, and heterocyclyl of R^d, the heterocyclyl or spiro heterocyclyl formed by R^f and R^g combining with the nitrogen to which they are attached, and the heterocyclyl formed by R^h and Rⁱ combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents selected from C₁₋₆ alkyl, hydroxy, hydroxyC₁₋₆ alkyl, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl; or

10 a pharmaceutically acceptable salt thereof.

[0244] Embodiment 3. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R² and R³ together with the carbon atom to which they are attached form 3- or 4- membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocyclyl is unsubstituted or substituted with 1 to 6 R^{2a}.

[0245] Embodiment 4. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R² and R³ together with the carbon atom to which they are attached form 3- or 4- membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocyclyl is unsubstituted.

20 [0246] Embodiment 5. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R² and R³ together with the carbon atom to which they are attached form 3- membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocyclyl is unsubstituted or substituted with 1 to 6 R^{2a}.

[0247] Embodiment 6. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R² and R³ together with the carbon atom to which they are attached form 4- membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocyclyl is unsubstituted or substituted with 1 to 6 R^{2a}.

[0248] Embodiment 7. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R² and R³ together with the carbon atom to which they are

attached form 3- membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocyclyl is unsubstituted.

[0249] Embodiment 8. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R² and R³ together with the carbon atom to which they are

5 attached form 4- membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocyclyl is unsubstituted.

[0250] Embodiment 9. The compound of embodiment 1 or 3 to 8, or a pharmaceutically acceptable salt thereof, wherein L^B is a bond, C₁₋₂ alkylene, or –O–;

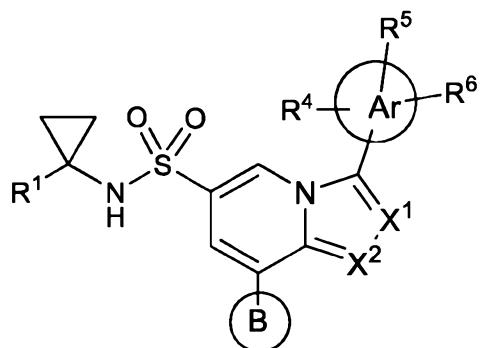
[0251] Embodiment 10. The compound of embodiment 1 or 3 to 8, or a pharmaceutically acceptable salt thereof, wherein L^B is a bond.

[0252] Embodiment 11. The compound of embodiment 1 or 3 to 8, or a pharmaceutically acceptable salt thereof, wherein L^B is C₁₋₂ alkylene.

[0253] Embodiment 12. The compound of embodiment 1 or 3 to 8, or a pharmaceutically acceptable salt thereof, wherein L^B is –O–.

15 **[0254]** Embodiment 13. The compound of embodiment 1 or 3 to 8, or a pharmaceutically acceptable salt thereof, wherein L^B is –NR^{LB}– or –S–.

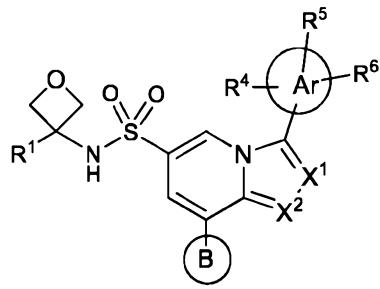
[0255] Embodiment 14. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof having the formula (Ia)



20

(Ia).

[0256] Embodiment 15. The compound of 1 or 2, or a pharmaceutically acceptable salt thereof having the formula (Ib)



[0257] Embodiment 16. The compound of any one of embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein at least one of X¹ and X² is N.

5 **[0258]** Embodiment 17. The compound of any one of embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein X¹ and X² are both N.

[0259] Embodiment 18. The compound of any one of embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein X¹ is N and X² is CR⁷.

10 **[0260]** Embodiment 19. The compound of any one of embodiments 1 to 15, or a pharmaceutically acceptable salt thereof, wherein X¹ is CR⁷ and X² is N.

[0261] Embodiment 20. The compound of any one of embodiments 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, fluoro, methyl, ethyl, difluoromethyl, or trifluoromethyl.

15 **[0262]** Embodiment 21. The compound of any one of embodiments 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen.

[0263] Embodiment 22. The compound of any one of embodiments 1 to 21, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen, cyano, methyl, or ethyl.

[0264] Embodiment 23. The compound embodiment 22, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen.

20 **[0265]** Embodiment 24. The compound embodiment 22, or a pharmaceutically acceptable salt thereof, wherein R¹ is cyano.

[0266] Embodiment 25. The compound embodiment 22, or a pharmaceutically acceptable salt thereof, wherein R¹ is methyl.

[0267] Embodiment 26. The compound of embodiment 1, 2 or any one of embodiments 17 to 25, or a pharmaceutically acceptable salt thereof, wherein R² and R³ are independently C₁₋₂ alkyl.

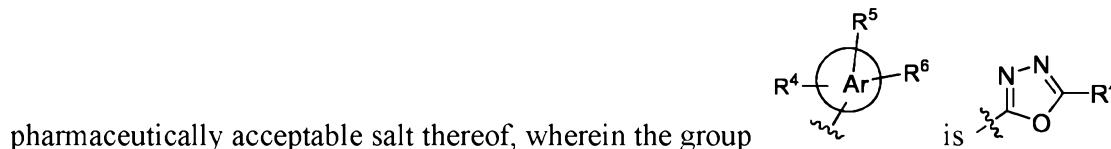
[0268] Embodiment 27. The compound of any one of embodiments 1 to 26, or a pharmaceutically acceptable salt thereof, wherein Ar is pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, or 1, 3, 5-triazinyl.

[0269] Embodiment 28. The compound of any one of embodiments 1 to 26, or a pharmaceutically acceptable salt thereof, wherein Ar is imidazolyl, isoxazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, or 10 1,3,4-thiadiazolyl.

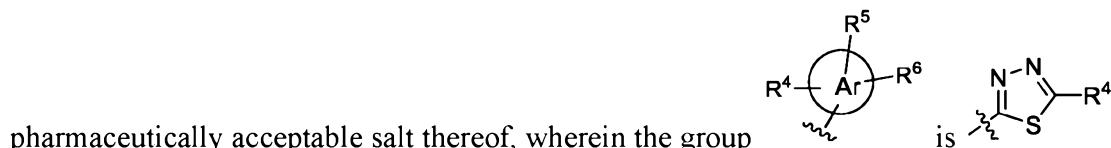
[0270] Embodiment 29. The compound of any one of embodiments 1 to 26, or a pharmaceutically acceptable salt thereof, wherein Ar is pyridazin-3-yl.

[0271] Embodiment 30. The compound of any one of embodiments 1 to 26, or a pharmaceutically acceptable salt thereof, wherein Ar is 1,3,4-oxadiazol-2-yl or 1,3,4-thiadiazol-15 2-yl.

[0272] Embodiment 31. The compound of any one of embodiments 1 to 26, or a



[0273] Embodiment 32. The compound of any one of embodiments 1 to 26, or a



[0274] Embodiment 33. The compound of any one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, wherein R⁴ is methyl, ethyl, difluoromethyl, trifluoromethyl, cyano, or C(O)H.

[0275] Embodiment 34. The compound of any one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, wherein R⁴ is difluoromethyl, methyl, trifluoromethyl, cyano, or C(O)H.

[0276] Embodiment 35. The compound of any one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, wherein R⁴ is methyl.

[0277] Embodiment 36. The compound of any one of embodiments 1 to 32, or a pharmaceutically acceptable salt thereof, wherein R⁴ is difluoromethyl.

[0278] Embodiment 37. The compound of any one of embodiments 1 to 36, or a pharmaceutically acceptable salt thereof, wherein R⁵ and R⁶ are independently hydrogen or absent.

[0279] Embodiment 38. The compound of any one of embodiments 1 to 36, or a pharmaceutically acceptable salt thereof, wherein R⁵ and R⁶ are each absent.

[0280] Embodiment 39. The compound of any one of embodiments 1 to 38, or a pharmaceutically acceptable salt thereof, wherein ring B is a 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, unsubstituted or substituted with R^a, R^b, and R^c.

[0281] Embodiment 40. The compound of embodiment 39, or a pharmaceutically acceptable salt thereof, wherein ring B is morpholinyl, 1,1-dioxothiomorpholinyl, azetinyl, pyrrolidinyl, piperidinyl, 6-oxo-1,6-dihydropyridinyl, or piperazinyl, each ring is independently unsubstituted or substituted with R^a, R^b, and R^c.

[0282] Embodiment 41. The compound of any one of embodiments 1 to 40, or a pharmaceutically acceptable salt thereof, wherein

R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, or C₁₋₆ haloalkyl; or R^f and R^g together with the nitrogen atom to which they are attached

form a 4- to 6- membered heterocycll, or 5- to 12-membered spiro heterocycll, each heterocycll having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), and

R^b is absent or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy;

5 R^c is absent or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy; and further wherein

the heterocycll of R^d, and the heterocycll or spiro heterocycll formed by R^f and R^g combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents independently selected from C₁₋₆ alkyl, 10 hydroxyC₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl.

[0283] Embodiment 42. The compound of any one of embodiments 1 to 40, or a pharmaceutically acceptable salt thereof, wherein

R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, -C(O)R^d (where R^d is hydrogen, C₁₋₆ 15 alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or 3- to 6- membered heterocycll having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, or C₁₋₆ haloalkyl; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocycll, or 5- to 12-membered spiro heterocycll, each 20 heterocycll having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), and

further wherein the heterocycll of R^d, and the heterocycll or spiro heterocycll formed by R^f and R^g combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents independently selected from C₁₋₆ 25 alkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl.

[0284] Embodiment 43. The compound of any one of embodiments 1 to 40 and 42, or a pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycll and combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring

comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

- 5 [0285] Embodiment 44. The compound of any one of embodiments 1 to 40 and 42, or a pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycl and combine to form a 4- to 6-membered saturated or partially unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 10 4- to 6-membered saturated or partially unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl, or oxo.

- [0286] Embodiment 45. The compound of any one of embodiments 1 to 40 and 42, or a pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycl and combine to form a 4- to 6-membered saturated ring comprising 1 additional heteroatom ring vertex, selected from N, O, and S, wherein the 4- to 6-membered saturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

- [0287] Embodiment 46. The compound of any one of embodiments 1 to 40 and 42, or a pharmaceutically acceptable salt thereof. wherein

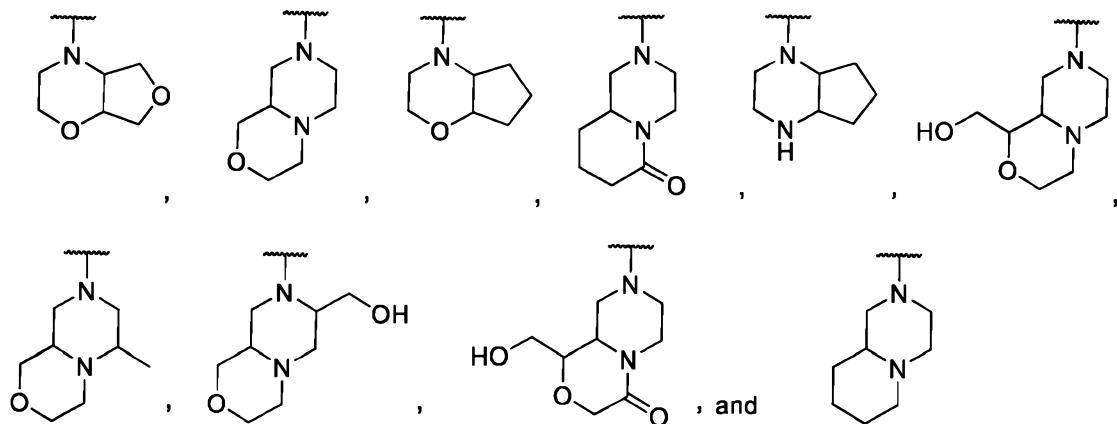
R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycl and combine to form a 4- to 6-membered saturated ring comprising 0 additional heteroatom ring vertices, wherein the 4- to 6-membered saturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

- 25 [0288] Embodiment 47. The compound of any one of embodiments 1 to 38 and 42, or a pharmaceutically acceptable salt thereof, wherein ring B is octahydropyrazino[2,1-c][1,4]oxazinyl, octahydro-2H-pyrido[1,2-a]pyrazinyl, 6-methyloctahydropyrazino[2,1-

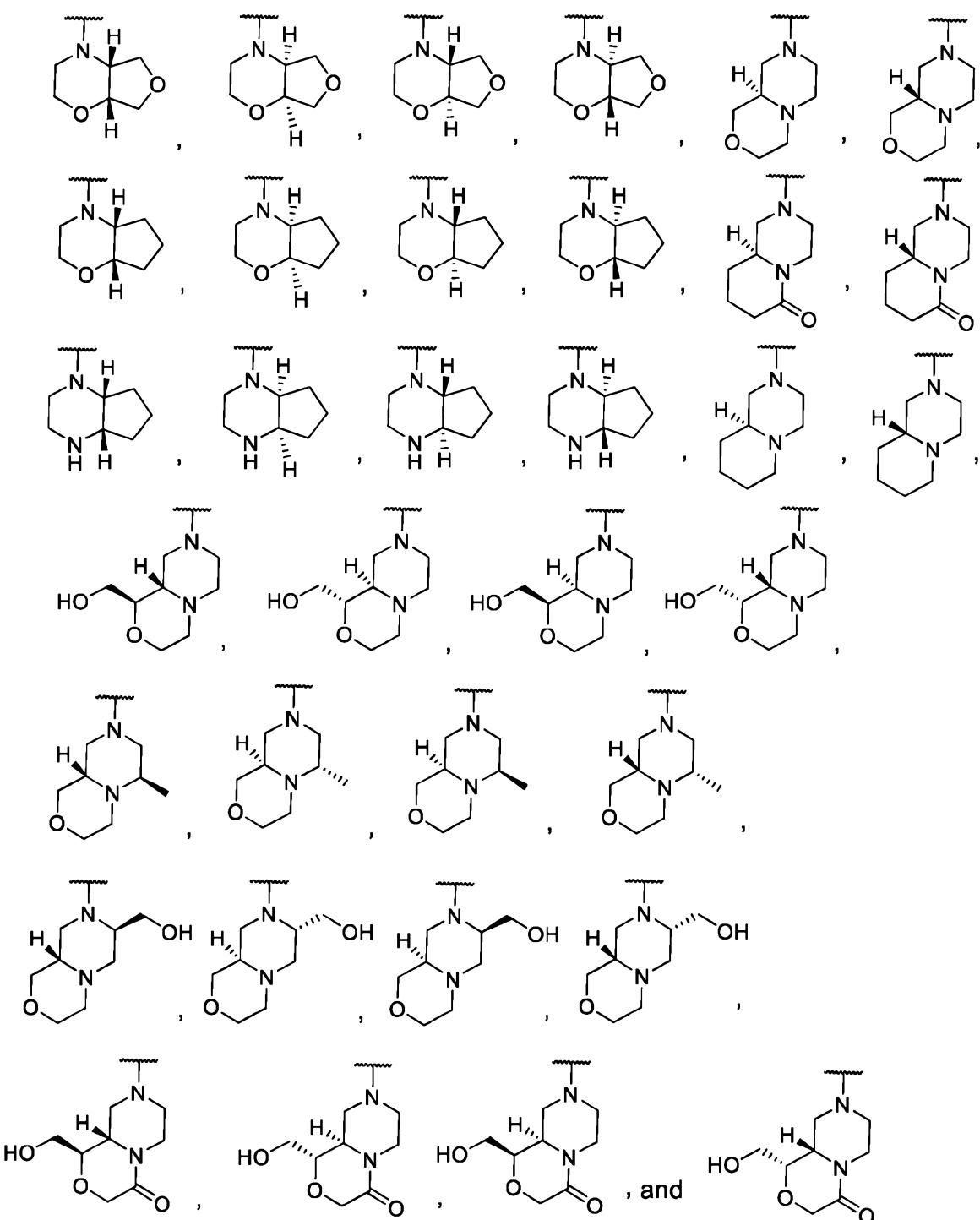
c][1,4]oxazinyl, octahydro-6H-pyrido[1,2-a]pyrazin-6-only, or octahdropyrazino[2,1-c][1,4]oxazinyl substituted with a hydroxymethyl.

[0289] Embodiment 48. The compound of any one of embodiments 1 to 38 and 42, or a pharmaceutically acceptable salt thereof, wherein ring B is octahydro-1H-5 cyclopenta[b]pyrazinyl.

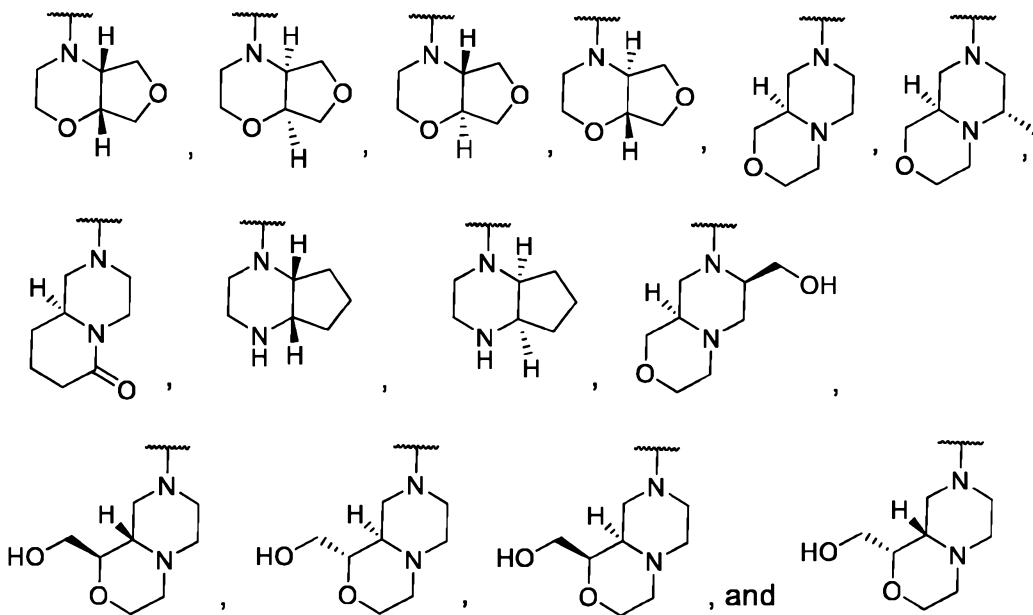
[0290] Embodiment 49. The compound of embodiment 39, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



[0291] Embodiment 50. The compound of embodiment 39, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



[0292] Embodiment 51. The compound of embodiment 39, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



[0293] Embodiment 52. The compound of any one of embodiments 1 to 38, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- to 12-membered spiro heterocyclyl, or 5- to 7- membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein each ring is substituted or unsubstituted with R^a, R^b, and R^c.

[0294] Embodiment 53. The compound of embodiment 52, or a pharmaceutically acceptable salt thereof, wherein ring B is 2-oxaspiro[3.5]non-6-en-7-yl, 2-oxaspiro[3.5]non-7-yl, 2-oxa-8-azaspiro[4.5]dec-8-yl, 9-oxa-3-azaspiro[5.5]undec-3-yl, 2-oxa-6-azaspiro[3.4]oct-6-yl, 1-oxa-7-azaspiro[3.5]non-7-yl, 1-oxa-8-azaspiro[4.5]dec-8-yl, 6-oxa-2-azaspiro[3.3]hept-2-yl, 2,8-diazaspiro[4.5]dec-8-yl, 2-oxa-6-azaspiro[3.5]non-6-yl, , 3,6-diazabicyclo[3.1.1]hept-3-yl, 2,7-diazaspiro[3.5]non-7-yl, each ring optionally substituted with R^a where R^a is hydrogen or alkyl.

[0295] Embodiment 54. A compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group in Table 1, Table 3, or Table 4.

[0296] Embodiment 55. A pharmaceutical composition comprising a compound of any one of embodiments 1 to 54, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[0297] Embodiment 56. A method of treating a disease or disorder in which PARG activity is implicated in a patient, said method comprising administering to said patient an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55.

5 [0298] Embodiment 57. The method of embodiment 56, wherein the patient is in recognized need of such treatment.

10 [0299] Embodiment 58. A method of treating cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55.

[0300] Embodiment 59. The method of embodiment 58, wherein said cancer is ovarian, gastric, or breast cancer.

15 [0301] Embodiment 60. The method of embodiment 58, wherein said cancer is ovarian cancer, prostate cancer, pancreatic cancer, colorectal cancer, gastric cancer, skin cancer, endometrial cancer, cervical cancer, brain cancer, liver cancer, bladder cancer, esophageal cancer, kidney cancer, stomach cancer, thyroid cancer, lymphoma, leukemia, melanoma, uterine cancer, mantle cell lymphoma, renal cell carcinoma, appendicle cancer, hematologic cancer, MYH-related polyposis, gallbladder cancer, bile duct cancer, testicular cancer, bone cancer, or head and neck cancer.

20 [0302] Embodiment 61. A compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55, for use in therapy.

[0303] Embodiment 62. The compound or pharmaceutically acceptable salt thereof or composition according to embodiments 61, wherein said therapy is the treatment of a cancer.

25 [0304] Embodiment 63. The compound or pharmaceutically acceptable salt thereof, or composition according to embodiments 62, wherein said cancer is ovarian, gastric, or breast cancer.

[0305] Embodiment 64. The method of embodiment 63, wherein said cancer is breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, colorectal cancer, gastric cancer, skin cancer, endometrial cancer, cervical cancer, brain cancer, liver cancer, bladder cancer, esophageal cancer, kidney cancer, stomach cancer, thyroid cancer, lymphoma, leukemia, 5 melanoma, uterine cancer, mantle cell lymphoma, renal cell carcinoma, appendiceal cancer, hematologic cancer, MYH-related polyposis, gallbladder cancer, bile duct cancer, testicular cancer, bone cancer, or head and neck cancer.

[0306] Embodiment 65. The use of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55 10 in the manufacture of a medicament for use in therapy.

[0307] Embodiment 66. The use of embodiment 65, wherein said therapy is the treatment of a cancer.

[0308] Embodiment 67. The use of embodiment 66, wherein said cancer is breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, gastric cancer, skin cancer, endometrial 15 cancer, cervical cancer, brain cancer, liver cancer, bladder cancer, esophageal cancer, kidney cancer, colorectal cancer, stomach cancer, thyroid cancer, lymphoma, leukemia, melanoma, uterine cancer, mantle cell lymphoma, renal cell carcinoma, appendiceal cancer, hematologic cancer, MYH-related polyposis, gallbladder cancer, bile duct cancer, testicular cancer, bone cancer, or head and neck cancer.

20 [0309] Embodiment 68. A method of inhibiting PARG *in vivo* in a patient, said method comprising administering to said patient an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55.

25 [0310] Embodiment 69. A method of inhibiting cell proliferation, *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55.

[0311] Embodiment 70. A method of treating a cancer resistant to one or more platins or one or more PARP inhibitors in a patient in need thereof, said method comprising administering to said patient an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55.

5 [0312] Embodiment 71. A method of treating a cancer resistant to one or more platins in a patient in need thereof, said method comprising administering to said patient an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55.

10 [0313] Embodiment 72. A method of treating a cancer resistant to one or more PARP inhibitors in a patient in need thereof, said method comprising administering to said patient an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55.

[0314] Embodiment 73. The method of embodiment 70 or 71, wherein the one or more platins is carboplatin, cisplatin, oxaliplatin, nedaplatin, saraplatin, lobaplatin, or heptaplatin.

15 [0315] Embodiment 74. The method of embodiment 70 or 72, wherein the one or more PARP inhibitors is niraparib, rucaparib, olaparib, talazoparib, or veliparib.

20 [0316] Embodiment 75. A method of treating and/or preventing a homologous recombinant deficient (HRD) cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55.

[0317] Embodiment 76. The method of embodiment 75, wherein the patient is in recognized need of such treatment.

25 [0318] Embodiment 77. A method of treating and/or preventing a cancer in a patient, where the cancer is characterized by a reduction or absence of BRCA1 and/or BRCA2 gene expression, the absence or mutation of BRCA1 and/or BRCA2 genes, or reduced function of BRCA1 and/or BRCA2 proteins, comprising administering to the patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55.

[0319] Embodiment 78. A method of treating and/or preventing a cancer in a patient, where the cancer is characterized by a reduction or absence of BRCA1 gene expression, the absence or mutation of BRCA1 genes, or reduced function of BRCA1 proteins, comprising administering to the patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55.

[0320] Embodiment 79. A method of treating and/or preventing a cancer in a patient, where the cancer is characterized by a reduction or absence of BRCA2 gene expression, the absence or mutation of BRCA2 genes, or reduced function of BRCA2 proteins, comprising administering to the patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 54, or a pharmaceutical composition of embodiment 55.

[0321] Embodiment 80. The method of any one of embodiments 77 to 79, wherein the patient is in recognized need of such treatment.

[0322] Embodiment 81. A PARG inhibitor for use in the treatment of cancer, wherein the PARG inhibitor is a compound of any one of embodiments 1 to 54, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 55.

[0323] Embodiment 82. Use of a PARG inhibitor in the manufacture of a medicament for treating cancer, wherein the PARG inhibitor is a compound of any one of embodiments 1 to 54, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 55.

[0324] Embodiment 83. The method or use of any one of embodiments 70 to 82, wherein said cancer is breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, colorectal cancer, gastric cancer, skin cancer, endometrial cancer, cervical cancer, brain cancer, liver cancer, bladder cancer, esophageal cancer, kidney cancer, colorectal cancer, stomach cancer, thyroid cancer, lymphoma, leukemia, melanoma, uterine cancer, mantle cell lymphoma, renal cell carcinoma, appendiceal cancer, hematologic cancer, MYH-related polyposis, gallbladder cancer, bile duct cancer, testicular cancer, bone cancer, or head and neck cancer.

EXAMPLES

[0325] The following references (intermediates), synthetic schemes, and examples (final compounds) are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to 5 limit the scope of what the inventors regard as their invention, nor are they intended to represent that the experiments below were performed or that they are all of the experiments that may be performed. It is to be understood that exemplary descriptions written in the present tense were not necessarily performed, but rather that the descriptions can be performed to generate data and the like of a nature described therein. Efforts have been made to ensure accuracy with respect to 10 numbers used (e.g., amounts, temperature, etc.), but some experimental errors and deviations should be accounted for.

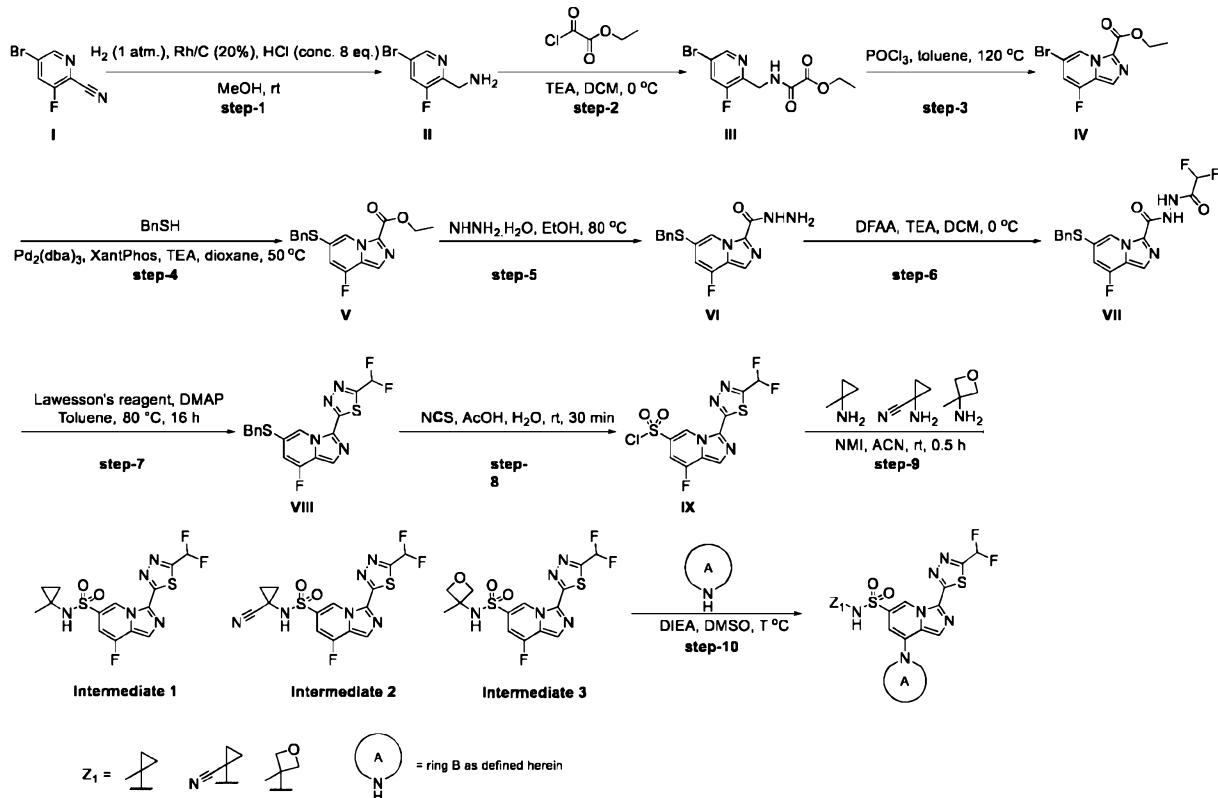
[0326] Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius (°C), and pressure is at or near atmospheric. Standard abbreviations are used, including the following: μg = microgram; μl or 15 μL = microliter; mM = millimolar; μM = micromolar; aa = amino acid(s); Ac_2O = acetic anhydride; AcCl = acetylchloride; ACN = acetonitrile; AIBN = 2,2'-Azobis(2- methylpropionitrile); BID = twice daily; BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; Boc_2O or $(\text{Boc})_2\text{O}$ = di-tert-butyl carbonate; bp = base pair(s); BSA = bovine serum albumin; BW = body weight; d = doublet; dd = doublet of doublets; DEAD = diethyl 20 azodicarboxylate; DIBAL = diisobutylaluminium hydride DIEA = N,N-diisopropylethylamine; DIPEA = N,N-diisopropylethylamine; dl or dL = deciliter; DMA = dimethylacetamide; DMAP = dimethylaminopyridine; DME = 1,2-dimethoxyethane; DMEM = Dulbecco's Modification of Eagle's Medium; DMF = N,N-dimethylformamide; DMSO = dimethylsulfoxide; dppf = 1,1'-Bis(diphenylphosphino)ferrocene; DTT = dithiothreitol; EDTA = ethylenediaminetetraacetic acid; ES = electrospray; EtOAc or EA = ethyl acetate; EtOH = ethanol; g = gram; h or hr = 25 hour(s); HATU = 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HEPES = 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HOAc = acetic acid; HPLC = high performance liquid chromatography; HPLC = high pressure liquid chromatography; i.m. = intramuscular(ly); i.p. = intraperitoneal(ly); IHC = 30 immunohistochemistry; IPA = isopropyl alcohol; kb = kilobase(s); kDa = kilodalton; kg =

kilogram; l or L = liter; LC = liquid chromatography; LCMS = liquid chromatography and mass spectrometry; m / z = mass to charge ratio; M = molar; m = multiplet; MeCN = acetonitrile; MeOH = methanol; MeSO₂Cl = methanesulfonylchloride; mg = milligram; min = minute(s); min = minutes; ml or mL = milliliter; mM = millimolar; MS = mass spectrometry; MsCl = 5 methanesulfonylchloride; N = normal; NADPH = nicotinamide adenine dinucleotide phosphate; NBS = N-bromosuccinamide; ng = nanogram; nm = nanometer; nM = nanomolar; NMP = N-methylpyrrolidone; NMR = nuclear magnetic resonance; ns = not statistically significant; nt = nucleotides(s); PBS = phosphate-buffered saline; Pd/C = palladium on carbon; Pd₂(dba)₃ = Tris(debenzylideneactone) dipalladium; Pd(dppf)Cl₂ = 1,1'-bis(diphenylphosphino)ferrocene-10 palladium(II)dichloride; PE = petroleum ether; QD = daily; QM = monthly; QW = weekly; rac = racemic; Rt = retention time; s = singlet; s or sec = second(s); sat. = saturated; SC or SQ = subcutaneous(ly); t = triplet; TBAB = tetra-n-butylammonium bromide; TEA = triethylamine; TFA = trifluoroacetic acid; THF = tetrahydrofuran; TLC = thin layer chromatography; TMSCl = trimethylsilylchloride; TsOH = p-toluenesulfonic acid; U = unit; wt = wildtype.

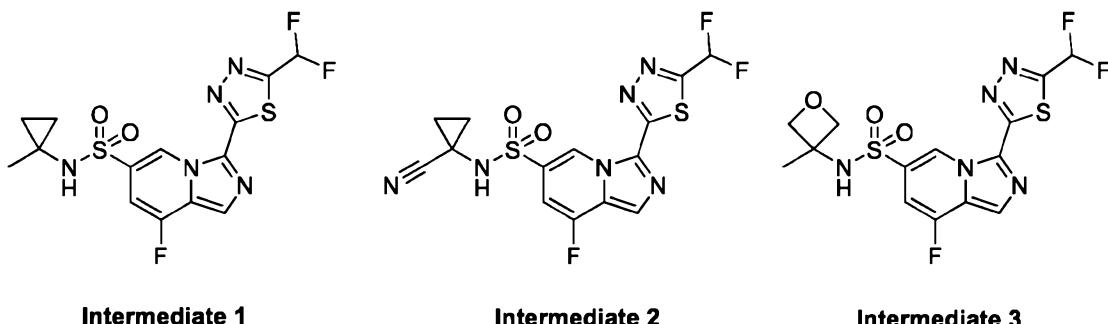
15 [0327] The following paragraphs outline and describe Schemes 1 to 6, which were used to prepare the compounds of the present disclosure. The first section, Preparation of Intermediates, provides detailed information on how intermediates 1-15 were prepared. The second section, Preparation of Exemplary Compounds, provides detailed information on how select exemplary compounds were prepared from the intermediates.

Preparation of Intermediates

Scheme 1

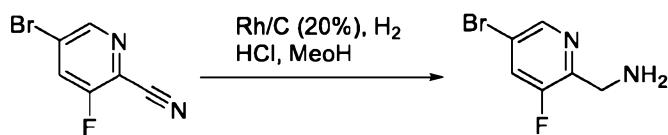


Preparation of Intermediates 1, 2 and 3



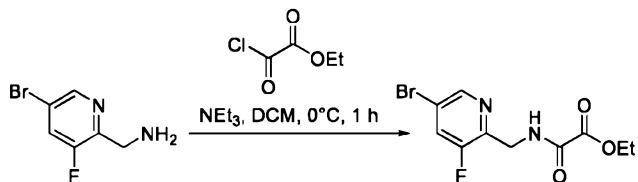
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Step-1: Synthesis of (5-bromo-3-fluoropyridin-2-yl)methanamine II:



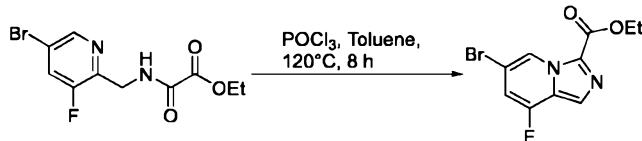
[0328] To a solution of 5-bromo-3-fluoropyridine-2-carbonitrile (100 g, 497.51 mmol) in MeOH (2 L) were added concentrated HCl (332 mL, 3984.00 mmol) and Rh/C (30.00 g, 5%) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 9 days under hydrogen atmosphere (1 atm). The resulting mixture was filtered; 5 the filter cake was washed with MeOH (500 mL X 2). The filtrate was collected and concentrated under vacuum. The residue was purified by triturated with heptane (500 mL) to afford 1-(5-bromo-3-fluoropyridin-2-yl)methanamine hydrochloride (125 g, crude) as a light yellow solid. *m/z* (ESI): [M+H]⁺, 204.9, 206.9; found, 205.0, 207.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.06 (s, 1H), 8.84 – 8.56 (m, 4H), 8.31 (dd, *J* = 9.2, 2.0 Hz, 1H), 4.19 (s, 2H).

10 **Step-2: Synthesis of ethyl 2-((5-bromo-3-fluoropyridin-2-yl)methyl)amino)-2-oxoacetate III:**



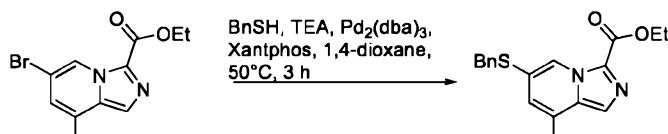
[0329] To a stirred solution of (5-bromo-3-fluoropyridin-2-yl)methanamine TFA salt (160 g, 780.374 mmol) in DCM (1600 mL) was added TEA (326 mL, 2341.121 mmol) at room 15 temperature. The reaction mixture was cooled at 0 °C, slowly added dropwise ethyl 2-chloro-2-oxoacetate (127.8 g, 936.4 mmol) at 0 °C and stirred for 1 h. The reaction mixture was diluted with water (800 mL) and extracted with DCM (2 x 1L). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford ethyl 2-((5-bromo-3-fluoropyridin-2-yl)methyl)amino)-2-oxoacetate (142 g, 59.64%) as an off white solid. MS ESI calculated for C₁₀H₁₀BrFN₂O₃ [M+H]⁺ 20 304.99, found 305.14.

Step-3: Synthesis of ethyl 6-bromo-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate IV:



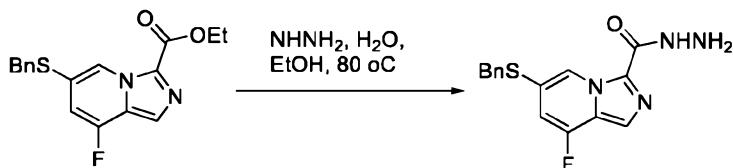
[0330] To a stirred solution of ethyl 2-(((5-bromo-3-fluoropyridin-2-yl)methyl)amino)-2-oxoacetate (142 g, 465.417 mmol) in toluene (1000 mL) was added POCl_3 (142 mL) at room temperature. The reaction mixture was stirred at 120 °C for 8 h. The reaction mixture was quenched with water (300 mL), added saturated aqueous NaHCO_3 solution and extracted with EtOAc (2 x 1 L). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford ethyl 6-bromo-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate (83 g, 62.12%) as an off white solid. MS ESI calculated for $\text{C}_{10}\text{H}_8\text{BrFN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 286.98, found 287.08.

Step-4: Synthesis of ethyl 6-(benzylthio)-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate V:



[0331] To a solution of ethyl 6-bromo-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate (83 g, 291.228 mmol) in 1,4 dioxane (830 mL) were added benzyl mercaptan (116.025 g, 232.982 mmol), Xanthphos (16.850 g, 29.123 mmol), $\text{Pd}_2(\text{dba})_3$ (26.668 g, 29.123 mmol) and triethyl amine (88.2 mL, 873.684 mmol) and the reaction mixture was heated at 50 °C for 3 h. The reaction mixture was diluted with water (500 mL) and extracted with EtOAc (2 x 600 mL). Combined organic layer was washed with brine solution (500 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude was purified by column chromatography using silica gel (100-200) and eluted at 30% EtOAc/Hexane. The pure fractions were collected and concentrated under reduced pressure to afford ethyl 6-(benzylthio)-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate (60 g, 62.82%) as a brown solid. MS ESI calculated for $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 331.08, found 331.27.

Step-5: Synthesis of 6-(benzylthio)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide VI:



[0332] To a stirred solution of ethyl 6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate (25.0 g, 75.67 mmol) in EtOH (250 mL) was added hydrazine hydrate (23.7 g,

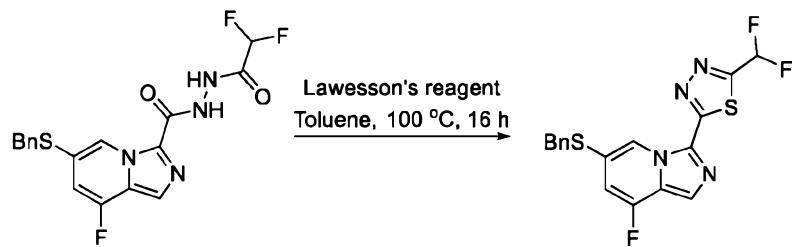
379.10 mmol, 80%) at room temperature. The resulting mixture was stirred at 80 °C for 1 h. The mixture was cooled at room temperature. The precipitated solids were collected by filtration and washed with ethanol, then dried over vacuum to afford 6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (22.2 g, 89%) as a light yellow solid. *m/z* (ESI): [M+H]⁺, 317.2.

5 **Step-6: Synthesis of 6-(benzylthio)-N'-(2,2-difluoroacetyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide VII:**



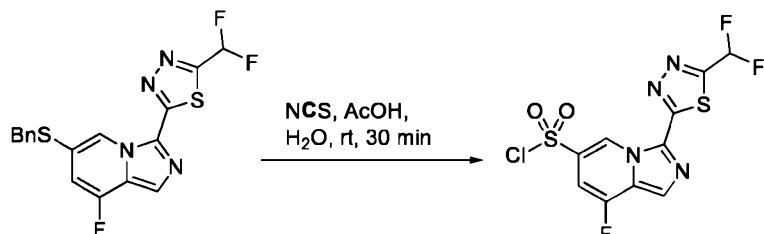
[0333] To a stirred solution of 6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (22.2 g, 70.17 mmol) and TEA (21.3 g, 210.48 mmol) in DCM (250 mL) was 10 added 2,2-difluoroacetyl 2,2-difluoroacetate (8.9 mL, 77.19 mmol) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction mixture was quenched by the addition of ice/water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was 15 purified by silica gel column chromatography, eluted with 0~10% methanol in dichloromethane to afford 6-(benzylsulfanyl)-N'-(2,2-difluoroacetyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (29 g, 97%) as a light brown solid. *m/z* (ESI): [M+H]⁻, 395.0.

Step-7: Synthesis of 2-(6-(benzylthio)-8-fluoroimidazo[1,5-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole VIII:



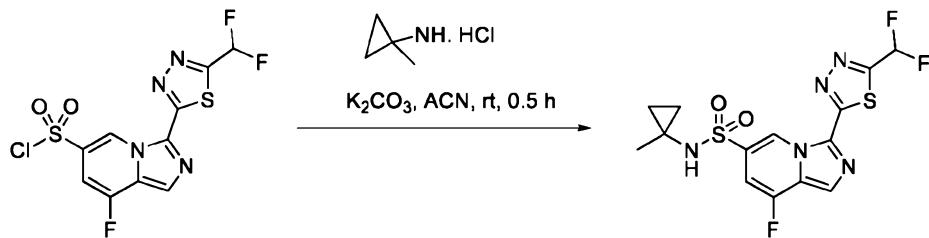
[0334] To a solution of 6-(benzylthio)-N¹-(2,2-difluoroacetyl)-8-fluoroimidazo[1,5-*a*]pyridine-3-carbohydrazide (30 g, 76.071 mmol) in dry toluene (300 mL) was added 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 1,3-dioxide (56.6 g, 152.14 mmol) and the mixture was stirred at 100°C for 16 h. The solvent was evaporated, crude was diluted with water (600 mL) and extracted with EtOAc (2 x 600 mL). The combined organic layer was washed with sat. aq. NaHCO₃ solution (1 Lit) and then brine solution (600 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude was purified by column chromatography using silica gel (100-200) and the product was eluted at 20% EtOAc/Hexane. The pure fractions were collected and concentrated under reduced pressure to afford 2-(6-(benzylthio)-8-fluoroimidazo[1,5-*a*]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (14 g, 46.90%) as a yellow solid. MS ESI calculated for C₁₇H₁₁F₃N₄S₂ [M+H]⁺ 393.04, found 393.30.

Step-8: Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoroimidazo[1,5-*a*]pyridine-6-sulfonyl chloride IX:



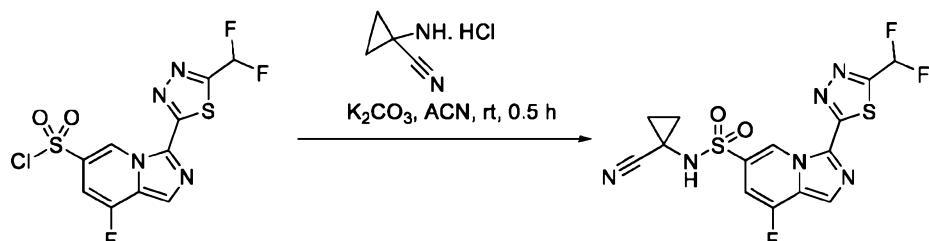
[0335] To a suspension of 2-(6-(benzylthio)-8-fluoroimidazo[1,5-*a*]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (14 g, 35.7 mmol) in acetic acid and water (84 mL: 28 mL) under N₂ was added 1-chloropyrrolidine-2,5-dione (14.292 g, 107.029 mmol) portion wise. The reaction was stirred at rt for 30 min. The reaction mixture was filtered and filtrate was dried under reduced pressure to obtain 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoroimidazo[1,5-*a*]pyridine-6-sulfonyl chloride (9.1 g, 69.18%) as a yellow solid. The obtained product was used in subsequent reactions without purification. MS ESI calculated for C₁₀H₄ClF₃N₄O₂S₂ [M+H]⁺ 368.94, found 369.15.

Step-9: Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(3-methyloxetan-3-yl)imidazo[1,5-*a*]pyridine-6-sulfonamide (Intermediate 1):



[0336] To a stirred solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoroimidazo[1,5-a]pyridine-6-sulfonyl chloride (3.0 g, 8.136 mmol, 1 equiv.) in ACN (30 mL) were added potassium carbonate (5.622 g, 40.680 mmol, 5 equiv.) followed by addition of 1-methylcyclopropan-1-amine hydrochloride (1.751 g, 16.272 mmol, 2 equiv.) and the reaction mixture stirred at RT for 0.5 h. Reaction progress was monitored by TLC and LCMS. TLC showed completion of SM. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layer was washed with brine solution (50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (2.35 g, 71.6 %) as an off white solid. MS ESI calculated for C₁₄H₁₂F₃N₅O₂S₂ [M+H]⁺ 404.05, found 404.40.

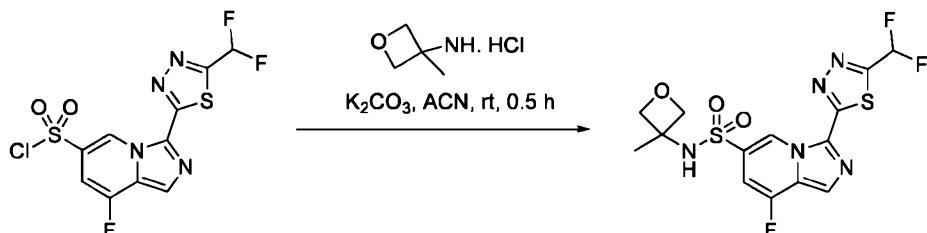
Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoroimidazo[1,5-a]pyridine-6-sulfonamide (Intermediate 2):



[0337] To a stirred solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoroimidazo[1,5-a]pyridine-6-sulfonyl chloride (2.5 g, 6.78 mmol) in ACN (25 mL, 10V) were added 1-cyanocyclopropan-1-amine hydrochloride (1.206 g, 10.170 mmol) dissolved in N-methylimidazole (5 mL) at 0°C and then the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with 1N aq. HCl solution (25 mL) and brine solution (50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and

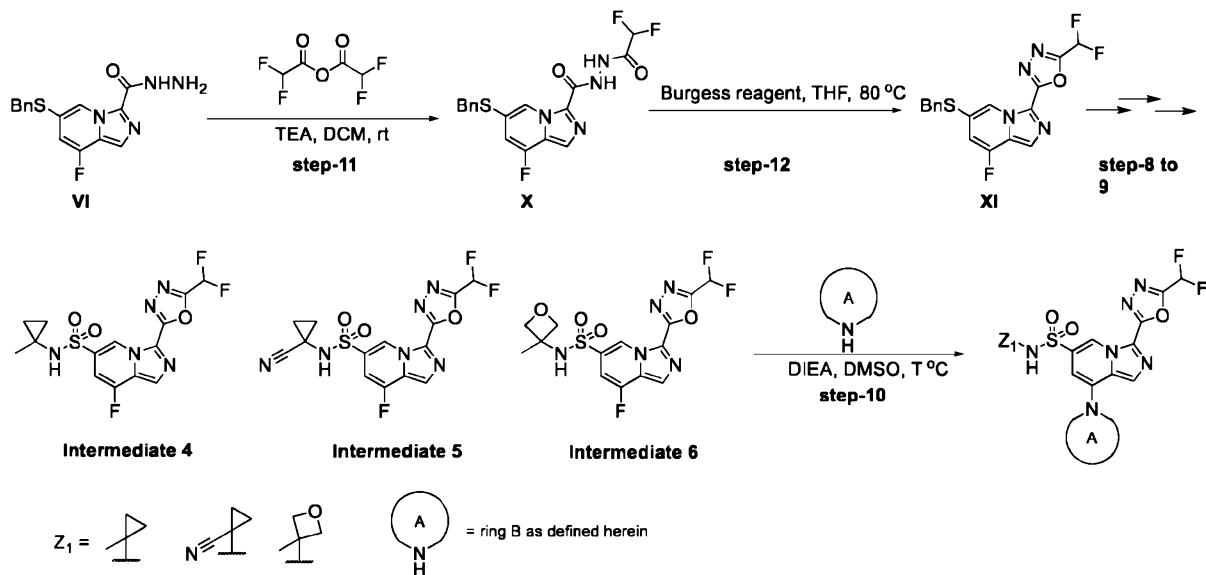
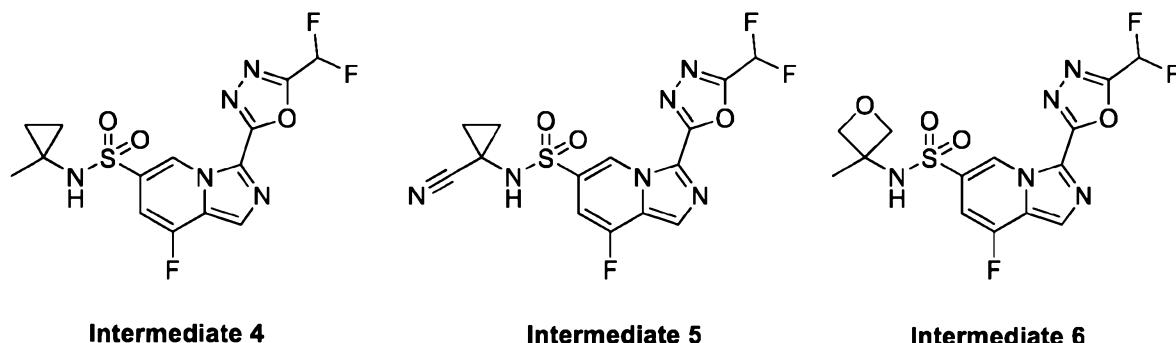
concentrated under reduced pressure to get N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoroimidazo[1,5-a]pyridine-6-sulfonamide (1.8 g, 64.07 %) as an off white solid. MS ESI calculated for $C_{14}H_9F_3N_6O_2S_2 [M+H]^+$ 415.02, found 415.28. 1H NMR (400 MHz, DMSO-d₆): δ (ppm) 9.83 (s, 1H), 9.67 (s, 1H), 8.18-8.10 (m, 1H), 7.84-7.57 (m, 1H), 5 7.27-7.23 (m, 1H), 1.52-1.37 (m, 4H).

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (Intermediate 3):



[0338] To a stirred solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoroimidazo[1,5-a]pyridine-6-sulfonate chloride (1.5 g, 4.068 mmol) in ACN (15 mL) were added K₂CO₃ (2.817 g, 20.340 mmol) followed by addition of 3-methyloxetan-3-amine hydrochloride (0.708 g, 8.136 mmol) and the reaction mixture stirred at RT for 0.5 h. Reaction progress was monitored by TLC and LCMS. TLC showed completion of SM. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 30 mL). The combined 15 organic layer was washed with brine solution (50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (1.21 g, 70.92 %) as a brown solid. MS ESI calculated for C₁₄H₁₂F₃N₅O₃S₂ [M-H]⁻ 418.03, found 418.18.

[0339] Step-10, providing compounds of Formula I, is further described in the Preparation of Exemplary Compounds section, below.

Scheme 2**Preparation of Intermediates 4, 5 and 6****Intermediate 4****Intermediate 5****Intermediate 6**

5 Step-11: Synthesis of 6-(benzylsulfanyl)-N'-(2,2-difluoroacetyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (X)

[0340] To a stirred solution of 6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (22.2 g, 70.17 mmol) and TEA (21.3 g, 210.48 mmol) in DCM (250 mL) was added 2,2-difluoroacetyl 2,2-difluoroacetate (8.9 mL, 77.19 mmol) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by the addition of ice/water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column

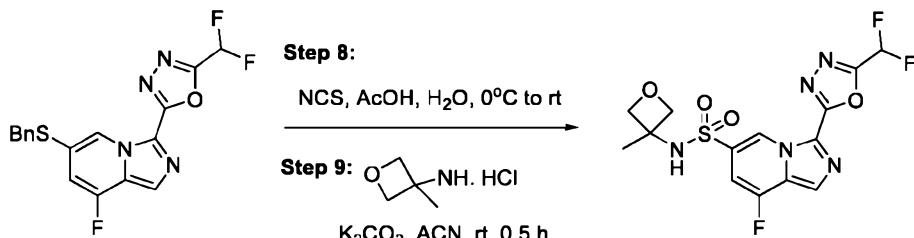
chromatography, eluted with DCM/MeOH (10:1) to afford 6-(benzylsulfanyl)-N'-(2,2-difluoroacetyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (29 g, 97%) as a light brown solid. *m/z* (ESI): [M+H]⁺ 395.00

Step-12: Synthesis of 2-[6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridin-3-yl]-5-

(difluoromethyl)-1,3,4-oxadiazole (XI)

[0341] To a stirred solution of 6-(benzylsulfanyl)-N'-(2,2-difluoroacetyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (25.0 g, 63.39 mmol) in THF (140 mL) was added Burgess reagent (30.2 g, 126.78 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at 80 °C overnight. The resulting mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (8:1) to afford 2-[6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridin-3-yl]-5-(difluoromethyl)-1,3,4-oxadiazole (15.2 g, 60%) as a yellow solid. *m/z* (ESI): [M+H]⁺ 377.05

15 Step-8 and 9: Synthesis of 3-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-8-fluoro-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (Intermediate 6)

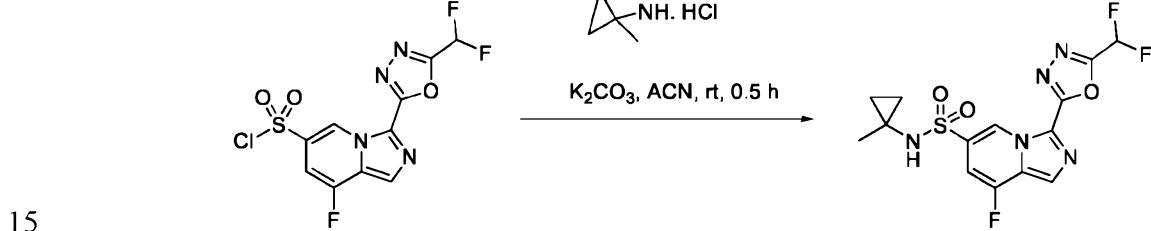


[0342] To a stirred mixture of 2-[6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridin-3-yl]-5-(difluoromethyl)-1,3,4-oxadiazole (6.0 g, 15.94 mmol) in AcOH (60 mL) and H₂O (20 mL) was added NCS (6.4 g, 47.82 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was diluted with water. The mixture was basified with NaHCO₃ (sat.) to pH 6. The resulting mixture was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford 3-[5-(difluoromethyl)-1,3,4-

oxadiazol-2-yl]-8-fluoroimidazo[1,5-a]pyridine-6-sulfonyl chloride (6.3 g, 85%) as a yellow solid. *m/z* (ESI): [M+H]⁺ 353.10

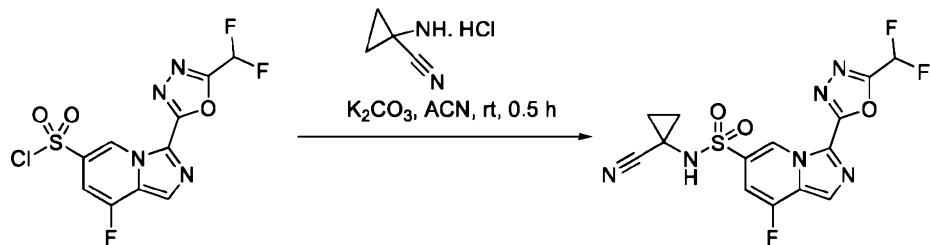
[0343] To a stirred mixture of 3-methyloxetan-3-amine (1.25 g, 14.29 mmol) and NMI (10 mL, 24.36 mmol) in MeCN (15 mL) was added 3-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-8-fluoroimidazo[1,5-a]pyridine-6-sulfonyl chloride (4.2 g, 11.91 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The resulting mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EtOAc (2:3) to afford 3-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-8-fluoro-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (2.1 g, 41%) as a white solid. *m/z* (ESI): [M+H]⁺ 404.05

Synthesis of 3-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-8-fluoro-N-(3-methylcyclopropyl-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (Intermediate 4):



[0344] Intermediate 4 was synthesized in same manner as intermediate 6, while using 1-methylcyclopropan-1-amine hydrochloride to afford 3-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-8-fluoro-N-(3-methylcyclopropyl-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide [M+H]⁺ 388.05, found 388.30.

20 **Synthesis of 3-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-8-fluoro-N-(3-cyanocyclopropyl-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (Intermediate 5):**

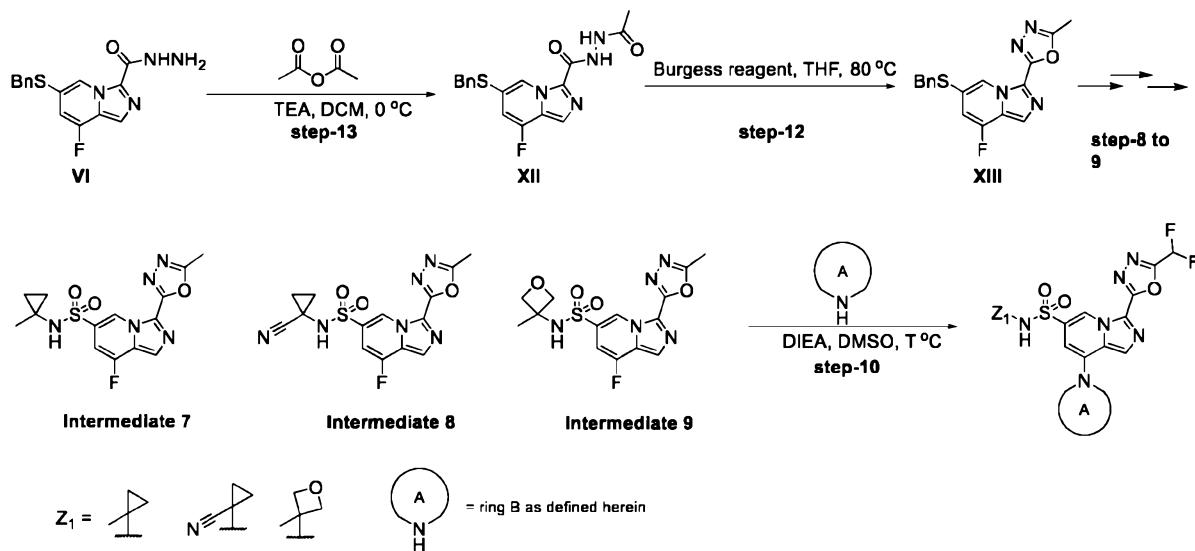


[0345] Intermediate 5 was synthesized in same manner as intermediate 6, while using 1-cyanocyclopropyl-1-amine hydrochloride to afford 3-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-8-fluoro-N-(3-cyanocyclopropyl-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide $[M+H]^+$ 415.02,

5 found 415.40.

[0346] Step-10, providing compounds of Formula I, is further described in the Preparation of Exemplary Compounds section, below.

Scheme 3a



10 **Step-13: Synthesis of N'-acetyl-6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (XII):**

[0347] To a stirred solution of 6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (3.80 g, 12.01 mmol) and TEA (3.65 g, 36.04 mmol) in DCM (200 mL) was added Ac_2O (1.23 g, 12.01 mmol) at 0°C under nitrogen atmosphere. The resulting mixture was warmed and stirred at room temperature for 2 h. The precipitated solids were collected by

filtration and washed with dichloromethane to afford N'-acetyl-6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (4.10 g, crude) as a white solid. MS (ESI) calc'd for (C₁₇H₁₅FN₄O₂S) [M+1]⁺, 359.1; found, 359.0.

Step-12: Synthesis of 2-[6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridin-3-yl]-5-methyl-

5 **1,3,4-oxadiazole (XIII):**

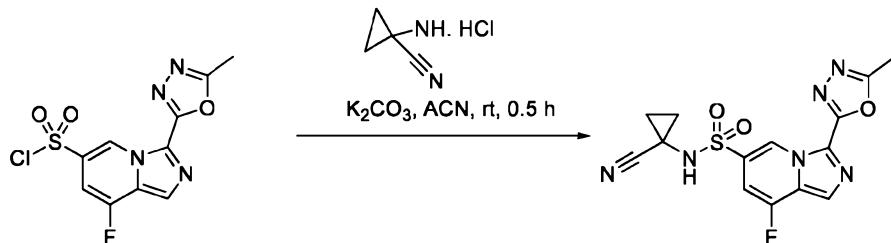
[0348] To a stirred solution of N'-acetyl-6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (4.10 g, 11.44 mmol) in THF (80 mL) was added Burgess reagent (9.54 g, 40.04 mmol) at room temperature. The resulting mixture was stirred at 80 °C for 16 h under nitrogen atmosphere. The resulting mixture was quenched with water and extracted with ethyl acetate.

10 The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 0~50% ethyl acetate in petroleum ether to afford 2-[6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridin-3-yl]-5-methyl-1,3,4-oxadiazole (3.40 g, 79%) as a yellow solid. MS (ESI) calc'd for (C₁₇H₁₃FN₄OS) [M+1]⁺, 341.1; found, 341.0. ¹H NMR (400 MHz, DMSO-d₆) δ 8.87 (s, 1H), 7.90 (s, 1H), 7.40 – 7.33 (m, 2H), 7.31 – 7.18 (m, 4H), 4.32 (s, 2H), 2.65 (s, 3H).

Step-8: Synthesis of 8-fluoro-3-(5-methyl-1,3,4-oxadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonyl chloride:

[0349] To a stirred mixture of 2-[6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridin-3-yl]-5-methyl-1,3,4-oxadiazole (1.00 g, 2.94 mmol) in AcOH (9 mL) and H₂O (3 mL) was added NCS (1.18 g, 8.81 mmol) in portions at room temperature. The resulting mixture was stirred at room temperature for 15 min. The resulting mixture was quenched with water and extracted with dichloromethane. The combined organic layers were washed with saturated NaHCO₃ (aq.) and dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure to afford 8-fluoro-3-(5-methyl-1,3,4-oxadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonyl chloride (1.50 g, crude) as a yellow oil. MS (ESI) calc'd for (C₁₀H₆ClFN₄O₃S) [M+1]⁺, 317.0; found, 316.9.

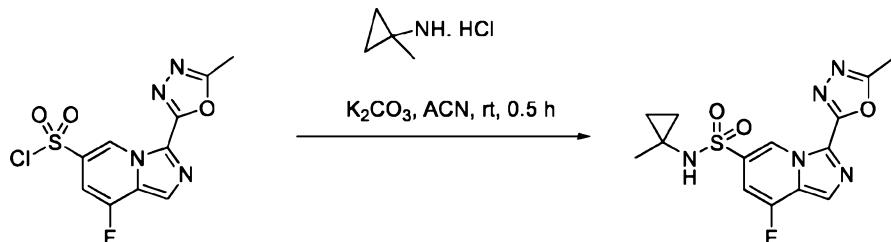
Step-9: Synthesis of N-(1-cyanocyclopropyl)-8-fluoro-3-(5-methyl-1,3,4-oxadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (intermediate 8):



[0350] To a stirred solution of 1-aminocyclopropane-1-carbonitrile hydrochloride (0.56 g, 4.73 mmol) and NMI (3 mL) in MeCN (20 mL) was added a solution of 8-fluoro-3-(5-methyl-1,3,4-

5 oxadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonyl chloride (1.50 g, 4.74 mmol) in MeCN (15 mL) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The resulting mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 0~70% ethyl acetate in petroleum ether to afford N-(1-cyanocyclopropyl)-8-fluoro-3-(5-methyl-1,3,4-oxadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (280 mg, 12%) as a white solid. MS (ESI) calc'd for (C₁₄H₁₁FN₆O₃S) [M+1]⁺, 363.1; found, 363.0. ¹H NMR (400 MHz, DMSO-d₆) δ 9.65 (s, 1H), 9.63 (s, 1H), 8.14 (s, 1H), 7.22 (d, *J* = 9.6 Hz, 1H), 2.69 (s, 3H), 1.53 – 1.46 (m, 2H), 1.42 – 1.35 (m, 2H).

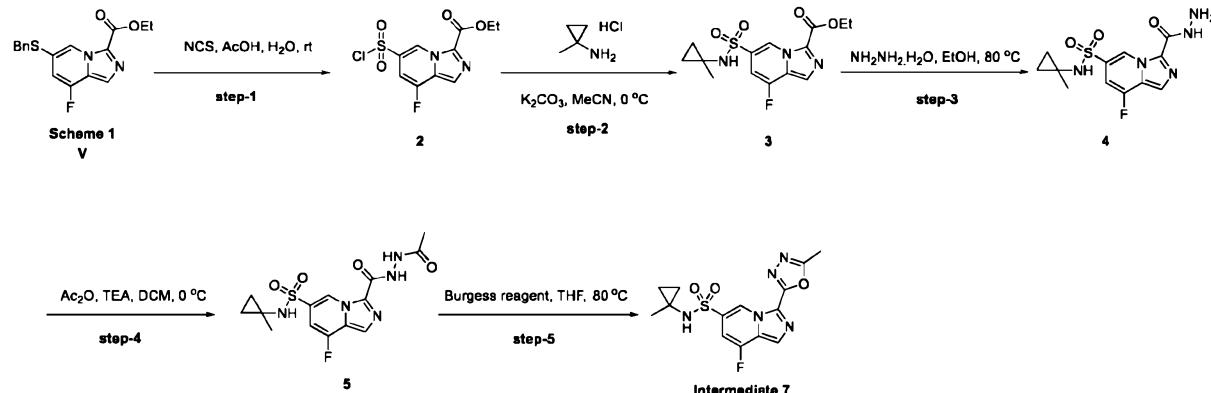
Synthesis of N-(1-methylcyclopropyl)-8-fluoro-3-(5-methyl-1,3,4-oxadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (intermediate 7):



20 [0351] Intermediate 7 was synthesized in same manner as intermediate 8, while using 1-methylcyclopropyl-1-amine hydrochloride to afford 3-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-8-fluoro-N-(3-methylcyclopropyl-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide. MS (ESI) calculated for (C₁₄H₁₄FN₅O₃S) [M+H]⁺, 352.1; found, 352.0. ¹H NMR (400 MHz, DMSO-d₆) δ

9.54 (s, 1H), 8.57 (s, 1H), 8.10 (d, $J = 0.8$ Hz, 1H), 7.18 (dd, $J = 10.0, 1.2$ Hz, 1H), 2.69 (s, 3H), 1.20 (s, 3H), 0.77 – 0.69 (m, 2H), 0.52 – 0.44 (m, 2H).

Scheme 3b



5 **Step-1: Synthesis of ethyl 6-(chlorosulfonyl)-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate (2):**

[0352] To a stirred solution ethyl 6-(benzylsulfanyl)-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate (30 g, 90.80 mmol) in AcOH (180 mL) and H₂O (60 mL) was added NCS (36.38 g, 272.41 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The resulting mixture was basified with saturated NaHCO₃ (aq.). The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under vacuum to afford ethyl 6-(chlorosulfonyl)-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate (34.0 g, 96.45%) as a yellow solid. MS (ESI) calculated for (C₁₀H₈ClFN₂O₄S) [M+1]⁺, 307.0; found, 307.0.

Step-2: Synthesis of ethyl 8-fluoro-6-[(1-methylcyclopropyl)sulfamoyl]imidazo[1,5-a]pyridine-3-carboxylate (3):

[0353] To a stirred solution 1-methylcyclopropan-1-amine hydrochloride (11.93 g, 110.86 mmol) and K₂CO₃ (91.93 g, 665.16 mmol) in ACN (350 mL) was added ethyl 6-(chlorosulfonyl)-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate (34 g, 110.86 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with ice/water at 0 °C and extracted with ethyl acetate. The combined organic layers were

washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 0~42% ethyl acetate in petroleum ether to afford ethyl 8-fluoro-6-[(1-methylcyclopropyl)sulfamoyl]imidazo[1,5-a]pyridine-3-carboxylate (15.8 g, 38%) as a yellow solid. MS (ESI) calculated for (C₁₄H₁₆FN₃O₄S) [M+1]⁺, 342.1; found, 342.1.

Step-3: Synthesis of 8-fluoro-3-(hydrazinecarbonyl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (4):

[0354] To a solution of ethyl 8-fluoro-6-[(1-methylcyclopropyl)sulfamoyl]imidazo[1,5-a]pyridine-3-carboxylate (2.00 g, 5.85 mmol) in EtOH (20 mL) was added NH₂NH₂·H₂O (2 mL). The resulting mixture was stirred at 80 °C for 1 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford 8-fluoro-3-(hydrazinecarbonyl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (1.80 g, crude) as a white solid. MS (ESI) calculated for (C₁₂H₁₄FN₅O₃S) [M+H]⁺, 328.1; found, 328.0.

Step-4: Synthesis of 3-(2-acetylhydrazine-1-carbonyl)-8-fluoro-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (5):

[0355] To a solution of 8-fluoro-3-(hydrazinecarbonyl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (1.30 g, 3.97 mmol) and TEA (1.20 g, 11.91 mmol) in DCM (13 mL) was added Ac₂O (0.53 g, 5.16 mmol) at 0 °C. The resulting mixture was then stirred at 0 °C for 2 h. The reaction mixture was quenched by the addition of water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford 3-(2-acetylhydrazine-1-carbonyl)-8-fluoro-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (1.5 g, crude) as a yellow solid. MS (ESI) calculated for (C₁₄H₁₆FN₅O₄S) [M+H]⁺, 370.1; found, 370.0.

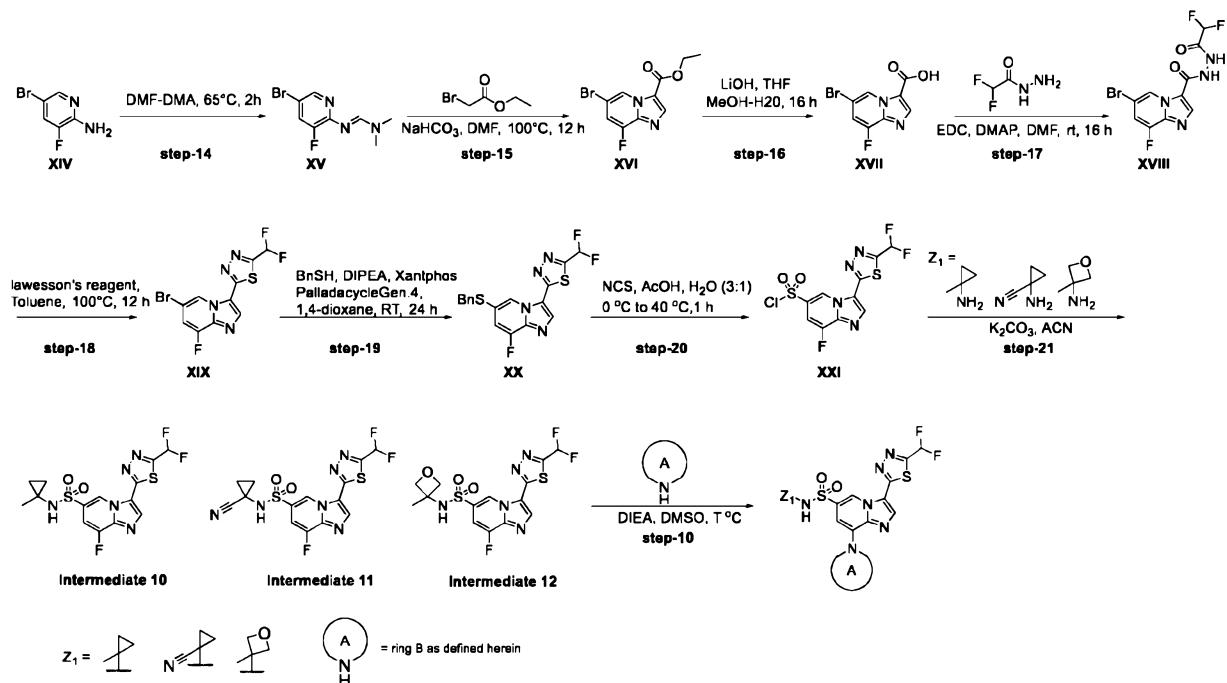
Step-5: Synthesis of 8-fluoro-3-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (PH-IDEA-P1-01-182-3), intermediate 7:

[0356] To a solution of 3-(N'-acetylhydrazinecarbonyl)-8-fluoro-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (1.50 g, 4.06 mmol) in THF (15 mL) was added Burgess reagent (1.90 g, 8.12 mmol). The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting residue was purified by flash column chromatography with 0~75% ethyl acetate in petroleum ether to afford 8-fluoro-3-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (0.69 g, 46% over 3 steps) as a yellow solid. MS (ESI) calculated for (C₁₄H₁₄FN₅O₃S) [M+H]⁺, 352.1; found, 352.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.54 (s, 1H), 8.57 (s, 1H), 8.10 (d, *J* = 0.8 Hz, 1H), 7.18 (dd, *J* = 10.0, 1.2 Hz, 1H), 2.69 (s, 3H), 1.20 (s, 3H), 0.77 – 0.69 (m, 2H), 0.52 – 0.44 (m, 2H).

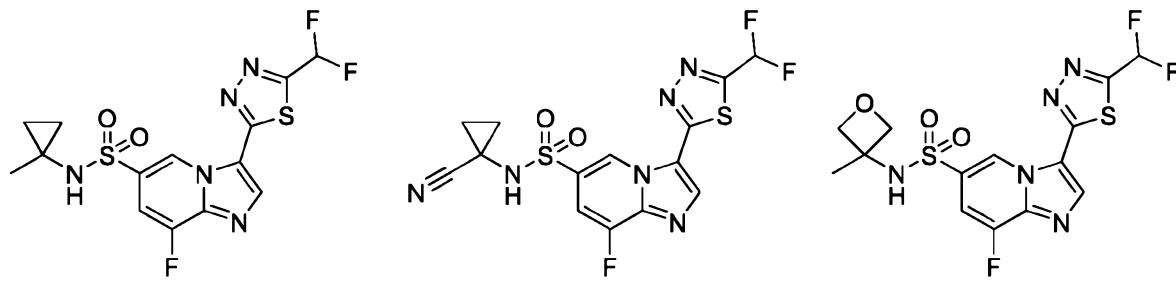
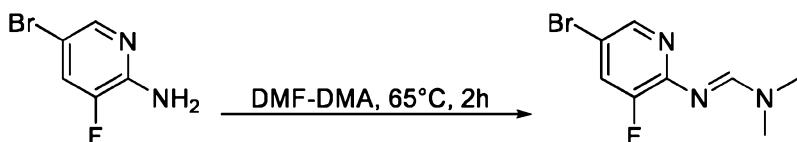
[0357] Step-10, providing compounds of Formula I, is further described in the Preparation of Exemplary Compounds section, below.

15

Scheme 4

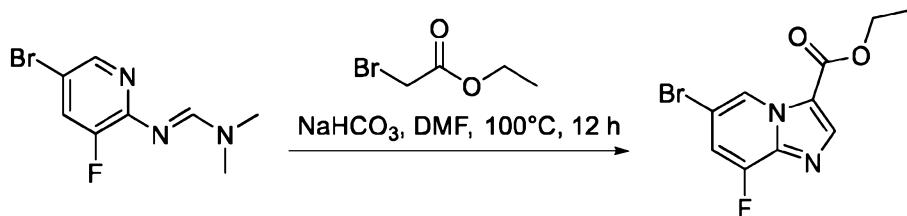


Preparation of Intermediates 10, 11 and 12

**Intermediate 10****Intermediate 11****Intermediate 12****Step 14: Synthesis of (*E*)-*N'*-(5-bromo-3-fluoropyridin-2-yl)-*N,N*-dimethylformimidamide**

[0358] To a stirred solution of 5-bromo-3-fluoropyridin-2-amine (**Source: BLD**) (250

5 g, 1308.893 mmol) in DMF (500 ml) was added 1,1-dimethoxy-*N,N*-dimethylmethanamine (0.869 L, 6544.465 mmol) and the reaction mixture was heated at 65 °C for 1 h. The reaction mixture was quenched with ice cold water (1000 mL) and stirred for 30 min. The solid was precipitated out which was filtered, washed with water (1000 mL) and dried under vacuum to afford (*E*)-*N'*-(5-bromo-3-fluoropyridin-2-yl)-*N,N*-dimethylformimidamide (250 g, 77.62%) as a brown solid. MS ESI calculated for C₈H₉BrFN₃ [M+H]⁺ 246.0, found 246.05.

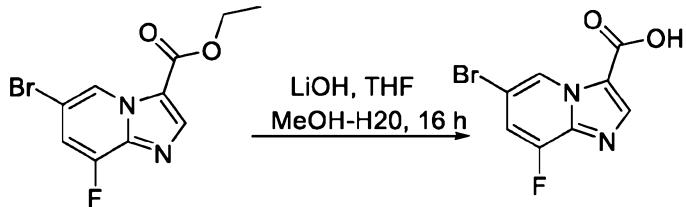
Step 15: Synthesis of ethyl 6-bromo-8-fluoroimidazo[1,2-a]pyridine-3-carboxylate

[0359] To a stirred solution of (*E*)-*N'*-(5-bromo-3-fluoropyridin-2-yl)-*N,N*-dimethylformimidamide (250 g, 1015.917 mmol) in DMF (2500 mL)

15 were added NaHCO₃ (128.016 g, 1523.876 mmol) and ethyl 2-bromoacetate (337.073 mL, 3047.752 mmol) and the reaction mixture was stirred at 100 °C for 12 h. The reaction mixture was quenched with ice cold water (1000 mL) and stirred for 30 min. The solid was precipitated out which was filtered, washed with water (1000 mL) and dried under vacuum

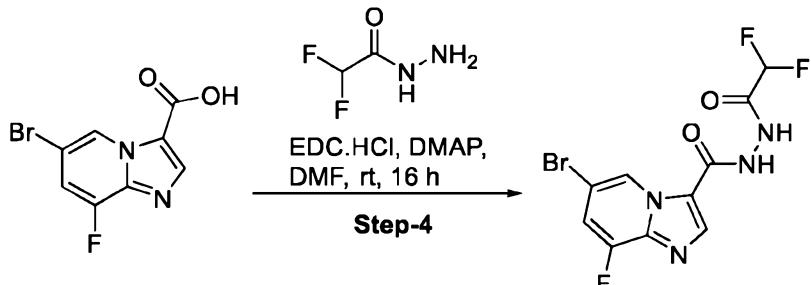
to afford ethyl 6-bromo-8-fluoroimidazo[1,2-*a*]pyridine-3-carboxylate (120 g, 41.14%) as a brown solid. MS ESI calculated for C₁₀H₈BrFN₂O₂ [M+H]⁺ 286.98, found 287.11.

Step 16: Synthesis of 6-Bromo-8-fluoroimidazo[1,2-*a*]pyridine-3-carboxylic acid



- 5 [0360] To a stirred solution of ethyl 6-bromo-8-fluoroimidazo[1,2-*a*]pyridine-3-carboxylate (125 g, 457.773 mmol) in THF (875 ml): Water (375 ml) was added lithium hydroxide (21.925 g, 915.546 mmol) at 0 °C and stirred for 16 h at rt. The reaction mixture was diluted with water (500 mL), acidified with 1N HCl (500 mL) and extracted with EtOAc (3x500 mL). The combined organic layers were separated, washed with brine solution (500 mL), dried over
10 anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get 6-bromo-8-fluoroimidazo[1,2-*a*]pyridine-3-carboxylic acid (80 g, 67.47 %) as an off white solid. MS ESI calculated for C₈H₄BrFN₂O₂ [M+H]⁺ 258.94, found 259.17 and 261.06.

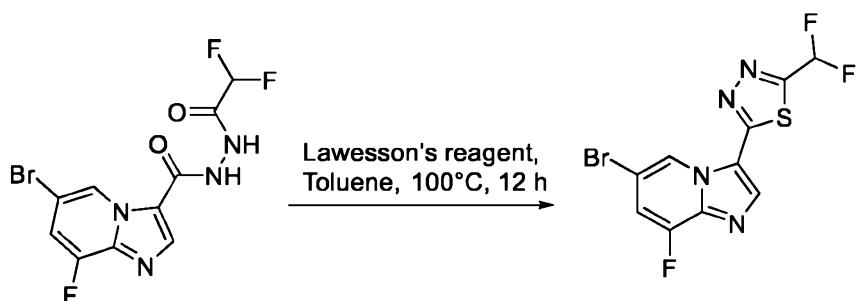
Step 17: Synthesis of 6-Bromo-N-(2,2-difluoroacetyl)-8-fluoroimidazo[1,2-*a*]pyridine-3-carbohydrazide



- 15 [0361] To a stirred solution of 6-bromo-8-fluoroimidazo[1,2-*a*]pyridine-3-carboxylic acid (14 g, 54.047 mmol) in DMF (140 mL) was added 1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide.hydrochloride (15.541 g, 81.070 mmol), 1-hydroxybenzotriazole (3.651 g, 1.737 mmol) and the reaction mixture was stirred for 15 min.
20 Subsequently, 2,2-difluoroacetohydrazide (8.923 g, 81.070 mmol) and triethylamine (22.6 ml, 162.141 mmol) was added and the reaction mixture was stirred for 16 h at rt. The reaction mixture was diluted with water (500 mL) and extracted with EtOAc (2 x 300 mL). The

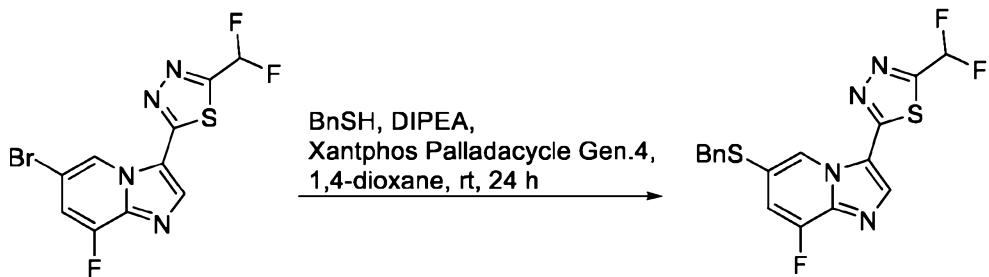
combined organic layers were separated, washed with brine solution (200 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude product as an oil. To this crude was added water (100 mL) and stirred for 30 min. The solid was precipitated out which was filtered, washed with water (100 mL) and dried under vacuum to afford 6-bromo-N'-(2,2-difluoroacetyl)-8-fluoroimidazo[1,2-*a*]pyridine-3-carbohydrazide (6 g, 31.62%) as a white solid. MS ESI calculated for C₁₀H₆BrF₃N₄O₂ [M+H]⁺ 350.96, found 351.11.

Step 18: Synthesis of 2-(6-bromo-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole



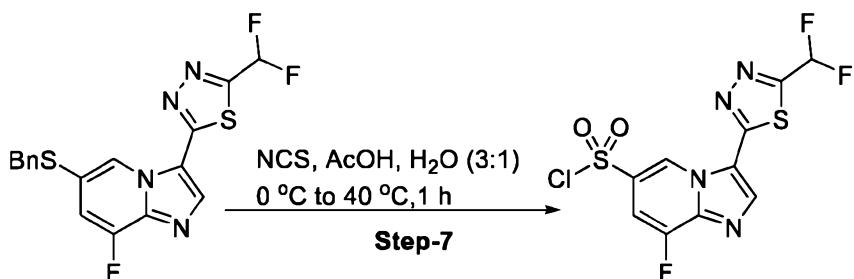
[0362] A solution of 6-bromo-N'-(2,2-difluoroacetyl)-8-fluoroimidazo[1,2-*a*]pyridine-3-carbohydrazide (6 g, 17.090 mmol) in dry Toluene (60 ml) was degassed with Argon, and to it was added 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 1,3-dioxide (12.726g, 34.180 mmol) and the reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with water (250 mL) and extracted with EtOAc (2 x 300 mL). The combined organic layers were separated, washed with brine solution (250 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product as a brown solid. The crude was purified by column chromatography using silica gel (100-200) and eluted with 50% EtOAc/Hexane as a gradient. The product was eluted at 30% EtOAc/Hexane. The pure fractions were collected and concentrated under reduced pressure to afford 2-(6-bromo-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (4 g, 67%) as a green solid. MS ESI calculated for C₁₀H₆BrF₃N₄S₁ [M+H]⁻ 348.93, found 349.11 and 351.07

Step 19: Synthesis of 2-(6-(benzylthio)-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole



[0363] To a stirred solution of 2-(6-bromo-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (13g, 37.236 mmol) and phenylmethanethiol (8.726 ml, 74.471 mmol) in 1,4-Dioxane (130 mL) was added DIPEA (19.458 mL, 111.707 mmol), and the reaction mixture was degassed for 5 min. Subsequently, to it was added XantPhos Pd G4 (3.583 mg, 3.724 mmol) and stirred at rt for 24 h. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (2 x 250 mL). The combined organic layers were separated, washed with brine solution (250 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product as an oil. The crude was purified by column chromatography using silica gel (100-200) and eluted with 30% EtOAc/Hexane. The pure fractions were collected and concentrated under reduced pressure to afford 2-(6-(benzylthio)-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-thiadiazole (9 g, 61.59 %) as a yellow solid. MS ESI calculated for C₁₇H₁₁F₃N₄S₂ [M+H]⁺ 393.04, found 393.11.

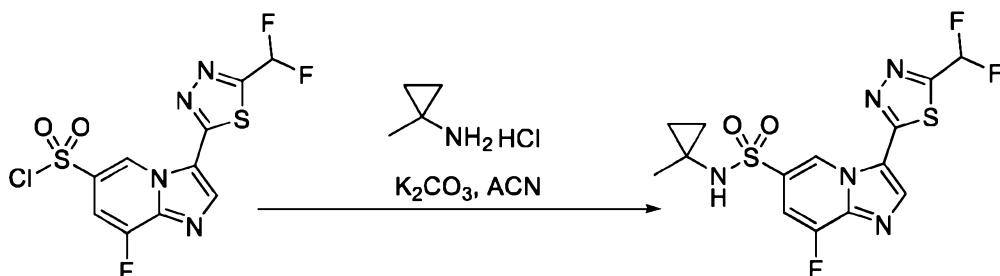
15 Step 20: Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoroimidazo[1,2-*a*]pyridine-6-sulfonyl chloride



[0364] To a dried 50 mL single neck RBF, was added 2-[6-(benzylsulfanyl)-8-fluoroimidazo[1,2-*a*]pyridin-3-yl]-5-(difluoromethyl)-1,3,4-thiadiazole (10 g, 25.483 mmol), in a mixture of Acetic acid and water (3:1; 80 mL). The reaction mixture was placed under N₂ and stirred at rt for 5 minutes to afford a yellow solution (if the material does not dissolve, the

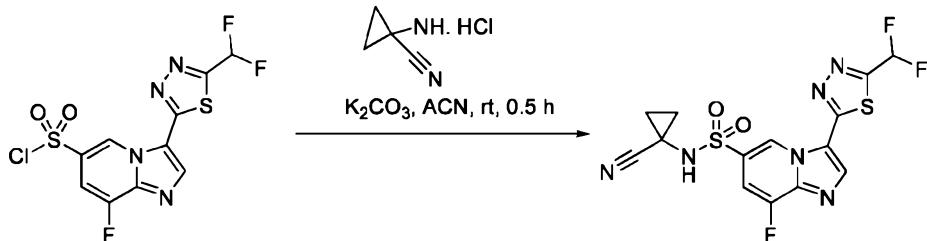
mixture was sonicated for several minutes). To the reaction mixture was subsequently added 1-chloropyrrolidine-2,5-dione (10.208g, 76.449 mmol) portion wise. The reaction mixture was heated to 40°C for 30 min. The reaction mixture was poured into DCM (200 ml). The organic fraction was washed with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over Sodium sulfate, filtered, 5 and evaporated, giving impure 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoroimidazo[1,2-*a*]pyridine-6-sulfonyl chloride (9 g, 95.78 %) as a reddish orange oil that eventually solidified to a reddish orange solid. The reddish orange film thus obtained was used in subsequent reactions without additional purification. MS ESI calculated for C₁₀H₄ClF₃N₄O₂S₂ [M+H]⁺ 368.94, found 369.29 and 371.10.

10 **Step 21: Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(1-methylcyclopropyl)imidazo[1,2-*a*]pyridine-6-sulfonamide (Intermediate 10)**



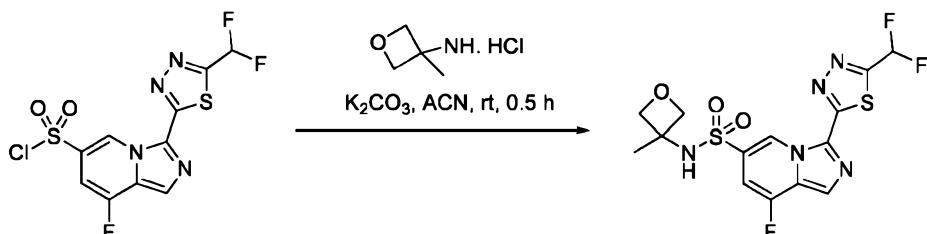
[0365] Procedure: To a stirred solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoroimidazo[1,2-*a*]pyridine-6-sulfonyl chloride (9 g, 24.408 mmol) in ACN (90 mL) was 15 added potassium carbonate (20.240g, 146.447mmol) followed by 1-methylcyclopropan-1-amine hydrochloride (2.888 g, 26.849 mmol) and stirred at rt for 4h. The reaction mixture was diluted with water (250 mL) and extracted with EtOAc (2x300 mL). The combined organic layers were separated, washed with brine solution (200 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude product as a solid. The crude was purified 20 by column chromatography using silica gel (100-200) and eluted with 50% EtOAC/Hexane as a gradient. The product was eluted at 30% EtOAC/Hexane. The pure fractions were collected and concentrated under reduced pressure to afford 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(1-methylcyclopropyl)imidazo[1,2-*a*]pyridine-6-sulfonamide (6 g, 60.94%) as a brown solid. MS ESI calculated for C₁₄H₁₂F₃N₅O₂S₂ [M+H]⁺ 404.04, found 404.28. ¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 9.87 (d, 1H), 8.78 (s, 1H), 8.57 (s, 1H), 7.72 (t, 1H), 7.69 (dd, 1H), 25 1.18 (s, 3H), 0.72(dd, 2H), 0.5 (dd, 2H).

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(1-cyanocyclopropyl)imidazo[1,2-*a*]pyridine-6-sulfonamide (Intermediate 11):



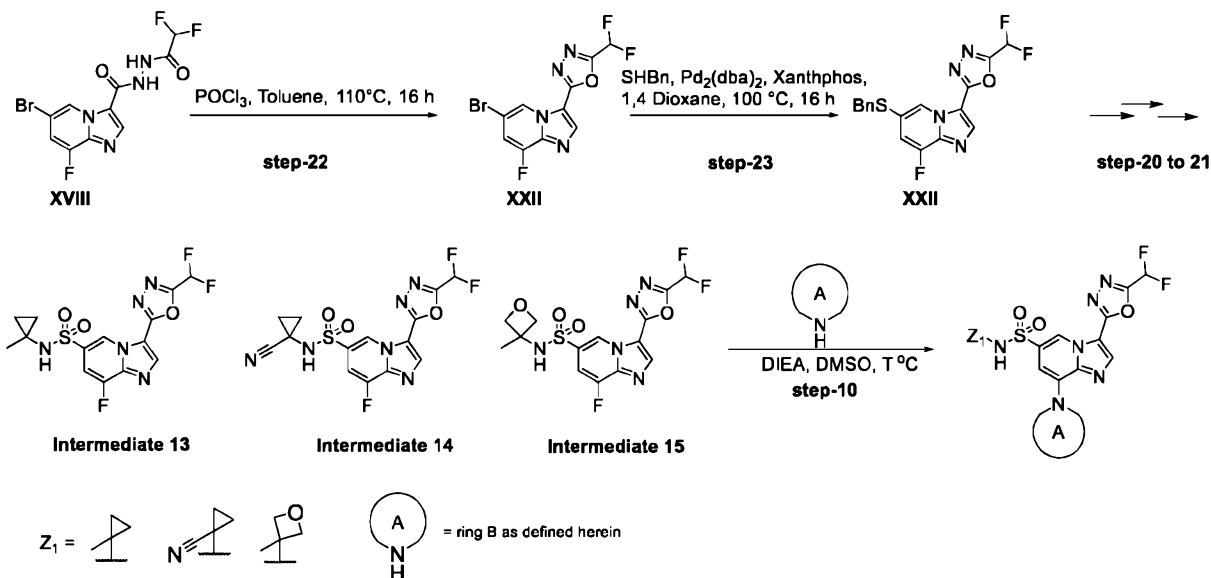
[0366] Intermediate 11 was synthesized in same manner as intermediate 10, while using 1-cyanocyclopropyl-1-amine hydrochloride to afford 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(1-cyanocyclopropyl)imidazo[1,2-*a*]pyridine-6-sulfonamide $[M+H]^+$ 415.02, found 415.28.

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(3-methyloxetan-3-yl)imidazo[1,2-*a*]pyridine-6-sulfonamide (Intermediate 12):



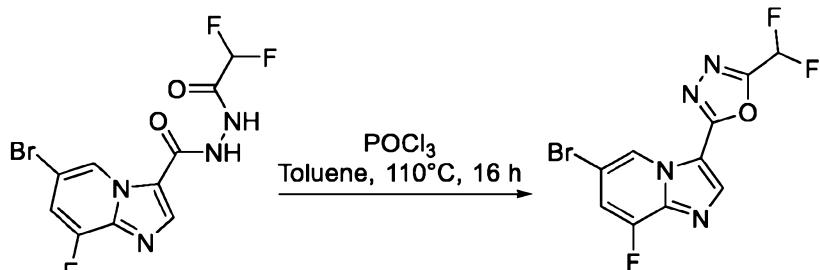
[0367] Intermediate 12 was synthesized in same manner as intermediate 10, while using 1-methyloxetan-1-amine hydrochloride to afford 3-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]-8-fluoro-N-(3-methyloxetan-3-yl)imidazo[1,2-*a*]pyridine-6-sulfonamide $[M-H]^-$ 418.03, found 418.18.

[0368] Step-10, providing compounds of Formula I, is further described in the Preparation of Exemplary Compounds section, below.

Scheme 5

Step 22: Synthesis of 2-(6-Bromo-8-fluoroimidazo[1,2-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (XXII)

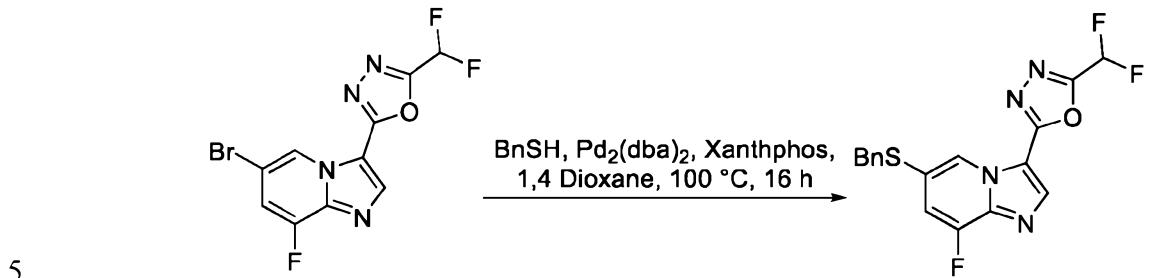
5



[0369] To a stirred solution of 6-bromo-*N'*-(2,2-difluoroacetyl)-8-fluoroimidazo[1,2-*a*]pyridine-3-carbohydrazide (2 g, 5.697 mmol) in Toluene (40 mL) was added POCl_3 (8 mL) at 0 °C and stirred at 110 °C for 16 h. After completion of the reaction, the reaction mixture was diluted with water (200 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were separated, washed with brine solution (100 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get a crude which was purified by column chromatography using silica gel (100-200) and eluted with 25% EtOAC/Hexane as a gradient. The pure fractions were collected and concentrated under reduced pressure to afford methyl 2-(6-bromo-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (1.2 g, 63.25%) as a yellow solid. MS ESI calculated for $\text{C}_{10}\text{H}_5\text{BrF}_3\text{N}_4\text{O}$

$[M+H]^+$ 332.96, found 333.26. **¹H NMR (400 MHz, CDCl₃):** δ (ppm) 9.45 (s, 1H), 8.37-8.93 (m, 1H), 7.36-7.39 (m, 1H), 6.96 (brt, J = 51.6 Hz, 1H).

Step 23: Synthesis of 2-(6-(Benzylthio)-8-fluoroimidazo[1,2-*a*] pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (XXIII)

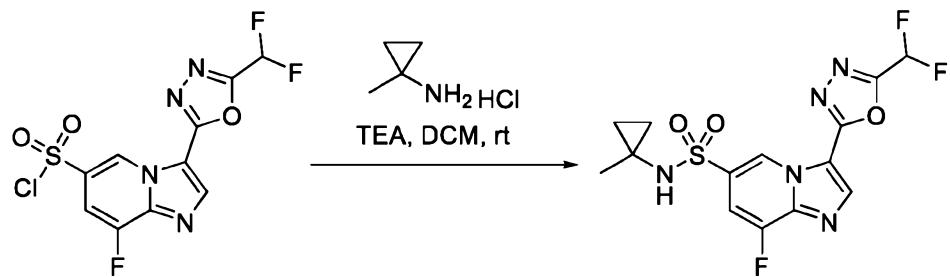


[0370] To a stirred solution of 2-(6-bromo-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (0.6 g, 1.801 mmol) and Benzyl mercaptan (0.329 mL, 2.702 mmol) in 1,4 Dioxane (12 mL) was added DIPEA (0.917 mL, 5.404 mmol) at rt and the reaction mixture was degassed with N₂ for 10 min. Subsequently, Xanthphos (0.208 g, 10 0.360 mmol) and Pd₂(dba)₃ (0.165 g, 0.180 mmol) were added, and the reaction mixture was degassed with N₂ for additional 5 min. The reaction mixture was stirred at 90 °C for 16 h. After completion of the reaction, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were separated, washed with brine solution (100 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product as an oil. The crude was purified by column chromatography using silica gel (100-200) and eluted with 30% EtOAc/Hexane as a gradient. The pure fractions were collected and concentrated under reduced pressure to afford 2-(6-(benzylthio)-8-fluoroimidazo[1,2-*a*] pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (0.5 g, 73.75%) as a brown solid. MS ESI calculated for C₁₇H₁₂F₃N₄OS [M+H]⁺ 377.07, found 377.42.

1H NMR (400 MHz, CDCl₃): δ (ppm) 9.12-9.13 (m, 1H), 8.33 (s, 1H), 7.26-7.29 (m, 4H), 7.26-7.23 (m, 1H), 7.11-7.08 (m, 1H), 6.96 (s, 1H), 4.16 (s, 2H).

[0371] Step-20 for Scheme 5 was performed as described in Step 8 for Scheme 2.

Step 21: Synthesis of 2-(6-(Benzylthio)-8-fluoroimidazo[1,2-*a*] pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Intermediate 13)

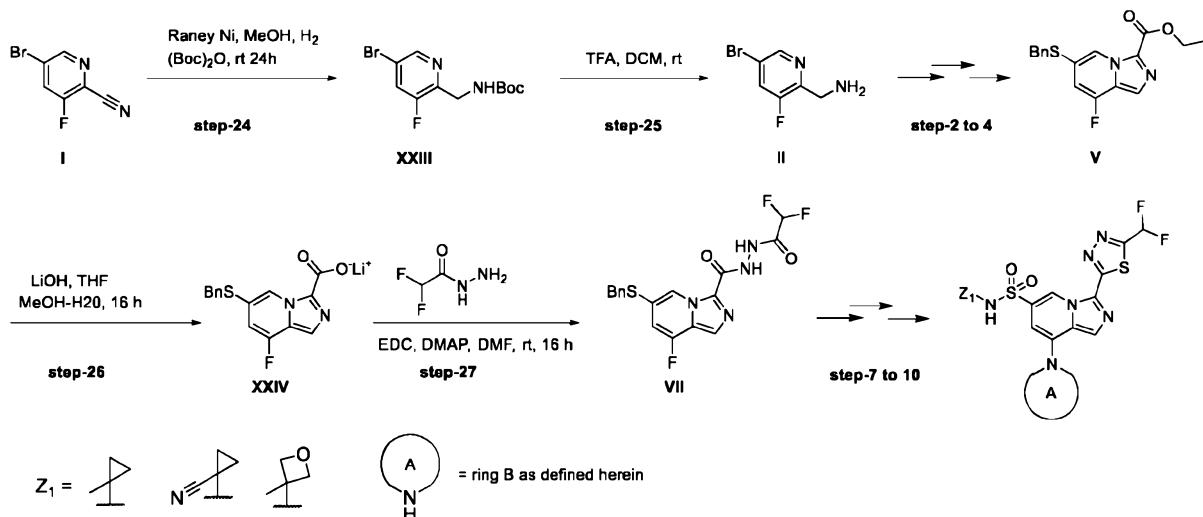


[0372] To a stirred solution of 3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-fluoroimidazo[1,2-a]pyridine-6-sulfonyl chloride (0.45 g, 1.276 mmol) in DCM (9 mL) was added 1-methylcyclopropan-1-amine hydrochloride (0.412 g, 3.828 mmol) followed by

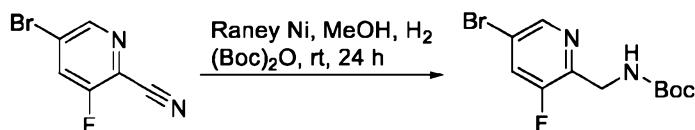
- 5 TEA (0.895 mL, 6.380 mmol) and stirred at rt for 4 h. After completion of the reaction, the reaction mixture was diluted with water (100 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were separated, washed with brine solution (100 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product as an oil. The crude was purified by column chromatography using silica gel (100-200)
- 10 and eluted with 50% EtOAc/Hexane as a gradient. The pure fractions were collected and concentrated under reduced pressure to afford 3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-fluoro-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (0.25 g, 50.58%) as an off-white solid. MS ESI calculated for $C_{14}H_{13}F_3N_5O_3S$ [M+H]⁺ 388.07, found 388.23. **¹H NMR (400 MHz, CDCl₃):** δ (ppm) 9.85-9.86 (m, 1H), 8.50 (s, 1H), 7.53-7.55 (m, 1H), 6.98 (brt, *J* = 51.6 Hz, 1H), 1.37 (s, 3H), 0.86-0.87 (m, 2H), 0.61-0.63 (m, 2H).
- 15

Scheme 6

[0373] Scheme 1 synthesis alternative to make Intermediates 1, 2, and 3.

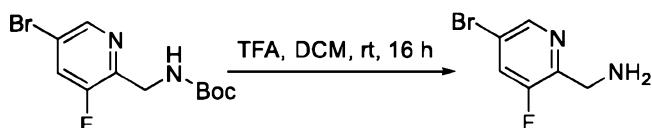


Step-24: Synthesis of tert-butyl ((5-bromo-3-fluoropyridin-2-yl)methyl)carbamate XXIII:



[0374] To a stirred solution of 5-bromo-3-Fluoropicolinonitrile (450 g, 2238.8 mmol) (Angene 5 Chemicals) in MeOH (5000 mL) was added Raney Ni (225 g, 50% Wt/Wt) followed by addition of Boc anhydride (976.139 g, 4477.703 mmol) at room temperature. The reaction mixture was stirred under hydrogen atmosphere (40 psi) using autoclave and stirred at room temperature for 16 h. The reaction mixture was filtered through celite bed, washed with methanol (2000 mL). The filtrate was concentrated under reduced pressure. Crude was purified by column chromatography using silica gel (100-200 mesh) and the product was eluted at 1-5% EtOAc/pet ether. The pure fractions were collected and concentrated under reduced pressure to afford *tert*-Butyl ((5-bromo-3-fluoropyridin-2-yl)methyl)carbamate (220 g, 32.20%) as an off white solid. MS ESI calculated for $\text{C}_{11}\text{H}_{14}\text{BrFN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 305.02, found 305.18.

Step-25: Synthesis of (5-Bromo-3-fluoropyridin-2-yl)methanamine II:



[0375] To a stirred solution of *tert*-butyl ((5-bromo-3-fluoropyridin-2-yl)methyl)carbamate (220 g, 723.684 mmol) in DCM (500 mL) was added TFA (220 mL) at

room temperature and stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure to afford (5-bromo-3-fluoropyridin-2-yl)methanamine as TFA salt (160 g, 73%) as pale brown semi solid. MS ESI calculated for $C_6H_6BrFN_2 [M+H]^+$ 204.97, found 205.11.

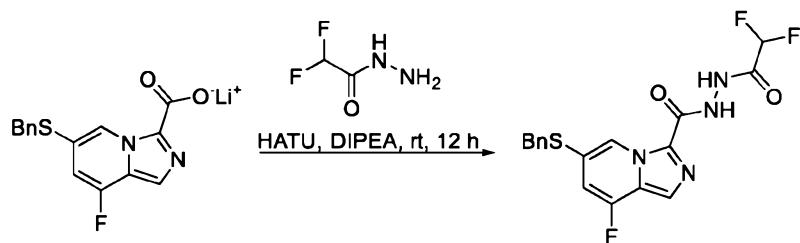
5 [0376] Steps-2 to 4 for Scheme 6 were performed as described in Scheme 1.

Step-26: Synthesis of lithium 6-(benzylthio)-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate XXIV:



[0377] To a stirred solution of ethyl 6-(benzylthio)-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate (50 g, 151.34 mmol) in THF:MeOH:H₂O (3:3:1) (150 mL:150 mL:50 mL) 10 was added Lithium hydroxide monohydrate (9.52 g, 227.01 mmol) and the reaction mixture was stirred rt for 3 h. The reaction mixture was concentrated under reduced pressure and co-distilled with toluene to get lithium 6-(benzylthio)-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate (45 g, 96.46%) as an off white solid. MS ESI calculated for $C_{15}H_{11}FN_2O_2S [M+H]^+$ 303.05, found 15 303.31.

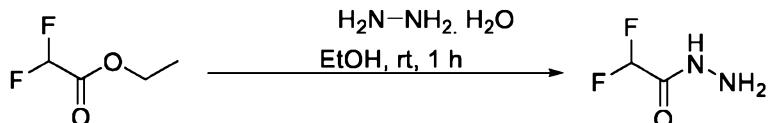
Step-27: Synthesis of 6-(benzylthio)-N'-(2,2-difluoroacetyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide VII:



[0378] To a stirred solution of lithium 6-(benzylthio)-8-fluoroimidazo[1,5-a]pyridine-3-carboxylate (45 g, 145.98 mmol) in DMF (180 mL, 4V) 20 were added HATU (61.05 g, 160.58 mmol), 2,2-difluoroacetohydrazide (17.66 g, 160.58 mmol) and DIPEA (59.1 mL, 321.1 mmol) and the reaction mixture was stirred at rt for 12 h. The reaction mixture was diluted with water (600 mL) and extracted with EtOAc (2x500 mL). The combined organic layer was washed

with brine solution (500 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure. The crude was purified by column chromatography using silica gel (100-200) and the product was eluted at 50% EtOAc/Hexane. The pure fractions were collected and concentrated under reduced pressure to afford 6-(benzylthio)-N'-(2,2-difluoroacetyl)-8-fluoroimidazo[1,5-a]pyridine-3-carbohydrazide (30 g, 52.11%) as a yellow solid. MS ESI calculated for $C_{17}H_{13}F_3N_4O_2S [M+H]^+$ 395.07, found 395.33.

Step-27a: Synthesis of 2,2-difluoroacetohydrazide:



[0379] To a solution of ethyl 2,2-difluoroacetate (25 g, 201.467 mmol, 1 equiv.) in Ethanol (250 mL) were added Hydrazine hydrate, 100% (12.910 g, 402.933 mmol, 2 equiv.) at room temperature. Then the reaction mixture was stirred rt for 1 h. The progress of the reaction was monitored by TLC. TLC showed completion of SM. The reaction mixture was concentrated under reduced pressure. The crude was purified by column chromatography using silica gel (100-200) and eluted with 2% MeOH/DCM. The pure fractions were collected and concentrated under reduced pressure to afford 2,2-difluoroacetohydrazide (20.1 g, 90.65%) as a Pale yellow liquid. MS ES⁺ calculated for $C_2H_4F_2N_2O [M+H]^+$ 111.04, found 111.14.

[0380] Steps-7 to 10 for Scheme 6 were performed as described in Scheme 1.

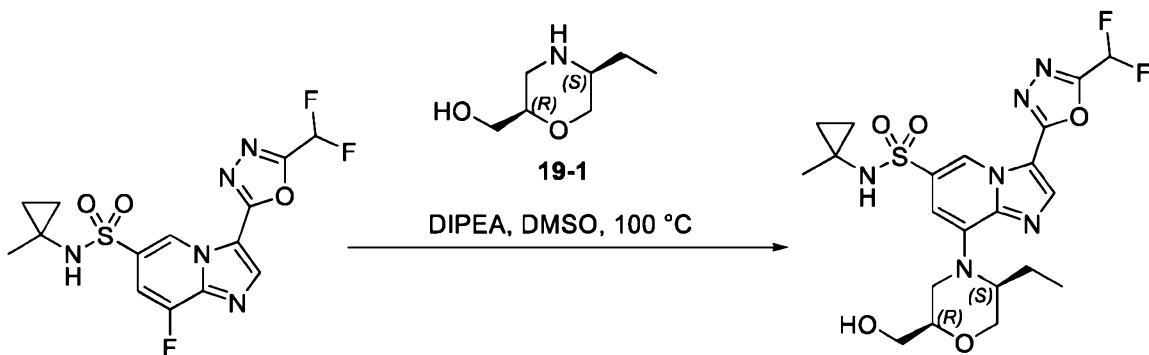
Preparation of Exemplary Compounds

Step-10: Synthestic procedure

20

Example 19

Step 10: Synthesis of 2-(6-(Benzylthio)-8-fluoroimidazo[1,2-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole



[0381] To a stirred solution of 3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-fluoro-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (0.2 g, 0.516 mmol) and ((2*R*,5*S*)-5-ethylmorpholin-2-yl)methanol (Compound 19-1) (0.225 g, 1.549 mmol) in DMSO (4 mL)

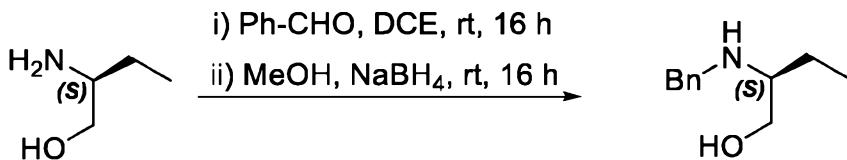
5 was added DIPEA (0.438 mL, 2.582 mmol) at rt. The reaction mixture was stirred at 80 °C for 48 h. After completion of the reaction, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were separated, washed with brine solution (20 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product as an oil. The crude was purified by Prep HPLC.

10 Purification conditions: ANL-MCL-5-PREP-015, Column Name XSCSH PACKED C18 (25*150 mm) 5 µm, Column No. PACKED, Mobile Phase-A AMMONIUM BICARBONATE IN WATER, Mobile Phase-B ACN, Gradient program (T/%B) 0/40,2/40,18.40/45,18.41/100,21/100,21.01/40,25/40, Flow Rate (mL/minute) 21,

SOLUBILITY: ACN, Fraction Volume: 150 mL. Fraction was collected and concentrated under 15 reduced pressure and lyophilized to afford 3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2*R*,5*S*)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide (0.111 g, 41.94%) as an off-white solid. MS ESI calculated for C₂₁H₂₇F₂N₆O₅S [M+H]⁺ 513.17, found 513.36. **¹H NMR (400 MHz, DMSO-d₆)**: δ (ppm) 9.34-9.35 (m, 1H), 8.54 (s, 1H), 8.46 (s, 1H), 6.28 (brt, *J* = 51.2 Hz, 1H), 6.93-6.94 (m, 1H), 5.13 (brs, 1H), 4.88-6.92 (m, 1H), 3.91-3.96 (m, 1H), 3.83-3.86 (m, 1H), 3.50-3.68 (m, 4H), 3.14-3.19 (m, 1H), 1.75-1.83 (m, 1H), 1.36-1.43 (m, 1H), 1.11 (s, 3H), 0.67-0.73 (m, 5H), 0.43-0.47 (m, 2H).

Synthesis of Compound 19-1

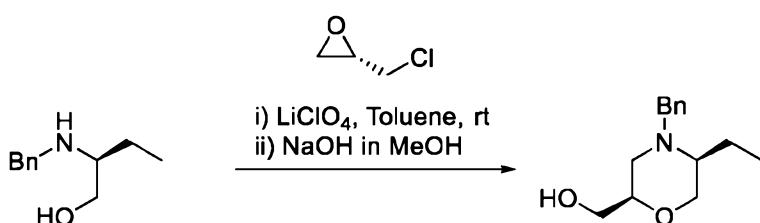
Synthesis of 2-(6-(Benzylthio)-8-fluoroimidazo[1,2-a]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole



[0382] To a stirred solution of (*S*)-2-aminobutan-1-ol (100 g, 1121.879 mmol) in DCE (1000 mL) was added Benzaldehyde (178.379 g, 1682.818 mmol) and stirred at 90 °C for 16 h. Then reaction mixture was cooled to 0°C and concentrated RM. Then dissolve in MeOH (2000

5 mL) and added Sodium borohydride (85.263 g, 2243.757 mmol) stirred at RT for 2 h. After completion of the reaction, the reaction mixture was quenched with ammonium chloride and diluted with water (1000 mL) and extracted with EtOAc (2 x 500 mL). The combined organic layers were separated, washed with brine solution (500 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude product as an oil. The 10 crude was purified by column chromatography using silica gel (100-200) and eluted with 5%MeOH in DCM as a gradient. The pure fractions were collected and concentrated under reduced pressure to afford methyl (*S*)-2-(benzylamino)butan-1-ol (100 g, 49.72%) as a white solid. MS ESI calculated for C₁₁H₁₈NO [M+H]⁺ 180.14, found 180.16. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.39-7.46 (m, 2H), 7.28-7.38 (m, 3H), 4.77 (brs, 1H), 3.88-4.00 (m, 2H), 3.72-15 3.76 (m, 1H), 3.46-3.52 (m, 1H), 2.72-2.78 (m, 2H), 1.55-1.70 (m, 2H), 0.91 (t, J = 7.6 Hz, 1H). Note: Exchangeable protons not observed.

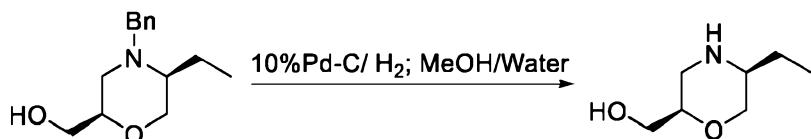
Synthesis of 2-(6-(Benzylthio)-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole



20 [0383] To a stirred solution of (*S*)-2-(benzylamino)butan-1-ol (101 g, 563.427 mmol) and (*S*)-2-(chloromethyl)oxirane (66.266 mL, 845.141 mmol) in Toluene (1000.000 mL) was added Lithium perchlorate (89.585 g, 845.141 mmol) at rt. The reaction mixture was stirred at room temperature for 24 h. Subsequently, NaOH (45.074 g, 1126.855 mmol) dissolved in 250 mL of MeOH, was added to the reaction mixture slowly and the reaction mixture was stirred at

room temperature for 2 days. After completion of the reaction, the reaction mixture was diluted with water (1000 mL) and extracted with EtOAc (2 x 800 mL). The combined organic layers were separated, washed with brine solution (500 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get the crude compound. The crude 5 compound was purified by column chromatography using silica gel (100-200) and eluted with 30% EtOAc/Hexane as a gradient. The product was eluted at 30% EtOAc/Hexane. The pure fractions were collected and concentrated under reduced pressure to afford ((5*S*)-4-benzyl-5-ethylmorpholin-2-yl)methanol (50 g, 37.71%) as a white solid. MS ESI calculated for C₁₄H₂₂NO₂ [M+H]⁺ 236.17, found 236.38. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.27-7.35 (m, 10 4H), 7.22-7.24 (m, 1H), 3.87-3.90 (m, 4H), 3.58-3.59 (m, 2H), 2.49-2.54 (m, 1H), 2.40-2.44 (m, 1H), 2.33-2.37 (m, 1H), 2.38-2.39 (m, 1H), 1.58-1.75 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H).

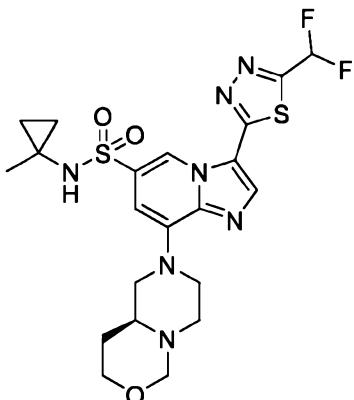
Synthesis of 2-(6-(Benzylthio)-8-fluoroimidazo[1,2-*a*]pyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole (Compound-19-1)



15 [0384] To a stirred solution of ((5*S*)-4-benzyl-5-ethylmorpholin-2-yl) methanol (25 g, 106.383 mmol) in MeOH (125 mL) and water (125 mL) was added Pd/C (15 g) at rt. The reaction mixture was stirred at room temperature under hydrogen balloon atmosphere for 16 h. Reaction progress was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was filtered through a celite pad with MeOH and concentrated under reduced pressure to afford ((5*S*)-5-ethylmorpholin-2-yl) methanol (15 g, 97.11%) as an off-white gummy liquid. ¹H NMR (400 MHz, CDCl₃): δ (ppm) 4.55 (m, 1H), 3.26-3.51 (m, 5H), 2.64-2.66 (m, 2H), 2.44-2.51 (m, 1H), 1.36-1.50 (m, 2H), 0.84-0.86 (m, 3H).
20

Example 36

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

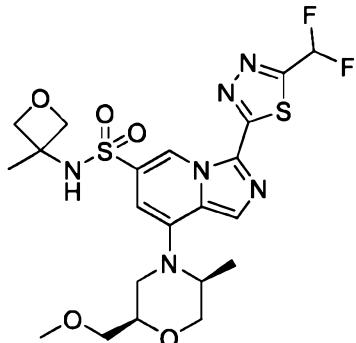


[0385] To a stirred solution of 3-(5-(Difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(1-methylcyclopropyl)imidazo[1,2-*a*]pyridine-6-sulfonamide (Intermediate 10) (150 mg, 0.372 mmol) in DMSO (2 mL) were added (*R*)-octahydropyrazino[2,1-*c*][1,4]oxazine (**Source: BLD**) (158.630 mg, 1.116 mmol), and DIPEA (0.390 mL, 2.231 mmol) at room temperature.

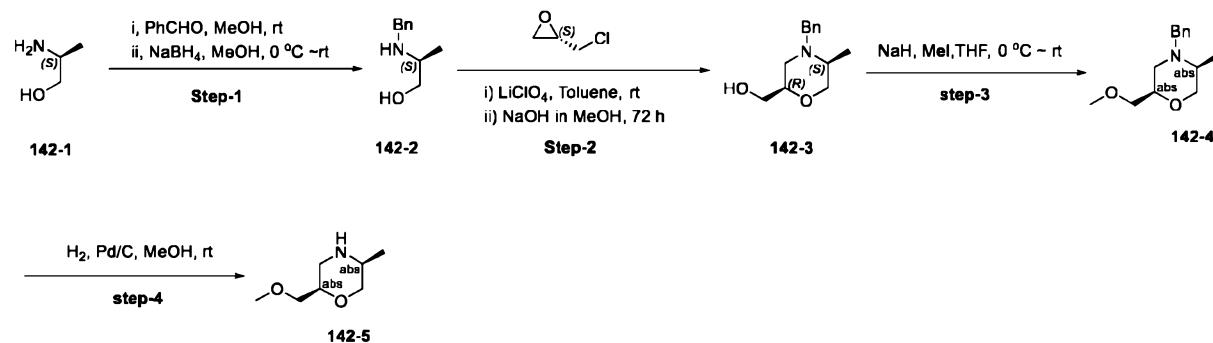
The reaction mixture was heated to 100 °C and stirred at same temperature for 16 h. After completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were separated, washed with brine solution (20 mL), dried over anhydrous sodium sulphate, filtered and filtrate was concentrated under reduced pressure to give the crude compound. The crude was purified by Prep HPLC. Purification conditions: COLUMN:- XS CSH (150*25 mm) 10□m BUFFER A:- ABC BUFFER B: Acetonitrile, MOBILE PHASE CONDITIONS (% of B):-0/20,2/20,12/71,12.72/100,20/20 FLOW-21 MI ANL-MCL5-APMS-003, Fraction was collected and concentrated under reduced pressure and lyophilized to afford (*R*)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)-N-(1-methylcyclopropyl)imidazo[1,2-*a*]pyridine-6-sulfonamide (66 mg, 33.77%) as an off white solid. MS ESI calculated for C₂₁H₂₆F₂N₇O₃S₂ [M+H]⁺ 526.15, found 526.43. **¹H NMR (400 MHz, DMSO-d₆):** δ (ppm) 9.65 (d, *J* = 1.2 Hz, 1H), 8.61 (s, 1H), 8.40 (br s, 1H), 7.70 (t, *J* = 53.2 Hz, 1H), 6.98 (d, *J* = 1.6 Hz, 1H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.10 (d, *J* = 11.2 Hz, 1H), 3.73-3.84 (m, 2H), 3.57 (td, *J* = 11.2 Hz, 2.0 Hz, 1H), 3.22 (t, *J* = 10.8 Hz, 1H), 2.95-3.04 (m, 1H), 2.89 (d, *J* = 11.2 Hz, 1H), 2.72 (d, *J* = 11.6 Hz, 1H), 2.58 (t, *J* = 11.0 Hz, 1H), 2.24-2.48 (m, 3H), 1.13 (s, 3H), 0.68-0.75 (m, 2H), 0.40-0.49 (m, 2H).

Example 142

Synthesis of 3-[5-(difluoromethyl)-1,3,4-thiadiazol-2-yl]-8-[(2R,5S)-2-(methoxymethyl)-5-methylmorpholin-4-yl]-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide



Synthesis of (2R,5S)-2-(methoxymethyl)-5-methylmorpholine (Compound 142-5)



5

Step 1: Synthesis of (2S)-2-(benzylamino)propan-1-ol (142-2):

[0386] To a solution of (2S)-2-aminopropan-1-ol (30.00 g, 399.41 mmol) (*Bide Pharmatech Ltd.*) in anhydrous MeOH (300 mL) was added benzaldehyde (42.39 g, 399.41 mmol) at room temperature. After stirring for 1 h at room temperature, the mixture was cooled at 0 °C, then 10 NaBH4 (15.11 g, 399.41 mmol) was added to the mixture in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for additional 2 h at room temperature. The reaction mixture was quenched by the addition of water. The organic solvent was removed under vacuum. The aqueous layer was acidified with HCl (2 N) to pH ~5 and extracted with ethyl acetate. The aqueous layer was collected and then basified with NaOH (10% aq.) to pH ~9. The 15 mixture was then extracted with ethyl acetate. The combined organic layers were washed with brine. The organic layer was dried over anhydrous sodium sulfate, then filtered through paper. The filtrate was concentrated under vacuum to afford (2S)-2-(benzylamino)propan-1-ol (54.00 g, 77%) as a light yellow oil. MS (ESI) calculated for (C₁₀H₁₅NO) [M+1]⁺, 166.1; found, 166.2.

Step 2: Synthesis of [(2R,5S)-4-benzyl-5-methylmorpholin-2-yl]methanol (142-3):

[0387] To a stirred solution of (2S)-2-(benzylamino)propan-1-ol (15.00 g, 90.36 mmol) and (S)-epichlorohydrin (12.60 g, 136.10 mmol) (*Accela ChemBio Co., Ltd.*) in anhydrous Toluene (150 mL) was added lithium perchlorate (14.48 g, 136.10 mmol) at room temperature. The

5 mixture was stirred at room temperature for 24 h. Then a solution of NaOH (7.26 g, 181.47 mmol) in MeOH (80 mL) was added slowly to the above mixture at 0 °C. The resulting mixture was warmed to room temperature and stirred for 3 days. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were separated, washed with brine. The organic layers were dried over anhydrous sodium sulphate, filtered and
10 concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography on C18 column-360 g with 5~55% acetonitrile in 10 mM ammonium bicarbonate aqueous solution. The product fractions were collected and concentrated under reduced pressure to afford [(2R,5S)-4-benzyl-5-methylmorpholin-2-yl]methanol (9.1 g) as a yellow oil. Then the product was further purified by Prep-HPLC with the following conditions:

15 [Column: XBridge Prep C18 Column, 19*250 mm, 5µm; Mobile Phase A: Water (10mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 18% B to 28% B in 15 min; Wave Length: 254nm/220nm] to afford [(2R,5S)-4-benzyl-5-methylmorpholin-2-yl]methanol (4.1 g, 20%) as colorless oil. MS (ESI) calculated for (C₁₃H₁₉NO₂) [M+1]⁺, 222.1; found, 222.2. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.18 (m, 5H), 3.82 (dd, *J* = 11.2, 3.2 Hz, 1H), 3.76 – 3.59 (m, 5H), 3.52 (d, *J* = 13.4 Hz, 1H), 2.83 – 2.77 (m, 1H), 2.63 – 2.45 (m, 1H), 2.38 (dd, *J* = 11.8, 3.0 Hz, 1H), 2.09 (br, 1H), 1.12 (d, *J* = 6.6 Hz, 3H).

Step-3: Synthesis of (2R,5S)-4-benzyl-2-(methoxymethyl)-5-methylmorpholine (142-4):

[0388] To a degassed solution of [(2R,5S)-4-benzyl-5-methylmorpholin-2-yl]methanol (1.00 g, 4.52 mmol) in anhydrous THF (10 mL) was added NaH (360 mg, 9.01 mmol, 60% in mineral oil) in portions at 0 °C. After stirring at 0 °C for 1 h under nitrogen, MeI (1.92 g, 13.56 mmol) was added dropwise to the above mixture at 0 °C. The resulting solution was warmed at 25 °C for 16 h with stirring. The reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by Combi Flash (Biotage Isolera Prime) with an 80 g silica gel column and eluted with 0~50% ethyl acetate

in petroleum ether within 30 min to afford (2R,5S)-4-benzyl-2-(methoxymethyl)-5-methylmorpholine (0.89 g, 83%) as a yellow oil. MS (ESI) calculated for ($C_{14}H_{21}NO_2$) [$M+1$]⁺, 236.1; found, 236.2.

Step-4: Synthesis of (2R,5S)-2-(methoxymethyl)-5-methylmorpholine (Compound 142-5):

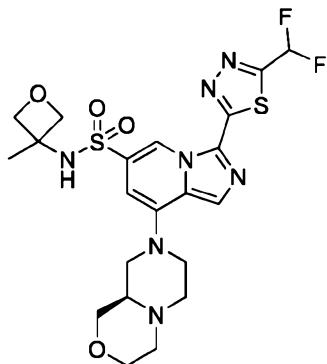
- 5 [0389] To a solution of (2R,5S)-4-benzyl-2-(methoxymethyl)-5-methylmorpholine (890 mg, 3.77 mmol) in MeOH (10 mL) was added Pd/C (100 mg, 5% active on carbon) at 25 °C. The mixture was placed under hydrogen atmosphere with a balloon (1 atm.). The reaction mixture degassed via vacuum evacuation, then backfilled with hydrogen, and this process was repeated three times. The reaction mixture was stirred at 25 °C for 16 h under hydrogen atmosphere. The 10 mixture was filtered through a Celite pad. The filtrate was collected and concentrated under vacuum to afford (2R,5S)-2-(methoxymethyl)-5-methylmorpholine (Compound 142-5) (490 mg, crude) as a yellow oil. MS (ESI) calculated for ($C_7H_{15}NO_2$) [$M+1$]⁻, 146.1; found, 146.1. ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.59 – 3.27 (m, 5H), 3.26 (s, 3H), 2.88 (br, 1H), 2.82 – 2.57 (m, 3H), 1.00 (d, *J* = 6.6 Hz, 3H).
- 15 **Synthesis of 3-[5-(difluoromethyl)-1,3,4-thiadiazol-2-yl]-8-[(2R,5S)-2-(methoxymethyl)-5-methylmorpholin-4-yl]-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (Example 142)**

- [0390] To a stirred solution of 3-[5-(difluoromethyl)-1,3,4-thiadiazol-2-yl]-8-fluoro-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (3.0 g, 7.15 mmol) in dry DMSO (30 mL) were sequentially added DIEA (2.8 g, 21.46 mmol) and (2R,5S)-2-(methoxymethyl)-5-methylmorpholine (Compound 142-5) (2.1 g, 14.31 mmol) at room temperature. The resulting 20 solution was stirred at 110 °C for 16 h. The resulting mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. The resulting residue was purified by flash column chromatography and eluted with 0~50% ethyl acetate in petroleum ether to afford 3-[5-(difluoromethyl)-1,3,4-thiadiazol-2-yl]-8-[(2R,5S)-2-(methoxymethyl)-5-methylmorpholin-4-yl]-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (2.8 g, 71%) as a yellow solid. *m/z* (ESI): [M+H]⁺ 545.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.59 (s, 1H), 8.76 (s, 1H), 8.08 (s, 1H), 7.68 (t, *J* = 53.2 Hz, 1H), 6.66 (d, *J* = 1.0 Hz, 1H), 4.62 (t, *J* = 6.2 Hz, 2H), 4.32 – 25

4.12 (m, 3H), 4.03 – 3.99 (m, 1H), 3.84 – 3.77 (m, 2H), 3.58 – 3.50 (m, 2H), 3.34 (s, 3H), 3.25 (t, J = 11.4 Hz, 1H), 3.11 – 3.08 (m, 1H), 1.49 (s, 3H), 1.02 (d, J = 6.6 Hz, 3H).

Example 171

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

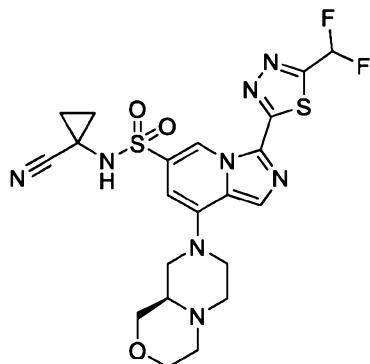


[0391] To a stirred solution of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (Intermediate 3) (150 mg, 0.358 mmol.) in dimethyl sulfoxide (2.0 mL) were added DIPEA (0.221 mL, 1.200 mmol.) and followed by addition of (*R*)-octahydropyrazino[2,1-*c*][1,4]oxazine (170.400 mg, 1.200 mmol, Source: BLD) at room temperature. The reaction mixture was heated to 100 °C and stirred at same temperature for 16 h. The reaction mixture was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 30 mL). Combined organic layers were separated, washed with brine solution (10 mL), dried over anhydrous sodium sulphate, filtered and filtrate was concentrated under reduced pressure to give the crude compound. The crude compound was purified by Prep HPLC. Purification conditions: COLUMN: X BRIDGE PACKED BUFFER A: 10 mM ABC BUFFER B:- ACN SOLUBILITY:- ACN –THF-WATER MOBILE PHASE CONDITIONS (% of B):- 0/20,2/20,10/60,14.55/60,15/98,18/98,18.10/20,20/20 FLOW-19 ML /MIN ANL-MCL-APMS - 05. Fractions were concentrated under reduced pressure and lyophilized to afford (*R*)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1H)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide (74.6 mg, 38.51%) as a yellow solid.

[0392] MS ESI calculated for C₂₁H₂₆F₂N₇O₄S₂: 542.15, found 542.42 [M+H]⁺. **1H NMR (400 MHz, DMSO-d₆)**: δ (ppm) 9.57 (s, 1H), 8.71 (s, 1H), 8.05 (s, 1H), 7.67 (t, J = 53.2 Hz, 1H),

6.68 (d, $J = 1.2$ Hz, 1H), 4.60-4.65 (m, 2H), 4.18 (d, $J = 6.0$ Hz, 2H), 3.77-3.86 (m, 2H), 3.73 (d, $J = 11.2$ Hz, 1H), 3.51-3.62 (m, 2H), 3.18 (t, $J = 10.4$ Hz, 1H), 2.98-3.07 (m, 1H), 2.89 (d, $J = 11.2$ Hz, 1H), 2.73 (d, $J = 11.2$ Hz, 1H), 2.57 (t, $J = 11.0$ Hz, 1H), 2.40-2.49 (m, 2H), 2.27-2.36 (m, 1H), 1.49 (s, 3H).

5

Example 172**Synthesis of (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide**

[0393] To a stirred solution of *N*-(1-Cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoroimidazo[1,5- α]pyridine-6-sulfonamide (Intermediate 2) (200 mg, 0.483 mmol, 1.0 equiv.) in DMSO (5 mL) were added (*R*)-octahydropyrazino[2,1-*c*][1,4]oxazine (102.948 mg, 0.724 mmol, 1.5 equiv.; Source: BLD, Catalog Number BD295204) and DIPEA (311.790 mg, 2.413 mmol, 5.0 equiv.) at room temperature. The reaction mixture was heated to 100 °C and stirred at same temperature for 48 h. After completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2x20 mL). The combined organic layers were separated, washed with brine solution (20 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to obtain the crude compound. The crude was purified by Prep HPLC. Purification conditions: Mobile phase A: - 10 mM Ammonium bicarbonate (Aq.), Mobile phase B: -ACN Column:- X-SELECT- C18 (150*25 mM) 10 μ Flow: - 19 ml/min, Method 0/30,2/30,10/55,12/55,12.1/98,17/98,17.1/30,20/30 Solubility: - ACN + THF + Water Temperature: - Ambient ID- apms-006. Fraction was collected and concentrated under reduced pressure and further lyophilized to afford (*R*)-*N*-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydropyrazino[2,1-*c*][1,4]oxazin-8(1*H*)-yl)imidazo[1,5-*a*]pyridine-6-sulfonamide (98.5 mg, 38.03%) as a yellow

solid. MS ESI calculated for $C_{21}H_{23}F_2N_8O_3S_{22}$ [M+H]⁻ 537.13, found 537.37. UPLC: 98.39% Chiral SFC: 97.08%. **¹H NMR (400 MHz, DMSO-d₆):** δ (ppm) 9.65 (s, 1H), 9.46 (br s, 1H), 8.06 (s, 1H), 7.68 (t, *J* = 53.2 Hz, 1H), 6.65 (d, *J* = 0.8 Hz, 1H), 3.77-3.86 (m, 2H), 3.73 (d, *J* = 10.8 Hz, 1H), 3.50-3.61 (m, 2H), 3.18 (t, *J* = 10.4 Hz, 1H), 2.97-3.07 (m, 1H), 2.89 (d, *J* = 11.2 Hz, 1H), 2.73 (d, *J* = 11.0 Hz, 1H), 2.54-2.62 (m, 2H), 2.43-2.47 (m, 1H), 2.26-2.36 (m, 1H), 1.30-1.50 (m, 4H).

Example 231 and 232

Synthesis of 4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide

[0394] To a stirred solution of 3-(5-(Difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (intermediate 1) (0.2 g, 0.496 mmol) in DMSO (10.0 mL) were added *N*-methylmorpholine-2-carboxamide TFA (Compound 231-1) salt (0.214 g, 1.487 mmol) and followed by the addition of DIPEA (0.192 g, 1.487 mmol) at room temperature. The reaction mixture was heated to 120°C and stirred at same temperature for 48 h. After completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2x20 mL). Combined organic layers were separated, washed with brine solution (20 mL), dried over *anhydrous sodium sulphate*, filtered and filtrate was concentrated under reduced pressure to give crude compound. The crude compound was purified by Prep HPLC Purification conditions: MOBILE PHASE: 0.1% Formic Acid in H₂O:

MeCN COLUMN: X-BRIDGE C18 (19X250) mm 5u, Flow-18mL/min, GRADIENT METHOD: 0/40.5.00/65.9.15/65.9.16/99.11.20/40.14.20/40 SOLUBILITY: MeOH. Fraction was collected and concentrated under reduced pressure and further lyophilized to afford 4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide (0.15 g) as an off white solid.

[0395] The racemic mixture was separated by SFC. Prep. to give **peak-1:** (R) 4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide (43 mg, 16.44%) and **peak-2:** (S) 4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-ethylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide (43 mg, 16.44%) as yellow solid.

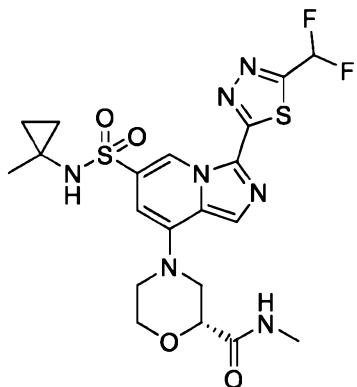
Analytical SFC Conditions:

[0396] SFC purification conditions: Column: **Chiralpak-IG (250X4.6X5μ)** Total flow: 4.0 g/min % of CO₂: 55, % of Co-Solvent: 45% (100% Methanol): 100. bar Temperature: 30°C).

[0397] Fractions were collected and concentrated under reduced pressure and lyophilized to afford **peak-1:**(R)4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-ethylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide (43 mg, 16.44%) and **peak-2:** (S) 4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide (43 mg, 16.44%) as pale yellow solid.

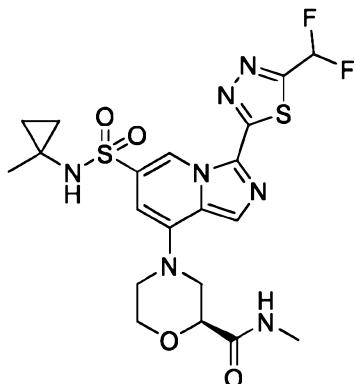
[0398] MS ESI calculated for C₂₀H₂₃F₂N₇O₄S₂ [M+H]⁺ 527.1, found 528.3

Example 232; (R)-4-(3-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide



[0399] **¹H NMR (400 MHz, DMSO-d₆):** δ (ppm) 9.61 (s, 1H), 8.46 (s, 1H), 8.14 (s, 1H), 8.00-7.99 (m, 1H), 7.68 (t, *J* = 53.2 Hz, 1H), 6.72 (s, 1H), 4.29-4.26 (m, 1H), 4.05-4.02 (m, 1H), 3.95-3.90 (m, 1H), 3.59 (t, *J* = 13.2 Hz, 2H), 3.22-3.16 (m, 1H), 3.03-2.97 (m, 1H), 2.67 (d, *J* = 4.8 Hz, 3H), 1.14 (s, 3H), 0.75-0.67 (m, 2H), 0.47-0.42 (m, 2H).

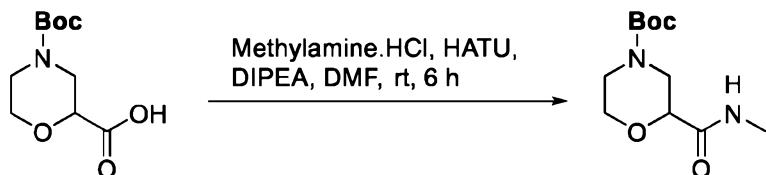
Example 231; (S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide



5 [0400] **¹H NMR (400 MHz, DMSO-d₆):** δ (ppm) 9.61 (s, 1H), 8.47 (s, 1H), 8.14 (s, 1H), 8.00-7.98 (m, 1H), 7.68 (t, *J* = 53.2 Hz, 1H), 6.73 (s, 1H), 4.29-4.26 (m, 1H), 4.05-4.02 (m, 1H), 3.94-3.90 (m, 1H), 3.59 (t, *J* = 13.0 Hz, 2H), 3.22-3.16 (m, 1H), 3.03-2.97 (m, 1H), 2.67 (d, *J* = 4.4 Hz, 3H), 1.19-1.14 (m, 3H), 0.75-0.68 (m, 2H), 0.47-0.44 (m, 2H).

[0401] The following paragraphs describe the preparation of Compound 231-1.

10 **Synthesis of tert-butyl 2-(methyl carbamoyl) morpholine-4-carboxylate:**

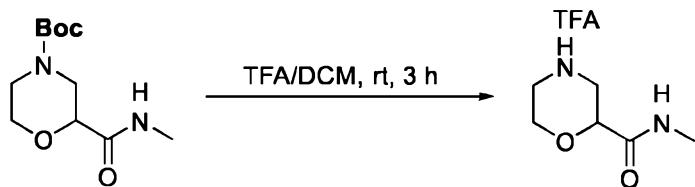


15 [0402] To a solution of 4-(*tert*-butoxycarbonyl) morpholine-2-carboxylic acid (**Source: BLD**) (10 g, 43.244 mmol) in *N,N*- Dimethylformamide (50 mL) were added HATU (24.6 g, 64.8657 mmol) at room temperature and followed by the portion wise addition of methylamine hydrochloride, 99% (8.759 g, 129.731 mmol) at 0 °C and followed by the addition DIPEA (38.525 mL, 216.218 mmol) at room temperature and the reaction mixture was stirred same temperature for 6 h. After completion of the reaction, the reaction mixture was diluted with water (500 mL) and extracted with EtOAc (2x300 mL). Combined organic layers were separated, washed with brine solution (200 mL), dried over *anhydrous sodium sulphate*, filtered and filtrate was concentrated under reduced pressure to give crude compound. The crude compound was

purified by column chromatography using silica gel (100-200) and eluted with 20% EtOAc/Hexane as a gradient. The product was eluted at 30% EtOAc/Hexane. Fractions were collected and concentrated under reduced pressure to afford *tert*-butyl 2-(methylcarbamoyl) morpholine-4-carboxylate (7 g, 66.26%) as a white solid. MS ESI calculated for C₁₁H₂₀N₂O₄

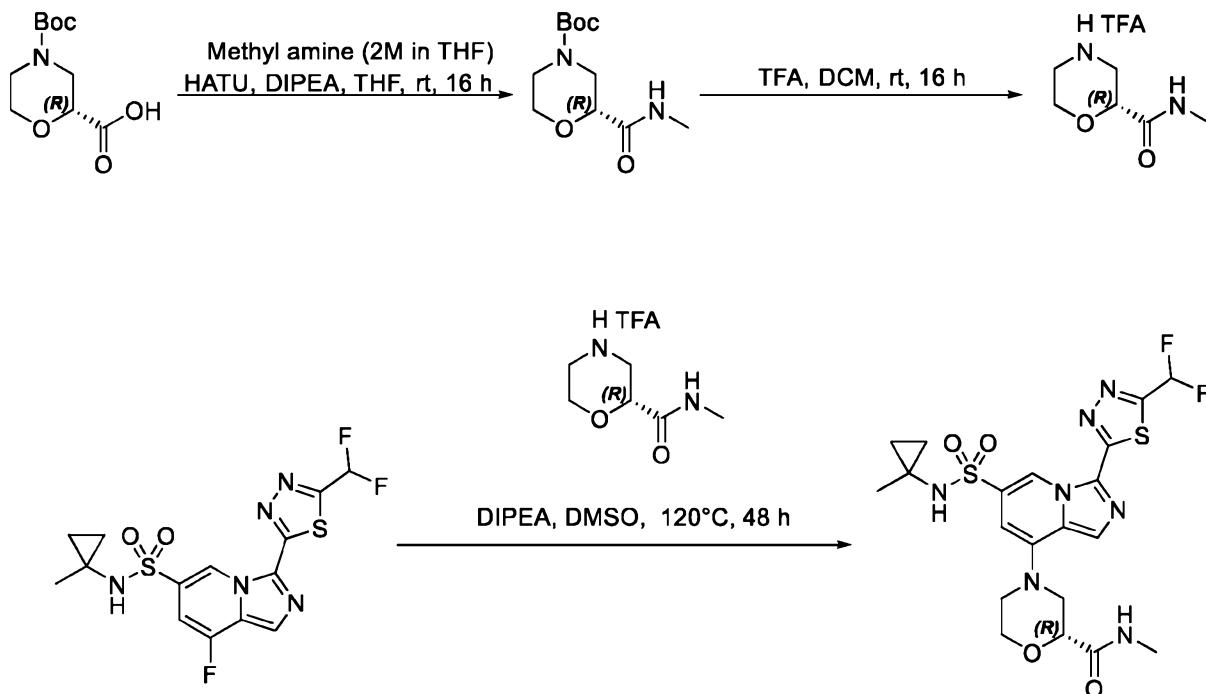
5 [M+H]⁺ 244.1, found 245.3.

Synthesis of TFA salt of N-methylmorpholine-2-carboxamide (Compound 231-1):

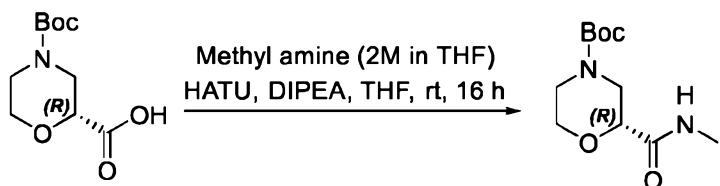


[0403] To a solution of *tert*-butyl 2-(methylcarbamoyl) morpholine-4-carboxylate (1.0 g, 4.097 mmol) in DCM (10 mL) was added trifluoroacetic acid (2.3 g, 20.483 mmol) at 0 °C and 10 the reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated under reduced pressure and co-distilled with DCM (3X30 mL) to afford *N*-methylmorpholine-2-carboxamide as a TFA salt (0.5 g, 84.65%) as a brown solid. MS ESI calculated for C₆H₁₂N₂O₂ [M+H]⁺ 144.1, found 145.2.

[0404] The following paragraphs describe the asymmetric synthesis of (R)-N-methylmorpholine-2-carboxamide (Compound 232-1)



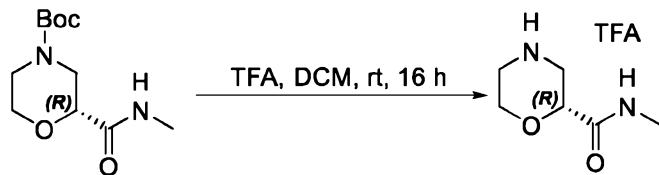
Synthesis of *tert*-Butyl (*R*)-2-(methylcarbamoyl)morpholine-4-carboxylate



[0405] To a stirred solution of (*R*)-4-(*tert*-Butoxycarbonyl)morpholine-2-carboxylic acid

- 5 (4.0 g, 17.298 mmol) and MeNH₂ (10.37 mL, 2M in THF, 20.757 mmol) (Combiblocks) in THF (80 mL) were added HATU (9.866 g, 25.946 mmol) followed by DIPEA (8.808 mL, 51.893 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was diluted with water (200 mL) and extracted with EtOAc (2 x 300 mL). The combined organic layers were separated, washed with brine (100 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get the crude compound. The crude residue was triturated with diethyl ether, decanted and dried under reduced pressure to afford *tert*-butyl (*R*)-2-(methylcarbamoyl)morpholine-4-carboxylate (4.0 g, 94.66%) as an off-white solid. MS ESI calculated for C₁₁H₂₁N₂O₄ [M+H]⁺ 245.15, found 245.21.

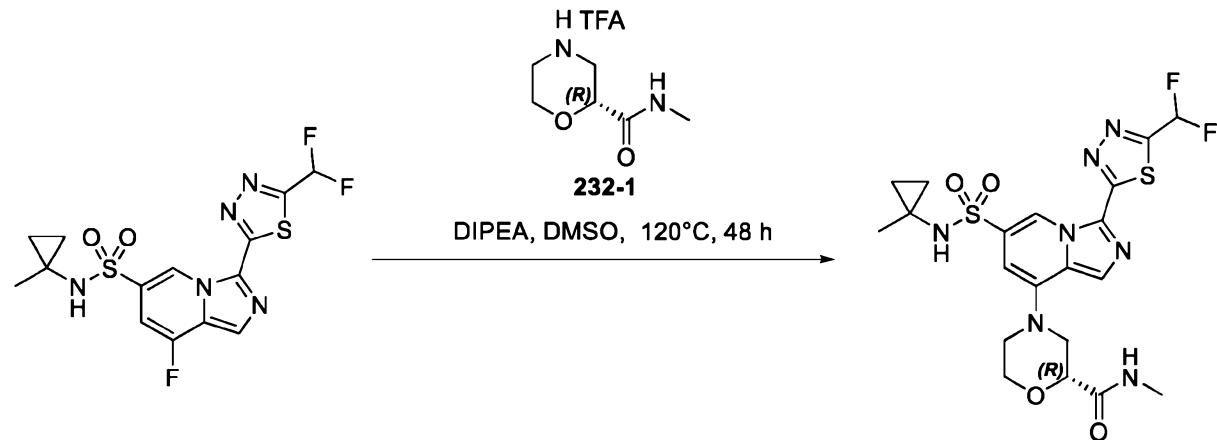
Synthesis of (*R*)-*N*-Methylmorpholine-2-carboxamide (TFA salt) (Compound 232-1)



[0406] To a stirred solution of *tert*-Butyl (*R*)-2-(methylcarbamoyl)morpholine-4-carboxylate (4.0 g, 16.374 mmol) in DCM (40 mL) was added TFA (3.210 mL, 3.210 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 16 h. Volatiles were removed under reduced pressure and the resulted crude residue was triturated with diethyl ether and pentane to afford (*R*)-*N*-methylmorpholine-2-carboxamide (2.1 g, TFA salt) as an off-white solid.

Step 10: Synthesis of (*R*)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-

methylocyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-*N*-methylmorpholine-2-carboxamide (Example 232):



[0407] To a stirred solution of 3-(5-(Difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-fluoro-*N*-(1-methylocyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide (5 mg, 0.012 mmol) in DMSO (0.5 mL) were added (*R*)-*N*-methylmorpholine-2-carboxamide (3.575 mg, 0.025 mmol) and followed by the addition of DIPEA (0.011 mL, 0.062 mmol) at room temperature. The reaction mixture was heated to 120°C and stirred at same temperature for 48 h. After completion of the reaction, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2x5 mL). Combined organic layers were separated, washed with brine solution (5 mL), dried over *anhydrous sodium sulphate*, filtered and filtrate was concentrated under reduced pressure to

give crude compound. The crude product was purified by Prep-TLC (Merck AL silica gel 60 F254 plate; 5% methanol/DCM) to obtain (R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide (3 mg, 45.84%) as an off white solid. MS ESI calculated for C₂₀H₂₃F₂N₇O₄S₂

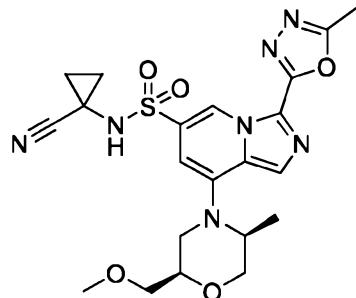
5 [M+H]⁺ 528.1, found 528.5. **¹H NMR (400 MHz, DMSO-d₆):** δ (ppm) 9.61 (s, 1H), 8.46 (s, 1H), 8.14 (s, 1H), 8.00-7.98 (m, 1H), 7.68 (t, *J* = 53.2 Hz, 1H), 6.73 (s, 1H), 4.29-4.26 (m, 1H), 4.05-4.02 (m, 1H), 3.94-3.90 (m, 1H), 3.59 (t, *J* = 13.0 Hz, 2H), 3.22-3.16 (m, 1H), 3.03-2.97 (m, 1H), 2.67 (d, *J* = 4.4 Hz, 3H), 1.19-1.14 (m, 3H), 0.75-0.68 (m, 2H), 0.47-0.44 (m, 2H). **RT 2.427 min as determined using** Column/dimensions: Chiraldak- IG-3(4.6*150mm) 3μm, CO₂:

10 60%, Co solvent: 40% (100% Methanol), Total Flow: 4 mL/min, ABPR: 1500 psi, Temperature: 30 °C, Wavelength: 268 nm.

Example 235

Synthesis of 8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)-3-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(1-cyanocyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

15



[0408] To a stirred solution of N-(1-cyanocyclopropyl)-8-fluoro-3-(5-methyl-1,3,4-oxadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (100 mg, 0.28 mmol) and DIEA (107 mg, 0.83 mmol) in DMSO (1 mL) was added (2R,5S)-2-(methoxymethyl)-5-methylmorpholine (Compound 142-5) (80 mg, 0.55 mmol) at room temperature. The resulting mixture was stirred 20 at 80 °C for 2 days under nitrogen atmosphere. The resulting mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC with the following conditions: [Column: Xselect CSH

OBD Column 30*150mm, 5um; Mobile Phase A: water (0.1% FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 40% B in 9 min; Wave Length: 254nm/220nm] to afford N-(1-cyanocyclopropyl)-8-[(2R,5S)-2-(methoxymethyl)-5-methylmorpholin-4-yl]-3-(5-methyl-1,3,4-oxadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide (29.0 mg, 21.47%) as a light yellow solid. MS (ESI) calc'd for ($C_{21}H_{25}N_7O_5S$) [M+1]⁺, 488.2; found, 488.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.54 (br, 1H), 9.48 (s, 1H), 8.08 (s, 1H), 6.57 (s, 1H), 4.30 – 4.21 (m, 1H), 4.04 – 3.97 (m, 1H), 3.87 – 3.73 (m, 2H), 3.58 – 3.48 (m, 2H), 3.34 (s, 3H), 3.29 – 3.21 (m, 1H), 3.13 – 3.07 (m, 1H), 2.67 (s, 3H), 1.53 – 1.33 (m, 4H), 1.03 (d, *J* = 6.8 Hz, 3H).

Examples Synthesis

10 [0409] The Examples below were made using intermediates and following the procedures disclosed in the paragraphs above.

Example 1

Synthesis of 3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

15 [0410] *m/z* [M+H]⁺ 513.29

Example 2

Synthesis of 8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-3-(5-methyl-1,3,4-oxadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0411] *m/z* [M+H]⁺ 477.32

Example 3

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-5-ethyl-2-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide

[0412] *m/z* [M+H]⁺ 524.26

Example 4

25 Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((S)-2-((S)-2-(hydroxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0413] m/z [M+H]⁺ 584.22

Example 5

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((R)-2-((S)-2-(hydroxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0414] m/z [M+H]⁺ 584.24

Example 6

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((S)-2-((R)-2-(hydroxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0415] m/z [M+H]⁺ 584.24

Example 7

Synthesis of (S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-ethylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide

[0416] m/z [M+H]⁺ 510.25

Example 8

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((R)-2-((R)-2-(hydroxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0417] m/z [M+H]⁺ 584.28

Example 9

Synthesis of S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-methoxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0418] m/z [M+H]⁺ 584.32

25

Example 10

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-methoxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0419] m/z [M+H]⁺ 584.21

Example 11

5 Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-hydroxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0420] m/z [M+H]⁺ 570.18

Example 12

10 Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-hydroxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0421] m/z [M+H]⁺ 570.29

Example 13

Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(2-(morpholine-4-carbonyl)morpholino)imidazo[1,2-a]pyridine-6-sulfonamide

15 [0422] m/z [M+H]⁺ 584.25

Example 14

Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(2-(morpholine-4-carbonyl)morpholino)imidazo[1,2-a]pyridine-6-sulfonamide

[0423] m/z [M+H]⁺ 584.25

20

Example 15

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aS,7aR)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0424] m/z [M+H]⁺ 513.23

Example 16

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aR,7aS)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0425] m/z [M+H]⁺ 513.23

Example 17

5 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aR,7aR)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0426] m/z [M+H]⁺ 513.23

Example 18

10 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aS,7aS)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0427] m/z [M+H]⁺ 513.27

Example 19

Synthesis of 3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

15 [0428] m/z [M+H]⁺ 513.36

Example 20

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(2,5-dioxa-8-azaspiro[3.5]nonan-8-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0429] ¹H NMR (400 MHz, DMSO) δ 9.69 (d, J = 1.5 Hz, 1H), 8.67 (s, 1H), 8.42 (s, 1H), 7.70 (t, J = 53.1 Hz, 1H), 7.06 (d, J = 1.6 Hz, 1H), 4.56 (q, J = 6.8 Hz, 4H), 3.95 (s, 2H), 3.85 (dd, J = 6.1, 3.5 Hz, 2H), 3.44 (d, J = 5.0 Hz, 2H), 1.13 (s, 3H), 0.71 (q, J = 4.6 Hz, 2H), 0.48 – 0.41 (m, 2H). m/z [M+H] = 513.2.

Example 21

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2,5-dimethylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide

[0430] m/z [M+H]⁺ 510.07

Example 22

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(methoxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

5 [0431] m/z [M+H]⁺ 559.29

Example 23

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(methoxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0432] m/z [M+H]⁺ 559.29

10 [0433] m/z [M+H]⁺ 554.09

Example 24

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(methoxymethyl)morpholino)imidazo[1,2-a]pyridine-6-sulfonamide

15 [0434] m/z [M+H]⁺ 531.13

Example 25

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0435] m/z [M+H]⁺ 522.36

Example 26

Synthesis of rel-(R)-N-(1-cyanocyclopropyl)-8-(3-cyclopropylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

20 [0436] m/z [M+H]⁺ 522.36

Example 27

Synthesis of rel-(S)-N-(1-cyanocyclopropyl)-8-(3-cyclopropylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

Example 28

Synthesis of (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-ethylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide

[0437] m/z [M+H]⁺ 510.11

5

Example 29

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2-(methoxymethyl)-5-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0438] m/z [M+H]⁺ 545.3

Example 30

10 Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0439] m/z [M+H]⁺ 545.3

Example 31

15 Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)imidazo[1,2-a]pyridine-6-sulfonamide

[0440] m/z [M+H]⁺ 540.1

Example 32

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2-(methoxymethyl)-5-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide

20 [0441] m/z [M+H]⁺ 540.35

Example 33

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide

[0442] m/z [M+H]⁺ 540.35

25

Example 34

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0443] m/z [M+H]⁺ 542.45

Example 35

- 5 Synthesis of (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahydro-2H,6H-pyrazino[1,2-c][1,3]oxazin-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0444] m/z [M+H]⁺ 537.4

Example 37

- Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2-hydroxymethyl)-5-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide

[0445] m/z [M+H]⁺ 526.37

Example 38

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-hydroxymethyl)-5-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide

- 15 [0446] m/z [M+H]⁺ 526.37

Example 39

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(hydroxymethyl)morpholino)imidazo[1,2-a]pyridine-6-sulfonamide

[0447] m/z [M+H]⁺ 540.35

- 20 [0446] m/z [M+H]⁺ 526.37

Example 40

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-((4aR,7aS)-octahydro-1H-cyclopenta[b]pyrazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0448] m/z [M+H]⁺ 510.36

Example 41

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-((4aS,7aR)-octahydro-1H-cyclopenta[b]pyrazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0449] m/z [M+H]⁺ 510.4

Example 42

- 5 Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-morpholinoimidazo[1,2-a]pyridine-6-sulfonamide

[0450] m/z [M+H]⁺ 471.23

Example 43

- Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0451] m/z [M+H]⁺ 545.36

Example 44

Synthesis of (S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide

- 15 [0452] m/z [M+H]⁺ 528.31

Example 45

Synthesis of (R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide

[0453] m/z [M+H]⁺ 528.35

20

Example 46

Synthesis of (S)-8-(2-(azetidine-1-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0454] m/z [M+H]⁺ 554.34

Example 47

Synthesis of (R)-8-(2-(azetidine-1-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0455] m/z [M+H]⁺ 554.34

Example 48

- 5 Synthesis of rel-(2R,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide

[0456] m/z [M+H]⁺ 542.29

Example 49

- 10 Synthesis of rel-(2S,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide

[0457] m/z [M+H]⁺ 542.29

Example 50

- 15 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0458] m/z [M+H]⁺ 545.3

Example 51

- 20 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0459] m/z [M+H]⁺ 545.33

Example 52

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

- 25 [0460] m/z [M+H]⁺ 545.33

Example 53

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0461] m/z [M+H]⁺ 545.33

5

Example 54

Synthesis of rel-N-(1-cyanocyclopropyl)-8-((3S,5R)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0462] m/z [M+H]⁺ 575.23

10

Example 55

Synthesis of rel-N-(1-cyanocyclopropyl)-8-((3R,5S)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0463] m/z [M+H]⁺ 575.23

15

Example 56

Synthesis of rel-8-((3S,5R)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0464] m/z [M+H]⁺ 580.28

20

Example 57

Synthesis of rel-8-((3R,5S)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0465] m/z [M+H]⁺ 580.28

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Example 58

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1S,9aS)-1-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0466] m/z [M+H]⁺ 556.31

5

Example 59

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1R,9aR)-1-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0467] m/z [M+H]⁺ 556.28

10

Example 60

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1S,9aR)-1-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0468] m/z [M+H]⁺ 556.14

15

Example 61

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1R,9aS)-1-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0469] m/z [M+H]⁺ 556.31

20

Example 62

Synthesis of (S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6,6-dimethylmorpholine-2-carboxamide

[0470] m/z [M+H]⁺ 542.26

25

Example 63

Synthesis of (R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6,6-dimethylmorpholine-2-carboxamide

[0471] m/z [M+H]⁺ 542.3

5

Example 64

Synthesis of rel-8-((3S,5R)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0472] m/z [M+H]⁺ 564.28

10

Example 65

Synthesis of rel-8-((3R,5S)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0473] m/z [M+H]⁺ 564.28

15

Example 66

Synthesis of rel-8-((2S,6R)-2-((difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0474] m/z [M+H]⁺ 565.35

20

Example 67

Synthesis of rel-8-((2R,6S)-2-((difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0475] m/z [M+H]⁺ 565.35

25

Example 68

Synthesis of rel-8-((2R,6R)-2-((difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0476] m/z [M+H]⁺ 565.31

5

Example 69

Synthesis of rel-8-((2S,6S)-2-((difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0477] m/z [M+H]⁺ 565.31

10

Example 70

Synthesis of rel-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide

[0478] m/z [M+H]⁺ 526.28

Example 71

15 Synthesis of rel-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-(hydroxymethyl)-6-methylmorpholino)imidazo[1,2-a]pyridine-6-sulfonamide

[0479] m/z [M+H]⁺ 526.11

Example 72

Synthesis of S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(6-
20 oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0480] m/z [M+H]⁺ 549.27

Example 73

Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(6-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

25 [0481] m/z [M+H]⁺ 554.33

Example 74

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0482] m/z [M+H]⁺ 529.23

5

Example 75

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0483] m/z [M+H]⁺ 529.28

Example 76

10 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0484] m/z [M+H]⁺ 515.25

Example 77

15 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0485] m/z [M+H]⁺ 515.25

Example 78

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

20 [0486] m/z [M+H]⁺ 515.24

Example 79

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0487] m/z [M+H]⁺ 515.29

25

Example 80

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0488] m/z [M+H]⁺ 593.28

Example 81

- 5 Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0489] m/z [M+H]⁺ 598.26

Example 82

- 10 Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(6-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0490] m/z [M+H]⁺ 538.36

Example 83

Synthesis of (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

- 15 [0491] m/z [M+H]⁺ 565.35

Example 84

Synthesis of rel-(2S,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide

[0492] m/z [M+H]⁺ 528.29

20

Example 85

Synthesis of rel-(2R,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide

[0493] m/z [M+H]⁺ 528.25

Example 86

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0494] m/z [M+H]⁺ 582.38

Example 87

- 5 Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0495] m/z [M+H]⁺ 525.22

Example 88

- 10 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0496] m/z [M+H]⁺ 529.32

Example 89

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

- 15 [0497] m/z [M+H]⁺ 529.32

Example 90

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0498] m/z [M+H]⁺ 570.33

- 20 [0497] m/z [M+H]⁺ 529.32

Example 91

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0499] m/z [M+H]⁺ 530.3

Example 92

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0500] m/z [M+H]⁺ 514.26

Example 93

- 5 Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0501] m/z [M+H]⁺ 514.3

Example 94

- Synthesis of rel-(S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-2-methylmorpholine-2-carboxamide

[0502] m/z [M+H]⁺ 528.33

Example 95

Synthesis of rel-(R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-2-methylmorpholine-2-carboxamide

- 15 [0503] m/z [M+H]⁺ 528.24

Example 96

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-(hydroxymethyl)-6-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0504] m/z [M+H]⁺ 531.29

- 20 Example 97

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0505] m/z [M+H]⁺ 531.29

Example 98

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0506] m/z [M+H]⁺ 509.26

Example 99

- 5 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0507] m/z [M+H]⁺ 515.19

Example 100

- 10 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-(hydroxymethyl)-6-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0508] m/z [M+H]⁺ 515.25

Example 101

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,2-a]pyridine-6-sulfonamide

- 15 [0509] m/z [M+H]⁺ 551.29

Example 102

Synthesis of rel-(2R,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide

[0510] m/z [M+H]⁺ 528.27

- 20 [0511] m/z [M+H]⁺ 528.27

Example 103

Synthesis of rel-(2S,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide

[0512] m/z [M+H]⁺ 528.27

Example 104

Synthesis of 3-(6-cyanopyridazin-3-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0512] m/z [M+H]⁺ 467.27

Example 105

- 5 Synthesis of (R)-3-(6-cyanopyridazin-3-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0513] m/z [M+H]⁺ 523.22

Example 106

- Synthesis of 3-(6-cyanopyridazin-3-yl)-N-(1-methylcyclopropyl)-8-((6S,9aR)-6-methylhexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0514] m/z [M+H]⁺ 509.39

Example 107

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

- 15 [0515] m/z [M+H]⁺ 498.26

Example 108

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1R,9aS)-1-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

- 20 [0516] m/z [M+H]⁺ 556.35

Example 109

Synthesis of (S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(3-methyloxetan-3-yl)sulfamoyl)imidazo[1,2-a]pyridin-8-yl)-N-methylmorpholine-2-carboxamide

[0517] ^1H NMR (400 MHz, MeOD) δ 9.90 (d, J = 1.6 Hz, 1H), 8.43 (s, 1H), 7.34 (t, J = 53.5 Hz, 1H), 7.11 (d, J = 1.6 Hz, 1H), 4.43 – 4.13 (m, 6H), 2.96 – 2.86 (m, 1H), 2.80 (s, 3H), 1.62 (d, J = 5.8 Hz, 5H), 1.43 – 1.32 (m, 2H). m/z [M+H]⁺ 392.8.

Example 110

5 Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0518] ^1H NMR (400 MHz, DMSO) δ 9.62 (d, J = 1.5 Hz, 1H), 8.68 (s, 1H), 8.61 (s, 1H), 7.70 (t, J = 53.2 Hz, 1H), 6.98 (d, J = 1.7 Hz, 1H), 4.63 (dd, J = 6.1, 3.6 Hz, 2H), 4.52 (d, J = 11.2 Hz, 1H), 4.18 (d, J = 6.1 Hz, 2H), 4.09 (q, J = 5.3 Hz, 1H), 3.90 (d, J = 11.2 Hz, 1H), 3.79 (dd, J = 10.6, 2.9 Hz, 2H), 3.60 – 3.49 (m, 1H), 3.22 – 3.06 (m, 5H), 2.94 (t, J = 10.3 Hz, 1H), 2.70 – 2.55 (m, 2H), 1.49 (s, 3H), 1.19 (d, J = 6.5 Hz, 3H). m/z [M+H]⁺ 556.0.

Example 111

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0519] ^1H NMR (400 MHz, DMSO) δ 9.56 (d, J = 1.5 Hz, 1H), 8.54 (s, 1H), 8.33 (s, 1H), 7.63 (t, J = 53.2 Hz, 1H), 6.89 (d, J = 1.7 Hz, 1H), 4.44 (d, J = 11.6 Hz, 1H), 3.85 – 3.76 (m, 1H), 3.72 (dd, J = 10.7, 2.9 Hz, 2H), 3.47 (td, J = 11.1, 2.4 Hz, 1H), 3.16 – 2.97 (m, 3H), 2.87 (td, J = 9.5, 8.4, 4.6 Hz, 1H), 2.59 (td, J = 11.4, 3.3 Hz, 1H), 2.52 (d, J = 11.1 Hz, 1H), 2.47 (s, 1H), 1.10 (d, J = 6.5 Hz, 3H), 1.06 (s, 3H), 0.70 – 0.57 (m, 2H), 0.38 (d, J = 1.9 Hz, 2H). m/z [M+H]⁺ 540.2

Example 112

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0520] ^1H NMR (400 MHz, DMSO) δ 9.65 (d, J = 1.5 Hz, 1H), 8.63 (s, 1H), 8.41 (s, 1H), 7.71 (t, J = 53.2 Hz, 1H), 6.99 (d, J = 1.6 Hz, 1H), 4.76 (s, 1H), 4.40 (d, J = 31.2 Hz, 2H), 4.20 (s, 1H), 3.99 (s, 1H), 3.59 (s, 1H), 3.09 (d, J = 12.3 Hz, 1H), 2.92 (h, J = 6.9 Hz, 2H), 1.31 (d, J = 60.9 Hz, 3H), 1.15 (s, 3H), 1.06 (d, J = 6.6 Hz, 6H), 0.70 (t, J = 9.5 Hz, 2H), 0.50 – 0.39 (m, 2H). m/z [M+H]⁺ 554.2.

Example 113

Synthesis of 8-((3R,5R)-3,5-dimethylpiperazin-1-yl)-N-(1-methylcyclopropyl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,2-a]pyridine-6-sulfonamide

[0521] ^1H NMR (400 MHz, DMSO) δ 9.59 (d, J = 1.5 Hz, 1H), 8.66 (s, 1H), 8.42 (s, 1H), 6.97 (d, J = 1.6 Hz, 1H), 3.51 (dd, J = 11.5, 3.3 Hz, 2H), 3.39 (dd, J = 11.5, 6.1 Hz, 4H), 1.21 – 1.08 (m, 9H), 0.70 (t, J = 8.9 Hz, 2H), 0.45 (d, J = 1.8 Hz, 2H). m/z [M+H]⁺ 516.0

Example 114

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,2-a]pyridine-6-sulfonamide

[0522] ^1H NMR (400 MHz, DMSO) δ 9.61 (d, J = 1.5 Hz, 1H), 8.60 (s, 1H), 8.40 (s, 1H), 7.70 (t, J = 53.2 Hz, 1H), 6.94 (d, J = 1.6 Hz, 1H), 3.50 (dd, J = 11.4, 3.3 Hz, 2H), 3.38 (dd, J = 11.4, 6.2 Hz, 2H), 3.28 (td, J = 6.2, 3.2 Hz, 2H), 1.21 – 1.07 (m, 9H), 0.71 (d, J = 7.1 Hz, 2H), 0.44 (d, J = 1.7 Hz, 2H). m/z [M+H]⁺ 498.0

Example 115

Synthesis of (S)-8-(2-(1-oxa-6-azaspiro[3.3]heptane-6-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0523] m/z [M+H]⁺ 596.17

Example 116

Synthesis of (R)-8-(2-(1-oxa-6-azaspiro[3.3]heptane-6-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0524] m/z [M+H]⁺ 596.17

Example 117

Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-(methoxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0525] m/z [M+H]⁺ 598.24

Example 118

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-(methoxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

5 [0526] m/z [M+H]⁺ 598.24

Example 119

Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-(hydroxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0527] m/z [M+H]⁺ 584.32

10 [0528] m/z [M+H]⁺ 584.32

Example 120

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-(hydroxymethyl)azetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0529] m/z [M+H]⁺ 584.28

Example 121

15 Synthesis of (S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methyl-N-(oxetan-3-yl)morpholine-2-carboxamide

[0530] m/z [M+H]⁺ 570.21

Example 122

20 Synthesis of (S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-(oxetan-3-yl)morpholine-2-carboxamide

Example 123

Synthesis of (R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-methyl-N-(oxetan-3-yl)morpholine-2-carboxamide

[0531] m/z [M+H]⁺ 584.25

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Example 124

Synthesis of (R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N-(oxetan-3-yl)morpholine-2-carboxamide

[0532] m/z [M+H]⁺ 570.23

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Example 125

Synthesis of N-(1-cyanocyclopropyl)-8-((2R,5S)-2-((difluoromethoxy)methyl)-5-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0533] ¹H NMR (400 MHz, DMSO-d₆) δ 9.56 (br, 1H), 9.46 (s, 1H), 8.18 (s, 1H), 7.65 (t, J = 51.2 Hz, 1H), 6.75 (t, J = 75.6 Hz, 1H), 6.64 (s, 1H), 4.26 – 4.25 (m, 1H), 4.08 – 4.01 (m, 3H), 3.92 – 3.89 (m, 1H), 3.82 – 3.79 (m, 1H), 3.32 – 3.17 (m, 2H), 1.51 – 1.41 (m, 4H), 1.06 (d, J = 6.8 Hz, 3H). m/z [M+H]⁺ 560.1

Example 126

Synthesis of 3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0534] ¹H NMR (400 MHz, DMSO-d₆) δ 9.35 (s, 1H), 8.77 (s, 1H), 8.14 (s, 1H), 7.65 (t, J = 51.2 Hz, 1H), 6.67 (s, 1H), 4.61 (t, J = 5.6 Hz, 2H), 4.32 – 4.21 (m, 1H), 4.20 – 4.13 (m, 2H), 4.06 – 3.95 (m, 1H), 3.89 – 3.71 (m, 2H), 3.65 – 3.44 (m, 2H), 3.33 (s, 3H), 3.27 – 3.21 (m, 1H), 3.16 – 3.04 (m, 1H), 1.47 (s, 3H), 1.02 (d, J = 6.4 Hz, 3H). m/z [M+H]⁺ 529.1

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Example 127

Synthesis of 8-((2R,5S)-2-((difluoromethoxy)methyl)-5-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0535] ^1H NMR (400 MHz, DMSO-*d*₆) δ 9.36 (s, 1H), 8.77 (s, 1H), 8.16 (s, 1H), 7.65 (t, *J* = 51.2 Hz, 1H), 6.75 (t, *J* = 75.6 Hz, 1H), 6.71 (s, 1H), 4.62 (t, *J* = 6.8 Hz, 2H), 4.29 – 4.20 (m, 1H), 4.19 – 4.17 (m, 2H), 4.10 – 3.98 (m, 3H), 3.93 – 3.86 (m, 1H), 3.83 – 3.81 (m, 1H), 3.27 – 3.25 (m, 1H), 3.21 – 3.14 (m, 1H), 1.49 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H). *m/z* [M+H]⁺ 565.1

Example 128

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-(hexahdropyrazino[2,1-

10 c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0536] ^1H NMR (400 MHz, DMSO-*d*₆) δ 9.37 (s, 1H), 8.45 (s, 1H), 8.10 (s, 1H), 7.66 (t, *J* = 51.2 Hz, 1H), 6.68 (d, *J* = 1.2 Hz, 1H), 3.88 – 3.69 (m, 3H), 3.63 – 3.48 (m, 2H), 3.19 (t, *J* = 10.4 Hz, 1H), 3.04 – 2.98 (m, 1H), 2.92 – 2.87 (m, 1H), 2.73 (d, *J* = 11.2 Hz, 1H), 2.60 – 2.54 (m, 2H), 2.48 – 2.44 (m, 1H), 2.34 – 2.28 (m, 1H), 1.15 (s, 3H), 0.75 – 0.69 (m, 2H), 0.48 – 0.43 (m, 2H). *m/z* [M+H]⁺ 510.2

Example 129

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-(hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0537] ^1H NMR (400 MHz, DMSO-*d*₆) δ 9.35 (s, 1H), 8.74 (s, 1H), 8.11 (s, 1H), 7.66 (t, *J* = 51.2 Hz, 1H), 6.70 (d, *J* = 1.2 Hz, 1H), 4.63 (dd, *J* = 6.0, 2.8 Hz, 2H), 4.24 – 4.07 (m, 2H), 3.92 – 3.68 (m, 3H), 3.59 – 3.54 (m, 2H), 3.19 (t, *J* = 10.4 Hz, 1H), 3.05 – 3.00 (m, 1H), 2.92 – 2.89 (m, 1H), 2.74 (d, *J* = 11.2 Hz, 1H), 2.63 – 2.54 (m, 2H), 2.48 – 2.41 (m, 1H), 2.35 – 2.28 (m, 1H), 1.49 (s, 3H). *m/z* [M+H]⁺ 526.2

Example 130

25 Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide

[0538] ^1H NMR (400 MHz, DMSO-*d*₆) δ 9.55 (br, 1H), 9.45 (s, 1H), 8.17 (s, 1H), 7.66 (t, *J* = 51.2 Hz, 1H), 6.64 (s, 1H), 4.27 – 4.26 (m, 1H), 4.03 – 4.00 (m, 1H), 3.84 – 3.76 (m, 2H), 3.58 –

3.54 (m, 2H), 3.54 (s, 3H), 3.34 – 3.23 (m, 1H), 3.13 – 3.10 (m, 1H), 1.47 – 1.35 (m, 4H), 1.04 (d, J = 6.8 Hz, 3H). m/z [M+H]⁺ 524.1

Example 131

Synthesis of (R)-8-(2-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)morpholino)-3-(5-difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0539] m/z [M+H]⁺ 596.36

Example 132

Synthesis of (S)-8-(2-(2-oxa-6-azaspiro[3.3]heptane-6-carbonyl)morpholino)-3-(5-difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0540] m/z [M+H]⁺ 596.36

Example 133

Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-methoxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0541] m/z [M+H]⁺ 584.32

Example 134

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-methoxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0542] m/z [M+H]⁺ 584.32

Example 135

Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(2-(3-hydroxyazetidine-1-carbonyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0543] m/z [M+H]⁺ 570.29

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Example 136

Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(2-(morpholine-4-carbonyl)morpholino)imidazo[1,5-a]pyridine-6-sulfonamide

[0544] m/z [M+H]⁺ 584.36

Example 137

- 5 Synthesis of 3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0545] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.38 (s, 1H), 8.48 (s, 1H), 8.14 (s, 1H), 7.66 (t, *J* = 51.2 Hz, 1H), 6.66 (s, 1H), 4.25 – 4.23 (m, 1H), 4.03 – 3.99 (m, 1H), 3.84 – 3.80 (m, 2H), 3.57 – 3.50 (m, 2H), 3.26 (s, 3H), 3.23 – 3.21 (m, 1H), 3.08 – 3.05 (m, 1H), 1.13 (s, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.79 – 0.72 (m, 2H), 0.48 – 0.44 (m, 2H). m/z [M+H]⁺ 513.2

Example 138

Synthesis of 3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,6S)-2-(methoxymethyl)-6-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0546] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.37 (s, 1H), 8.45 (s, 1H), 7.97 (s, 1H), 7.66 (t, *J* = 51.2 Hz, 1H), 6.70 (d, *J* = 1.2 Hz, 1H), 4.17 – 4.14 (m, 2H), 3.81 – 3.77 (m, 1H), 3.63 – 3.59 (m, 1H), 3.47 – 3.44 (m, 1H), 3.37 (s, 3H), 3.32 – 3.28 (m, 1H), 3.20 – 3.16 (m, 1H), 3.04 – 3.00 (m, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.16 (s, 3H), 0.76 – 0.70 (m, 2H), 0.48 – 0.43 (m, 2H). m/z [M+H]⁺ 513.2

Example 139

- 20 Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(2,5-dioxa-8-azaspiro[3.5]nonan-8-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0547] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.64 (s, 1H), 8.39 (br, 1H), 8.02 (s, 1H), 7.69 (t, *J* = 52.8 Hz, 1H), 6.78 (s, 1H), 4.74 (s, 4H), 4.04 – 3.76 (m, 2H), 3.51 (s, 2H), 3.29 – 3.15 (m, 2H), 1.17 (s, 3H), 0.87 – 0.62 (m, 2H), 0.53 – 0.35 (m, 2H). m/z [M+H]⁺ 513.1

Example 140

Synthesis of (2R,5S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,5-dimethylmorpholine-2-carboxamide

[0548] m/z [M+H]⁺ 542.26

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Example 141

Synthesis of (2S,5S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,5-dimethylmorpholine-2-carboxamide

[0549] m/z [M+H]⁺ 542.22

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Example 143

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(methoxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0550] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.56 (s, 1H), 8.74 (s, 1H), 8.10 (s, 1H), 7.68 (t, *J* = 53.2 Hz, 1H), 6.65 (d, *J* = 0.8 Hz, 1H), 4.62 (dd, *J* = 6.8, 3.2 Hz, 2H), 4.17 (d, *J* = 6.4 Hz, 2H), 3.96 – 3.92 (m, 3H), 3.83 – 3.79 (m, 1H), 3.53 – 3.49 (m, 2H), 3.50 (s, 3H), 3.228 – 3.22 (m, 1H), 3.19 – 3.15 (m, 1H), 1.81 – 1.78 (m, 1H), 1.48 (s, 3H), 1.38 – 1.35 (m, 1H), 0.73 (t, *J* = 7.2 Hz, 3H). m/z [M+H]⁺ 559.2

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Example 144

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(methoxymethyl)-5-methylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide

[0551] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.70 (s, 1H), 9.50 (br, 1H), 8.12 (s, 1H), 7.69 (t, *J* = 53.2 Hz, 1H), 6.63 (d, *J* = 1.2 Hz, 1H), 4.33 – 4.19 (m, 1H), 4.04 – 4.00 (m, 1H), 3.85 – 3.80 (m, 2H), 3.58 – 3.50 (m, 2H), 3.35 (s, 3H), 3.29 – 3.23 (m, 1H), 3.13 – 3.10 (m, 1H), 1.58 – 1.32 (m, 4H), 1.04 (d, *J* = 6.4 Hz, 3H). m/z [M+H]⁺ 540

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Example 145

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aR,7aS)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0552] m/z [M+H]⁺ 513.09

Example 146

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aS,7aR)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

5 [0553] m/z [M+H]⁺ 513.09

Example 147

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aR,7aR)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0554] m/z [M+H]⁺ 513.23

10 **Example 148**

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((4aS,7aS)-hexahydro-4H-furo[3,4-b][1,4]oxazin-4-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0555] m/z [M+H]⁺ 513.27

Example 149

15 Synthesis of (2S,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide

[0556] ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.62 (s, 1H), 8.44 (s, 1H), 8.06 (s, 1H), 7.84 (s, 1H), 7.69 (t, *J* = 52.8 Hz, 1H), 6.74 (s, 1H), 4.33 – 4.28 (m, 1H), 4.06 – 3.96 (m, 1H), 3.82 – 3.73 (m, 2H), 2.79 (t, *J* = 11.6 Hz, 1H), 2.67 (d, *J* = 4.8 Hz, 3H), 2.62 – 2.54 (m, 1H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.15 (s, 3H), 0.77 – 0.68 (m, 2H), 0.49 – 0.42 (m, 2H). m/z [M+H]⁺ 542.1

Example 150

Synthesis of rel-(2S,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide

25 [0557] Compounds **150** and **152** are pairs, **150** has longer retention time on chiral column CHIRALPAK IE-3. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.60 (s, 1H), 8.46 (s, 1H), 8.43 (s, 1H),

8.05 (d, $J = 3.2$ Hz, 1H), 7.68 (t, $J = 53.2$ Hz, 1H), 6.69 (s, 1H), 4.47 – 4.46 (m, 1H), 4.34 (d, $J = 12.4$ Hz, 1H), 4.07 – 3.94 (m, 1H), 3.35 – 3.34 (m, 1H), 2.95 – 2.86 (m, 1H), 2.83 – 2.77 (m, 1H), 2.74 (d, $J = 4.4$ Hz, 3H), 1.32 (d, $J = 6.0$ Hz, 3H), 1.15 (s, 3H), 0.80 – 0.73 (m, 1H), 0.73 – 0.66 (m, 1H), 0.52 – 0.40 (m, 2H). m/z [M+H]⁺ 542.2

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Example 151

Synthesis of (2R,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide

[0558] 1 H NMR (400 MHz, DMSO-*d*₆) δ 9.62 (s, 1H), 8.46 (s, 1H), 8.07 (s, 1H), 7.84 (s, 1H), 7.69 (t, $J = 52.8$ Hz, 1H), 6.74 (d, $J = 0.8$ Hz, 1H), 4.32 – 4.27 (m, 1H), 4.05 – 3.94 (m, 1H), 3.81 – 3.72 (m, 2H), 2.83 – 2.74 (m, 1H), 2.67 (d, $J = 4.8$ Hz, 3H), 2.62 – 2.54 (m, 1H), 1.29 (d, $J = 6.8$ Hz, 3H), 1.15 (s, 3H), 0.77 – 0.68 (m, 2H), 0.50 – 0.40 (m, 2H). m/z [M+H]⁺ 542.1

Example 152

Synthesis of rel-(2R,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-N,6-dimethylmorpholine-2-carboxamide

[0559] Compounds **150** and **152** are pairs, **152** has shorter retention time on chiral column CHIRALPAK IE-3. 1 H NMR (400 MHz, DMSO-*d*₆) δ 9.61 (s, 1H), 8.45 (s, 1H), 8.41 (s, 1H), 8.05 (d, $J = 4.4$ Hz, 1H), 7.68 (t, $J = 53.2$ Hz, 1H), 6.69 (s, 1H), 4.47 – 4.46 (m, 1H), 4.34 (d, $J = 12.0$ Hz, 1H), 4.05 – 3.94 (m, 1H), 3.35 – 3.34 (m, 1H), 2.95 – 2.86 (m, 1H), 2.83 – 2.77 (m, 1H), 2.74 (d, $J = 4.8$ Hz, 3H), 1.32 (d, $J = 6.4$ Hz, 3H), 1.16 (s, 3H), 0.80 – 0.74 (m, 1H), 0.74 – 0.66 (m, 1H), 0.50 – 0.41 (m, 2H). m/z [M+H]⁺ 542.1

Example 153

Synthesis of 3-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0560] 1 H NMR (400 MHz, DMSO-*d*₆) δ 9.38 (s, 1H), 8.47 (s, 1H), 8.13 (s, 1H), 7.65 (t, $J = 51.2$ Hz, 1H), 6.67 (d, $J = 1.2$ Hz, 1H), 4.89 (t, $J = 5.6$ Hz, 1H), 4.24 – 4.23 (m, 1H), 4.03 – 4.00

(m, 1H), 3.79 – 3.77 (m, 1H), 3.71 – 3.49 (m, 3H), 3.25 – 3.12 (m, 2H), 1.14 (s, 3H), 1.02 (d, J = 6.4 Hz, 3H), 0.79 – 0.72 (m, 2H), 0.51 – 0.39 (m, 2H). m/z [M+H]⁺ 499.1

Example 154

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)imidazo[1,5-a]pyridine-6-sulfonamide

[0561] m/z [M+H]⁺ 540.29

Example 155

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide

[0562] m/z [M+H]⁺ 526.12

Example 156

Synthesis of rel-(S)-N-(1-cyanocyclopropyl)-8-(3-cyclopropylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0563] m/z [M+H]⁺ 522.29

[0564] m/z [M+H]⁺ 522.29

Example 157

Synthesis of rel-(R)-N-(1-cyanocyclopropyl)-8-(3-cyclopropylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0565] m/z [M+H]⁺ 510.34

Example 158

Synthesis of (S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(3-ethylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide

[0566] m/z [M+H]⁺ 510.34

Example 159

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0566] m/z [M+H]⁺ 531.09

Example 160

Synthesis of rel- (R)-8-(2-(azetidine-1-carbonyl)-2-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

5 [0567] m/z [M+H]⁺ 568.12

Example 161

Synthesis of rel- (S)-8-(2-(azetidine-1-carbonyl)-2-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0568] m/z [M+H]⁺ 568.16

10 [0569] m/z [M+H]⁺ 531.09

Example 163

15 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-(hydroxymethyl)-6-methylmorpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0570] m/z [M+H]⁺ 531.13

Example 164

20 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-(hydroxymethyl)-6-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0571] m/z [M+H]⁺ 515.12

Example 165

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

25 [0572] m/z [M+H]⁺ 515.12

Example 166

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-((4aS,7aR)-octahydro-1H-cyclopenta[b]pyrazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0573] m/z [M+H]⁺ 510.34

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Example 167

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-((4aR,7aS)-octahydro-1H-cyclopenta[b]pyrazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0574] m/z [M+H]⁺ 510.29

Example 168

10 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1S,9aS)-1-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0575] m/z [M+H]⁺ 556.28

Example 169

15 Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-morpholinoimidazo[1,5-a]pyridine-6-sulfonamide

[0576] m/z [M+H]⁺ 471.34

Example 170

20 Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1R,9aR)-1-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0577] m/z [M+H]⁺ 556.28

Example 173

25 Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0578] m/z [M+H]⁺ 526.37

Example 174

Synthesis of rel-8-((2R,6R)-2-(azetidine-1-carbonyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0579] m/z [M+H]⁺ 568.31

Example 175

Synthesis of rel-8-((2S,6S)-2-(azetidine-1-carbonyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0580] m/z [M+H]⁺ 568.32

Example 176

Synthesis of rel-(S)-8-(2-(azetidine-1-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0581] m/z [M+H]⁺ 554.34

Example 177

Synthesis of rel-(R)-8-(2-(azetidine-1-carbonyl)morpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0582] m/z [M+H]⁺ 554.34

Example 178

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0583] m/z [M+H]⁺ 545.3

Example 179

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0584] m/z [M+H]⁺ 545.3

Example 180

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

5 [0585] m/z [M+H]⁺ 545.33

Example 181

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0586] m/z [M+H]⁺ 593.34

10

Example 182

Synthesis of rel-N-(1-cyanocyclopropyl)-8-((3S,5R)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0587] m/z [M+H]⁺ 575.29

15

Example 183

Synthesis of rel-N-(1-cyanocyclopropyl)-8-((3R,5S)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0588] m/z [M+H]⁺ 575.29

20

Example 184

Synthesis of rel-8-((3S,5R)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0589] m/z [M+H]⁺ 580.25

25

Example 185

Synthesis of rel-8-((3R,5S)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0590] m/z [M+H]⁺ 580.28

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Example 186

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((7R,9aR)-7-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0591] m/z [M+H]⁺ 572.28

10

Example 187

Synthesis of rel-8-((2S,6R)-2-((difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0592] m/z [M+H]⁺ 565.24

15

Example 188

Synthesis of rel-8-((2R,6S)-2-((difluoromethoxy)methyl)-6-methylmorpholino)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0593] m/z [M+H]⁺ 565.24

20

Example 189

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0594] m/z [M+H]⁺ 598.34

Example 190

Synthesis of rel-8-((3S,5R)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0595] m/z [M+H]⁺ 564.28

5

Example 191

Synthesis of rel-8-((3R,5S)-3-((difluoromethoxy)methyl)-5-methylpiperazin-1-yl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0596] m/z [M+H]⁺ 564.28

10

Example 192

Synthesis of rel-(2S,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide

[0597] m/z [M+H]⁺ 528.27

15

Example 193

Synthesis of rel-(2R,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide

[0598] m/z [M+H]⁺ 528.27

20

Example 194

Synthesis of rel-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,6R)-2-(hydroxymethyl)-6-methylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide

[0599] m/z [M+H]⁺ 526.07

25

Example 195

Synthesis of rel-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,6S)-2-(hydroxymethyl)-6-methylmorpholino)imidazo[1,5-a]pyridine-6-sulfonamide

[0600]

m/z [M+H]⁺ 526.21

Example 196

Synthesis of rel- 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0601] m/z [M+H]⁺ 529.23

5

Example 197

Synthesis of rel- 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0602] m/z [M+H]⁺ 529.26

Example 198

10 Synthesis of rel- 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0603] m/z [M+H]⁺ 529.26

Example 199

15 Synthesis of rel- 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-5-ethyl-2-(hydroxymethyl)morpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0604] m/z [M+H]⁺ 529.3

Example 200

20 Synthesis of (R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6,6-dimethylmorpholine-2-carboxamide

[0605] m/z [M+H]⁺ 542.28

Example 201

25 Synthesis of (S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6,6-dimethylmorpholine-2-carboxamide

[0606] m/z [M+H]⁺ 542.32

Example 202

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((7R,9aR)-7-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0607] m/z [M+H]⁺ 567.32

Example 203

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0608] m/z [M+H]⁺ 525.25

Example 204

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0609] m/z [M+H]⁺ 530.25

Example 205

Synthesis of (S)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(6-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0610] m/z [M+H]⁺ 549.19

Example 206

Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(3-methyloxetan-3-yl)-8-(6-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0611] m/z [M+H]⁺ 554.22

Example 207

Synthesis of (R)-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0612] m/z [M+H]⁺ 565.27

Example 208

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(4-(piperazine-1-carbonyl)piperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

5 [0613] m/z [M+H]⁺ 582.27

Example 209

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((7R,9aR)-7-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

10 [0614] m/z [M+H]⁺ 556.25

Example 210

Synthesis of rel-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((1S,9aR)-1-(hydroxymethyl)hexahdropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

15 [0615] m/z [M+H]⁺ 556.28

Example 211

Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0616] m/z [M+H]⁺ 509.25

20 [0617] m/z [M+H]⁺ 514.29

Example 212

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0618] m/z [M+H]⁺ 514.29

Example 213

25 Synthesis of rel-(2S,6S)-4-(1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide

[0618] m/z [M+H]⁺ 562.21

Example 214

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

5 [0619] m/z [M+H]⁺ 515.24

Example 215

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5R)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0620] m/z [M+H]⁺ 515.24

10 [0621] m/z [M+H]⁺ 515.24

Example 216

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2R,5S)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0622] m/z [M+H]⁺ 515.24

Example 217

15 Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((2S,5R)-2-(hydroxymethyl)-5-methylmorpholino)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0623] m/z [M+H]⁺ 514.34

Example 218

20 Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3R,5S)-3-(hydroxymethyl)-5-methylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0624] m/z [M+H]⁺ 604.17

Example 219

Synthesis of (R)-1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

25 [0624] m/z [M+H]⁺ 604.17

Example 220

Synthesis of 1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0625] m/z [M+H]⁺ 590.28

5

Example 221

Synthesis of (R)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-(4-isobutyryl-3-methylpiperazin-1-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0626] m/z [M+H]⁺ 570.33

Example 222

10 Synthesis of rel-(2R,6R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide

[0627] m/z [M+H]⁺ 528.29

Example 223

15 Synthesis of rel-(2S,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide

[0628] m/z [M+H]⁺ 528.33

Example 224

20 Synthesis of 1-chloro-N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0629] m/z [M+H]⁺ 585.26

Example 225

Synthesis of (S)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-(6-oxooctahydro-2H-pyrido[1,2-a]pyrazin-2-yl)imidazo[1,5-a]pyridine-6-sulfonamide

25 [0630] m/z [M+H]⁺ 538.26

Example 226

Synthesis of (R)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-2-methylmorpholine-2-carboxamide

[0631] m/z [M+H]⁺ 528.33

5

Example 227

Synthesis of (S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-2-methylmorpholine-2-carboxamide

[0632] m/z [M+H]⁺ 528.29

Example 228

10 Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)-N-(3-methyloxetan-3-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0633] m/z [M+H]⁺ 556.26

Example 229

15 Synthesis of N-(1-cyanocyclopropyl)-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide

[0634] m/z [M+H]⁺ 551.32

Example 230

20 Synthesis of 1-chloro-3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-8-((3S,5S)-3,5-dimethylpiperazin-1-yl)-N-(1-methylcyclopropyl)imidazo[1,5-a]pyridine-6-sulfonamide

[0635] m/z [M+H]⁺ 532.22

Example 233

Synthesis of 3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-N-(1-methylcyclopropyl)-8-((6S,9aR)-6-methylhexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)imidazo[1,5-a]pyridine-6-sulfonamide

25 [0636] m/z [M+H]⁺ 540.3

Example 234

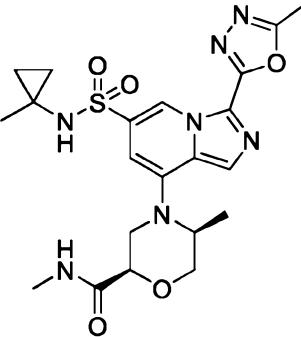
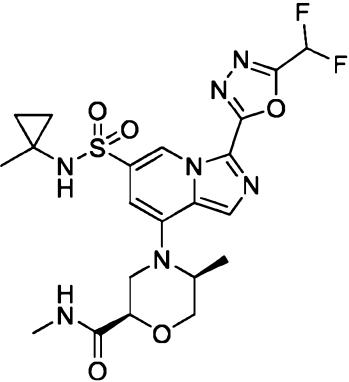
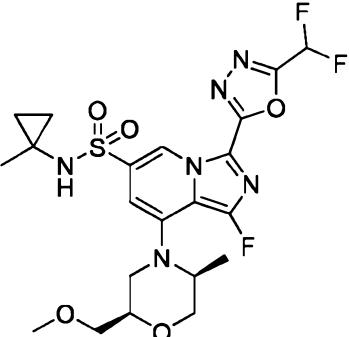
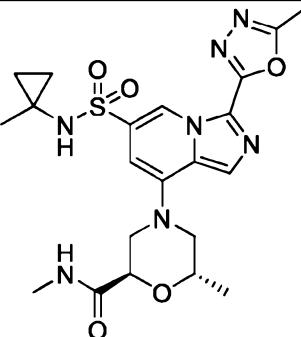
Synthesis of (2S,6S)-4-(3-(5-(difluoromethyl)-1,3,4-thiadiazol-2-yl)-6-(N-(1-methylcyclopropyl)sulfamoyl)imidazo[1,5-a]pyridin-8-yl)-6-methylmorpholine-2-carboxamide

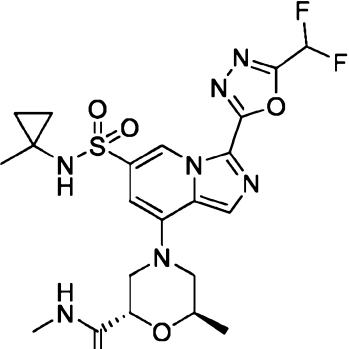
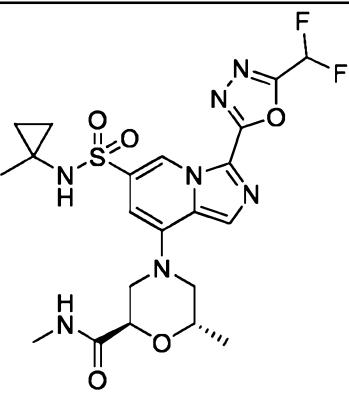
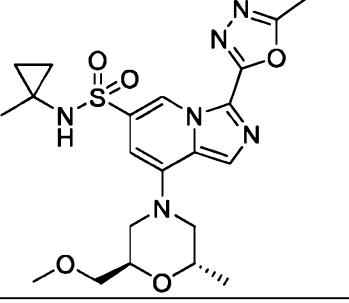
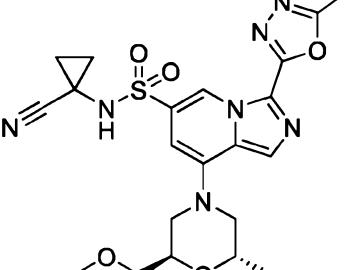
[0637] ^1H NMR (400 MHz, DMSO) δ 9.62 (s, 1H), 8.47 (s, 1H), 8.07 (s, 1H), 7.68 (t, J = 53.2 Hz, 1H), 7.38 (dd, J = 62.1, 2.4 Hz, 2H), 6.74 (d, J = 1.3 Hz, 1H), 4.26 (dd, J = 10.8, 2.5 Hz, 1H), 3.99 (ddt, J = 13.9, 7.7, 3.9 Hz, 1H), 3.76 (td, J = 10.8, 2.4 Hz, 2H), 2.79 (t, J = 11.5 Hz, 1H), 2.58 (dd, J = 12.4, 10.3 Hz, 1H), 1.28 (d, J = 6.2 Hz, 3H), 1.15 (s, 3H), 0.80 – 0.65 (m, 2H), 0.52 – 0.39 (m, 2H). m/z [M+H] $^+$ 528.2

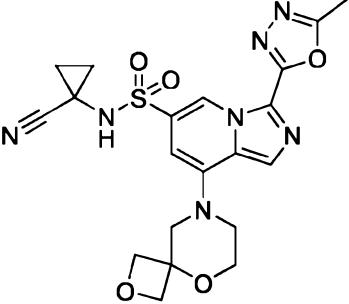
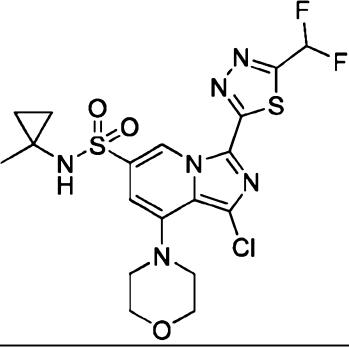
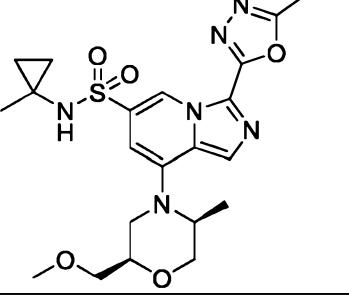
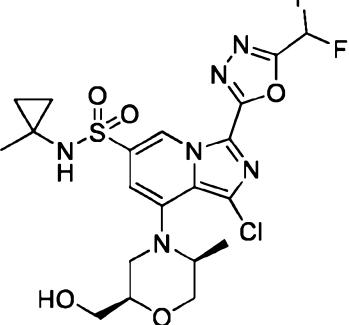
[0638] Examples 236 to 277 are disclosed Table 3 and were synthesized by, for example, methods disclosed herein.

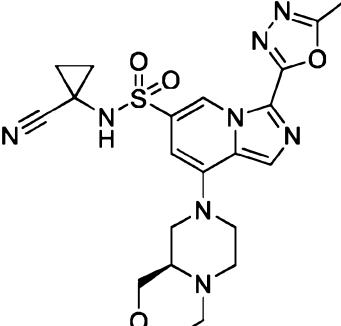
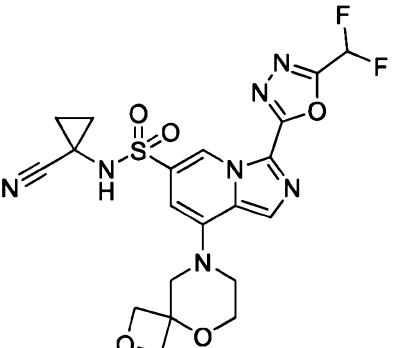
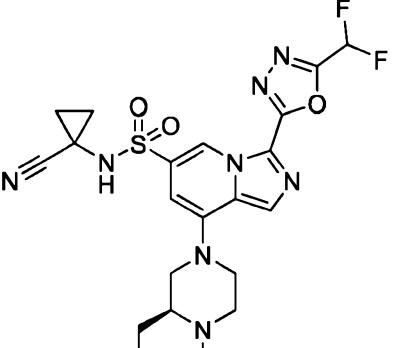
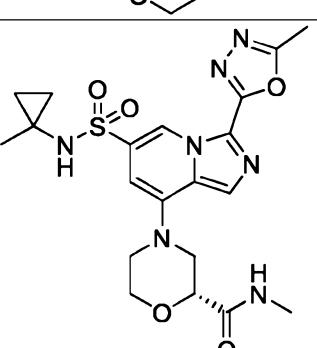
Table 3

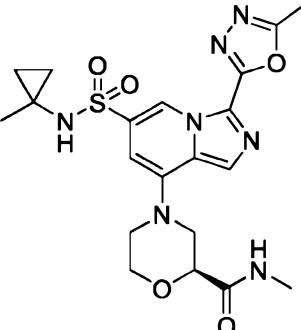
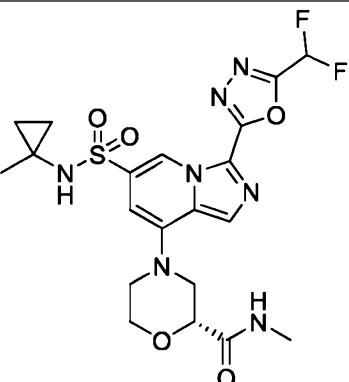
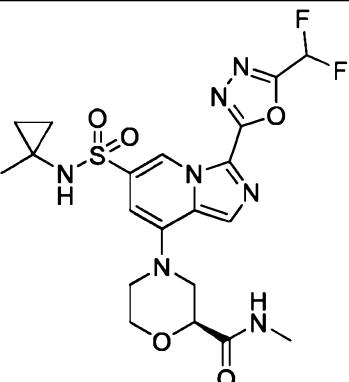
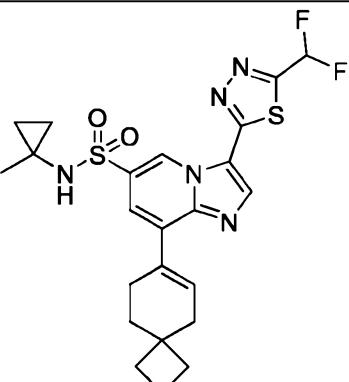
Example	Structure	m/z [M+H] $^+$
236		m/z [M+H] $^+$ 487.1
237		m/z [M+H] $^+$ 486.1

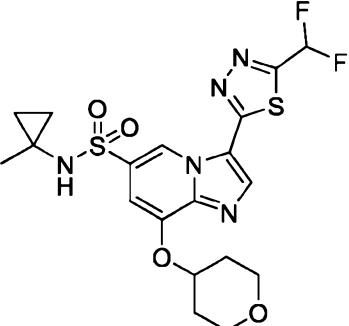
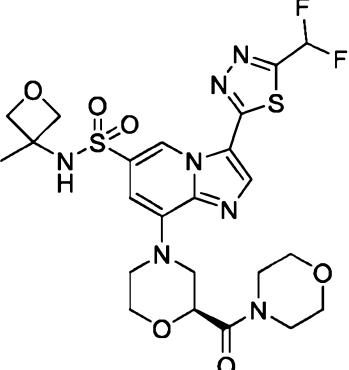
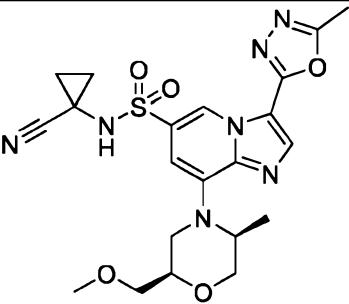
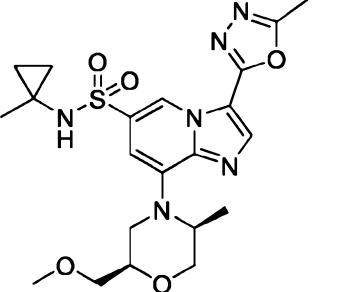
238		$m/z [M+H]^+ 490.29$
239		$m/z [M+H]^+ 526.35$
240		$m/z [M+H]^+ 531.31$
241		$m/z [M+H]^+ 490.25$

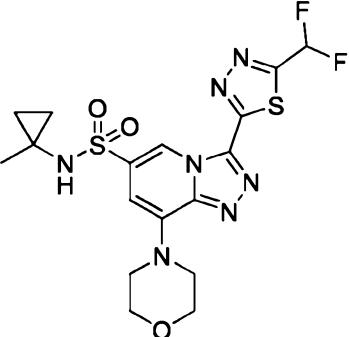
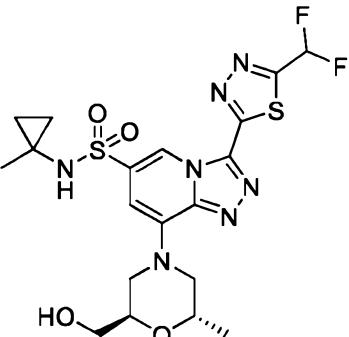
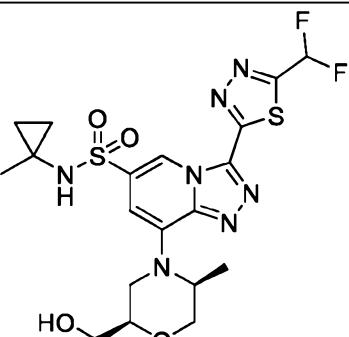
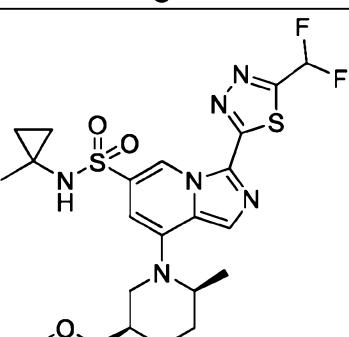
242		$m/z [M+H]^+ 526.35$
243		$m/z [M+H]^+ 526.35$
244		$m/z [M+H]^+ 477.15$
245		$m/z [M+H]^+ 488.15$

246		$m/z [M+H]^+$ 472.15
247		$m/z [M+H]^+$ 505.14
248		$m/z [M+H]^+$ 477.36
249		$m/z [M+H]^+$ 533.2

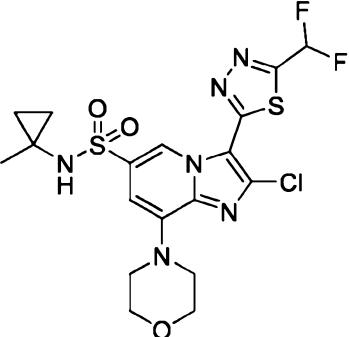
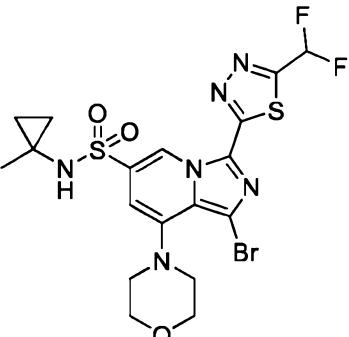
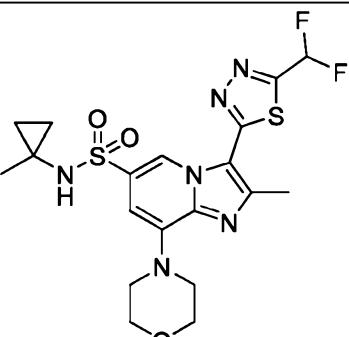
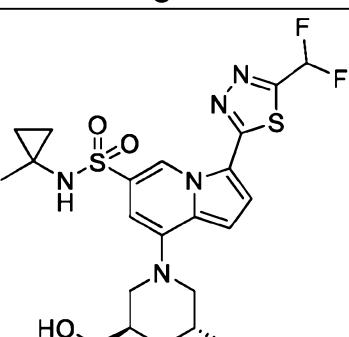
250		$m/z [M+H]^+$ 485.15
251		$m/z [M+H]^+$ 508.0
252		$m/z [M+H]^+$ 521.1
253		$m/z [M+H]^+$ 476.36

254		$m/z [M+H]^+$ 476.36
255		$m/z [M+H]^+$ 512.32
256		$m/z [M+H]^+$ 512.32
257		$m/z [M+H]^+$ 508.22

258		$m/z [M+H]^+$ 486.19
260		$m/z [M+H]^+$ 600.2
261		$m/z [M+H]^+$ 488.2
262		$m/z [M+H]^+$ 477.2

263		$m/z [M+H]^+$ 472.2
264		$m/z [M+H]^+$ 516.2
265		$m/z [M+H]^+$ 516.2
266		$m/z [M+H]^+$ 529.15

267		$m/z [M+H]^+ 529.15$
268		$m/z [M+H]^+ 486.05$
269		$m/z [M+H]^+ 485.1$
270		$m/z [M+H]^+ 485.15$

271		$m/z [M+H]^+ 504.9$
272		$m/z [M+H]^+ 549.0$
273		$m/z [M+H]^+ 485.2$
274		$m/z [M+H]^+ 514.05$

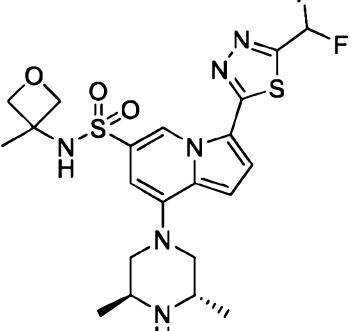
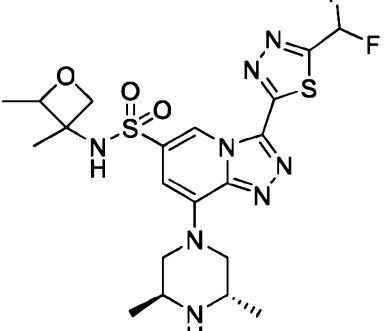
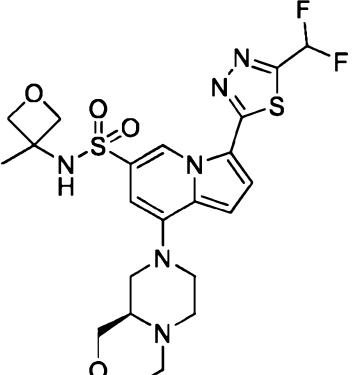
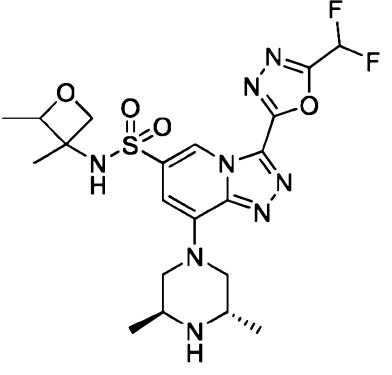
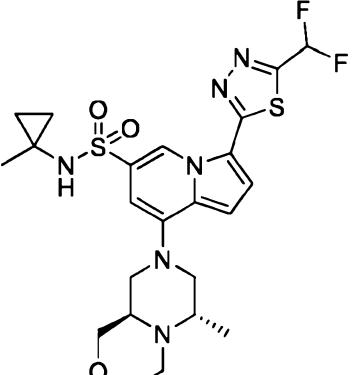
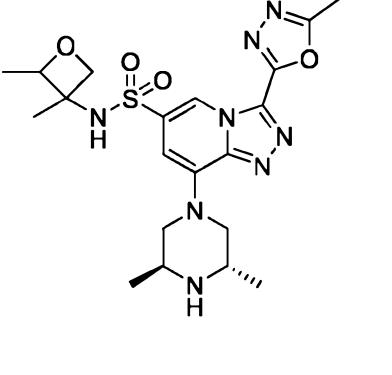
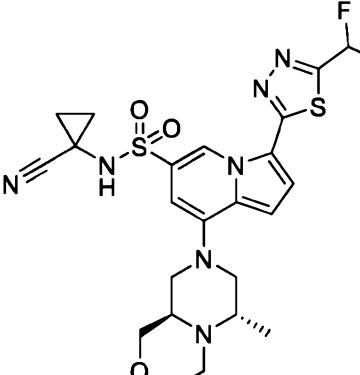
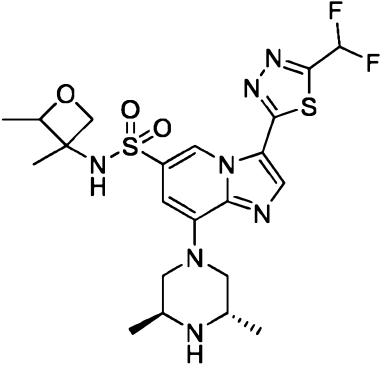
275		$m/z [M+H]^+$ 487.0
276		$m/z [M+H]^+$ 486.05
277		$m/z [M+H]^+$ 486.0
395		$m/z [M+H]^+$ 486.1

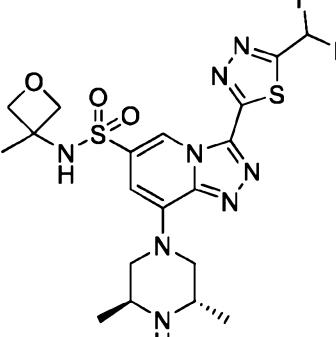
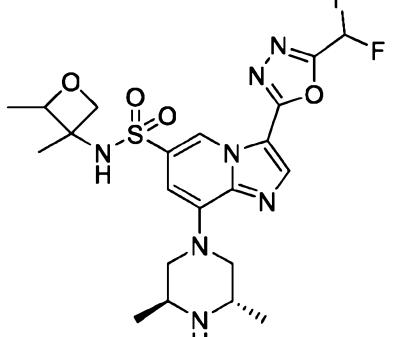
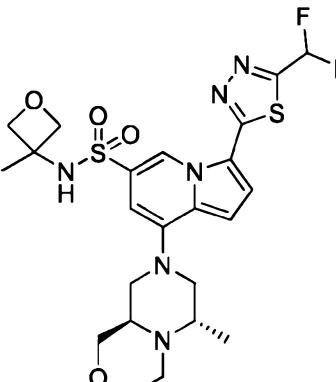
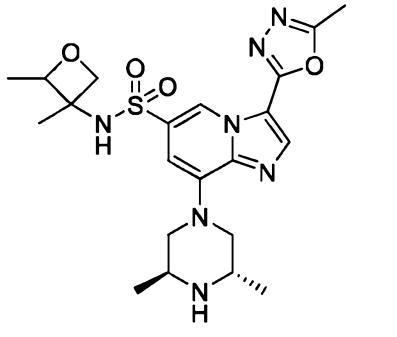
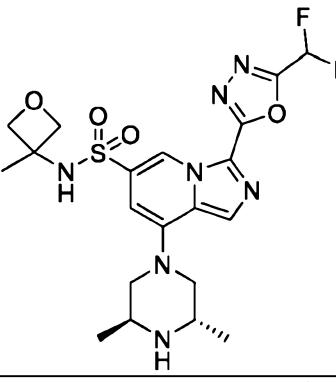
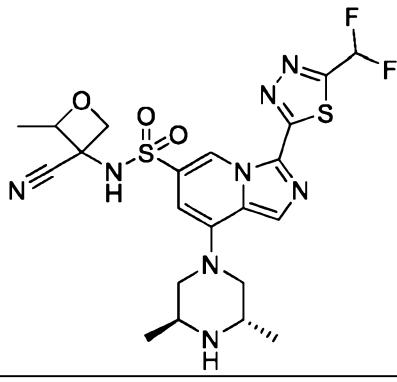
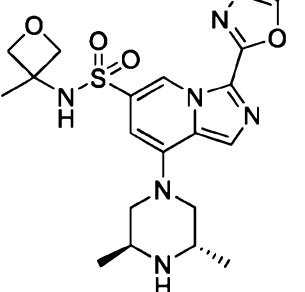
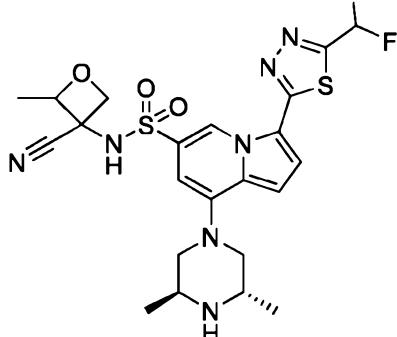
[0639] Examples disclosed in Table 4 (Ex. 278 to 393) can be prepared using the methods disclosed herein as well as general synthetic methods known in the art.

Table 4

Ex.	Structure	Ex.	Structure
278		336	
279		337	
280		338	
281		339	

282		340	
283		341	
284		342	
285		343	

286		344	
287		345	
288		346	
289		347	

290		348	
291		349	
292		350	
293		351	

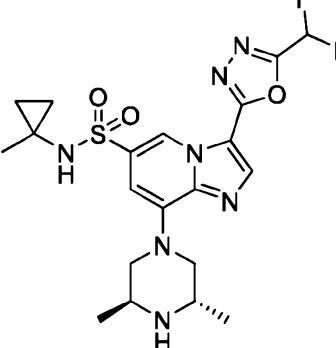
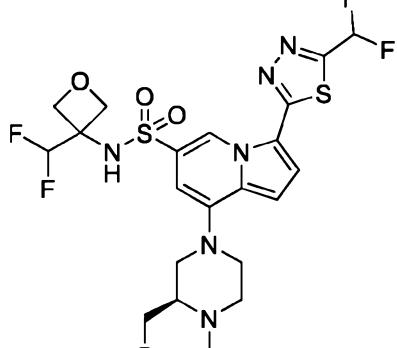
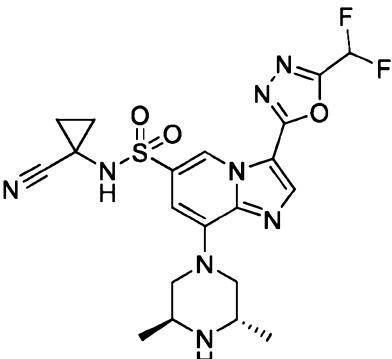
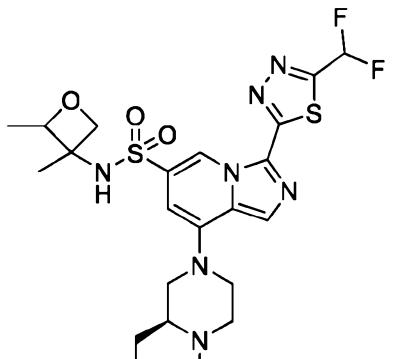
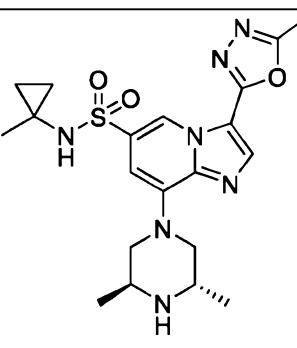
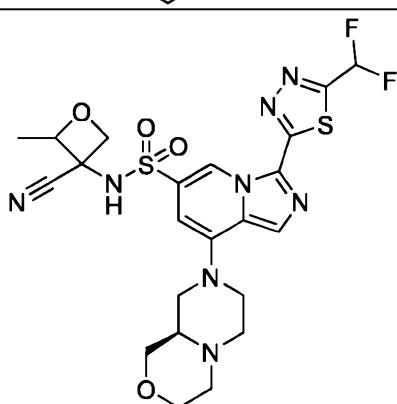
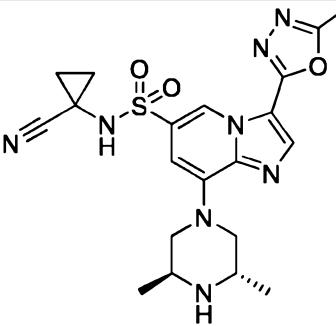
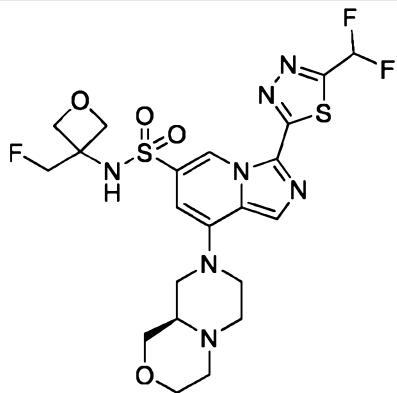
294		352	
295		353	
296		354	
297		355	

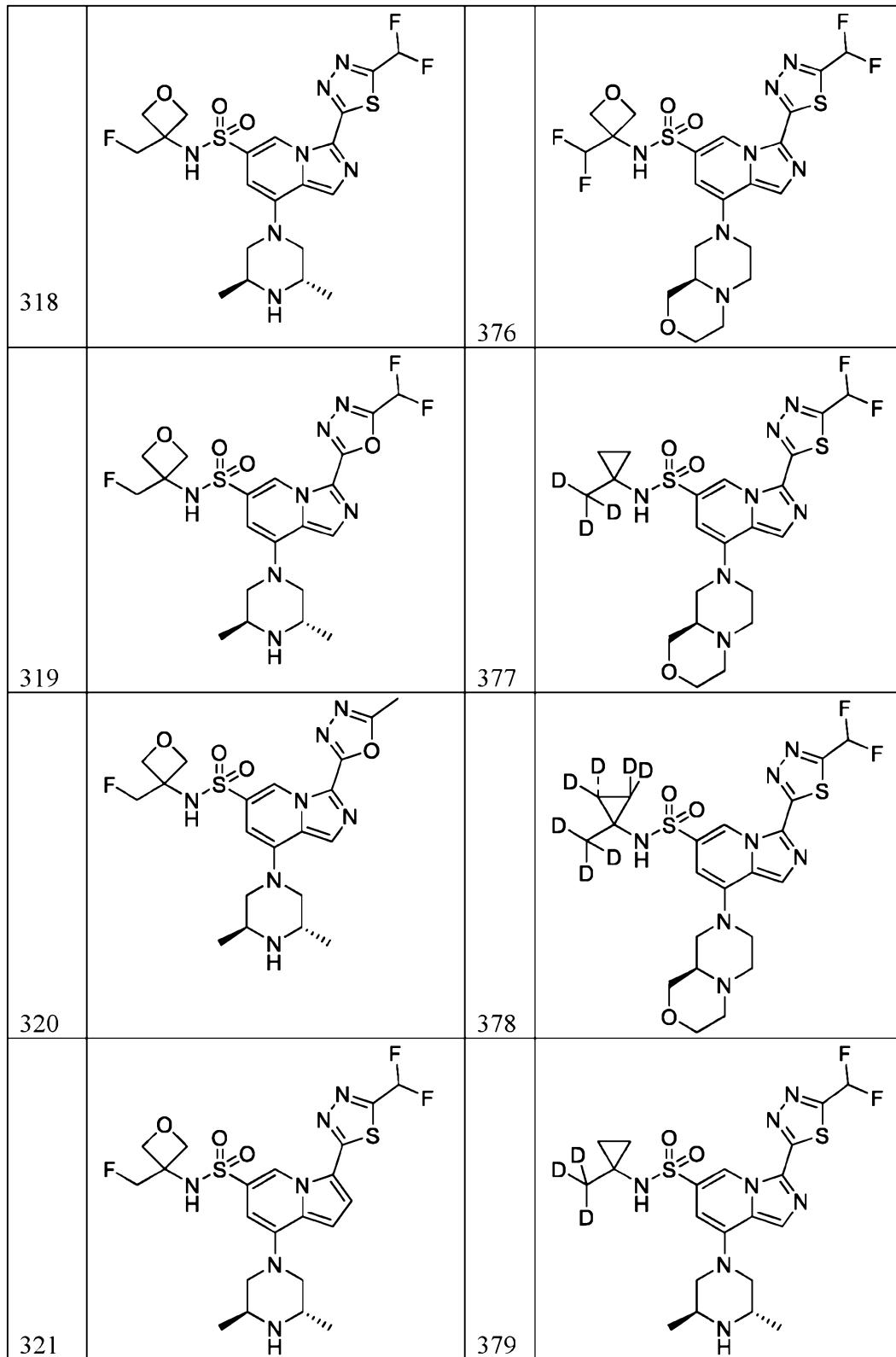
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299		357	
300		358	
301		359	

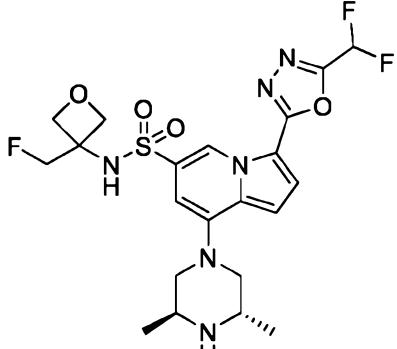
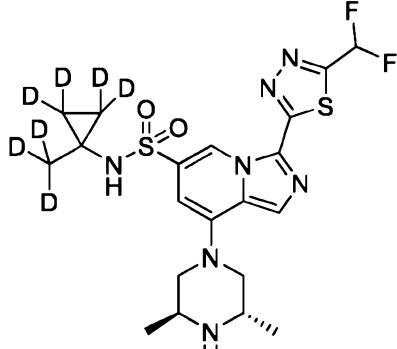
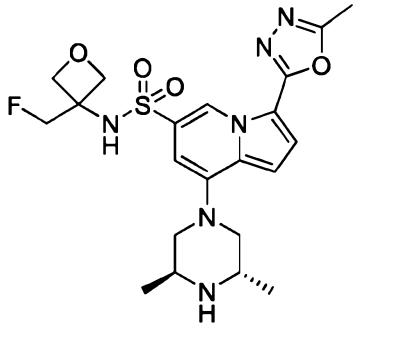
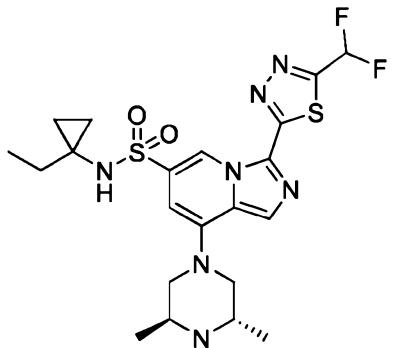
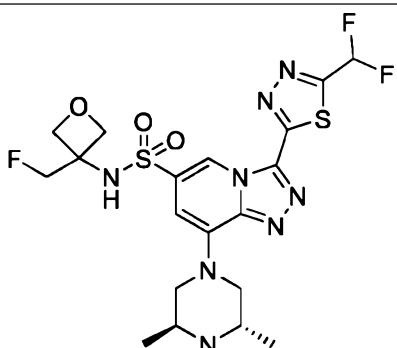
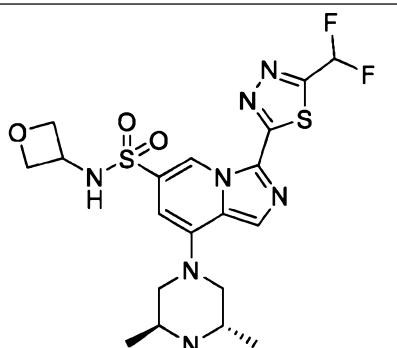
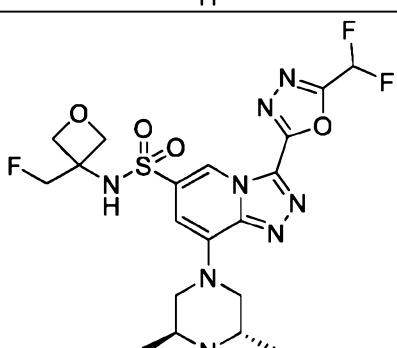
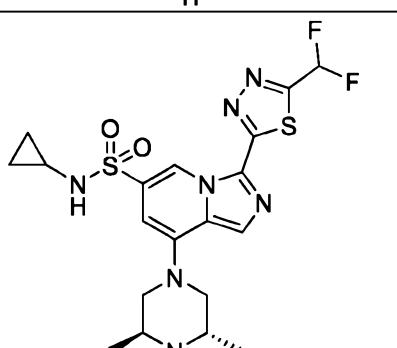
302		360	
303		361	
304		362	
305		363	

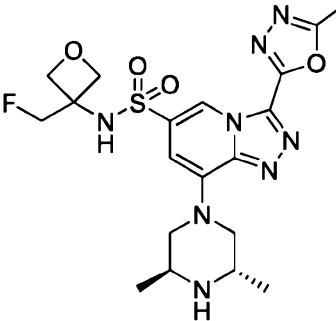
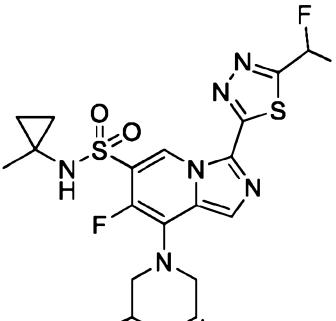
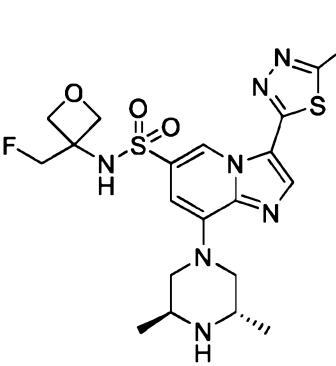
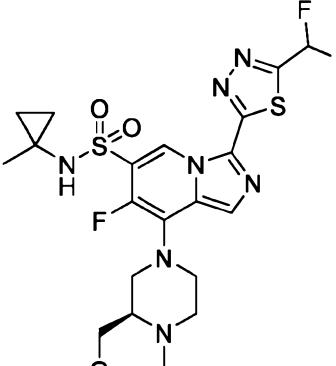
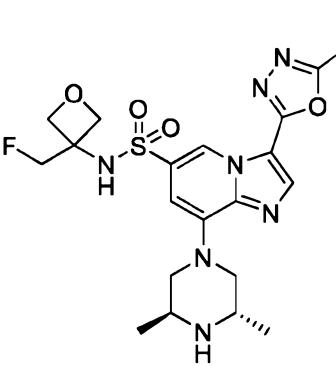
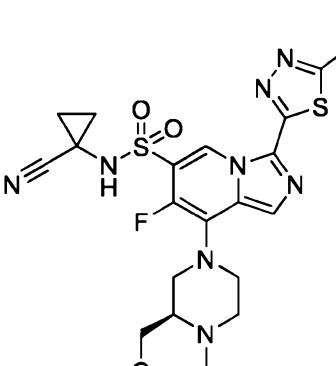
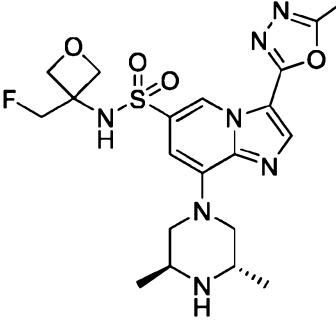
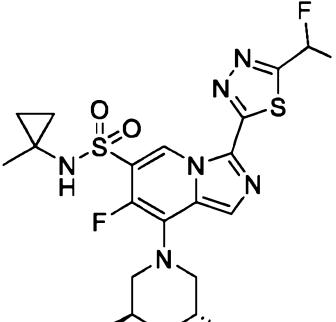
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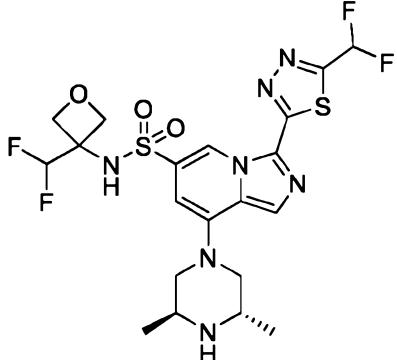
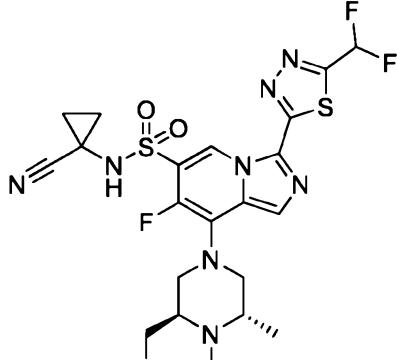
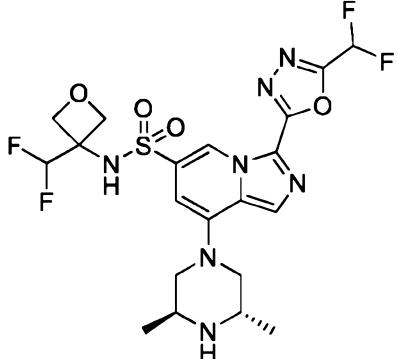
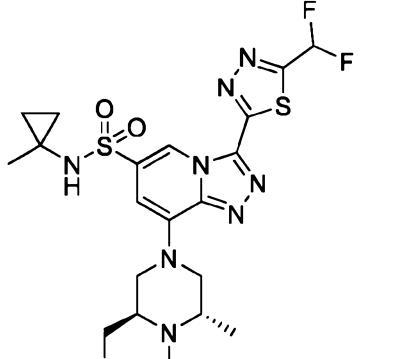
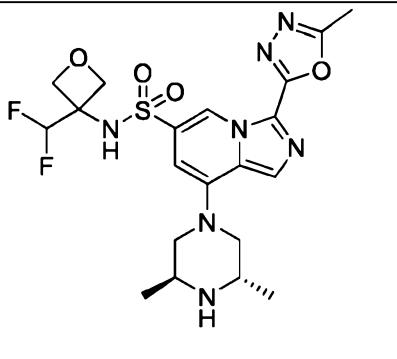
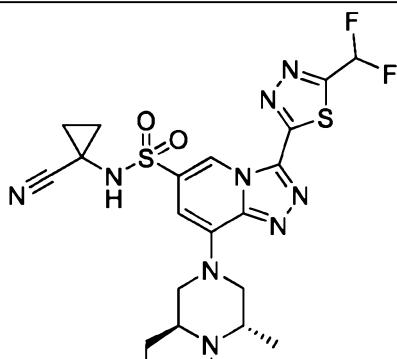
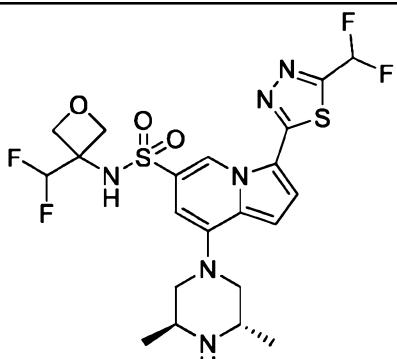
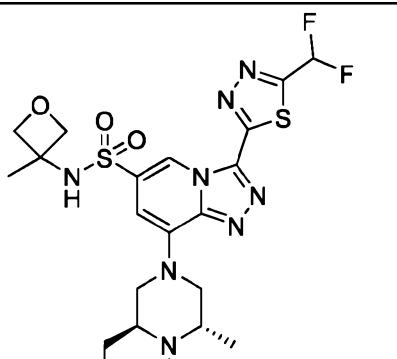
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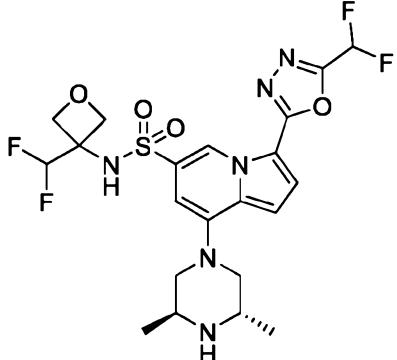
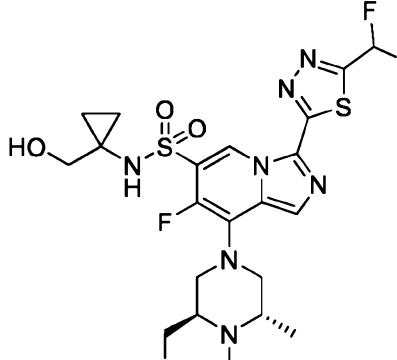
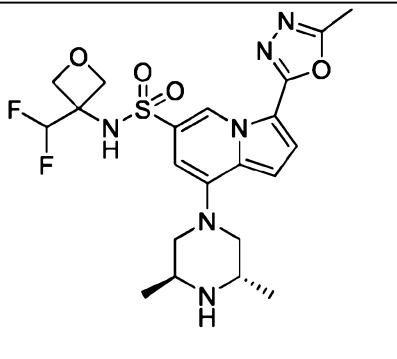
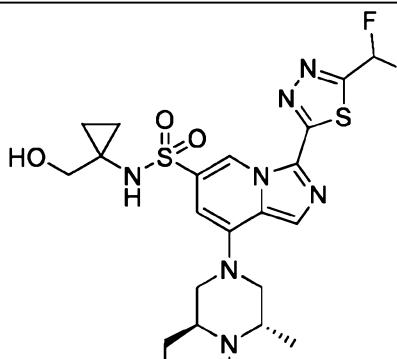
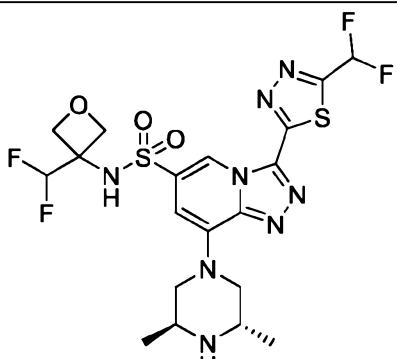
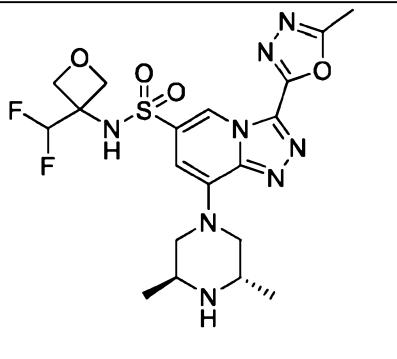
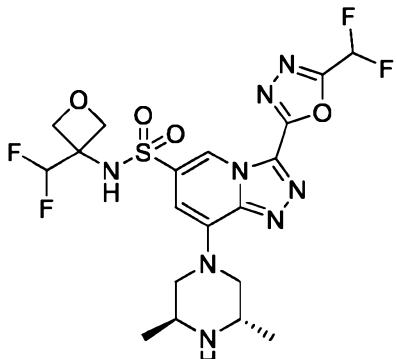
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Biological Examples

Example 1

Inhibition of PARG enzymatic assay

5

Enzymatic EC₅₀ Assay

[0640] PARG enzyme was incubated with compound or vehicle (DMSO) and the biotinylated-PARYlated PARP-1 substrate in a microtiter plate. After adding detection antibody and streptavidin-europium, and then incubating, the plate was read for fluorescence intensity. The low control (DMSO) with low fluorescence intensity represents no inhibition of enzymatic activity, while the high control (no enzyme) with high fluorescence intensity represents full inhibition of enzymatic activity.

Materials:

Enzyme:

- 15 • PARG
- hPARG: 250 pM, 1-976, His-tagged, Proteos, 2.0 mg/mL (17.9 μM)
 - Substrate: 30 nM
 - Test Compound/Enzyme Pre-incubation time: 1 hr
 - Enzyme/Substrate Reaction time: 10 minutes
- 20 Substrate: hPARP1, His6-TEV tagged, 1.2 mg/mL (10.3 μM)
Detection Antibody: anti-His monoclonal antibody-ULight, Perkin Elmer catalog # TRF0134-M
Streptavidin-Europium: Perkin Elmer catalog # AD0062
Assay Buffer: 50mM Tris-HCL pH 7.4, 50mM KCL, 3mM EDTA, 0.4mM EGTA, 1mM DTT, 0.01% Tween 20, 0.01% BSA
- 25 Temperature: 23°C

Total reaction volume: 20 μL

Controls:

- 0% inhibition: DMSO
- 100% inhibititon: No enzyme

Enzyme reaction and Detection:

1. Transfer 200nL of 100x compound or DMSO to the appropriate wells of a 384 well white polystyrene microtitre plate (Corning Catalog#3574).
2. Transfer 10 uL of 2x final concentration of enzyme in assay buffer or assay buffer alone to the appropriate wells.
3. Centrifuge the plate at 1000 rpm for 30 seconds.
4. Incubate the plate at room temperature for 1 hour.
5. Transfer 10 uL of 2x substrate in assay buffer to all test wells.
6. Incubate the plate at room temperature for 10 minutes
10. Transfer 10 uL of 3x mixture of 42nM detection antibody and 2.25nM streptavidin-europium in 50mM Tris-HCL pH 7.4 to all test wells.
8. Incubate the plate at room temperature for 1 hour.
9. Read the plate on a plate reader (Envision)

Excitation: 317nM

15 Emission: 620nM

Emission: 665nM

Data Analysis:

[0641] EC₅₀ values were calculated in Collaborative Drug Discovery vault (CDD). Curves

were fitted by CDD as response (%) vs compound concentration (uM) using a 4-parameter

20 inhibition model using Formula 1.

[0642] Formula 1:

$$\text{Fit} = (A + ((B - A) / (1 + ((C/x)^D))))$$

$$\text{Res} = (y - \text{fit})$$

[0643] The TR-FRET EC₅₀ values for a representative number of compounds of Formula (I) or

25 Formula (I') are provided in Table 2 below.

TR-FRET

**** <= 0.1 μM, 0.1 μM < *** <= 0.3 μM, 0.3 μM < ** <= 1 μM, 1 μM < * < 10 μM

Table 2

Example	TR-FRET EC ₅₀ (μM)						
1	****	20	****	39	***	58	****
2	****	21	****	40	****	59	***
3	****	22	***	41	****	60	****
4	****	23	****	42	****	61	***
5	***	24	****	43	***	62	***
6	****	25	****	44	****	63	****
7	****	26	**	45	****	64	****
8	>10 μM	27	****	46	****	65	****
9	>10 μM	28	**	47	****	66	****
10	>10 μM	29	***	48	****	67	***
11	****	30	****	49	****	68	**
12	****	31	****	50	****	69	****
13	****	32	***	51	***	70	****
14	*	33	****	52	**	71	****
15	***	34	****	53	****	72	****
16	*	35	****	54	****	73	***
17	*	36	****	55	****	74	****
18	****	37	***	56	***	75	****
19	****	38	****	57	****	76	****
77	****	105	****	133	****	161	***
78	****	106	***	134	**	162	****
79	****	107	***	135	****	163	****
80	****	108	***	136	****	164	****
81	****	109	***	137	****	165	****
82	****	110	***	138	****	166	****
83	****	111	***	139	****	167	****
84	****	112	***	140	****	168	***
85	****	113	***	141	**	169	****

Example	TR-FRET EC ₅₀ (μM)						
86	****	114	****	142	****	170	****
87	****	115	****	143	****	171	****
88	**	116	***	144	****	172	****
89	****	117	****	145	**	173	****
90	****	118	****	146	**	174	****
91	****	119	****	147	****	175	****
92	****	120	****	148	***	176	****
93	****	121	****	149	****	177	****
94	****	122	****	150	****	178	***
95	****	123	****	151	****	179	****
96	****	124	***	152	****	180	****
97	****	125	****	153	****	181	****
98	****	126	****	154	****	182	****
99	****	127	****	155	****	183	****
100	****	128	****	156	****	184	****
101	****	129	****	157	*	185	****
102	****	130	****	158	****	186	****
103	****	131	***	159	****	187	***
104	****	132	****	160	**	188	****
189	****	217	****	247	****		
190	****	218	****	248	****		
191	****	219	***	249	****		
192	****	220	****	250	***		
193	****	221	****	251	***		
194	****	222	****	252	****		
195	****	223	****	253	***		
196	****	224	****	254	***		
197	****	225	****	255	*		

Example	TR-FRET EC ₅₀ (μM)						
198	****	226	****	256	****		
199	****	227	****	257	****		
200	****	228	****	258	****		
201	**	229	****				
202	****	230	****	260	****		
203	***	231	****	261	****		
204	****	232	****	262	****		
205	***	233	****	263	****		
206	****	234	****	264	****		
207	***	235	****	265	****		
208	****	236	NT	266	****		
209	****	237	****	267	****		
210	**	238	****				
211	****	239	****				
212	**	240	****				
213	***	241	****				
214	****	242	****				
215	****	243	****				
216	****	244	****				
245	***	246	**				

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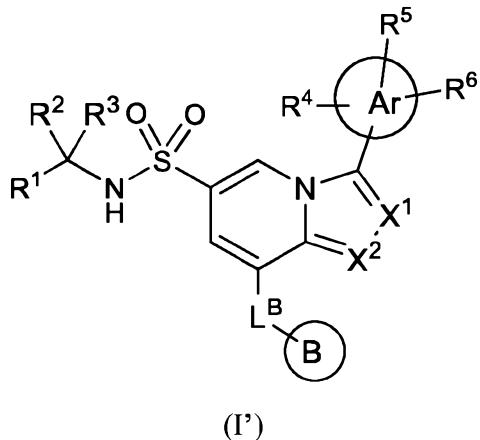
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WHAT IS CLAIMED IS:

1. A compound of Formula (I'):



wherein:

- 5 X^1 is selected from CR⁷ and N, X^2 is selected from CR⁷ and N;
- R¹ is hydrogen, cyano, formyl, -CONH₂, -CH₂OH, -CH₂OC₁₋₂ alkyl, C₁₋₂ alkyl, C₁₋₂ deuteroalkyl, or C₁₋₂ haloalkyl;
- R² and R³ are independently C₁₋₂ alkyl; or
- R² and R³ together with the carbon atom to which they are attached form C₃₋₄ cycloalkyl, or 3- or
10 4- membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S,
 wherein the cycloalkyl or heterocyclyl is unsubstituted or substituted with 1 to 6 R^{2a};
 each R^{2a} is independently deuterium, C₁₋₄ alkyl, halo, or C₁₋₄ haloalkyl;
- Ar is a 5- or 6-membered heteroaryl having 1 to 3 heteroatom ring vertices, each independently
 selected from N, O, and S;
- 15 R⁴ is C₁₋₃ alkyl, C₁₋₃ haloalkyl, hydroxyC₁₋₃alkyl, -C(O)H, or cyano;
- R⁵ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆
 haloalkoxy;
- R⁶ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆
 haloalkoxy;
- 20 each R⁷ is independently hydrogen, deuterium, halo, C₁₋₆ alkyl, C₁₋₆ haloalkyl, NR^{7a}R^{7b}, or
 hydroxy;
- each R^{7a} and R^{7b} is independently H or C₁₋₄ alkyl;

L^B is a bond, C₁₋₂ alkylene, -O-, -NR^{LB}-, or -S-;

R^{LB} is hydrogen or C₁₋₄ alkyl;

ring B is a 3- to 6- membered heterocyclyl, a 5- to 12-membered spiro heterocyclyl, or a 5- to 7- membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein ring B is unsubstituted or substituted with R^a, R^b, and R^c, wherein

5 R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, 5- or 6- membered

10 heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each

independently selected from N, O, and S, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl having 1 to 2 heteroatom

15 ring vertices, each independently selected from N, O, and S, or 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where

R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl,

hydroxyC₁₋₆ alkyl, or 3- or 6-membered heterocyclyl having 1 to 2 heteroatom ring

vertices, each independently selected from N, O, and S; or R^f and R^g together with the

nitrogen atom to which they are attached form a 4- to 6- membered heterocyclyl, or 5- to

20 12-membered spiro heterocyclyl, each heterocyclyl having 0 to 2 additional heteroatom

ring vertices, each independently selected from N, O, and S), or -S(O)₂NR^hRⁱ (where R^h

and Rⁱ are independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, or

hydroxyC₁₋₆ alkyl; or R^h and Rⁱ together with the nitrogen atom to which they are attached

form a 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each

25 independently selected from N, O, and S);

R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R^c is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; or

30 R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocyclyl combine to form

a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2

additional heteroatom ring vertices, each independently selected from N, O, and S,

wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and

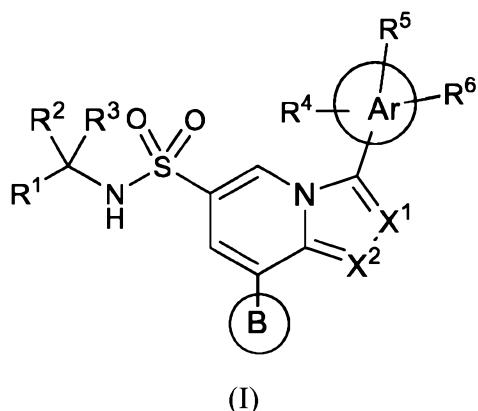
further wherein the heteroaryl and heterocycll of R^a, the phenyl, heteroaryl, and heterocycll of

5 R^d, the heterocycll or spiro heterocycll formed by R^f and R^g combining with the nitrogen to which they are attached, and the heterocycll formed by R^h and Rⁱ combining with the nitrogen to which they are attached are each independently unsubstituted or substituted with one, two, or three substituents selected from C₁₋₆ alkyl, hydroxy, hydroxyC₁₋₆ alkyl, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₂₋₈ alkoxyalkyl, and

10 C₂₋₈ haloalkoxyalkyl; or

a pharmaceutically acceptable salt thereof.

2. A compound of Formula (I):



15 wherein:

X¹ is selected from CR⁷ and N, X² is selected from CR⁷ and N, and at least one of X¹ and X² is N;

R¹ is hydrogen, cyano, formyl, -CONH₂, -CH₂OH, -CH₂OC₁₋₂ alkyl, C₁₋₂ alkyl, or C₁₋₂ haloalkyl;

20 R² and R³ are independently C₁₋₂ alkyl; or

R² and R³ together with the carbon atom to which they are attached form C₃₋₄ cycloalkyl, or 3- or 4- membered heterocycll having 1 heteroatom ring vertex, selected from N, O, and S;

Ar is a 5- or 6-membered heteroaryl having 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S;

R⁴ is C₁₋₃ alkyl, C₁₋₃ haloalkyl, hydroxyC₁₋₃alkyl, -C(O)H, or cyano;

R⁵ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R⁶ is absent or hydrogen, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

each R⁷ is independently hydrogen, deuterium, halo, C₁₋₆ alkyl, or C₁₋₆ haloalkyl;

ring B is a 3- to 6- membered heterocyclyl, a 5- to 12-membered spiro heterocyclyl, or a 5- to 7-

10 membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein ring B is unsubstituted or substituted with R^a, R^b, and R^c, wherein

R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, 5- or 6- membered

15 heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, phenyl, 5- to 6-membered heteroaryl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, or 3- to 6- membered

20 heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, or 3- or 6-membered heterocyclyl having 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S; or R^f and R^g together with the

25 nitrogen atom to which they are attached form a 4- to 6- membered heterocyclyl, or 5- to 12-membered spiro heterocyclyl, each heterocyclyl having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), or -S(O)₂NR^hRⁱ (where R^h and Rⁱ are independently hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, aminoC₁₋₆ alkyl, or hydroxyC₁₋₆ alkyl; or R^h and Rⁱ together with the nitrogen atom to which they are attached

form a 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S);

R^b is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy;

R^c is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, or C₁₋₆ haloalkoxy; or

5 R^b and R^c when on adjacent ring vertices of the 3- to 6- membered heterocyclyl combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxy, C₁₋₆ alkoxy, hydroxyC₁₋₆ alkyl, or oxo; and

10 further wherein the heteroaryl and heterocyclyl of R^a, the phenyl, heteroaryl, and heterocyclyl of R^d, the heterocyclyl or spiro heterocyclyl formed by R^f and R^g combining with the nitrogen to which they are attached, and the heterocyclyl formed by R^h and Rⁱ combining with the nitrogen to which they are attached are each independently unsubstituted or
15 substituted with one, two, or three substituents selected from C₁₋₆ alkyl, hydroxy, hydroxyC₁₋₆ alkyl, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl; or

a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof,

20 wherein R² and R³ together with the carbon atom to which they are attached form 3- or 4-membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocyclyl is unsubstituted or substituted with 1 to 6 R^{2a}.

4. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof,

wherein R² and R³ together with the carbon atom to which they are attached form 3- or 4-
25 membered heterocyclyl having 1 heteroatom ring vertex, selected from N, O, and S, wherein the heterocyclyl is unsubstituted.

5. The compound of any one of claims 1, 3 and 4, or a pharmaceutically acceptable salt thereof, wherein L^B is a bond, C₁₋₂ alkylene, or -O-;

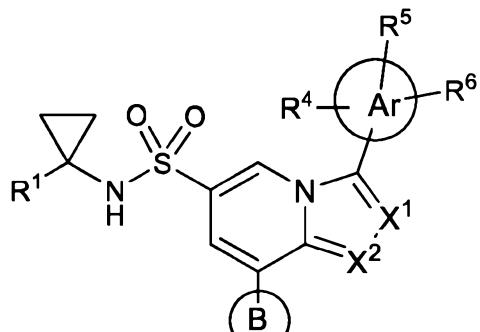
6. The compound of any one of claims 1, **3** and **4**, or a pharmaceutically acceptable salt thereof, wherein L^B is a bond.

7. The compound of any one of claims 1, **3** and **4**, or a pharmaceutically acceptable salt thereof, wherein L^B is C₁₋₂ alkylene.

8. The compound of any one of claims 1, **3** and **4**, or a pharmaceutically acceptable salt thereof, wherein L^B is -O-.

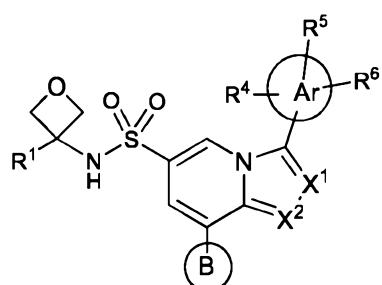
9. The compound of any one of claims 1, **3** and **4**, or a pharmaceutically acceptable salt thereof, wherein L^B is -NR^{LB}- or -S-.

10. The compound of claim **1** or **2**, or a pharmaceutically acceptable salt thereof having the formula (Ia)



(Ia).

11. The compound of any one of claims 1 to **4**, or a pharmaceutically acceptable salt thereof having the formula (Ib)



(Ib).

12. The compound of any one of claims 1 to **11**, or a pharmaceutically acceptable salt thereof, wherein at least one of X¹ and X² is N.

13. The compound of any one of claims 1 to **11**, or a pharmaceutically acceptable salt thereof, wherein X¹ and X² are both N.
5

14. The compound of any one of claims 1 to **11**, or a pharmaceutically acceptable salt thereof, wherein X¹ is N and X² is CR⁷.

15. The compound of any one of claims 1 to **11**, or a pharmaceutically acceptable salt thereof, wherein X¹ is CR⁷ and X² is N.

10 **16.** The compound of any one of claims **1** to **15**, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, fluoro, methyl, ethyl, difluoromethyl, or trifluoromethyl.

17. The compound of any one of claims **1** to **15**, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen.

15 **18.** The compound of any one of claims **1** to **17**, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen, cyano, methyl, or ethyl.

19. The compound claim **18**, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen.

20. The compound claim **18**, or a pharmaceutically acceptable salt thereof, wherein R¹ is cyano.

20 **21.** The compound claim **18**, or a pharmaceutically acceptable salt thereof, wherein R¹ is methyl.

22. The compound of any one of claims 1, 2, **12** to **21**, or a pharmaceutically acceptable salt thereof, wherein R² and R³ are independently C₁₋₂ alkyl.

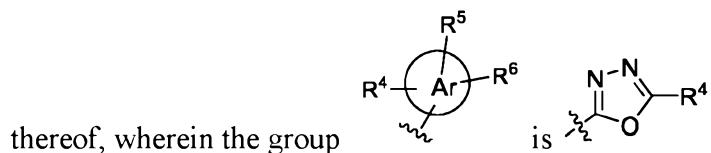
23. The compound of any one of claims 1 to **22**, or a pharmaceutically acceptable salt thereof, wherein Ar is pyridyl, pyridazinyl, pyrdimidinyl, pyrazinyl, or 1, 3, 5-triazinyl.

24. The compound of any one of claims 1 to **22**, or a pharmaceutically acceptable salt thereof, wherein Ar is imidazolyl, isoxazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, thiazolyl, 5 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-thiadiazolyl, or 1,3,4-thiadiazolyl.

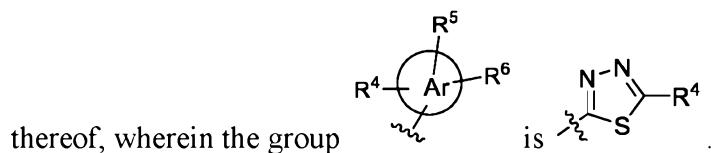
25. The compound of any one of claims 1 to **22**, or a pharmaceutically acceptable salt thereof, wherein Ar is pyridazin-3-yl.

26. The compound of any one of claims 1 to **22**, or a pharmaceutically acceptable salt thereof, wherein Ar is 1,3,4-oxadiazol-2-yl or 1,3,4-thiadiazol-2-yl.

10 **27.** The compound of any one of claims 1 to **22**, or a pharmaceutically acceptable salt



28. The compound of any one of claims 1 to **22**, or a pharmaceutically acceptable salt



15 **29.** The compound of any one of claims 1 to **28**, or a pharmaceutically acceptable salt thereof, wherein R⁴ is methyl, ethyl, difluoromethyl, trifluoromethyl, cyano, or C(O)H.

30. The compound of any one of claims 1 to **28**, or a pharmaceutically acceptable salt thereof, wherein R⁴ is difluoromethyl, methyl, trifluoromethyl, cyano, or C(O)H.

31. The compound of any one of claims 1 to **28**, or a pharmaceutically acceptable salt thereof, wherein R⁴ is methyl.

32. The compound of any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, wherein R⁴ is difluoromethyl.

33. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein R⁵ and R⁶ are independently hydrogen or absent.

5 34. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt thereof, wherein R⁵ and R⁶ are each absent.

10 35. The compound of any one of claims 1 to 34, or a pharmaceutically acceptable salt thereof, wherein ring B is a 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S, unsubstituted or substituted with R^a, R^b, and R^c.

36. The compound of claim 35, or a pharmaceutically acceptable salt thereof, wherein ring B is morpholinyl, 1,1-dioxothiomorpholinyl, azetinyl, pyrrolidinyl, piperidinyl, 6-oxo-1,6-dihdropyridinyl, or piperazinyl, each ring is independently unsubstituted or substituted with R^a, R^b, and R^c.

15 37. The compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof, wherein

R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, hydroxyC₁₋₆ alkyl, C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or 3- to 6- membered heterocyclyl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, or C₁₋₆ haloalkyl; or R^f and R^g together with the nitrogen atom to which they are attached form a 4- to 6- membered heterocyclyl, or 5- to 12-membered spiro heterocyclyl, each heterocyclyl having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), and

R^b is absent or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy;

R^c is absent or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, and C₁₋₆ haloalkoxy; and further wherein

the heterocycl of R^d, and the heterocycl or spiro heterocycl formed by R^f and R^g combining with the nitrogen to which they are attached are each independently unsubstituted or 5 substituted with one, two, or three substituents independently selected from C₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl.

38. The compound of any one of claims 1 to **36**, or a pharmaceutically acceptable salt thereof, wherein

R^a is absent, or C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, halo, C₁₋₆ haloalkyl, hydroxyC₁₋₆ alkyl, 10 C₂₋₈ alkoxyalkyl, C₂₋₈ haloalkoxyalkyl, C₃₋₆ cycloalkyl, -C(O)R^d (where R^d is hydrogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or 3- to 6- membered heterocycl having from 1 to 2 heteroatom ring vertices, each independently selected from N, O, and S), -C(O)OR^e (where R^e is hydrogen or C₁₋₆ alkyl), -C(O)NR^fR^g (where R^f and R^g are each independently hydrogen, C₁₋₆ alkyl, or C₁₋₆ haloalkyl; or R^f and R^g together with the nitrogen atom to which they are attached 15 form a 4- to 6- membered heterocycl, or 5- to 12-membered spiro heterocycl, each heterocycl having 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S), and

further wherein the heterocycl of R^d, and the heterocycl or spiro heterocycl formed by R^f and R^g combining with the nitrogen to which they are attached are each independently 20 unsubstituted or substituted with one, two, or three substituents independently selected from C₁₋₆ alkyl, hydroxyC₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₈ alkoxyalkyl, and C₂₋₈ haloalkoxyalkyl.

39. The compound of any one of claims 1 to **36** and **38**, or a pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycl and 25 combine to form a 4- to 6-membered saturated, partially unsaturated, or unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated, partially unsaturated, or unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

40. The compound of any one of claims 1 to **36** and **38**, or a pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycll and combine to form a 4- to 6-membered saturated or partially unsaturated ring comprising 0 to 2 additional heteroatom ring vertices, each independently selected from N, O, and S, wherein the 4- to 6-membered saturated or partially unsaturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl, or oxo.

41. The compound of any one of claims 1 to **36** and **38**, or a pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycll and combine to form a 4- to 6-membered saturated ring comprising 1 additional heteroatom ring vertex, selected from N, O, and S, wherein the 4- to 6-membered saturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

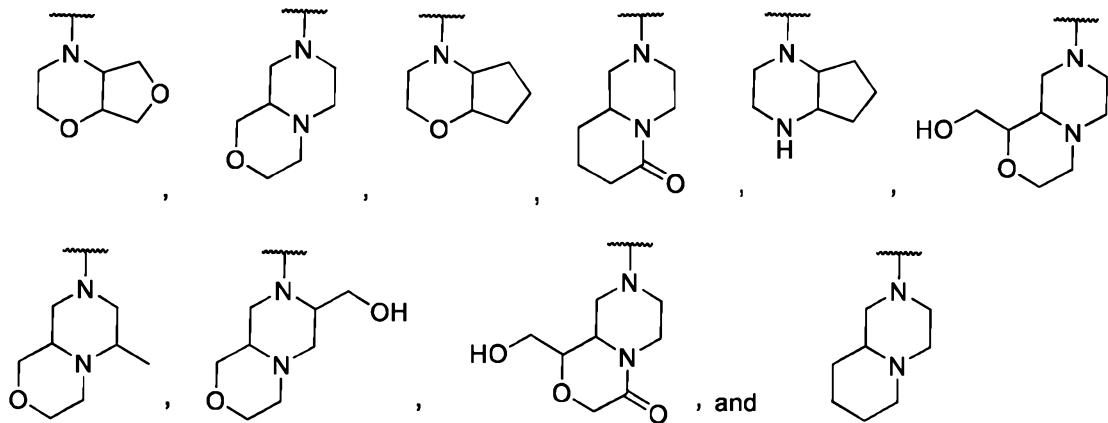
42. The compound of any one of claims 1 to **36** and **38**, or a pharmaceutically acceptable salt thereof, wherein

R^b and R^c are on adjacent ring vertices of the 3- to 6- membered heterocycll and combine to form a 4- to 6-membered saturated ring comprising 0 additional heteroatom ring vertices, wherein the 4- to 6-membered saturated ring is substituted with 0 to 3 moieties, each of which is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, halo, hydroxyC₁₋₆ alkyl or oxo.

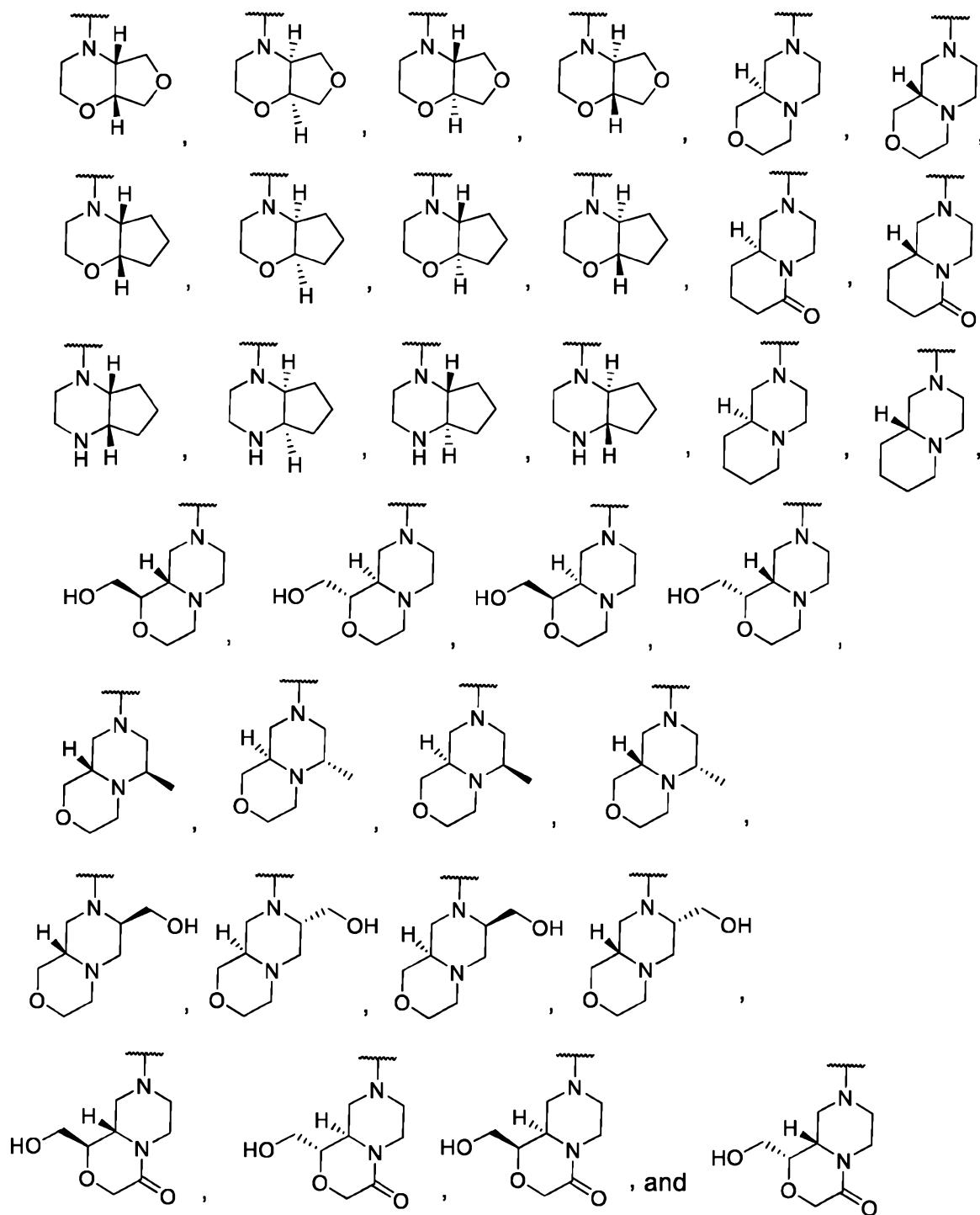
43. The compound of any one of claims 1 to **34** and **38**, or a pharmaceutically acceptable salt thereof, wherein ring B is octahydropyrazino[2,1-c][1,4]oxazinyl, octahydro-2H-pyrido[1,2-a]pyrazinyl, 6-methyloctahydropyrazino[2,1-c][1,4]oxazinyl, octahydro-6H-pyrido[1,2-a]pyrazin-6-only, or octahydropyrazino[2,1-c][1,4]oxazinyl substituted with a hydroxymethyl.

44. The compound of any one of claims 1 to **34** and **38**, or a pharmaceutically acceptable salt thereof, wherein ring B is octahydro-1H-cyclopenta[b]pyrazinyl.

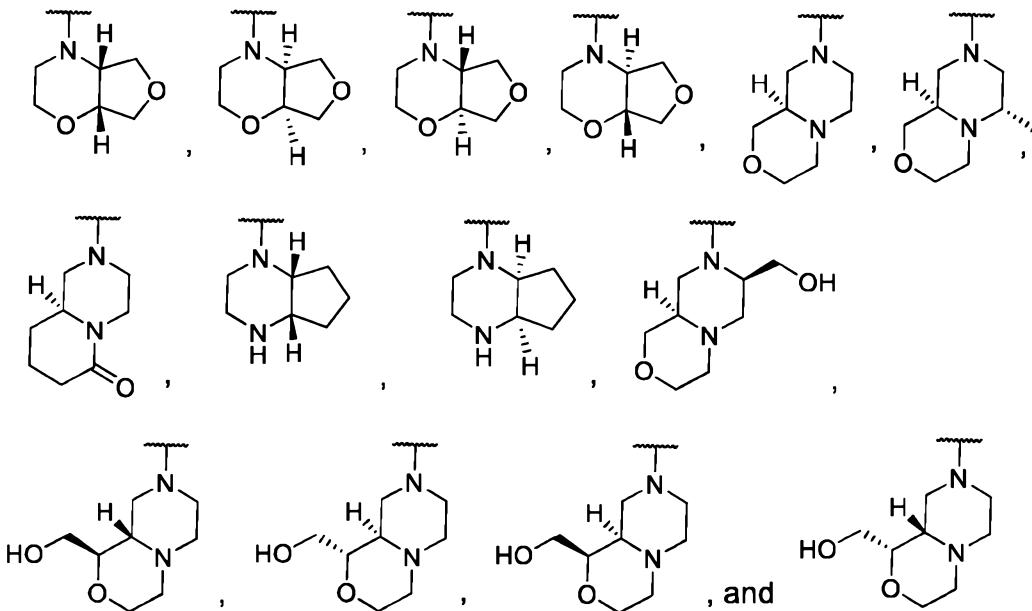
45. The compound of claim 35, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



46. The compound of claim 35, or a pharmaceutically acceptable salt thereof, wherein
5 R^b and R^c combined with ring B form the moiety selected from the group consisting of:



47. The compound of claim **35**, or a pharmaceutically acceptable salt thereof, wherein R^b and R^c combined with ring B form the moiety selected from the group consisting of:



48. The compound of any one of claims 1 to **34**, or a pharmaceutically acceptable salt thereof, wherein ring B is 5- to 12-membered spiro heterocyclyl, or 5- to 7- membered bridged heterocyclyl, each heterocyclyl having from 1 to 3 heteroatom ring vertices, each independently selected from N, O, and S, wherein each ring is substituted or unsubstituted with R^a, R^b, and R^c.

49. The compound of claim **48**, or a pharmaceutically acceptable salt thereof, wherein ring B is 2-oxaspiro[3.5]non-6-en-7-yl, 2-oxaspiro[3.5]non-7-yl, 2-oxa-8-azaspiro[4.5]dec-8-yl, 9-oxa-3-azaspiro[5.5]undec-3-yl, 2-oxa-6-azaspiro[3.4]oct-6-yl, 1-oxa-7-azaspiro[3.5]non-7-yl, 1-oxa-8-azaspiro[4.5]dec-8-yl, 6-oxa-2-azaspiro[3.3]hept-2-yl, 2,8-diazaspiro[4.5]dec-8-yl, 2-oxa-6-azaspiro[3.5]non-6-yl, 3,6-diazabicyclo[3.1.1]hept-3-yl, 2,7-diazaspiro[3.5]non-7-yl, each ring optionally substituted with R^a where R^a is hydrogen or alkyl.

50. A compound of claim **1**, or a pharmaceutically acceptable salt thereof, wherein said compound is selected from the group in Table 1.

51. A pharmaceutical composition comprising a compound of any one of claims **1** to **50**, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

52. A method of treating a disease or disorder in which PARG activity is implicated in a patient, said method comprising administering to said patient an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 50, or a pharmaceutical composition of claim 51.

5 **53.** The method of claim 52, wherein the patient is in recognized need of such treatment.

10 **54.** A method of treating cancer in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 50, or a pharmaceutical composition of claim 51.

55. The method of claim 54, wherein said cancer is ovarian, gastric, or breast cancer.

15 **56.** The method of claim 54, wherein said cancer is ovarian cancer, prostate cancer, pancreatic cancer, colorectal cancer, gastric cancer, skin cancer, endometrial cancer, cervical cancer, brain cancer, liver cancer, bladder cancer, esophageal cancer, kidney cancer, rectal cancer, stomach cancer, thyroid cancer, lymphoma, leukemia, melanoma, uterine cancer, mantle cell lymphoma, renal cell carcinoma, appendicle cancer, hematologic cancer, MYH-related polyposis, gallbladder cancer, bile duct cancer, testicular cancer, bone cancer, or head and neck cancer.

20 **57.** A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 50, or a pharmaceutical composition of claim 51, for use in therapy.

58. The compound or pharmaceutically acceptable salt thereof or composition according to claims 57, wherein said therapy is the treatment of a cancer.

59. The compound or pharmaceutically acceptable salt thereof, or composition according to claims 58, wherein said cancer is ovarian, gastric, or breast cancer.

60. The method of claim **59**, wherein said cancer is breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, colorectal cancer, gastric cancer, skin cancer, endometrial cancer, cervical cancer, brain cancer, liver cancer, bladder cancer, esophageal cancer, kidney cancer, stomach cancer, thyroid cancer, lymphoma, leukemia, melanoma, uterine cancer, mantle cell lymphoma, renal cell carcinoma, appendicle cancer, hematologic cancer, MYH-related polyposis, gallbladder cancer, bile duct cancer, testicular cancer, bone cancer, or head and neck cancer.

61. The use of a compound or a pharmaceutically acceptable salt thereof of any one of claims **1** to **50**, or a pharmaceutical composition of claim **51** in the manufacture of a medicament for use in therapy.

62. The use of claim **61**, wherein said therapy is the treatment of a cancer.

63. The use of claim **62**, wherein said cancer is breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, colorectal cancer, gastric cancer, skin cancer, endometrial cancer, cervical cancer, brain cancer, liver cancer, bladder cancer, esophageal cancer, kidney cancer, colorectal cancer, stomach cancer, thyroid cancer, lymphoma, leukemia, melanoma, uterine cancer, mantle cell lymphoma, renal cell carcinoma, appendicle cancer, hematologic cancer, MYH-related polyposis, gallbladder cancer, bile duct cancer, testicular cancer, bone cancer, or head and neck cancer.

64. A method of inhibiting PARG *in vivo* in a patient, said method comprising administering to said patient an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of claims **1** to **50**, or a pharmaceutical composition of claim **51**.

65. A method of inhibiting cell proliferation, *in vitro* or *in vivo*, said method comprising contacting a cell with an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of claims **1** to **50**, or a pharmaceutical composition of claim **51**.

66. A method of treating a cancer resistant to one or more platins or one or more PARP inhibitors in a patient in need thereof, said method comprising administering to said patient an effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 50, or a pharmaceutical composition of claim 51.

5 **67.** The method of claim 66, wherein the one or more platins is carboplatin, cisplatin, oxaliplatin, nedaplatin, saraplatin, lobaplatin, or heptaplatin.

68. The method of claim 66, wherein the one or more PARP inhibitors is niraparib, rucaparib, olaparib, talazoparib, or veliparib.

10 **69.** A method of treating and/or preventing a homologous recombinant deficient (HRD) cancer in a patient comprising administering to the patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 50, or a pharmaceutical composition of claim 51.

15 **70.** The method of claim 69, wherein the patient is in recognized need of such treatment.

20 **71.** A method of treating and/or preventing a cancer in a patient, where the cancer is characterized by a reduction or absence of BRCA1 and/or BRCA2 gene expression, the absence or mutation of BRCA1 and/or BRCA2 genes, or reduced function of BRCA1 and/or BRCA2 proteins, comprising administering to the patient a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 50, or a pharmaceutical composition of claim 51.

25 **72.** The method of claim 71, wherein the patient is in recognized need of such treatment.

73. A PARG inhibitor for use in the treatment of cancer, wherein the PARG inhibitor is a compound of any one of claims 1 to 50, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 51.

74. Use of a PARG inhibitor in the manufacture of a medicament for treating cancer, wherein the PARG inhibitor is a compound of any one of claims 1 to 50, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 51.

75. The method or use of any one of claims 66 to 74, wherein said cancer is breast
5 cancer, ovarian cancer, prostate cancer, pancreatic cancer, colorectal cancer, gastric cancer, skin
cancer, endometrial cancer, cervical cancer, brain cancer, liver cancer, bladder cancer,
esophageal cancer, kidney cancer, colorectal cancer, stomach cancer, thyroid cancer, lymphoma,
leukemia, melanoma, uterine cancer, mantle cell lymphoma, renal cell carcinoma, appendiceal
cancer, hematologic cancer, MYH-related polyposis, gallbladder cancer, bile duct cancer,
10 testicular cancer, bone cancer, or head and neck cancer.

INTERNATIONAL SEARCH REPORT

International application No PCT/US2024/015669
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A. CLASSIFICATION OF SUBJECT MATTER INV. C07D471/04 C07D519/00 A61P35/00 A61K31/437 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2021/055744 A1 (IDEAYA BIOSCIENCES INC [US]) 25 March 2021 (2021-03-25) abstract page 39 – page 130; examples 1-115 claim 1 ----- WO 2016/092326 A1 (CANCER REC TECH LTD [GB]) 16 June 2016 (2016-06-16) abstract page 328 – page 398; examples 1-631 claim 1 ----- WO 2023/057389 A1 (FORX THERAPEUTICS AG [CH]) 13 April 2023 (2023-04-13) abstract page 387 – page 474; examples 1-299 claim 1 ----- -/-	1-75 1-75 1-75
X, P		

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
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25 April 2024

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Bissmire, Stewart

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