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(54) **Title:** SMALL MOLECULE MODULATORS OF GLUCOCEREBROSIDASE ACTIVITY AND USES THEREOF

(57) **Abstract:** Provided herein are compounds that modulate glucocerebrosidase (GCase), an enzyme whose activity is associated with neurological diseases and disorders (e.g., Gaucher's disease, Parkinson's disease). Also provided are pharmaceutical compositions and kits comprising the compounds, and methods of treating GCase-related diseases and disorders (e.g., Gaucher's disease, Parkinson's disease) with the compounds in a subject, by administering the compounds and/or compositions described herein.

WO 2022/232360 A1

SMALL MOLECULE MODULATORS OF GLUCOCEREBROSIDASE ACTIVITY AND USES THEREOF

RELATED APPLICATION

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application 63/182,734, filed April 30, 2021, the entirety of which is incorporated herein by reference

BACKGROUND

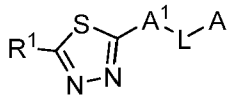
[0002] Glucocerebrosidase (EC 3.2.1.45), also is called β-glucocerebrosidase, β-glucosidase, D-glucosyl-N-acylsphingosine glucohydrolase, or GCase, is an enzyme having glucosylceramidase activity. Glucocerebrosidase is required to cleave the beta-glucosidic linkage of the chemical glucocerebroside, which is an intermediate in glycolipid metabolism. Glucocerebrosidase is localized in the lysosome and disabling mutations in the gene for glucocerebrosidase (GBA1) are associated with abnormal accumulation of lipids in lysosomes.

[0003] Genetic diseases caused by mutations in GBA1 include neurodegenerative diseases such as Gaucher's disease and Parkinson's disease. Current treatments for diseases such Type 1 Gaucher's disease are limited to enzyme replacement therapy (ERT) administered every two weeks. ERT is very expensive and not effective for neuronopathic forms of Gaucher's disease. Efforts to discover and employ small molecule compounds to activate Gcase have been met with limited success. Thus, there is a need for new compounds that effectively activate Gcase and are useful in the treatment of neurodegenerative diseases (e.g., Gaucher's disease and Parkinson's disease).

SUMMARY

[0004] The present disclosure provides compounds that are modulators of GCase. These compounds provide new compositions and methods for the treatment of diseases associated with GCase activity (*e.g.*, neurodegenerative diseases, such as Gaucher's disease and Parkinson's disease).

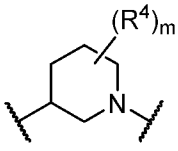
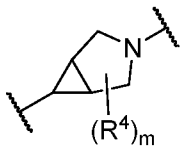
[0005] In one aspect, provided are compounds of Formula (**I**):



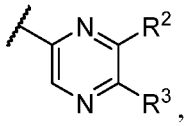
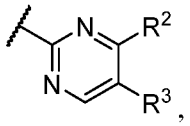
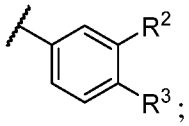
(**I**),

and pharmaceutically acceptable salts, co-crystals, tautomers, stereoisomers, solvates, hydrates, polymorphs, isotopically enriched derivatives, or prodrugs thereof, wherein:

R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

A^1 is  or ;

L is a bond or –C(=O)-;

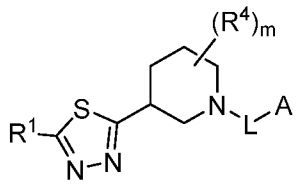
A is , , or ;

R^2 and R^3 are each independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

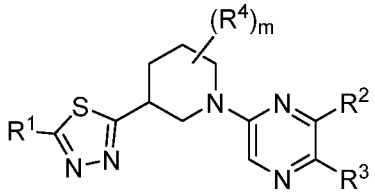
each R^4 is independently halogen, substituted or unsubstituted alkyl, or two instances of R^4 on the same carbon form with that carbon a carbonyl; and

m is 0, 1, 2, 3, or 4.

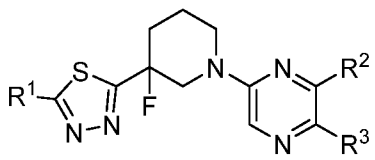
[0006] In certain embodiments, the compounds of Formula (**I**) are compounds of Formula (**I-a**), (**I-b**), (**I-c**), (**I-d**), (**I-e**), (**I-f**), (**I-g**), (**I-h**), (**I-i**), (**I-j**), (**I-k**), (**I-l**), (**I-m**), (**I-n**), (**I-o**), or (**I-p**):



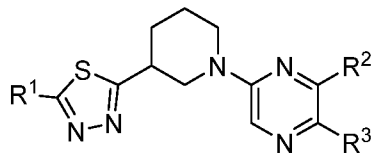
(**I-a**)

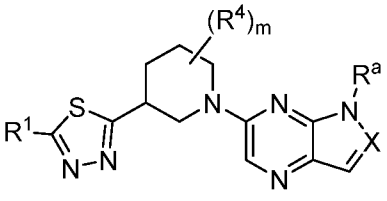


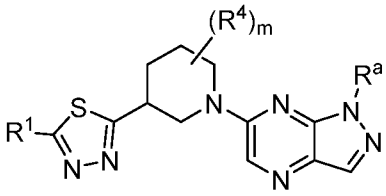
(**I-b**),

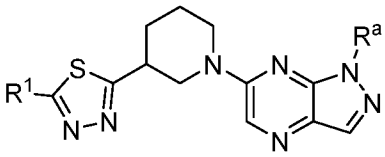


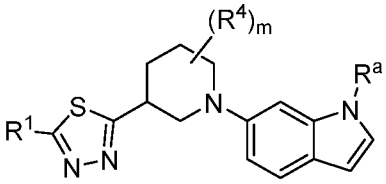
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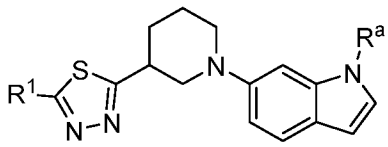

(**I-d**),

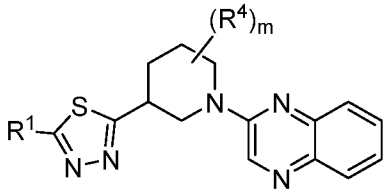

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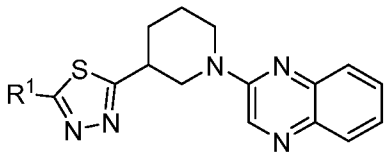

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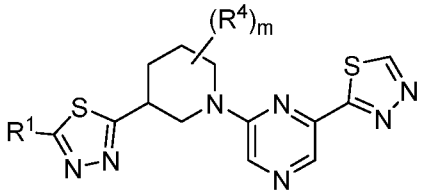

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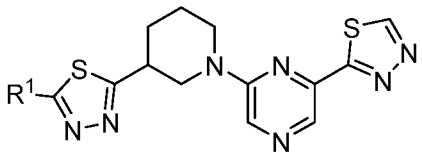

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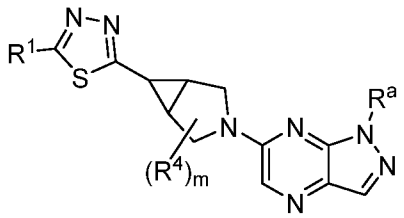

(**I-i**),

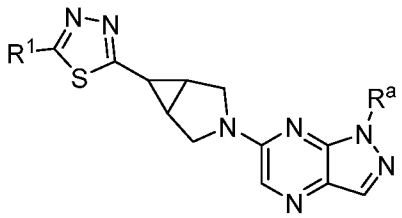

(**I-j**),

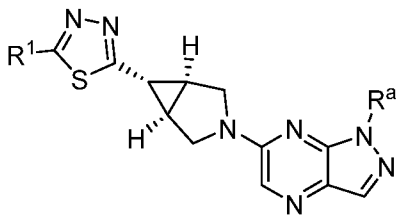

(**I-k**),


(**I-l**),


(**I-m**),

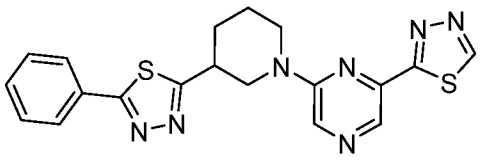
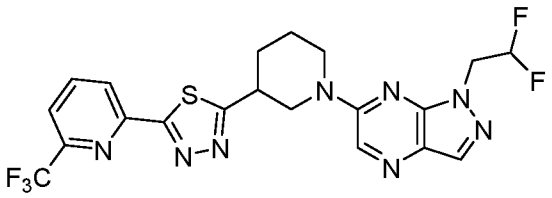
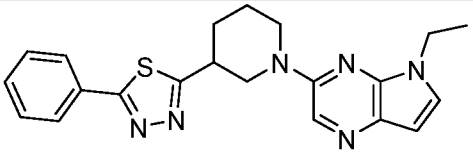
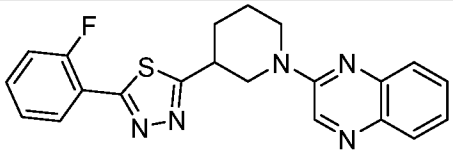
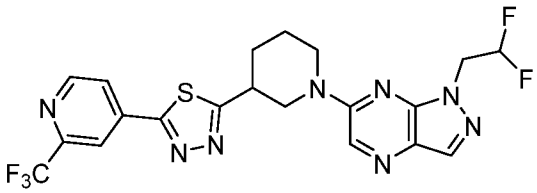
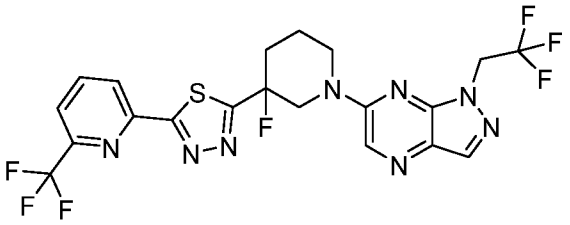
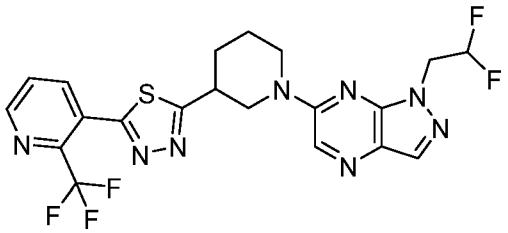
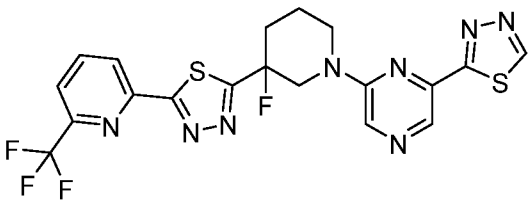
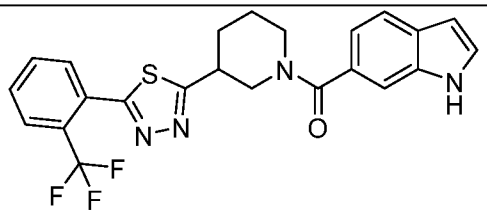
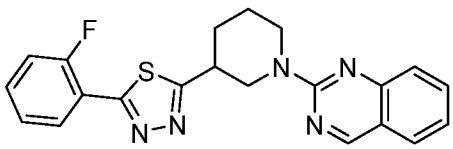
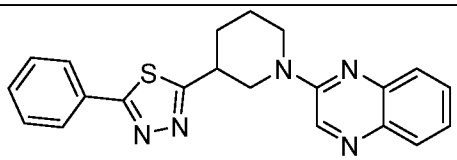
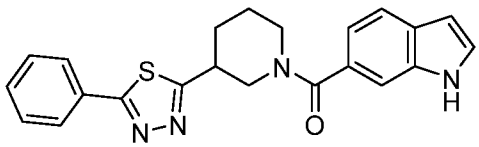
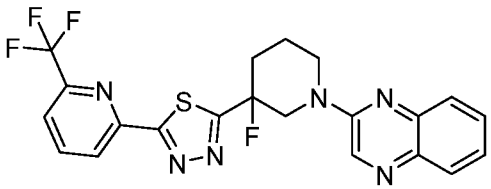
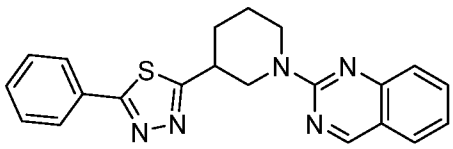
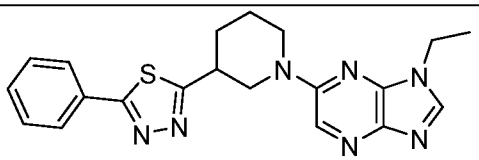
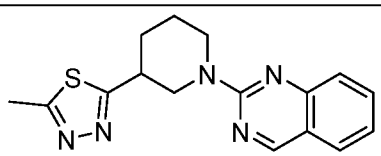

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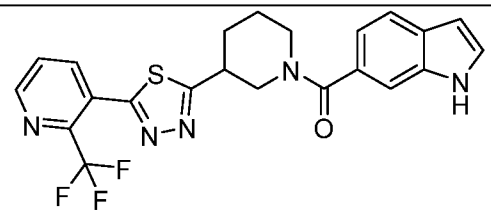
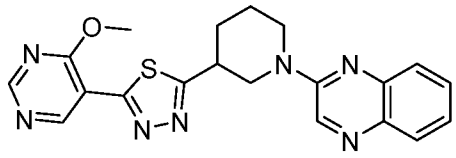
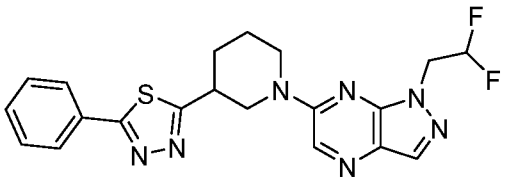
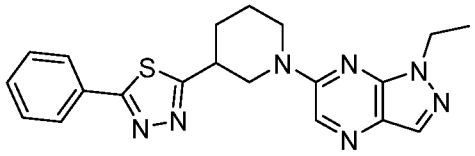
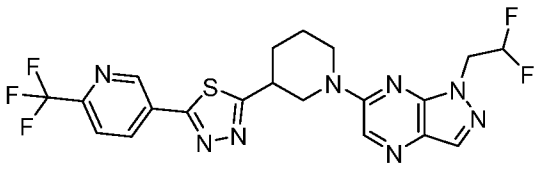
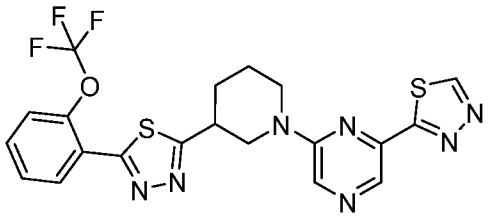
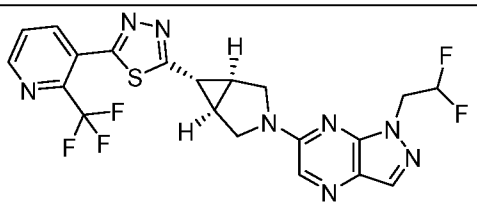
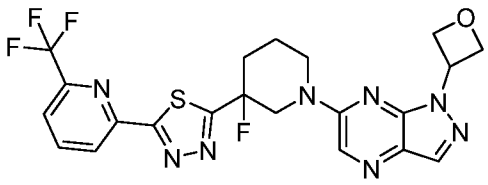
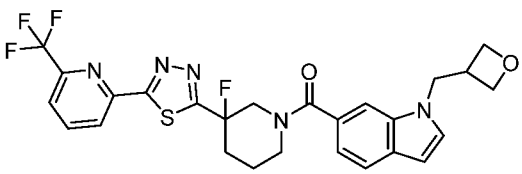
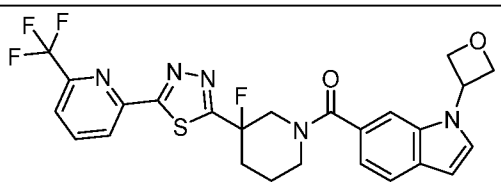
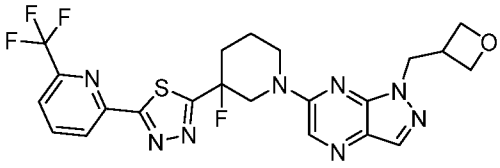
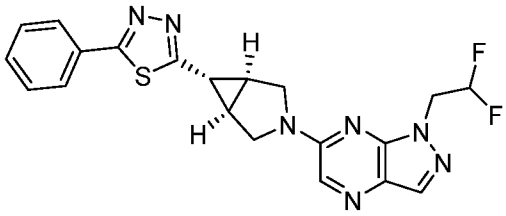
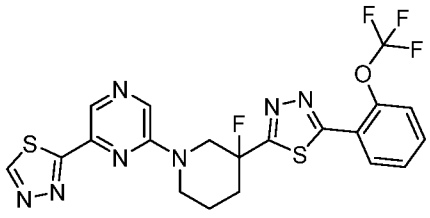

(**I-o**),


(**I-p**),

or pharmaceutically acceptable salts thereof.

[0007] Exemplary compounds of Formula (**I**) include, but are not limited to:

 1	 2
 3	 4
 5	 6
 7	 8
 9	 10
 11	 12
 13	 14
 15	 16

 17	 18
 19	 20
 21	 22
 23	 24
 25	 26
 27	 28
 29	

and pharmaceutically acceptable salts thereof.

[0008] In another aspect, provided are pharmaceutical compositions comprising a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

[0009] In another aspect, provided are methods of treating a disease or disorder in a subject in need thereof, the method comprising administering a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) to the subject.

[0010] In certain embodiments, the disease or disorder is associated with glucocerebrosidase activity. In certain embodiments, the disease or disorder is a neurological disease or disorder. In certain embodiments, the neurological disease or disorder is Parkinson's disease or Gaucher's disease.

[0011] In another aspect, provided are methods of activating glucocerebrosidase, the method comprising contacting glucocerebrosidase with an effective amount of a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**) to the subject.

[0012] In another aspect, provided are kits comprising a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof. In certain embodiments, the kits further comprise instructions for administration (*e.g.*, human administration).

[0013] The details of certain embodiments of the invention are set forth in the Detailed Description of Certain Embodiments, as described below. Other features, objects, and advantages of the invention will be apparent from the Definitions, Examples, and Claims.

DEFINITIONS

Chemical definitions

[0014] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers,

Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0015] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen *et al.*, Tetrahedron 33:2725 (1977); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S.H., Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0016] In a formula, ~~~ is a single bond where the stereochemistry of the moieties immediately attached thereto is not specified, --- is absent or a single bond, and ═══ or ═══ is a single or double bond.

[0017] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, replacement of ^{19}F with ^{18}F, or the replacement of ^{12}C with ^{13}C or ^{14}C are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0018] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C_{1-6} alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0019] The term "aliphatic" refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. Likewise, the term "heteroaliphatic" refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

[0020] The term "alkyl" refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("C_{1-9} alkyl"). In some embodiments, an alkyl group

has 1 to 8 carbon atoms ("C_{1-8} alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("C_{1-7} alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_{1-6} alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("C_{1-5} alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("C_{1-4} alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("C_{1-3} alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("C_{1-2} alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_{2-6} alkyl"). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), propyl (C_3) (*e.g.*, n-propyl, isopropyl), butyl (C_4) (*e.g.*, n-butyl, tert-butyl, sec-butyl, iso-butyl), pentyl (C_5) (*e.g.*, n-pentyl, 3-pentanyl, amyl, neopentyl, 3-methyl-2-butanyl, tertiary amyl), and hexyl (C_6) (*e.g.*, n-hexyl). Additional examples of alkyl groups include n-heptyl (C_7), n-octyl (C_8), and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents (*e.g.*, halogen, such as F). In certain embodiments, the alkyl group is an unsubstituted C_{1-10} alkyl (such as unsubstituted C_{1-6} alkyl, *e.g.*, $-CH_3$ (Me), unsubstituted ethyl (Et), unsubstituted propyl (Pr, *e.g.*, unsubstituted n-propyl (n-Pr), unsubstituted isopropyl (i-Pr)), unsubstituted butyl (Bu, *e.g.*, unsubstituted n-butyl (n-Bu), unsubstituted tert-butyl (tert-Bu or t-Bu), unsubstituted sec-butyl (sec-Bu), unsubstituted isobutyl (i-Bu)). In certain embodiments, the alkyl group is a substituted C_{1-10} alkyl (such as substituted C_{1-6} alkyl, *e.g.*, $-CF_3$, Bn).

[0021] The term "haloalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} haloalkyl"). Examples of haloalkyl groups include $-CHF_2$, $-CH_2F$, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, and the like.

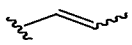
[0022] The term "alkoxy" refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. In some embodiments, the alkoxy moiety has 1 to 8 carbon atoms ("C_{1-8} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 6 carbon atoms ("C_{1-6} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 4 carbon atoms ("C_{1-4} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 3 carbon atoms

("C_{1-3} alkoxy"). In some embodiments, the alkoxy moiety has 1 to 2 carbon atoms ("C_{1-2} alkoxy"). Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy and tert-butoxy.

[0023] The term "alkoxyalkyl" is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by an alkoxy group, as defined herein. In some embodiments, the alkoxyalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} alkoxyalkyl"). In some embodiments, the alkoxyalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} alkoxyalkyl").

[0024] The term "heteroalkyl" refers to an alkyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 20 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-20} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 18 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-18} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 16 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-16} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 14 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-14} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 12 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-12} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-3} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-2} alkyl"). In some embodiments, a heteroalkyl group is a saturated

group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In some embodiments, the heteroalkyl group defined herein is a partially unsaturated group having 1 or more heteroatoms within the parent chain and at least one unsaturated carbon, such as a carbonyl group. For example, a heteroalkyl group may comprise an amide or ester functionality in its parent chain such that one or more carbon atoms are unsaturated carbonyl groups. Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-20} alkyl. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-10} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-20} alkyl. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-10} alkyl.

[0025] The term "alkenyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is a substituted C_{2-10} alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is not specified (*e.g.*, $-CH=CHCH_3$ or ) may be an (E)- or (Z)-double bond.

[0026] The term "heteroalkenyl" refers to an alkenyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-4} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC_{2-10} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{2-10} alkenyl.

[0027] The term "alkynyl" refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some

embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon-carbon triple bonds can be internal (such as in 2-butynyl) or terminal (such as in 1-butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butynyl (C_4), 2-butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is a substituted C_{2-10} alkynyl.

[0028] The term "heteroalkynyl" refers to an alkynyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1or 2 heteroatoms within the parent chain ("heteroC_{2-4} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl

group is an unsubstituted heteroC_{2-10} alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC_{2-10} alkynyl.

[0029] The term "carbocyclyl" or "carbocyclic" refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("C_{3-7} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("C_{4-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("C_{5-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1H-indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or polycyclic (*e.g.*, containing a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") or tricyclic system ("tricyclic carbocyclyl")) and can be saturated or can contain one or more carbon-carbon double or triple bonds. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C_{3-14} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-14} carbocyclyl.

[0030] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms ("C_{4-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6} cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C_{3-14} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_{3-14} cycloalkyl.

[0031] The term "heterocyclyl" or "heterocyclic" refers to a radical of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3-14 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or polycyclic (*e.g.*, a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl")), and can be saturated or can contain one or more carbon-carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is an

unsubstituted 3-14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3-14 membered heterocyclyl.

[0032] In some embodiments, a heterocyclyl group is a 5-10 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-8 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-6 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heterocyclyl"). In some embodiments, the 5-6 membered heterocyclyl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0033] Exemplary 3-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazinyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl,

tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydrofuro[2,3-b]pyridinyl, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

[0034] The term "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has 6 ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("C_{14} aryl"; *e.g.*, anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is an unsubstituted C_{6-14} aryl. In certain embodiments, the aryl group is a substituted C_{6-14} aryl.

[0035] "Arylalkyl" is a subset of "alkyl" and refers to an alkyl group substituted by an aryl group, wherein the point of attachment is on the alkyl moiety.

[0036] The term "heteroaryl" refers to a radical of a 5-14 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-14 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" includes ring systems wherein the heteroaryl

ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

[0037] In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-8 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5-14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5-14 membered heteroaryl.

[0038] Exemplary 5-membered heteroaryl groups containing 1 heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing 2 heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing 3 heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing 4 heteroatoms include, without limitation,

tetrazolyl. Exemplary 6-membered heteroaryl groups containing 1 heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing 2 heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing 3 or 4 heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing 1 heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include, without limitation, phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, and phenazinyl.

[0039] "Heteroarylalkyl" is a subset of "alkyl" and refers to an alkyl group substituted by a heteroaryl group, wherein the point of attachment is on the alkyl moiety.

[0040] The term "unsaturated bond" refers to a double or triple bond.

[0041] The term "unsaturated" or "partially unsaturated" refers to a moiety that includes at least one double or triple bond.

[0042] The term "saturated" refers to a moiety that does not contain a double or triple bond, *i.e.*, the moiety only contains single bonds.

[0043] Affixing the suffix "-ene" to a group indicates the group is a divalent moiety, *e.g.*, alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl, heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl.

[0044] A group is optionally substituted unless expressly provided otherwise. The term "optionally substituted" refers to being substituted or unsubstituted. In certain embodiments, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are optionally substituted. "Optionally substituted" refers to a group which may be substituted or unsubstituted (*e.g.*, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl,

"substituted" or "unsubstituted" heteroalkyl, "substituted" or "unsubstituted" heteroalkenyl, "substituted" or "unsubstituted" heteroalkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted" means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, and includes any of the substituents described herein that results in the formation of a stable compound. The present disclosure contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this disclosure, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety. The disclosure is not intended to be limited in any manner by the exemplary substituents described herein.

[0045] When substituted, exemplary carbon atom substituents include, but are not limited to, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-ON(R^{bb})_2$, $-N(R^{bb})_2$, $-N(R^{bb})_3{}^+X^-$, $-N(OR^{cc})R^{bb}$, $-SH$, $-SR^{aa}$, $-SSR^{cc}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-C(OR^{cc})_3$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-OC(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-C(=O)NR^{bb}SO_2R^{aa}$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$, $-S(=O)R^{aa}$, $-OS(=O)R^{aa}$, $-Si(R^{aa})_3$, $-OSi(R^{aa})_3$ $-C(=S)N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=S)SR^{aa}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-OC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, $-SC(=O)R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-P(=O)(N(R^{bb})_2)_2$, $-OP(=O)(N(R^{bb})_2)_2$, $-NR^{bb}P(=O)(R^{aa})_2$, $-NR^{bb}P(=O)(OR^{cc})_2$, $-NR^{bb}P(=O)(N(R^{bb})_2)_2$, $-P(R^{cc})_2$, $-P(OR^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_3{}^+X^-$, $-P(R^{cc})_4$, $-P(OR^{cc})_4$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3{}^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3{}^+X^-$, $-OP(R^{cc})_4$, $-OP(OR^{cc})_4$, $-B(R^{aa})_2$, $-B(OR^{cc})_2$, $-BR^{aa}(OR^{cc})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl,

carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^- is a counterion;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-CN$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)(N(R^{cc})_2)_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^- is a counterion;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3{}^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$,

$-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)(OR^{ee})_2$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S; wherein X^- is a counterion;

each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl and 5-10 membered heteroaryl, or two R^{ff} groups are joined to form a 3-10 membered heterocyclyl or 5-10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}$ alkyl, $-ON(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_2$, $-N(C_{1-6}$ alkyl$)_3{}^+X^-$, $-NH(C_{1-6}$ alkyl$)_2{}^+X^-$, $-NH_2(C_{1-6}$ alkyl$){}^+X^-$, $-NH_3{}^+X^-$, $-N(OC_{1-6}$ alkyl$)(C_{1-6}$ alkyl$)$, $-N(OH)(C_{1-6}$ alkyl$)$, $-NH(OH)$, $-SH$, $-SC_{1-6}$ alkyl, $-SS(C_{1-6}$ alkyl$)$, $-C(=O)(C_{1-6}$ alkyl$)$, $-CO_2H$, $-CO_2(C_{1-6}$ alkyl$)$, $-OC(=O)(C_{1-6}$ alkyl$)$, $-OCO_2(C_{1-6}$ alkyl$)$, $-C(=O)NH_2$, $-C(=O)N(C_{1-6}$ alkyl$)_2$, $-OC(=O)NH(C_{1-6}$ alkyl$)$, $-NHC(=O)(C_{1-6}$ alkyl$)$, $-N(C_{1-6}$ alkyl$)C(=O)($ C_{1-6} alkyl$)$, $-NHCO_2(C_{1-6}$ alkyl$)$, $-NHC(=O)N(C_{1-6}$ alkyl$)_2$, $-NHC(=O)NH(C_{1-6}$ alkyl$)$, $-NHC(=O)NH_2$, $-C(=NH)O(C_{1-6}$ alkyl$)$, $-OC(=NH)(C_{1-6}$ alkyl$)$, $-OC(=NH)OC_{1-6}$ alkyl, $-C(=NH)N(C_{1-6}$ alkyl$)_2$, $-C(=NH)NH(C_{1-6}$ alkyl$)$, $-C(=NH)NH_2$, $-OC(=NH)N(C_{1-6}$ alkyl$)_2$, $-OC(=NH)NH(C_{1-6}$ alkyl$)$, $-OC(=NH)NH_2$, $-NHC(=NH)N(C_{1-6}$ alkyl$)_2$, $-NHC(=NH)NH_2$, $-NHSO_2(C_{1-6}$ alkyl$)$, $-SO_2N(C_{1-6}$ alkyl$)_2$, $-SO_2NH(C_{1-6}$ alkyl$)$, $-SO_2NH_2$, $-SO_2(C_{1-6}$ alkyl$)$, $-SO_2O(C_{1-6}$ alkyl$)$, $-OSO_2(C_{1-6}$ alkyl$)$, $-SO(C_{1-6}$ alkyl$)$, $-Si(C_{1-6}$ alkyl$)_3$, $-OSi(C_{1-6}$ alkyl$)_3$ $-C(=S)N(C_{1-6}$ alkyl$)_2$, $C(=S)NH(C_{1-6}$ alkyl$)$, $C(=S)NH_2$, $-C(=O)S(C_{1-6}$ alkyl$)$, $-C(=S)SC_{1-6}$

alkyl, $-SC(=S)SC_{1-6}$ alkyl, $-P(=O)(OC_{1-6}$ alkyl$)_2$, $-P(=O)(C_{1-6}$ alkyl$)_2$, $-OP(=O)(C_{1-6}$ alkyl$)_2$, $-OP(=O)(OC_{1-6}$ alkyl$)_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6} alkyl, heteroC_{2-6} alkenyl, heteroC_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein X^- is a counterion.

[0046] The term "halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0047] The term "hydroxyl" or "hydroxy" refers to the group –OH. The term "substituted hydroxyl" or "substituted hydroxyl," by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $-OR^{aa}$, $-ON(R^{bb})_2$, $-OC(=O)SR^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})N(R^{bb})_2$, $-OS(=O)R^{aa}$, $-OSO_2R^{aa}$, $-OSi(R^{aa})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3{}^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3{}^+X^-$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, and $-OP(=O)(N(R^{bb})_2)_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein.

[0048] The term "amino" refers to the group $-NH_2$. The term "substituted amino," by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino. In certain embodiments, the "substituted amino" is a monosubstituted amino or a disubstituted amino group.

[0049] The term "monosubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one hydrogen and one group other than hydrogen, and includes groups selected from $-NH(R^{bb})$, $-NHC(=O)R^{aa}$, $-NHCO_2R^{aa}$, $-NHC(=O)N(R^{bb})_2$, $-NHC(=NR^{bb})N(R^{bb})_2$, $-NHSO_2R^{aa}$, $-NHP(=O)(OR^{cc})_2$, and $-NHP(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb} and R^{cc} are as defined herein, and wherein R^{bb} of the group $-NH(R^{bb})$ is not hydrogen.

[0050] The term "disubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than hydrogen, and includes groups selected from $-N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}SO_2R^{aa}$, $-NR^{bb}P(=O)(OR^{cc})_2$, and $-NR^{bb}P(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with hydrogen.

[0051] The term "trisubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three groups, and includes groups selected from $-N(R^{bb})_3$ and $-N(R^{bb})_3{}^+X^-$, wherein R^{bb} and X^- are as defined herein.

[0052] The term "sulfonyl" refers to a group selected from $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, and $-SO_2OR^{aa}$, wherein R^{aa} and R^{bb} are as defined herein.

[0053] The term "sulfinyl" refers to the group $-S(=O)R^{aa}$, wherein R^{aa} is as defined herein.

[0054] The term "acyl" refers to a group having the general formula: $-C(=O)R^{X1}$, $-C(=O)OR^{X1}$, $-C(=O)-O-C(=O)R^{X1}$, $-C(=O)SR^{X1}$, $-C(=O)N(R^{X1})_2$, $-C(=S)R^{X1}$, $-C(=S)N(R^{X1})_2$, $-C(=S)O(R^{X1})$, $-C(=S)S(R^{X1})$, $-C(=NR^{X1})R^{X1}$, $-C(=NR^{X1})OR^{X1}$, $-C(=NR^{X1})SR^{X1}$, or $-C(=NR^{X1})N(R^{X1})_2$, wherein R^{X1} is hydrogen; halogen; substituted or unsubstituted hydroxyl; substituted or unsubstituted thiol; substituted or unsubstituted amino; substituted or unsubstituted acyl, cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkyl; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, mono- or di- aliphaticamino, mono- or di- heteroaliphaticamino, mono- or di- alkylamino, mono- or di- heteroalkylamino, mono- or di-arylamino, or mono- or di-heteroarylamino; or two R^{X1} groups taken together form a 5- to 6-membered heterocyclic ring. Exemplary acyl groups include aldehydes (–CHO), carboxylic acids ($-CO_2H$), ketones, acyl halides, esters, amides, imines, carbonates, carbamates, and ureas. Acyl substituents include, but are not limited to, any of the substituents described herein, that result in the formation of a stable moiety (*e.g.*, aliphatic, alkyl, alkenyl, alkynyl, heteroaliphatic, heterocyclic, aryl, heteroaryl, acyl, oxo, imino, thiooxo, cyano, isocyano, amino, azido, nitro, hydroxyl, thiol, halo, aliphaticamino, heteroaliphaticamino, alkylamino, heteroalkylamino, arylamino, heteroarylamino, alkylaryl, arylalkyl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, acyloxy, and the like, each of which may or may not be further substituted).

[0055] The term "oxo" refers to the group =O, and the term "thiooxo" refers to the group =S.

[0056] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, –OH, $-OR^{aa}$, $-N(R^{cc})_2$, –CN, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{cc})OR^{aa}$,

$-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)(OR^{cc})_2$, $-P(=O)(R^{aa})_2$, $-P(=O)(N(R^{cc})_2)_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10}alkyl, heteroC_{2-10}alkenyl, heteroC_{2-10}alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein.

[0057] In certain embodiments, the substituent present on the nitrogen atom is a nitrogen protecting group (also referred to herein as an "amino protecting group"). Nitrogen protecting groups include, but are not limited to, $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, C_{1-10} alkyl (*e.g.*, aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0058] For example, nitrogen protecting groups such as amide groups (*e.g.*, $-C(=O)R^{aa}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, N-benzoylphenylalanyl derivative, benzamide, p-phenylbenzamide, o-nitophenylacetamide, o-nitrophenoxyacetamide, acetoacetamide, (N'-dithiobenzyloxyacylamino)acetamide, 3-(p-hydroxyphenyl)propanamide, 3-(o-nitrophenyl)propanamide, 2-methyl-2-(o-nitrophenoxy)propanamide, 2-methyl-2-(o-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, o-nitrocinnamide, N-acetylmethionine derivative, o-nitrobenzamide and o-(benzoyloxymethyl)benzamide.

[0059] Nitrogen protecting groups such as carbamate groups (*e.g.*, $-C(=O)OR^{aa}$) include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluoroenylmethyl carbamate,

2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-t-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenylyl)ethyl carbamate (Bpoc), 1-(3,5-di-t-butylphenyl)-1-methylethyl carbamate (t-Bumeoc), 2-(2′- and 4′-pyridyl)ethyl carbamate (Pyoc), 2-(N,N-dicyclohexylcarboxamido)ethyl carbamate, t-butyl carbamate (BOC or Boc), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, N-hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), p-methoxybenzyl carbamate (Moz), p-nitobenzyl carbamate, p-bromobenzyl carbamate, p-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (Msz), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(p-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, m-chloro-p-acyloxybenzyl carbamate, p-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc), m-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, o-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(o-nitrophenyl)methyl carbamate, t-amyl carbamate, S-benzyl thiocarbamate, p-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, p-decyloxybenzyl carbamate, 2,2-dimethoxyacylvinyl carbamate, o-(N,N-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(N,N-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, p-(p'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(p-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate,

p-(phenylazo)benzyl carbamate, 2,4,6-tri-t-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[0060] Nitrogen protecting groups such as sulfonamide groups (*e.g.*, $-S(=O)_2R^{aa}$) include, but are not limited to, p-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β-trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4′,8′-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0061] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, N′-p-toluenesulfonylaminoacyl derivative, N′-phenylaminothioacyl derivative, N-benzoylphenylalanyl derivative, N-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, N-phthalimide, N-dithiasuccinimide (Dts), N-2,3-diphenylmaleimide, N-2,5-dimethylpyrrole, N-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, N-methylamine, N-allylamine, N-[2-(trimethylsilyl)ethoxy]methylamine (SEM), N-3-acetoxypropylamine, N-(1-isopropyl-4-nitro-2-oxo-3-pyroolin-3-yl)amine, quaternary ammonium salts, N-benzylamine, N-di(4-methoxyphenyl)methylamine, N-5-dibenzosuberylamine, N-triphenylmethylamine (Tr), N-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), N-9-phenylfluorenylamine (PhF), N-2,7-dichloro-9-fluorenylmethyleneamine, N-ferrocenylmethylamino (Fcm), N-2-picolylamino N'-oxide, N-1,1-dimethylthiomethyleneamine, N-benzylideneamine, N-p-methoxybenzylideneamine, N-diphenylmethyleneamine, N-[(2-pyridyl)mesityl]methyleneamine, N-(N',N'-dimethylaminomethylene)amine, N,N'-isopropylidenediamine, N-p-nitrobenzylideneamine, N-salicylideneamine, N-5-chlorosalicylideneamine, N-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, N-cyclohexylideneamine, N-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, N-borane derivative, N-diphenylborinic acid derivative, N-[phenyl(pentaacylchromium- or tungsten)acyl]amine, N-copper chelate, N-zinc chelate, N-nitroamine, N-nitrosoamine, amine N-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt),

diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, o-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys). In certain embodiments, a nitrogen protecting group is benzyl (Bn), tert-butyloxycarbonyl (BOC), carbobenzyloxy (Cbz), 9-flurenylmethyloxycarbonyl (Fmoc), trifluoroacetyl, triphenylmethyl, acetyl (Ac), benzoyl (Bz), p-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP), 2,2,2-trichloroethyloxycarbonyl (Troc), triphenylmethyl (Tr), tosyl (Ts), brosyl (Bs), nosyl (Ns), mesyl (Ms), triflyl (Tf), or dansyl (Ds).

[0062] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to herein as an "hydroxyl protecting group"). Oxygen protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0063] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), t-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), p-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (p-AOM), guaiacolmethyl (GUM), t-butoxymethyl, 4-pentenyloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, t-butyl, allyl, p-chlorophenyl, p-methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn), p-

methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, p-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl N-oxido, diphenylmethyl, p,p'-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α-naphthyldiphenylmethyl, p-methoxyphenyldiphenylmethyl, di(p-methoxyphenyl)phenylmethyl, tri(p-methoxyphenyl)methyl, 4-(4'-bromophenacyloxyphenyl)diphenylmethyl, 4,4′,4″-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4′,4″-tris(levulinoyloxyphenyl)methyl, 4,4′,4″-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-yl)bis(4′,4″-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1′-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, benzisothiazolyl S,S-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, t-butyldimethylsilyl (TBDMS), t-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), t-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, p-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, t-butyl carbonate (BOC or Boc), p-nitrophenyl carbonate, benzyl carbonate, p-methoxybenzyl carbonate, 3,4-dimethoxybenzyl carbonate, o-nitrobenzyl carbonate, p-nitrobenzyl carbonate, S-benzyl thiocarbonate, 4-ethoxy-1-napththyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, o-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (E)-2-methyl-2-butenoate, o-(methoxyacyl)benzoate, α-naphthoate, nitrate, alkyl N,N,N',N'-tetramethylphosphorodiamidate, alkyl N-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts). In certain embodiments, an oxygen protecting group is silyl. In certain

embodiments, an oxygen protecting group is t-butyldiphenylsilyl (TBDPS), t-butyldimethylsilyl (TBDMS), triisoproylsilyl (TIPS), triphenylsilyl (TPS), triethylsilyl (TES), trimethylsilyl (TMS), triisopropylsiloxymethyl (TOM), acetyl (Ac), benzoyl (Bz), allyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-trimethylsilylethyl carbonate, methoxymethyl (MOM), 1-ethoxyethyl (EE), 2-methyoxy-2-propyl (MOP), 2,2,2-trichloroethoxyethyl, 2-methoxyethoxymethyl (MEM), 2-trimethylsilylethoxymethyl (SEM), methylthiomethyl (MTM), tetrahydropyranyl (THP), tetrahydrofuranyl (THF), p-methoxyphenyl (PMP), triphenylmethyl (Tr), methoxytrityl (MMT), dimethoxytrityl (DMT), allyl, p-methoxybenzyl (PMB), t-butyl, benzyl (Bn), allyl, or pivaloyl (Piv).

[0064] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a "thiol protecting group"). Sulfur protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3{}^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3{}^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference. In certain embodiments, a sulfur protecting group is acetamidomethyl, t-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl.

[0065] A "counterion" or "anionic counterion" is a negatively charged group associated with a positively charged group in order to maintain electronic neutrality. An anionic counterion may be monovalent (*i.e.*, including one formal negative charge). An anionic counterion may also be multivalent (*i.e.*, including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (*e.g.*, F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HCO_3^-, HSO_4^-, sulfonate ions (*e.g.*, methansulfonate, trifluoromethanesulfonate, *p*–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), carboxylate ions (*e.g.*, acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like), BF_4^-, PF_4^-, PF_6^-, AsF_6^-, SbF_6^-, $B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$, $B(C_6F_5)_4^-$, BPh_4^-, $Al(OC(CF_3)_3)_4^-$, and carborane anions (*e.g.*, $CB_{11}H_{12}^-$ or $(HCB_{11}Me_5Br_6)^-$). Exemplary counterions which may be multivalent include CO_3^{2-}, HPO_4^{2-}, PO_4^{3-}, $B_4O_7^{2-}$, SO_4^{2-}, $S_2O_3^{2-}$, carboxylate anions (*e.g.*, tartrate, citrate, fumarate, maleate, malate, malonate, gluconate, succinate, glutarate, adipate, pimelate, suberate, azelate, sebacate, salicylate, phthalates, aspartate, glutamate, and the like), and carboranes.

[0066] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and Claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other definitions

[0067] The following definitions are more general terms used throughout the present application.

[0068] As used herein, the term "salt" refers to any and all salts, and encompasses pharmaceutically acceptable salts.

[0069] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and/or animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}\ alkyl)_4^-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine

cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0070] The term "solvate" refers to forms of the compound, or a salt thereof, that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds described herein may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[0071] The term "hydrate" refers to a compound that is associated with water molecules. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula R·x H_2O, wherein R is the compound, and x is a number greater than 0. A given compound may form more than one type of hydrate, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates (R·0.5 H_2O)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates (R·2 H_2O) and hexahydrates (R·6 H_2O)).

[0072] The term "tautomers" or "tautomeric" refers to two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a single bond, or vice versa). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

[0073] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

[0074] Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers".

When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (−)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[0075] The term "polymorph" refers to a crystalline form of a compound (or a salt, hydrate, or solvate thereof). Many compounds can adopt a variety of different crystal forms (i.e., different polymorphs). Typically, such different crystalline forms have different X-ray diffraction patterns, infrared spectra, and/or can vary in some or all properties such as melting points, density, hardness, crystal shape, optical and electrical properties, stability, solubility, and bioavailability. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate a given preparation. Various polymorphs of a compound can be prepared by crystallization under different conditions.

[0076] The term "co-crystal" refers to a crystalline structure composed of at least two components. In certain embodiments, a co-crystal contains a compound of the present disclosure and one or more other component(s), including, but not limited to, atoms, ions, molecules, or solvent molecules. In certain embodiments, a co-crystal contains a compound of the present disclosure and one or more solvent molecules. In certain embodiments, a co-crystal contains a compound of the present disclosure and one or more acid or base. In certain embodiments, a co-crystal contains a compound of the present disclosure and one or more components related to said compound, including, but not limited to, an isomer, tautomer, salt, solvate, hydrate, synthetic precursor, synthetic derivative, fragment, or impurity of said compound.

[0077] The term "prodrugs" refers to compounds that have cleavable groups that are removed, by solvolysis or under physiological conditions, to provide the compounds described herein, which are pharmaceutically active in vivo. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like. Other derivatives of the compounds described herein have activity in both their acid and acid derivative forms, but in the acid sensitive form often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the

parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides, and anhydrides derived from acidic groups pendant on the compounds described herein are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, aryl, C_{7-12} substituted aryl, and C_{7-12} arylalkyl esters of the compounds described herein may be preferred.

[0078] The terms "composition" and "formulation" are used interchangeably.

[0079] The term "modulate" means decreasing or inhibiting activity and/or increasing or augmenting activity. For example, modulating glucocerebrosidase activity means decreasing or inhibiting glucocerebrosidase activity and/or increasing or augmenting glucocerebrosidase activity. The compounds disclosed herein may be administered to modulate glucocerebrosidase activity for example, as a chaperone or activator.

[0080] A "subject" to which administration is contemplated refers to a human (*i.e.*, male or female of any age group, *e.g.*, pediatric subject (*e.g.*, infant, child, or adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) or non-human animal. In certain embodiments, the non-human animal is a mammal (*e.g.*, primate (*e.g.*, cynomolgus monkey or rhesus monkey), commercially relevant mammal (*e.g.*, cattle, pig, horse, sheep, goat, cat, or dog), or bird (*e.g.*, commercially relevant bird, such as chicken, duck, goose, or turkey)). In certain embodiments, the non-human animal is a fish, reptile, or amphibian. The non-human animal may be a male or female at any stage of development. The non-human animal may be a transgenic animal or genetically engineered animal. The term "patient" refers to a human subject in need of treatment of a disease. The subject may also be a plant. In certain embodiments, the plant is a land plant. In certain embodiments, the plant is a non-vascular land plant. In certain embodiments, the plant is a vascular land plant. In certain embodiments, the plant is a seed plant. In certain embodiments, the plant is a cultivated plant. In certain embodiments, the plant is a dicot. In certain embodiments, the plant is a monocot. In certain embodiments, the plant is a flowering plant. In some embodiments, the plant is a cereal plant, *e.g.*, maize, corn, wheat, rice, oat, barley, rye, or millet. In some embodiments, the plant is a legume, *e.g.*, a bean plant, *e.g.*, soybean plant. In some embodiments, the plant is a tree or shrub.

[0081] The term "biological sample" refers to any sample including tissue samples (such as tissue sections and needle biopsies of a tissue); cell samples (*e.g.*, cytological smears (such as Pap or blood smears) or samples of cells obtained by microdissection); samples of whole

organisms (such as samples of yeasts or bacteria); or cell fractions, fragments or organelles (such as obtained by lysing cells and separating the components thereof by centrifugation or otherwise). Other examples of biological samples include blood, serum, urine, semen, fecal matter, cerebrospinal fluid, interstitial fluid, mucous, tears, sweat, pus, biopsied tissue (*e.g.*, obtained by a surgical biopsy or needle biopsy), nipple aspirates, milk, vaginal fluid, saliva, swabs (such as buccal swabs), or any material containing biomolecules that is derived from a first biological sample.

[0082] The term "administer," "administering," or "administration" refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound described herein, or a composition thereof, in or on a subject.

[0083] The terms "treatment," "treat," and "treating" refer to reversing, alleviating, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed. Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[0084] The terms "condition," "disease," and "disorder" are used interchangeably.

[0085] An "effective amount" of a compound described herein refers to an amount sufficient to elicit the desired biological response. An effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. In certain embodiments, an effective amount is a therapeutically effective amount. In certain embodiments, an effective amount is a prophylactic treatment. In certain embodiments, an effective amount is the amount of a compound described herein in a single dose. In certain embodiments, an effective amount is the combined amounts of a compound described herein in multiple doses.

[0086] A "therapeutically effective amount" of a compound described herein is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent. In certain embodiments, a therapeutically effective amount is an amount sufficient for GCase activation (*e.g.*, at least 5%, at least 10%,

at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 100%, at least 150%, at least 200%, at least 250%, at least 300%, or at least 500% increase in the enzymatic activity of GCase). In certain embodiments, a therapeutically effective amount is an amount sufficient for treating a disease or disorder (*e.g.*, neurological disorder). In certain embodiments, a therapeutically effective amount is an amount sufficient for GCase activation and treating a disease or disorder (*e.g.*, neurological disorder).

[0087] A "prophylactically effective amount" of a compound described herein is an amount sufficient to prevent a condition, or one or more signs or symptoms associated with the condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent. In certain embodiments, a prophylactically effective amount is an amount sufficient for GCase activation. In certain embodiments, a prophylactically effective amount is an amount sufficient for treating a disease or disorder (*e.g.*, neurological disorder). In certain embodiments, a prophylactically effective amount is an amount sufficient for GCase activation and treating a disease or disorder (*e.g.*, neurological disorder).

[0088] As used herein, the term "activate" or "activation" in the context of enzymes, for example, in the context of GCase, refers to an increase in the activity of the enzyme. In some embodiments, the term refers to an increase of the level of enzyme activity, *e.g.*, GCase activity, to a level that is statistically significantly higher than an initial level, which may, for example, be a baseline level of enzyme activity (e.g., of wild-type GCase). In some embodiments, the term refers to an increase in the level of enzyme activity, *e.g.*, GCase activity, to a level that is greater than 1%, greater than 5%, greater than 10%, greater than 25%, greater than 50%, greater than 75%, greater than 100%, greater than 150%, greater than 200%, greater than 300%, greater than 400%, greater than 500%, or greater than 1000% of an initial level, which may, for example, be a baseline level of enzyme activity.

[0089] The term "immunotherapy" refers to a therapeutic agent that promotes the treatment of disease by inducing, enhancing, or suppressing an immune response. Immunotherapies designed to elicit or amplify an immune response are classified as activation immunotherapies, while immunotherapies that reduce or suppress are classified as suppression immunotherapies. Immunotherapies are typically, but not always, biotherapeutic

agents. Numerous immunotherapies are used to treat cancer. These include, but are not limited to, monoclonal antibodies, adoptive cell transfer, cytokines, chemokines, vaccines, and small molecule inhibitors.

[0090] The terms "biologic," "biologic drug," and "biological product" refer to a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, nucleic acids, and proteins. Biologics may include sugars, proteins, or nucleic acids, or complex combinations of these substances, or may be living entities, such as cells and tissues. Biologics may be isolated from a variety of natural sources (*e.g.*, human, animal, microorganism) and may be produced by biotechnological methods and other technologies.

[0091] The term "small molecule" or "small molecule therapeutic" refers to molecules, whether naturally occurring or artificially created (*e.g.*, via chemical synthesis) that have a relatively low molecular weight. Typically, a small molecule is an organic compound (*i.e.*, it contains carbon). The small molecule may contain multiple carbon-carbon bonds, stereocenters, and other functional groups (*e.g.*, amines, hydroxyl, carbonyls, and heterocyclic rings, etc.). In certain embodiments, the molecular weight of a small molecule is not more than about 1,000 g/mol, not more than about 900 g/mol, not more than about 800 g/mol, not more than about 700 g/mol, not more than about 600 g/mol, not more than about 500 g/mol, not more than about 400 g/mol, not more than about 300 g/mol, not more than about 200 g/mol, or not more than about 100 g/mol. In certain embodiments, the molecular weight of a small molecule is at least about 100 g/mol, at least about 200 g/mol, at least about 300 g/mol, at least about 400 g/mol, at least about 500 g/mol, at least about 600 g/mol, at least about 700 g/mol, at least about 800 g/mol, or at least about 900 g/mol, or at least about 1,000 g/mol. Combinations of the above ranges (*e.g.*, at least about 200 g/mol and not more than about 500 g/mol) are also possible. In certain embodiments, the small molecule is a therapeutically active agent such as a drug (*e.g.*, a molecule approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (C.F.R.)). The small molecule may also be complexed with one or more metal atoms and/or metal ions. In this instance, the small molecule is also referred to as a "small organometallic molecule." Preferred small molecules are biologically active in that they produce a biological effect in animals, preferably mammals, more preferably humans. Small molecules include, but are not limited to, radionuclides and imaging agents. In certain embodiments, the small molecule is a drug. Preferably, though not necessarily, the drug is one that has already been deemed safe and effective for use in humans or animals by the appropriate governmental agency or

regulatory body. For example, drugs approved for human use are listed by the FDA under 21 C.F.R. §§ 330.5, 331 through 361, and 440 through 460, incorporated herein by reference; drugs for veterinary use are listed by the FDA under 21 C.F.R. §§ 500 through 589, incorporated herein by reference. All listed drugs are considered acceptable for use in accordance with the present invention.

[0092] The term "therapeutic agent" refers to any substance having therapeutic properties that produce a desired, usually beneficial, effect. For example, therapeutic agents may treat, ameliorate, and/or prevent disease. Therapeutic agents, as disclosed herein, may be biologics or small molecule therapeutics, or combinations thereof.

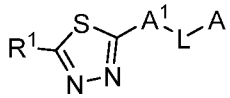
DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0093] Provided herein are compounds that are modulators of GCase (*e.g.*, GCase activators). In one aspect, the provided GCase modulators are compounds of Formula (**I**), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and pharmaceutical compositions thereof. Accordingly, the compounds are useful for the treatment and/or prevention of diseases and disorders associated with GCase activity (*e.g.*, neurological diseases and disorders) in a subject in need thereof.

[0094] The compounds described herein interact with GCase. As described herein, the therapeutic effect may be a result of modulation (e.g., activation), binding, and/or modification of GCase by the compounds described herein. The compounds may be provided for use in any composition, kit, or method described herein as a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

Compounds of Formula (I)

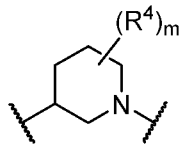
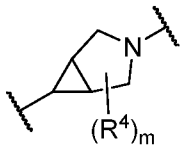
[0095] In one aspect, disclosed is a compound of Formula (**I**):



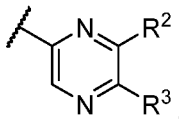
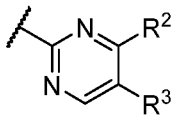
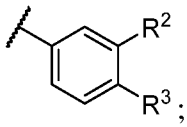
(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

A^1 is  or ;

L is a bond or –C(=O)-;

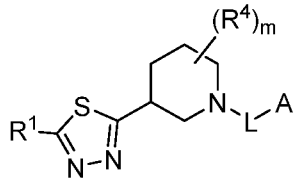
A is , , or ;

R^2 and R^3 are each independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^4 is independently halogen, substituted or unsubstituted alkyl, or two instances of R^4 on the same carbon form with that carbon a carbonyl; and

m is 0, 1, 2, 3, or 4.

[0096] In an embodiment, disclosed is a compound of Formula (**I-a**):

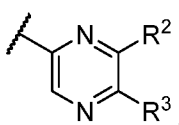
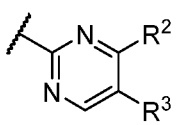
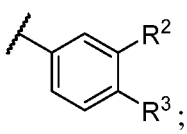


(**I-a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof, wherein:

R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

L is a bond or –C(=O)-;

A is , , or ;

R^2 and R^3 are each independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted

carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^4 is independently halogen, substituted or unsubstituted alkyl, or two instances of R^4 on the same carbon form with that carbon a carbonyl; and

m is 0, 1, 2, 3, or 4.

R^1

[0097] As described herein, R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl. In certain embodiments, R^1 is substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl. In certain embodiments, R^1 is substituted or unsubstituted heteroaryl, or substituted or unsubstituted phenyl. In certain embodiments, R^1 is substituted or unsubstituted pyridinyl, or substituted or unsubstituted aryl. In certain embodiments, R^1 is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted aryl.

[0098] In certain embodiments, R^1 is substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted phenyl. In certain embodiments, R^1 is substituted or unsubstituted pyridinyl, or substituted or unsubstituted phenyl. In certain embodiments, R^1 is substituted pyridinyl, substituted or unsubstituted pyrimidinyl, or substituted or unsubstituted phenyl. In certain embodiments, R^1 is substituted pyridinyl, or substituted or unsubstituted phenyl.

[0099] In certain embodiments, R^1 is substituted or unsubstituted pyrimidinyl. In certain embodiments, R^1 is substituted pyrimidinyl. In certain embodiments, R^1 is pyrimidinyl substituted with alkoxy. In certain embodiments, R^1 is pyrimidinyl substituted with C_{1-4} alkoxy.

[00100] In certain embodiments, R^1 is pyridinyl substituted with halogen, haloalkyl or haloalkoxy; pyrimidinyl substituted with alkoxy; unsubstituted phenyl; or phenyl substituted with halogen, haloalkyl, or alkyl. In certain embodiments, R^1 is pyridinyl substituted with halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; is pyrimidinyl substituted with C_{1-4} alkoxy; unsubstituted phenyl; or phenyl substituted with halogen, C_{1-4} haloalkyl, or C_{1-4} alkyl.

[00101] In certain embodiments, R^1 is pyridinyl substituted with halogen, haloalkyl or haloalkoxy; unsubstituted phenyl; or phenyl substituted with halogen, haloalkyl, or alkyl. In certain embodiments, R^1 is pyridinyl substituted with halogen, C_{1-4} haloalkyl or C_{1-4} haloalkoxy; unsubstituted phenyl; or phenyl substituted with halogen, C_{1-4} haloalkyl, or C_{1-4} alkyl.

[00102] In certain embodiments, R^1 is pyridinyl substituted with halogen or haloalkyl; unsubstituted phenyl; or phenyl substituted with halogen or haloalkyl. In certain embodiments, R^1 is pyridinyl substituted with halogen or C_{1-4} haloalkyl; unsubstituted phenyl; or phenyl substituted with halogen or C_{1-4} haloalkyl.

[00103] In certain embodiments, R^1 is pyridinyl substituted with halogen or haloalkyl; unsubstituted phenyl; or phenyl substituted with halogen, haloalkoxy, or haloalkyl. In certain embodiments, R^1 is pyridinyl substituted with halogen or C_{1-4} haloalkyl; unsubstituted phenyl; or phenyl substituted with halogen, C_{1-4} haloalkoxy, or C_{1-4} haloalkyl.

[00104] In certain embodiments, R^1 is pyridinyl substituted with fluoro or fluoroalkyl; unsubstituted phenyl; or phenyl substituted with fluoro or fluoroalkyl. In certain embodiments, R^1 is pyridinyl substituted with fluoro or C_{1-4} fluoroalkyl; unsubstituted phenyl; or phenyl substituted with fluoro or C_{1-4} fluoroalkyl.

[00105] In certain embodiments, R^1 is pyridinyl substituted with fluoro or fluoroalkyl; unsubstituted phenyl; or phenyl substituted with fluoro, fluoroalkoxy, or fluoroalkyl. In certain embodiments, R^1 is pyridinyl substituted with fluoro or C_{1-4} fluoroalkyl; unsubstituted phenyl; or phenyl substituted with fluoro, C_{1-4} fluoroalkoxy, or C_{1-4} fluoroalkyl.

[00106] In certain embodiments, R^1 is pyridinyl substituted with halogen or haloalkyl. In certain embodiments, R^1 is pyridinyl substituted with halogen or C_{1-4} haloalkyl.

[00107] In certain embodiments, R^1 is pyridinyl substituted with fluoro or fluoroalkyl. In certain embodiments, R^1 is pyridinyl substituted with fluoro or C_{1-4} fluoroalkyl.

[00108] In certain embodiments, R^1 is pyridinyl substituted with haloalkyl. In certain embodiments, R^1 is pyridinyl substituted with C_{1-4} haloalkyl. In certain embodiments, R^1 is pyridinyl substituted with fluoroalkyl. In certain embodiments, R^1 is pyridinyl substituted with C_{1-4} fluoroalkyl.

[00109] In certain embodiments, R^1 is substituted or unsubstituted pyrimidinyl. In certain embodiments, R^1 is substituted pyrimidinyl. In certain embodiments, R^1 is pyrimidinyl substituted with alkoxy. In certain embodiments, R^1 is pyrimidinyl substituted with C_{1-4} alkoxy.

[00110] In certain embodiments, R^1 is unsubstituted phenyl.

[00111] In certain embodiments, R^1 is phenyl substituted with halogen or haloalkyl. In certain embodiments, R^1 is phenyl substituted with halogen or C_{1-4} haloalkyl. In certain embodiments, R^1 is phenyl substituted with fluoro or fluoroalkyl. In certain embodiments, R^1 is phenyl substituted with fluoro or C_{1-4} fluoroalkyl.

[00112] In certain embodiments, R^1 is phenyl substituted with halogen, haloalkoxy, or haloalkyl. In certain embodiments, R^1 is phenyl substituted with halogen, C_{1-4} haloalkoxy, or C_{1-4} haloalkyl. In certain embodiments, R^1 is phenyl substituted with fluoro, fluoroalkoxy, or fluoroalkyl. In certain embodiments, R^1 is phenyl substituted with fluoro, C_{1-4} fluoroalkoxy, or C_{1-4} fluoroalkyl.

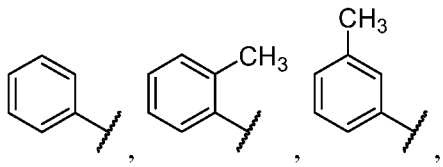
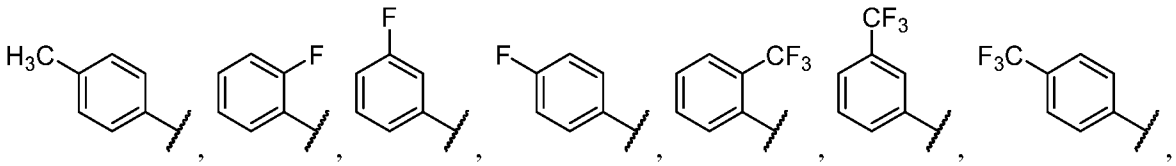
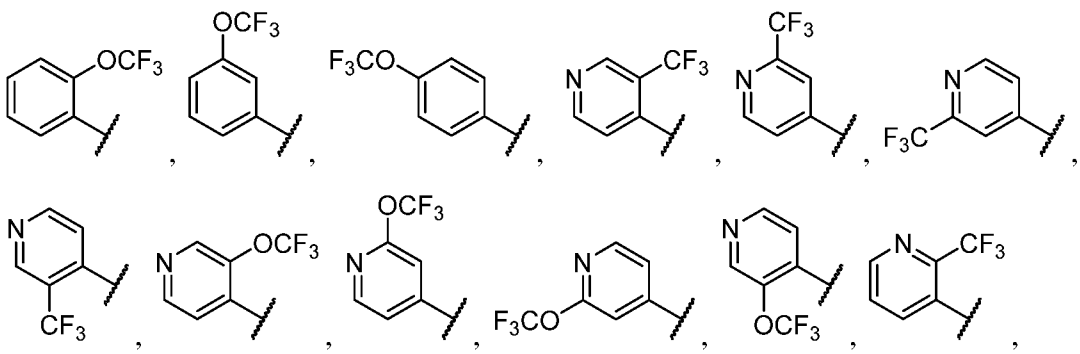
[00113] In certain embodiments, R^1 is phenyl substituted with halogen. In certain embodiments, R^1 is phenyl substituted with fluoro.

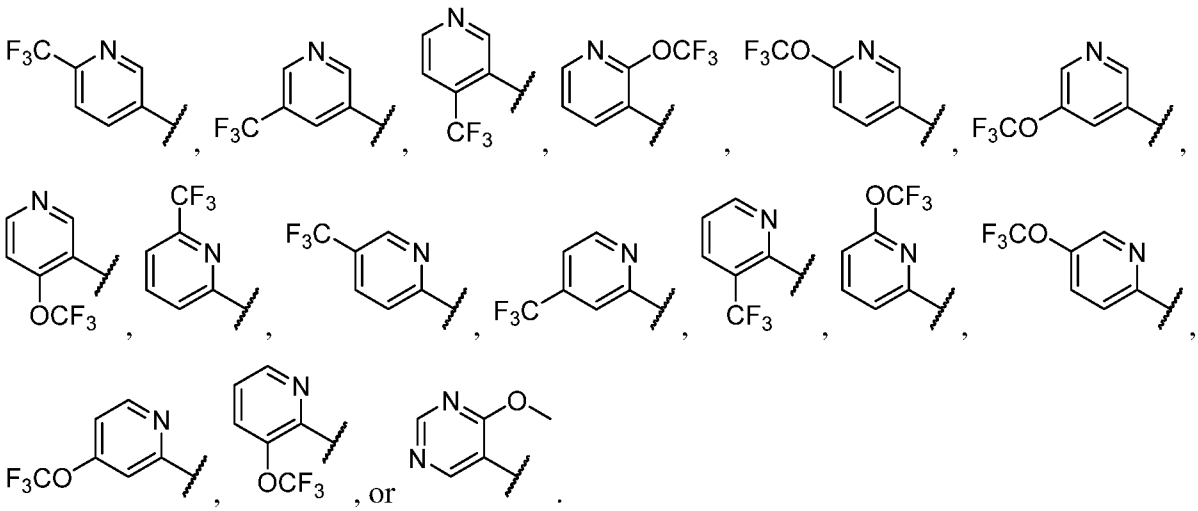
[00114] In certain embodiments, R^1 is phenyl substituted with haloalkyl. In certain embodiments, R^1 is phenyl substituted with C_{1-4} haloalkyl. In certain embodiments, R^1 is phenyl substituted with fluoroalkyl. In certain embodiments, R^1 is phenyl substituted with C_{1-4} fluoroalkyl.

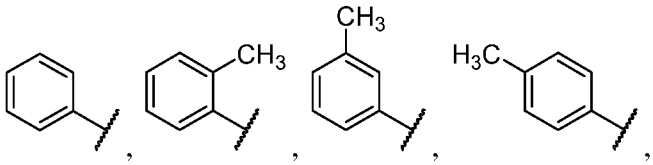
[00115] In certain embodiments, R^1 is phenyl substituted with haloalkoxy. In certain embodiments, R^1 is phenyl substituted with C_{1-4} haloalkoxy. In certain embodiments, R^1 is phenyl substituted with fluoroalkoxy. In certain embodiments, R^1 is phenyl substituted with C_{1-4} fluoroalkoxy.

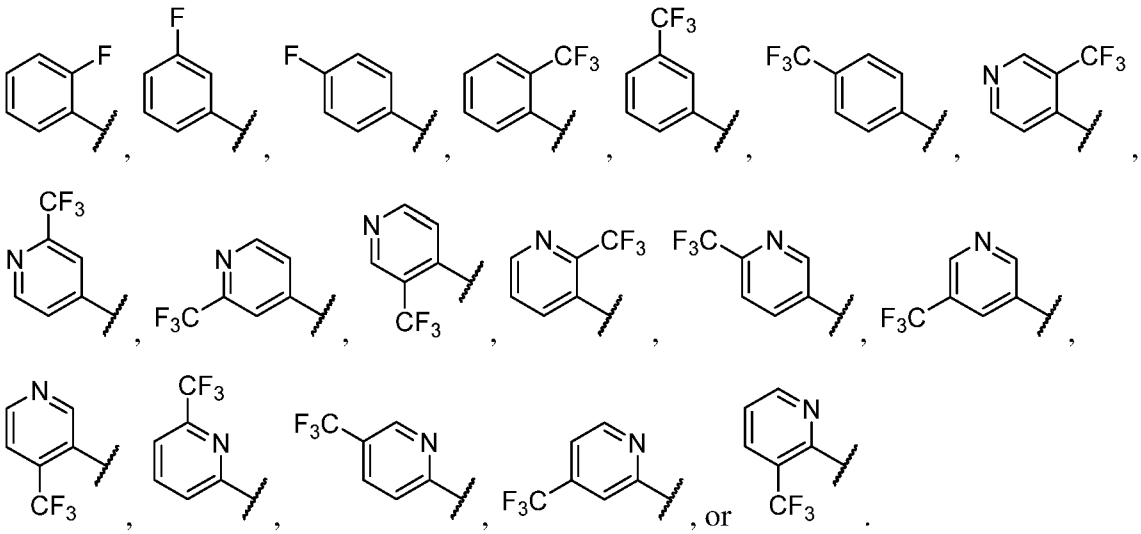
[00116] In certain embodiments, R^1 is phenyl substituted with alkyl. In certain embodiments, R^1 is phenyl substituted with C_{1-4} alkyl.

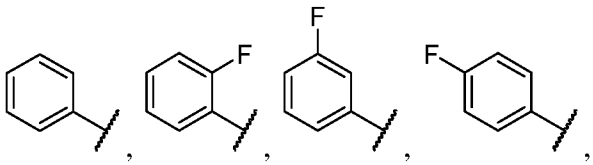
[00117] In certain embodiments, R^1 is substituted or unsubstituted alkyl. In certain embodiments, R^1 is unsubstituted alkyl. In certain embodiments, R^1 is unsubstituted C_{1-4} alkyl. In certain embodiments, R^1 is methyl.

[00118] In certain embodiments, R^1 is methyl, , , .

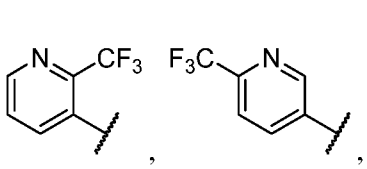


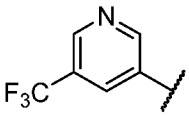
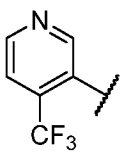
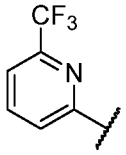
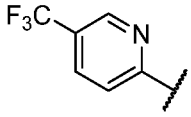
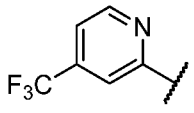
[00119] In certain embodiments, R^1 is 

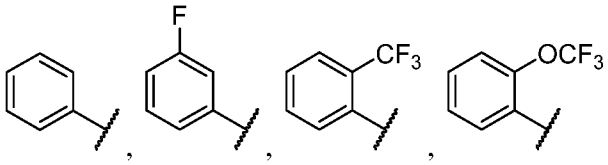


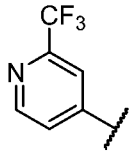
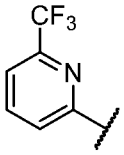
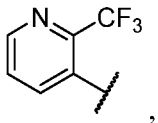
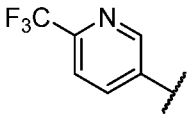
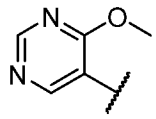
[00120] In certain embodiments, R^1 is 

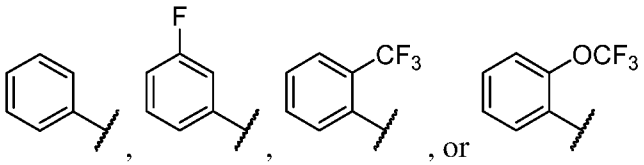


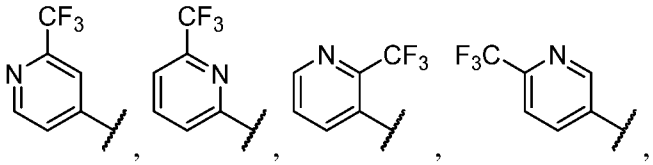


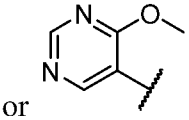






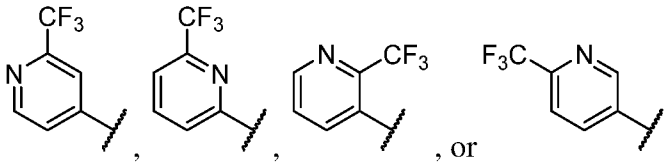

[00121] In certain embodiments, R^1 is 

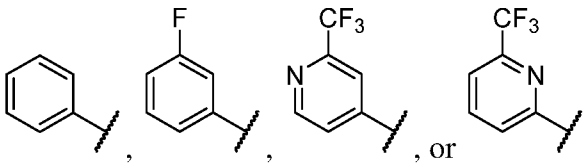






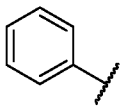
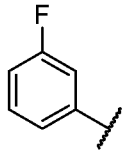
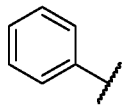
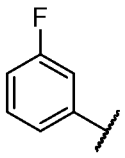
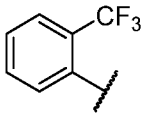
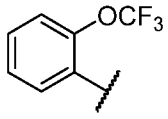
[00122] In certain embodiments, R^1 is 

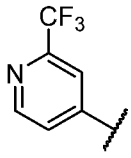
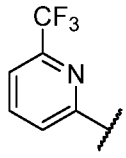
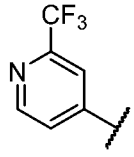
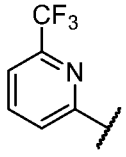
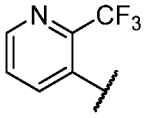
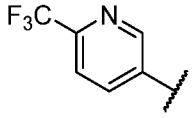
[00123] In certain embodiments, R^1 is 



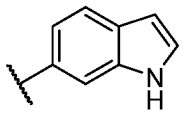
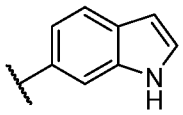
[00124] In certain embodiments, R^1 is 

[00125] In certain embodiments, R^1 is 

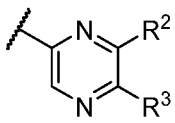
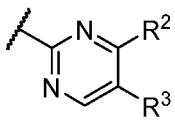
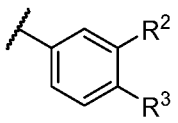
[00126] In certain embodiments, R^1 is , or . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is .

[00127] In certain embodiments, R^1 is  or . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is . In certain embodiments, R^1 is .

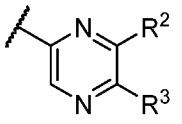
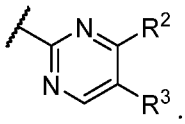
L

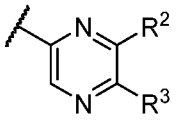
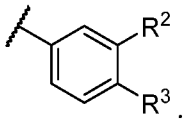
[00128] As described herein, L is a bond or –C(=O)-. In certain embodiments, L is a bond. In certain embodiments, L is–C(=O)-. In certain embodiments, when L is –C(=O)-, then A is . In certain embodiments, L is only –C(=O)- when A is .

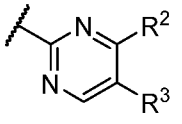
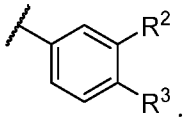
A

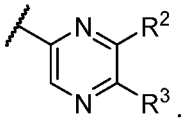
[00129] As described herein, A is , , or ; wherein R^2 and R^3 are each independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl,

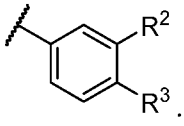
substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

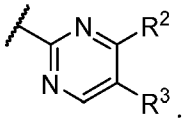
[00130] In certain embodiments, A is  or .

[00131] In certain embodiments, A is  or .

[00132] In certain embodiments, A is  or .

[00133] In certain embodiments, A is .

[00134] In certain embodiments, A is .

[00135] In certain embodiments, A is .

[00136] In certain embodiments, R^2 and R^3 are each independently hydrogen or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00137] In certain embodiments, R^2 is substituted or unsubstituted heteroaryl. In certain embodiments, R^2 is unsubstituted heteroaryl. In certain embodiments, R^2 is substituted or unsubstituted thiadizaolyl. In certain embodiments, R^2 is unsubstituted thiadizaolyl.

[00138] In certain embodiments, R^3 is hydrogen.

[00139] In certain embodiments, R^2 is substituted or unsubstituted heteroaryl; and R^3 is hydrogen. In certain embodiments, R^2 is unsubstituted heteroaryl; and R^3 is hydrogen. In certain embodiments, R^2 is substituted or unsubstituted thiadizaolyl; and R^3 is hydrogen. In certain embodiments, R^2 is unsubstituted thiadizaolyl; and R^3 is hydrogen.

[00140] In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00141] In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted phenyl. In

certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted phenyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form an unsubstituted phenyl.

[00142] In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrrolyl, or substituted or unsubstituted pyrazolyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted pyrrolyl or substituted or unsubstituted pyrazolyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted imidazolyl, substituted pyrrolyl, or substituted pyrazolyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl or substituted pyrazolyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted imidazolyl, substituted pyrrolyl, or substituted pyrazolyl, wherein the imidazolyl, pyrrolyl, or pyrazolyl is substituted with substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted imidazolyl, substituted pyrrolyl, or substituted pyrazolyl, wherein the imidazolyl, pyrrolyl, or pyrazolyl is substituted with substituted or unsubstituted alkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl or substituted pyrazolyl, wherein the pyrrolyl or pyrazolyl is substituted with substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl or substituted pyrazolyl, wherein the pyrrolyl or pyrazolyl is substituted with substituted or unsubstituted alkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted imidazolyl, substituted pyrrolyl, or substituted pyrazolyl, wherein the imidazolyl, pyrrolyl, or pyrazolyl is substituted with unsubstituted alkyl, heterocyclylalkyl, heterocyclyl, or haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted imidazolyl, substituted pyrrolyl, or substituted pyrazolyl, wherein the imidazolyl, pyrrolyl, or pyrazolyl is substituted with unsubstituted alkyl or haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl or substituted pyrazolyl, wherein the pyrrolyl or pyrazolyl is substituted with unsubstituted alkyl, heterocyclylalkyl, heterocyclyl, or haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a

substituted pyrrolyl or substituted pyrazolyl, wherein the pyrrolyl or pyrazolyl is substituted with unsubstituted alkyl or haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted imidazolyl, substituted pyrrolyl, or substituted pyrazolyl, wherein the imidazolyl, pyrrolyl, or pyrazolyl is substituted with unsubstituted C_{1-4} alkyl, 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, or C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted imidazolyl, substituted pyrrolyl, or substituted pyrazolyl, wherein the imidazolyl, pyrrolyl, or pyrazolyl is substituted with unsubstituted C_{1-4} alkyl or C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl or substituted pyrazolyl, wherein the pyrrolyl or pyrazolyl is substituted with unsubstituted C_{1-4} alkyl, 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, or C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl or substituted pyrazolyl, wherein the pyrrolyl or pyrazolyl is substituted with unsubstituted C_{1-4} alkyl or C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted imidazolyl, substituted pyrrolyl, or substituted pyrazolyl, wherein the imidazolyl, pyrrolyl, or pyrazolyl is substituted with unsubstituted C_{1-4} alkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl or substituted pyrazolyl, wherein the pyrrolyl or pyrazolyl is substituted with unsubstituted C_{1-4} alkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted imidazolyl, substituted pyrrolyl, or substituted pyrazolyl, wherein the imidazolyl, pyrrolyl, or pyrazolyl is substituted with C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl or substituted pyrazolyl, wherein the pyrrolyl or pyrazolyl is substituted with C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted imidazolyl, substituted pyrrolyl, or substituted pyrazolyl, wherein the imidazolyl, pyrrolyl, or pyrazolyl is substituted with 4-5 membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl or substituted pyrazolyl, wherein the pyrrolyl or pyrazolyl is substituted with 4-5 membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted imidazolyl, substituted pyrrolyl, or substituted pyrazolyl, wherein the imidazolyl, pyrrolyl, or pyrazolyl is substituted with 4-5 membered heterocyclyl. In certain embodiments, R^2 and R^3 together with the atoms to which

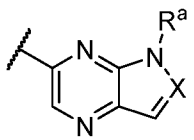
they are attached form a substituted pyrrolyl or substituted pyrazolyl, wherein the pyrrolyl or pyrazolyl is substituted with 4-5 membered heterocyclyl.

[00143] In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted pyrazolyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrazolyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrazolyl, wherein the pyrazolyl is substituted with substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrazolyl, wherein the pyrazolyl is substituted with substituted or unsubstituted alkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrazolyl, wherein the pyrazolyl is substituted with unsubstituted alkyl, heterocyclylalkyl, heterocyclyl, or haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrazolyl, wherein the pyrazolyl is substituted with unsubstituted alkyl or haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrazolyl, wherein the pyrazolyl is substituted with unsubstituted C_{1-4} alkyl, 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, or C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrazolyl, wherein the pyrazolyl is substituted with unsubstituted C_{1-4} alkyl or C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrazolyl, wherein the pyrazolyl is substituted with unsubstituted C_{1-4} alkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrazolyl, wherein the pyrazolyl is substituted with C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrazolyl, wherein the pyrazolyl is substituted with 4-5 membered heterocyclyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrazolyl, wherein the pyrazolyl is substituted with 4-5 membered heterocyclyl C_{1-4} alkyl.

[00144] In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted pyrrolyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted, wherein the pyrrolyl is substituted with substituted or unsubstituted heterocyclyl, or substituted or unsubstituted alkyl. In certain embodiments, R^2 and R^3 together with the

atoms to which they are attached form a substituted, wherein the pyrrolyl is substituted with substituted or unsubstituted alkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl, wherein the pyrrolyl is substituted with heterocyclyl, unsubstituted alkyl, or haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl, wherein the pyrrolyl is substituted with unsubstituted alkyl or haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl, wherein the pyrrolyl is substituted with 4-5 membered heterocyclyl, unsubstituted C_{1-4} alkyl, or C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl, wherein the pyrrolyl is substituted with unsubstituted C_{1-4} alkyl or C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl, wherein the pyrrolyl is substituted with unsubstituted C_{1-4} alkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl, wherein the pyrrolyl is substituted with C_{1-4} haloalkyl. In certain embodiments, R^2 and R^3 together with the atoms to which they are attached form a substituted pyrrolyl, wherein the pyrrolyl is substituted with 4-5 membered heterocyclyl.

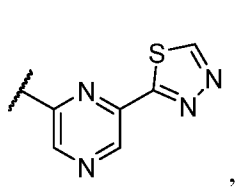
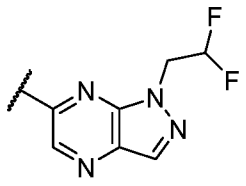
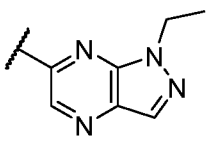
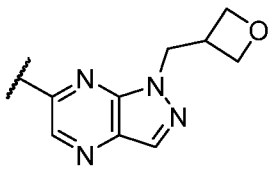
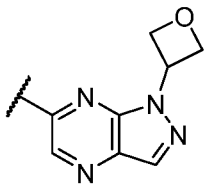
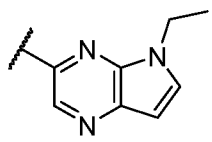
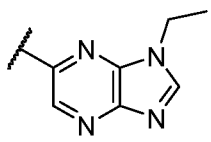
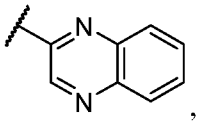
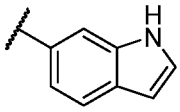
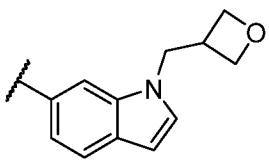
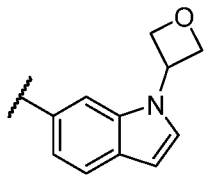
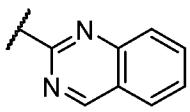
[00145] In certain embodiments, A is

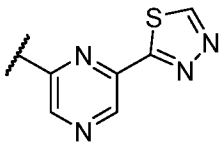
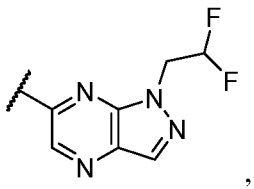
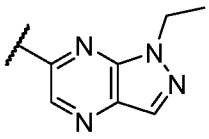
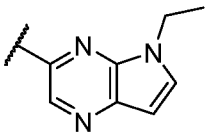
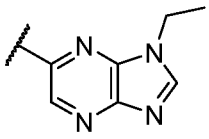
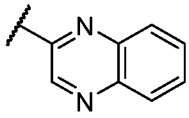
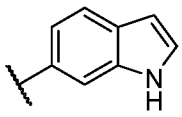
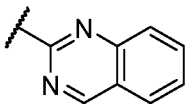


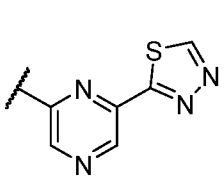
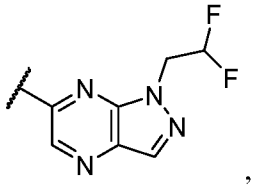
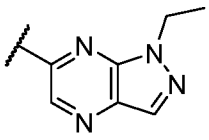
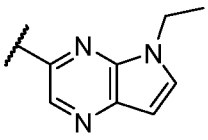
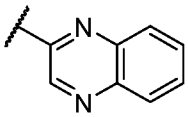
wherein X is N or CH; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

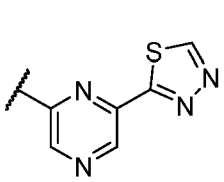
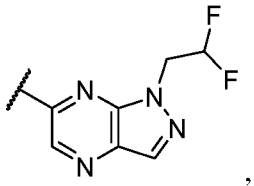
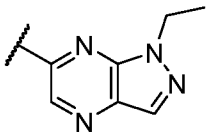
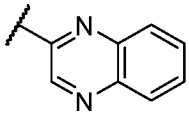
[00146] In certain embodiments, X is N or CH; and R^a is substituted or unsubstituted alkyl. In certain embodiments, X is N or CH; and R^a is heterocyclyl, haloalkyl, or alkyl. In certain embodiments, X is N or CH; and R^a is haloalkyl or alkyl. In certain embodiments, X is N or CH; and R^a is 4-5 membered heterocyclyl, fluoroalkyl, or alkyl. In certain embodiments, X is N or CH; and R^a is fluoroalkyl or alkyl. In certain embodiments, X is N or CH; and R^a is 4-5 membered heterocyclyl, C_{1-4} haloalkyl, or C_{1-4} alkyl. In certain embodiments, X is N or CH; and R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, X is N or CH; and R^a is 4-membered heterocyclyl, C_{1-4} fluoroalkyl, or C_{1-4} alkyl. In certain embodiments, X is N or CH; and R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, X is N; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl. In certain embodiments, X is N; and R^a is substituted or unsubstituted alkyl. In certain embodiments, X is N; and R^a is

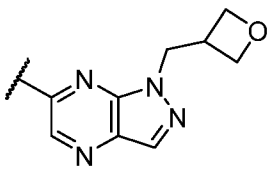
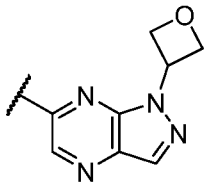
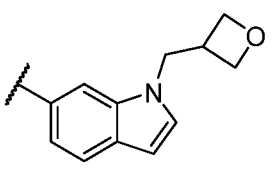
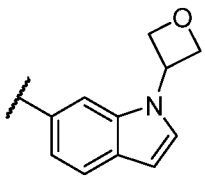
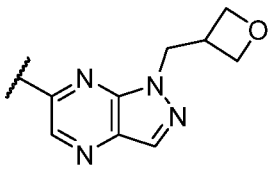
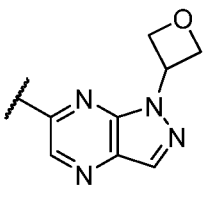
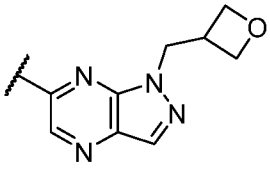
heterocyclyl, haloalkyl, or alkyl. In certain embodiments, X is N; and R^a is haloalkyl or alkyl. In certain embodiments, X is N; and R^a is 4-5 membered heterocyclyl, fluoroalkyl, or alkyl. In certain embodiments, X is N; and R^a is fluoroalkyl or alkyl. In certain embodiments, X is N; and R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, X is N or CH; and R^a is 4-membered heterocyclyl, C_{1-4} fluoroalkyl, or C_{1-4} alkyl. In certain embodiments, X is N; and R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is substituted or unsubstituted alkyl. In certain embodiments, X is CH; and R^a is 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, haloalkyl or alkyl. In certain embodiments, X is CH; and R^a is haloalkyl or alkyl. In certain embodiments, X is CH; and R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, fluoroalkyl or alkyl. In certain embodiments, X is CH; and R^a is fluoroalkyl or alkyl. In certain embodiments, X is CH; and R^a is 4-membered heterocyclyl C_{1-4} alkyl, 4-membered heterocyclyl, C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is ethyl. In certain embodiments, X is CH; and R^a is oxetanyl. In certain embodiments, X is CH; and R^a is oxetanylmethyl.

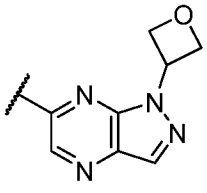
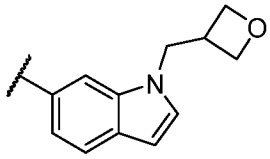
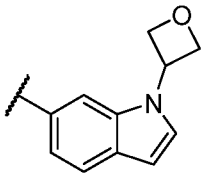
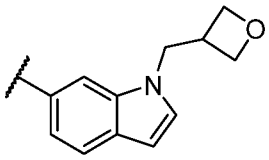
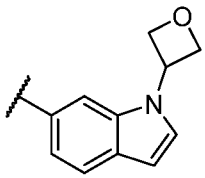
[00147] In certain embodiments, A is , , , , , , , , , , , or .

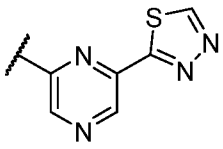
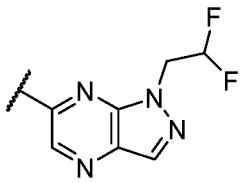
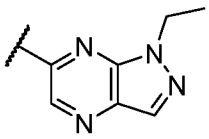
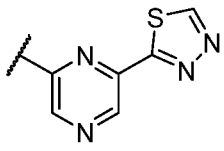
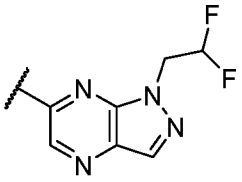
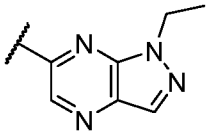
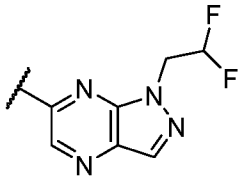
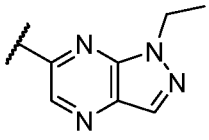
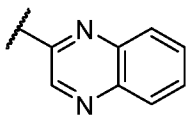
[00148] In certain embodiments, A is , , , , , , , or .

[00149] In certain embodiments, A is , , , , or .

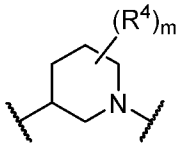
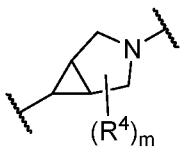
[00150] In certain embodiments, A is , , , or .

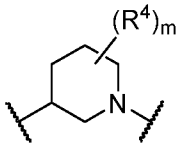
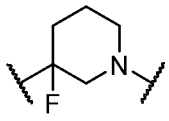
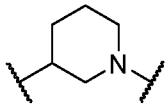
[00151] In certain embodiments, A is , , , or . In certain embodiments, A is , or . In certain embodiments, A is . In certain

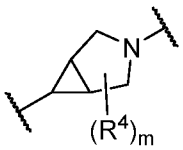
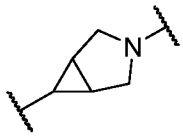
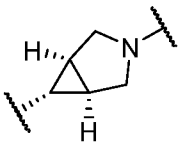
embodiments, A is  . In certain embodiments, A is  or  . In certain embodiments, A is  . In certain embodiments, A is  .

[00152] In certain embodiments, A is  ,  , or  . In certain embodiments, A is  . In certain embodiments, A is  or  . In certain embodiments, A is  . In certain embodiments, A is  . In certain embodiments, A is  .

A^1

[00153] As described herein, A^1 is  or  .

[00154] In certain embodiments, A^1 is . In certain embodiments, A^1 is . In certain embodiments, A^1 is .

[00155] In certain embodiments, A^1 is . In certain embodiments, A^1 is . In certain embodiments, A^1 is .

R^4

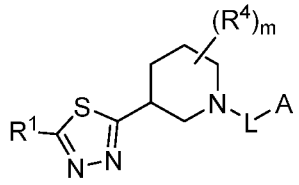
[00156] As described herein, each R^4 is independently halogen, substituted or unsubstituted alkyl, or two instances of R^4 on the same carbon form with that carbon a carbonyl; and m is 0, 1, 2, 3, or 4.

[00157] In certain embodiments, R^4 is halogen, or two instances of R^4 on the same carbon form with that carbon a carbonyl . In certain embodiments, R^4 is fluoro, or two instances of R^4 on the same carbon form with that carbon a carbonyl . In certain embodiments, R^4 is halogen. In certain embodiments, R^4 is fluoro. In certain embodiments, two instances of R^4 on the same carbon form with that carbon a carbonyl . In certain embodiments, m is 0, 1, 2, or 3. In certain embodiments, m is 0, 1, or 2. In certain embodiments, m is 0 or 2. In certain embodiments, m is 0 or 1. In certain embodiments, m is 1 or 2. In certain embodiments, m is 0. In certain embodiments, m is 2. In certain embodiments, m is 1.

[00158] In certain embodiments, R^4 is halogen, or two instances of R^4 on the same carbon form with that carbon a carbonyl ; and m is 2. In certain embodiments, R^4 is fluoro, or two instances of R^4 on the same carbon form with that carbon a carbonyl ; and m is 2. In certain embodiments, R^4 is halogen; and m is 2. In certain embodiments, R^4 is fluoro; and m is 2. In certain embodiments, two instances of R^4 on the same carbon form with that carbon a carbonyl ; and m is 2.

Certain Embodiments

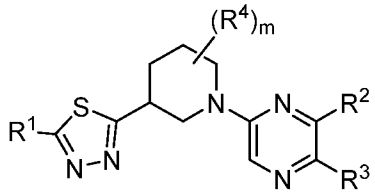
[00159] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-a**):



(**I-a**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^4, m, L, and A are as defined herein.

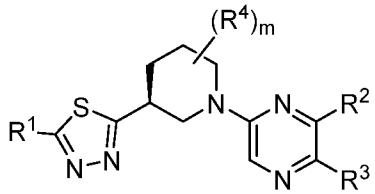
[00160] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-b**):



(**I-b**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^2, R^3, R^4, and m are as defined herein.

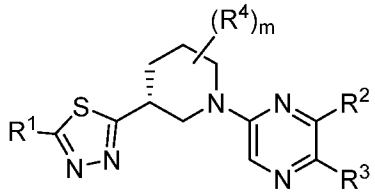
[00161] In certain embodiments, the compound of Formula (**I-b**) is of Formula (**I-b-1**):



(**I-b-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^2, R^3, R^4, and m are as defined herein.

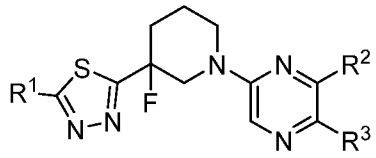
[00162] In certain embodiments, the compound of Formula (**I-a**) is of Formula (**I-b-2**):



(**I-b-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^2, R^3, R^4, and m are as defined herein.

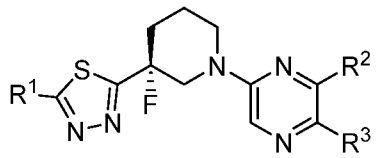
[00163] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-c**):



(**I-c**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^2, and R^3 are as defined herein.

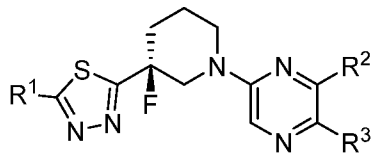
[00164] In certain embodiments, the compound of Formula (**I-c**) is of Formula (**I-c-1**):



(**I-c-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^2, and R^3 are as defined herein.

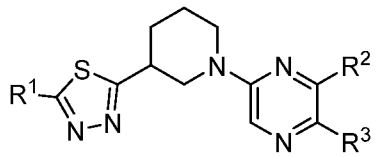
[00165] In certain embodiments, the compound of Formula (**I-c**) is of Formula (**I-c-2**):



(**I-c-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^2, and R^3 are as defined herein.

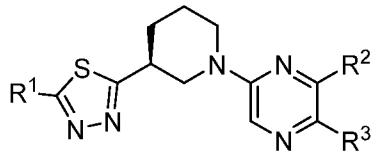
[00166] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-d**):



(**I-d**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^2, and R^3 are as defined herein.

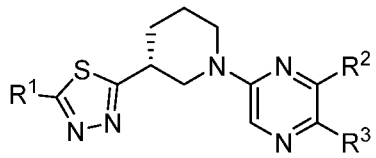
[00167] In certain embodiments, the compound of Formula (**I-d**) is of Formula (**I-d-1**):



(**I-d-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^2, and R^3 are as defined herein.

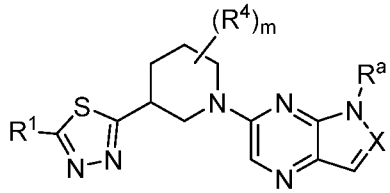
[00168] In certain embodiments, the compound of Formula (**I-d**) is of Formula (**I-d-2**):



(**I-d-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^2, and R^3 are as defined herein.

[00169] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-e**):



(**I-e**),

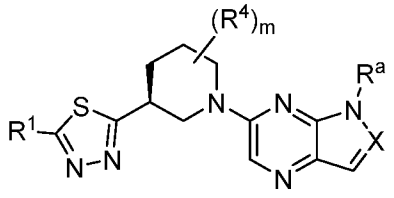
or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^4, and m are as defined herein; X is N or CH; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

[00170] In certain embodiments, X is N or CH; and R^a is substituted or unsubstituted alkyl.

[00171] In certain embodiments, X is N or CH; and R^a is heterocyclyl, haloalkyl, or alkyl. In certain embodiments, X is N or CH; and R^a is haloalkyl or alkyl. In certain embodiments, X is N or CH; and R^a is 4-5 membered heterocyclyl, fluoroalkyl, or alkyl. In certain

embodiments, X is N or CH; and R^a is fluoroalkyl or alkyl. In certain embodiments, X is N or CH; and R^a is 4-5 membered heterocyclyl, C_{1-4} haloalkyl, or C_{1-4} alkyl. In certain embodiments, X is N or CH; and R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, X is N or CH; and R^a is 4-membered heterocyclyl, C_{1-4} fluoroalkyl, or C_{1-4} alkyl. In certain embodiments, X is N or CH; and R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, X is N; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl. In certain embodiments, X is N; and R^a is substituted or unsubstituted alkyl. In certain embodiments, X is N; and R^a is heterocyclyl, haloalkyl, or alkyl. In certain embodiments, X is N; and R^a is haloalkyl or alkyl. In certain embodiments, X is N; and R^a is 4-5 membered heterocyclyl, fluoroalkyl, or alkyl. In certain embodiments, X is N; and R^a is fluoroalkyl or alkyl. In certain embodiments, X is N; and R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, X is N or CH; and R^a is 4-membered heterocyclyl, C_{1-4} fluoroalkyl, or C_{1-4} alkyl. In certain embodiments, X is N; and R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is substituted or unsubstituted alkyl. In certain embodiments, X is CH; and R^a is 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, haloalkyl or alkyl. In certain embodiments, X is CH; and R^a is haloalkyl or alkyl. In certain embodiments, X is CH; and R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, fluoroalkyl or alkyl. In certain embodiments, X is CH; and R^a is fluoroalkyl or alkyl. In certain embodiments, X is CH; and R^a is 4-membered heterocyclyl C_{1-4} alkyl, 4-membered heterocyclyl, C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is C_{1-4} alkyl. In certain embodiments, X is CH; and R^a is ethyl. In certain embodiments, X is CH; and R^a is oxetanyl. In certain embodiments, X is CH; and R^a is oxetanylmethyl.

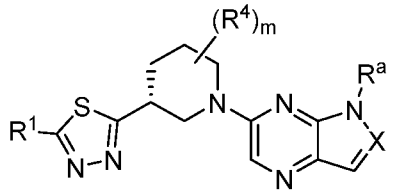
[00172] In certain embodiments, the compound of Formula (**I-e**) is of Formula (**I-e-1**):



(**I-e-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

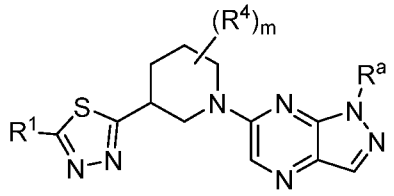
[00173] In certain embodiments, the compound of Formula (**I-e**) is of Formula (**I-e-2**):



(**I-e-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

[00174] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-f**):



(**I-f**),

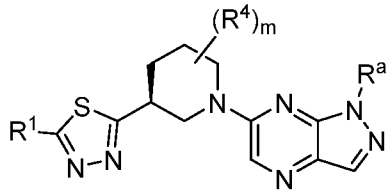
or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^4, and m are as defined herein; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

[00175] In certain embodiments, R^a is substituted or unsubstituted alkyl.

[00176] In certain embodiments, 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, haloalkyl or alkyl. In certain embodiments, R^a is haloalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, fluoroalkyl or alkyl. In certain embodiments, R^a is fluoroalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} fluoroalkyl, or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl. In certain embodiments, R^a is 2,2-difluoroethyl. In certain embodiments, R^a is C_{1-4} alkyl. In certain embodiments, R^a is ethyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is 4-membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is oxetanylmethyl. In

certain embodiments, R^a is 4-5 membered heterocyclyl. In certain embodiments, R^a is 4-membered heterocyclyl. In certain embodiments, R^a is oxetanyl.

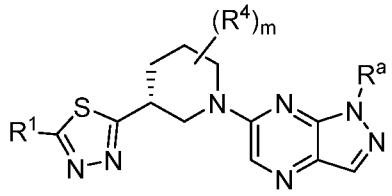
[00177] In certain embodiments, the compound of Formula (**I-f**) is of Formula (**I-f-1**):



(**I-f-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

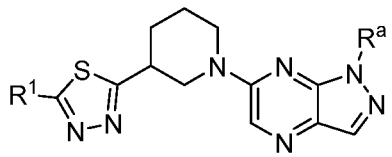
[00178] In certain embodiments, the compound of Formula (**I-f**) is of Formula (**I-f-2**):



(**I-f-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

[00179] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-g**):



(**I-g**),

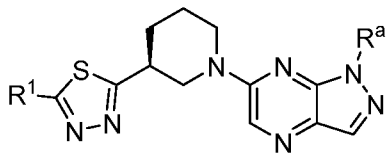
or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1 is as defined herein; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

In certain embodiments, R^a is substituted or unsubstituted alkyl.

[00180] In certain embodiments, 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, haloalkyl or alkyl. In certain embodiments, R^a is haloalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, fluoroalkyl or alkyl. In certain embodiments, R^a is fluoroalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is 4-5

membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} fluoroalkyl, or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl. In certain embodiments, R^a is 2,2-difluoroethyl. In certain embodiments, R^a is C_{1-4} alkyl. In certain embodiments, R^a is ethyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is 4-membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is oxetanylmethyl. In certain embodiments, R^a is 4-5 membered heterocyclyl. In certain embodiments, R^a is 4-membered heterocyclyl. In certain embodiments, R^a is oxetanyl.

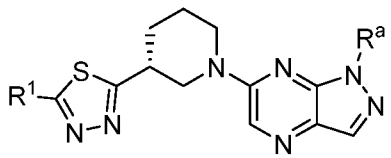
[00181] In certain embodiments, the compound of Formula (**I-g**) is of Formula (**I-g-1**):



(**I-g-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

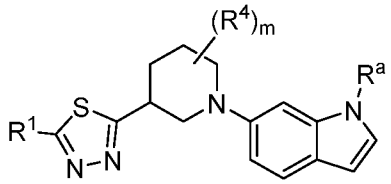
[00182] In certain embodiments, the compound of Formula (**I-g**) is of Formula (**I-g-2**):



(**I-g-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

[00183] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-h**):



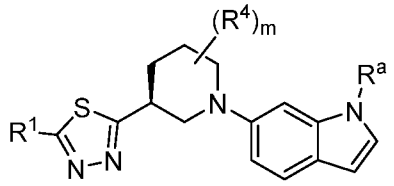
(**I-h**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^4, and m are as defined herein; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

In certain embodiments, R^a is substituted or unsubstituted alkyl.

[00184] In certain embodiments, 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, haloalkyl or alkyl. In certain embodiments, R^a is haloalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, fluoroalkyl or alkyl. In certain embodiments, R^a is fluoroalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} fluoroalkyl, or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl. In certain embodiments, R^a is 2,2-difluoroethyl. In certain embodiments, R^a is C_{1-4} alkyl. In certain embodiments, R^a is ethyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is 4-membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is oxetanylmethyl. In certain embodiments, R^a is 4-5 membered heterocyclyl. In certain embodiments, R^a is 4-membered heterocyclyl. In certain embodiments, R^a is oxetanyl.

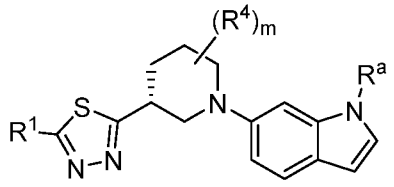
[00185] In certain embodiments, the compound of Formula (**I-g**) is of Formula (**I-h-1**):



(**I-h-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

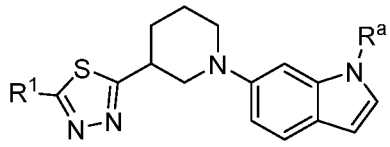
[00186] In certain embodiments, the compound of Formula (**I-h**) is of Formula (**I-h-2**):



(**I-h-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

[00187] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-i**):



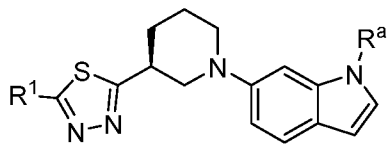
(**I-i**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1 is as defined herein; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

In certain embodiments, R^a is substituted or unsubstituted alkyl.

[00188] In certain embodiments, 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, haloalkyl or alkyl. In certain embodiments, R^a is haloalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, fluoroalkyl or alkyl. In certain embodiments, R^a is fluoroalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} fluoroalkyl, or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl. In certain embodiments, R^a is 2,2-difluoroethyl. In certain embodiments, R^a is C_{1-4} alkyl. In certain embodiments, R^a is ethyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is 4-membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is oxetanylmethyl. In certain embodiments, R^a is 4-5 membered heterocyclyl. In certain embodiments, R^a is 4-membered heterocyclyl. In certain embodiments, R^a is oxetanyl.

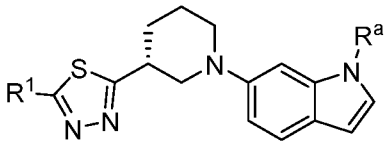
[00189] In certain embodiments, the compound of Formula (**I-i**) is of Formula (**I-i-1**):



(**I-i-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

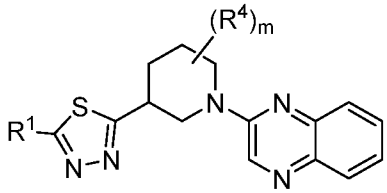
[00190] In certain embodiments, the compound of Formula (**I-i**) is of Formula (**I-i-2**):



(**I-i-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

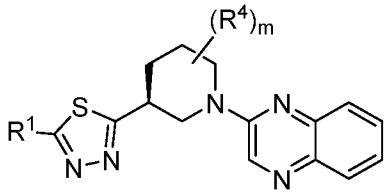
[00191] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-j**):



(**I-j**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^4, and m are as defined herein.

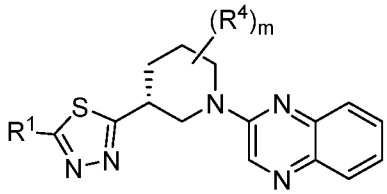
[00192] In certain embodiments, the compound of Formula (**I-j**) is of Formula (**I-j-1**):



(**I-j-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

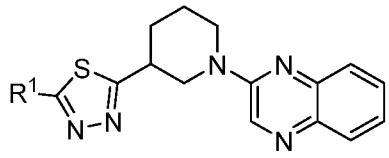
[00193] In certain embodiments, the compound of Formula (**I-j**) is of Formula (**I-j-2**):



(**I-j-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

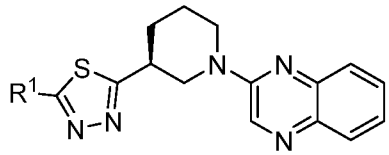
[00194] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-k**):



(**I-k**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1 is as defined herein.

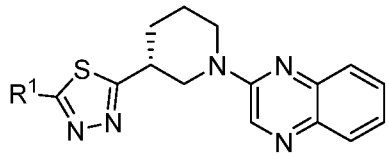
[00195] In certain embodiments, the compound of Formula (**I-k**) is of Formula (**I-k-1**):



(**I-k-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

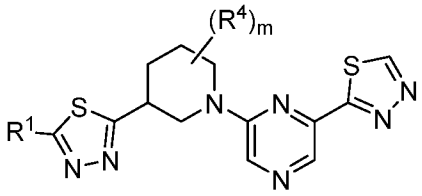
[00196] In certain embodiments, the compound of Formula (**I-k**) is of Formula (**I-k-2**):



(**I-k-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

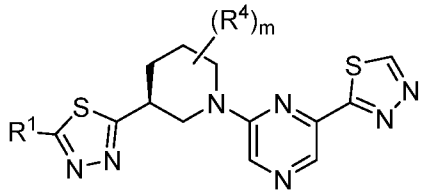
[00197] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-l**):



(**I-l**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^4, and m are as defined herein.

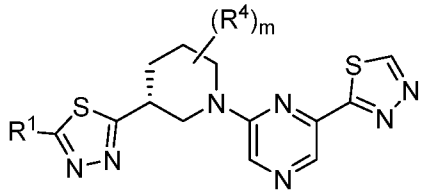
[00198] In certain embodiments, the compound of Formula (**I-l**) is of Formula (**I-l-1**):



(**I-l-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

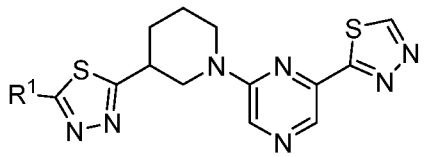
[00199] In certain embodiments, the compound of Formula (**I-l**) is of Formula (**I-l-2**):



(**I-l-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

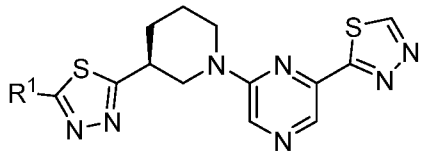
[00200] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-m**):



(**I-m**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1 is as defined herein.

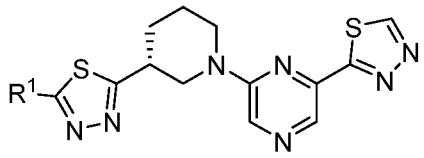
[00201] In certain embodiments, the compound of Formula (**I-m**) is of Formula (**I-m-1**):



(**I-m-1**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

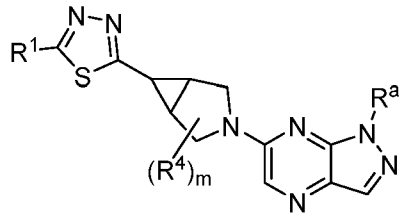
[00202] In certain embodiments, the compound of Formula (**I-m**) is of Formula (**I-m-2**):



(**I-m-2**),

or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof.

[00203] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-n**):



(**I-n**),

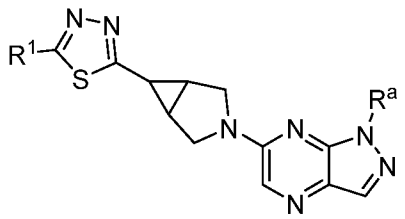
or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1, R^4, and m are as defined herein; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

[00204] In certain embodiments, R^a is substituted or unsubstituted alkyl.

[00205] In certain embodiments, 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, haloalkyl or alkyl. In certain embodiments, R^a is haloalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, fluoroalkyl or alkyl. In certain embodiments, R^a is fluoroalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} fluoroalkyl, or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4}

haloalkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl. In certain embodiments, R^a is 2,2-difluoroethyl. In certain embodiments, R^a is C_{1-4} alkyl. In certain embodiments, R^a is ethyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is 4-membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is oxetanylmethyl. In certain embodiments, R^a is 4-5 membered heterocyclyl. In certain embodiments, R^a is 4-membered heterocyclyl. In certain embodiments, R^a is oxetanyl.

[00206] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-o**):



(**I-o**),

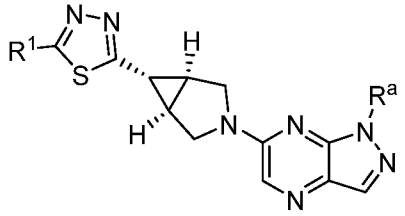
or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1 is as defined herein; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

[00207] In certain embodiments, R^a is substituted or unsubstituted alkyl.

[00208] In certain embodiments, 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, haloalkyl or alkyl. In certain embodiments, R^a is haloalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, fluoroalkyl or alkyl. In certain embodiments, R^a is fluoroalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} fluoroalkyl, or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl. In certain embodiments, R^a is 2,2-difluoroethyl. In certain embodiments, R^a is C_{1-4} alkyl. In certain embodiments, R^a is ethyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is 4-membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is oxetanylmethyl. In

certain embodiments, R^a is 4-5 membered heterocyclyl. In certain embodiments, R^a is 4-membered heterocyclyl. In certain embodiments, R^a is oxetanyl.

[00209] In certain embodiments, the compound of Formula (**I**) is of Formula (**I-p**):



(**I-p**),

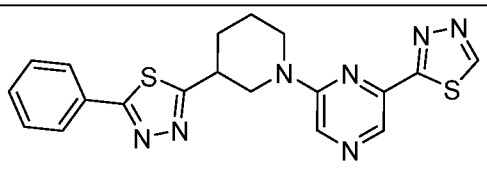
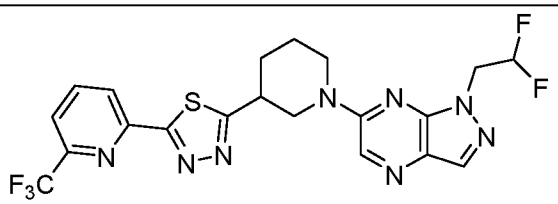
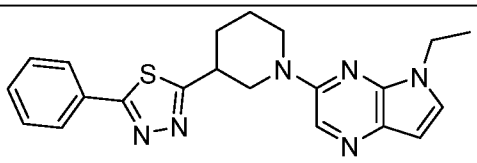
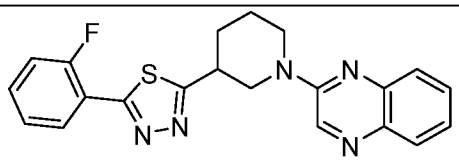
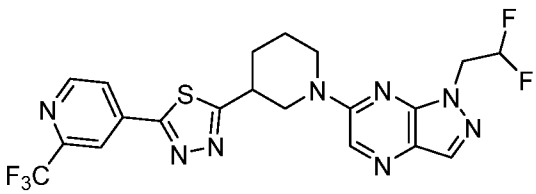
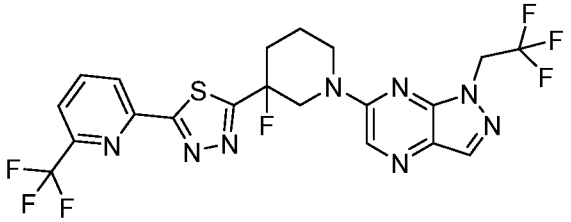
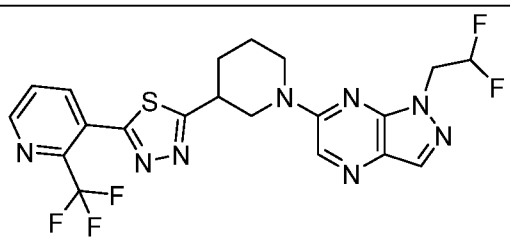
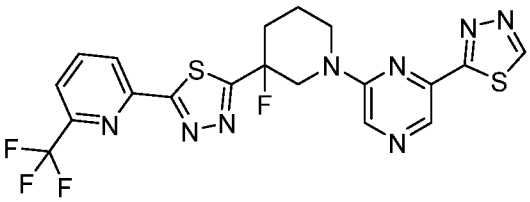
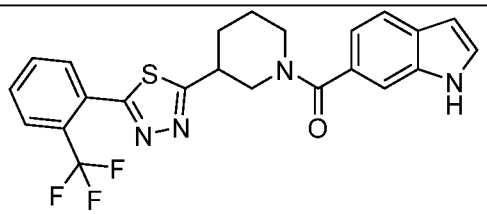
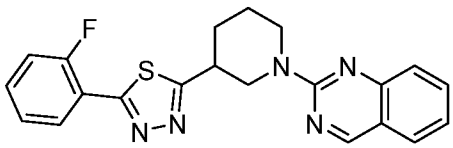
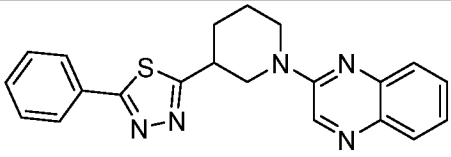
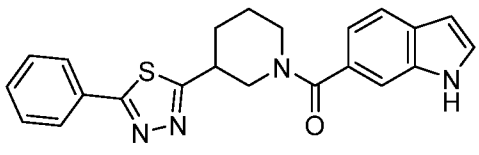
or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof; wherein R^1 is as defined herein; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

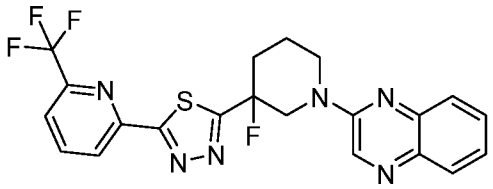
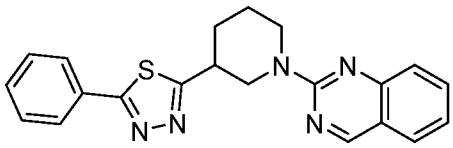
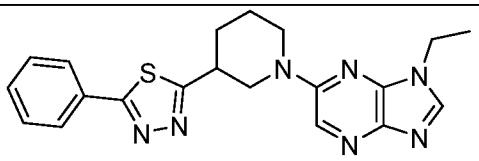
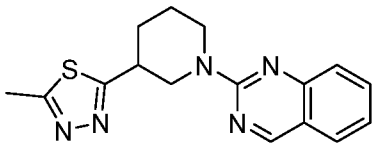
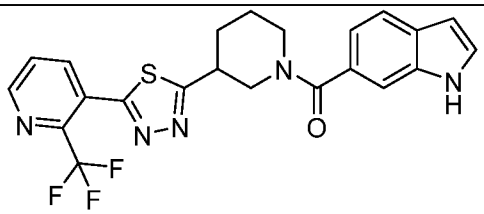
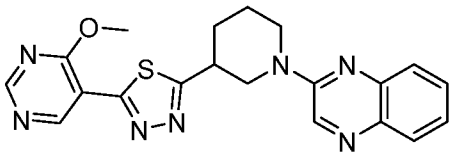
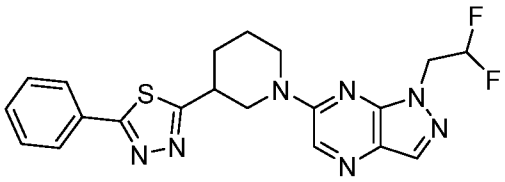
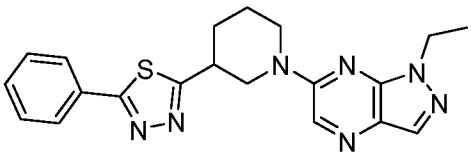
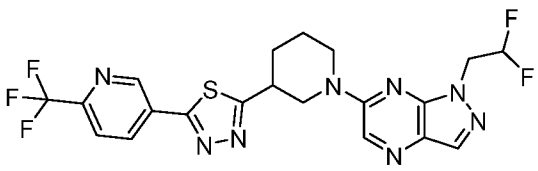
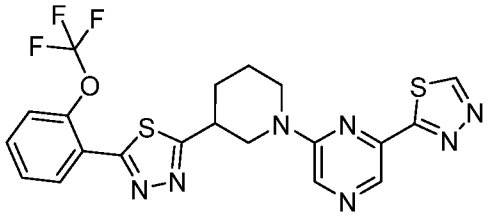
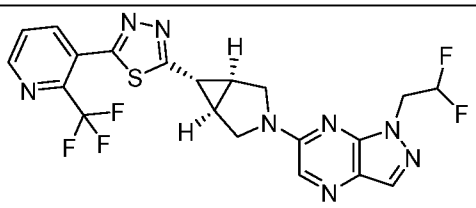
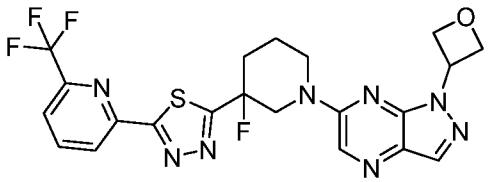
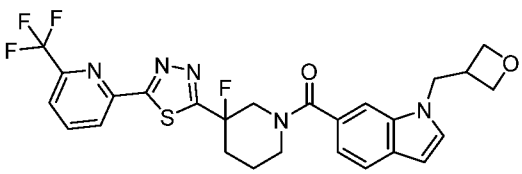
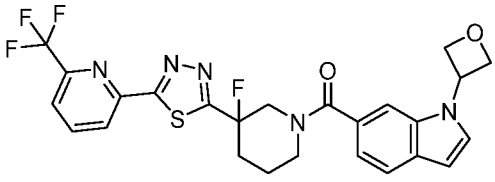
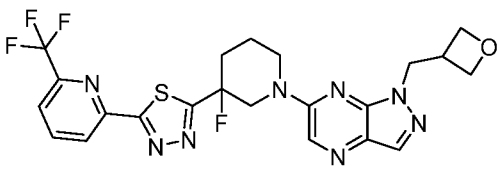
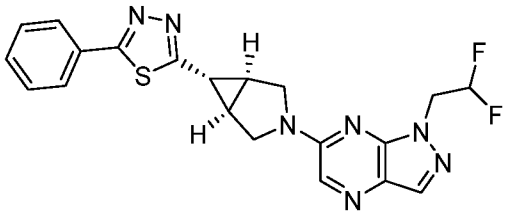
[00210] In certain embodiments, R^a is substituted or unsubstituted alkyl.

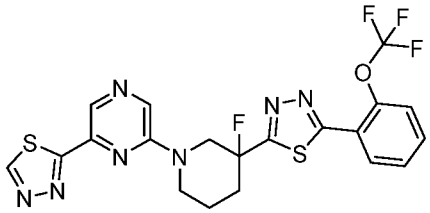
[00211] In certain embodiments, 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, haloalkyl or alkyl. In certain embodiments, R^a is haloalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclylalkyl, 4-5 membered heterocyclyl, fluoroalkyl or alkyl. In certain embodiments, R^a is fluoroalkyl or alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl or C_{1-4} alkyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl, 4-5 membered heterocyclyl, C_{1-4} fluoroalkyl, or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl or C_{1-4} alkyl. In certain embodiments, R^a is C_{1-4} haloalkyl. In certain embodiments, R^a is C_{1-4} fluoroalkyl. In certain embodiments, R^a is 2,2-difluoroethyl. In certain embodiments, R^a is C_{1-4} alkyl. In certain embodiments, R^a is ethyl. In certain embodiments, R^a is 4-5 membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is 4-membered heterocyclyl C_{1-4} alkyl. In certain embodiments, R^a is oxetanylmethyl. In

certain embodiments, R^a is 4-5 membered heterocyclyl. In certain embodiments, R^a is 4-membered heterocyclyl. In certain embodiments, R^a is oxetanyl.

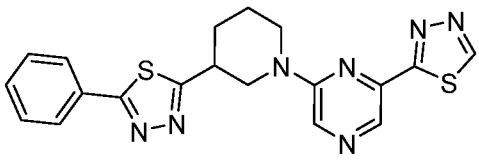
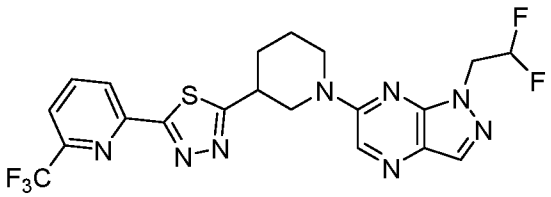
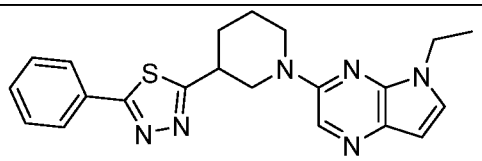
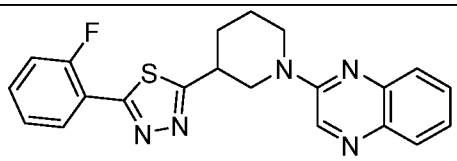
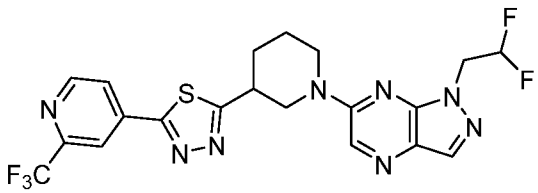
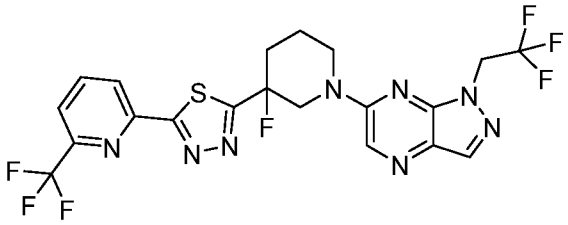
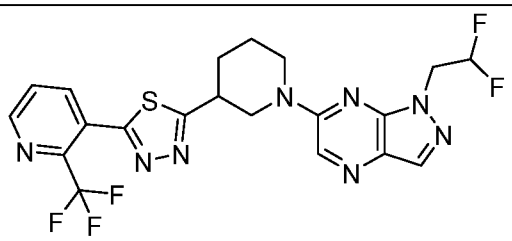
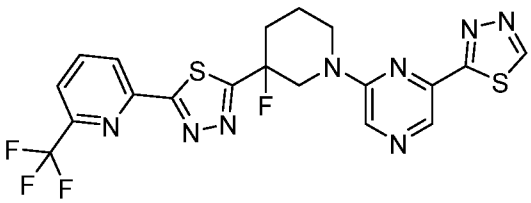
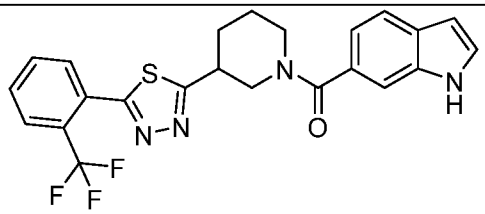
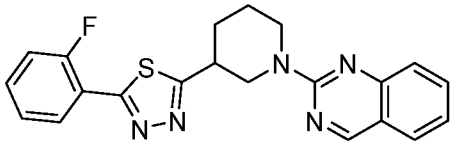
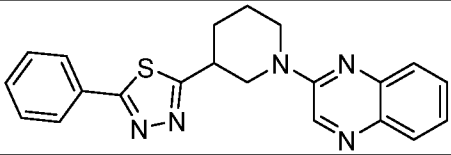
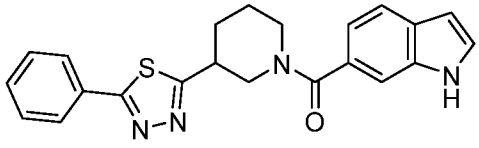
[00212] In certain embodiments, the compound of Formula (**I**) is one of the following compounds, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof:

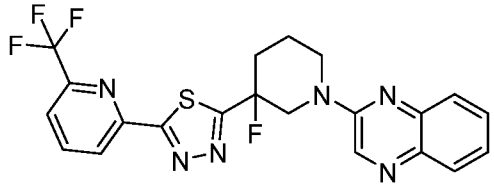
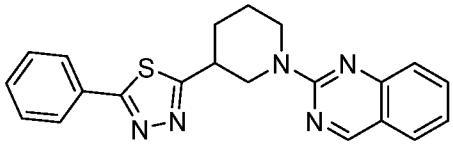
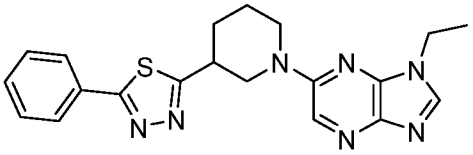
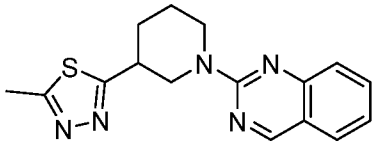
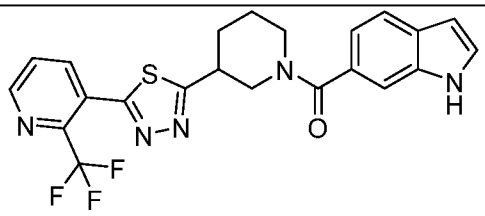
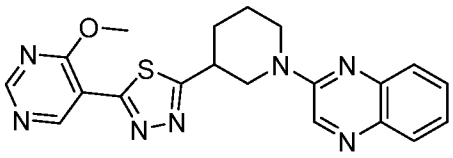
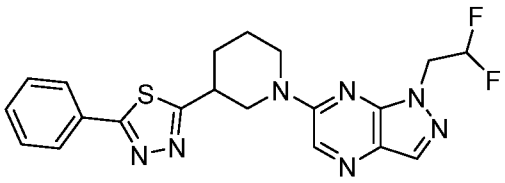
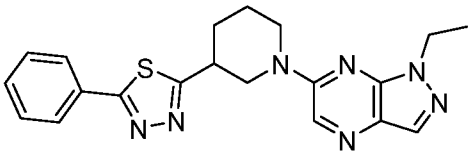
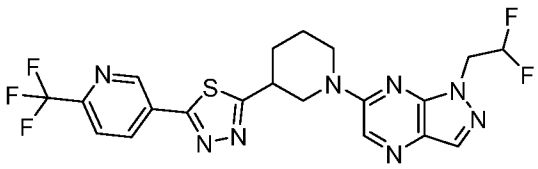
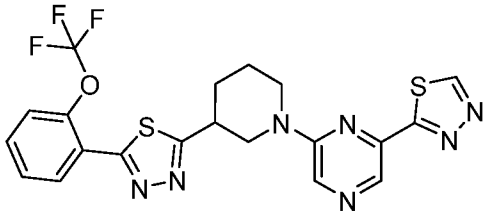
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[00213] In certain embodiments, the compound of Formula (**I**) is one of the following compounds, or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof:

 1	 2
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[00214] In certain embodiments, the provided compounds (*e.g.*, compounds of Formula (**I**)), activate GCase with an EC_{50} of less than 100,000 nM, less than 50,000 nM, less than 20,000 nM, less than 10,000 nM, less than 5,000 nM, less than 2,500 nM, less than 1,000 nM, less than 900 nM, less than 800 nM, less than 700 nM, less than 600 nM, less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 90 nM, less than 80 nM, less than 70 nM, less than 60 nM, less than 50 nM, less than 40 nM, less than 30 nM, less than 20 nM, less than 10 nM, less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, or less than 1 nM.

Pharmaceutical Compositions, Kits, and Administration

[00215] The present disclosure provides pharmaceutical compositions comprising a disclosed compound (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition described herein comprises a compound of Formula (**I**), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00216] In certain embodiments, the compound of Formula (**I**) is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective for treating a disease or disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for treating a neurological disease or disorder in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for preventing a neurological disease or disorder in a subject in need thereof.

[00217] In certain embodiments, the effective amount is an amount effective for reducing the risk of developing a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof.

[00218] In certain embodiments, the effective amount is an amount effective for increasing the activity of GCase in a subject, tissue, biological sample, or cell.

[00219] In certain embodiments, the subject being treated or administered a compound described herein is an animal. The animal may be of either sex and may be at any stage of development. In certain embodiments, the subject described herein is a human. In certain embodiments, the subject is a non-human animal. In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a non-human mammal. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal, such as a dog or cat. In certain embodiments, the subject is a livestock animal, such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal, such as a rodent (*e.g.*, mouse, rat), dog, pig, or non-human primate. In certain embodiments, the animal is a genetically engineered animal. In certain embodiments,

the animal is a transgenic animal (*e.g.*, transgenic mice and transgenic pigs). In certain embodiments, the subject is a fish or reptile.

[00220] In certain embodiments, the effective amount is an amount effective for increasing the activity of GCase by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, at least about 300%, at least about 400%, at least about 500%, or at least about 1000%. In certain embodiments, the effective amount is an amount effective for iincreasing the activity of GCase by a range between a percentage described in this paragraph and another percentage described in this paragraph, inclusive.

[00221] The present disclosure provides pharmaceutical compositions comprising a compound that interacts with (*e.g.*, activates) GCase for use in treating a GCase-related disease or disorder in a subject in need thereof. The present disclosure provides pharmaceutical compositions comprising a compound that interacts with (*e.g.*, activates) GCase for use in treating a disease or disorder associated with aberrant activity of GCase in a subject in need thereof. The present disclosure provides pharmaceutical compositions comprising a compound that interacts with (*e.g.*, activates) GCase for use in treating a disease or disorder associated with mutated GCase in a subject in need thereof.

[00222] In certain embodiments, the composition is for use in treating a disease or disorder. In certain embodiments, the composition is for use in treating a neurological disease or disorder. In certain embodiments, the composition is for use in treating Gaucher's disease or Parkinson's disease. In certain embodiments, the composition is for use in treating Gaucher's disease. In certain embodiments, the composition is for use in treating Parkinson's disease.

[00223] A compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents (*e.g.*, therapeutically and/or prophylactically active agents). The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their activity (*e.g.*, activity (*e.g.*, potency and/or efficacy) in treating a disease in a subject in need thereof, in preventing a disease in a subject in need thereof, and/or in reducing the risk to develop a disease in a subject in need thereof), improve bioavailability, improve safety, reduce drug resistance, reduce and/or modify metabolism, inhibit excretion, and/or modify distribution in a subject or cell. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects. In certain embodiments, a pharmaceutical composition described herein including a compound described herein and an

additional pharmaceutical agent exhibit a synergistic effect that is absent in a pharmaceutical composition including one of the compound and the additional pharmaceutical agent, but not both.

[00224] The compound or composition can be administered concurrently with, prior to, or subsequent to one or more additional pharmaceutical agents, which may be useful as, *e.g.*, combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved for human or veterinary use by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful for treating and/or preventing a disease (*e.g.*, neurological disease or disorder). Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the compound described herein with the additional pharmaceutical agent(s) and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agent(s) in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00225] In certain embodiments, the compound or pharmaceutical composition is a solid. In certain embodiments, the compound or pharmaceutical composition is a powder. In certain embodiments, the compound or pharmaceutical composition can be dissolved in a liquid to make a solution. In certain embodiments, the compound or pharmaceutical composition is dissolved in water to make an aqueous solution. In certain embodiments, the pharmaceutical composition is a liquid for parental injection. In certain embodiments, the pharmaceutical composition is a liquid for oral administration (*e.g.*, ingestion). In certain embodiments, the pharmaceutical composition is a liquid (*e.g.*, aqueous solution) for intravenous injection. In

certain embodiments, the pharmaceutical composition is a liquid (*e.g.*, aqueous solution) for subcutaneous injection.

[00226] After formulation with an appropriate pharmaceutically acceptable excipient in a desired dosage, the pharmaceutical compositions of the present dislcosure can be administered to humans and other animals orally, parenterally, intracisternally, intraperitoneally, topically, bucally, or the like, depending on the disease or condition being treated.

[00227] In certain embodiments, a pharmaceutical composition comprising a compound of Formula (**I**) is administered, orally or parenterally, at dosage levels of each pharmaceutical composition sufficient to deliver from about 0.001 mg/kg to about 200 mg/kg in one or more dose administrations for one or several days (depending on the mode of administration). In certain embodiments, the effective amount per dose varies from about 0.001 mg/kg to about 200 mg/kg, about 0.001 mg/kg to about 100 mg/kg, about 0.01 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic and/or prophylactic effect. In certain embodiments, the compounds described herein may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 200 mg/kg, from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic and/or prophylactic effect. The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage may be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). In certain embodiments, the composition described herein is administered at a dose that is below the dose at which the agent causes non-specific effects.

[00228] In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.001 mg to about 1000 mg per unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.01 mg to about 200 mg per

unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.01 mg to about 100 mg per unit dose. In certain embodiments, pharmaceutical composition is administered at a dose of about 0.01 mg to about 50 mg per unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.01 mg to about 10 mg per unit dose. In certain embodiments, the pharmaceutical composition is administered at a dose of about 0.1 mg to about 10 mg per unit dose.

[00229] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the composition comprising a compound of Formula (**I**) into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[00230] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage, such as, for example, one-half or one-third of such a dosage.

[00231] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00232] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00233] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[00234] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar,

bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[00235] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.* bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.* polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60), sorbitan tristearate (Span 65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (*e.g.* polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.* Cremophor™), polyoxyethylene ethers, (*e.g.* polyoxyethylene lauryl ether (Brij 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F-68, Poloxamer-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[00236] Exemplary binding agents include starch (*e.g.*, cornstarch and starch paste), gelatin, sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone),

magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[00237] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[00238] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00239] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00240] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00241] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00242] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00243] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl.

[00244] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[00245] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00246] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazelnut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[00247] Liquid dosage forms for oral and parenteral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active agents, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and

sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, agents of the invention are mixed with solubilizing agents such CREMOPHOR EL® (polyethoxylated castor oil), alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and combinations thereof.

[00248] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. Sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00249] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00250] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00251] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00252] The active agents can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active agent may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[00253] Formulations suitable for topical administration include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments, or pastes; or solutions or suspensions such as drops. Formulations for topical administration to the skin surface can be prepared by dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream, ointment, or soap. Useful carriers are capable of forming a film or layer over the skin to localize application and inhibit removal. For topical administration to internal tissue surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue-coating solutions, such as pectin-containing formulations can be used.

Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present disclosure contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of an agent to the body. Such dosage forms can be made by dissolving or dispensing the agent in the proper medium. Absorption enhancers can also be used to increase the flux of the agent across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the agent in a polymer matrix or gel.

[00254] Additionally, the carrier for a topical formulation can be in the form of a hydroalcoholic system (*e.g.*, liquids and gels), an anhydrous oil or silicone based system, or an emulsion system, including, but not limited to, oil-in-water, water-in-oil, water-in-oil-in-water, and oil-in-water-in-silicone emulsions. The emulsions can cover a broad range of consistencies including thin lotions (which can also be suitable for spray or aerosol delivery), creamy lotions, light creams, heavy creams, and the like. The emulsions can also include microemulsion systems. Other suitable topical carriers include anhydrous solids and semisolids (such as gels and sticks); and aqueous based mousse systems.

[00255] Also encompassed by the disclosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a pharmaceutical composition or compound described herein and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a pharmaceutical composition or compound described herein. In some embodiments, the pharmaceutical composition or compound described herein provided in the first container and the second container are combined to form one unit dosage form.

[00256] Thus, in one aspect, provided are kits including a first container comprising a compound or pharmaceutical composition described herein. In certain embodiments, the kits are useful for treating a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits are useful for preventing a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits are useful for reducing the risk of developing a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits are useful for increasing the activity of GCase in a subject or cell.

[00257] In certain embodiments, a kit described herein further includes instructions for using the kit. A kit described herein may also include information as required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). In certain embodiments, the

information included in the kits is prescribing information. In certain embodiments, the kits and instructions provide for treating a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for preventing a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for reducing the risk of developing a disease (*e.g.*, neurological disease or disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for increasing the activity of GCase in a subject or cell. A kit described herein may include one or more additional pharmaceutical agents described herein as a separate composition.

Methods of Treatment

[00258] The present disclosure provides methods for treating a disease or disorder in a subject in need thereof. In certain embodiments, the present disclosure provides methods for treating a disease or disorder associated with GCase activity. In certain embodiments, the application provides a method of treating a neurological disease or disorder. In certain embodiments, the application provides a method of treating Gaucher's disease or Parkinson's disease. In certain embodiments, the application provides a method of treating Gaucher's disease. In certain embodiments, the application provides a method of treating Parkinson's disease.

[00259] The present disclosure provides a method of activating GCase. The present disclosure provides a method of increasing the activity of GCase. In certain embodiments, the application provides a method of activating GCase (e.g., increasing the activity of GCase) *in vitro*. In certain embodiments, the application provides a method of activating GCase (e.g., increasing the activity of GCase) *in vivo*. In certain embodiments, the application provides a method of increasing the activity of GCase in a cell. In certain embodiments, the application provides a method of increasing the activity of GCase in a human cell.

[00260] In certain embodiments, the methods comprise administering to a subject in need thereof (*e.g.*, a subject with a neurological disease or disorder) a compound that interacts with GCase, for example, a compound that is a modulator of GCase (e.g., an activator of GCase), a binder of GCase, or a compound that modifies GCase. In certain embodiments, the methods comprise administering a compound of the disclosure (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug, or composition thereof, to a subject in need thereof. In some embodiments, the method comprises administering a pharmaceutical

composition comprising a compound of the disclosure (*e.g.*, a compound of Formula (**I**)), or a pharmaceutically acceptable salt, co-crystal, tautomer, stereoisomer, solvate, hydrate, polymorph, isotopically enriched derivative, or prodrug, or composition thereof, to a subject in need thereof.

[00261] Another object of the present disclosure is the use of a compound as described herein (e.g., of any formulae herein) in the manufacture of a medicament for use in the treatment of a disorder or disease described herein. Another object of the present disclosure is the use of a compound as described herein (e.g., of any formulae herein) for use in the treatment of a disorder or disease described herein.

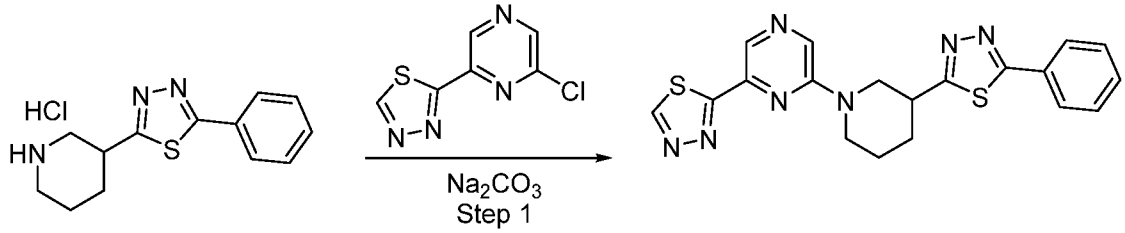
EXAMPLES

[00262] In order that the invention described herein may be more fully understood, the following examples are set forth. The examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

Synthetic Methods

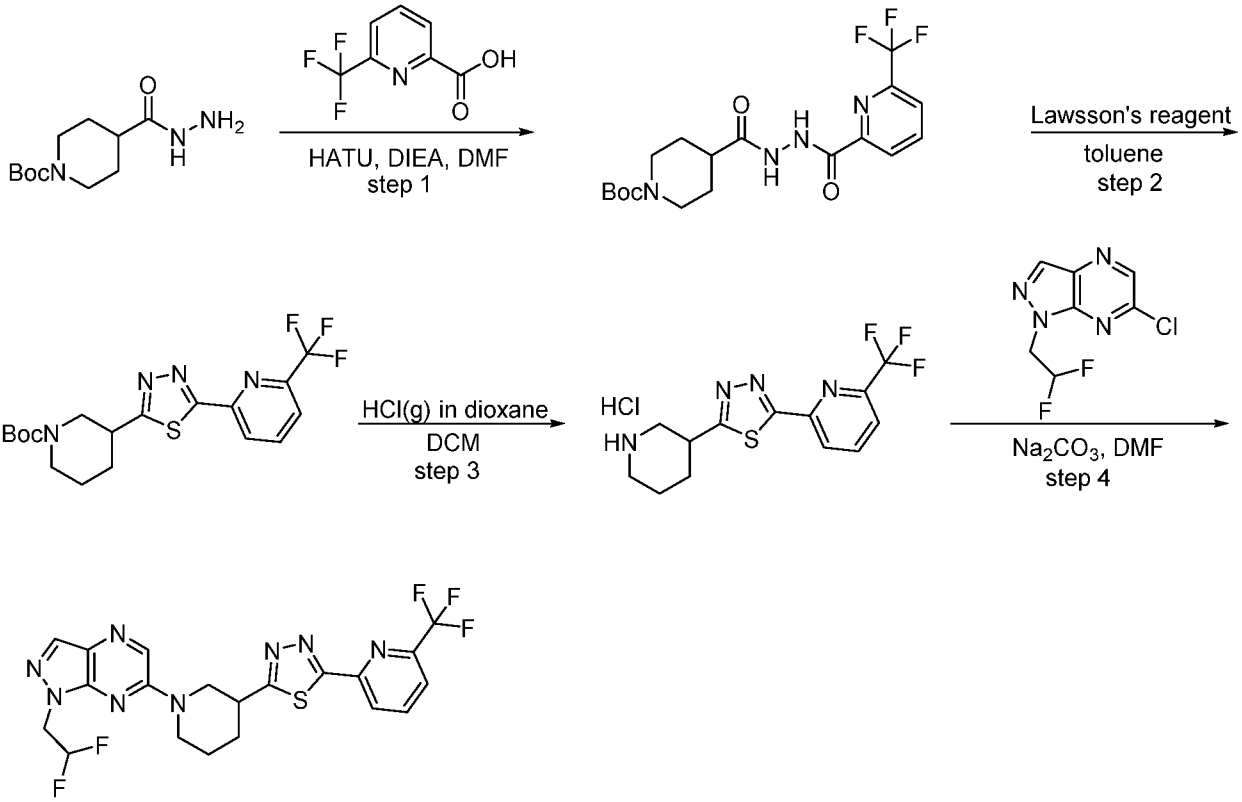
[00263] Compounds of Formula (**I**) were prepared following the synthetic schemes and procedures described in detail below. The examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope. Compounds of the disclosure that are not explicitly described in the following procedures may be prepared by analogous methods. Those having ordinary skill in the art would understand how to make such compounds from the disclosure provided herein and by means known in the art of organic synthesis. For example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and subsequent editions thereof are representative and instructive. Methods for optimizing reaction conditions, if necessary minimizing competing by products, are known in the art.

2-[3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl]-6-(1,3,4-thiadiazol-2-yl)pyrazine (1)



[00264] 2-[3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl]-6-(1,3,4-thiadiazol-2-yl)pyrazine: To a stirred solution of 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine hydrochloride (102 mg, 0.362 mmol, 1.2 equiv) and 2-chloro-6-(1,3,4-thiadiazol-2-yl)pyrazine (60.0 mg, 0.302 mmol, 1.00 equiv) in DMF (1 mL) was added Na_2CO_3 (96.0 mg, 0.906 mmol, 3 equiv) . The resulting mixture was stirred for 3 hours at 100 °C. The reaction mixture was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 60% gradient in 15 min; detector, UV 254 nm. This resulted in 2-[3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl]-6-(1,3,4-thiadiazol-2-yl)pyrazine (34.0 mg, 27.62%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (s, 1H), 8.65-8.62 (m, 2H), 8.08-7.88 (m, 2H), 7.59-7.54 (m, 3H), 4.67-4.58 (m, 1H), 4.25-4.21 (m, 1H), 3.68-3.51 (m, 2H), 3.44-3.36 (m, 1H) ,2.25 (s, 1H), 2.09- 1.83 (m, 2H), 1.77-1.69 (m, 1H). MS m/z: 407.8 $[M+H]^+$.

2-(5-{1-[1-(2,2-difluoroethyl)pyrazolo[3,4-b]pyrazin-6-yl]piperidin-3-yl}-1,3,4-thiadiazol-2-yl)-6-(trifluoromethyl)pyridine (2)



[00265] Step 1: *tert*-butyl 3-({[6-(trifluoromethyl)pyridin-2-yl]formohydrazido}carbonyl)piperidine-1-carboxylate: To a stirred solution of 6-(trifluoromethyl)pyridine-2-carboxylic acid and HATU (656 mg, 1.70 mmol, 1.1 equiv) in DCM (10 mL) were added DIEA (405 mg, 3.10 mmol, 2 equiv) and tert-butyl 3-(hydrazinecarbonyl)piperidine-1-carboxylate (458 mg, 1.80 mmol, 1.2 equiv) dropwise at 0 °C. The resulting mixture was stirred for 3 hours at room temperature. The reaction was diluted with water (20 mL) and extracted with EtOAc (25 mL x 2). The combined organic phases were washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under vacuum to give the crude product. It was purified by chromatography on silica gel (Flash 40 g, 30-60% EA:PE) to afford *tert*-butyl 3-({[6-(trifluoromethyl)pyridin-2-yl]formohydrazido}carbonyl)piperidine-1-carbo- xylate (450 mg, 99.0%) as a light yellow oil. MS *m/z*: 417[M+H]$^+$.

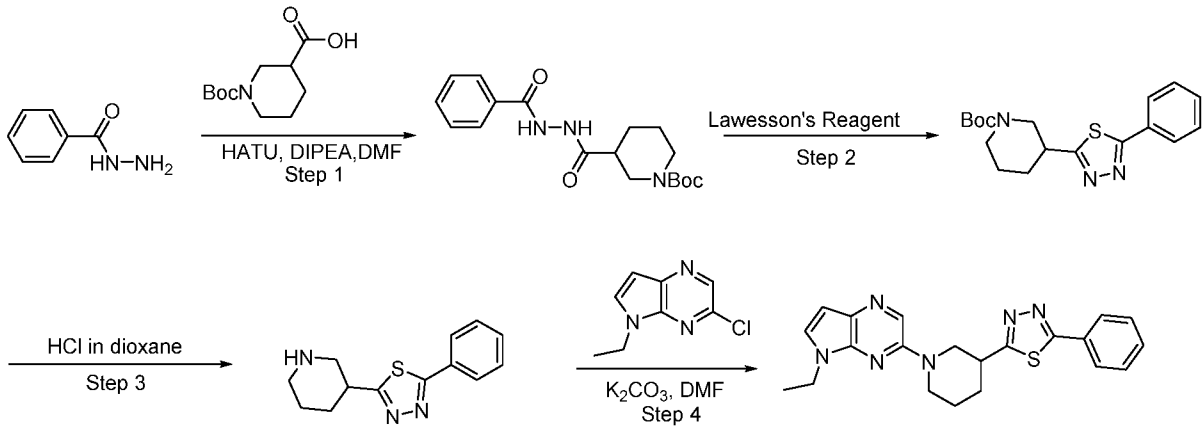
[00266] Step 2: *tert*-butyl 3-{5-[6-(trifluoromethyl)pyridin-2-yl]-1,3,4-thiadiazol-2-yl}piperidine-1-carboxylate: A solution of *tert*-butyl 3-({[6-(trifluoromethyl)pyridin-2-yl]formohydrazido} carbonyl)piperidine-1-carboxylate and Lawesson Reagent (233 mg, 0.570 mmol, 0.6 equiv) in toluene (5 mL) was stirred for 2 hours at 60 °C. The reaction mixture was purified by chromatography on silica gel (Flash 40 g, 40-60% EtOAc:PE) to

afford 3-{5-[6-(trifluoromethyl)pyridin-2-yl]-1,3,4-thiadiazol-2-yl}piperidine-1-carboxylate (450 mg, 99.0%) as a white solid. MS *m/z*: 415[M+H]$^+$.

[00267] Step 3: 2-[5-(piperidin-3-yl)-1,3,4-thiadiazol-2-yl]-6-(trifluoromethyl)pyridine hydrochloride: To a stirred solution of tert-butyl 3-{5-[6-(trifluoromethyl)pyridin-2-yl]-1,3,4-thiadiazol-2-yl}piperidine-1-carboxylate (240 mg, 0.579 mmol, 1.00 equiv) in DCM (4mL) was added HCl(gas) in 1,4-dioxane (4M, 2 mL) dropwise at 0 °C. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated to dryness under vacuum. This resulted in 2-[5-(piperidin-3-yl)-1,3,4-thiadiazol-2-yl]-6-(trifluoromethyl)pyridine hydrochloride (150 mg, 92.0%) as a white solid. MS *m/z*: 315[M+H]$^+$.

[00268] Step 4: 2-(5-{1-[1-(2,2-difluoroethyl)pyrazolo[3,4-b]pyrazin-6-yl]piperidin-3-yl}-1,3,4-thiadiazol-2-yl)-6-(trifluoromethyl) pyridine: To a stirred solution of 2-[5-(piperidin-3-yl)-1,3,4-thiadiazol-2-yl]-6-(trifluoromethyl)pyridine hydrochloride (114 mg, 0.326 mmol, 1.2 equiv) and 6-chloro-1-(2,2-difluoroethyl)pyrazolo[3,4-b]pyrazine (50.0 mg, 0.272 mmol, 1.00 equiv) in DMF (1mL) was added Na_2CO_3 (86.3 mg, 0.816 mmol, 3 equiv) . The resulting mixture was stirred for 3 hours at 100 °C. The reaction mixture was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 2-(5-{1-[1-(2,2-difluoroethyl)pyrazolo[3,4-b]pyrazin-6-yl]piperidin-3-yl}-1,3,4-thiadiazol-2-yl)-6-(trifluoro methyl) pyridine (73.0 mg, 54.1%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61-8.50 (m, 2H), 8.36-8.32 (m, 1H), 8.15 (s, 1H), 8.13-8.04 (m, 1H), 6.60-6.27 (m, 1H), 4.75-4.66 (m, 3H), 4.38-4.35 (m, 1H), 3.71-3.54 (m, 2H), 3.43-3.38 (m, 1H), 2.30-2.27 (m, 1H), 2.10-1.96 (m, 1H), 1.94-1.82 (m, 1H), 1.73-1.70 (m, 1H). MS m/z: 497.2 [M+H]$^+$.

2-(1-(5-ethyl-5*H*-pyrrolo[2,3-b]pyrazin-3-yl)piperidin-3-yl)-5-phenyl-1,3,4-thiadiazole (3)



[00269] Step 1: *tert*-butyl 3-(2-benzoylhydrazine-1-carbonyl)piperidine-1-carboxylate: To a stirred solution of 1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid and HATU (656 mg, 1.70 mmol, 1.1 equiv) in DCM (10 mL) were added DIEA (406 mg, 3.10 mmol, 2 equiv) and benzohydrazide (458 mg, 1.80 mmol, 1.2 equiv) at 0 °C. The resulting mixture was stirred for 3 hours at room temperature. The reaction was diluted with water (20 mL) and extracted with EtOAc (25 mLx2). The combined organic phases were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to give the crude product. It was purified by chromatography on silica gel (Flash 40 g, 40-60% EtOAc:PE) to afford *tert*-butyl 3-(2-benzoylhydrazine-1-carbonyl)piperidine-1-carboxylate (450 mg, 99.0%) as a light yellow oil. MS *m/z*: 347[M+H]$^+$.

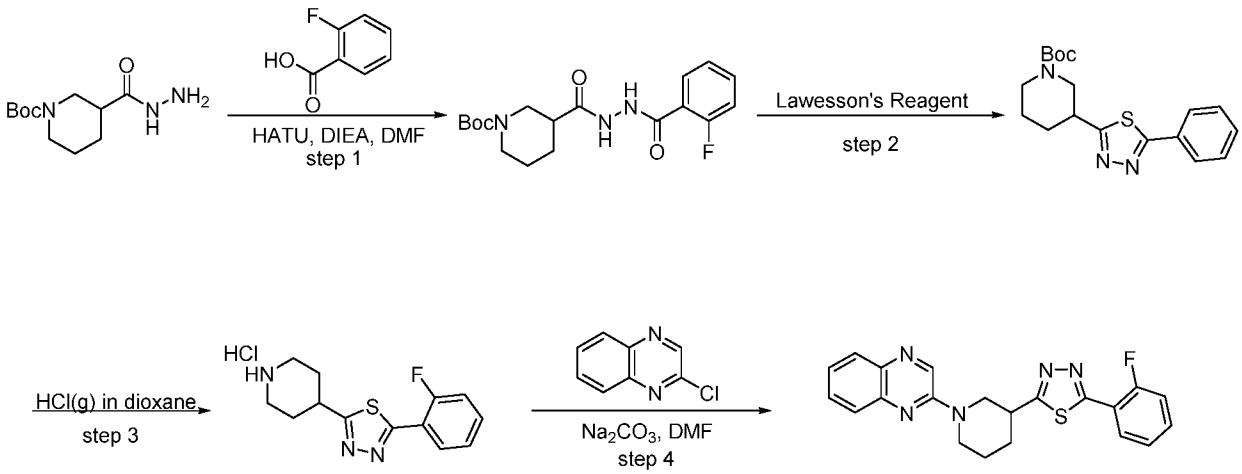
[00270] Step 2: *tert*-butyl 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: A solution of *tert*-butyl 3-(2-benzoylhydrazine-1-carbonyl)piperidine-1-carboxylate and Lawesson Reagent (233.12 mg, 0.57 mmol, 0.6 equiv) in toluene (5 mL) was stirred for 2 hours at 60 °C. The reaction mixture was purified by chromatography on silica gel (Flash 40 g, 40-60% EtOAc:PE) to afford tert-butyl 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (450.2 mg, 99.0%) as a white solid. MS *m/z*: 346[M+H]$^+$.

[00271] Step 3: 2-phenyl-5-(piperidin-3-yl)-1,3,4-thiadiazole: To a stirred solution of tert-butyl 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (240 mg, 0.579 mmol, 1.00 equiv) in DCM (4mL) was added HCl(gas) in 1,4-dioxane (4M, 2 mL) dropwise at 0 °C. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated to dryness under vacuum. This resulted in 2-phenyl-5-(piperidin-3-yl)-1,3,4-thiadiazole (150 mg, 95.0%) as a white solid. MS *m/z*: 246 [M+H]$^+$.

[00272] Step 4: 2-(1-(5-ethyl-5*H*-pyrrolo[2,3-b]pyrazin-3-yl)piperidin-3-yl)-5-phenyl-1,3,4-thiadiazole: To a stirred solution of 3-chloro-5-methyl-6-phenylpyrrolo[2,3-*b*]pyrazine

(50.0 mg, 0.205 mmol, 1.00 equiv) and 3-(2-methylphenoxymethyl)piperidine (54.8 mg, 0.267 mmol, 1.3 equiv) in dioxane (1 mL) were added Pd-PEPPSI-IPentCl 2-methylpyridine (17.26 mg, 0.021 mmol, 0.1 equiv) and Cs_2CO_3 (200 mg, 0.615 mmol, 3 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 2 hours at 100 °C under N_2 atmosphere. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 2-(1-(5-ethyl-5H-pyrrolo[2,3-*b*]pyrazin-3-yl)piperidin-3-yl)-5-phenyl-1,3,4-thiadiazole (14.0 mg, 16.5%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.04-8.01 (m, 2H), 7.64-7.53 (m, 4H), 6.51-6.50 (d,J=4.8 Hz, 1H), 4.59-4.55 (m, 1H), 4.26-4.16 (m, 3H), 3.65-3.50 (m, 2H), 3.39-3.37 (m, 1H), 2.35-1.81 (m, 4H), 1.47-1.43 (m, 3H). MS m/z: 391.0 $[M+H]^+$.

2-(2-fluorophenyl)-5-(1-(quinoxalin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (4)



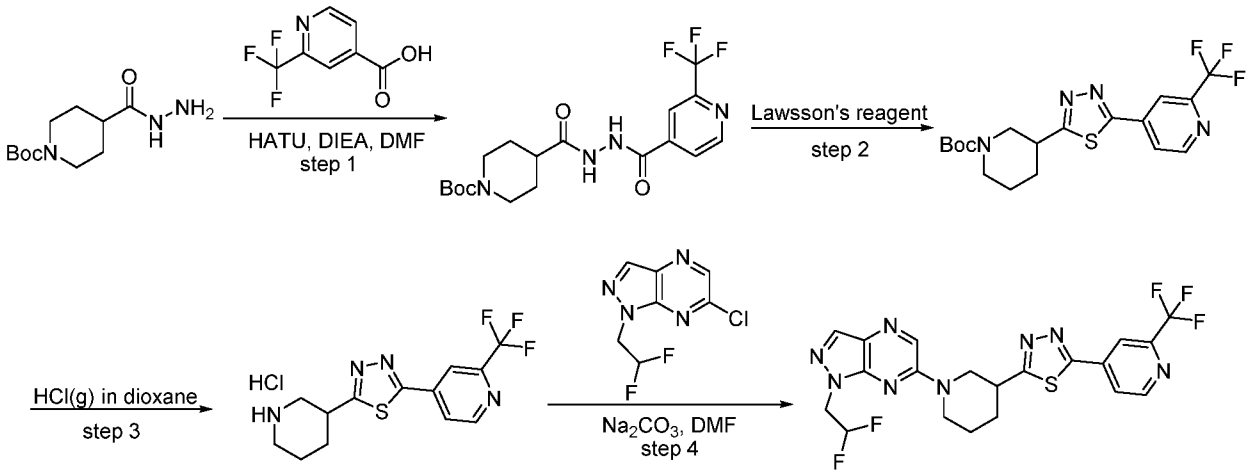
[00273] Step 1: *tert*-butyl 3-(2-(2-fluorobenzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate: To a stirred solution of 2-fluorobenzoic acid (202 mg, 1.44 mmol, 1.0 eq.) and HATU (547 mg, 1.44 mmol, 1.0 equiv) in DMF (5 mL) were added DIEA (557 mg, 4.32 mmol, 4 equiv) and tert-butyl 3-(hydrazinecarbonyl)piperidine-1-carboxylate (350 mg, 1.44 mmol, 1.0 equiv) dropwise at 0 °C. The resulting mixture was stirred for 3 hours at room temperature. The reaction was diluted with water (20 mL) and extracted with EtOAc (25 mLx2). The combined organic phases were washed with water (40 mL), brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under vacuum to give the crude product. It was purified by chromatography on silica gel (Flash 40 g, 40-60% EA:PE) to afford *tert*-butyl 3-(2-(2-fluorobenzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (250 mg, 47.6%) as a light yellow oil. MS *m/z*: 310 $[M-tBu+H]^+$.

[00274] Step 2: *tert*-butyl 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: A solution of *tert*-butyl 3-(2-(2-fluorobenzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (250 mg, 0.685 mmol, 1 equiv) and Lawesson Reagent (168 mg, 0.410 mmol, 0.6 equiv) in toluene (5 mL) was stirred for 16 hours at 100 °C. The reaction mixture was purified by chromatography on silica gel (Flash 40 g, 40-60% EtOAc:PE) to afford *tert*-butyl 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (120 mg,50.1%) as a white solid. MS *m/z*: 290 $[M\text{-}tBu+H]^+$.

[00275] Step 3: 2-(2-fluorophenyl)-5-(piperidin-4-yl)-1,3,4-thiadiazole hydrochloride: To a stirred solution of *tert*-butyl 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (120 mg, 0.347 mmol, 1.00 equiv) in DCM (1 mL) was added HCl(gas) in 1,4-dioxane (4M, 1 mL) dropwise at 0 °C. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated to dryness under vacuum. This resulted in 2-[5-(piperidin-3-yl)-1,3,4-thiadiazol-2-yl]-6-(trifluoromethyl)pyridine hydrochloride (100 mg, 96.0%) as a white solid. MS *m/z*: 264 $[M+H]^+$.

[00276] Step 4: 2-(2-fluorophenyl)-5-(1-(quinoxalin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole: To a stirred solution of 2-[5-(piperidin-3-yl)-1,3,4-thiadiazol-2-yl]-6-(trifluoromethyl) pyridine hydrochloride (90.0 mg, 0.300 mmol, 1.2 equiv) and 2-chloroquinoxaline (41.0 mg, 0.250 mmol, 1.00 equiv) in DMF (1mL) was added Na_2CO_3 (79.5 mg, 0.750 mmol, 3 equiv). The resulting mixture was stirred for 3 h at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (15 mL x3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (1:1) to afford the product. The product was further purified by reversed phase Combi-flash chromatography with the following conditions (column, C18 gel; mobile phase, B phase: MeCN, A phase: water; 35% to 75% B gradient in 20 min; detector: UV 254/220 nm). The pure fraction was concentrated under vacuum to afford 2-(2-fluorophenyl)-5-(1-(quinoxalin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (50.0 mg, 51.2%) as a white solid. ^1H NMR (300 MHz, DMSO-*d6*) δ 8.93 (s, 1H), 8.25 (td, J = 7.6, 1.8 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.72 – 7.54 (m, 3H), 7.55 – 7.32 (m, 3H), 4.79 (q, J = 9.7, 9.3 Hz, 1H), 4.41 (dd, J = 9.7, 3.6 Hz, 1H), 3.79 – 3.52 (m, 2H), 3.50 – 3.35 (m, 1H), 2.40 – 2.22 (m, 1H), 2.14 – 1.82 (m, 2H), 1.82 – 1.62 (m, 1H). MS *m/z*: 392.0 $[M+H]^+$.

2-(1-(1-(2,2-difluoroethyl)-1*H*-pyrazolo[3,4-*b*]pyrazin-6-yl)piperidin-3-yl)-5-(2-(trifluoromethyl)pyridin-4-yl)-1,3,4-thiadiazole (5)



[00277] Step 1: *tert*-butyl 4-(2-(2-(trifluoromethyl)isonicotinoyl)hydrazine-1-carbonyl)piperidine -1-carboxylate: To a solution of *tert*-butyl 4-(hydrazinecarbonyl)piperidine-1-carboxylate (231 mg, 0.952 mmol, 1.00 equiv) , HATU (434 mg, 1.14 mmol, 1.2 equiv) and DIPEA (246 mg, 1.90 mmol, 2.0 equiv) in DCM (10 mL) was added *tert*-butyl 3-(hydrazinecarbonyl)piperidine-1-carboxylate (458.3 mg, 1.8 mmol, 1.2 equiv) dropwise at 0 °C. The resulting mixture was stirred for overnight at room temperature. The reaction was diluted by water (20 mL) and extracted by EtOAc (25 mL x 2). The combined organic phases were washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under vacuum to give the crude product.. It was purified by chromatography on silica gel (Flash 40 g, 30-60% EA:PE) to afford *tert*-butyl 4-(2-(2-(trifluoromethyl)isonicotinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (350 mg, 88.3%) as a white solid. MS *m/z*: 417[M+H]$^+$.

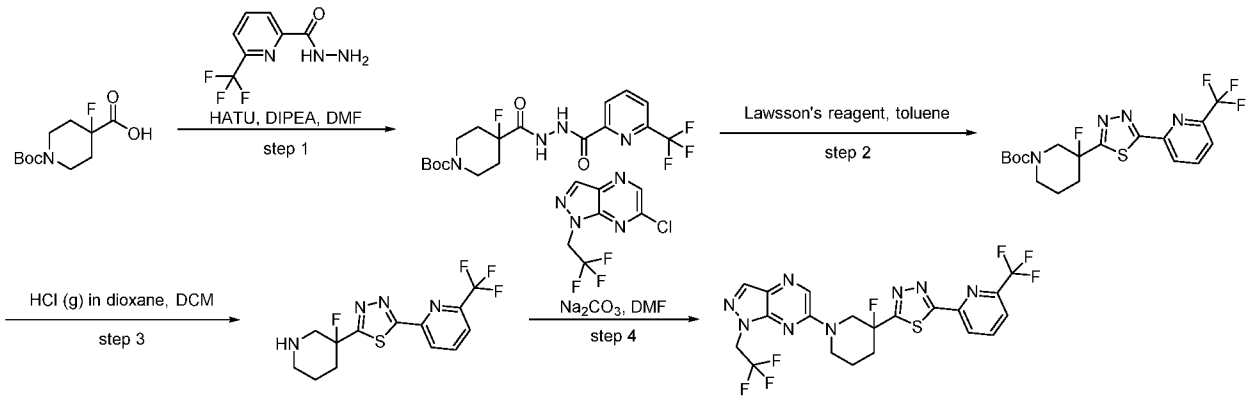
[00278] Step 2: *tert*-butyl 3-(5-(2-(trifluoromethyl)pyridin-4-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: A solution of *tert*-butyl 4-(2-(2-(trifluoromethyl)isonicotinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (350 mg, 0.841 mmol, 1.00 equiv) and Lawesson Reagent (203.98 mg, 0.505 mmol, 0.6 equiv) in toluene (5 mL) was stirred for 3 h at 100 °C. The resulting mixture was concentrated to dryness under reduced pressure. The reaction mixture was purified by chromatography on silica gel (Flash 40 g, 40-60% EtOAc:PE) to to afford tert-butyl 3-(5-(2-(trifluoromethyl)pyridin-4-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (150 mg, 43.1%) as a white solid. MS *m/z*: 415[M+H]$^+$.

[00279] Step 3: 2-(piperidin-3-yl)-5-(2-(trifluoromethyl)pyridin-4-yl)-1,3,4-thiadiazole: A stirred solution of *tert*-butyl 3-{5-[2-(trifluoromethyl)pyridin-4-yl]-1,3,4-thiadiazol-2-

yl}piperidine-1-carboxylate (150 mg, 0.362 mmol, 1.00 equiv) in 4M HCl(g)/dioxane (5 mL) was stirred for overnight at 0 °C. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated to dryness under reduced pressure. This resulted in 2-(piperidin-3-yl)-5-(2-(trifluoromethyl)pyridin-4-yl)-1,3,4-thiadiazole (150 mg, 93.0%) as a white solid. MS *m/z*: 315[M+H]$^+$.

[00280] Step 4: 2-(1-(1-(2,2-difluoroethyl)-1*H*-pyrazolo[3,4-*b*]pyrazin-6-yl)piperidin-3-yl)-5-(2-(trifl uoro- methyl)pyridin-4-yl)-1,3,4-thiadiazole: A solution of 6-chloro-1-(oxetan-3-ylmethyl)pyrazolo[3,4-b]pyrazine (65.0 mg, 0.289 mmol, 1.00 equiv), Na_2CO_3 (92.0 mg, 0.867 mmol, 3 equiv) and 3-(piperidin-3-ylmethoxy)-2-(trifluoromethyl)pyridine (82.8 mg, 0.318 mmol, 1.1 equiv) in DMF (1.30 mL) was stirred for 1 h at 100 °C. The reaction mixture was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 10% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 2-(1-(1-(2,2-difluoroethyl)-1*H*-pyrazolo[3,4-*b*]pyrazin-6-yl)piperidin-3-yl)-5-(2-(trifluoromethyl)pyridin-4-yl)-1,3,4-thiadia zole (60.0 mg, 46.2%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (d, *J* = 5.1 Hz, 1H), 8.56 (s, 1H), 8.35 (s, 1H), 8.26 (dd, *J* = 5.1, 1.6 Hz, 1H), 8.16 (s, 1H), 6.59 – 6.28 (m, 1H), 4.78 – 4.65 (m, 3H), 4.31 (d, *J* = 13.5 Hz, 1H), 3.72 – 3.65 (m, 2H), 3.53 – 3.41 (m, 1H), 2.36 – 2.29 (m, 1H), 2.06 – 1.96 (m, 1H), 1.95 – 1.84 (m, 1H), 1.79 –1.69(m, 1H). MS m/z: 497.2 [M+H]$^+$.

2-(3-Fluoro-1-(1-(2,2,2-trifluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole (6)



[00281] Step 1: tert-butyl 4-fluoro-4-(2-(6-(trifluoromethyl)picolinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate: To a stirred mixture of 1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carboxylic acid (500 mg, 2.02 mmol, 1.00 equiv) and 6-(trifluoromethyl)pyridine-2-carbohydrazide (456 mg, 2.22 mmol, 1.10 equiv) in DMF (8 mL) were added HATU (922 mg, 2.42 mmol, 1.2 equiv) and DIPEA (784 mg, 6 mmol, 3 equiv).

The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water, 5% to 95% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl 4-fluoro-4-(2-(6-(trifluoromethyl)picolinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (850 mg, 96.7%) as an off-white solid. MS *m/z*: 379 $[M\text{-}tBu+H]^+$.

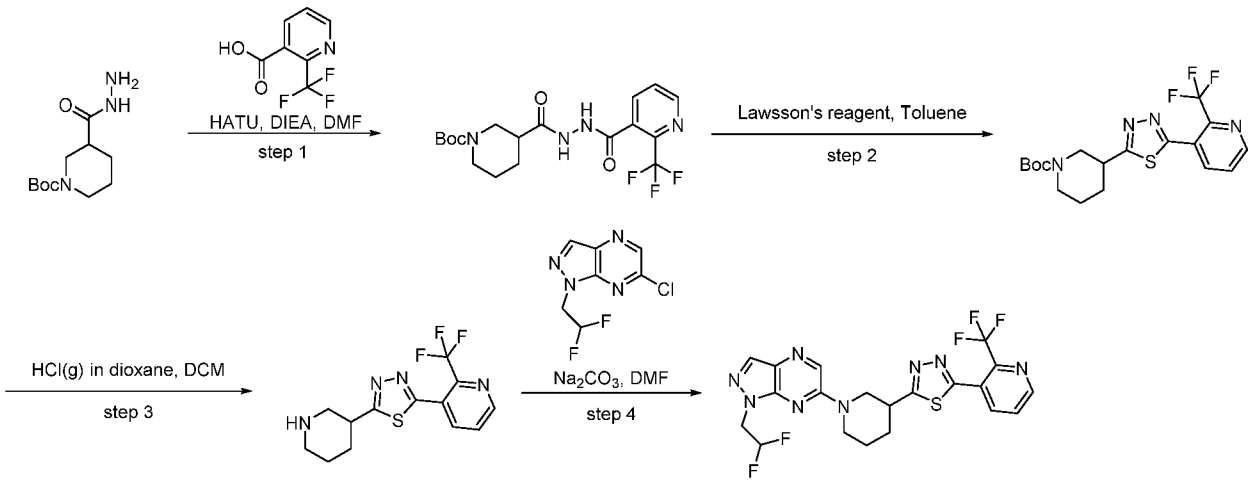
[00282] Step 2: tert-butyl 3-fluoro-3-(5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: To a stirred solution of tert-butyl 4-fluoro-4-(2-(6-(trifluoromethyl)picolinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (900 mg, 2.07 mmol, 1.00 equiv) in toluene (12 mL) was added Lawesson Reagent (670 mg, 1.65 mmol, 0.80 equiv). The resulting mixture was stirred for 3 h at 80 °C. The reaction was quenched with sat. $NaHCO_3$ (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water (0.1% FA), 5 to 95% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl 3-fluoro-3-(5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (480 mg, 53.5%) as a light yellow solid. MS *m/z*: 377 $[M\text{-}tBu+H]^+$.

[00283] Step 3: 2-(3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole hydrochloride: To a stirred solution of tert-butyl 3-fluoro-3-(5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (480 mg, 1.110 mmol, 1.00 equiv) in DCM (3 mL) was added HCl(gas)in 1,4-dioxane (3 mL). The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The crude product 2-(3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole hydrochloride (450 mg) was used in the next step directly without further purification. MS *m/z*: 333 $[M+H]^+$.

[00284] Step 4: 2-(3-fluoro-1-(1-(2,2,2-trifluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole: To a stirred mixture of 6-chloro-1-(2,2,2-trifluoroethyl)pyrazolo[3,4-b]pyrazine (50 mg, 0.211 mmol, 1.00 equiv) and 2-(3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole hydrochloride (81.8 mg, 0.222 mmol, 1.05 equiv) in DMF (3 mL) was added Na_2CO_3 (67.2 mg, 0.633 mmol, 3.00 equiv). The resulting mixture was stirred for overnight at 100 °C. The

resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 1:1) to afford the crude product. The crude product was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water (0.1% FA), 40% to 95% gradient in 16 min; detector, UV 254 nm. This resulted in 2-(3-fluoro-1-(1-(2,2,2-trifluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole (57.8 mg, 51.3%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.63 (s, 1H), 8.62-8.56 (m, 1H), 8.38 (t, J = 8.1 Hz, 1H), 8.22 (s, 1H), 8.20-8.12 (m, 1H), 5.19 (dd, J = 18.3, 9.0 Hz, 2H), 5.10-4.94 (m, 1H), 4.64-4.51 (m, 1H), 4.03 (dd, J = 32.4, 14.4 Hz, 1H), 3.50-3.39 (m, 1H), 2.46-2.39 (m, 2H), 2.02-1.81 (m, 2H). MS m/z: 533.2 $[M+H]^+$.

2-(1-(1-(2,2-Difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole (7)



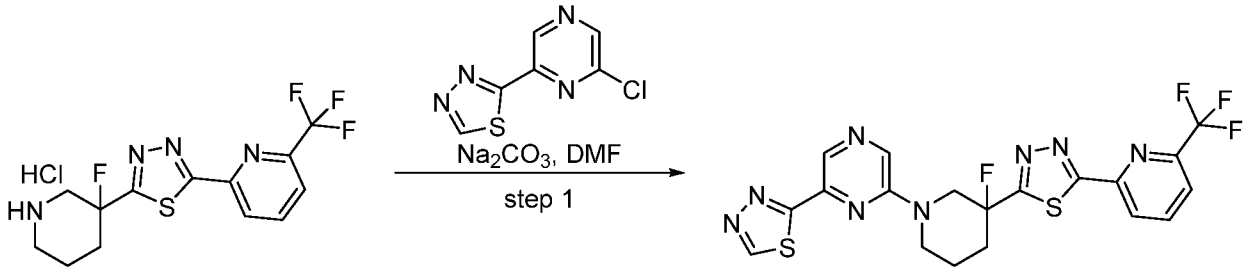
[00285] Step 1: tert-butyl 3-(2-(2-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate: To a stirred solution of 2-(trifluoromethyl)pyridine-3-carboxylic acid (300 mg, 1.57 mmol, 1.00 equiv) and HATU (656 mg, 1.73 mmol, 1.1 equiv) in DCM (10 mL) were added DIEA (405 mg, 3.14 mmol, 2 equiv) and tert-butyl 3-(hydrazinecarbonyl)piperidine-1-carboxylate (458 mg, 1.88 mmol, 1.2 equiv) dropwise at 0 °C. The resulting mixture was stirred for 3 hours at room temperature. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford tert-butyl 3-(2-(2-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate as a light yellow oil. MS m/z: 417 $[M+H]^+$.

[00286] Step 2: tert-butyl 3-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: A solution of tert-butyl 3-(2-(2-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (400 mg, 0.961 mmol, 1.00 equiv) and Lawesson Reagent (233 mg, 0.577 mmol, 0.6 equiv) in Toluene (5 mL) was stirred for 2 hours at 60 °C. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:2) to afford tert-butyl 3-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (230 mg, 57.8%) as a white solid. MS *m/z*: 415 $[M+H]^+$.

[00287] Step 3: 3-[5-(piperidin-3-yl)-1,3,4-thiadiazol-2-yl]-2-(trifluoromethyl)pyridine hydrochloride: To a stirred solution of tert-butyl 3-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (230 mg, 0.555 mmol, 1.00 equiv) in DCM (2 mL) was added HCl(gas)in 1,4-dioxane (2 mL) dropwise at 0 °C. The resulting mixture was stirred for 1 hours at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 3-[5-(piperidin-3-yl)-1,3,4-thiadiazol-2-yl]-2-(trifluoromethyl)pyridine hydrochloride (180 mg) as a white solid. MS *m/z*: 315 $[M+H]^+$

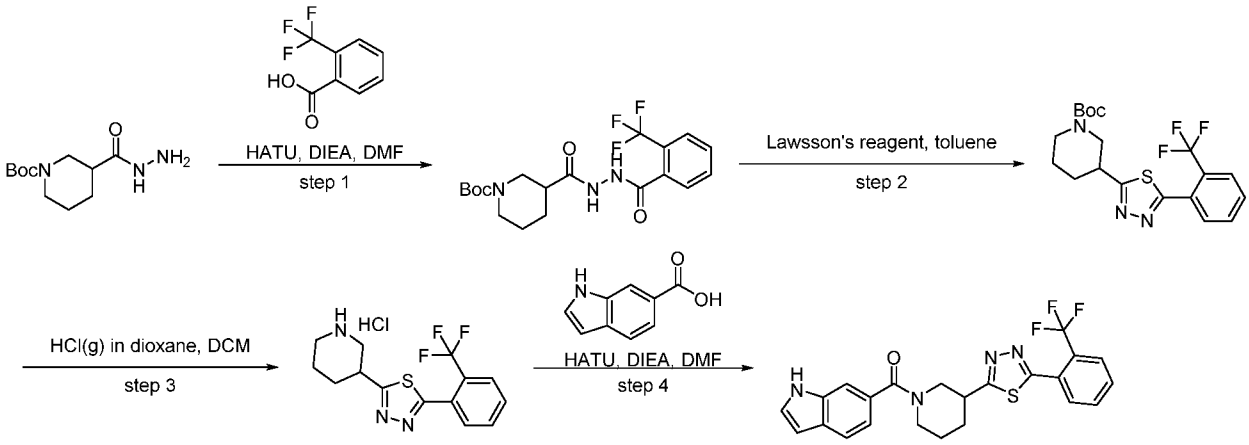
[00288] Step 4: 2-(1-(1-(2,2-difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole: To a stirred solution of 3-[5-(piperidin-3-yl)-1,3,4-thiadiazol-2-yl]-2-(trifluoromethyl)pyridine hydrochloride (95.3 mg, 0.272 mmol, 1.00 equiv) and 1-(2,2-difluoroethyl)pyrazolo[3,4-b]pyrazine (50 mg, 0.272 mmol, 1.00 equiv) in DMF (1 mL) was added Na_2CO_3 (86.3 mg, 0.816 mmol, 3 equiv). The resulting mixture was stirred for 3 hours at 100 °C. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 2-(1-(1-(2,2-difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole (73 mg, 54.1%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.04 (d, J = 5.1 Hz, 1H), 8.63 (s, 1H), 8.42 (d, J = 1.2 Hz, 1H), 8.37 – 8.31 (m, 1H), 8.23 (s, 1H), 6.73 – 6.30 (m, 1H), 4.84-4.73 (m, 3H), 4.41-4.36 (m, 1H), 3.81-3.75 (m, 2H), 3.61 – 3.46 (m, 1H), 2.36-2.31 (m, 1H),2.14-2.07 (m, 1H), 1.97-1.93 (m, 1H), 1.86-1.80 (m, 1H). MS *m/z*: 497.2 $[M+H]^+$.

2-(3-Fluoro-3-{5-[6-(trifluoromethyl)pyridin-2-yl]-1,3,4-thiadiazol-2-yl}piperidin-1-yl)-6-(1,3,4-thiadiazol-2-yl)pyrazine (8)



[00289] To a stirred mixture of 2-chloro-6-(1,3,4-thiadiazol-2-yl)pyrazine (90 mg, 0.453 mmol, 1.00 equiv) and 2-(3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole hydrochloride (175 mg, 0.476 mmol, 1.05 equiv) in DMF (4 mL) was added Na_2CO_3 (144 mg, 1.36 mmol, 3.00 equiv). The resulting mixture was stirred for overnight at 100 °C. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 1:1) to afford the crude product. The crude product was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water (0.1% FA), 40% to 95% gradient in 16 min; detector, UV 254 nm. This resulted in 2-(1-(6-(1,3,4-thiadiazol-2-yl)pyrazin-2-yl)-3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole (56.3 mg, 25.1%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.70 (s, 1H), 8.68 (s, 1H), 8.65 (s, 1H), 8.61-8.54 (m, 1H), 8.38 (t, J = 8.1 Hz, 1H), 8.18-8.12 (m, 1H), 4.87 (dd, J = 14.7, 9.0 Hz, 1H), 4.50-4.34 (m, 1H), 4.00 (dd, J = 31.5, 14.4 Hz, 1H), 3.50-3.37 (m, 1H), 2.66-2.52 (m, 1H), 2.47-2.41 (m, 1H), 2.03-1.83 (m, 2H). MS *m/z*: 495.1 $[M+H]^+$.

(1H-Indol-6-yl)(3-(5-(2-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)piperidin-1-yl)methanone (9)



[00290] Step 1: tert-butyl 3-(2-(2-(trifluoromethyl)benzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate: To a stirred mixture of tert-butyl 3-(hydrazinecarbonyl)piperidine-1-carboxylate (350 mg, 1.43 mmol, 1 equiv) and 2-(trifluoromethyl)benzoic acid (218 mg, 1.15 mmol, 0.8 equiv) in DMF (3 mL) were added HATU (546 mg, 1.43 mmol, 1 equiv) and DIEA (557 mg, 4.31 mmol, 3 equiv), The resulting mixture was stirred for 1 h at room temperature under argon atmosphere. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in tert-butyl tert-butyl 3-(2-(2-(trifluoromethyl)benzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (280 mg, 47.2%) as a white solid. MS *m/z*: 416 $[M+H]^+$.

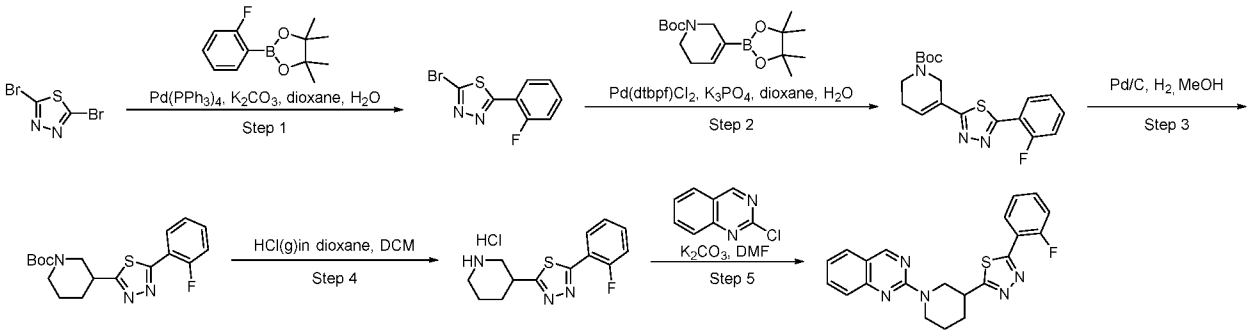
[00291] Step 2: tert-butyl 3-(5-(2-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: To a stirred solution of tert-butyl 3-(2-(2-(trifluoromethyl)benzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (280 mg, 0.675 mmol, 1 equiv) in Toluene (2 mL) was added Lawesson Reagent (164 mg, 0.405 mmol, 0.6 equiv). The resulting mixture was stirred for overnight at 60 °C. Desired product could be detected by LCMS. the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:2) to afford tert-butyl 3-(5-(2-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (140 mg, 50.2%) as a yellow solid. MS *m/z*: 414 $[M+H]^+$.

[00292] Step 3: 2-(piperidin-3-yl)-5-(2-(trifluoromethyl)phenyl)-1,3,4-thiadiazole hydrochloride: A solution of t tert-butyl 3-(5-(2-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (140 mg, 0.339 mmol, 1 equiv) and HCl (gas) in 1,4-dioxane (1 mL) in DCM (1 mL) was stirred for 2 h at room temperature. After removing the solvent, the crude product 2-(piperidin-3-yl)-5-(2-(trifluoromethyl)phenyl)-1,3,4-thiadiazole hydrochloride (130 mg) was used for next step without further purification. MS *m/z*: 314 $[M+H]^+$.

[00293] Step 4: (1H-indol-6-yl)(3-(5-(2-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)piperidin-1-yl)methanone: To a stirred mixture of 2-(piperidin-3-yl)-5-(2-(trifluoromethyl)phenyl)-1,3,4-thiadiazole hydrochloride (80 mg, 0.229 mmol, 1 equiv) and 1H-indole-6-carboxylic acid (36.9 mg, 0.229 mmol, 1 equiv) in DMF (2 mL) were added HATU (104 mg, 0.275 mmol, 1.2 equiv) and DIEA (88.6 mg, 0.687 mmol, 3 equiv).

The resulting mixture was stirred for 1 h at room temperature under argon atmosphere. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 90% gradient in 10 min; detector, UV 254 nm. This resulted in (1H-indol-6-yl)(3-(5-(2-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)piperidin-1-yl)methanone (60 mg, 67.4%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.32 (s, 1H), 8.02 – 7.94 (m, 1H), 7.88 – 7.73 (m, 3H), 7.59 (d, J = 8.2 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.07 (dd, J = 8.2, 1.4 Hz, 1H), 6.52 – 6.46 (m, 1H), 4.70 – 4.0 (m, 1H), 3.61 – 3.55 (m, 1H), 3.24 – 3.07 (m, 1H), 2.00 – 1.57 (m, 3H). MS m/z: 457.0 $[M+H]^+$.

2-(2-Fluorophenyl)-5-(1-(quinazolin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (10)



[00294] Step 1: 2-bromo-5-(2-fluorophenyl)-1,3,4-thiadiazole: To a stirred mixture of dibromo-1,3,4-thiadiazole (2 g, 8.20 mmol, 1.00 equiv) and 2-(2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.82 g, 8.20 mmol, 1.00 equiv) in dioxane (10 mL)/H_2O (2 mL) were added $Pd(PPh_3)_4$ (0.95 g, 0.820 mmol, 0.10 equiv) and K_2CO_3 (2.27 g, 16.4 mmol, 2.00 equiv). The resulting mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. The residue was purified by silica gel column chromatography, eluted with PE / EA (8 : 1) to afford 2-bromo-5-(2-fluorophenyl)-1,3,4-thiadiazole (540 mg, 25.4%) as an off-white solid. MS m/z: 259 $[M-tBu+H]^+$.

[00295] Step 2: tert-butyl 5-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate: To a stirred mixture of 2-bromo-5-(2-fluorophenyl)-1,3,4-thiadiazole (200 mg, 0.772 mmol, 1.00 equiv) and tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyridine-1-carboxylate (477 mg, 1.54 mmol, 2.00 equiv) in dioxane (2.5 mL)/H_2O (0.5 mL) were added $Pd(dtbpf)Cl_2$ (50.3 mg, 0.077 mmol, 0.10 equiv) and K_3PO_4 (327 mg, 1.54 mmol, 2.00 equiv). The resulting mixture was stirred for overnight at 60 °C

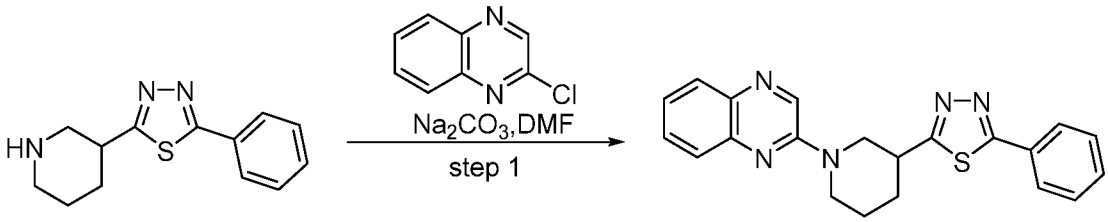
under nitrogen atmosphere. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford tert-butyl tert-butyl 5-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (170 mg, 60.9%) as a light yellow solid. MS *m/z*: 306 $[M\text{-}tBu+H]^+$.

[00296] Step 3: tert-butyl 3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: To a stirred solution of tert-butyl 5-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (170 mg, 0.470 mmol, 1.00 equiv) in MeOH (5 mL) were added Pd/C (20 mg, 10% Pd on carbon, wetted with water). The resulting mixture was stirred for 3 h at room temperature under hydrogen atmosphere. The resulting mixture was filtered, and the filter cake was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure. This resulted in tert-butyl 3-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (170 mg, 99.4%) as a light yellow solid. MS *m/z*: 308 $[M\text{-}tBu+H]^+$.

[00297] Step 4: 2-(2-fluorophenyl)-5-(piperidin-3-yl)-1,3,4-thiadiazole: To a stirred solution of tert-butyl 4-[5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl]piperidine-1-carboxylate (170 mg, 0.468 mmol, 1.00 equiv) in DCM (2 mL) were added HCl (gas) in 1,4-dioxane (2 mL). The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum and used in the next step directly without further purification. MS *m/z*: 264 $[M+H]^+$.

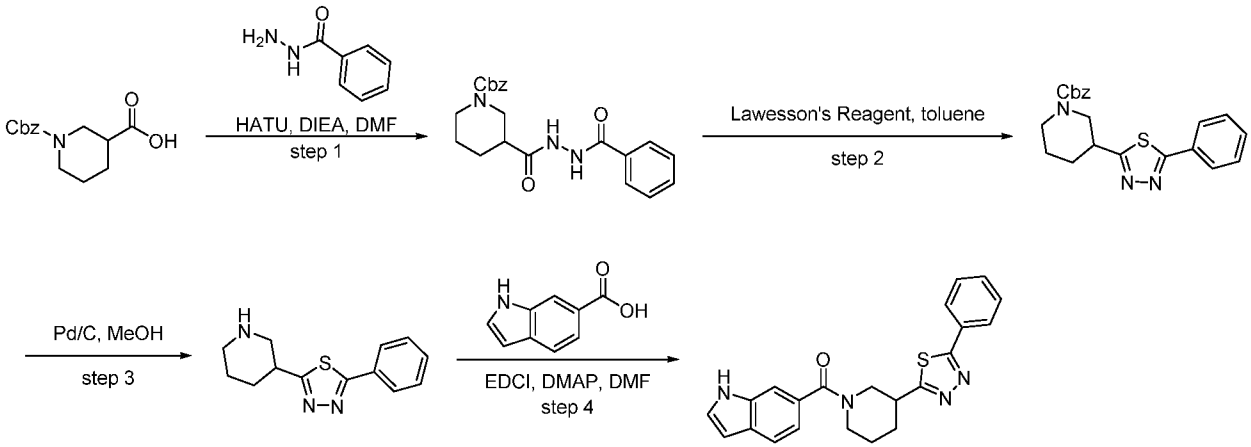
[00298] Step 5: 2-(2-fluorophenyl)-5-(1-(quinazolin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole: To a stirred mixture of 2-chloroquinoxaline (50 mg, 0.304 mmol, 1.00 equiv) and 2-(2-fluorophenyl)-5-(piperidin-3-yl)-1,3,4-thiadiazole (109 mg, 0.365 mmol, 1.20 equiv) in DMF (2 mL) was added K_2CO_3 (126 mg, 0.912 mmol, 3.00 equiv). The resulting mixture was stirred for 4 h at 80 °C. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed phase Combi-Flash with the following conditions: column, C18 gel; mobile phase, MeCN in water, 5% to 95% gradient in 20 min; detector, UV 254 nm. This resulted in 2-(2-fluorophenyl)-5-(1-(quinazolin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (46.1 mg, 38.8%) as a light yellow solid. ^1H NMR (300 MHz, DMSO-d_6): δ 9.25 (s, 1H), 8.31-8.21 (m, 1H), 7.90-7.83 (m, 1H), 7.79-7.70 (m, 1H), 7.70-7.60 (m, 1H), 7.58-7.39 (m, 3H), 7.35-7.24 (m, 1H), 5.09-4.98 (m, 1H), 4.74-4.59 (m, 1H), 3.64-3.45 (m, 2H), 3.43-3.33 (m, 1H), 2.39-2.24 (m, 1H), 2.207-1.82 (m, 2H), 1.79-1.56(m, 1H). MS *m/z*: 392.10 $[M+H]^+$.

2-Phenyl-5-(1-(quinoxalin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (11)



[00299] Step 1: 2-phenyl-5-(1-(quinoxalin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole: To a stirred solution of 2-phenyl-5-(piperidin-3-yl)-1,3,4-thiadiazole (70 mg, 0.286 mmol, 1 equiv) and 2-chloroquinoxaline (46.8 mg, 0.286 mmol, 1.00 equiv) in DMF (1 mL) was added Na_2CO_3 (90.9 mg, 0.858 mmol, 3 equiv). The resulting mixture was stirred for 2 h at 100 °C. The residue was purified by reverse flash chromatography with the following conditions (column, C18 gel; mobile phase, B phase: MeCN, A phase: water; 5% to 95% B gradient in 20 min; detector: UV 254/220 nm). This resulted in 2-phenyl-5-(1-(quinoxalin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (15 mg, 14.1%) as a white solid. MS *m/z*: 374.1 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.02 – 7.90 (m, 2H), 7.88 – 7.79 (m, 1H), 7.68 – 7.49 (m, 5H), 7.49 – 7.35 (m, 1H), 4.79 (q, J = 9.1 Hz, 1H), 4.40 (d, J = 13.5 Hz, 1H), 3.65 – 3.50 (m, 2H), 3.48 – 3.33 (m, 3H), 2.34 – 2.23 (m, 1H), 2.02 – 1.83 (m, 2H), 1.82 – 1.64 (m, 1H).

(1H-Indol-6-yl)(3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)methanone (12)



[00300] Step 1: benzyl 3-(2-benzoylhydrazine-1-carbonyl)piperidine-1-carboxylate: To a stirred mixture of 1-((benzyloxy)carbonyl)piperidine-3-carboxylic acid (1 g, 3.79 mmol, 1.00 equiv) and benzohydrazide (0.775 g, 5.69 mmol, 1.5 equiv) in DMF (6 mL) were added HATU (1.73 g, 4.56 mmol, 1.2 equiv) and DIEA (0.981 g, 7.59 mmol, 2 equiv). The resulting mixture was stirred for 1 h at room temperature under argon atmosphere. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with

EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 90% gradient in 10 min; detector, UV 254 nm. This resulted in benzyl 3-(2-benzoylhydrazine-1-carbonyl)piperidine-1-carboxylate (1.02 g, 70.4%) as a white solid. MS *m/z*: 382 $[M+H]^+$.

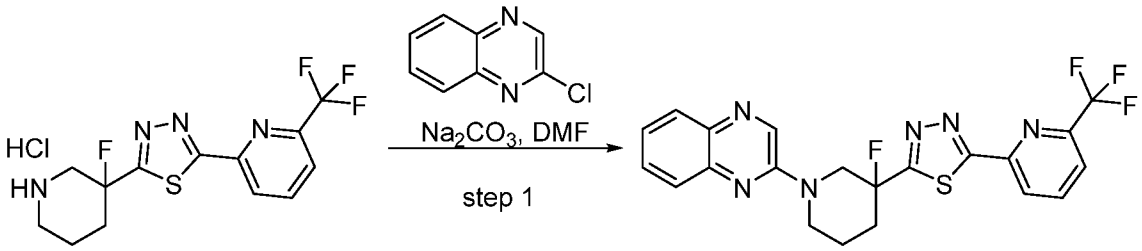
[00301] Step 2: benzyl 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: To a stirred solution of benzyl 3-(2-benzoylhydrazine-1-carbonyl)piperidine-1-carboxylate (500 mg, 1.31 mmol, 1 equiv) in Toluene (5 mL) was added Lawesson Reagent (318 mg, 0.787 mmol, 0.6 equiv). The resulting mixture was stirred for overnight at 110 °C. Desired product could be detected by LCMS. the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:2) to afford benzyl 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (50 mg, 10.0%) as a yellow solid. MS m/z: 380 $[M+H]^+$.

[00302] Step 3: 2-phenyl-5-(piperidin-3-yl)-1,3,4-thiadiazole: To the solution of benzyl 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (50 mg, 0.132 mmol, 1 equiv) in MeOH (1 mL) was added Pd/C (5 mg, 10% Pd on carbon, wetted with water). The resulted mixture was hydrogenated overnight at room temperature. Desired product could be detected by LCMS. The reaction system was filtrated through celite and the filtrate was concentrated. The crude product 2-phenyl-5-(piperidin-3-yl)-1,3,4-thiadiazole (30 mg) was used directly for next step. MS m/z: 246 $[M+H]^+$.

[00303] Step 4: (1H-indol-6-yl)(3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)methanone: To a stirred mixture of 1H-indole-6-carboxylic acid (7.88 mg, 0.049 mmol, 0.8 equiv) and 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine (15 mg, 0.061 mmol, 1.00 equiv) in DMF (1 mL) were added EDCI (12.8 mg, 0.067 mmol, 1.1 equiv) and DMAP (8.22 mg, 0.067 mmol, 1.1 equiv), The resulting mixture was stirred for 1 h at room temperature under argon atmosphere. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in (1H-indol-6-yl)(3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidin-1-yl)methanone (7.2 mg, 29.0%) as a white solid. ^1H NMR (400 MHz, DMSO-*d6*) δ 11.30 (s, 1H), 7.94 (s, 2H), 7.64 – 7.54 (m, 4H), 7.51 – 7.45 (m, 2H),

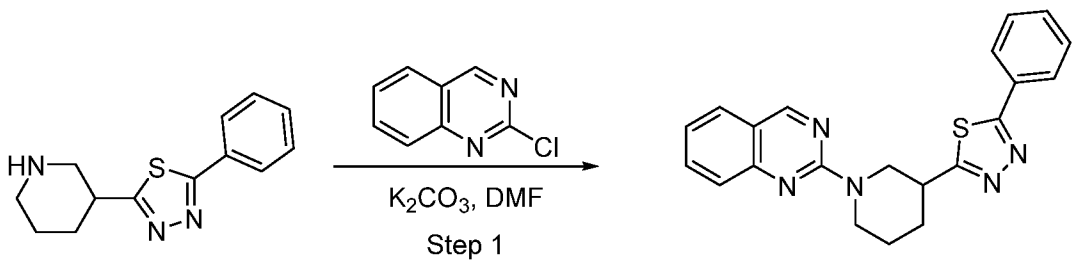
7.16 – 6.98 (m, 1H), 6.48 (d, *J* = 2.7 Hz, 1H), 4.42 (s, 2H), 3.58 – 3.48 (m, 1H), 3.40 (d, *J* = 12.1 Hz, 1H), 3.16 (s, 1H), 2.28 (d, *J* = 13.4 Hz, 1H), 1.91 (d, *J* = 11.6 Hz, 1H), 1.80 (s, 1H), 1.65 (s, 1H). MS *m/z*: 389.0 $[M+H]^+$.

2-(3-Fluoro-3-{5-[6-(trifluoromethyl)pyridin-2-yl]-1,3,4-thiadiazol-2-yl}piperidin-1-yl)quinoxaline (13)



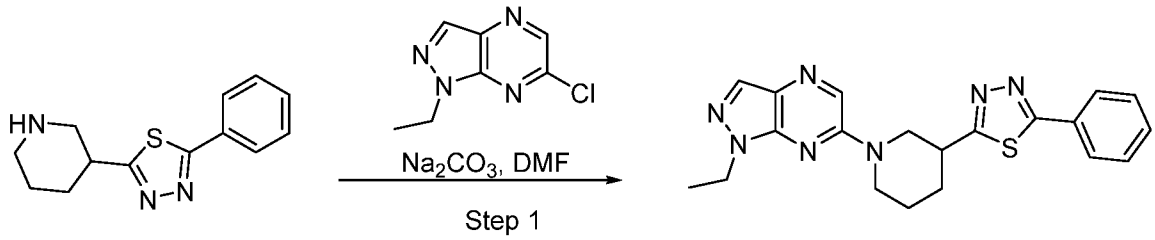
[00304] To a stirred mixture of 2-chloroquinoxaline (50 mg, 0.304 mmol, 1.00 equiv) and 2-(3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole hydrochloride (117 mg, 0.319 mmol, 1.05 equiv) in DMF (3 mL) was added Na_2CO_3 (96.6 mg, 0.912 mmol, 3.00 equiv). The resulting mixture was stirred for overnight at 100 °C. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA = 2:3) to afford the crude product. The crude product was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water (0.1% FA), 40% to 95% gradient in 16 min; detector, UV 254 nm. This resulted in 2-(3-fluoro-1-(quinoxalin-2-yl)piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole (27.9 mg, 19.9%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.98 (s, 1H), 8.63-8.53 (m, 1H), 8.38 (t, *J* = 8.1 Hz, 1H), 8.19-8.08 (m, 1H), 7.89-7.81 (m, 1H), 7.68-7.56 (m, 2H), 7.48-7.38 (m, 1H), 5.08 (dd, *J* = 14.4, 9.6 Hz, 1H), 4.72-4.57 (m, 1H), 4.00 (dd, *J* = 32.7, 14.4 Hz, 1H), 3.49-3.35 (m, 1H), 2.65-2.52 (m, 1H), 2.47-2.40 (m, 1H), 2.04-1.82 (m, 2H). MS *m/z*: 461.1 $[M+H]^+$.

2-Phenyl-5-(1-(quinazolin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (14)



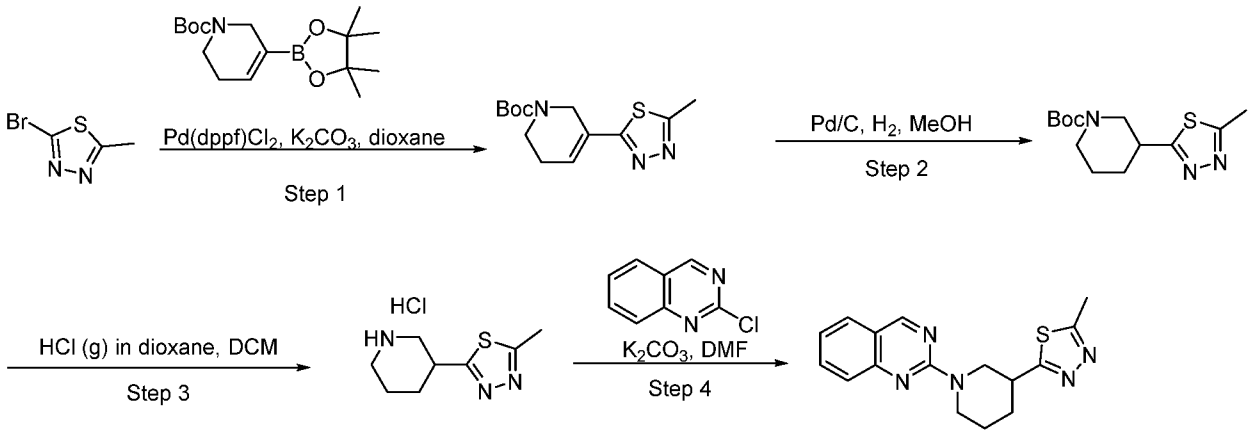
[00305] To a stirred mixture of 2-chloroquinoxaline (50 mg, 0.304 mmol, 1.00 equiv) and 2-phenyl-5-(piperidin-3-yl)-1,3,4-thiadiazole (89.4 mg, 0.365 mmol, 1.20 equiv) in DMF (2 mL) was added K_2CO_3 (126 mg, 0.912 mmol, 3.00 equiv). The resulting mixture was stirred for 4 h at 80 °C. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed phase Combi-Flash with the following conditions: column, C18 gel; mobile phase, MeCN in water, 5% to 95% gradient in 20 min; detector, UV 254 nm. This resulted in 2-phenyl-5-(1-(quinazolin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (24 mg, 21.1%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.25 (d, J = 0.8 Hz, 1H), 8.02 – 7.90 (m, 2H), 7.86 (dd, J = 8.1, 1.5 Hz, 1H), 7.74 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H), 7.63 – 7.49 (m, 4H), 7.29 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 5.05 (d, J = 9.4 Hz, 1H), 4.68 (d, J = 13.2 Hz, 1H), 3.59 – 3.41 (m, 2H), 3.39 – 3.24 (m, 1H), 2.35 – 2.28 (m, 1H), 1.94 – 1.88 (m, 1H), 1.76 – 1.62 (m, 1H). MS *m/z*: 374.1 $[M+H]^+$.

2-(1-(1-Ethyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-phenyl-1,3,4-thiadiazole (15)



[00306] To a stirred solution of 2-phenyl-5-(piperidin-3-yl)-1,3,4-thiadiazole (120 mg, 0.585 mmol, 1.00 equiv) and 6-chloro-1-ethyl-1H-pyrazolo[3,4-b]pyrazine (153 mg, 0.702 mmol, 1.2 equiv) in DMF (2 mL) was added Na_2CO_3 (381 mg, 1.17 mmol, 2 equiv) at 0 °C. The resulting mixture was stirred for 2 h at 100 °C. The mixture was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 0% to 100% gradient in 30 min; detector, UV 254 nm. This resulted in 2-(1-(1-ethyl-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-phenyl-1,3,4-thiadiazole (20.1 mg, 7.25%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.50 (s, 1H), 8.04 (s, 1H), 7.94 – 7.96 (m, 2H), 7.80 – 7.85 (m, 3H), 4.74-4,78 (m, 1H), 4.34 – 4.44 (m, 3H), 3.57 – 3.60 (m, 2H), 3.39 – 3.41 (m, 1H), 2.33 – 2.36 (m, 1H), 2.03 – 1.55 (m, 3H), 1.45 – 1.47 (m, 3H). MS *m/z*: 392.2 $[M+H]^+$.

2-methyl-5-(1-(quinazolin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (16)



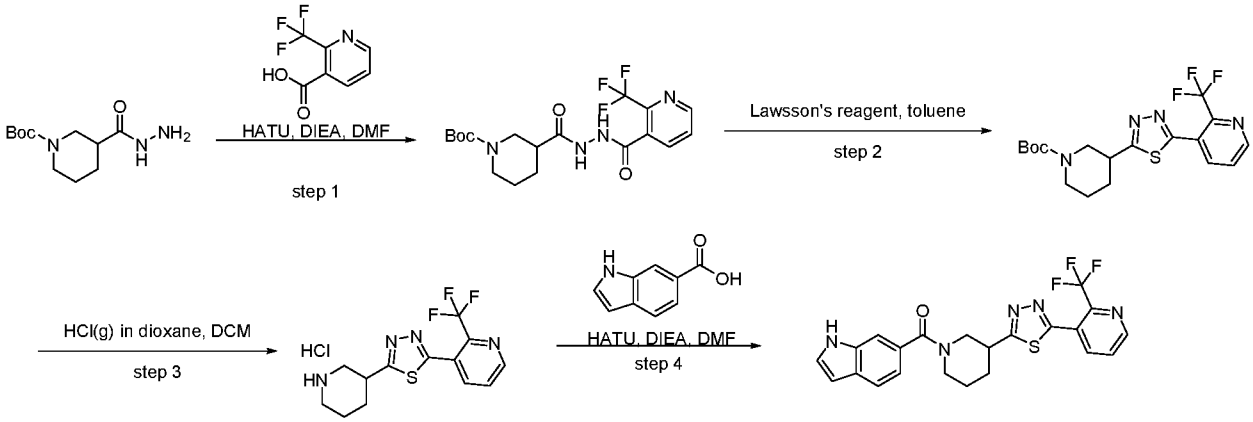
[00307] Step 1: tert-butyl 5-(5-methyl-1,3,4-thiadiazol-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate: To a stirred mixture of 2-bromo-5-methyl-1,3,4-thiadiazole (100 mg, 0.559 mmol, 1.00 equiv) and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (224 mg, 0.727 mmol, 1.30 equiv) in 1,4-dioxane (4 mL)/H_2O (1 mL) were added $Pd(dppf)Cl_2$ (40.87 mg, 0.056 mmol, 0.10 equiv) and K_2CO_3 (231.58 mg, 1.677 mmol, 3.00 equiv). The resulting mixture was stirred for 3 h at 80 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EA 2:1) to afford tert-butyl 5-(5-methyl-1,3,4-thiadiazol-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (150 mg, 95.4%) as a light yellow solid. MS *m/z*: 226 $[M\text{-}tBu+H]^+$.

[00308] Step 2: tert-butyl 3-(5-methyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: To a stirred solution of tert-butyl 5-(5-methyl-1,3,4-thiadiazol-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (150 mg, 0.533 mmol, 1.00 equiv) in MeOH (5 mL) were added Pd/C (15 mg, 10% Pd on carbon, wetted with water). The resulting mixture was stirred for 3 h at room temperature under hydrogen atmosphere. The resulting mixture was filtered, and the filter cake was washed with MeOH (3 x 8 mL). The filtrate was concentrated under reduced pressure. This resulted in tert-butyl 3-(5-methyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (150 mg, 99.29%) as a light yellow solid. MS *m/z*: 228 $[M\text{-}tBu+H]^+$.

[00309] Step 3: 2-methyl-5-(piperidin-3-yl)-1,3,4-thiadiazole hydrochloride: To a stirred solution of tert-butyl 3-(5-methyl-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (150 mg, 0.529 mmol, 1.00 equiv) in DCM (1 mL) were added HCl (gas) in 1,4-dioxane (1 mL). The resulting mixture was stirred for 3 h at room temperature. The resulting mixture was concentrated under vacuum and used in the next step directly without further purification. MS *m/z*: 184 $[M+H]^+$.

[00310] Step 4: 2-methyl-5-(1-(quinazolin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole: To a stirred mixture of 2-chloroquinoxaline (50 mg, 0.304 mmol, 1.00 equiv) and 2-methyl-5-(piperidin-3-yl)-1,3,4-thiadiazole hydrochloride (80.1 mg, 0.365 mmol, 1.20 equiv) in DMF (3 mL) was added K_2CO_3 (1256 mg, 0.912 mmol, 3.00 equiv). The resulting mixture was stirred for 4 h at 80 °C. The resulting mixture was diluted with water (10 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed phase Combi-Flash with the following conditions: column, C18 gel; mobile phase, MeCN in water, 5% to 95% gradient in 16 min; detector, UV 254 nm. This resulted in 2-methyl-5-(1-(quinazolin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (30 mg, 31.7%) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.23 (d, J = 0.8 Hz, 1H), 7.85 (dd, J = 8.1, 1.5 Hz, 1H), 7.74 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.52 (dd, J = 8.5, 1.0 Hz, 1H), 7.29 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 5.00 – 4.90 (m, 1H), 4.63 (d, J = 13.1 Hz, 1H), 3.52 – 3.41 (m, 1H), 3.40 – 3.35 (m, 1H), 3.32 – 3.23 (m, 1H), 2.70 (s, 3H), 2.25 – 2.15 (m, 1H), 1.96 – 1.75 (m, 2H), 1.72 – 1.58 (m, 1H). MS *m/z*: 312.15 $[M+H]^+$.

(1H-Indol-6-yl)(3-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidin-1-yl)methanone (17)



[00311] Step 1: tert-butyl 3-(2-(2-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate: To a stirred mixture of tert-butyl 3-(hydrazinecarbonyl)piperidine-1-carboxylate (350 mg, 1.43 mmol, 1 equiv) and 2-(trifluoromethyl)nicotinic acid (219 mg, 1.15 mmol, 0.8 equiv) in DMF (3 mL) were added HATU (546 mg, 1.43 mmol, 1 equiv) and DIEA (557 mg, 4.31 mmol, 3 equiv), The resulting mixture was stirred for 1 h at room temperature under argon atmosphere. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with

EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in tert-butyl 3-(2-(2-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (230 mg, 38.4%) as a white solid. MS *m/z*: 417 $[M+H]^+$.

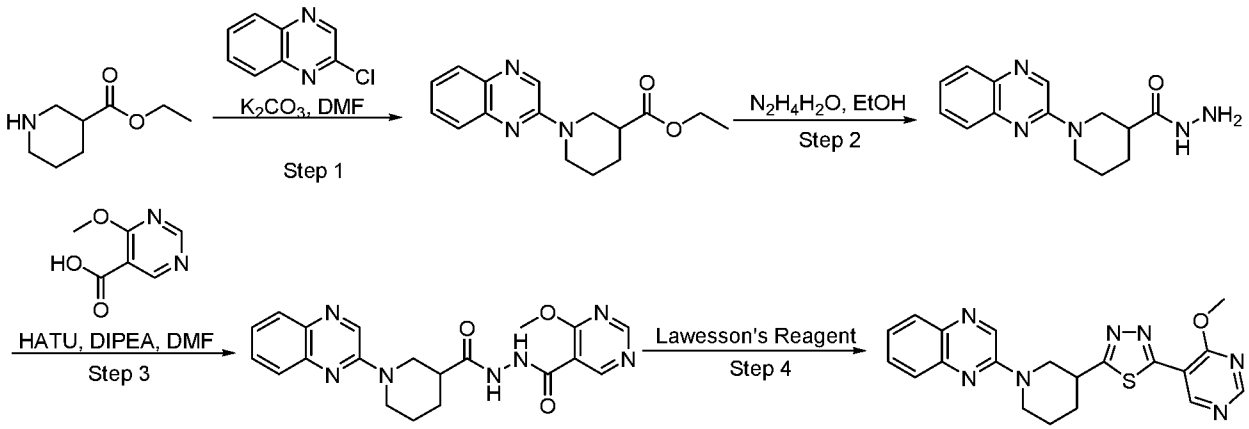
[00312] Step 2: tert-butyl 3-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: To a stirred solution of tert-butyl 3-(2-(2-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (230 mg, 0.552 mmol, 1 equiv) in Toluene (2 mL) was added Lawesson Reagent (134 mg, 0.331 mmol, 0.6 equiv). The resulting mixture was stirred for overnight at 60 °C. Desired product could be detected by LCMS. the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:2) to afford tert-butyl 3-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (110 mg, 48.0%) as a yellow solid. MS *m/z*: 415 $[M+H]^+$.

[00313] Step 3: 2-(piperidin-3-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole hydrochloride: A solution of tert-butyl 3-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (110 mg, 0.265 mmol, 1 equiv) and HCl (gas) in 1,4-dioxane (1 mL) in DCM (1 mL) was stirred for 2 h at room temperature. After removing the solvent, the crude product 2-(piperidin-3-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole hydrochloride (60 mg) was used for next step without further purification. MS *m/z*: 315 $[M+H]^+$.

[00314] Step 4: (1H-indol-6-yl)(3-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidin-1-yl)methanone: To a stirred mixture of 2-(piperidin-3-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole hydrochloride (130 mg, 0.371 mmol, 1 equiv) and 1H-indole-6-carboxylic acid (59.7 mg, 0.371 mmol, 1 equiv) in DMF (2 mL) were added HATU (169 mg, 0.445 mmol, 1.2 equiv) and DIEA (143 mg, 1.11 mmol, 3 equiv), The resulting mixture was stirred for 1 h at room temperature under argon atmosphere. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 90% gradient in 10 min; detector, UV 254 nm. This resulted in (1H-indol-6-yl)(3-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidin-1-

yl)methanone(59.3 mg, 34.0%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1H), 9.02 – 8.88 (m, 1H), 8.27 (d, J = 8.0 Hz, 1H), 8.00 – 7.79 (m, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.14 – 6.91 (m, 1H), 6.56 – 6.36 (m, 1H), 4.11 (d, J = 249.8 Hz, 2H), 3.59 (d, J = 10.7 Hz, 1H), 3.51 – 3.39 (m, 1H), 3.18 (s, 1H), 2.36 – 2.23 (m, 1H), 1.94 (d, J = 11.7 Hz, 1H), 1.80 (s, 1H), 1.66 (s, 1H). MS *m/z*: 458.1 $[M+H]^+$.

2-(4-Methoxypyrimidin-5-yl)-5-(1-(quinoxalin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (18)



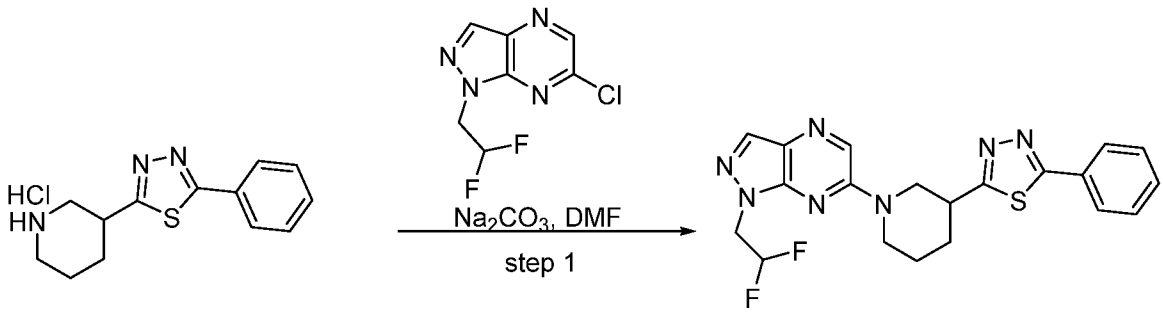
[00315] Step 1: ethyl 1-(quinoxalin-2-yl)piperidine-3-carboxylate: To a stirred solution of 2-chloroquinoxaline (500 mg, 3.04 mmol, 1.00 equiv) and ethyl piperidine-3-carboxylate (478 mg, 3.04 mmol, 1 equiv) in DMF (12 mL) was added Cs_2CO_3 (1980 mg, 6.08 mmol, 2 equiv) . The resulting mixture was stirred at 100 °C for 1 h. The resulting mixture was diluted with water (10 mL). The residue was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in ethyl 1-(quinoxalin-2-yl)piperidine-3-carboxylate (600 mg, 48.4%) as a brown solid. MS *m/z*: 286 $[M+H]^+$.

[00316] Step 2: 1-(quinoxalin-2-yl)piperidine-3-carbohydrazide: To a stirred solution of ethyl 1-(quinoxalin-2-yl)piperidine-3-carboxylate (600 mg, 2.10 mmol, 1.00 equiv) in EtOH (6 mL) was added hydrazine (202 mg, 6.31 mmol, 3 equiv). The resulting mixture was stirred at 80 °C for 1 h. The resulting mixture was diluted with water (10 mL). The residue was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 1-(quinoxalin-2-yl)piperidine-3-carbohydrazide (500 mg, 78.9%) as a dark grey solid. MS *m/z*: 272 $[M+H]^+$.

[00317] Step 3: 4-methoxy-N'-(1-(quinoxalin-2-yl)piperidine-3-carbonyl)pyrimidine-5-carbohydrazide: To a stirred solution of 1-(quinoxalin-2-yl)piperidine-3-carbohydrazide (500 mg, 1.84 mmol, 1.00 equiv) and 4-methoxypyrimidine-5-carboxylic acid (284 mg, 1.84 mmol, 1 equiv) in DMF (7 mL) were added HATU (770 mg, 2.03 mmol, 1.1 equiv) and DIPEA (714 mg, 5.53 mmol, 3 equiv) dropwise at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (10 mL). The residue was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silca gel, eluted by PE/EA (1/1) This resulted in 4-methoxy-N'-(1-(quinoxalin-2-yl)piperidine-3-carbonyl)pyrimidine-5-carbohydrazide (400 mg, 37.3%) as a dark yellow solid. MS *m/z*: 408 $[M+H]^+$.

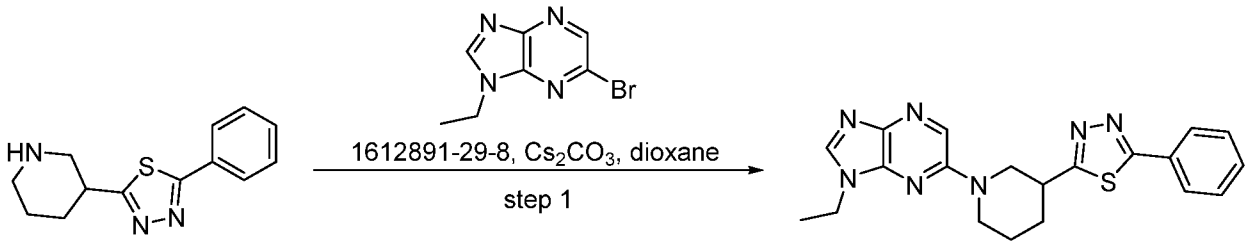
[00318] Step 4: 2-(4-methoxypyrimidin-5-yl)-5-(1-(quinoxalin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole: To a stirred solution of 4-methoxy-N-(1-(quinoxalin-2-yl)piperidine-3-carbonyl)pyrimidine-5-carbohydrazide acid (400 mg, 0.982 mmol, 1.00 equiv) and Lawesson's reagent (238 mg, 0.589 mmol, 0.6 equiv) in Toluene (6 mL) was dropwise at 100 °C for 2 h. The resulting mixture was extracted with water (3 x 15 mL). The combined organic layers were washed with EtOAc (3 x 15 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase Combi-Flash with the following conditions: column, C18 gel; mobile phase, MeCN in water (0.1% FA), 5% to 70% gradient in 20 min; detector, UV 220 nm. This resulted in 2-(4-methoxypyrimidin-5-yl)-5-(1-(quinoxalin-2-yl)piperidin-3-yl)-1,3,4-thiadiazole (27.5 mg, 6.87%) as a yellow green solid. ^1H NMR (400 MHz, DMSO-d_6) δ: 9.34 (s, 1H), 8.98 (s, 1H), 8.92 (s, 1H), 7.86 – 7.73 (m, 1H), 7.64 – 7.49 (m, 2H), 7.41 – 7.38(m, 1H), 4.77 – 4.40 (m, 1H), 4.39 (d, J = 13.3 Hz, 1H), 4.11 (s, 3H), 3.68 – 3.52 (m, 2H), 3.43 – 3.34 (m, 1H), 2.34 – 2.26 (m, 1H), 2.02 (t, J = 10.4 Hz, 1H), 1.87 – 1.84 (m, 1H), 1.75 – 1.74 (m, 1H). MS *m/z*: 406.1 $[M+H]^+$.

2-(1-(1-(2,2-Difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-phenyl-1,3,4-thiadiazole (19)



[00319] To a stirred solution of 6-chloro-1-(2,2-difluoroethyl)pyrazolo[3,4-b]pyrazine (107 mg, 0.490 mmol, 1.2 equiv) and 3-(5-phenyl-1,3,4-thiadiazol-2-yl)piperidine (100 mg, 0.408 mmol, 1.00 equiv) in DMF (2 mL) was added Na_2CO_3 (129 mg, 1.22 mmol, 3 equiv). The resulting mixture was stirred for 3 hours at 100 °C. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 5% to 95% gradient in 30 min; detector, UV 254 nm. This resulted in 2-(1-(1-(2,2-difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-phenyl-1,3,4-thiadiazole (36.1 mg, 20.2%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.16 (s, 1H), 7.97 – 7.92 (m, 2H), 7.61 – 7.52(m, 3H), 6.60 –6.28(m, 1H), 4.81 – 4.63 (m, 3H), 4.43 – 4.26 (m, 1H), 3.65 – 3.54 (m, 2H), 3.45 – 3.36 (m, 1H), 2.31 – 2.23 (m, 1H), 2.04 – 1.92 (m, 1H), 1.92 – 1.83 (m, 1H), 1.78 – 1.65 (m, 1H). MS *m/z*: 428.1 $[M+H]^+$.

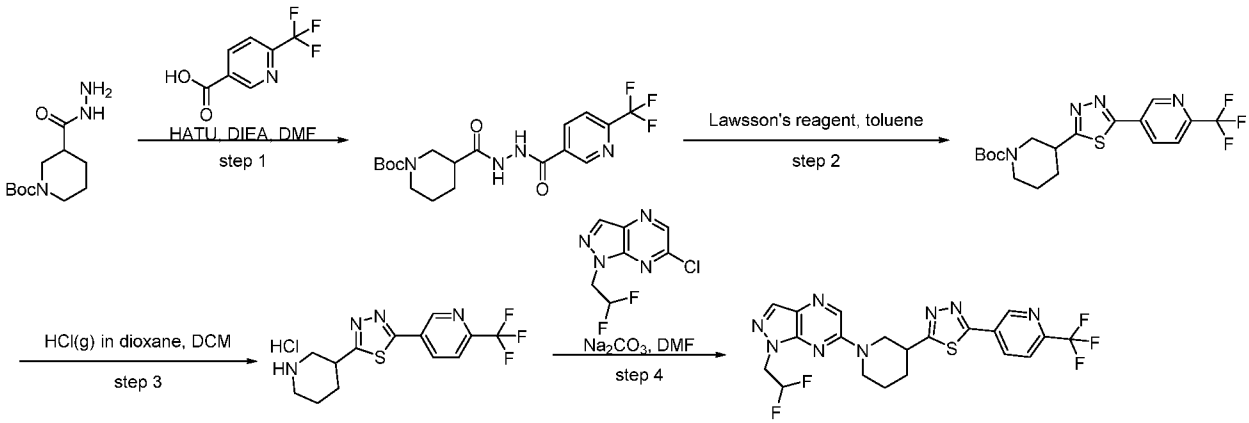
2-(1-(1-Ethyl-1H-imidazo[4,5-b]pyrazin-6-yl)piperidin-3-yl)-5-phenyl-1,3,4-thiadiazole (20)



[00320] To a stirred solution of 2-phenyl-5-(piperidin-3-yl)-1,3,4-thiadiazole (64.8 mg, 0.264 mmol, 1.2 equiv) and 6-bromo-1-ethyl-1H-imidazo[4,5-b]pyrazine (50 mg, 0.220 mmol, 1.00 equiv) in dioxane (1 mL) was added 1612891-29-8 (18.5 mg, 0.022 mmol, 0.1 equiv) and Cs_2CO_3 (143 mg, 0.440 mmol, 2 equiv). The resulting mixture was stirred for 2 h at 100 °C. The residue was purified by reverse flash chromatography with the following conditions (column, C18 gel; mobile phase, B phase: MeCN, A phase: water; 0% to 100% B gradient in 20 min; detector: UV 254/220 nm). This resulted in 2-(1-(1-ethyl-1H-imidazo[4,5-b]pyrazin-6-yl)piperidin-3-yl)-5-phenyl-1,3,4-thiadiazole (16.7 mg, 19.1%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, J = 7.5 Hz, 2H), 8.02 – 7.87 (m, 2H),

7.64 – 7.45 (m, 3H), 4.54 (d, *J* = 13.1 Hz, 1H), 4.22 – 4.12 (m, 3H), 3.63 – 3.45 (m, 2H), 2.30 – 2.20 (m, 1H), 2.01 – 1.90 (m, 1H), 1.89 – 1.80 (m, 1H), 1.78 – 1.66 (m, 1H), 1.48 – 1.40 (m, 3H). MS *m/z*: 392.2 $[M+H]^+$.

2-(1-(1-(2,2-Difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole (21)



[00321] Step 1: tert-butyl 3-(2-(6-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate: To a stirred solution of 6-(trifluoromethyl)pyridine-3-carboxylic acid (300 mg, 1.57 mmol, 1.00 equiv) and HATU (656 mg, 1.72 mmol, 1.1 equiv) in DMF (5 mL) were added DIEA (406 mg, 3.14 mmol, 2 equiv) and tert-butyl 3-(hydrazinecarbonyl)piperidine-1-carboxylate (458 mg, 1.88 mmol, 1.20 equiv) dropwise at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The resulting mixture was diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 5% to 95% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl 3-(2-(6-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (400 mg, 61.2%) as a yellow solid. MS *m/z*: 417 $[M+H]^+$.

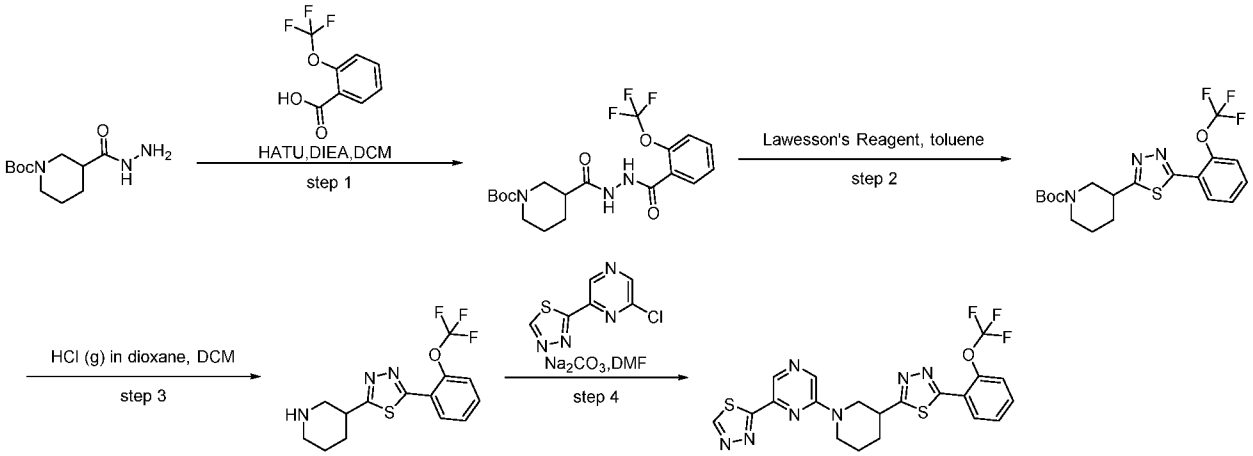
[00322] Step 2: tert-butyl 3-(5-(6-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: A solution of tert-butyl 3-(2-(6-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (200 mg, 0.48 mmol, 1.00 equiv) and Lawesson Reagent (117 mg, 0.288 mmol, 0.6 equiv) in Toluene (2 mL)was stirred for 2 hours at 60 °C. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford tert-butyl 3-(5-(6-

(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (130 mg, 65.3%) as a white solid. MS *m/z*: 415 $[M+H]^+$.

[00323] Step 3: 2-(piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole hydrochloride: To a stirred solution of tert-butyl 3-(5-(6-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (130 mg, 0.314 mmol, 1.00 equiv) in DCM (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL) dropwise at 0 °C. The resulting mixture was concentrated under vacuum. This resulted in 2-(piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole hydrochloride (130 mg, crude) as a white solid. MS *m/z*: 315 $[M+H]^+$

[00324] Step 4: 2-(1-(1-(2,2-difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole: To a stirred solution of 2-(piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole hydrochloride (115 mg, 0.329 mmol, 1.2 equiv) and Na_2CO_3 (87.3 mg, 0.822 mmol, 3 equiv) in DMF (1 mL) was added 6-chloro-1-(2,2-difluoroethyl)pyrazolo[3,4-b]pyrazine (60 mg, 0.274 mmol, 1.00 equiv). The resulting mixture was stirred for 2 hours at 100 °C. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 40% to 70% gradient in 15 min; detector, UV 254 nm. This resulted in 2-(1-(1-(2,2-difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole (30 mg, 22.0%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.34-9.33 (m, 1H), 8.65-8.63 (m, 1H), 8.56 (s, 1H), 8.16 (s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 6.59-6.30 (m, 1H), 4.80 – 4.63 (m, 3H), 4.35-4.32 (m, 1H), 3.72 – 3.60 (m, 2H), 3.51 – 3.38 (m, 1H), 2.30-2.27 (m, 1H), 2.09 – 1.95 (m, 1H), 1.94 – 1.83 (m, 1H), 1.79 – 1.66 (m, 1H). MS *m/z*: 497.2 $[M+H]^+$.

2-(1-(6-(1,3,4-thiadiazol-2-yl)pyrazin-2-yl)piperidin-3-yl)-5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole (22)



[00325] Step 1: tert-butyl 3-(2-(2-(trifluoromethoxy)benzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate: To a stirred solution of 2-(trifluoromethoxy)benzoic acid (300 mg, 1.45 mmol, 1.00 equiv) and HATU (553 mg, 1.45 mmol, 1 equiv) in DCM (10 mL) were added DIEA (282 mg, 2.18 mmol, 1.5 equiv) and tert-butyl 3-(hydrazinecarbonyl)piperidine-1-carboxylate (425 mg, 1.74 mmol, 1.2 equiv) dropwise at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford tert-butyl 3-(2-(2-(trifluoromethoxy)benzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (500 mg, 79.6%) as a light yellow oil. MS *m/z*: 432[M+H]$^+$.

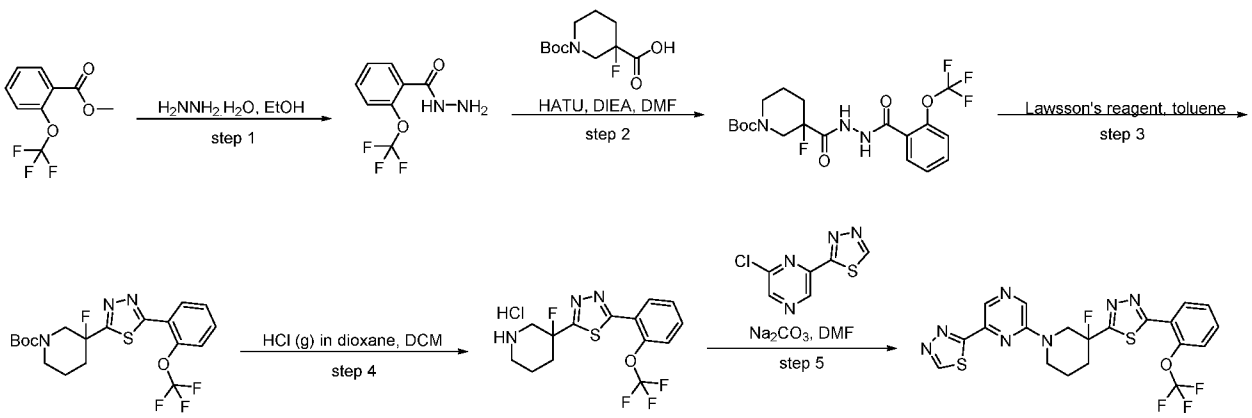
[00326] Step 2: tert-butyl 3-(5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: A solution of tert-butyl 3-(2-(2-(trifluoromethoxy)benzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (400 mg, 0.93 mmol, 1.00 equiv) and Lawesson Reagent (225 mg, 0.556 mmol, 0.6 equiv) in Toluene (4 mL) was stirred for 3 hours at 60 °C. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford tert-butyl 3-(5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate as a light yellow oil. MS *m/z*: 430 [M+H]$^+$.

[00327] Step 3: 2-(piperidin-3-yl)-5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole hydrochloride: To a stirred solution of tert-butyl 3-(5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (180 mg, 0.410 mmol, 1.00 equiv) in DCM (1 mL) was added HCl in dioxane (1 mL) dropwise at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The resulting mixture was concentrated under vacuum. This provided 2-(piperidin-3-yl)-5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole hydrochloride (140 mg, crude) as a white solid. MS *m/z*: 315[M+H]$^+$

[00328] Step 4: 2-(1-(6-(1,3,4-thiadiazol-2-yl)pyrazin-2-yl)piperidin-3-yl)-5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole: To a stirred solution of 2-chloro-6-(1,3,4-thiadiazol-2-yl)pyrazine (60 mg, 0.302 mmol, 1.00 equiv) and Na_2CO_3 (96.05 mg, 0.906 mmol, 3 equiv) in DMF (1 mL) was added 2-(piperidin-3-yl)-5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole hydrochloride (132 mg, 0.362 mmol, 1.2 equiv). The resulting mixture was stirred for 2 hours at 100 °C. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 100% gradient in 30 min; detector, UV 254 nm. This provided 2-(1-(6-(1,3,4-thiadiazol-2-yl)pyrazin-2-yl)piperidin-3-yl)-5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole (19 mg, 12.8%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 1H), 8.66-8.62 (m, 2H),

8.31-8.28 (m, 1H), 7.75-7.71 (m, 1H), 7.66 – 7.57 (m, 2H), 4.58-4.53 (m, 1H), 4.18-4.15 (m, 1H), 3.75 – 3.61 (m, 2H), 3.49-3.43 (m, 1H), 2.33 – 2.23 (m, 1H), 2.10 – 1.98 (m, 1H), 1.88-1.84 (m, 1H), 1.76-1.67 (m, 1H). MS *m/z*: 492.1 $[M+H]^+$.

2-(1-(6-(1,3,4-Thiadiazol-2-yl)pyrazin-2-yl)-3-fluoropiperidin-3-yl)-5-(2-(trifluoromethoxy) phenyl)-1,3,4-thiadiazole (29)



[00329] Step 1: 2-(trifluoromethoxy)benzohydrazide: Into a EtOH (10 mL) were added methyl 2-(trifluoromethoxy)benzoate (1 g, 4.54 mmol, 1 equiv) and hydrazine (0.44 g, 13.6 mmol, 3 equiv) at 80 °C. The residue product was purified by reverse phase flash with the following conditions (MeCN in water (0.1% FA), 40% to 95% gradient in 16 min; detector, UV 254 nm.) to afford 2-(trifluoromethoxy)benzohydrazide (900 mg, 90.0%) as a yellow oil. MS *m/z*: 221 $[M+H]^+$.

[00330] Step 2: tert-butyl 3-fluoro-3-(2-(2-(trifluoromethoxy)benzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate: To a stirred mixture of 1-(tert-butoxycarbonyl)-3-fluoropiperidine-3-carboxylic acid (500 mg, 2.02 mmol, 1 equiv) and 2-(trifluoromethoxy)benzohydrazide (490 mg, 2.22 mmol, 1.1 equiv) in DMF (8 mL) were added HATU (923 mg, 2.43 mmol, 1.2 equiv) and DIPEA (314 mg, 2.43 mmol, 1.2 equiv). The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water, 5% to 95% gradient in 20 min; detector, UV 254 nm. This provided tert-butyl 3-fluoro-3-(2-(2-(trifluoromethoxy)benzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (900 mg, 90.3%) as an off-white solid. MS *m/z*: 450 $[M+H]^+$.

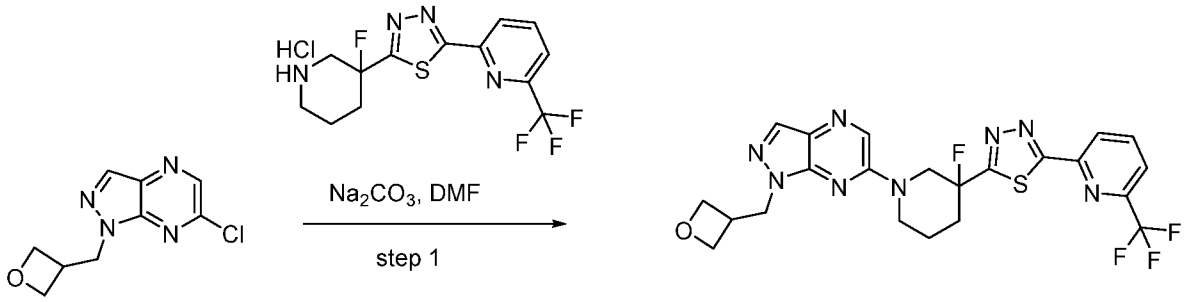
[00331] Step 3: tert-butyl 3-fluoro-3-(5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: To a stirred solution of tert-butyl 3-fluoro-3-(2-(2-(trifluoromethoxy)benzoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (900 mg, 2. mmol, 1 equiv) in toluene (12 mL) was added Lawesson Reagent (670 mg, 1.6 mmol, 0.80 equiv). The resulting mixture was stirred for 3 h at 80 °C. The reaction was quenched with sat. $NaHCO_3$ (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water (0.1% FA), 5% to 95% gradient in 20 min; detector, UV 254 nm. This provided tert-butyl 3-fluoro-3-(5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (150 mg, 16.4%) as a light yellow solid. MS *m/z*: 448 $[M+H]^{+}$.

[00332] Step 4: 2-(3-fluoropiperidin-3-yl)-5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole hydrochloride: To a stirred solution of tert-butyl 3-fluoro-3-(5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (150 mg, 0.335 mmol, 1 equiv) in DCM (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL). The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The crude product 2-(3-fluoropiperidin-3-yl)-5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole hydrochloride (120 mg) was used in the next step directly without further purification. MS *m/z*: 348 $[M+H]^{+}$.

[00333] Step 5: 2-(1-(6-(1,3,4-thiadiazol-2-yl)pyrazin-2-yl)-3-fluoropiperidin-3-yl)-5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole: To a stirred mixture of 2-(3-fluoropiperidin-3-yl)-5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole hydrochloride (120 mg, 0.314 mmol, 1 equiv) and methyl 2-(6-chloropyrazin-2-yl)-1,3,4-thiadiazole (62.2 mg, 0.314 mmol, 1.2 equiv) in DMF (1 mL) was added Na_2CO_3 (66.6 mg, 0.628 mmol, 2 equiv) . The resulting mixture was stirred for overnight at 80 °C. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL) and brine (1 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 1:1) to afford the crude product. The crude product was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water (0.1% FA), 40% to 95% gradient in 16 min; detector, UV 254 nm. This provided 2-(1-(6-(1,3,4-thiadiazol-2-yl)pyrazin-2-yl)-3-fluoropiperidin-3-yl)-5-(2-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole (15 mg, 8.83%) as a white solid. ^1H NMR (400

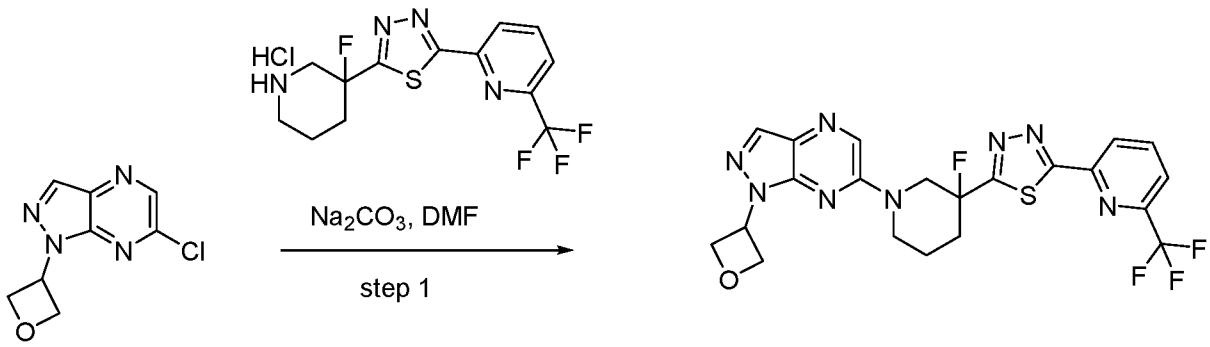
MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.66 (d, J = 6.0 Hz, 2H), 8.33 (dd, J = 8.0, 1.6 Hz, 1H), 7.82 – 7.74 (m, 1H), 7.71 – 7.62 (m, 2H), 4.88 (dd, J = 14.4, 9.0 Hz, 1H), 4.47 – 4.36 (m, 1H), 4.01 (dd, J = 31.6, 14.4 Hz, 1H), 3.50 – 3.38 (m, 1H), 2.48 – 2.40 (m, 2H), 2.01 – 1.81 (m, 2H). MS m/z: 510.1 $[M+H]^+$.

2-(3-Fluoro-1-(1-(oxetan-3-ylmethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole (27)



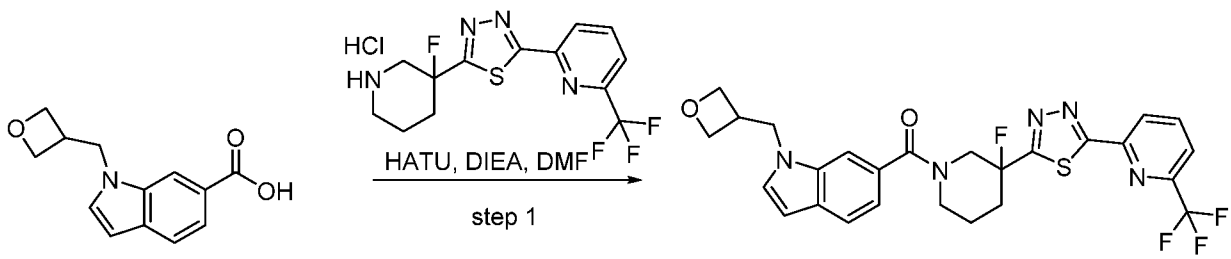
[00334] To a stirred mixture of 6-chloro-1-(oxetan-3-ylmethyl)pyrazolo[3,4-b]pyrazine (60 mg, 0.267 mmol, 1 equiv) and 2-(3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole hydrochloride (106 mg, 0.320 mmol, 1.2 equiv) in DMF (2 mL) was added Na_2CO_3 (56.6 mg, 0.534 mmol, 2 equiv). The resulting mixture was stirred for overnight at 80 °C. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL) and brine (1 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 1:1) to afford the crude product. The crude product was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water (0.1% FA), 40% to 95% gradient in 16 min; detector, UV 254 nm. This provided 2-(3-fluoro-1-(1-(oxetan-3-ylmethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole (30 mg, 20.50%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.58 (d, J = 8.6 Hz, 2H), 8.38 (t, J = 7.9 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H), 8.07 (s, 1H), 5.00 – 4.95 (m, 1H), 4.67 – 4.45 (m, 7H), 4.00 – 3.91 (m, 1H), 3.54 – 3.35 (m, 2H), 2.43 (s, 2H), 1.99 (d, J = 52.8 Hz, 2H). MS m/z: 520.9 $[M+H]^+$.

2-(3-fluoro-1-(1-(oxetan-3-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole (24)



[00335] To a stirred mixture of 6-chloro-1-(oxetan-3-yl)pyrazolo[3,4-b]pyrazine (60 mg, 0.285 mmol, 1 equiv) and 2-(3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole hydrochloride (113 mg, 0.342 mmol, 1.2 equiv) in DMF (2 mL) was added Na_2CO_3 (56.6 mg, 0.534 mmol, 2 equiv). The resulting mixture was stirred for overnight at 80 °C. The resulting mixture was diluted with water (15 mL). The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL) and brine (1 x 10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EA 1:1) to afford the crude product. The crude product was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water (0.1% FA), 40% to 95% gradient in 16 min; detector, UV 254 nm. This provided 2-(3-fluoro-1-(1-(oxetan-3-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)piperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole (27.2 mg, 17.49%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.59 (t, J = 3.9 Hz, 2H), 8.39 (t, J = 7.9 Hz, 1H), 8.22 (s, 1H), 8.16 (d, J = 7.5 Hz, 1H), 5.93 (t, J = 6.9 Hz, 1H), 5.11 – 4.74 (m, 5H), 4.55 (d, J = 12.9 Hz, 1H), 4.00 (d, J = 17.7 Hz, 1H), 3.42 (s, 1H), 2.43 (s, 2H), 1.91 (s, 2H). MS m/z: 506.9 $[M+H]^+$.

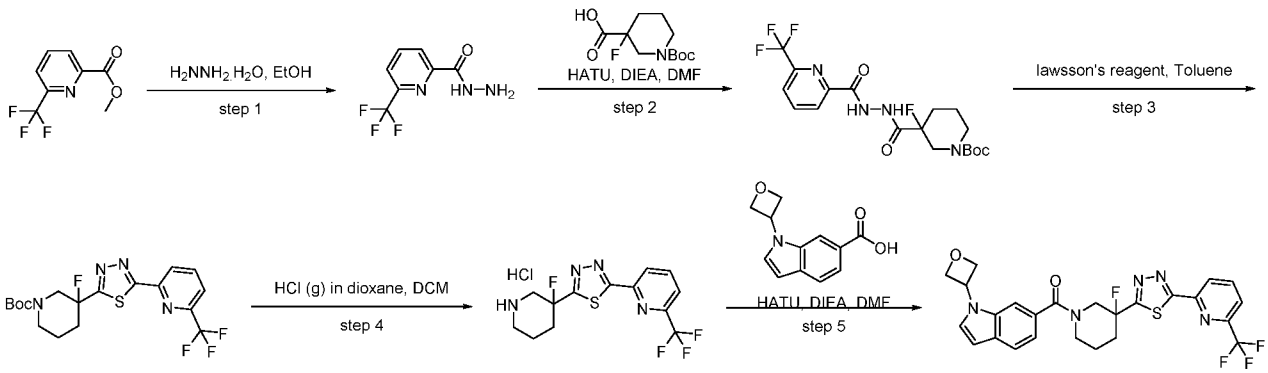
(3-Fluoro-3-(5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazol-2-yl)piperidin-1-yl)(1-(oxetan-3-ylmethyl)-1H-indol-6-yl)methanone (25)



[00336] To a stirred mixture of 1-(oxetan-3-ylmethyl)-1H-indole-6-carboxylic acid (60 mg, 0.260 mmol, 1 equiv) in DMF (1 mL) was added HATU (98.8 mg, 0.260 mmol, 1 equiv) in portions at 0 °C .The mixture was stirred for 10 min under this temperature. To the above

mixture was added DIEA (101 mg, 0.780 mmol, 3 equiv) and 2-(3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole hydrochloride (95.7 mg, 0.260 mmol, 1 equiv) sequentially at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with water (10 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (1 x 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (EtOAc/PE = 1/1) to afford crude product. The crude product was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 35% to 65% gradient in 10 min; detector, UV 254 nm. This resulted (3-fluoro-3-(5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazol-2-yl)piperidin-1-yl)(1-(oxetan-3-ylmethyl)-1H-indol-6-yl)methanone (50.0 mg, 35.2%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.56 (d, J = 8.1 Hz, 1H), 8.36 (t, J = 7.8 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.67 – 7.52 (m, 3H), 7.08 (dd, J = 8.1, 1.2 Hz, 1H), 6.49 (d, J = 3.0 Hz, 1H), 4.60 (t, J = 6.9 Hz, 2H), 4.53 (d, J = 7.5 Hz, 2H), 4.40 (td, J = 6.0, 2.4 Hz, 2H), 4.18 – 3.60 (m, 2H), 3.54 – 3.35 (m, 2H), 3.30 – 3.06 (m, 1H), 2.49 – 2.19 (m, 2H), 2.04 – 1.67 (m, 2H). MS *m/z*: 546.2 $[M+H]^+$.

(3-Fluoro-3-(5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazol-2-yl)piperidin-1-yl)(1-(oxetan-3-yl)-1H-indol-6-yl)methanone (26)



[00337] Step 1: 6-(trifluoromethyl)picolinohydrazide: Into a EtOH (15 mL) were added methyl 6-(trifluoromethyl)picolinate (2.5 g, 12.2 mmol, 1 equiv) and hydrazine (1.83 g, 36.5 mmol, 3 equiv) at 80 °C. The resulting mixture was purified by reverse phase flash with the following conditions (MeCN in water (0.1% FA), 40% to 95% gradient in 16 min; detector, UV 254 nm.) to afford 6-(trifluoromethyl)picolinohydrazide (2000 mg, 79.6%) as a yellow oil. MS *m/z*: 206 $[M+H]^+$.

[00338] Step 2: tert-butyl 3-fluoro-3-(2-(6-(trifluoromethyl)picolinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate: To a stirred mixture of 1-(tert-butoxycarbonyl)-3-

fluoropiperidine-3-carboxylic acid (842 mg, 3.41 mmol, 1 equiv) and 6-(trifluoromethyl)picolinohydrazide (700 mg, 3.41 mmol, 1.0 equiv) in DMF (8 mL) were added HATU (1.29 g, 3.41 mmol, 1.0 equiv) and DIPEA (1.32 g, 10.2 mmol, 3 equiv). The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with water (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water, 5% to 95% gradient in 20 min; detector, UV 254 nm. This provided tert-butyl 3-fluoro-3-(2-(6-(trifluoromethyl)picolinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (1.29 g, 87.0%) as an off-white solid. MS *m/z*: 435 $[M+H]^+$.

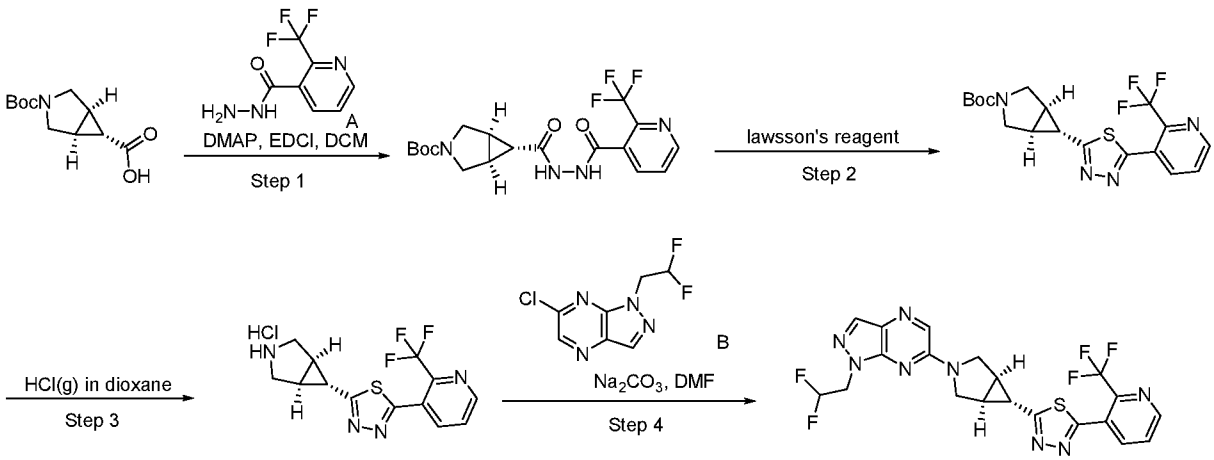
[00339] Step 3: tert-butyl 3-fluoro-3-(5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate: To a stirred solution of tert-butyl 3-fluoro-3-(2-(6-(trifluoromethyl)picolinoyl)hydrazine-1-carbonyl)piperidine-1-carboxylate (1.29 g, 2.97 mmol, 1 equiv) in toluene (12 mL) was added Lawesson Reagent (1.20 g, 2.97 mmol, 1.0 equiv). The resulting mixture was stirred for 3 h at 80 °C. The reaction was quenched with sat. $NaHCO_3$ (aq.) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash with the following conditions: column, C18 gel; mobile phase, MeCN in water (0.1% FA), 5% to 95% gradient in 20 min; detector, UV 254 nm. This provided tert-butyl 3-fluoro-3-(5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (450 mg, 35.1%) as a light yellow solid. MS *m/z*: 433 $[M+H]^+$.

[00340] Step 4: 2-(3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole hydrochloride: To a stirred solution of tert-butyl 3-fluoro-3-(5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazol-2-yl)piperidine-1-carboxylate (450 mg, 1.04 mmol, 1 equiv) in DCM (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL). The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The crude product 2-(3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole hydrochloride (400 mg) was used in the next step directly without further purification. MS *m/z*: 333 $[M+H]^+$.

[00341] Step 5: (3-fluoro-3-(5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazol-2-yl)piperidin-1-yl)(1-(oxetan-3-yl)-1H-indol-6-yl)methanone: To a stirred mixture of 1-(oxetan-3-yl)indole-6-carboxylic acid (65.4 mg, 0.301 mmol, 1 equiv) in DMF (1 mL) was

added HATU (114 mg, 0.301 mmol, 1 equiv) in portion at 0 °C .The mixture was stirred for 10 min under this temperature. To the above mixture was added DIEA (117 mg, 0.903 mmol, 3 equiv) and 2-(3-fluoropiperidin-3-yl)-5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazole hydrochloride (111 mg, 0.301 mmol, 1.00 equiv) sequentially at 0 °C. The resulting mixture was stirred for additional 1 h at room temperature. The reaction was quenched with water (10 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (1 x 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (EtOAc/PE = 1/1) to afford crude product. The crude product was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 35% to 65% gradient in 10 min; detector, UV 254 nm. This resulted (3-fluoro-3-(5-(6-(trifluoromethyl)pyridin-2-yl)-1,3,4-thiadiazol-2-yl)piperidin-1-yl)(1-(oxetan-3-yl)-1H-indol-6-yl)methanone (57.3 mg, 34.1%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.55 (s, 1H), 8.36 (t, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 3.3 Hz, 1H), 7.68 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.14 – 7.09 (m, 1H), 6.62 (d, *J* = 3.2 Hz, 1H), 5.84 (d, *J* = 7.4 Hz, 1H), 5.05 (t, *J* = 7.2 Hz, 2H), 4.98 – 4.87 (m, 2H), 4.38 (d, *J* = 75.2 Hz, 1H), 3.85 (s, 2H), 2.48 – 2.32 (m, 2H), 1.97 – 1.75 (m, 2H). MS *m/z*: 532.0 $[M+H]^+$.

2-((1R,5S,6r)-3-(1-(2,2-Difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3-azabicyclo[3.1.0]hexan-6-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole (23)



[00342] Step 1: tert-butyl (1*R*,5*S*,6*r*)-6-(2-(2-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate: To a stirred solution of (1*R*,5*S*,6*r*)-3-(tert-butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (500 mg, 2.20 mmol, 1.0 equiv) and DMAP (672 mg, 5.50 mmol, 2.50 equiv) in DCM (5 mL) were added EDCI (632 mg, 3.30 mmol, 1.5 equiv) and 2-(trifluoromethyl)nicotinohydrazide (451 mg, 2.20 mmol,

1.0 equiv). The resulting mixture was stirred for overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse flash chromatography with the following conditions (column, C18 gel; mobile phase, B phase: MeCN, A phase: water; 0% to 100% B gradient in 20 min; detector: UV 254/220 nm). This provided tert-butyl (1*R*,5*S*,6*r*)-6-(2-(2-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (600 mg, 65.8%) as a red solid. MS *m/z*: 415 $[M+H]^+$.

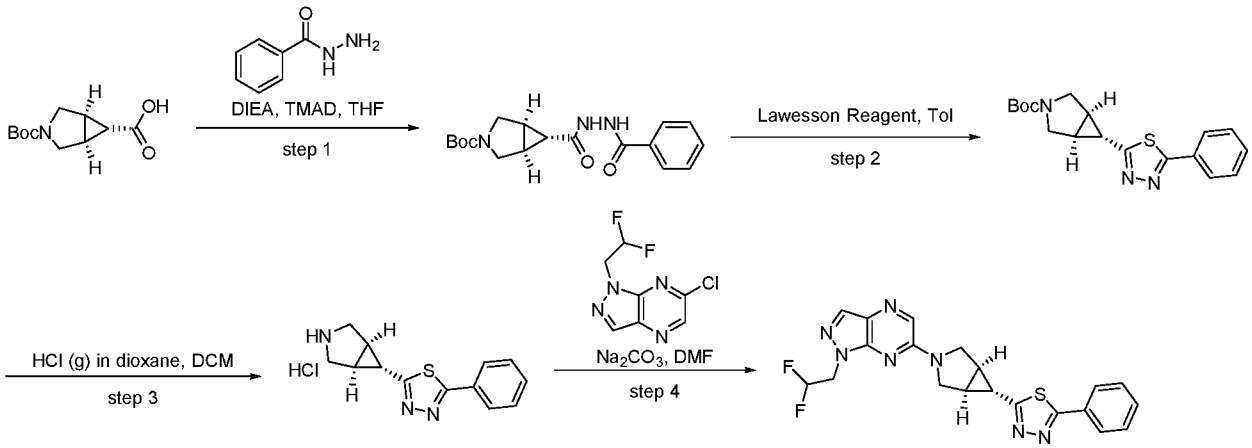
[00343] Step 2: tert-butyl (1*R*,5*S*,6*r*)-6-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate: A solution of tert-butyl (1*R*,5*S*,6*r*)-6-(2-(2-(trifluoromethyl)nicotinoyl)hydrazine-1-carbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (600 mg, 1.45 mmol, 1.00 equiv) and Lawesson reagent (352 mg, 0.870 mmol, 0.6 equiv) in Toluene (3 mL) was stirred for 2 h at 60 °C . The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/1) to afford tert-butyl (1*R*,5*S*,6*r*)-6-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (300 mg, 40.2%) as a yellow oil. MS *m/z*: 413 $[M+H]^+$.

[00344] Step 3: 2-((1*R*,5*S*,6*r*)-3-azabicyclo[3.1.0]hexan-6-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole hydrochloride: A solution of tert-butyl (1*R*,5*S*,6*r*)-6-(5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazol-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (200 mg, 0.485 mmol, 1 equiv) and HCl(gas)in 1,4-dioxane (1.00 mL) in DCM (2.00 mL) was stirred for 2 h at room temperature. After removing the solvent, the crude product 2-((1*R*,5*S*,6*r*)-3-azabicyclo[3.1.0]hexan-6-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole hydrochloride (100 mg) was used for next step without further purification. MS *m/z*: 313 $[M+H]^+$.

[00345] Step 4: 2-((1*R*,5*S*,6*r*)-3-(1-(2,2-difluoroethyl)-1*H*-pyrazolo[3,4-*b*]pyrazin-6-yl)-3-azabicyclo[3.1.0]hexan-6-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole: To a stirred solution of 2-((1*R*,5*S*,6*r*)-3-azabicyclo[3.1.0]hexan-6-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole hydrochloride (79.9 mg, 0.229 mmol, 1.00 equiv) and 6-chloro-1-(2,2-difluoroethyl)-1*H*-pyrazolo[3,4-*b*]pyrazine (50.0 mg, 0.229 mmol, 1.00 equiv) in DMF (1.00 mL) was added Na_2CO_3 (72.7 mg, 0.687 mmol, 3.00 equiv). The resulting mixture was stirred for 3 h at 100 °C. The residue was purified by reverse flash chromatography with the following conditions (column, C18 gel; mobile phase, B phase: MeCN, A phase: water; 0% to 100% B gradient in 20 min; detector: UV 254/220 nm). This provided 2-((1*R*,5*S*,6*r*)-3-(1-(2,2-difluoroethyl)-1*H*-pyrazolo[3,4-*b*]pyrazin-6-yl)-3-azabicyclo[3.1.0]hexan-6-yl)-5-(2-(trifluoromethyl)pyridin-3-yl)-1,3,4-thiadiazole (5 mg,

4.42%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 – 8.93 (m, 1H), 8.28 – 8.26 (m, 1H), 8.17 – 8.13(m, 2H), 7.93 – 7.90 (m, 1H), 6.61 – 6.32 (m, 1H), 4.75 – 4.67 (m, 2H), 4.16 – 4.13 (m, 2H), 3.77 – 3.74 (m, 2H), 2.69 – 2.67(m, 1H), 2.61 – 2.59 (m, 2H). MS *m/z*: 495.1 $[M+H]^+$.

2-((1R,5S,6R)-3-(1-(2,2-Difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3-azabicyclo[3.1.0]hexan-6-yl)-5-phenyl-1,3,4-thiadiazole (28)



[00346] Step 1: tert-butyl (1R,5S,6r)-6-(2-benzoylhydrazine-1-carbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate: To a stirred mixture of (1R,5S,6r)-3-(tert-butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (500 mg, 2.20 mmol, 1.00 equiv) and benzohydrazide (360 mg, 2.64 mmol, 1.2 equiv) in DMF (11 mL) were added HATU (921 mg, 2.42 mmol, 1.10 equiv) and DIEA (427 mg, 3.30 mmol, 1.50 equiv). The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was diluted with EtOAc (50 mL). The organic layer was washed by water (2 x 45 mL), and brine (45 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 5% to 100% gradient in 20 min; detector, UV 254 nm. This provided tert-butyl (1R,5S,6r)-6-(2-benzoylhydrazine-1-carbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (600 mg, 79.0%) as a white oil. MS *m/z*: 346 $[M+H]^+$.

[00347] Step 2: tert-butyl (1R,5S,6r)-6-(5-phenyl-1,3,4-thiadiazol-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate: To a stirred mixture of tert-butyl (1R,5S,6r)-6-(2-benzoylhydrazine-1-carbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (500 mg, 1.45 mmol, 1.00 equiv) and Lawsson reagent (352 mg, 0.869 mmol, 0.600 equiv) in toluene. The resulting mixture was stirred for 3 h at 100 ° C. The mixture was allowed to cool down

to room temperature. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford tert-butyl (1R,5S,6r)-6-(5-phenyl-1,3,4-thiadiazol-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (350 mg, 70.4%) as a white oil. MS *m/z*: 344 $[M+H]^+$.

[00348] Step 3: 2-((1R,5S,6r)-3-azabicyclo[3.1.0]hexan-6-yl)-5-phenyl-1,3,4-thiadiazole hydrochloride: A solution of tert-butyl tert-butyl (1R,5S,6r)-6-(5-phenyl-1,3,4-thiadiazol-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (300 mg, 0.873 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (2.00 mL) in DCM (2.00 mL) was stirred for 2 h at room temperature. After removing the solvent, the crude product 2-((1R,5S,6r)-3-azabicyclo[3.1.0]hexan-6-yl)-5-phenyl-1,3,4-thiadiazole hydrochloride (100 mg) was used for next step without further purification. MS *m/z*: 244 $[M+H]^+$.

[00349] Step 4: 2-((1R,5S,6r)-3-(1-(2,2-difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3-azabicyclo [3.1.0]hexan-6-yl)-5-phenyl-1,3,4-thiadiazole: To a stirred solution of 2-((1R,5S,6r)-3-azabicyclo[3.1.0]hexan-6-yl)-5-phenyl-1,3,4-thiadiazole hydro chloride (90.0 mg, 0.370 mmol, 1.00 equiv) and 6-chloro-1-(2,2-difluoroethyl)-1H-pyrazolo[3,4-b]pyrazine (60.0 mg, 0.274 mmol, 0.740 equiv) in DMF (1.50 mL) was added Na_2CO_3 (118 mg, 1.11 mmol, 3.00 equiv). The resulting mixture was stirred for 2 h at 100 °C. The residue was purified by reverse flash chromatography with the following conditions (column, C18 gel; mobile phase, B phase: MeCN, A phase: water; 5% to 100% B gradient in 20 min; detector: UV 254/220 nm). This provided 2-((1R,5S,6r)-3-(1-(2,2-difluoroethyl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3-azabicyclo[3.1.0]hexan-6-yl)-5-phenyl-1,3,4-thiadiazole (92.0 mg, 58.4%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16 (d, J = 6.5 Hz, 2H), 7.98 – 7.87 (m, 2H), 7.61 – 7.51 (m, 3H), 6.47 (tt, J = 54.9, 3.8 Hz, 1H), 4.71 (td, J = 15.0, 3.8 Hz, 2H), 4.14 (d, J = 11.4 Hz, 2H), 3.79 – 3.69 (m, 2H), 2.62 – 2.58 (m, 1H), 2.57 – 2.53 (m, 2H). MS *m/z*: 426.1 $[M+H]^+$.

Biological assay data and procedures

[00350] Exemplary compounds were evaluated for activation of GCase in a live cell PFB assay in HELA cells (essentially as described in Ysselstein et al., "LRRK2 kinase activity regulates lysosomal glucocerebrosidase in neurons derived from Parkinson's disease patients" *Nature Communications* (2019) 10:5570). The results in Table 3 demonstrate that compounds of the disclosure are potent activators of GCase. EC_{50} ranges: A: <10 μM; B: >10-50 μM; C: >50-100 μM; D: >100 μM.

Table 3. In vitro enzymatic EC_{50} values for exemplary compounds

Compound	GCase EC50: (μM)
1	B
2	B
3	B
4	B
5	A
6	B
7	B
8	B
9	B
10	B
11	B
12	B
13	B
14	B
15	C
16	D
17	B
18	B
19	A
20	A
21	A
22	A
23	D
24	D
25	B
26	B
27	A
28	B
29	B

EQUIVALENTS AND SCOPE

[00351] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is

present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00352] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

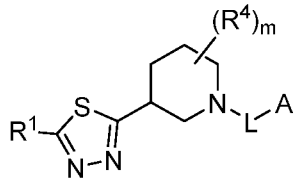
[00353] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00354] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made

without departing from the spirit or scope of the present invention, as defined in the following claims.

[00355] For reasons of completeness, various aspects of the present disclosure are set out in the following numbered clauses:

[00356] Clause 1. A compound of Formula (**I**):

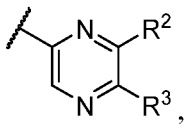
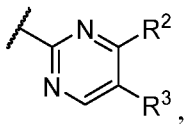
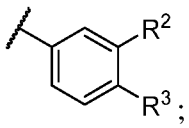


(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

L is a bond or –C(=O)-;

A is , , or ;

R^2 and R^3 are each independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^4 is independently halogen, substituted or unsubstituted alkyl, or two instances of R^4 on the same carbon form with that carbon a carbonyl ; and

m is 0, 1, 2, 3, or 4.

[00357] Clause 2. The compound of clause 1, or a pharmaceutically acceptable salt thereof, wherein: R^1 is substituted or unsubstituted pyridinyl, or substituted or unsubstituted phenyl.

[00358] Clause 3. The compound of clause 1 or 2, or a pharmaceutically acceptable salt thereof, wherein: R^1 is substituted pyridinyl, or substituted or unsubstituted phenyl.

[00359] Clause 4. The compound of any of clauses 1-3, or a pharmaceutically acceptable salt thereof, wherein: R^1 is pyridinyl substituted with halogen or haloalkyl, phenyl substituted with halogen or haloalkyl, or unsubstituted phenyl.

[00360] Clause 5. The compound of any of clauses 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is pyridinyl substituted with halogen or haloalkyl.

[00361] Clause 6. The compound of any of clauses 1-5, or a pharmaceutically acceptable salt thereof, wherein: R^1 is pyridinyl substituted with haloalkyl.

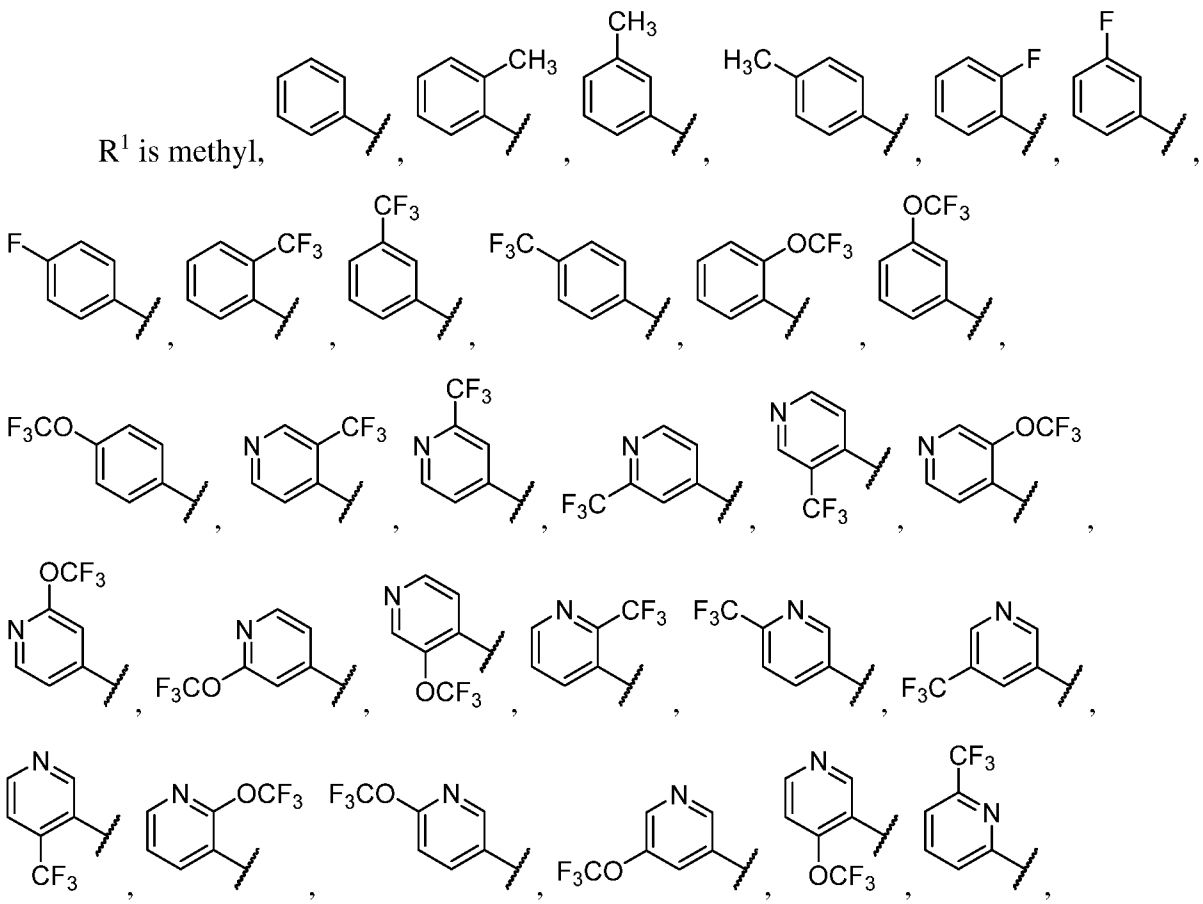
[00362] Clause 7. The compound of any of clauses 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is unsubstituted phenyl.

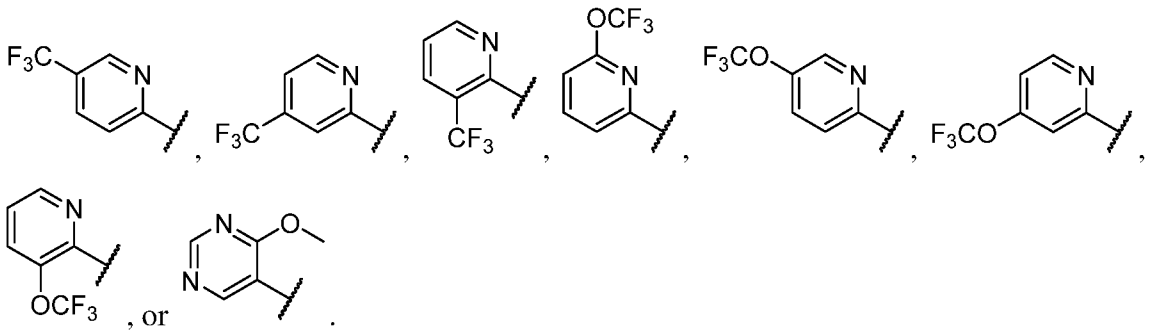
[00363] Clause 8. The compound of any of clauses 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is phenyl substituted with halogen or haloalkyl.

[00364] Clause 9. The compound of any of clauses 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is phenyl substituted with halogen.

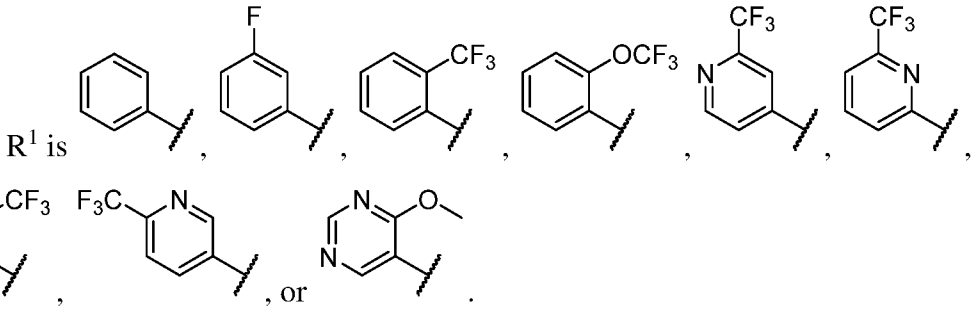
[00365] Clause 10. The compound of any of clauses 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is phenyl substituted with haloalkyl.

[00366] Clause 11. The compound of any of clauses 1-4, or a pharmaceutically acceptable salt thereof, wherein:

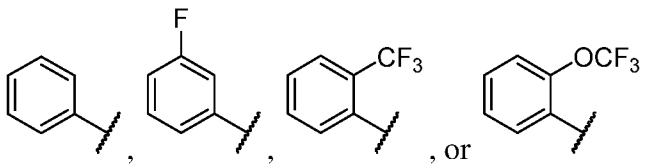
R^1 is methyl, 



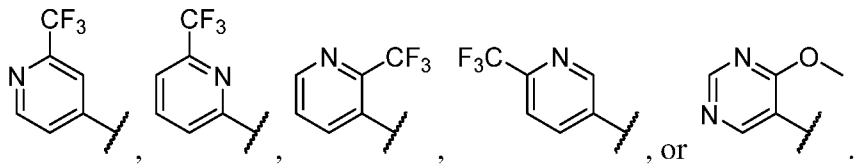
[00367] Clause 12. The compound of any of clauses 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is 

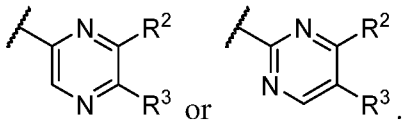
[00368] Clause 13. The compound of any of clauses 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is 

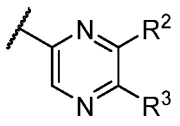
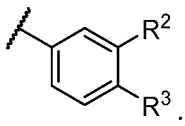
[00369] Clause 14. The compound of any of clauses 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is 

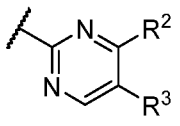
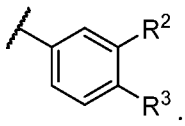
[00370] Clause 15. The compound of any of clauses 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is 

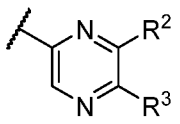
[00371] Clause 16. The compound of any of clauses 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is  or .

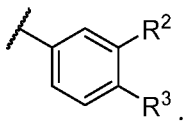
[00372] Clause 17. The compound of any of clauses 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is  or .

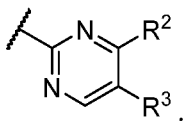
[00373] Clause 18. The compound of any of clauses 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is .

[00374] Clause 19. The compound of any of clauses 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is .

[00375] Clause 20. The compound of any of clauses 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is .

[00376] Clause 21. The compound of any of clauses 1-20, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 are each independently hydrogen or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00377] Clause 22. The compound of any of clauses 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 is heteroaryl.

[00378] Clause 23. The compound of any of clauses 1-22, or a pharmaceutically acceptable salt thereof, wherein: R^2 is thiadiazolyl.

[00379] Clause 24. The compound of any of clauses 1-23, or a pharmaceutically acceptable salt thereof, wherein: R^3 is hydrogen.

[00380] Clause 25. The compound of any of clauses 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00381] Clause 26. The compound of any of clauses 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl.

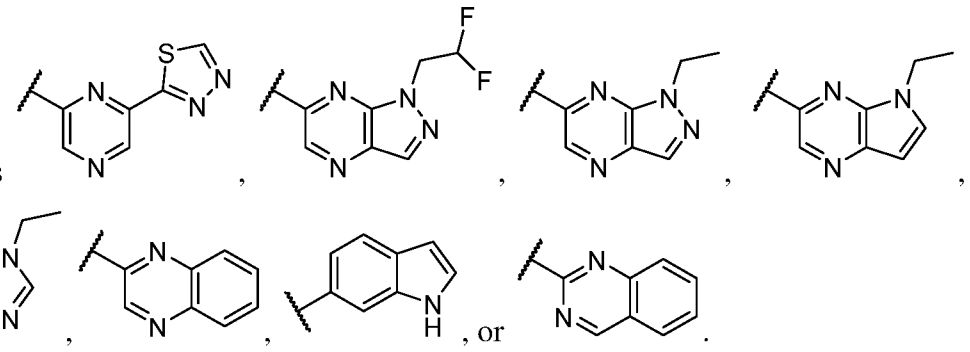
[00382] Clause 27. The compound of any of clauses 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted phenyl.

[00383] Clause 28. The compound of any of clauses 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl.

[00384] Clause 29. The compound of any of clauses 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrrolyl or a substituted or unsubstituted pyrazolyl.

[00385] Clause 30. The compound of any of clauses 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted pyrazolyl.

[00386] Clause 31. The compound of any of clauses 1-30, or a pharmaceutically acceptable salt thereof, wherein:

A is 

[00387] Clause 32. The compound of any of clauses 1-31, or a pharmaceutically acceptable salt thereof, wherein: R^4 is halogen or two instances of R^4 on the same carbon form with that carbon a carbonyl.

[00388] Clause 33. The compound of any of clauses 1-32, or a pharmaceutically acceptable salt thereof, wherein: R^4 is fluoro or two instances of R^4 on the same carbon form with that carbon a carbonyl.

[00389] Clause 34. The compound of any of clauses 1-33, or a pharmaceutically acceptable salt thereof, wherein: R^4 is fluoro.

[00390] Clause 35. The compound of any of clauses 1-34, or a pharmaceutically acceptable salt thereof, wherein: m is 0.

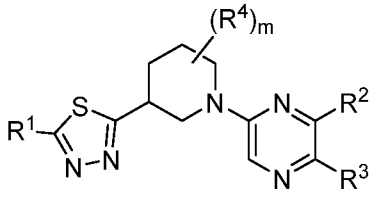
[00391] Clause 36. The compound of any of clauses 1-35, or a pharmaceutically acceptable salt thereof, wherein: m is 2.

[00392] Clause 37. The compound of any of clauses 1-35, or a pharmaceutically acceptable salt thereof, wherein: m is 1.

[00393] Clause 38. The compound of any of clauses 1-37, or a pharmaceutically acceptable salt thereof, wherein: L is a bond.

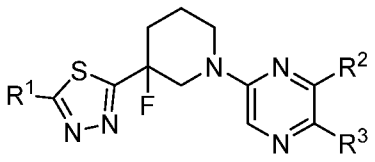
[00394] Clause 39. The compound of any of clauses 1-37, or a pharmaceutically acceptable salt thereof, wherein: L is –C(=O)-.

[00395] Clause 40. The compound of clause 1, wherein the compound is of formula (**I-a**):



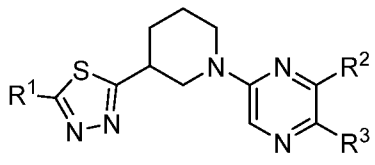
(**I-a**), or a pharmaceutically acceptable salt thereof.

[00396] Clause 41. The compound of clause 1, wherein the compound is of formula (**I-b**)



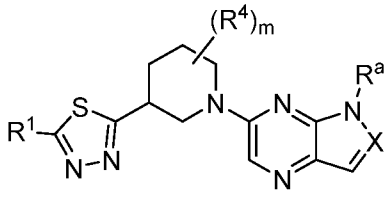
(**I-b**), or a pharmaceutically acceptable salt thereof.

[00397] Clause 42. The compound of clause 1, wherein the compound is of formula (**I-c**):



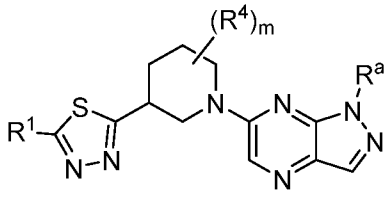
(**I-c**), or a pharmaceutically acceptable salt thereof.

[00398] Clause 43. The compound of clause 1, wherein the compound is of formula (**I-d**):



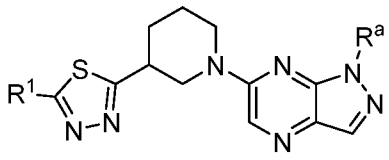
(**I-d**), or a pharmaceutically acceptable salt thereof, wherein: X is N or CH; and R^a is substituted or unsubstituted alkyl.

[00399] Clause 44. The compound of clause 1, wherein the compound is of formula (**I-e**):



(**I-e**), or a pharmaceutically acceptable salt thereof, wherein: R^a is substituted or unsubstituted alkyl.

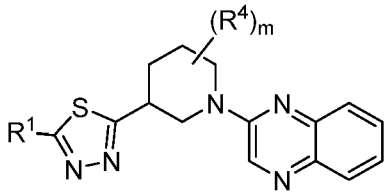
[00400] Clause 45. The compound of clause 1, wherein the compound is of formula (**I-f**):



(**I-f**), or a pharmaceutically acceptable salt thereof, wherein: R^a is substituted or unsubstituted alkyl.

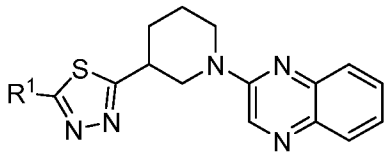
[00401] Clause 46. The compound of any of clauses 43-45, or a pharmaceutically acceptable salt thereof, wherein: R^a is unsubstituted alkyl or haloalkyl.

[00402] Clause 47. The compound of clause 1, wherein the compound is of formula (**I-g**):



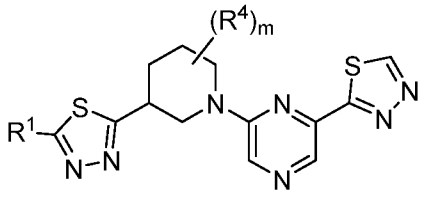
(**I-g**), or a pharmaceutically acceptable salt thereof.

[00403] Clause 48. The compound of clause 1, wherein the compound is of formula (**I-h**):



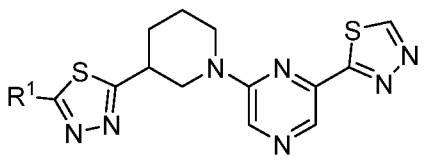
(**I-h**), or a pharmaceutically acceptable salt thereof.

[00404] Clause 49. The compound of clause 1, wherein the compound is of formula (**I-i**):



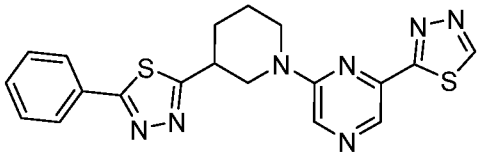
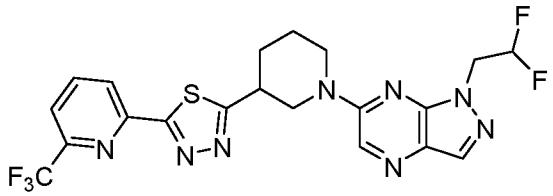
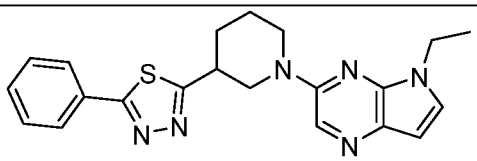
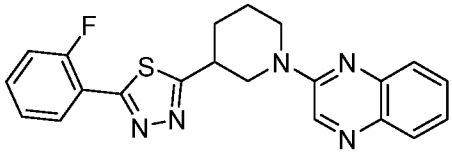
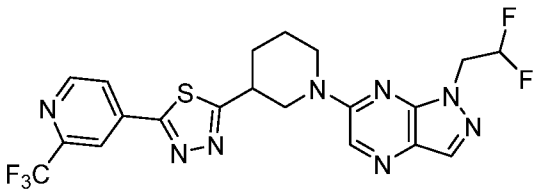
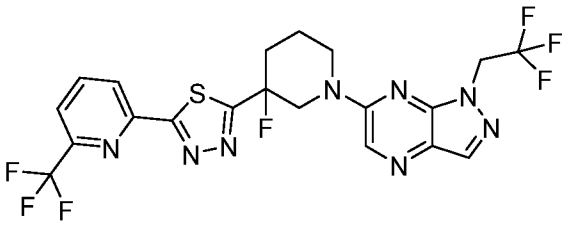
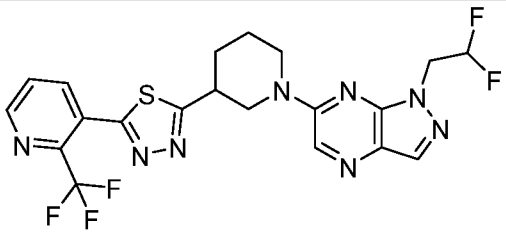
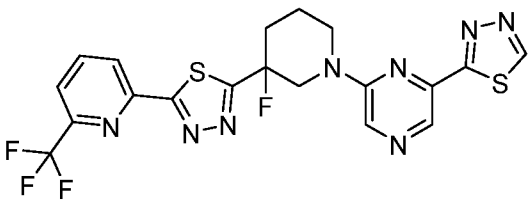
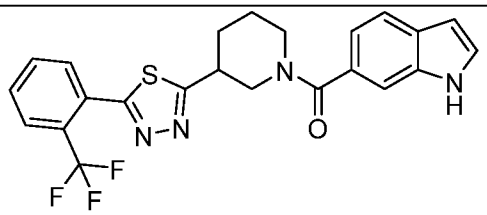
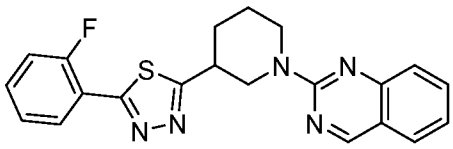
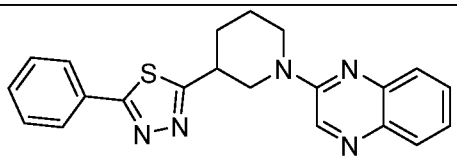
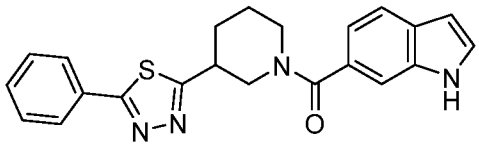
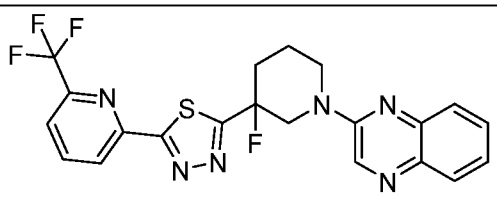
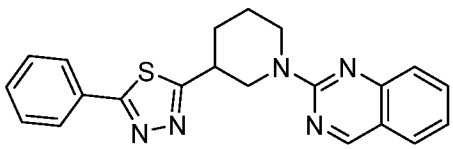
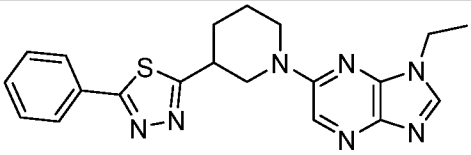
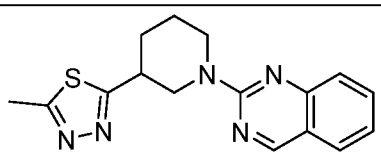
(**I-i**), or a pharmaceutically acceptable salt thereof.

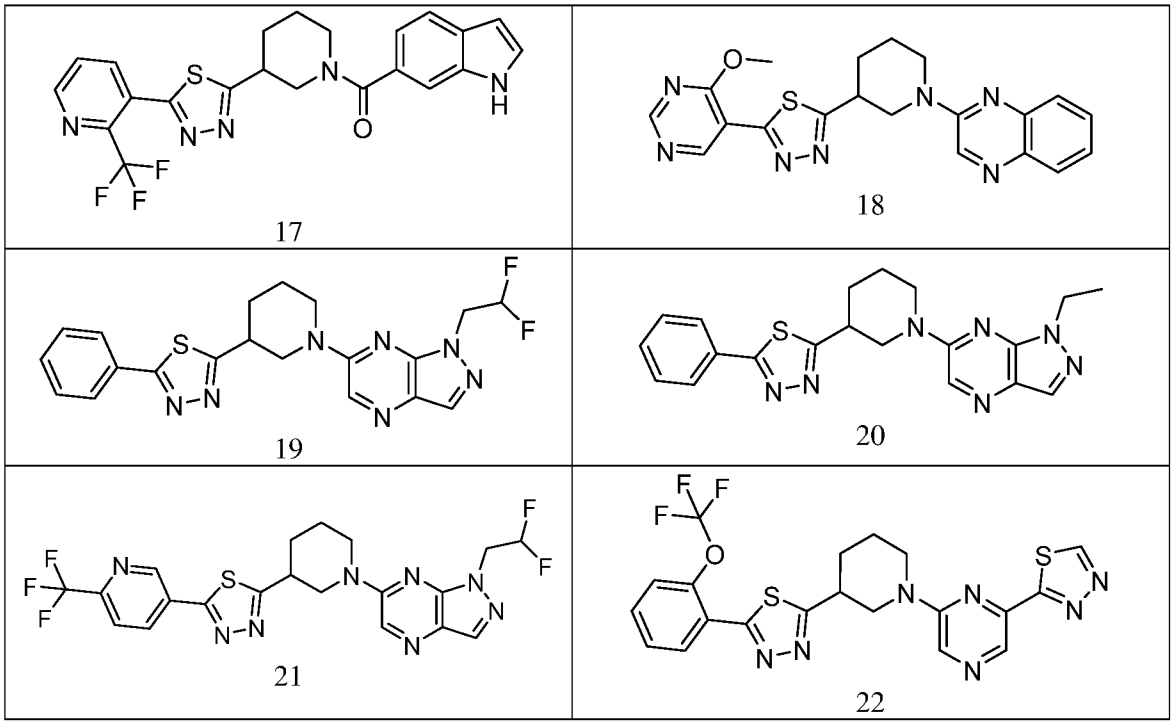
[00405] Clause 50. The compound of clause 1, wherein the compound is of formula (**I-j**):



(**I-j**), or a pharmaceutically acceptable salt thereof.

[00406] Clause 51. The compound of clause 1, wherein the compound is:

 1	 2
 3	 4
 5	 6
 7	 8
 9	 10
 11	 12
 13	 14
 15	 16



or a pharmaceutically acceptable salt thereof.

[00407] Clause 52. A pharmaceutical composition comprising a compound of any of clauses 1-51, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00408] Clause 53. A kit comprising a compound of any of clauses 1-51, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of clause 52, and instructions for administering the compound or pharmaceutical composition to a subject in need thereof.

[00409] Clause 54. A method of treating a disease or disorder in a subject in need thereof, the method comprising administering an effective amount of a compound of any of clauses 1-51, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of clause 52.

[00410] Clause 55. The method of clause 54, wherein the disease or disorder is associated with glucocerebrosidase activity.

[00411] Clause 56. The method of clause 54 or 55, wherein the disease or disorder is a neurological disease or disorder.

[00412] Clause 57. The method of clause 56, wherein the neurological disease or disorder is Parkinson's disease or Gaucher's disease.

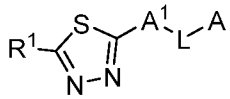
[00413] Clause 58. A method of activating glucocerebrosidase, the method comprising contacting glucocerebrosidase with an effective amount of a compound of any of clauses 1-51, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of clause 52.

[00414] Clause 59. The method of clause 58, wherein the contacting is *in vitro*.

[00415] Clause 60. The method of clause 58, wherein the contacting is *in vivo*.

[00416] Additional various aspects of the present disclosure are set out in the following numbered embodiments:

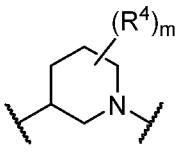
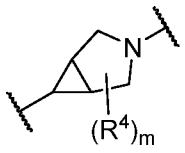
[00417] Embodiment 1. A compound of Formula (**I**):



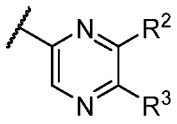
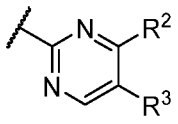
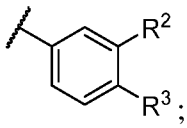
(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

A^1 is  or ;

L is a bond or –C(=O)-;

A is , , or ;

R^2 and R^3 are each independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^4 is independently halogen, substituted or unsubstituted alkyl, or two instances of R^4 on the same carbon form with that carbon a carbonyl; and

m is 0, 1, 2, 3, or 4.

[00418] Embodiment 2. The compound of embodiment 1, or a pharmaceutically acceptable salt thereof, wherein: R^1 is substituted or unsubstituted pyridinyl, or substituted or unsubstituted phenyl.

[00419] Embodiment 3. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt thereof, wherein: R^1 is substituted pyridinyl, or substituted or unsubstituted phenyl.

[00420] Embodiment 4. The compound of any of embodiments 1-3, or a pharmaceutically acceptable salt thereof, wherein: R^1 is pyridinyl substituted with halogen or haloalkyl, unsubstituted phenyl, or phenyl substituted with halogen, haloalkoxy, or haloalkyl.

[00421] Embodiment 5. The compound of any of embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is pyridinyl substituted with halogen or haloalkyl.

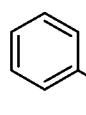
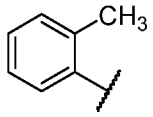
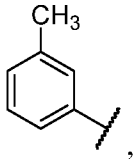
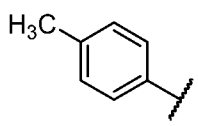
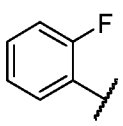
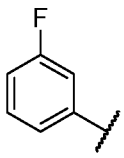
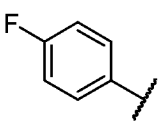
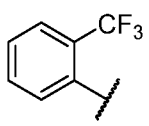
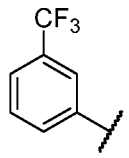
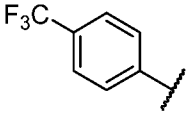
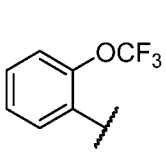
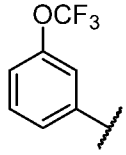
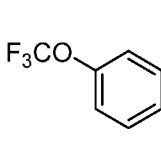
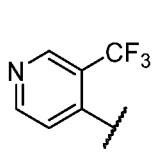
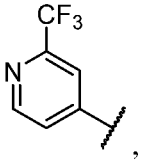
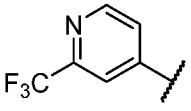
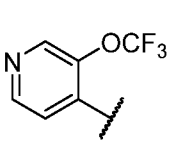
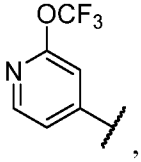
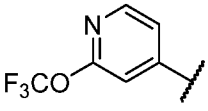
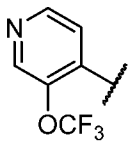
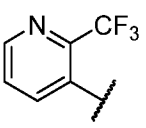
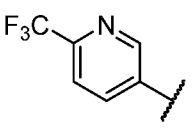
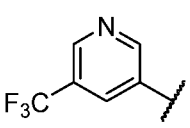
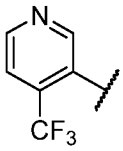
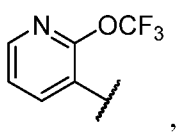
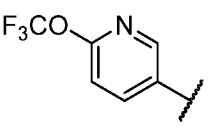
[00422] Embodiment 6. The compound of any of embodiments 1-5, or a pharmaceutically acceptable salt thereof, wherein: R^1 is pyridinyl substituted with haloalkyl.

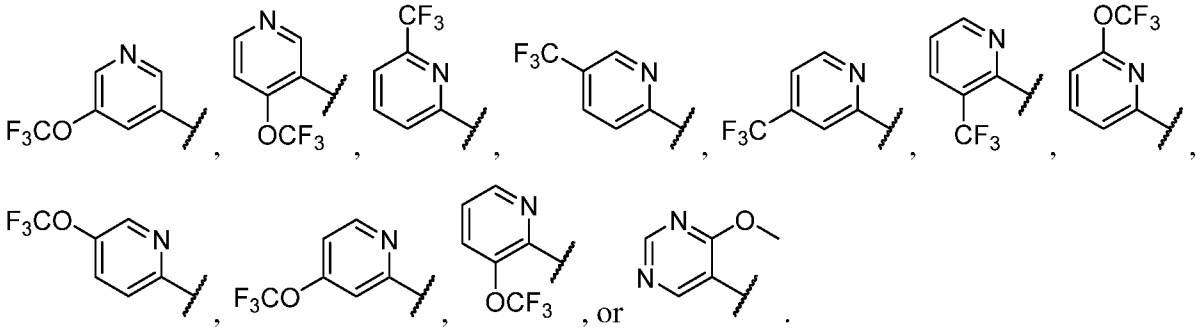
[00423] Embodiment 7. The compound of any of embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is unsubstituted phenyl.

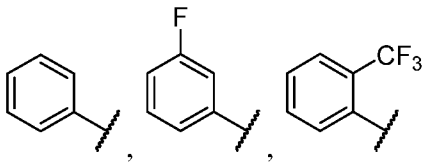
[00424] Embodiment 8. The compound of any of embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is phenyl substituted with halogen, haloalkoxy, or haloalkyl.

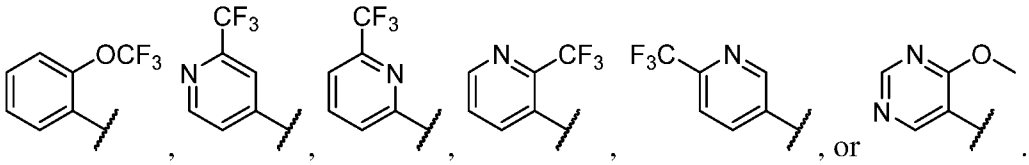
[00425] Embodiment 9. The compound of any of embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is phenyl substituted with halogen.

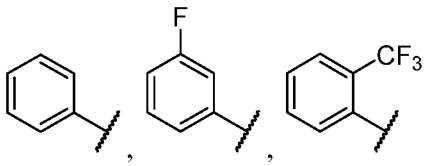
[00426] Embodiment 10. The compound of any of embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is phenyl substituted with haloalkyl.

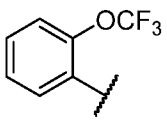
[00427] Embodiment 11. The compound of any of embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is methyl, , , , , , , , , , , , , , , , , , , , , , , , , , , .

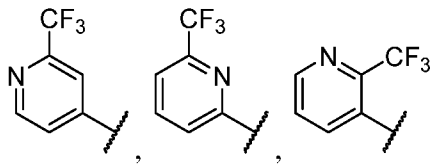


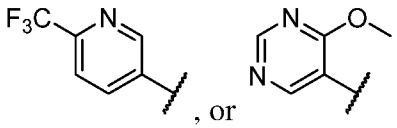
[00428] Embodiment 12. The compound of any of embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is 

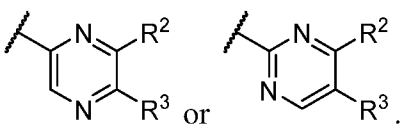


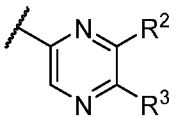
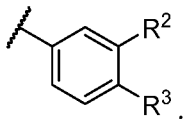
[00429] Embodiment 13. The compound of any of embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is 

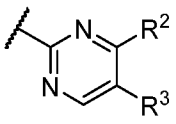
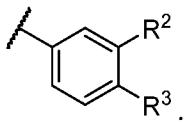


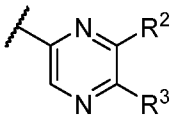
[00430] Embodiment 14. The compound of any of embodiments 1-4, or a pharmaceutically acceptable salt thereof, wherein: R^1 is 

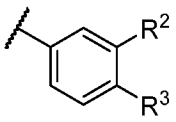


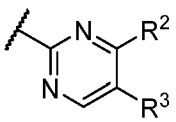
[00431] Embodiment 15. The compound of any of embodiments 1-14, or a pharmaceutically acceptable salt thereof, wherein: A is .

[00432] Embodiment 16. The compound of any of embodiments 1-14, or a pharmaceutically acceptable salt thereof, wherein: A is  or .

[00433] Embodiment 17. The compound of any of embodiments 1-14, or a pharmaceutically acceptable salt thereof, wherein: A is  or .

[00434] Embodiment 18. The compound of any of embodiments 1-14, or a pharmaceutically acceptable salt thereof, wherein: A is .

[00435] Embodiment 19. The compound of any of embodiments 1-14, or a pharmaceutically acceptable salt thereof, wherein: A is .

[00436] Embodiment 20. The compound of any of embodiments 1-14, or a pharmaceutically acceptable salt thereof, wherein: A is .

[00437] Embodiment 21. The compound of any of embodiments 1-20, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 are each independently hydrogen or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[00438] Embodiment 22. The compound of any of embodiments 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 is heteroaryl.

[00439] Embodiment 23. The compound of any of embodiments 1-22, or a pharmaceutically acceptable salt thereof, wherein: R^2 is thiadiazolyl.

[00440] Embodiment 24. The compound of any of embodiments 1-23, or a pharmaceutically acceptable salt thereof, wherein: R^3 is hydrogen.

[00441] Embodiment 25. The compound of any of embodiments 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

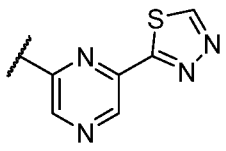
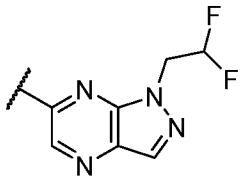
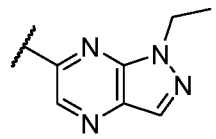
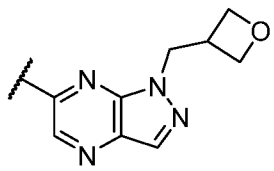
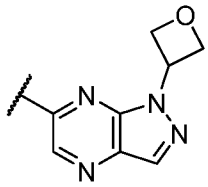
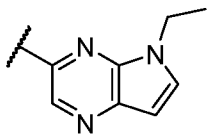
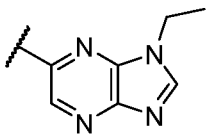
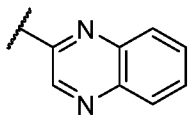
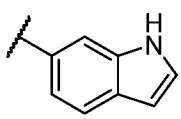
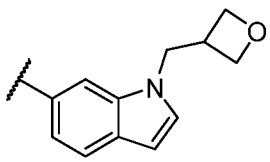
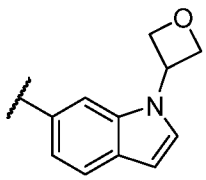
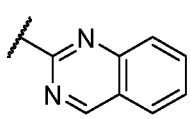
[00442] Embodiment 26. The compound of any of embodiments 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl.

[00443] Embodiment 27. The compound of any of embodiments 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted phenyl.

[00444] Embodiment 28. The compound of any of embodiments 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl.

[00445] Embodiment 29. The compound of any of embodiments 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrrolyl, or a substituted or unsubstituted pyrazolyl.

[00446] Embodiment 30. The compound of any of embodiments 1-21, or a pharmaceutically acceptable salt thereof, wherein: R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted pyrazolyl.

[00447] Embodiment 31. The compound of any of embodiments 1-30, or a pharmaceutically acceptable salt thereof, wherein: A is , , , , , , , , , , , or .

[00448] Embodiment 32. The compound of any of embodiments 1-31, or a pharmaceutically acceptable salt thereof, wherein: R^4 is halogen or two instances of R^4 on the same carbon form with that carbon a carbonyl.

[00449] Embodiment 33. The compound of any of embodiments 1-32, or a pharmaceutically acceptable salt thereof, wherein: R^4 is fluoro or two instances of R^4 on the same carbon form with that carbon a carbonyl.

[00450] Embodiment 34. The compound of any of embodiments 1-33, or a pharmaceutically acceptable salt thereof, wherein: R^4 is fluoro.

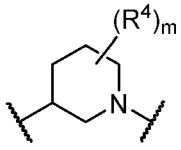
[00451] Embodiment 35. The compound of any of embodiments 1-34, or a pharmaceutically acceptable salt thereof, wherein: m is 0.

[00452] Embodiment 36. The compound of any of embodiments 1-35, or a pharmaceutically acceptable salt thereof, wherein: m is 2.

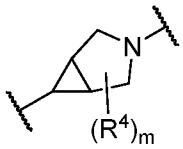
[00453] Embodiment 37. The compound of any of embodiments 1-35, or a pharmaceutically acceptable salt thereof, wherein: m is 1.

[00454] Embodiment 38. The compound of any of embodiments 1-37, or a pharmaceutically acceptable salt thereof, wherein: L is a bond.

[00455] Embodiment 39. The compound of any of embodiments 1-37, or a pharmaceutically acceptable salt thereof, wherein: L is –C(=O)-.

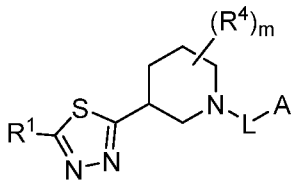
[00456] Embodiment 40. The compound of any of embodiments 1-39, or a pharmaceutically acceptable salt thereof, wherein: A^1 is 

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[00457] Embodiment 41. The compound of any of embodiments 1-39, or a pharmaceutically acceptable salt thereof, wherein: A^1 is 

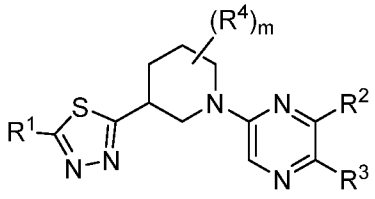
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[00458] Embodiment 42. The compound of embodiment 1, wherein the compound is of formula (**I-a**):



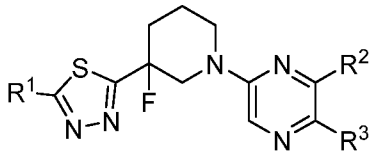
(**I-a**), or a pharmaceutically acceptable salt thereof.

[00459] Embodiment 43. The compound of embodiment 1, wherein the compound is of formula (**I-b**):



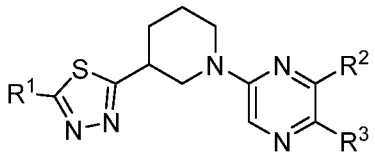
(**I-b**), or a pharmaceutically acceptable salt thereof.

[00460] Embodiment 44. The compound of embodiment 1, wherein the compound is of formula (**I-c**):



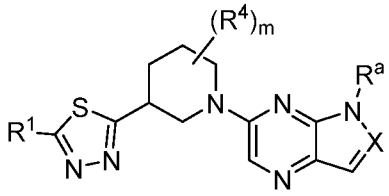
(**I-c**), or a pharmaceutically acceptable salt thereof.

[00461] Embodiment 45. The compound of embodiment 1, wherein the compound is of formula (**I-d**):



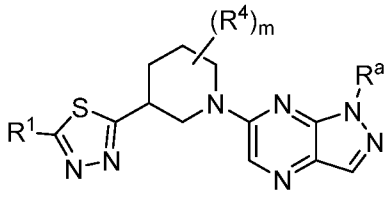
(**I-d**), or a pharmaceutically acceptable salt thereof.

[00462] Embodiment 46. The compound of embodiment 1, wherein the compound is of formula (**I-e**):



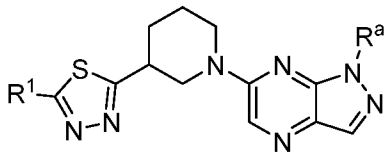
(**I-e**), or a pharmaceutically acceptable salt thereof, wherein: X is N or CH; and R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

[00463] Embodiment 47. The compound of embodiment 1, wherein the compound is of formula (**I-f**):



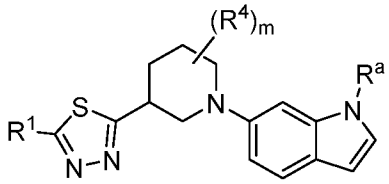
(**I-f**), or a pharmaceutically acceptable salt thereof, wherein: R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

[00464] Embodiment 48. The compound of embodiment 1, wherein the compound is of formula (**I-g**):



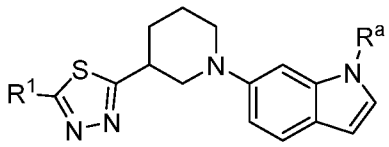
(**I-g**), or a pharmaceutically acceptable salt thereof, wherein: R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

[00465] Embodiment 49. The compound of embodiment 1, wherein the compound is of formula (**I-h**):



(**I-h**), or a pharmaceutically acceptable salt thereof, wherein: R^a is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

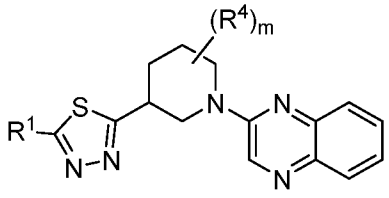
[00466] Embodiment 50. The compound of embodiment 1, wherein the compound is of formula (**I-i**):



(**I-i**), or a pharmaceutically acceptable salt thereof, wherein: R^a is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

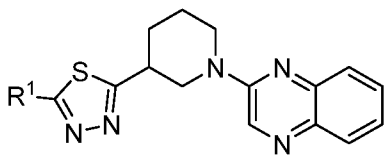
[00467] Embodiment 51. The compound of any of embodiments 46-50, or a pharmaceutically acceptable salt thereof, wherein: R^a is unsubstituted heterocyclyl, unsubstituted alkyl, or haloalkyl.

[00468] Embodiment 52. The compound of embodiment 1, wherein the compound is of formula (**I-j**):



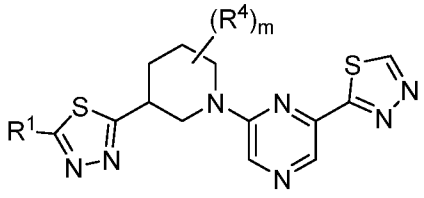
(**I-j**), or a pharmaceutically acceptable salt thereof.

[00469] Embodiment 53. The compound of embodiment 1, wherein the compound is of formula (**I-k**):



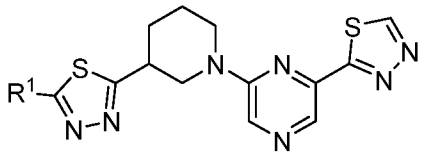
(**I-k**), or a pharmaceutically acceptable salt thereof.

[00470] Embodiment 54. The compound of embodiment 1, wherein the compound is of formula (**I-l**):



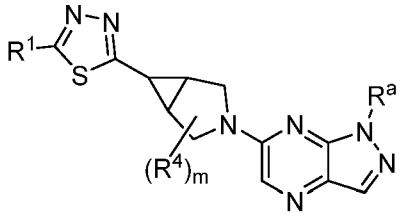
(**I-l**), or a pharmaceutically acceptable salt thereof.

[00471] Embodiment 55. The compound of embodiment 1, wherein the compound is of formula (**I-m**):



(**I-m**), or a pharmaceutically acceptable salt thereof.

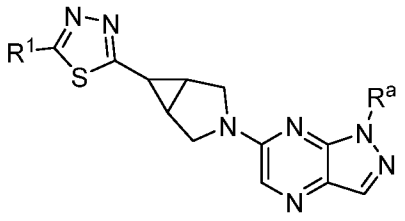
[00472] Embodiment 56. The compound of embodiment 1, wherein the compound is of formula (**I-n**):



(**I-n**), or a pharmaceutically acceptable salt thereof, wherein:

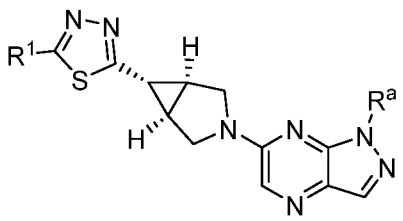
R^a is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

[00473] Embodiment 57. The compound of embodiment 1, wherein the compound is of formula (**I-o**):



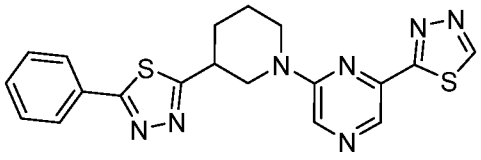
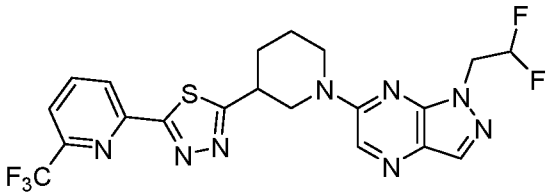
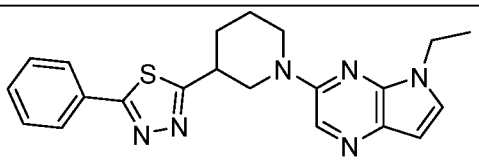
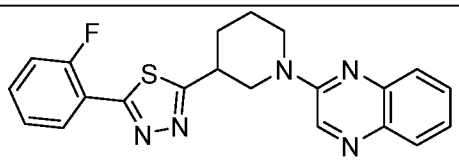
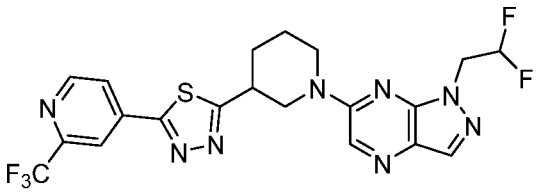
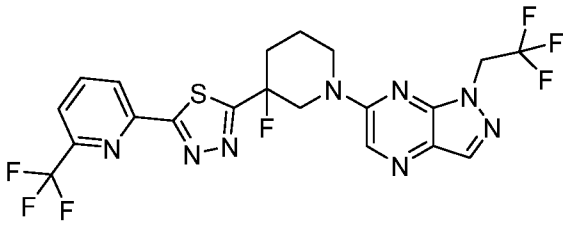
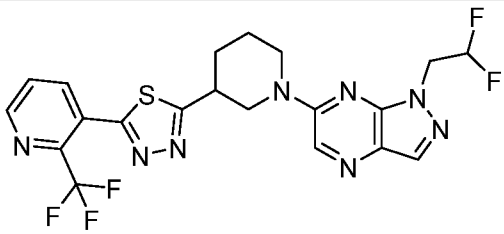
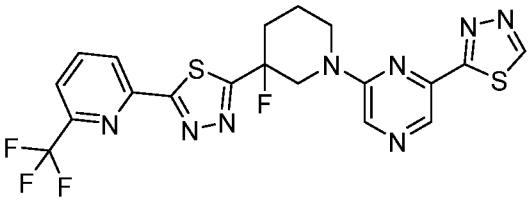
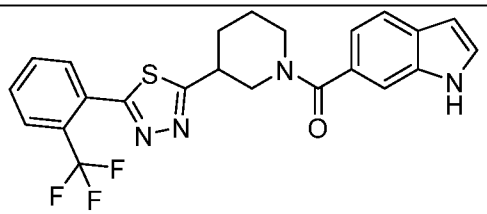
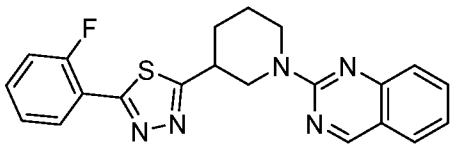
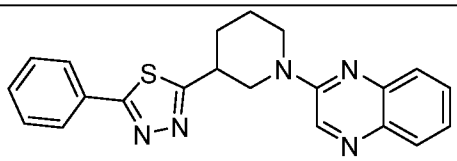
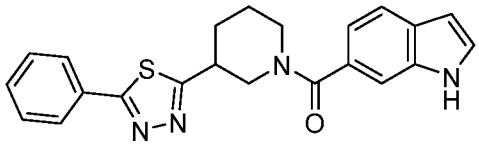
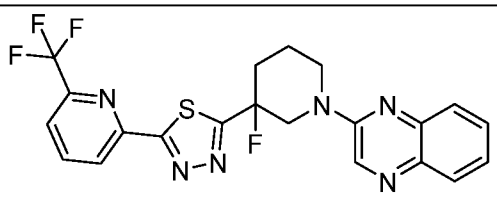
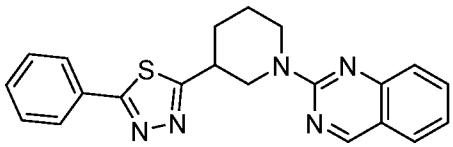
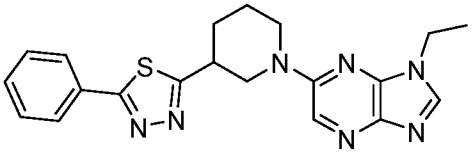
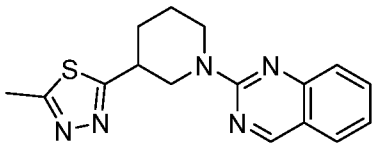
(**I-o**), or a pharmaceutically acceptable salt thereof.

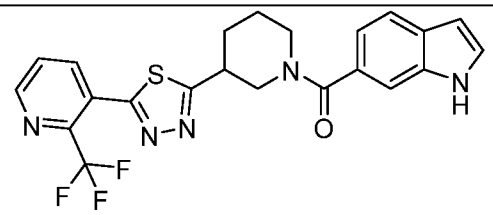
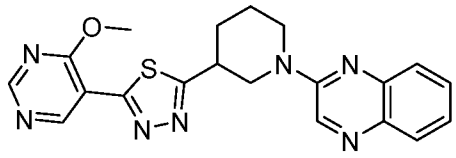
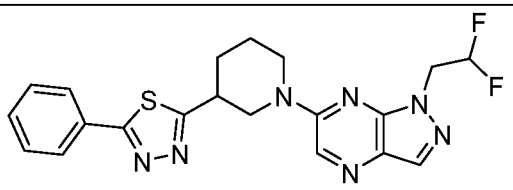
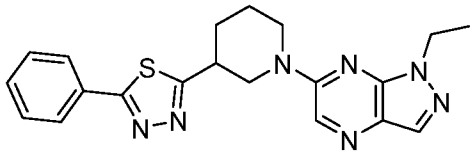
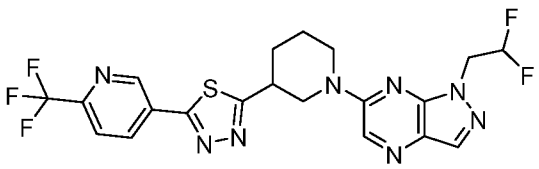
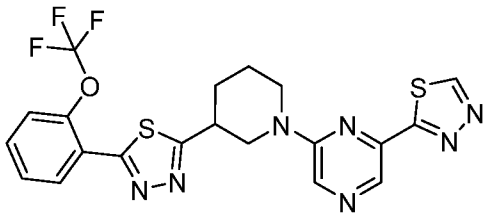
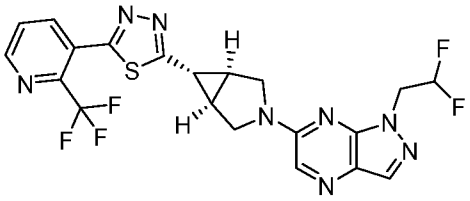
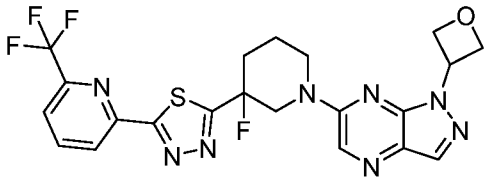
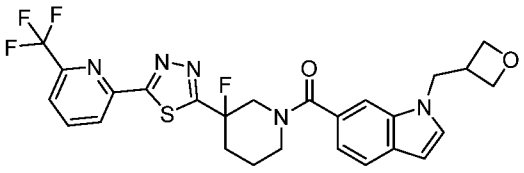
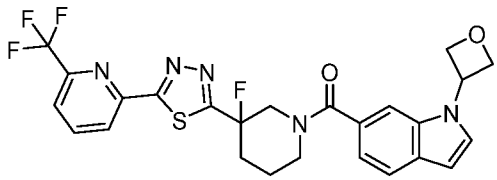
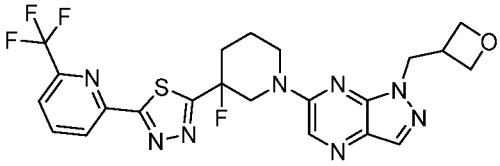
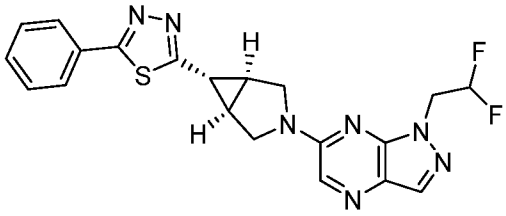
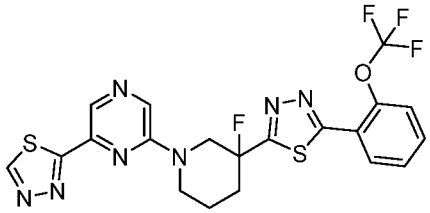
[00474] Embodiment 58. The compound of embodiment 1, wherein the compound is of formula (**I-p**):



(**I-p**), or a pharmaceutically acceptable salt thereof.

[00475] Embodiment 59. The compound of embodiment 1, wherein the compound is:

 1	 2
 3	 4
 5	 6
 7	 8
 9	 10
 11	 12
 13	 14
 15	 16

 17	 18
 19	 20
 21	 22
 23	 24
 25	 26
 27	 28
 29	

or a pharmaceutically acceptable salt thereof.

[00476] Embodiment 60. A pharmaceutical composition comprising a compound of any of embodiments 1-59, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00477] Embodiment 61. A kit comprising a compound of any of embodiments 1-59, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 60, and instructions for administering the compound or pharmaceutical composition to a subject in need thereof.

[00478] Embodiment 62. A method of treating a disease or disorder in a subject in need thereof, the method comprising administering an effective amount of a compound of any of embodiments 1-59, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 60.

[00479] Embodiment 63. The method of embodiment 62, wherein the disease or disorder is associated with glucocerebrosidase activity.

[00480] Embodiment 64. The method of embodiment 62 or 63, wherein the disease or disorder is a neurological disease or disorder.

[00481] Embodiment 65. The method of embodiment 64, wherein the neurological disease or disorder is Parkinson's disease or Gaucher's disease.

[00482] Embodiment 66. A method of activating glucocerebrosidase, the method comprising contacting glucocerebrosidase with an effective amount of a compound of any of embodiments 1-59, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 60.

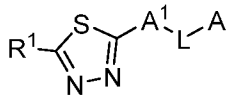
[00483] Embodiment 67. The method of embodiment 66, wherein the contacting is *in vitro*.

[00484] Embodiment 68. The method of embodiment 66, wherein the contacting is *in vivo*.

CLAIMS

What is claimed is:

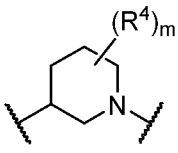
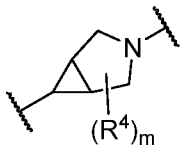
1. A compound of Formula (**I**):



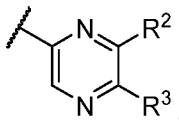
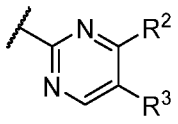
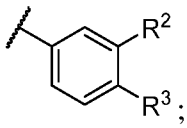
(**I**),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

A^1 is  or ;

L is a bond or –C(=O)-;

A is , , or ;

R^2 and R^3 are each independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^4 is independently halogen, substituted or unsubstituted alkyl, or two instances of R^4 on the same carbon form with that carbon a carbonyl; and

m is 0, 1, 2, 3, or 4.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted or unsubstituted pyridinyl, or substituted or unsubstituted phenyl.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is substituted pyridinyl, or substituted or unsubstituted phenyl.

4. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is pyridinyl substituted with halogen or haloalkyl, unsubstituted phenyl, or phenyl substituted with halogen, haloalkoxy, or haloalkyl.

5. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is pyridinyl substituted with halogen or haloalkyl.

6. The compound of any of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is pyridinyl substituted with haloalkyl.

7. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is unsubstituted phenyl.

8. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is phenyl substituted with halogen, haloalkoxy, or haloalkyl.

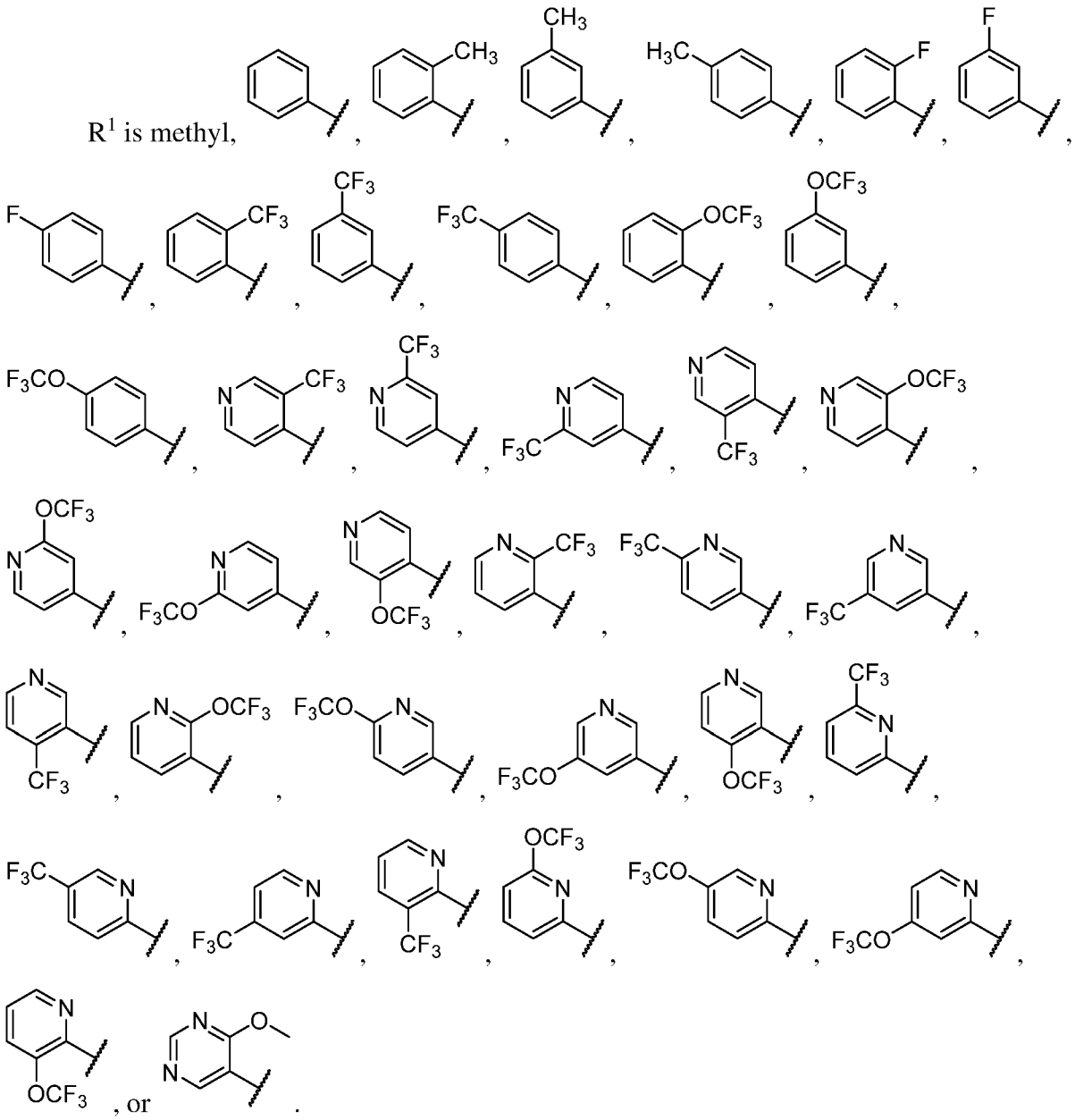
9. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is phenyl substituted with halogen.

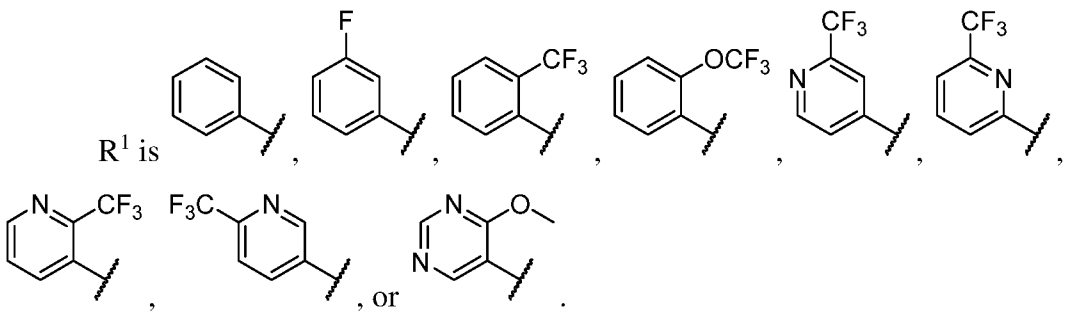
10. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is phenyl substituted with haloalkyl.

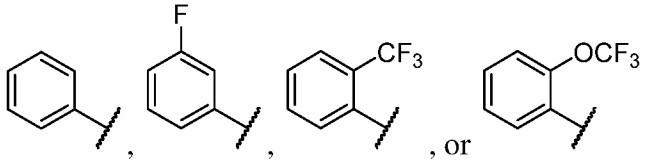
11. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is methyl, , or .

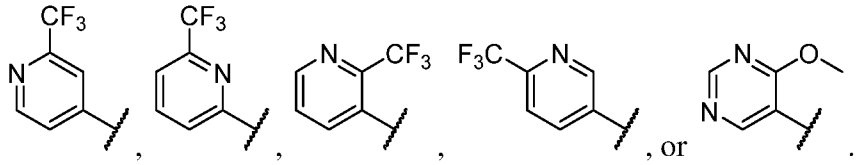
12. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is , or .

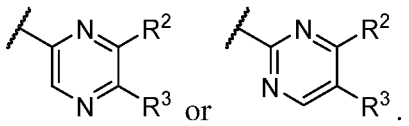
13. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is .

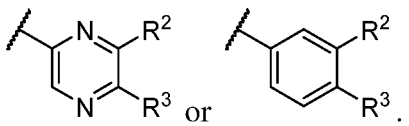
14. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is .

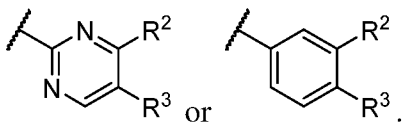
15. The compound of any of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is .

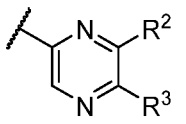
16. The compound of any of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is .

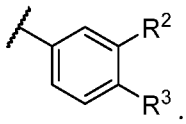
17. The compound of any of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is .

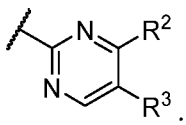
18. The compound of any of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is .

19. The compound of any of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is .

20. The compound of any of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein:

A is .

21. The compound of any of claims 1-20, or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 are each independently hydrogen or substituted or unsubstituted heteroaryl; or R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

22. The compound of any of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein:

R^2 is heteroaryl.

23. The compound of any of claims 1-22, or a pharmaceutically acceptable salt thereof, wherein:

R^2 is thiadiazolyl.

24. The compound of any of claims 1-23, or a pharmaceutically acceptable salt thereof, wherein:

R^3 is hydrogen.

25. The compound of any of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

26. The compound of any of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted aryl.

27. The compound of any of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted phenyl.

28. The compound of any of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted heteroaryl.

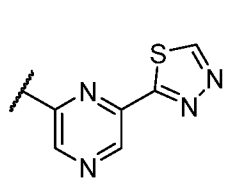
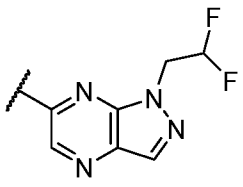
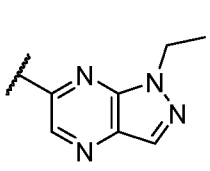
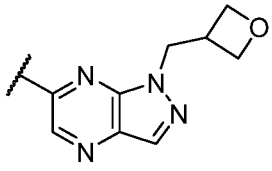
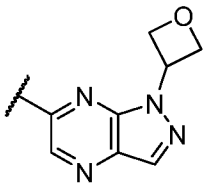
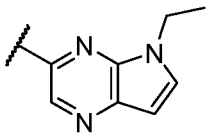
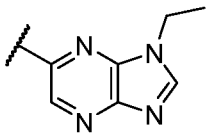
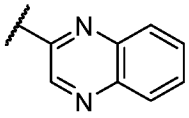
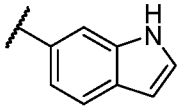
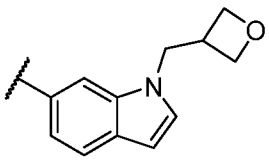
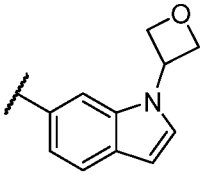
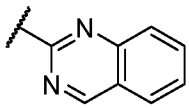
29. The compound of any of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrrolyl, or a substituted or unsubstituted pyrazolyl.

30. The compound of any of claims 1-21, or a pharmaceutically acceptable salt thereof, wherein:

R^2 and R^3 together with the atoms to which they are attached form a substituted or unsubstituted pyrazolyl.

31. The compound of any of claims 1-30, or a pharmaceutically acceptable salt thereof, wherein:

A is , , , , , , , , , , , or .

32. The compound of any of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein:

R^4 is halogen or two instances of R^4 on the same carbon form with that carbon a carbonyl.

33. The compound of any of claims 1-32, or a pharmaceutically acceptable salt thereof, wherein:

R^4 is fluoro or two instances of R^4 on the same carbon form with that carbon a carbonyl.

34. The compound of any of claims 1-33, or a pharmaceutically acceptable salt thereof, wherein:

R^4 is fluoro.

35. The compound of any of claims 1-34, or a pharmaceutically acceptable salt thereof, wherein:

m is 0.

36. The compound of any of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein:

m is 2.

37. The compound of any of claims 1-35, or a pharmaceutically acceptable salt thereof, wherein:

m is 1.

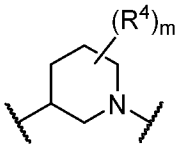
38. The compound of any of claims 1-37, or a pharmaceutically acceptable salt thereof, wherein:

L is a bond.

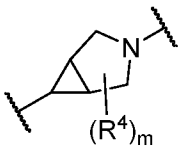
39. The compound of any of claims 1-37, or a pharmaceutically acceptable salt thereof, wherein:

L is –C(=O)-.

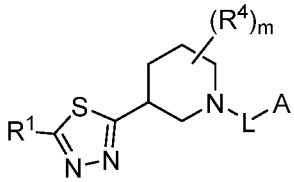
40. The compound of any of claims 1-39, or a pharmaceutically acceptable salt thereof, wherein:

A^1 is .

41. The compound of any of claims 1-39, or a pharmaceutically acceptable salt thereof, wherein:

A^1 is .

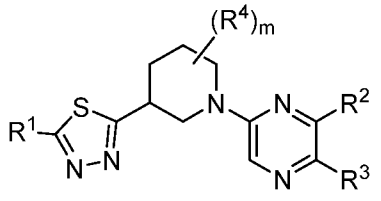
42. The compound of claim 1, wherein the compound is of formula (**I-a**):



(**I-a**),

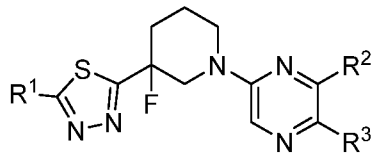
or a pharmaceutically acceptable salt thereof.

43. The compound of claim 1, wherein the compound is of formula (**I-b**):


(**I-b**),

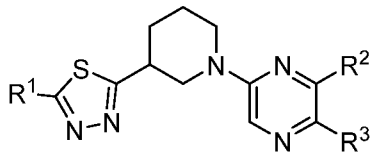
or a pharmaceutically acceptable salt thereof.

44. The compound of claim 1, wherein the compound is of formula (**I-c**):


(**I-c**),

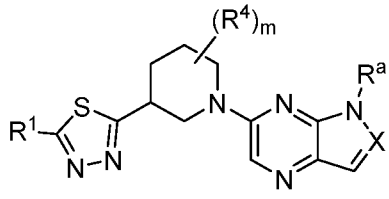
or a pharmaceutically acceptable salt thereof.

45. The compound of claim 1, wherein the compound is of formula (**I-d**):


(**I-d**),

or a pharmaceutically acceptable salt thereof.

46. The compound of claim 1, wherein the compound is of formula (**I-e**):

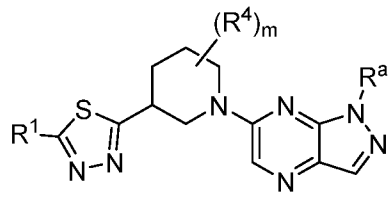

(**I-e**),

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH; and

R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

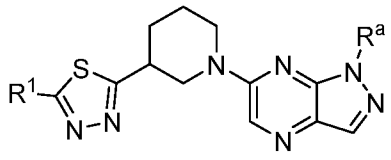
47. The compound of claim 1, wherein the compound is of formula (**I-f**):


(**I-f**),

or a pharmaceutically acceptable salt thereof, wherein:

R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

48. The compound of claim 1, wherein the compound is of formula (**I-g**):

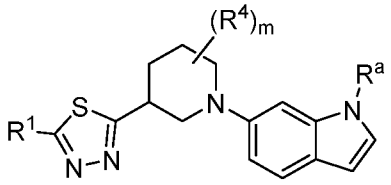


(**I-g**),

or a pharmaceutically acceptable salt thereof, wherein:

R^a is substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

49. The compound of claim 1, wherein the compound is of formula (**I-h**):

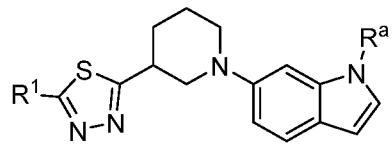


(**I-h**),

or a pharmaceutically acceptable salt thereof, wherein:

R^a is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

50. The compound of claim 1, wherein the compound is of formula (**I-i**):



(**I-i**),

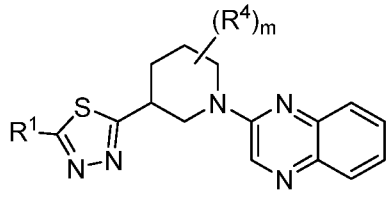
or a pharmaceutically acceptable salt thereof, wherein:

R^a is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

51. The compound of any of claims 46-50, or a pharmaceutically acceptable salt thereof, wherein:

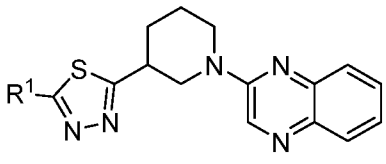
R^a is unsubstituted heterocyclyl, unsubstituted alkyl, or haloalkyl.

52. The compound of claim 1, wherein the compound is of formula (**I-j**):


(**I-j**),

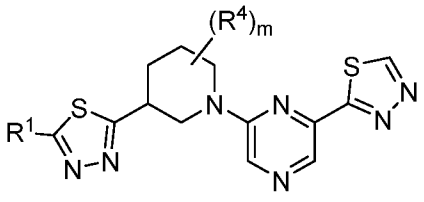
or a pharmaceutically acceptable salt thereof.

53. The compound of claim 1, wherein the compound is of formula (**I-k**):


(**I-k**),

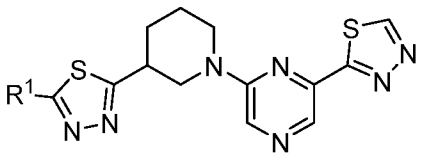
or a pharmaceutically acceptable salt thereof.

54. The compound of claim 1, wherein the compound is of formula (**I-l**):


(**I-l**),

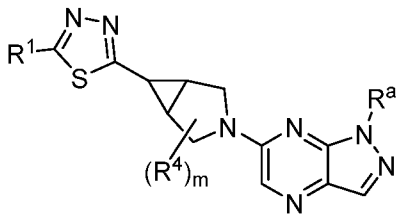
or a pharmaceutically acceptable salt thereof.

55. The compound of claim 1, wherein the compound is of formula (**I-m**):


(**I-m**),

or a pharmaceutically acceptable salt thereof.

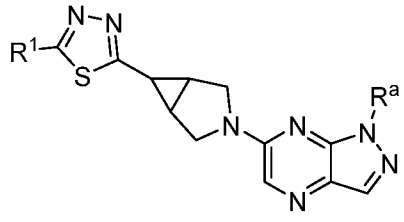
56. The compound of claim 1, wherein the compound is of formula (**I-n**):


(**I-n**),

or a pharmaceutically acceptable salt thereof, wherein:

R^a is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heterocyclyl.

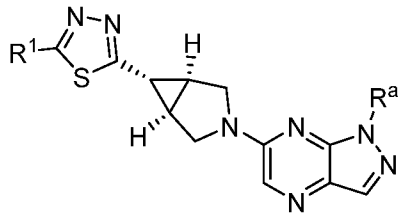
57. The compound of claim 1, wherein the compound is of formula (**I-o**):



(**I-o**),

or a pharmaceutically acceptable salt thereof.

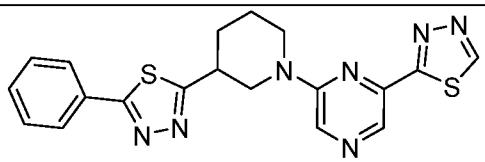
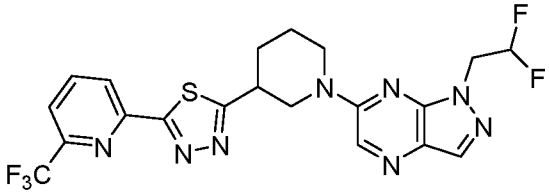
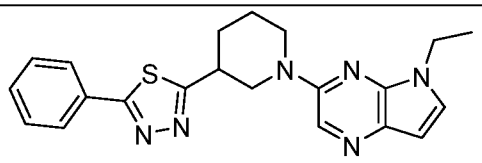
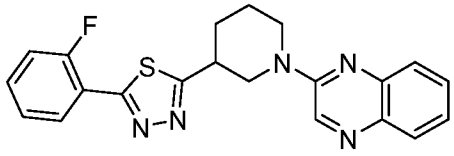
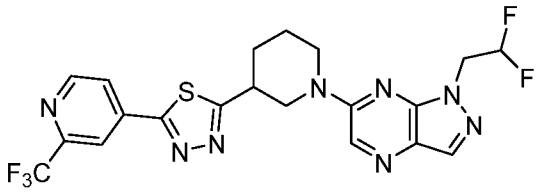
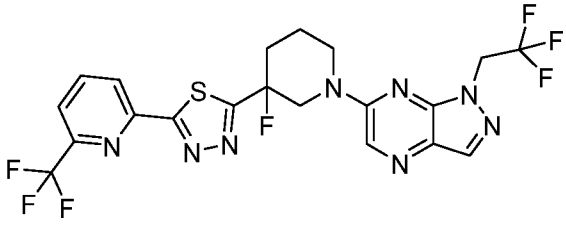
58. The compound of claim 1, wherein the compound is of formula (**I-p**):

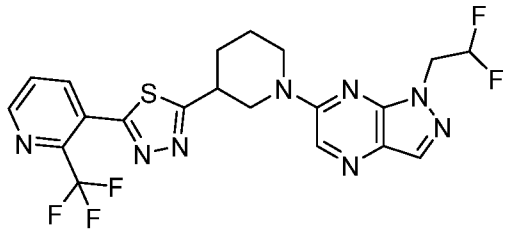
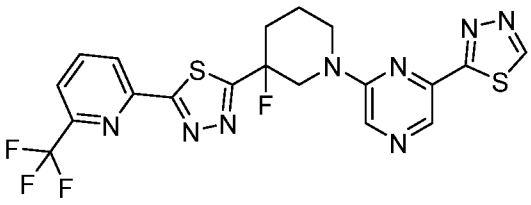
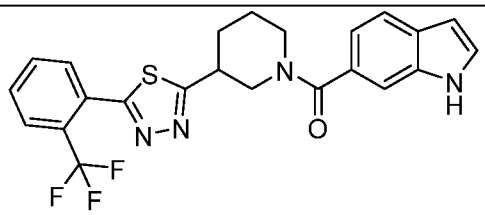
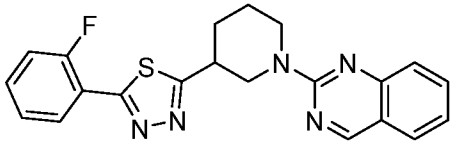
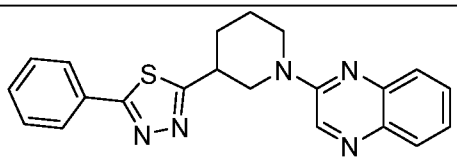
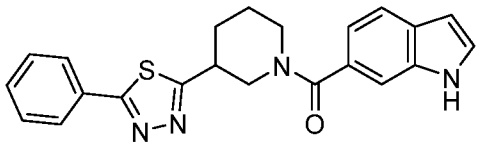
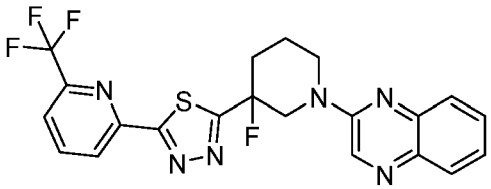
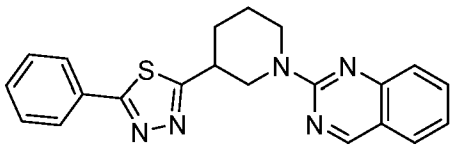
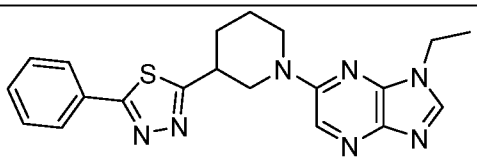
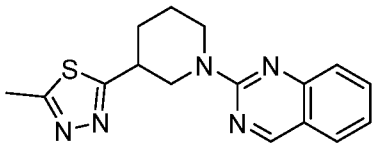
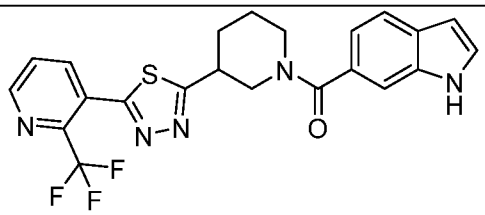
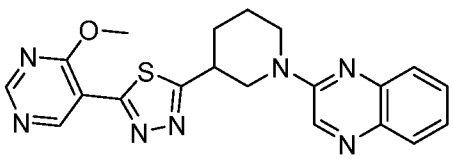
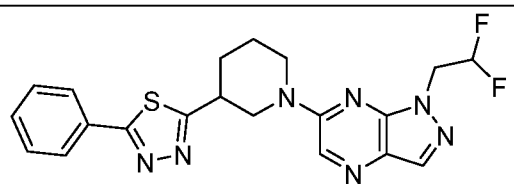
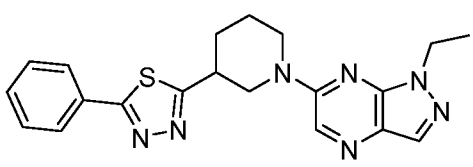


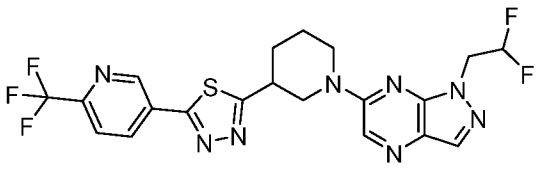
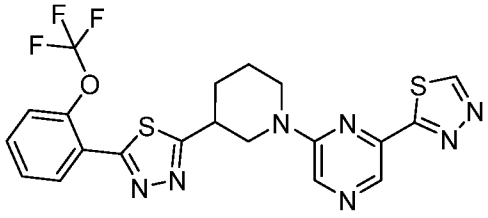
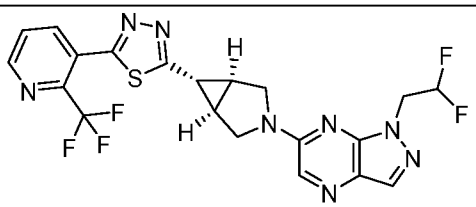
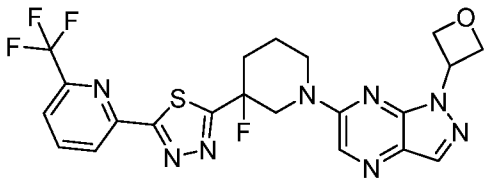
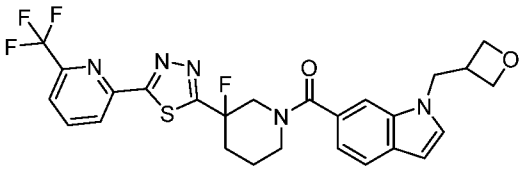
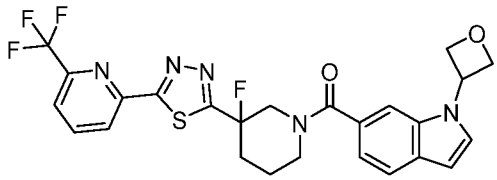
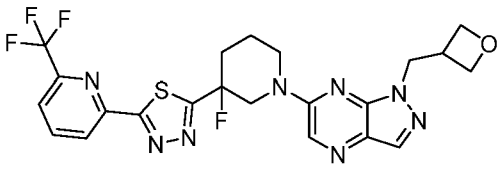
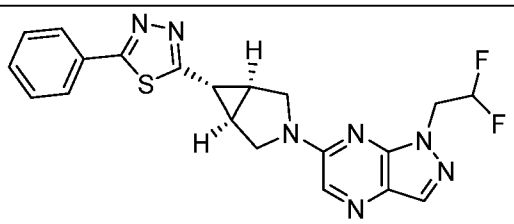
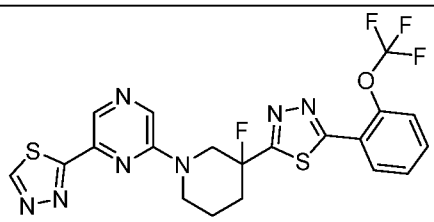
(**I-p**),

or a pharmaceutically acceptable salt thereof.

59. The compound of claim 1, wherein the compound is:

 1	 2
 3	 4
 5	 6

 7	 8
 9	 10
 11	 12
 13	 14
 15	 16
 17	 18
 19	 20

 21	 22
 23	 24
 25	 26
 27	 28
 29	

or a pharmaceutically acceptable salt thereof.

60. A pharmaceutical composition comprising a compound of any of claims 1-59, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

61. A kit comprising a compound of any of claims 1-59, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 60, and instructions for administering the compound or pharmaceutical composition to a subject in need thereof.

62. A method of treating a disease or disorder in a subject in need thereof, the method comprising administering an effective amount of a compound of any of claims 1-59, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 60.

63. The method of claim 62, wherein the disease or disorder is associated with glucocerebrosidase activity.

64. The method of claim 62 or 63, wherein the disease or disorder is a neurological disease or disorder.

65. The method of claim 64, wherein the neurological disease or disorder is Parkinson's disease or Gaucher's disease.

66. A method of activating glucocerebrosidase, the method comprising contacting glucocerebrosidase with an effective amount of a compound of any of claims 1-59, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 60.

67. The method of claim 66, wherein the contacting is *in vitro*.

68. The method of claim 66, wherein the contacting is *in vivo*.