

HETEROARYL AMINE COMPOUNDS AND USES THEREOF**RELATED APPLICATIONS**

[001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Applications, U.S.S.N. 63/520,171, filed August 17, 2023, and U.S.S.N. 63/567,980, filed March 21, 2024, the entire contents of each of which is incorporated herein by reference.

BACKGROUND

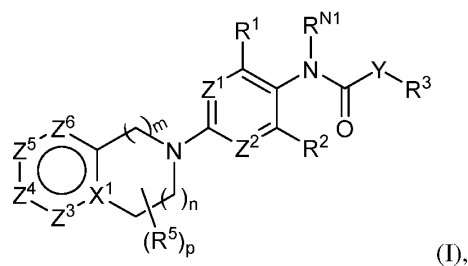
[002] Voltage-gated potassium channels, including the voltage-gated potassium channels Kv7.2 and Kv7.3 (Kv7.2/Kv7.3), are important in controlling neuronal excitability. Kv7.2/Kv7.3 underlie the neuronal “M-current,” named according to its initial characterization as a neuronal current decreased in response to muscarinic/cholinergic agonists (see Brown, D.A. *et al.*, *Nature* (1980), 283:673-676). The M-current is a non-inactivating, hyperpolarizing current known to act as a brake on neuronal hyperexcitability. Consequently, a decrease in the Kv7.2-mediated M-current, for example through genetic loss-of-function, can cause neuronal depolarization and an increase in membrane and neuronal excitability that can lead to action potential bursts that manifest as, *e.g.*, epileptic seizures. In contrast, an increase in the Kv7.2-mediated M-current can hyperpolarize the cell membrane and thereby reduce neuronal excitability and prevent the initiation and propagation of action potential bursts and the resultant seizures. Enhancing the open state of Kv7.2/Kv7.3 channels in neurons favors a hyperpolarized resting state, which reduces rapid action potential spiking (*i.e.*, burst firing). Such enhancement can provide a stabilizing effect on excitable, particularly hyper-excitable, neurons and can therefore be useful in treating certain seizure disorders. This enhancement has been clinically proven to be effective for treatment of seizure disorders, such as partial onset seizures in adults with epilepsy, with retigabine (ezogabine), a known Kv7.2/Kv7.3 potentiator.

[003] While significant advances have been made in this field, there remains a substantial need for improved compounds and methods for potentiating voltage-gated potassium channels, including the voltage-gated potassium channels Kv7.2/Kv7.3. Such compounds and methods can be used to treat diseases, disorders, and conditions in which potassium channel dysfunction is implicated.

SUMMARY

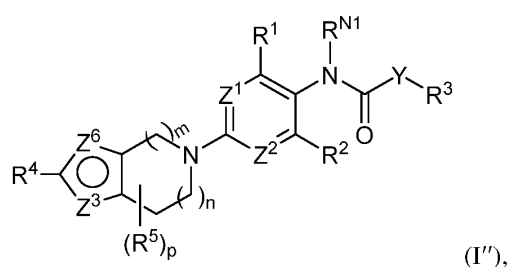
[004] Provided herein are compounds, including compounds of any of the formulae described herein (*e.g.*, Formula (I)), and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, hydrates, isotopically labeled derivatives, and prodrugs thereof. Compounds provided herein can act as potentiators of voltage-gated potassium channels (*e.g.*, Kv7 potassium channels such as Kv7.2/Kv7.3) and are therefore useful in the treatment and/or prevention of diseases, disorders, and conditions (*e.g.*, diseases, disorders, and conditions associated with Kv7 potassium channel dysfunction). Also provided herein are pharmaceutical compositions comprising the compounds provided herein, and kits comprising the same. Additionally, the disclosure provides methods of preparing the compounds and pharmaceutical compositions described herein, and intermediates useful thereto.

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



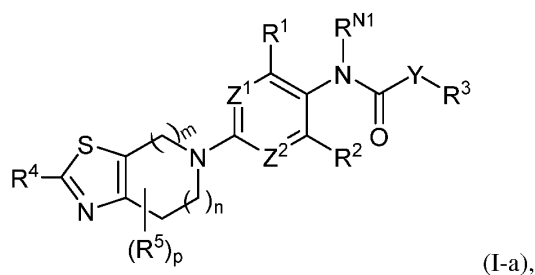
and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof, wherein X^1 , Z^1 , Z^2 , Z^3 , Z^4 , Z^5 , Z^6 , R^1 , R^2 , R^3 , R^5 , Y , R^{N1} , m , n , and p are as defined herein.

[006] In certain embodiments, the compound of Formula (I) is of Formula (I''):



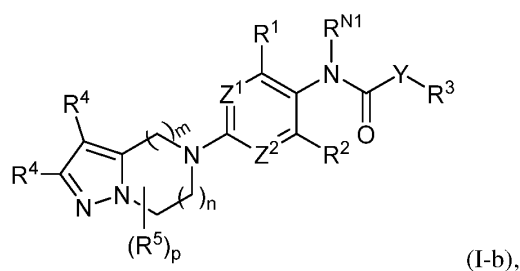
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof. In certain embodiments of Formula (I''), Z^3 is N and Z^6 is S. In certain embodiments of Formula (I''), Z^3 is S and Z^6 is N. In certain embodiments of Formula (I''), Z^3 is N and Z^6 is O. In certain embodiments of Formula (I''), Z^3 is O and Z^6 is N.

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



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



derivative, or prodrug thereof, or a pharmaceutical composition thereof.

- (d) Methods of potentiating a Kv7 potassium channel (*e.g.*, Kv7.2/Kv7.3) in a cell *in vitro* comprising contacting the cell with a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

[014] In another aspect, provided herein are compounds disclosed herein, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof, and pharmaceutical compositions thereof, for use in any of the methods provided herein. In another aspect, provided herein are compounds disclosed herein, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof, and pharmaceutical compositions thereof, for use as medicaments and/or in the preparation of medicaments.

[015] In another aspect, provided herein are kits comprising a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof. The kits described herein may include a single dose or multiple doses of the compound or pharmaceutical composition thereof. The kits described herein are useful in any method or use provided herein, and optionally further comprise instructions for using the kit (*e.g.*, instructions for using the compound or composition included in the kit).

[016] Also provided herein are methods of preparing compounds disclosed herein, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof, and pharmaceutical compositions thereof. Synthetic intermediates useful in the preparation of the compounds and compositions are also provided herein.

[017] The details of certain embodiments of the disclosure are set forth in the Detailed Description, as described below. Other embodiments of the disclosure will be apparent from the Definitions, Examples, Abstract, and Claims.

DEFINITIONS

Chemical Definitions

[018] 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 Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Michael B. Smith, *March's Advanced Organic Chemistry*, 7th Edition, John Wiley & Sons, Inc., New York, 2013; Richard C. Larock, *Comprehensive Organic Transformations*, John Wiley & Sons, Inc., New York, 2018; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[019] 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 present disclosure additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[020] Unless otherwise provided, formulae and structures depicted herein include compounds that do not include isotopically enriched atoms, and also include compounds that include isotopically enriched atoms (“isotopically labeled derivatives”). 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 a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays. In certain embodiments, one or more hydrogen atoms of a compound are replaced by deuterium (“deuterated derivatives”).

[021] The term “isotopes” refers to variants of a particular chemical element such that, while all isotopes of a given element share the same number of protons in each atom of the element, those isotopes differ in the number of neutrons.

[022] When a range of values (“range”) is listed, it encompasses each value and sub-range within the range. A range is inclusive of the values at the two ends of the range unless otherwise provided. For example, “ C_{1-6} alkyl” encompasses, 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.

[023] Use of the phrase “at least one instance” refers to 1, 2, 3, 4, or more instances, but also encompasses a range, *e.g.*, for example, from 1 to 4, from 1 to 3, from 1 to 2, from 2 to 4, from 2 to 3, or from 3 to 4 instances, inclusive.

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

[025] The term “alkyl” refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms (“ C_{1-20} alkyl”). In some embodiments, an alkyl group has 1 to 12 carbon atoms (“ C_{1-12} alkyl”). In some embodiments, an alkyl group has 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

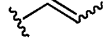
alkyl group has 1 to 3 carbon atoms (“C₁₋₃ alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“C₁₋₂ alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“C₁ alkyl”). In some embodiments, an alkyl group has 2 to 6 carbon atoms (“C₂₋₆ alkyl”). Examples of C₁₋₆ alkyl groups include methyl (C₁), ethyl (C₂), propyl (C₃) (*e.g.*, *n*-propyl, isopropyl), butyl (C₄) (*e.g.*, *n*-butyl, *tert*-butyl, *sec*-butyl, isobutyl), pentyl (C₅) (*e.g.*, *n*-pentyl, 3-pentanyl, amyl, neopentyl, 3-methyl-2-butanyl, *tert*-amyl), and hexyl (C₆) (*e.g.*, *n*-hexyl). Additional examples of alkyl groups include *n*-heptyl (C₇), *n*-octyl (C₈), *n*-dodecyl (C₁₂), 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 C₁₋₁₂ alkyl (such as unsubstituted C₁₋₆ alkyl, *e.g.*, –CH₃ (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 or *s*-Bu), unsubstituted isobutyl (*i*-Bu)). In certain embodiments, the alkyl group is a substituted C₁₋₁₂ alkyl (such as substituted C₁₋₆ alkyl, *e.g.*, –CH₂F, –CHF₂, –CF₃, –CH₂CH₂F, –CH₂CHF₂, –CH₂CF₃, or benzyl (Bn)).

[026] 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. “Perhaloalkyl” is a subset of haloalkyl and refers to an alkyl group wherein all 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 20 carbon atoms (“C₁₋₂₀ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 10 carbon atoms (“C₁₋₁₀ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 9 carbon atoms (“C₁₋₉ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms (“C₁₋₈ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 7 carbon atoms (“C₁₋₇ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms (“C₁₋₆ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 5 carbon atoms (“C₁₋₅ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms (“C₁₋₄ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms (“C₁₋₃ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms (“C₁₋₂ haloalkyl”). In some embodiments, all of the haloalkyl hydrogen atoms are independently replaced with fluoro to provide a “perfluoroalkyl” group. In some embodiments, all of the haloalkyl hydrogen atoms are independently replaced with chloro to provide a “perchloroalkyl” group. Examples of haloalkyl groups include –CHF₂, –CH₂F, –CF₃, –CH₂CF₃, –CF₂CF₃, –CF₂CF₂CF₃, –CCl₃, –CFCl₂, –CF₂Cl, and the like.

[027] 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, sulfur, silicon, boron, and phosphorous within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, the heteroalkyl group is an alkyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, and sulfur within (*e.g.*, 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 (“C₁₋₂₀ heteroalkyl”). In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 12 carbon atoms and 1 or more heteroatoms within the parent chain (“C₁₋₁₂ heteroalkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 11 carbon atoms and 1 or more heteroatoms within the parent chain (“C₁₋₁₁ heteroalkyl”). 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 (“C₁₋₁₀ heteroalkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain (“C₁₋₉ heteroalkyl”). 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 (“C₁₋₈ heteroalkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain (“C₁₋₇ heteroalkyl”). 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 (“C₁₋₆ heteroalkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms within the parent chain (“C₁₋₅ heteroalkyl”). 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 (“C₁₋₄ heteroalkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain (“C₁₋₃ heteroalkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain (“C₁₋₂ heteroalkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom (“C₁ heteroalkyl”). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms within the parent chain (“C₂₋₆ heteroalkyl”). 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.

[028] The term “alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 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 20 carbon atoms (“C₂₋₂₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 12 carbon atoms (“C₂₋₁₂ alkenyl”). In some embodiments, an alkenyl group has 2 to 11 carbon atoms (“C₂₋₁₁ alkenyl”). In some embodiments, an alkenyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 9 carbon atoms (“C₂₋₉ alkenyl”). In some embodiments, an alkenyl group has 2 to 8 carbon atoms (“C₂₋₈ alkenyl”). In some embodiments, an alkenyl group has 2 to 7 carbon atoms (“C₂₋₇ alkenyl”). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C₂₋₆ alkenyl”). In some embodiments, an alkenyl group has 2 to 5 carbon atoms (“C₂₋₅ alkenyl”). In some embodiments, an alkenyl group has 2 to 4 carbon atoms (“C₂₋₄ alkenyl”). In some embodiments, an alkenyl group has 2 to 3 carbon atoms (“C₂₋₃ alkenyl”). In some embodiments, an alkenyl group has 2 carbon atom (“C₂ 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 C₂₋₄ alkenyl

groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Additional examples of alkenyl include heptenyl (C₇), octenyl (C₈), octatrienyl (C₈), 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 an alkenyl group, a C=C double bond for which the stereochemistry is not specified (*e.g.*, $-\text{CH}=\text{CHCH}_3$ or ) may be in the (*E*)- or (*Z*)-configuration.

[029] 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, sulfur, silicon, boron, and phosphorous within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, the heteroalkenyl group is an alkenyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, and sulfur within (*e.g.*, 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 20 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“C₂₋₂₀ heteroalkenyl”). In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 12 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“C₂₋₁₂ heteroalkenyl”). In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 11 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“C₂₋₁₁ heteroalkenyl”). 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 (“C₂₋₁₀ heteroalkenyl”). 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 (“C₂₋₉ heteroalkenyl”). 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 (“C₂₋₈ heteroalkenyl”). 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 (“C₂₋₇ heteroalkenyl”). 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 (“C₂₋₆ heteroalkenyl”). 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 (“C₂₋₅ heteroalkenyl”). 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 (“C₂₋₄ heteroalkenyl”). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain (“C₂₋₃ heteroalkenyl”). In some embodiments, a heteroalkenyl group has 2 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain (“C₂ heteroalkenyl”). 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 (“C₂₋₆ heteroalkenyl”). 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.

[030] The term “alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) (“C₂₋₂₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 9 carbon atoms (“C₂₋₉ alkynyl”). In some embodiments, an alkynyl group has 2 to 8 carbon atoms (“C₂₋₈ alkynyl”). In some embodiments, an alkynyl group has 2 to 7 carbon atoms (“C₂₋₇ alkynyl”). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ alkynyl”). In some embodiments, an alkynyl group has 2 to 5 carbon atoms (“C₂₋₅ alkynyl”). In some embodiments, an alkynyl group has 2 to 4 carbon atoms (“C₂₋₄ alkynyl”). In some embodiments, an alkynyl group has 2 to 3 carbon atoms (“C₂₋₃ alkynyl”). In some embodiments, an alkynyl group has 2 carbon atoms (“C₂ alkynyl”). The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of C₂₋₄ alkynyl groups include, without limitation, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkynyl groups as well as pentynyl (C₅), hexynyl (C₆), and the like. Additional examples of alkynyl include heptynyl (C₇), octynyl (C₈), 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.

[031] 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, sulfur, silicon, boron, and phosphorous within (*e.g.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, the heteroalkynyl group is an alkynyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, and sulfur within (*e.g.*, 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 20 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“C₂₋₂₀ heteroalkynyl”). 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 (“C₂₋₁₀ heteroalkynyl”). 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 (“C₂₋₉ heteroalkynyl”). 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 (“C₂₋₈ heteroalkynyl”). 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 (“C₂₋₇ heteroalkynyl”). 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 (“C₂₋₆ heteroalkynyl”). 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 (“C₂₋₅ heteroalkynyl”). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain (“C₂₋₄ heteroalkynyl”). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the

parent chain (“C₂₋₃ heteroalkynyl”). In some embodiments, a heteroalkynyl group has 2 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain (“C₂ heteroalkynyl”). 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 (“C₁₋₆ heteroalkynyl”). 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.

[032] The term “carbocyclyl” or “carbocyclic” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms (“C₃₋₁₄ carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 14 ring carbon atoms (“C₃₋₁₄ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 13 ring carbon atoms (“C₃₋₁₃ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 12 ring carbon atoms (“C₃₋₁₂ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 11 ring carbon atoms (“C₃₋₁₁ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms (“C₃₋₇ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms (“C₄₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms (“C₅₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups include the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like. Exemplary C₃₋₈ carbocyclyl groups include the aforementioned C₃₋₁₀ carbocyclyl groups as well as cycloundecyl (C₁₁), spiro[5.5]undecanyl (C₁₁), cyclododecyl (C₁₂), cyclododecenyl (C₁₂), cyclotridecane (C₁₃), cyclotetradecane (C₁₄), 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 includes 0, 1, or 2 C=C double bonds in the carbocyclic ring system, as valency permits.

[033] “Cycloalkyl” refers to a saturated carbocyclyl group. In some embodiments, a cycloalkyl group has from 3 to 14 ring carbon atoms (“C₃₋₁₄ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms (“C₃₋₁₀ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C₃₋₈ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 7 ring carbon atoms (“C₃₋₇ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms (“C₄₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C₅₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ cycloalkyl”). Examples of C₅₋₆ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃₋₆ cycloalkyl groups include the aforementioned C₅₋₆ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ cycloalkyl groups include the aforementioned C₃₋₆ cycloalkyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). 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.

[034] 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, sulfur, silicon, boron, and phosphorous (“3-14 membered heterocyclyl”). In certain embodiments, the heterocyclyl group is 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. The point of attachment can be either to a ring carbon atom or a ring heteroatom of the heterocyclyl group, as valency permits. For example, 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 is substituted or unsubstituted, 3- to 8-membered, monocyclic heterocyclyl, wherein 1, 2, or 3 atoms in the heterocyclic ring system are independently oxygen, nitrogen, or sulfur, as valency permits.

[035] 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.

[036] Exemplary 3-membered heterocyclyl groups containing 1 heteroatom include azirdinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing 1 heteroatom include azetidiny, oxetanyl, and thietanyl. Exemplary 5-membered heterocyclyl groups containing 1 heteroatom include tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include piperidinyl, tetrahydropyranly, dihydropyridiny, and thianly. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include piperazinyl, morpholinyl, dithianly, and dioxanly. Exemplary 6-membered heterocyclyl groups containing 3 heteroatoms include triazinyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include azepanly, oxepanly and thiepanly. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include azocanly, oxecanly and thiocanly. Exemplary bicyclic heterocyclyl groups include indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinoliny, tetrahydroisoquinoliny, decahydroquinoliny, decahydroisoquinoliny, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridiny, decahydro-1,8-naphthyridiny, octahydropyrrolo[3,2-b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanly, chromenyl, 1H-benzo[e][1,4]diazepiny, 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]pyranly, 5,7-dihydro-4H-thieno[2,3-c]pyranly, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridiny, 2,3-dihydrofuro[2,3-b]pyridiny, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridiny, 4,5,6,7-tetrahydrofuro[3,2-c]pyridiny, 4,5,6,7-tetrahydrothieno[3,2-b]pyridiny, 1,2,3,4-tetrahydro-1,6-naphthyridiny, and the like.

[037] 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 (“C₆₋₁₄ aryl”). In some embodiments, an aryl group has 6–10 ring carbon atoms (“C₆₋₁₀ aryl”). In some embodiments, an aryl

group has 6 ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has 10 ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms (“C₁₄ 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.

[038] 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, sulfur, silicon, boron, and phosphorous (“5-14 membered heteroaryl”). In certain embodiments, the heteroaryl group is 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. The point of attachment can be either to a ring carbon atom or a ring heteroatom of the heteroaryl group, as valency permits. For example, 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, *e.g.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl). In certain embodiments, the heteroaryl is substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur. In certain embodiments, the heteroaryl is substituted or unsubstituted, 9- or 10-membered, bicyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur.

[039] 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.

[040] Exemplary 5-membered heteroaryl groups containing 1 heteroatom include pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing 2 heteroatoms include imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing 3 heteroatoms include triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing 4 heteroatoms include tetrazolyl. Exemplary 6-membered heteroaryl groups containing 1 heteroatom include pyridinyl. Exemplary 6-membered heteroaryl groups containing 2 heteroatoms include pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing 3 or 4 heteroatoms include triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing 1 heteroatom include azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indoliziny, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, and phenazinyl.

[041] The term “acyl” refers to a group having the general formula $-C(=O)R^{aa}$, $-C(=O)OR^{aa}$, $-C(=O)-O-C(=O)R^{aa}$, $-C(=O)SR^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=S)R^{aa}$, $-C(=S)N(R^{bb})_2$, $-C(=S)S(R^{aa})$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})SR^{aa}$, and $-C(=NR^{bb})N(R^{bb})_2$, wherein R^{aa} and R^{bb} are as defined herein. Exemplary acyl groups include aldehydes ($-CHO$), carboxylic acids ($-CO_2H$), ketones, acyl halides, esters, amides, imines, carbonates, carbamates, and ureas.

[042] The term “halo” or “halogen” refers to fluorine (fluoro, $-F$), chlorine (chloro, $-Cl$), bromine (bromo, $-Br$), or iodine (iodo, $-I$).

[043] The term “silyl” refers to the group $-Si(R^{aa})_3$, wherein R^{aa} is as defined herein.

[044] 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 is 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, oxygen, and sulfur 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 embodiments described herein are not limited in any manner by the exemplary substituents described herein.

[045] Exemplary substituents (*e.g.*, carbon atom substituents) include halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_3\text{H}$, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{ON}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_3^+\text{X}^-$, $-\text{N}(\text{OR}^{\text{cc}})\text{R}^{\text{bb}}$, $-\text{SH}$, $-\text{SR}^{\text{aa}}$, $-\text{SSR}^{\text{cc}}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{H}$, $-\text{CHO}$, $-\text{C}(\text{OR}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{OR}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{OP}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{OR}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(\text{OR}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(\text{R}^{\text{cc}})_4$, $-\text{P}(\text{OR}^{\text{cc}})_4$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3^+\text{X}^-$, $-\text{OP}(\text{OR}^{\text{cc}})_2$, $-\text{OP}(\text{OR}^{\text{cc}})_3^+\text{X}^-$, $-\text{OP}(\text{R}^{\text{cc}})_4$, $-\text{OP}(\text{OR}^{\text{cc}})_4$, $-\text{B}(\text{R}^{\text{aa}})_2$, $-\text{B}(\text{OR}^{\text{cc}})_2$, $-\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}})$, C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-20} heteroalkyl, C_{2-20} heteroalkenyl, C_{2-20} heteroalkynyl, 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, and wherein X^- is a counterion;

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

wherein:

each instance of R^{aa} is, independently, selected from C_{1-20} alkyl, C_{1-20} perhaloalkyl, C_{2-20}

alkenyl, C₂₋₂₀ alkynyl, C₁₋₂₀ heteroalkyl, C₂₋₂₀ heteroalkenyl, C₂₋₂₀ heteroalkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ 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 of the 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, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{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, C₁₋₂₀ alkyl, C₁₋₂₀ perhaloalkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, C₁₋₂₀ heteroalkyl, C₂₋₂₀ heteroalkenyl, C₂₋₂₀ heteroalkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ 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;

each instance of R^{cc} is, independently, selected from hydrogen, C₁₋₂₀ alkyl, C₁₋₂₀ perhaloalkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, C₁₋₂₀ heteroalkyl, C₂₋₂₀ heteroalkenyl, C₂₋₂₀ heteroalkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ 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, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{ee}, -ON(R^{ff})₂, -N(R^{ff})₂, -N(R^{ff})₃X⁻, -N(OR^{ee})R^{ff}, -SH, -SR^{ee}, -SSR^{ee}, -C(=O)R^{ee}, -CO₂H, -CO₂R^{ee}, -OC(=O)R^{ee}, -OCO₂R^{ee}, -C(=O)N(R^{ff})₂, -OC(=O)N(R^{ff})₂, -NR^{ff}C(=O)R^{ee}, -NR^{ff}CO₂R^{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}SO₂R^{ee}, -SO₂N(R^{ff})₂, -SO₂R^{ee}, -SO₂OR^{ee}, -OSO₂R^{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, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ heteroalkyl, C₂₋₁₀ heteroalkenyl, C₂₋₁₀ heteroalkynyl, C₃₋₁₀ carbocyclyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl, and 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^{ee} groups, or two geminal R^{dd} substituents are joined to form =O or =S, and wherein X⁻ is a counterion;

each instance of R^{ee} is, independently, selected from C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ heteroalkyl, C₂₋₁₀ heteroalkenyl, C₂₋₁₀ heteroalkynyl, C₃₋₁₀ carbocyclyl, C₆₋₁₀ 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^{ss} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} heteroalkyl, C_{2-10} heteroalkenyl, C_{2-10} heteroalkynyl, 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^{ss} groups;

each instance of R^{ss} is, independently, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}$ alkyl, $-ON(C_{1-6} \text{ alkyl})_2$, $-N(C_{1-6} \text{ alkyl})_2$, $-N(C_{1-6} \text{ alkyl})_3^+X^-$, $-NH(C_{1-6} \text{ alkyl})_2^+X^-$, $-NH_2(C_{1-6} \text{ alkyl})^+X^-$, $-NH_3^+X^-$, $-N(OC_{1-6} \text{ alkyl})(C_{1-6} \text{ alkyl})$, $-N(OH)(C_{1-6} \text{ alkyl})$, $-NH(OH)$, $-SH$, $-SC_{1-6}$ alkyl, $-SS(C_{1-6} \text{ alkyl})$, $-C(=O)(C_{1-6} \text{ alkyl})$, $-CO_2H$, $-CO_2(C_{1-6} \text{ alkyl})$, $-OC(=O)(C_{1-6} \text{ alkyl})$, $-OCO_2(C_{1-6} \text{ alkyl})$, $-C(=O)NH_2$, $-C(=O)N(C_{1-6} \text{ alkyl})_2$, $-OC(=O)NH(C_{1-6} \text{ alkyl})$, $-NHC(=O)(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})C(=O)(C_{1-6} \text{ alkyl})$, $-NHCO_2(C_{1-6} \text{ alkyl})$, $-NHC(=O)N(C_{1-6} \text{ alkyl})_2$, $-NHC(=O)NH(C_{1-6} \text{ alkyl})$, $-NHC(=O)NH_2$, $-C(=NH)O(C_{1-6} \text{ alkyl})$, $-OC(=NH)(C_{1-6} \text{ alkyl})$, $-OC(=NH)OC_{1-6}$ alkyl, $-C(=NH)N(C_{1-6} \text{ alkyl})_2$, $-C(=NH)NH(C_{1-6} \text{ alkyl})$, $-C(=NH)NH_2$, $-OC(=NH)N(C_{1-6} \text{ alkyl})_2$, $-OC(NH)NH(C_{1-6} \text{ alkyl})$, $-OC(NH)NH_2$, $-NHC(NH)N(C_{1-6} \text{ alkyl})_2$, $-NHC(=NH)NH_2$, $-NHSO_2(C_{1-6} \text{ alkyl})$, $-SO_2N(C_{1-6} \text{ alkyl})_2$, $-SO_2NH(C_{1-6} \text{ alkyl})$, $-SO_2NH_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2OC_{1-6}$ alkyl, $-OSO_2C_{1-6}$ alkyl, $-SOC_{1-6}$ alkyl, $-Si(C_{1-6} \text{ alkyl})_3$, $-OSi(C_{1-6} \text{ alkyl})_3$, $-C(=S)N(C_{1-6} \text{ alkyl})_2$, $C(=S)NH(C_{1-6} \text{ alkyl})$, $C(=S)NH_2$, $-C(=O)S(C_{1-6} \text{ alkyl})$, $-C(=S)SC_{1-6}$ alkyl, $-SC(=S)SC_{1-6}$ alkyl, $-P(=O)(OC_{1-6} \text{ alkyl})_2$, $-P(=O)(C_{1-6} \text{ alkyl})_2$, $-OP(=O)(C_{1-6} \text{ alkyl})_2$, $-OP(=O)(OC_{1-6} \text{ alkyl})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} heteroalkyl, C_{2-10} heteroalkenyl, C_{2-10} heteroalkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, or 5-10 membered heteroaryl; or two geminal R^{ss} substituents can be joined to form $=O$ or $=S$; and each X^- is a counterion.

[046] In certain embodiments, the molecular weight of a substituent (*e.g.*, carbon atom substituent) is lower than 250, lower than 200, lower than 150, lower than 100, or lower than 50 g/mol. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, nitrogen, and/or silicon atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, iodine, oxygen, sulfur, and/or nitrogen atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, chlorine, bromine, and/or iodine atoms. In certain embodiments, a substituent consists of carbon, hydrogen, fluorine, and/or chlorine atoms.

[047] In certain embodiments, exemplary substituents (*e.g.*, carbon atom substituents) include halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{aa}$, $-N(R^{bb})_2$, $-N(R^{bb})_3^+X^-$, $-SH$, $-SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2H$, $-CHO$, $-CO_2R^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-OC(=O)N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-NR^{bb}SO_2R^{aa}$, $-SO_2N(R^{bb})_2$, $-SO_2R^{aa}$, $-SO_2OR^{aa}$, $-OSO_2R^{aa}$,

$-\text{S}(=\text{O})\text{R}^{\text{aa}}, -\text{OS}(=\text{O})\text{R}^{\text{aa}}, -\text{Si}(\text{R}^{\text{aa}})_3, -\text{OSi}(\text{R}^{\text{aa}})_3, -\text{P}(=\text{O})(\text{R}^{\text{aa}})_2, -\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2, -\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2,$
 $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2, -\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2, -\text{OP}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2, -\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{R}^{\text{aa}})_2, -\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2,$
 $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2, -\text{B}(\text{R}^{\text{aa}})_2, -\text{B}(\text{OR}^{\text{cc}})_2, -\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}}), \text{C}_{1-10} \text{ alkyl}, \text{C}_{1-10} \text{ perhaloalkyl}, \text{C}_{2-10} \text{ alkenyl},$
 $\text{C}_{2-10} \text{ alkynyl}, \text{C}_{1-10} \text{ heteroalkyl}, \text{C}_{2-10} \text{ heteroalkenyl}, \text{C}_{2-10} \text{ heteroalkynyl}, \text{C}_{3-10} \text{ carbocyclyl}, 3\text{-}14 \text{ membered}$
 $\text{heterocyclyl}, \text{C}_{6-14} \text{ aryl}, \text{ and } 5\text{-}14 \text{ membered heteroaryl}, \text{ wherein } \text{X}^- \text{ is a counterion};$

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

each instance of R^{aa} is, independently, selected from $\text{C}_{1-10} \text{ alkyl}, \text{C}_{1-10} \text{ perhaloalkyl}, \text{C}_{2-10} \text{ alkenyl},$
 $\text{C}_{2-10} \text{ alkynyl}, \text{C}_{1-10} \text{ heteroalkyl}, \text{C}_{2-10} \text{ heteroalkenyl}, \text{C}_{2-10} \text{ heteroalkynyl}, \text{C}_{3-10} \text{ carbocyclyl}, 3\text{-}14 \text{ membered}$
 $\text{heterocyclyl}, \text{C}_{6-14} \text{ aryl}, \text{ and } 5\text{-}14 \text{ membered heteroaryl}, \text{ or two } \text{R}^{\text{aa}} \text{ groups are joined to form a } 3\text{-}14$
 $\text{membered heterocyclyl or } 5\text{-}14 \text{ membered heteroaryl ring};$

each instance of R^{bb} is, independently, selected from hydrogen, $-\text{OH}, -\text{OR}^{\text{aa}}, -\text{N}(\text{R}^{\text{cc}})_2, -\text{CN},$
 $-\text{C}(=\text{O})\text{R}^{\text{aa}}, -\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2, -\text{CO}_2\text{R}^{\text{aa}}, -\text{SO}_2\text{R}^{\text{aa}}, -\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}, -\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2, -\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2,$
 $-\text{SO}_2\text{R}^{\text{cc}}, -\text{SO}_2\text{OR}^{\text{cc}}, -\text{SOR}^{\text{aa}}, -\text{P}(=\text{O})(\text{R}^{\text{aa}})_2, -\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2, -\text{P}(=\text{O})(\text{N}(\text{R}^{\text{cc}})_2)_2, \text{C}_{1-10} \text{ alkyl}, \text{C}_{1-10}$
 $\text{perhaloalkyl}, \text{C}_{2-10} \text{ alkenyl}, \text{C}_{2-10} \text{ alkynyl}, \text{C}_{1-10} \text{ heteroalkyl}, \text{C}_{2-10} \text{ heteroalkenyl}, \text{C}_{2-10} \text{ heteroalkynyl}, \text{C}_{3-10}$
 $\text{carbocyclyl}, 3\text{-}14 \text{ membered heterocyclyl}, \text{C}_{6-14} \text{ aryl}, \text{ and } 5\text{-}14 \text{ membered heteroaryl}, \text{ or two } \text{R}^{\text{bb}} \text{ groups}$
 $\text{are joined to form a } 3\text{-}14 \text{ membered heterocyclyl or } 5\text{-}14 \text{ membered heteroaryl ring}; \text{ and}$

each instance of R^{cc} is, independently, selected from hydrogen, $\text{C}_{1-10} \text{ alkyl}, \text{C}_{1-10} \text{ perhaloalkyl}, \text{C}_{2-10}$
 $\text{alkenyl}, \text{C}_{2-10} \text{ alkynyl}, \text{C}_{1-10} \text{ heteroalkyl}, \text{C}_{2-10} \text{ heteroalkenyl}, \text{C}_{2-10} \text{ heteroalkynyl}, \text{C}_{3-10} \text{ carbocyclyl}, 3\text{-}14$
 $\text{membered heterocyclyl}, \text{C}_{6-14} \text{ aryl}, \text{ and } 5\text{-}14 \text{ membered heteroaryl}, \text{ or two } \text{R}^{\text{cc}} \text{ groups are joined to form a}$
 $3\text{-}14 \text{ membered heterocyclyl or } 5\text{-}14 \text{ membered heteroaryl ring}.$

[048] In certain embodiments, each carbon atom substituent is independently halogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted $\text{C}_{1-6} \text{ alkyl}, -\text{OR}^{\text{aa}}, -\text{SR}^{\text{aa}}, -\text{N}(\text{R}^{\text{bb}})_2, -\text{CN}, -\text{NO}_2,$
 $-\text{C}(=\text{O})\text{R}^{\text{aa}}, -\text{CO}_2\text{R}^{\text{aa}}, -\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2, -\text{OC}(=\text{O})\text{R}^{\text{aa}}, -\text{OCO}_2\text{R}^{\text{aa}}, -\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2, -\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}},$
 $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}, \text{ or } -\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2.$ In certain embodiments, each carbon atom substituent is
independently halogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-10}
 $\text{alkyl}, -\text{OR}^{\text{aa}}, -\text{SR}^{\text{aa}}, -\text{N}(\text{R}^{\text{bb}})_2, -\text{CN}, -\text{NO}_2, -\text{C}(=\text{O})\text{R}^{\text{aa}}, -\text{CO}_2\text{R}^{\text{aa}}, -\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2, -\text{OC}(=\text{O})\text{R}^{\text{aa}},$
 $-\text{OCO}_2\text{R}^{\text{aa}}, -\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2, -\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}, -\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}, \text{ or } -\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2,$ wherein R^{aa} is
hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted $\text{C}_{1-6} \text{ alkyl},$ an oxygen
protecting group (*e.g.*, silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl,
pivaloyl, or benzoyl) when attached to an oxygen atom, or a sulfur protecting group (*e.g.*,
acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfonyl, 2-pyridine-sulfonyl, or triphenylmethyl) when
attached to a sulfur atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one
or more halogen) or unsubstituted $\text{C}_{1-6} \text{ alkyl},$ or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc,
trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, each carbon atom substituent is
independently halogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C_{1-6}
 $\text{alkyl}, -\text{OR}^{\text{aa}}, -\text{SR}^{\text{aa}}, -\text{N}(\text{R}^{\text{bb}})_2, -\text{CN}, \text{ or } -\text{NO}_2.$ In certain embodiments, each carbon atom substituent is
independently halogen, substituted (*e.g.*, substituted with one or more halogen moieties) or unsubstituted

C₁₋₆ alkyl, -OR^{aa}, -SR^{aa}, -N(R^{bb})₂, -CN, -SCN, or -NO₂, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, an oxygen protecting group (*e.g.*, silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl) when attached to an oxygen atom, or a sulfur protecting group (*e.g.*, acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₁₀ alkyl, or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[049] In certain embodiments, each nitrogen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, -C(=O)R^{aa}, -CO₂R^{aa}, -C(=O)N(R^{bb})₂, or a nitrogen protecting group. In certain embodiments, each nitrogen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, -C(=O)R^{aa}, -CO₂R^{aa}, -C(=O)N(R^{bb})₂, or a nitrogen protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, or an oxygen protecting group when attached to an oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, or a nitrogen protecting group. In certain embodiments, each nitrogen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl or a nitrogen protecting group.

[050] 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 -OH, -OR^{aa}, -N(R^{cc})₂, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{cc})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, C₁₋₁₀ alkyl (*e.g.*, aralkyl, heteroaralkyl), C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, C₁₋₂₀ heteroalkyl, C₂₋₂₀ heteroalkenyl, C₂₋₂₀ heteroalkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ 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.

[051] For example, in certain embodiments, at least one nitrogen protecting group is an amide group (*e.g.*, a moiety that includes the nitrogen atom to which the nitrogen protecting groups (*e.g.*, -C(=O)R^{aa}) is directly attached). In certain such embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivatives, benzamide, *p*-phenylbenzamide, *o*-nitrophenylacetamide, *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 derivatives, *o*-nitrobenzamide, and *o*-(benzoyloxymethyl)benzamide.

[052] In certain embodiments, at least one nitrogen protecting group is a carbamate group (*e.g.*, a moiety that includes the nitrogen atom to which the nitrogen protecting groups (*e.g.*, $-\text{C}(=\text{O})\text{OR}^{\text{aa}}$) is directly attached). In certain such embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluorenylmethyl 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-biphenyl)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, alkylthio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitrobenzyl 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.

[053] In certain embodiments, at least one nitrogen protecting group is a sulfonamide group (*e.g.*, a moiety that includes the nitrogen atom to which the nitrogen protecting groups (*e.g.*, $-S(=O)_2R^{aa}$) is directly attached). In certain such embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of *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), benzyisulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[054] In certain embodiments, each nitrogen protecting group, together with the nitrogen atom to which the nitrogen protecting group is attached, is independently selected from the group consisting of phenothiazinyl-(10)-acyl derivatives, *N'*-*p*-toluenesulfonylaminoacyl derivatives, *N'*-phenylaminothioacyl derivatives, *N*-benzoylphenylalanyl derivatives, *N*-acetylmethionine derivatives, 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-pyroloin-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*-*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 derivatives, *N*-diphenylborinic acid derivatives, *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 some embodiments, two instances of a nitrogen protecting group together with the nitrogen atoms to which the nitrogen protecting

groups are attached are *N,N'*-isopropylidenediamine.

[055] In certain embodiments, a nitrogen protecting group is benzyl (Bn), *tert*-butoxycarbonyl (BOC), carbobenzyloxy (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), trifluoroacetyl, triphenylmethyl, acetyl (Ac), benzoyl (Bz), *p*-methoxybenzyl (PMB), 3,4-dimethoxybenzyl (DMPM), *p*-methoxyphenyl (PMP), 2,2,2-trichloroethoxycarbonyl (Troc), triphenylmethyl (Tr), tosyl (Ts), brosyl (Bs), nosyl (Ns), mesyl (Ms), triflyl (Tf), or dansyl (Ds).

[056] In certain embodiments, at least one nitrogen protecting group is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[057] In certain embodiments, each oxygen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or an oxygen protecting group. In certain embodiments, each oxygen atom substituents is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, or an oxygen protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, or an oxygen protecting group when attached to an oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, or a nitrogen protecting group. In certain embodiments, each oxygen atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl or an oxygen protecting group.

[058] 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 $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, 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.

[059] In certain embodiments, each oxygen protecting group, together with the oxygen atom to which the oxygen protecting group is attached, is selected from the group consisting of methoxy, methoxymethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (*p*-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenylloxymethyl (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 (PMB), 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 -naphthylidiphenylmethyl, *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, 4,4'-Dimethoxy-3'''-[N-(imidazolylmethyl)]trityl Ether (IDTr-OR), 4,4'-Dimethoxy-3'''-[N-(imidazolylethyl)carbonyl]trityl Ether (IETr-OR), 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), dimethylhexylsilyl, *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, adamantate, 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-naphthyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl carbonate (MTMEC-OR), 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-butenate, *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).

[060] In certain embodiments, an oxygen protecting group is silyl. In certain embodiments, an oxygen protecting group is *t*-butyldiphenylsilyl (TBDPS), *t*-butyldimethylsilyl (TBDMS), triisopropylsilyl (TIPS), triphenylsilyl (TPS), triethylsilyl (TES), trimethylsilyl (TMS), triisopropylsiloxyethyl (TOM), acetyl (Ac), benzoyl (Bz), allyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-trimethylsilylethyl carbonate, methoxymethyl (MOM), 1-ethoxyethyl (EE), 2-methoxy-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).

[061] In certain embodiments, at least one oxygen protecting group is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl.

[062] In certain embodiments, each sulfur atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, or a sulfur protecting group. In certain embodiments, each sulfur atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, or a sulfur protecting group, wherein R^{aa} is hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, or an oxygen protecting group when attached to an oxygen atom; and each R^{bb} is independently hydrogen, substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl, or a nitrogen protecting group. In certain embodiments, each sulfur atom substituent is independently substituted (*e.g.*, substituted with one or more halogen) or unsubstituted C₁₋₆ alkyl or a sulfur protecting group.

[063] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a “thiol protecting group”). In some embodiments, each sulfur protecting group is selected from the group consisting of $-\text{R}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(\text{OR}^{\text{cc}})_2$, $-\text{P}(\text{OR}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, and $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, 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.

[064] In certain embodiments, a sulfur protecting group is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl.

[065] 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 (*e.g.*, including one formal negative charge). An anionic counterion may also be multivalent (*e.g.*, including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (*e.g.*, F⁻, Cl⁻, Br⁻, I⁻), NO₃⁻, ClO₄⁻, OH⁻, H₂PO₄⁻, HCO₃⁻, HSO₄⁻, sulfonate ions (*e.g.*, methanesulfonate, 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), BF₄⁻, PF₄⁻, PF₆⁻, AsF₆⁻, SbF₆⁻, B[3,5-(CF₃)₂C₆H₃]₄⁻, B(C₆F₅)₄⁻, BPh₄⁻, Al(OC(CF₃)₃)₄⁻, and carborane anions (*e.g.*, CB₁₁H₁₂⁻ or (HCB₁₁Me₅Br₆)⁻). Exemplary counterions which may be multivalent include CO₃²⁻, HPO₄²⁻, PO₄³⁻, B₄O₇²⁻, SO₄²⁻, S₂O₃²⁻, 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.

[066] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and Claims. The embodiments provided herein are not limited in any manner by the above exemplary listing of substituents.

Other Definitions

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

[068] As used herein, the term “salt” refers to any and all salts and encompasses pharmaceutically acceptable salts. Salts include ionic compounds that result from the neutralization reaction of an acid and a base. A salt is composed of one or more cations (positively charged ions) and one or more anions (negative ions) so that the salt is electrically neutral (without a net charge). Salts of the compounds of the present disclosure include those derived from inorganic and organic acids and bases. Examples of 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 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, hippurate, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further salts include ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[069] 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 lower 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 the present 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 $N^+(C_{1-4} \text{ alkyl})_4^-$ 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.

[070] 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”.

[071] “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.”

[072] 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 be 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.

[073] The term “solvate” refers to forms of a compound, including salts 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, ethanولات, and methanولات.

[074] The term “hydrate” refers to a solvate wherein the compound is associated with water. 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 $R \times x H_2O$, 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 ($R \times 0.5 H_2O$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \times 2 H_2O$) and hexahydrates ($R \times 6 H_2O$)).

[075] The term “prodrugs” refers to compounds that have cleavable groups and become by solvolysis or under physiological conditions the compounds described herein, which are pharmaceutically active *in vivo*. See, *e.g.*, Bundgard, H., *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985. Prodrugs include acid derivatives 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. 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 subject.

[076] Throughout the present disclosure, references to “the compound” and “a compound” provided herein are intended to encompass the compound or group of compounds, and also pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof. Isotopically labeled derivatives are also included.

[077] The terms “composition” and “formulation” are used interchangeably.

[078] 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, disorder, or condition.

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

[080] The terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, 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. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[081] The term “prevent,” “preventing,” or “prevention” refers to a prophylactic treatment of a subject who is not and was not with a disease but is at risk of developing the disease or who was with a disease, is not with the disease, but is at risk of regression of the disease. In certain embodiments, the subject is at a higher risk of developing the disease or at a higher risk of regression of the disease than an average healthy member of a population.

[082] The terms “condition,” “disease,” and “disorder” are used interchangeably.

[083] 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, severity of side effects, disease, or disorder, the identity, pharmacokinetics, and pharmacodynamics of the particular compound, the condition being treated, the mode, route, and desired or required frequency of administration, the species, age and health or general condition 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. In certain embodiments, an effective amount is an amount sufficient for potentiating a Kv7 potassium channel (*e.g.*, in a subject or in a cell *in vitro*).

[084] 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 treating a disease, disorder, or condition (*e.g.*, a disease, disorder, or condition associated with Kv7 potassium channel dysfunction) in a subject. In certain embodiments, a therapeutically effective amount is an amount sufficient for potentiating a Kv7 potassium channel in a subject.

[085] A “prophylactically effective amount” of a compound described herein is an amount sufficient to prevent a condition, or one or more 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 preventing a disease, disorder, or condition (*e.g.*, a disease, disorder, or condition associated with Kv7 potassium channel dysfunction) in a subject. In certain embodiments, a prophylactically effective amount is an amount sufficient for potentiating a Kv7 potassium channel in a subject.

[086] “Voltage-gated potassium channels” (VGKCs) are transmembrane channels specific for potassium and sensitive to voltage changes in a cell’s membrane potential. During action potentials, they play an important role in returning the depolarized cell to a resting state. In VGKCs, alpha subunits form the actual conductance pore. Based on sequence homology of the hydrophobic transmembrane cores, the alpha subunits of voltage-gated potassium channels are grouped into 12 families (Kv1-12), of which Kv7 is one family. The Kv7 family of voltage-gated potassium channels consists of five members (Kv7.1-7.5) which are encoded for by the *KCNQ1-5* genes, respectively. Of the five, Kv7.2/Kv7.3 is the active heterotetramer that is the main active Kv7 current in neurons (M-current). A Kv7 potassium channel can be a member selected from Kv7.1, Kv7.2, Kv7.3, Kv7.4, and/or Kv7.5.

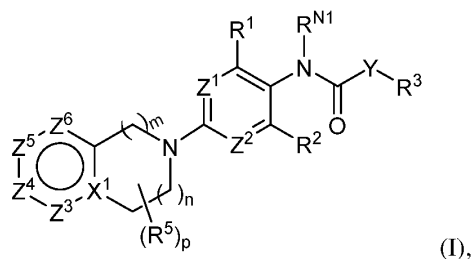
[087] “Potassium channel potentiator” and “potassium channel opener” are used interchangeably and refer to an agent that restores, enhances, or increases the activity of a potassium channel (*e.g.*, voltage-gated potassium channel, *e.g.*, Kv7 potassium channel), for example, by facilitating ion transmission through the potassium channel. “Potentiating,” “potentiation,” and the like, for the purposes of this disclosure, refer to restoring, enhancing, or increasing the activity or effect of a potassium channel.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[088] Provided herein are compounds, including compounds of any of the formulae described herein (*e.g.*, Formula (I)), and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, hydrates, isotopically labeled derivatives, and prodrugs thereof. Compounds provided herein can act as potentiators of voltage-gated potassium channels (*e.g.*, Kv7 potassium channels such as Kv7.2/Kv7.3) and can therefore be used in the treatment and/or prevention of diseases, disorders, and conditions (*e.g.*, diseases, disorders, and conditions associated with Kv7 potassium channel dysfunction). Also provided herein are pharmaceutical compositions comprising the compounds provided herein, and kits comprising the same. Additionally, the disclosure provides methods of preparing the compounds and pharmaceutical compositions described herein, and intermediates useful thereto.

Compounds

[089] Provided herein are compounds of Formula (I):



and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof, wherein:

X^1 is C or N;

Z^3 , Z^4 , and Z^6 are each independently CR⁴, N, NR^N, S, or O;

Z^5 is a bond, CR⁴, N, NR^N, S, or O;

provided that least one of Z^3 , Z^4 , Z^5 , and Z^6 is N, NR^N, S, or O, and no more than one of Z^3 , Z^4 , Z^5 , and Z^6 is S or O;

R^1 and R^2 are each independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, -SR^S, -S(=O)₂R^{S1}, or C₁₋₆ acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

R^3 is C₁₋₈ alkyl, C₃₋₁₀ cycloalkyl, 3-7 membered heterocyclyl, or -(CR'R'')_w-Ar¹, wherein the alkyl, cycloalkyl, or heterocyclyl is optionally substituted; w is 0, 1, or 2; Ar¹ is C₆₋₁₀ aryl or 5-10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted;

Y is a bond, -CR'R''-, -O-, or -NR^Y-;

R^Y is H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or a nitrogen protecting group, or R^Y and R³ are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein the alkyl, cycloalkyl, acyl, or heterocyclyl is optionally substituted;

Z^1 and Z^2 are each independently CR^Z or N;

each instance of R^Z is independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C₁₋₆ acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R⁴ is independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C₁₋₆ acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R⁵ is independently halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, -CN, -OR^O, -N(R^N)₂, or C₁₋₆ acyl, or two R⁵ attached to the same carbon atom are joined together with the intervening atoms to form C₃₋₇ cycloalkyl or 3-7 membered heterocyclyl, or two R⁵ attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl, is independently optionally substituted;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

m is 1 or 2;

n is 0, 1, or 2;

each instance of R' is independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3-7 membered heterocyclyl, each instance of R'' is independently H, halogen, C₁₋₆ alkyl, -OR^O, or -N(R^N)₂, or R' and R'' attached to the same carbon atom are joined together with the intervening atoms to form C₃₋₇ cycloalkyl or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted, or R' and R'' attached to the same carbon atom are taken together to form =O;

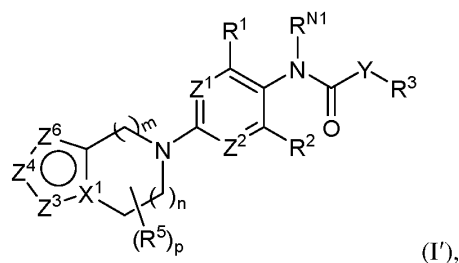
each instance of R^{N1} and R^N is independently H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ acyl, or a nitrogen protecting group, or two R^N attached to the same nitrogen atom are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, acyl, or heterocyclyl is independently optionally substituted;

each instance of R^O is independently H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₁₋₆ acyl, or an oxygen protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted;

each instance of R^S is independently H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₁₋₆ acyl, or a sulfur protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted; and

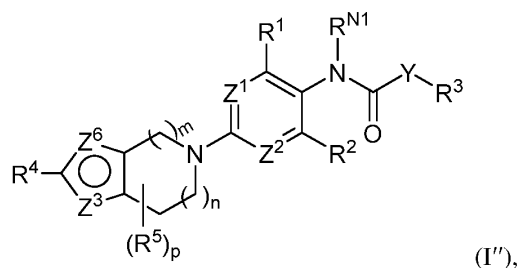
each instance of R^{S1} is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted.

[090] In certain embodiments, the compound of Formula (I) is of Formula (I'):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[091] In certain embodiments, the compound of Formula (I) is of Formula (I''):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or

prodrug thereof. In certain embodiments of Formula (I''):

Z^3 is N and Z^6 is S;

Z^3 is S and Z^6 is N;

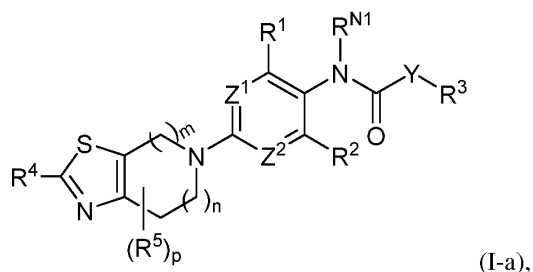
Z^3 is N and Z^6 is O; or

Z^3 is O and Z^6 is N.

[092] In certain embodiments of Formula (I''), Z^3 is N and Z^6 is S, or Z^3 is S and Z^6 is N. In certain embodiments of Formula (I''), Z^3 is N and Z^6 is S. In certain embodiments of Formula (I''), Z^3 is S and Z^6 is N.

[093] In certain embodiments of Formula (I''), Z^3 is N and Z^6 is O, or Z^3 is O and Z^6 is N. In certain embodiments of Formula (I''), Z^3 is N and Z^6 is O. In certain embodiments of Formula (I''), Z^3 is O and Z^6 is N.

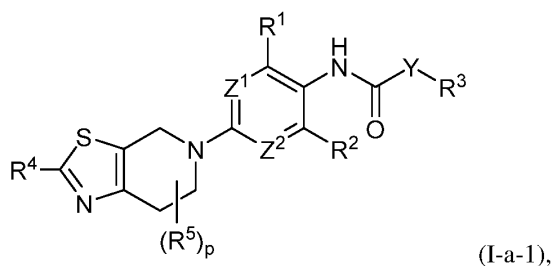
[094] In certain embodiments, the compound of Formula (I) is of Formula (I-a):



(I-a),

or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

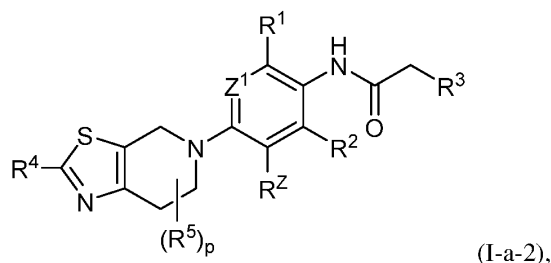
[095] In certain embodiments, the compound of Formula (I) is of Formula (I-a-1):



(I-a-1),

or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

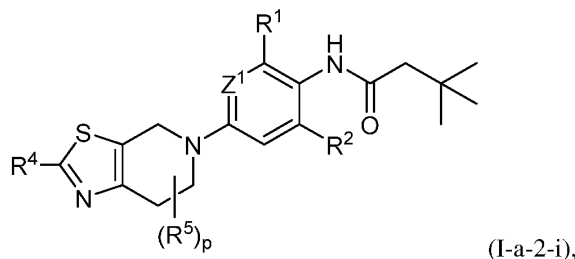
[096] In certain embodiments, the compound of Formula (I) is of Formula (I-a-2):



(I-a-2),

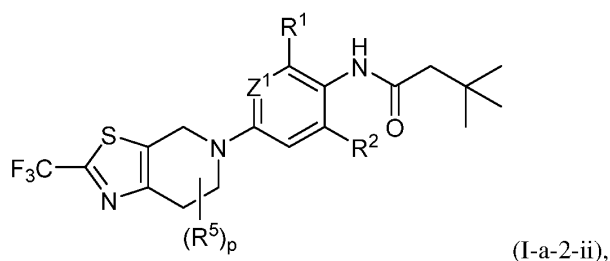
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof. In certain embodiments, Z^1 is CR^Z . In certain embodiments, Z^1 is CH. In certain embodiments, Z^1 is N. In certain embodiments, R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, R^1 and R^2 are methyl. In certain embodiments, R^1 is halogen and R^2 is unsubstituted C_{1-3} alkyl. In certain embodiments, R^1 is F and R^2 is methyl. In certain embodiments, R^2 is halogen and R^1 is unsubstituted C_{1-3} alkyl. In certain embodiments, R^2 is F and R^1 is methyl. In certain embodiments, R^1 is unsubstituted C_{3-6} cycloalkyl and R^2 is unsubstituted C_{1-3} alkyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are methyl. In certain embodiments, Z^1 is N, R^1 is halogen, and R^2 is unsubstituted C_{1-3} alkyl. In certain embodiments, Z^1 is N, R^1 is F, and R^2 is methyl. In certain embodiments, Z^1 is CH, R^1 is unsubstituted C_{1-3} alkyl, and R^2 is halogen. In certain embodiments, Z^1 is CH, R^1 is methyl, and R^2 is F. In certain embodiments, Z^1 is N, R^1 is unsubstituted C_{3-6} cycloalkyl, and R^2 is unsubstituted C_{1-3} alkyl. In certain embodiments, Z^1 is N, R^1 is cyclopropyl, and R^2 is methyl.

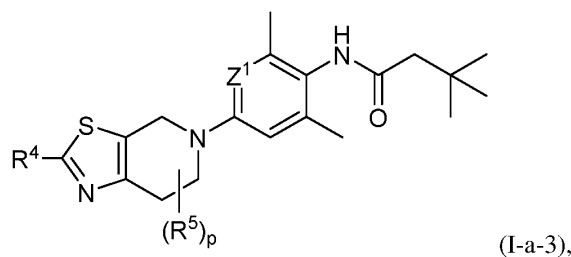
[098] In certain embodiments, the compound of Formula (I) is of Formula (I-a-2-ii):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof. In certain embodiments, Z^1 is CR^Z . In certain embodiments, Z^1 is CH. In certain embodiments, Z^1 is N. In certain embodiments, R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, R^1 and R^2 are methyl. In certain embodiments, R^1 is halogen and R^2 is unsubstituted C_{1-3} alkyl. In certain embodiments, R^1 is F and R^2 is methyl. In certain embodiments, R^2 is halogen and R^1 is unsubstituted C_{1-3} alkyl. In certain embodiments, R^2 is F and R^1 is methyl. In certain embodiments, R^1 is unsubstituted C_{3-6} cycloalkyl and R^2 is unsubstituted C_{1-3} alkyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are methyl. In certain embodiments, Z^1 is N, R^1 is halogen, and R^2

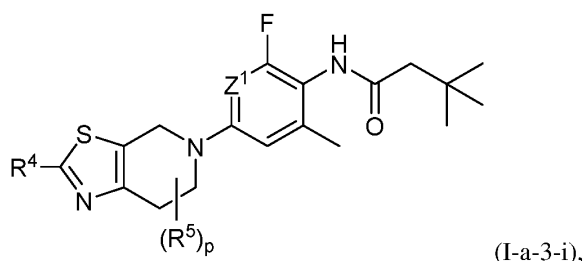
is unsubstituted C₁₋₃ alkyl. In certain embodiments, Z¹ is N, R¹ is F, and R² is methyl. In certain embodiments, Z¹ is CH, R¹ is unsubstituted C₁₋₃ alkyl, and R² is halogen. In certain embodiments, Z¹ is CH, R¹ is methyl, and R² is F. In certain embodiments, Z¹ is N, R¹ is unsubstituted C₃₋₆ cycloalkyl, and R² is unsubstituted C₁₋₃ alkyl. In certain embodiments, Z¹ is N, R¹ is cyclopropyl, and R² is methyl.

[099] In certain embodiments, the compound of Formula (I) is of Formula (I-a-3):



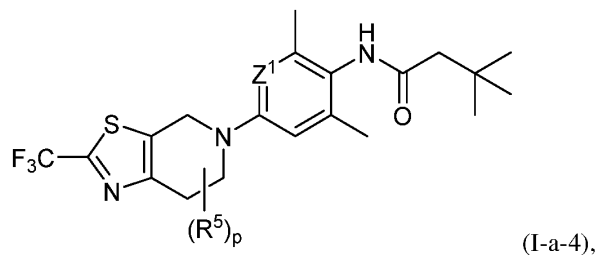
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[100] In certain embodiments, the compound of Formula (I) is of Formula (I-a-3-i):



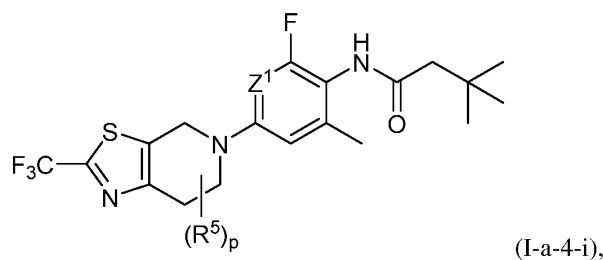
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[101] In certain embodiments, the compound of Formula (I) is of Formula (I-a-4):



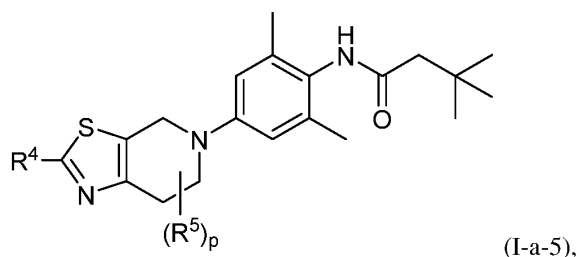
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[102] In certain embodiments, the compound of Formula (I) is of Formula (I-a-4-i):



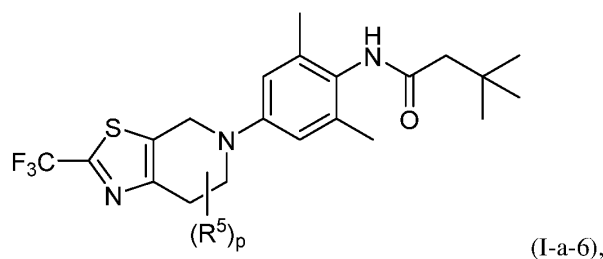
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[103] In certain embodiments, the compound of Formula (I) is of Formula (I-a-5):



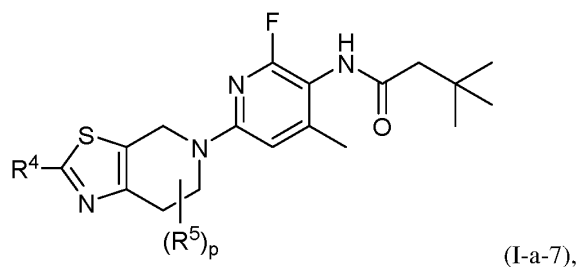
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[104] In certain embodiments, the compound of Formula (I) is of Formula (I-a-6):



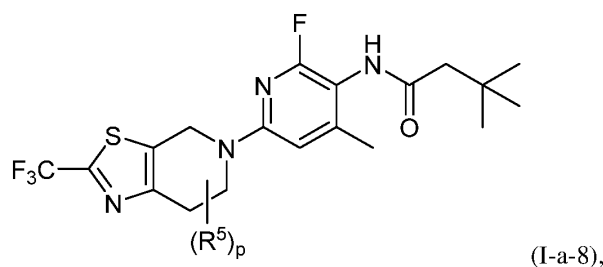
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[105] In certain embodiments, the compound of Formula (I) is of Formula (I-a-7):



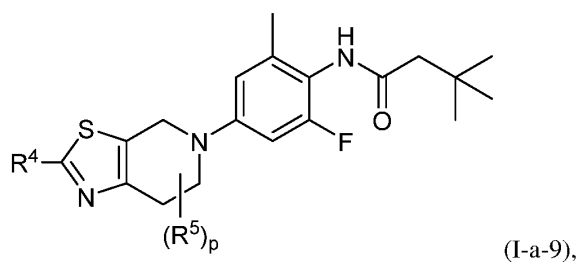
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[106] In certain embodiments, the compound of Formula (I) is of Formula (I-a-8):



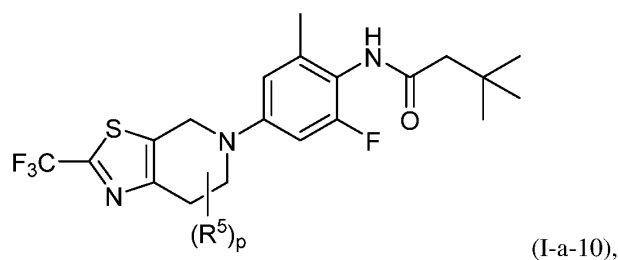
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[107] In certain embodiments, the compound of Formula (I) is of Formula (I-a-9):



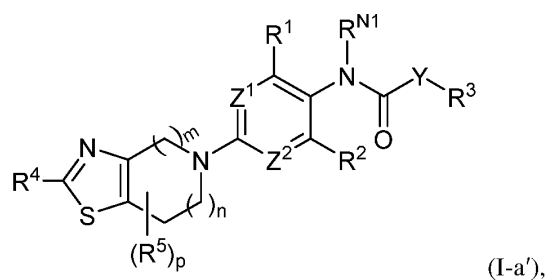
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[108] In certain embodiments, the compound of Formula (I) is of Formula (I-a-10):



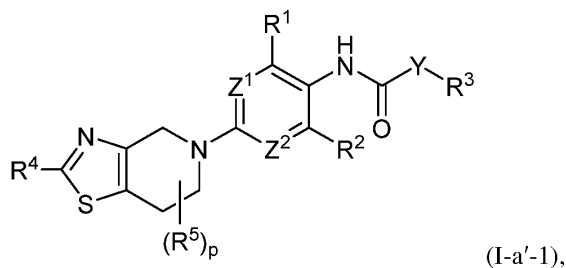
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



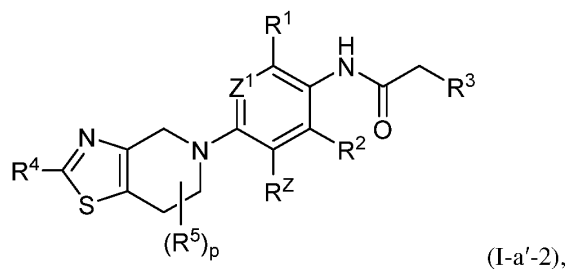
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[110] In certain embodiments, the compound of Formula (I) is of Formula (I-a'-1):



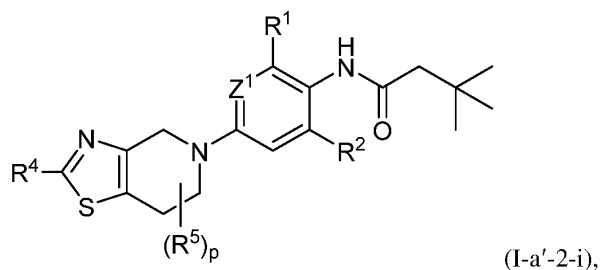
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[111] In certain embodiments, the compound of Formula (I) is of Formula (I-a'-2):



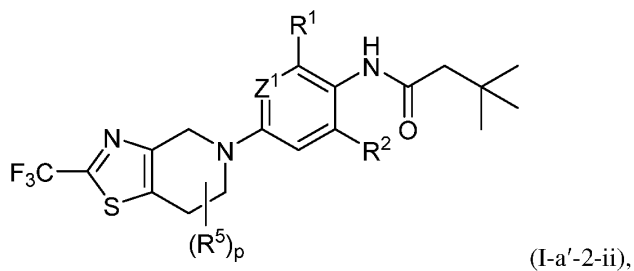
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[112] In certain embodiments, the compound of Formula (I) is of Formula (I-a'-2-i):



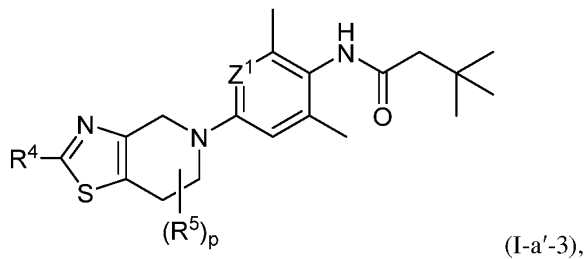
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[113] In certain embodiments, the compound of Formula (I) is of Formula (I-a'-2-ii):



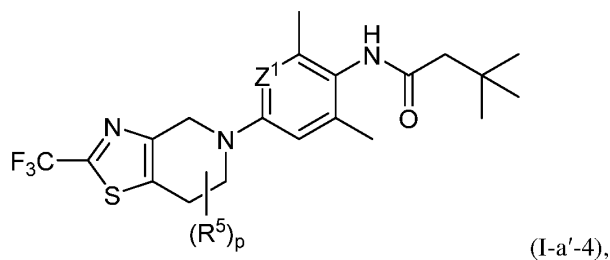
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[114] In certain embodiments, the compound of Formula (I) is of Formula (I-a'-3):



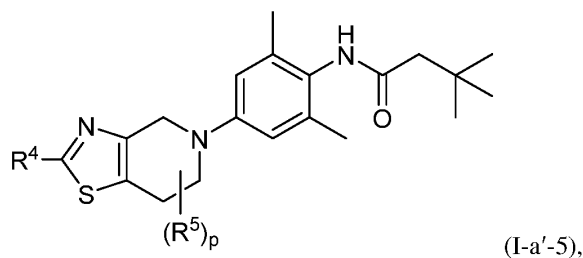
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[115] In certain embodiments, the compound of Formula (I) is of Formula (I-a'-4):



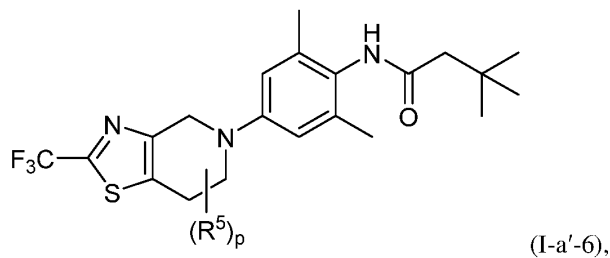
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[116] In certain embodiments, the compound of Formula (I) is of Formula (I-a'-5):



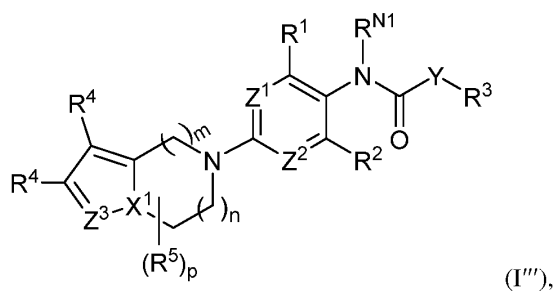
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[117] In certain embodiments, the compound of Formula (I) is of Formula (I-a'-6):



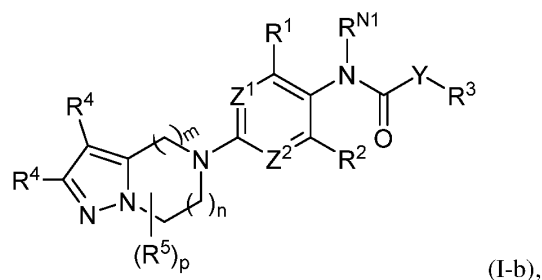
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[118] In certain embodiments, the compound of Formula (I) is of Formula (I'''):



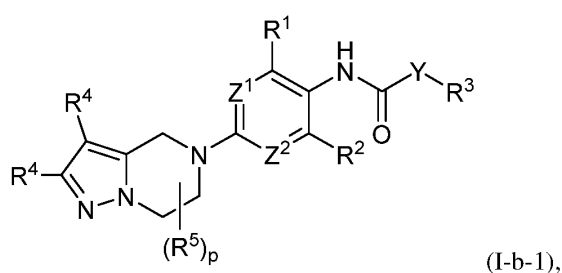
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



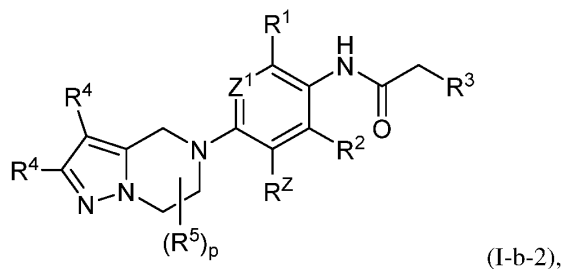
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



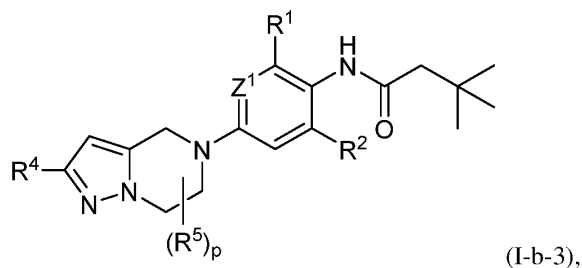
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

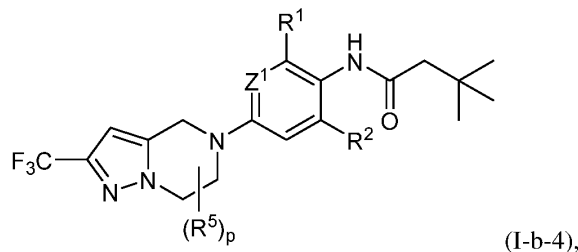
[122] In certain embodiments, the compound of Formula (I) is of Formula (I-b-3):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof. In certain embodiments, Z¹ is CR^Z. In certain embodiments, Z¹ is CH. In certain

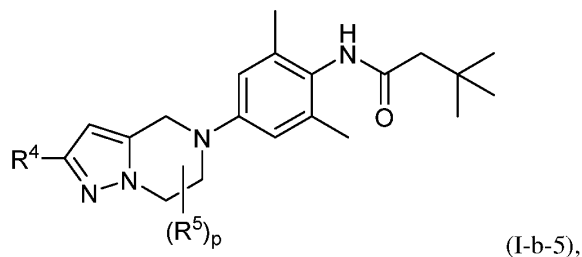
embodiments, R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, R^1 and R^2 are methyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are methyl.

[123] In certain embodiments, the compound of Formula (I) is of Formula (I-b-4):



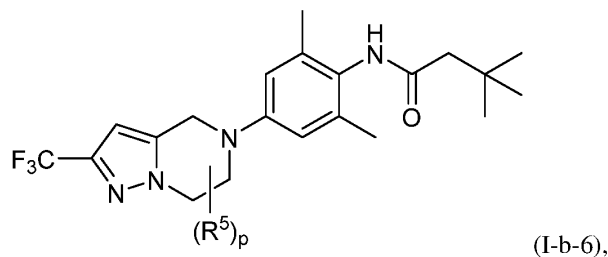
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof. In certain embodiments, Z^1 is CR^Z . In certain embodiments, Z^1 is CH. In certain embodiments, R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, R^1 and R^2 are methyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are methyl.

[124] In certain embodiments, the compound of Formula (I) is of Formula (I-b-5):



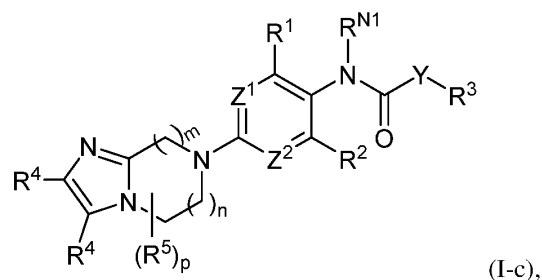
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[125] In certain embodiments, the compound of Formula (I) is of Formula (I-b-6):



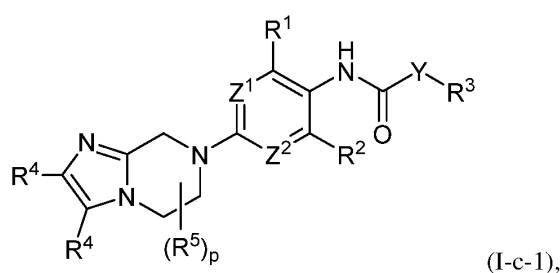
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



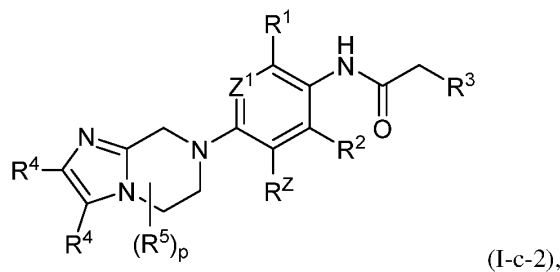
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



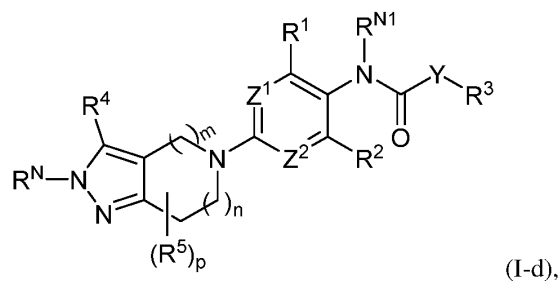
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



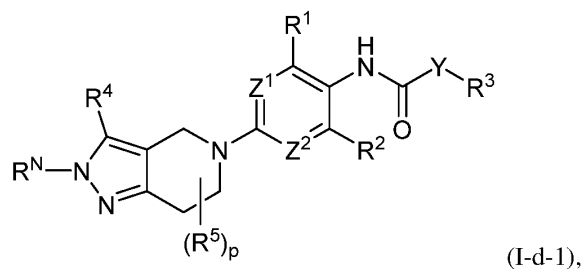
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



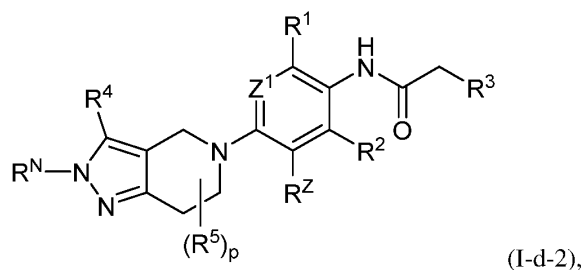
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



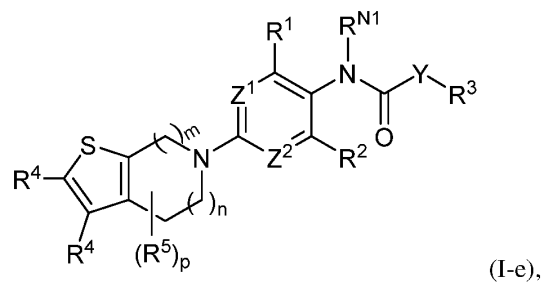
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



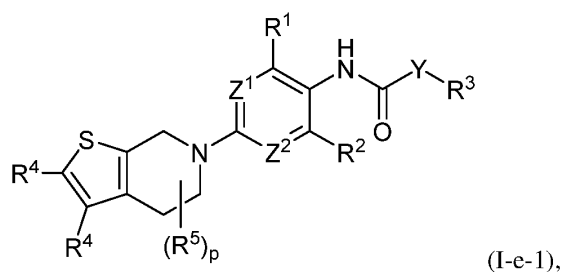
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



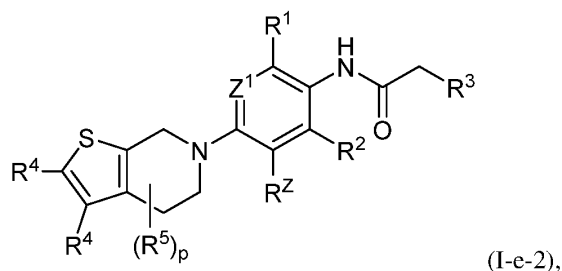
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



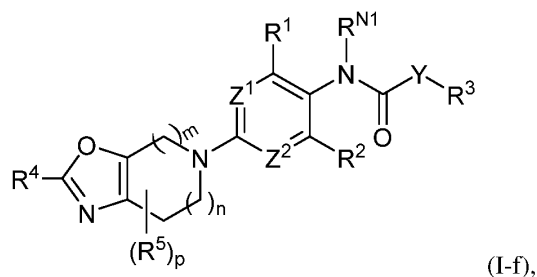
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



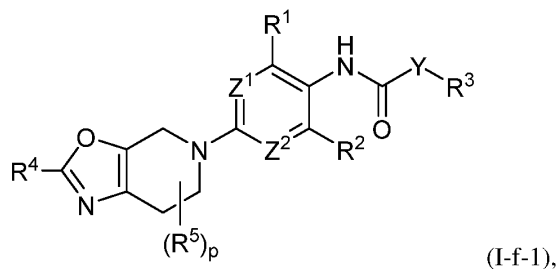
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



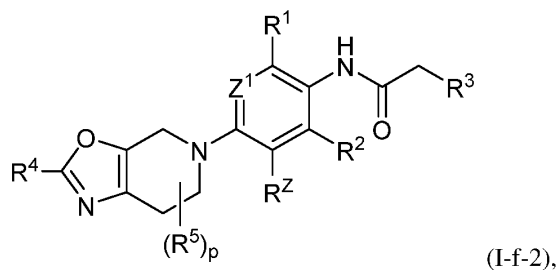
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



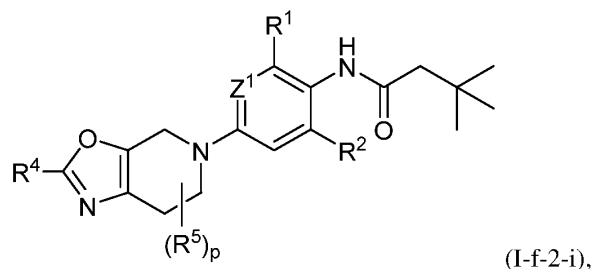
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



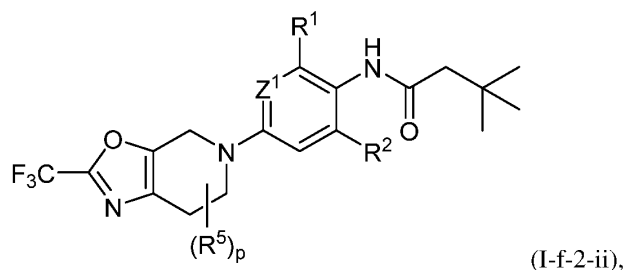
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



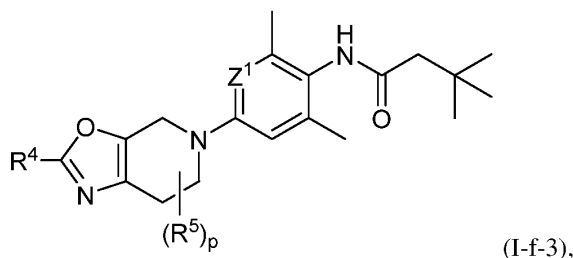
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof. In certain embodiments, Z^1 is CR^Z . In certain embodiments, Z^1 is CH. In certain embodiments, R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, R^1 and R^2 are methyl. In certain embodiments, R^1 and R^2 are independently halogen. In certain embodiments, R^1 is Cl and R^2 is F. In certain embodiments, Z^1 is CH, and R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are methyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are independently halogen. In certain embodiments, Z^1 is CH, R^1 is Cl, and R^2 is F.

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



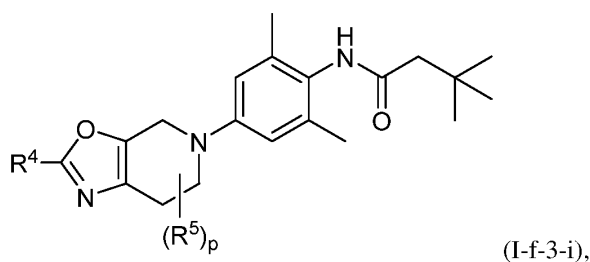
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof. In certain embodiments, Z^1 is CR^Z . In certain embodiments, Z^1 is CH. In certain embodiments, R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, R^1 and R^2 are methyl. In certain embodiments, R^1 and R^2 are independently halogen. In certain embodiments, R^1 is Cl and R^2 is F. In certain embodiments, Z^1 is CH, and R^1 and R^2 are independently unsubstituted C_{1-3} alkyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are methyl. In certain embodiments, Z^1 is CH, and R^1 and R^2 are independently halogen. In certain embodiments, Z^1 is CH, R^1 is Cl, and R^2 is F.

[140] In certain embodiments, the compound of Formula (I) is of Formula (I-f-3):



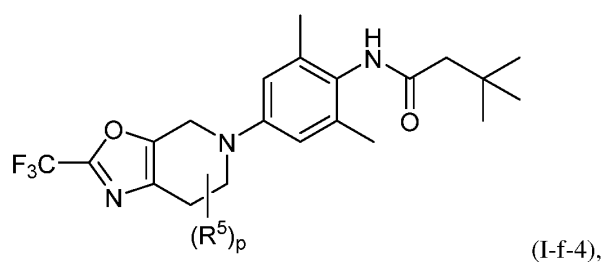
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[141] In certain embodiments, the compound of Formula (I) is of Formula (I-f-3-i):



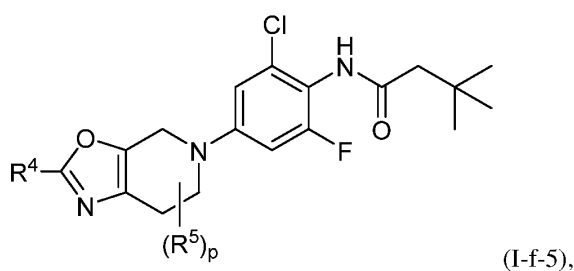
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[142] In certain embodiments, the compound of Formula (I) is of Formula (I-f-4):



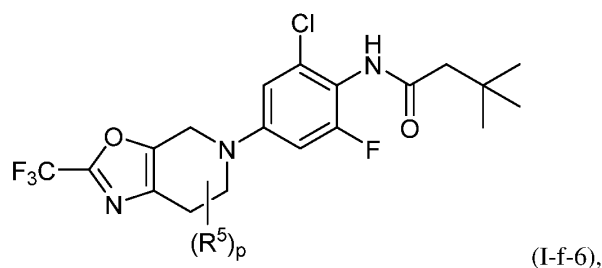
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[143] In certain embodiments, the compound of Formula (I) is of Formula (I-f-5):



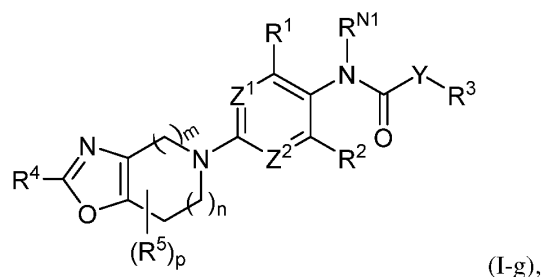
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[144] In certain embodiments, the compound of Formula (I) is of Formula (I-f-6):



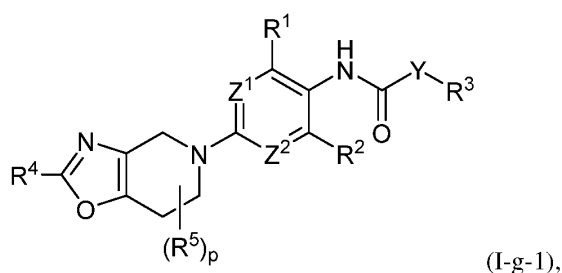
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



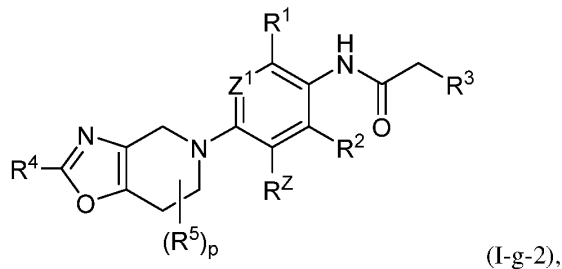
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



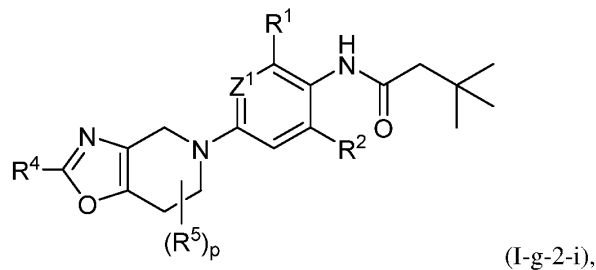
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



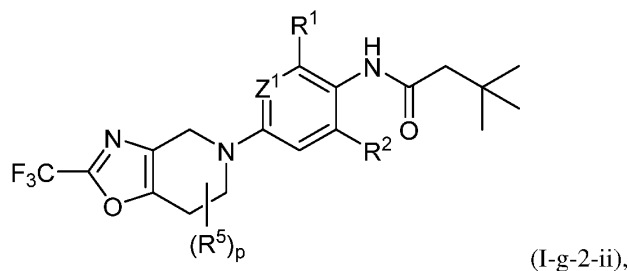
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



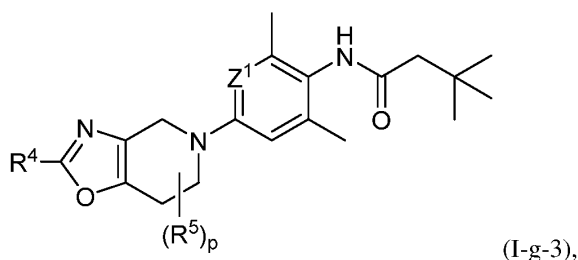
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

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



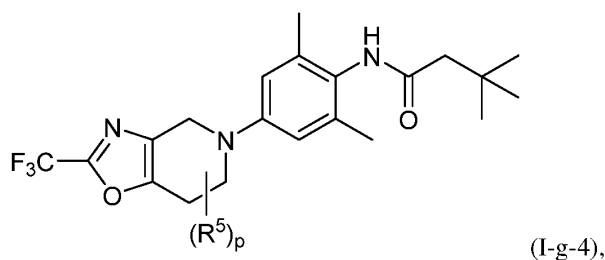
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[150] In certain embodiments, the compound of Formula (I) is of Formula (I-g-3):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[151] In certain embodiments, the compound of Formula (I) is of Formula (I-g-4):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

[152] In certain embodiments, a compound provided herein is a compound of Formula (I) or any subgenus or species thereof, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or solvate thereof. In certain embodiments, a compound provided herein is a compound of Formula (I) or any subgenus or species thereof, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof. In certain embodiments, a compound provided herein is a compound of Formula (I) or any subgenus or species thereof, or a pharmaceutically acceptable salt thereof. In certain embodiments, a compound provided herein is a compound of Formula (I) or any subgenus or species thereof, as a free base.

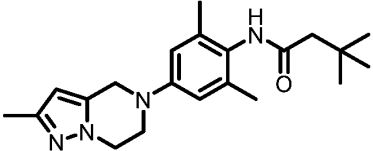
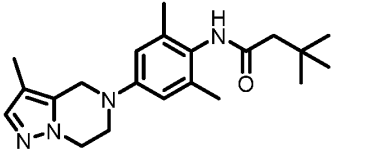
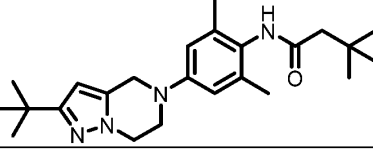
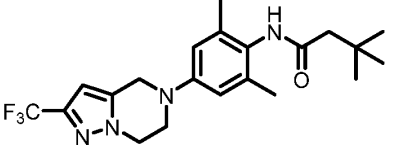
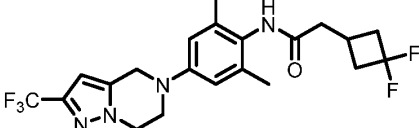
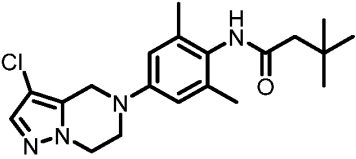
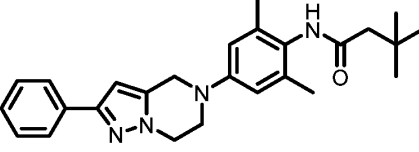
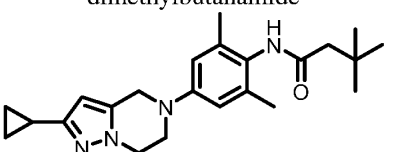
[153] In certain embodiments, a compound provided herein is an isotopically labeled derivative of a compound of Formula (I) or any subgenus or species thereof, or a pharmaceutically acceptable salt thereof. In certain embodiments, a compound provided herein is a deuterated

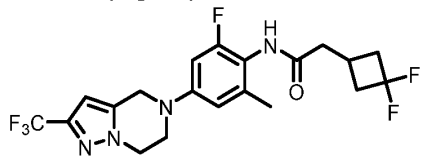
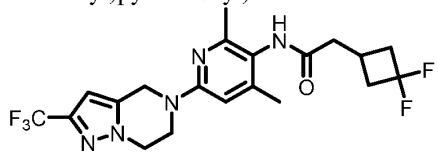
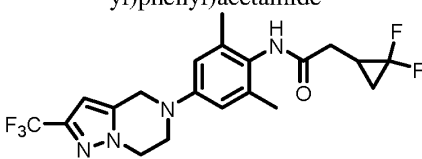
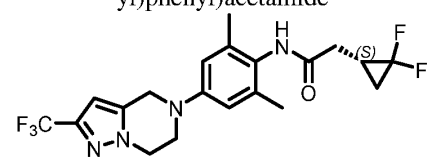
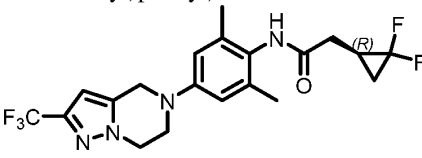
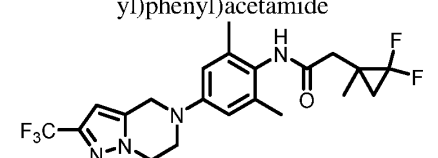
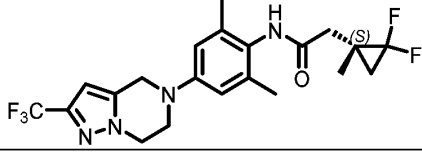
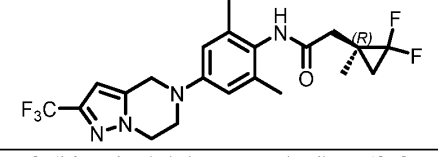
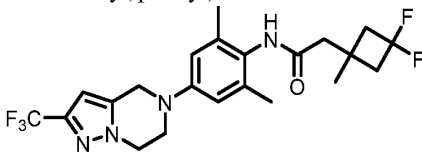
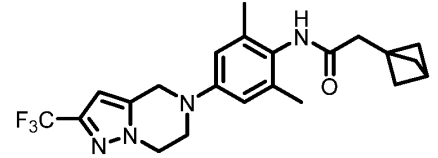
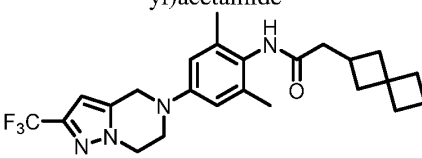
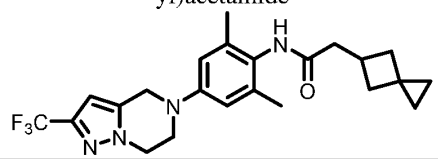
derivative of a compound of Formula (I) or any subgenus or species thereof, or a pharmaceutically acceptable salt thereof.

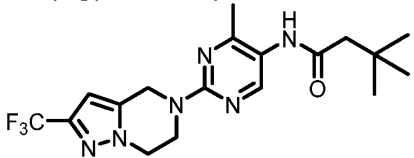
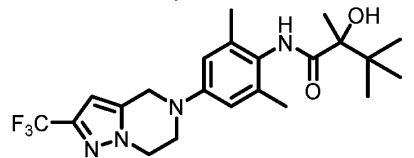
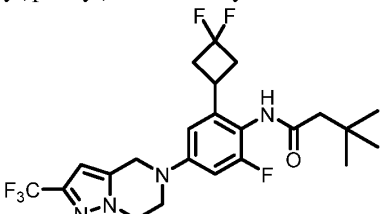
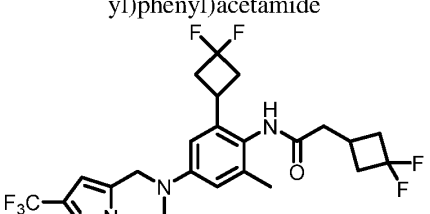
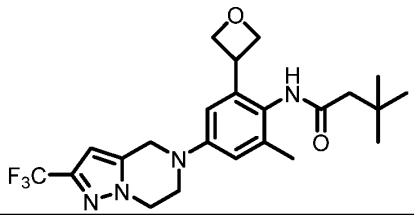
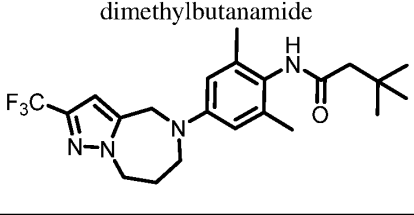
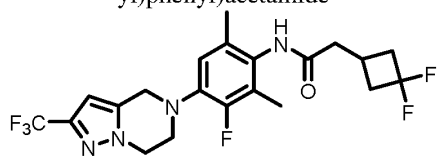
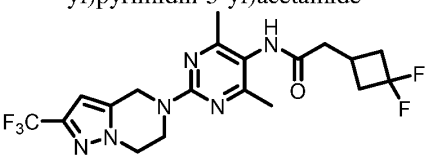
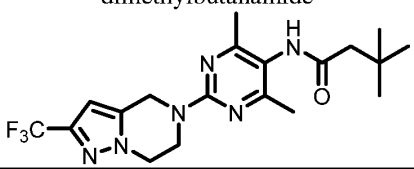
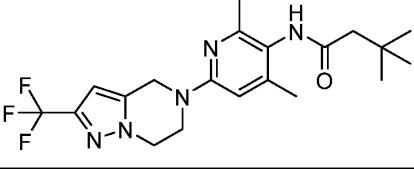
[154] In the various aspects and embodiments disclosed herein, express reference to a compound of Formula (I) is understood to alternatively refer to a compound of any disclosed subgenus or species thereof, for example, to a compound of any one of **Tables 1A-1C**.

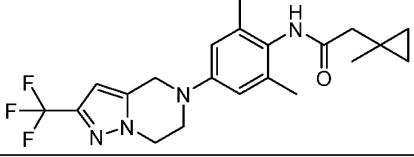
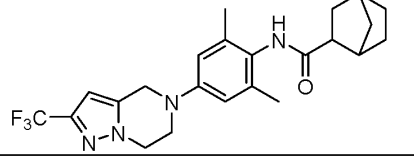
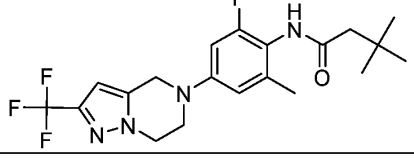
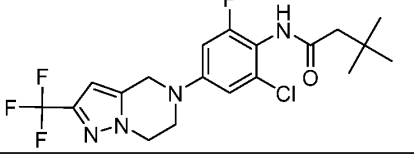
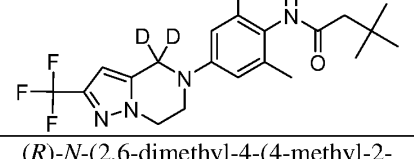
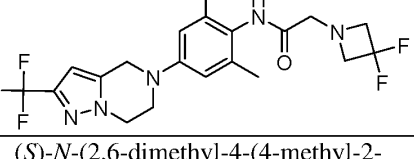
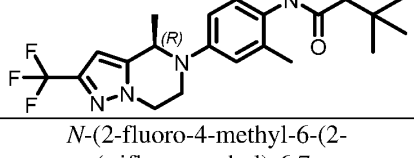
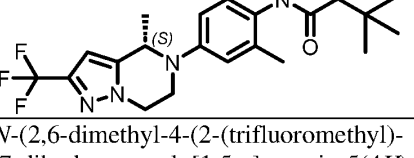
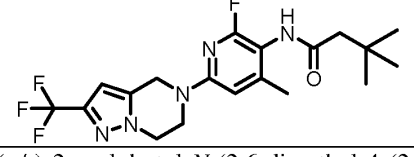
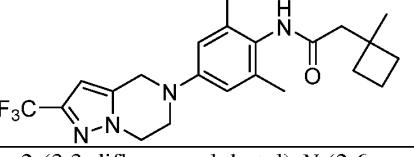
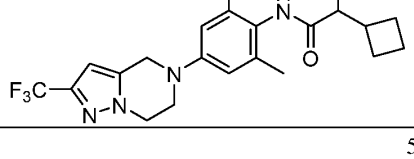
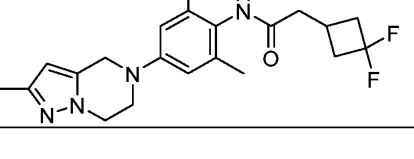
[155] In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1A**, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1A**, and pharmaceutically acceptable salts, stereoisomers, and tautomers thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1A**, and pharmaceutically acceptable salts thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1A** (in free base form).

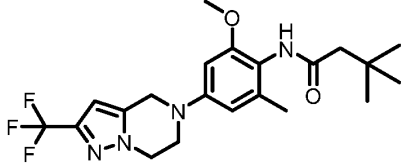
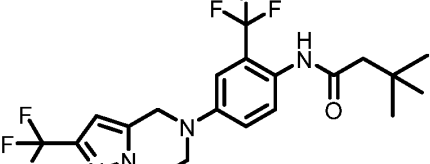
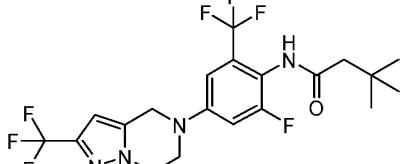
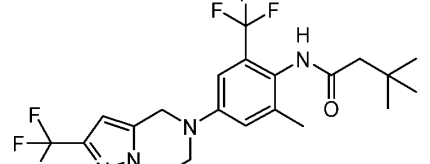
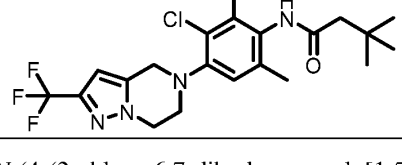
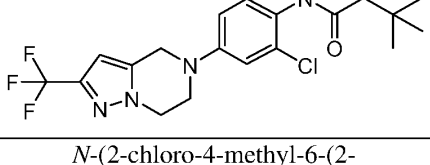
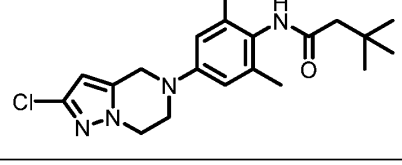
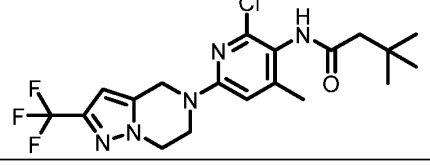
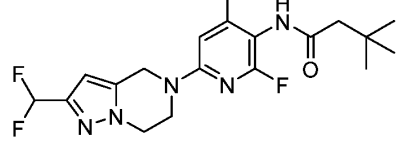
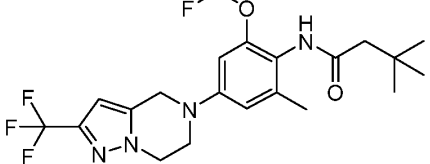
Table 1A

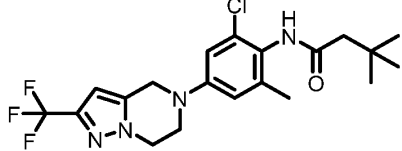
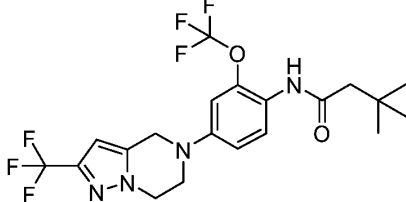
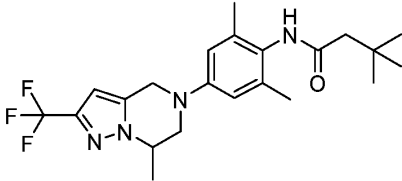
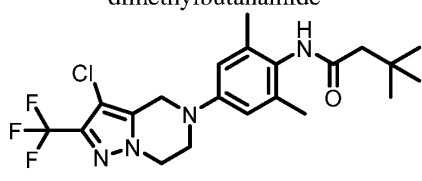
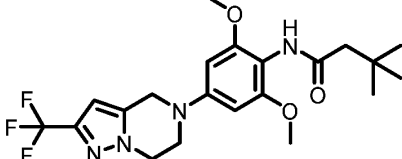
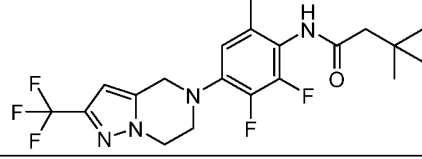
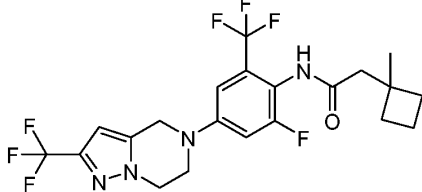
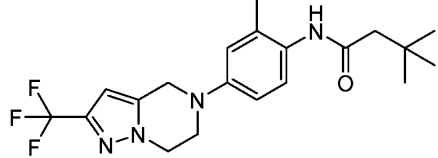
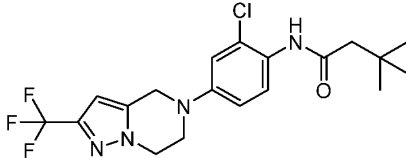
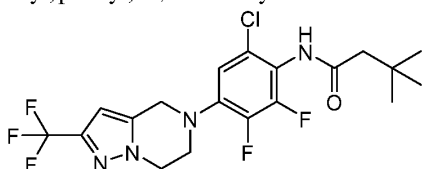
Ex.	Name and Structure	Ex.	Name and Structure
2	<i>N</i> -(2,6-dimethyl-4-(2-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	5	<i>N</i> -(2,6-dimethyl-4-(3-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 
6	<i>N</i> -(4-(2-(tert-butyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 	7	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 
10	2-(3,3-difluorocyclobutyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 	12	<i>N</i> -(4-(3-chloro-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 
13	<i>N</i> -(2,6-dimethyl-4-(2-phenyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	14	<i>N</i> -(4-(2-cyclopropyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 

Ex.	Name and Structure	Ex.	Name and Structure
15	2-(3,3-difluorocyclobutyl)- <i>N</i> -(2-fluoro-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 	16	2-(3,3-difluorocyclobutyl)- <i>N</i> -(2,4-dimethyl-6-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)pyridin-3-yl)acetamide 
18	2-(3,3-difluoro-1-methylcyclobutyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 	18a ^a	(<i>S</i>)-2-(3,3-difluoro-1-methylcyclobutyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 
18b ^a	(<i>R</i>)-2-(3,3-difluoro-1-methylcyclobutyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 	19	(+/-)-2-(2,2-difluoro-1-methylcyclopropyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 
19a ^b	(<i>S</i>)-2-(2,2-difluoro-1-methylcyclopropyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 	19b ^b	(<i>R</i>)-2-(2,2-difluoro-1-methylcyclopropyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 
20	2-(3,3-difluoro-1-methylcyclobutyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 	21	2-(bicyclo[1.1.1]pentan-1-yl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 
22	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-2-(spiro[3.3]heptan-2-yl)acetamide 	23	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-2-(spiro[2.3]hexan-5-yl)acetamide 

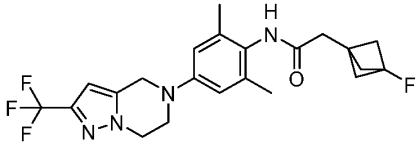
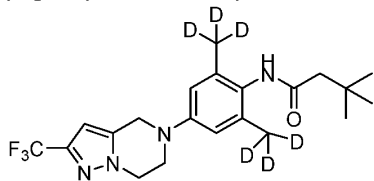
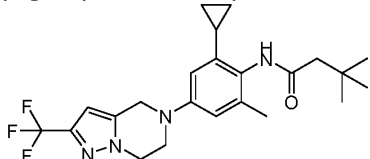
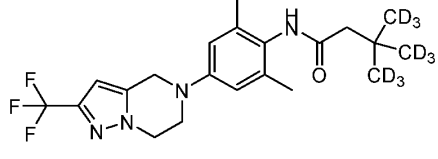
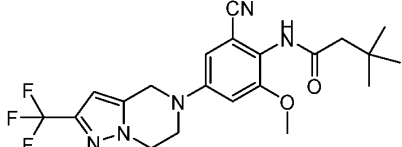
Ex.	Name and Structure	Ex.	Name and Structure
24	3,3-dimethyl-N-(4-methyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)pyrimidin-5-yl)butanamide 	25	N-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)-2-hydroxy-2,3,3-trimethylbutanamide 
27	N-(2-(3,3-difluorocyclobutyl)-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)-3,3-dimethylbutanamide 	28	2-(3,3-difluorocyclobutyl)-N-(2-(3,3-difluorocyclobutyl)-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)acetamide 
29	3,3-dimethyl-N-(2-methyl-6-(oxetan-3-yl)-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)butanamide 	30	N-(2,6-dimethyl-4-(2-(trifluoromethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)phenyl)-3,3-dimethylbutanamide 
31	2-(3,3-difluorocyclobutyl)-N-(3-fluoro-2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)acetamide 	32	2-(3,3-difluorocyclobutyl)-N-(4,6-dimethyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)pyrimidin-5-yl)acetamide 
33	N-(4,6-dimethyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)pyrimidin-5-yl)-3,3-dimethylbutanamide 	34	N-(2,4-dimethyl-6-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)pyridin-3-yl)-3,3-dimethylbutanamide 

Ex.	Name and Structure	Ex.	Name and Structure
36	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-2-(1-methylcyclopropyl)acetamide 	37	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)bicyclo[2.2.1]heptane-2-carboxamide 
38	<i>N</i> -(2-fluoro-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	39	<i>N</i> -(2-chloro-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 
40	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl-4,4-d2)phenyl)-3,3-dimethylbutanamide 	41	2-(3,3-difluoroazetidin-1-yl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 
42 ^c	(<i>R</i>)- <i>N</i> -(2,6-dimethyl-4-(4-methyl-2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	43 ^c	(<i>S</i>)- <i>N</i> -(2,6-dimethyl-4-(4-methyl-2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 
44	<i>N</i> -(2-fluoro-4-methyl-6-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)pyridin-3-yl)-3,3-dimethylbutanamide 	46	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-2-(1-methylcyclobutyl)acetamide 
47	(+/-)-2-cyclobutyl- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)propanamide 	48	2-(3,3-difluorocyclobutyl)- <i>N</i> -(2,6-dimethyl-4-(2-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 

Ex.	Name and Structure	Ex.	Name and Structure
49	<i>N</i> -[2-methoxy-6-methyl-4-[2-(trifluoromethyl)-6,7-dihydro-4 <i>H</i> -pyrazolo[1,5- <i>a</i>]pyrazin-5-yl]phenyl]-3,3-dimethylbutanamide 	50	3,3-dimethyl- <i>N</i> -(2-(trifluoromethyl)-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)phenyl)butanamide 
51	<i>N</i> -(2-fluoro-6-(trifluoromethyl)-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	52	3,3-dimethyl- <i>N</i> -(2-methyl-6-(trifluoromethyl)-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)phenyl)butanamide 
60	<i>N</i> -(3-chloro-2-fluoro-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	61	<i>N</i> -(2,6-dichloro-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 
62	<i>N</i> -(4-(2-chloro-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)-2-fluoro-6-methylphenyl)-3,3-dimethylbutanamide 	63	<i>N</i> -(2-chloro-4-methyl-6-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)pyridin-3-yl)-3,3-dimethylbutanamide 
64	<i>N</i> -(6-(2-(difluoromethyl)-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)-2-fluoro-4-methylpyridin-3-yl)-3,3-dimethylbutanamide 	65	3,3-dimethyl- <i>N</i> -(2-methyl-6-(trifluoromethoxy)-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5- <i>a</i>]pyrazin-5(4 <i>H</i>)-yl)phenyl)butanamide 

Ex.	Name and Structure	Ex.	Name and Structure
66	<i>N</i> -(2-chloro-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	69	3,3-dimethyl- <i>N</i> -(2-(trifluoromethoxy)-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)butanamide 
70	<i>N</i> -(2,6-dimethyl-4-(7-methyl-2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	71	<i>N</i> -(4-(3-chloro-2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 
72	<i>N</i> -(2,6-dimethoxy-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	73	<i>N</i> -(2,3-difluoro-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 
75	<i>N</i> -(2-fluoro-6-(trifluoromethyl)-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-2-(1-methylcyclobutyl)acetamide 	76	3,3-dimethyl- <i>N</i> -(2-methyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)butanamide 
77	<i>N</i> -(2-chloro-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	78	<i>N</i> -(6-chloro-2,3-difluoro-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 

Ex.	Name and Structure	Ex.	Name and Structure
94	<i>N</i> -(4-(2-chloro-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 	103 ^d	2-(2,2-difluoro-1-methylcyclopropyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide
104	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-2-(1-methylcyclobutyl)acetamide 	105 ^d	2-(2,2-difluoro-1-methylcyclopropyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide
106	2-(2,4-difluorophenyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 	107	2-(4,4-difluorocyclohexyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide
108	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-2-(4-fluorophenyl)acetamide 	109	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-2-(3-fluorophenyl)acetamide
110	2-(3,5-difluorophenyl)- <i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)acetamide 	111	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-2-(2-fluorophenyl)acetamide
115	<i>N</i> -(2,4-dimethyl-6-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)pyridin-3-yl)-2-(1-methylcyclobutyl)acetamide 	116	<i>N</i> -(2-chloro-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-2-(1-methylcyclobutyl)acetamide

Ex.	Name and Structure	Ex.	Name and Structure
117	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-2-(3-fluorobicyclo[1.1.1]pentan-1-yl)acetamide 	121	<i>N</i> -(2,6-bis(methyl- <i>d</i> 3)-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 
124	<i>N</i> -(2-cyclopropyl-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	125	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-bis(methyl- <i>d</i> 3)butanamide 
135	<i>N</i> -(2-cyano-6-methoxy-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	--	--

^a The absolute stereochemistry of Examples 18a and 18b have been arbitrarily defined.

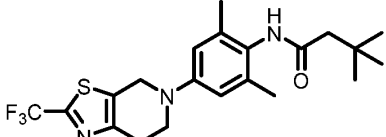
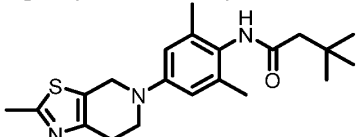
^b The absolute stereochemistry of Examples 19a and 19b have been arbitrarily defined.

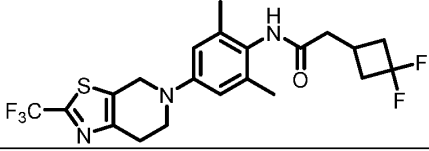
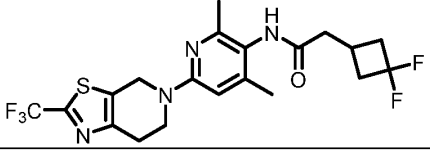
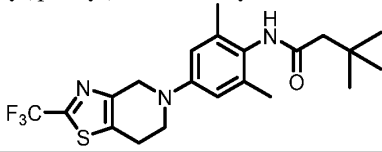
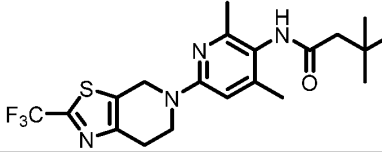
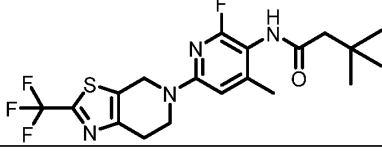
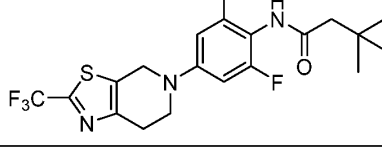
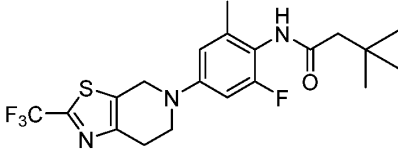
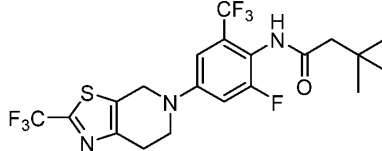
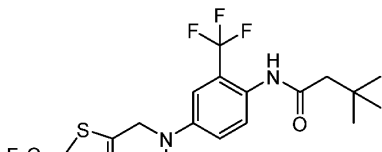
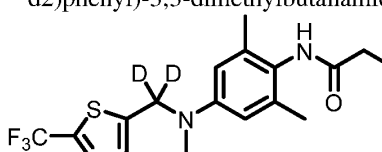
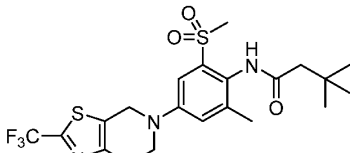
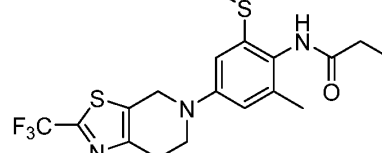
^c The absolute stereochemistry of Examples 42 and 43 have been arbitrarily defined.

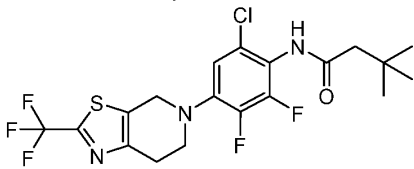
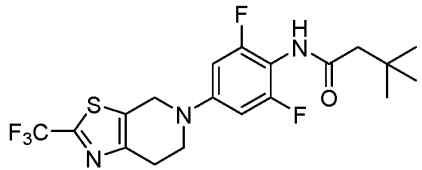
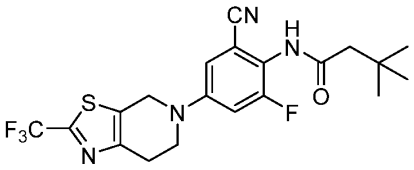
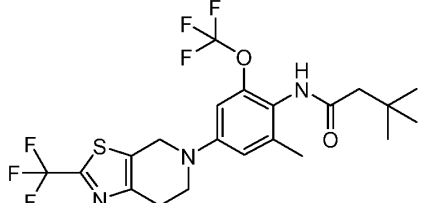
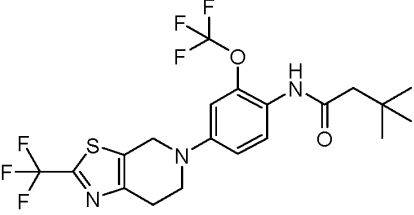
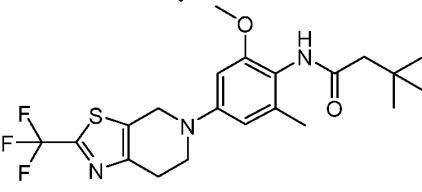
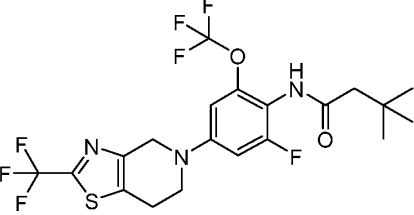
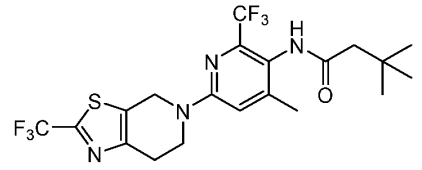
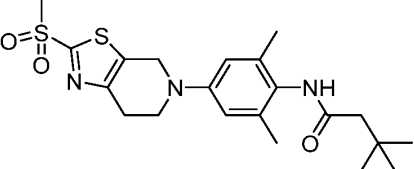
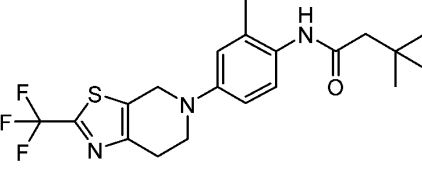
^d The absolute stereochemistry of Examples 103 and 105 have been arbitrarily defined.

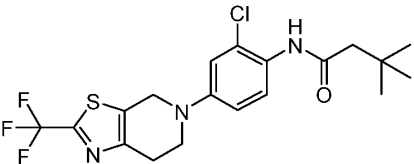
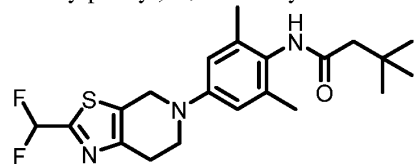
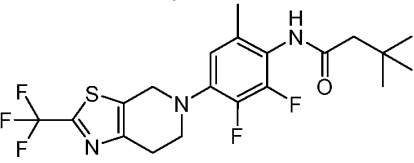
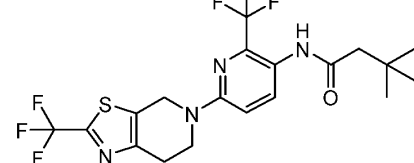
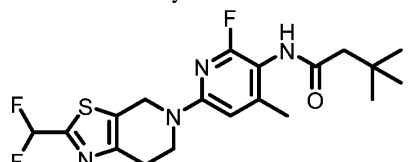
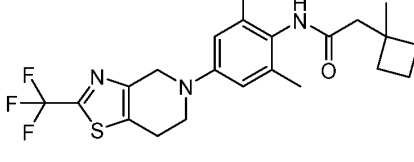
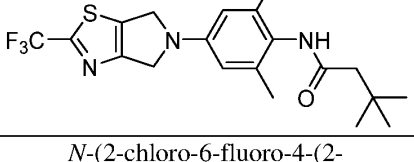
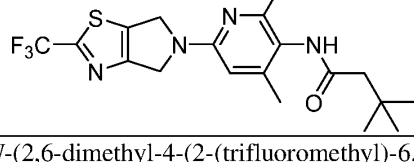
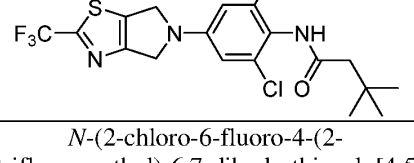
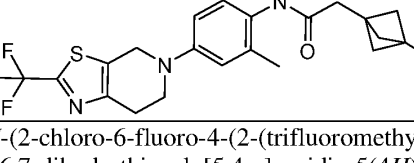
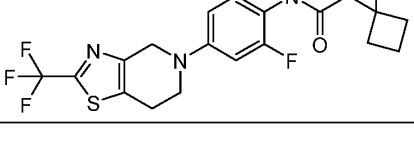
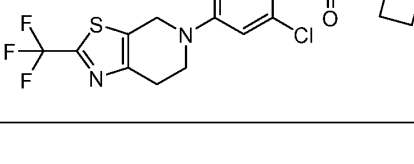
[156] In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1B**, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1B**, and pharmaceutically acceptable salts, stereoisomers, and tautomers thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1B**, and pharmaceutically acceptable salts thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1B** (in free base form).

Table 1B

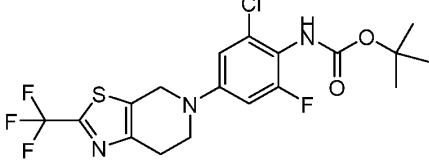
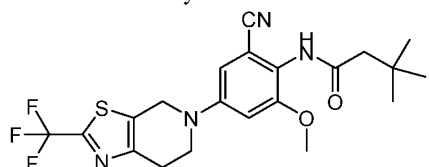
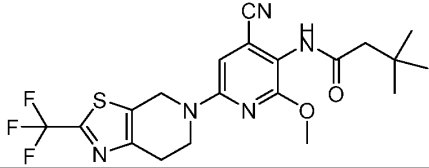
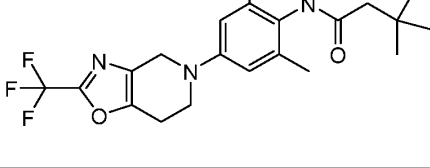
Ex.	Name and Structure	Ex.	Name and Structure
1	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	4	<i>N</i> -(2,6-dimethyl-4-(2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 

Ex.	Name and Structure	Ex.	Name and Structure
9	2-(3,3-difluorocyclobutyl)-N-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)phenyl)acetamide 	17	2-(3,3-difluorocyclobutyl)-N-(2,4-dimethyl-6-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)pyridin-3-yl)acetamide 
26	N-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)phenyl)-3,3-dimethylbutanamide 	35	N-(2,4-dimethyl-6-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)pyridin-3-yl)-3,3-dimethylbutanamide 
45	N-(2-fluoro-4-methyl-6-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)pyridin-3-yl)-3,3-dimethylbutanamide 	53	N-(2-chloro-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)phenyl)-3,3-dimethylbutanamide 
54	N-(2-fluoro-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)phenyl)-3,3-dimethylbutanamide 	55	N-(2-fluoro-6-(trifluoromethyl)-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)phenyl)-3,3-dimethylbutanamide 
56	3,3-dimethyl-N-(2-(trifluoromethyl)-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)phenyl)butanamide 	59	N-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl-4,4-d2)phenyl)-3,3-dimethylbutanamide 
67	3,3-dimethyl-N-(2-methyl-6-(methylsulfonyl)-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)phenyl)butanamide 	68	3,3-dimethyl-N-(2-methyl-6-(methylthio)-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)phenyl)butanamide 

Ex.	Name and Structure	Ex.	Name and Structure
74	<i>N</i> -(6-chloro-2,3-difluoro-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	79	<i>N</i> -(2,6-difluoro-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 
80	<i>N</i> -(2-cyano-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	81	3,3-dimethyl- <i>N</i> -(2-methyl-6-(trifluoromethoxy)-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)butanamide 
82	3,3-dimethyl- <i>N</i> -(2-(trifluoromethoxy)-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)butanamide 	83	<i>N</i> -(2-methoxy-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 
84	<i>N</i> -(2-fluoro-6-(trifluoromethoxy)-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[4,5-c]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	85	3,3-dimethyl- <i>N</i> -(4-methyl-2-(trifluoromethyl)-6-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)pyridin-3-yl)butanamide 
86	<i>N</i> -(2,6-dimethyl-4-(2-(methylsulfonyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	87	3,3-dimethyl- <i>N</i> -(2-methyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)butanamide 

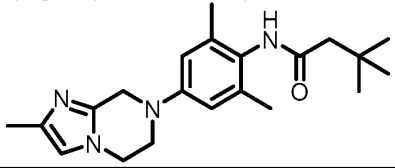
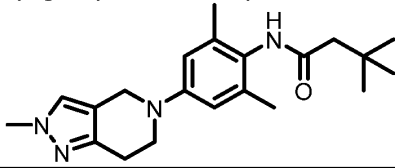
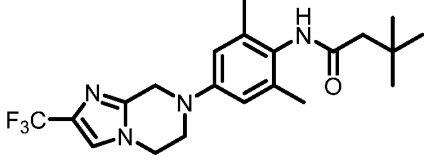
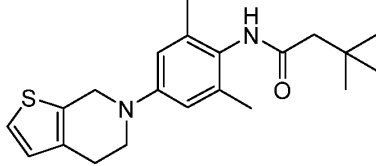
Ex.	Name and Structure	Ex.	Name and Structure
88	<i>N</i> -(2-chloro-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	89	<i>N</i> -(4-(2-(difluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 
90	<i>N</i> -(2,3-difluoro-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	122	3,3-dimethyl- <i>N</i> -(2-(trifluoromethyl)-6-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)pyridin-3-yl)butanamide 
91	<i>N</i> -(6-(2-(difluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)-2-fluoro-4-methylpyridin-3-yl)-3,3-dimethylbutanamide 	92	<i>N</i> -(2-chloro-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[4,5- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)phenyl)-2-(1-methylcyclobutyl)acetamide 
98	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-4,6-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>d</i>]thiazol-5-yl)phenyl)-3,3-dimethylbutanamide 	99	<i>N</i> -(2-fluoro-4-methyl-6-(2-(trifluoromethyl)-4,6-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>d</i>]thiazol-5-yl)pyridin-3-yl)-3,3-dimethylbutanamide 
100	<i>N</i> -(2-chloro-6-fluoro-4-(2-(trifluoromethyl)-4,6-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>d</i>]thiazol-5-yl)phenyl)-3,3-dimethylbutanamide 	112	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)phenyl)-2-(3-fluorobicyclo[1.1.1]pentan-1-yl)acetamide 
113	<i>N</i> -(2-chloro-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[4,5- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)phenyl)-2-(1-methylcyclobutyl)acetamide 	114	<i>N</i> -(2-chloro-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)phenyl)-2-(1-methylcyclobutyl)acetamide 

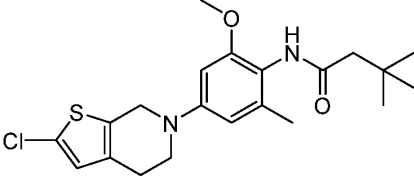
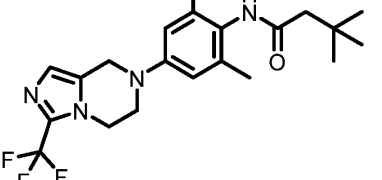
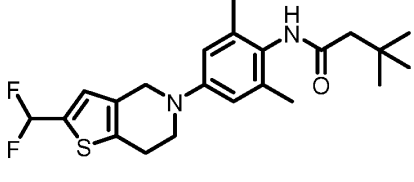
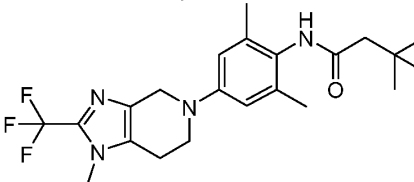
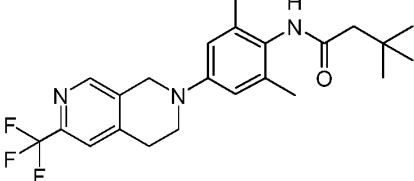
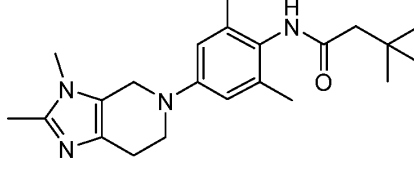
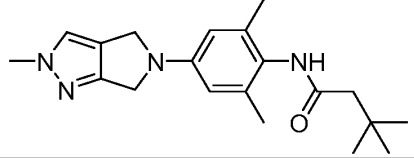
Ex.	Name and Structure	Ex.	Name and Structure
118	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-4,6,7,8-tetrahydro-5 <i>H</i> -thiazolo[5,4- <i>c</i>]azepin-5-yl)phenyl)-3,3-dimethylbutanamide 	119	<i>N</i> -[2,6-dimethyl-4-[2-(trifluoromethyl)-6,7-dihydro-4 <i>H</i> -oxazolo[5,4- <i>c</i>]pyridin-5-yl]phenyl]-3,3-dimethyl-butnamide
120	<i>N</i> -(2,6-bis(methyl- <i>d</i> 3)-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	123	<i>N</i> -(2-cyclopropyl-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide
126	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-bis(methyl- <i>d</i> 3)butanamide 	127	4,4,4-trifluoro- <i>N</i> -(2-fluoro-4-methyl-6-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)pyridin-3-yl)butanamide
128	<i>N</i> -(2-chloro-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)phenyl)-4,4,4-trifluorobutanamide 	129	<i>N</i> -(2-cyclopropyl-4-methyl-6-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)pyridin-3-yl)-3,3-dimethylbutanamide
130	<i>N</i> -(2-chloro-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydrooxazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	131	<i>N</i> -(4-fluoro-2-methyl-6-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4- <i>c</i>]pyridin-5(4 <i>H</i>)-yl)pyridin-3-yl)-3,3-dimethylbutanamide

Ex.	Name and Structure	Ex.	Name and Structure
132	<i>tert</i> -butyl (2-chloro-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)carbamate 	133	<i>N</i> -(2-cyano-6-methoxy-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 
134	<i>N</i> -(4-cyano-2-methoxy-6-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4 <i>H</i>)-yl)pyridin-3-yl)-3,3-dimethylbutanamide 	136	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrooxazolo[4,5-c]pyridin-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 

[157] In certain embodiments, a compound disclosed herein is selected from the compounds recited in Table 1C, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in Table 1C, and pharmaceutically acceptable salts, stereoisomers, and tautomers thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in Table 1C, and pharmaceutically acceptable salts thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in Table 1C (in free base form).

Table 1C

Ex.	Name and Structure	Ex.	Name and Structure
3	<i>N</i> -(2,6-dimethyl-4-(2-methyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	8	<i>N</i> -(2,6-dimethyl-4-(2-methyl-2,4,6,7-tetrahydro-5 <i>H</i> -pyrazolo[4,3-c]pyridin-5-yl)phenyl)-3,3-dimethylbutanamide 
11	<i>N</i> -(2,6-dimethyl-4-(2-(trifluoromethyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	57	<i>N</i> -(4-(4,7-dihydrothieno[2,3-c]pyridin-6(5 <i>H</i>)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 

Ex.	Name and Structure	Ex.	Name and Structure
58	<i>N</i> -(4-(2-chloro-4,7-dihydrothieno[2,3-c]pyridin-6(5 <i>H</i>)-yl)-2-methoxy-6-methylphenyl)-3,3-dimethylbutanamide 	93	<i>N</i> -(2,6-dimethyl-4-(3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 
95	<i>N</i> -(4-(2-(difluoromethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4 <i>H</i>)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 	96	<i>N</i> -(2,6-dimethyl-4-(1-methyl-2-(trifluoromethyl)-1,4,6,7-tetrahydro-5 <i>H</i> -imidazo[4,5-c]pyridin-5-yl)phenyl)-3,3-dimethylbutanamide 
97	<i>N</i> -(2,6-dimethyl-4-(6-(trifluoromethyl)-3,4-dihydro-2,7-naphthyridin-2(1 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	101	<i>N</i> -(4-(2,3-dimethyl-3,4,6,7-tetrahydro-5 <i>H</i> -imidazo[4,5-c]pyridin-5-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 
102	<i>N</i> -(2,6-dimethyl-4-(2-methyl-2,6-dihydropyrrolo[3,4-c]pyrazol-5(4 <i>H</i>)-yl)phenyl)-3,3-dimethylbutanamide 	--	--

[158] The following definitions and embodiments apply to all generic formulae comprising the relevant groups (*e.g.*, Formula (I) or any subgeneric formula thereof) provided herein. The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[159] As defined herein, X^1 is C or N. In certain embodiments, X^1 is C. In certain embodiments, X^1 is N.

[160] As defined herein, Z^3 is CR^4 , N, NR^N , S, or O. In certain embodiments, Z^3 is CR^4 . In certain embodiments, Z^3 is N. In certain embodiments, Z^3 is NR^N . In certain embodiments, Z^3 is S. In certain embodiments, Z^3 is O.

[161] As defined herein, Z^4 is CR^4 , N, NR^N , S, or O. In certain embodiments, Z^4 is CR^4 . In certain embodiments, Z^4 is C- CF_3 . In certain embodiments, Z^4 is N. In certain embodiments, Z^4 is NR^N . In certain embodiments, Z^4 is S. In certain embodiments, Z^4 is O.

[162] As defined herein, Z^5 is a bond, CR^4 , N, NR^N , S, or O. In certain embodiments, Z^5 is a bond. In certain embodiments, Z^5 is CR^4 . In certain embodiments, Z^5 is S. In certain embodiments, Z^5 is O. In certain embodiments, Z^5 is N. In certain embodiments, Z^5 is NR^N .

[163] As defined herein, Z^6 is CR^4 , N, NR^N , S, or O. In certain embodiments, Z^6 is CR^4 . In certain embodiments, Z^6 is N. In certain embodiments, Z^6 is NR^N . In certain embodiments, Z^6 is S. In certain embodiments, Z^6 is O.

[164] As described herein, at least one of Z^3 , Z^4 , Z^5 , and Z^6 is N, NR^N , S, or O, and no more than one of Z^3 , Z^4 , Z^5 , and Z^6 is S or O. In certain embodiments, at least two of Z^3 , Z^4 , Z^5 , and Z^6 are independently selected from N, NR^N , S, and O, provided that no more than one of Z^3 , Z^4 , Z^5 , and Z^6 is S or O.

[165] In certain embodiments:

Z^3 is N and Z^6 is S;

Z^3 is S and Z^6 is N;

Z^3 is N and Z^6 is O; or

Z^3 is O and Z^6 is N.

[166] In certain embodiments, Z^3 is N and Z^6 is S, or Z^3 is S and Z^6 is N. In certain embodiments, Z^3 is N and Z^6 is S. In certain embodiments, Z^3 is S and Z^6 is N.

[167] In certain embodiments, Z^3 is N and Z^6 is O, or Z^3 is O and Z^6 is N. In certain embodiments, Z^3 is N and Z^6 is O. In certain embodiments, Z^3 is O and Z^6 is N.

[168] As defined herein, each instance of R^4 is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted.

[169] In certain embodiments, at least one instance of R^4 is H.

[170] In certain embodiments, at least one instance of R^4 is halogen. In certain embodiments, at least one instance of R^4 is Cl. In certain embodiments, at least one instance of R^4 is F.

[171] In certain embodiments, at least one instance of R^4 is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^4 is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^4 is optionally substituted C_{1-4} alkyl. In certain embodiments, at least one instance of R^4 is unsubstituted C_{1-4} alkyl. In certain embodiments, at least one instance of R^4 is methyl. In certain embodiments, at least one instance of R^4 is *tert*-butyl.

[172] In certain embodiments, at least one instance of R^4 is C_{1-6} haloalkyl. In certain embodiments, at least one instance of R^4 is C_{1-3} haloalkyl. In certain embodiments, at least one instance of R^4 is C_1 haloalkyl. In certain embodiments, at least one instance of R^4 is - CF_2H .

[173] In certain embodiments, at least one instance of R^4 is - CF_3 .

[174] In certain embodiments, at least one instance of R^4 is optionally substituted C_{3-7} cycloalkyl. In

certain embodiments, at least one instance of R^4 is optionally substituted C_{3-5} cycloalkyl. In certain embodiments, at least one instance of R^4 is optionally substituted C_{3-4} cycloalkyl. In certain embodiments, at least one instance of R^4 is unsubstituted C_{3-4} cycloalkyl. In certain embodiments, at least one instance of R^4 is cyclopropyl.

[175] In certain embodiments, at least one instance of R^4 is optionally substituted C_{6-10} aryl. In certain embodiments, at least one instance of R^4 is optionally substituted C_6 aryl (phenyl). In certain embodiments, at least one instance of R^4 is unsubstituted phenyl.

[176] In certain embodiments, at least one instance of R^4 is optionally substituted 3-7 membered heterocyclyl. In certain embodiments, at least one instance of R^4 is optionally substituted 5-10 membered heteroaryl. In certain embodiments, at least one instance of R^4 is -CN. In certain embodiments, at least one instance of R^4 is -OR^O. In certain embodiments, at least one instance of R^4 is -N(R^N)₂. In certain embodiments, at least one instance of R^4 is optionally substituted C_{1-6} acyl.

[177] In other embodiments, at least one instance of R^4 is -SR^S. In certain embodiments, at least one instance of R^4 is -SMe.

[178] In other embodiments, at least one instance of R^4 is -S(=O)₂R^{S1}. In certain embodiments, at least one instance of R^4 is -S(=O)₂Me.

[179] As defined herein, p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 3. In certain embodiments, p is 4. In certain embodiments, p is 5. In certain embodiments, p is 6. In certain embodiments, p is 7. In certain embodiments, p is 8. In certain embodiments, p is 9. In certain embodiments, p is 10.

[180] As defined herein, m is 1 or 2. In certain embodiments, m is 1. In certain embodiments, m is 2.

[181] As defined herein, n is 0, 1, or 2. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2.

[182] In certain embodiments, m and n are both 1.

[183] In certain embodiments, m is 1, and n is 0.

[184] In certain embodiments, m is 1, and n is 2.

[185] As defined herein, R^1 is H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, -SR^S, -S(=O)₂R^{S1}, or C_{1-6} acyl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is optionally substituted.

[186] In certain embodiments, R^1 is H.

[187] In certain embodiments, R^1 is halogen. In certain embodiments, R^1 is F. In certain embodiments, R^1 is Cl.

[188] In certain embodiments, R^1 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^1 is optionally substituted C_{1-3} alkyl. In certain embodiments, R^1 is unsubstituted C_{1-3} alkyl. In certain embodiments, R^1 is methyl.

[189] In certain embodiments, R^1 is C_{1-6} haloalkyl. In certain embodiments, R^1 is C_{1-3} haloalkyl. In certain embodiments, R^1 is C_1 haloalkyl. In certain embodiments, R^1 is -CF₃.

[190] In certain embodiments, R¹ is optionally substituted C₃₋₇ cycloalkyl. In certain embodiments, R¹ is unsubstituted C₃₋₇ cycloalkyl. In certain embodiments, R¹ is C₃₋₇ cycloalkyl substituted with one or more instances of halogen and/or unsubstituted C₁₋₆ alkyl. In certain embodiments, R¹ is C₃₋₇ cycloalkyl substituted with one or more instances of halogen. In certain embodiments, R¹ is C₃₋₇ cycloalkyl substituted with one or more instances of F.

[191] In certain embodiments, R¹ is optionally substituted C₃₋₅ cycloalkyl. In certain embodiments, R¹ is C₃₋₅ cycloalkyl optionally substituted with one or more instances of halogen and/or unsubstituted C₁₋₆ alkyl. In certain embodiments, R¹ is C₄ cycloalkyl optionally substituted with one or more instances of halogen and/or unsubstituted C₁₋₆ alkyl. In certain embodiments, R¹ is C₄ cycloalkyl optionally substituted with one or more instances of halogen. In certain embodiments, R¹ is C₄ cycloalkyl optionally substituted with one or more instances of F.

[192] In certain embodiments, R¹ is unsubstituted C₃ cycloalkyl (cyclopropyl). In certain embodiments, R¹ is cyclopropyl substituted with one or more instances of halogen and/or unsubstituted C₁₋₆ alkyl. In certain embodiments, R¹ is cyclopropyl substituted with one or more instances of halogen. In certain embodiments, R¹ is cyclopropyl substituted with one or more instances of F.

[193] In certain embodiments, R¹ is unsubstituted C₄ cycloalkyl (cyclobutyl). In certain embodiments, R¹ is cyclobutyl substituted with one or more instances of halogen and/or unsubstituted C₁₋₆ alkyl. In certain embodiments, R¹ is cyclobutyl substituted with one or more instances of halogen. In certain embodiments, R¹ is cyclobutyl substituted with one or more instances of F.

[194] In certain embodiments, R¹ is unsubstituted C₅ cycloalkyl (*e.g.*, cyclopentyl). In certain embodiments, R¹ is cyclopentyl substituted with one or more instances of halogen and/or unsubstituted C₁₋₆ alkyl. In certain embodiments, R¹ is cyclopentyl substituted with one or more instances of halogen. In certain embodiments, R¹ is cyclopentyl substituted with one or more instances of F.

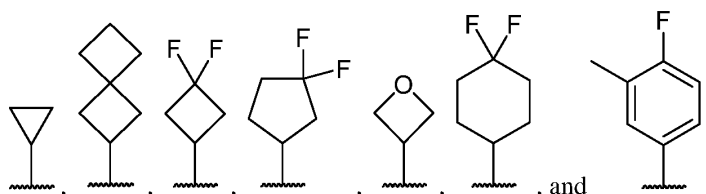
[195] In certain embodiments, R¹ is unsubstituted C₆ cycloalkyl (*e.g.*, cyclohexyl). In certain embodiments, R¹ is cyclohexyl substituted with one or more instances of halogen and/or unsubstituted C₁₋₆ alkyl. In certain embodiments, R¹ is cyclohexyl substituted with one or more instances of halogen. In certain embodiments, R¹ is cyclohexyl substituted with one or more instances of F.

[196] In certain embodiments, R¹ is optionally substituted 3-7 membered heterocyclyl. In certain embodiments, R¹ is optionally substituted 3-7 membered heterocyclyl having 1 or 2 ring heteroatoms independently selected from O, N, and S. In certain embodiments, R¹ is optionally substituted 3-6 membered heterocyclyl. In certain embodiments, R¹ is optionally substituted 3-6 membered heterocyclyl with 1 or 2 ring heteroatoms independently selected from O, N, and S. In certain embodiments, R¹ is optionally substituted 3-5 membered heterocyclyl. In certain embodiments, R¹ is optionally substituted 3-5 membered heterocyclyl having 1 ring heteroatom selected from O, N, and S. In certain embodiments, R¹ is optionally substituted 4-membered heterocyclyl having 1 ring heteroatom selected from O, N, and S. In certain embodiments, R¹ is optionally substituted 4-membered heterocyclyl with 1 ring heteroatoms independently selected from O and N. In certain embodiments, R¹ is optionally substituted oxetanyl. In certain embodiments, R¹ is unsubstituted oxetanyl.

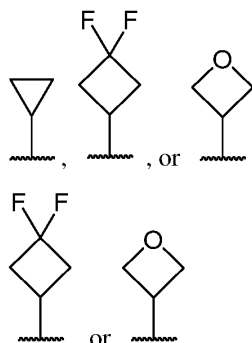
[197] In certain embodiments, R^1 is optionally substituted C_{6-10} aryl. In certain embodiments, R^1 is optionally substituted C_6 aryl (phenyl). In certain embodiments, R^1 is phenyl optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl.

[198] In certain embodiments, R^1 is optionally substituted 5-10 membered heteroaryl. In certain embodiments, R^1 is optionally substituted 5-10 membered heteroaryl with 1, 2, or 3 ring heteroatoms independently selected from O, N, and S. In certain embodiments, R^1 is optionally substituted 5-6 membered heteroaryl. In certain embodiments, R^1 is optionally substituted 5-6 membered heteroaryl with 1, 2, or 3 ring heteroatoms independently selected from O, N, and S.

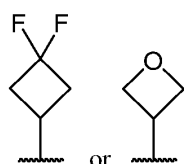
[199] In certain embodiments, R^1 is selected from:



[200] In certain embodiments, R^1 is:



[201] In certain embodiments, R^1 is:



[202] In certain embodiments, R^1 is $-OR^O$.

[203] In certain embodiments, R^1 is $-OR^O$, wherein R^O is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is $-OR^O$, wherein R^O is optionally substituted C_{1-3} alkyl. In certain embodiments, R^1 is $-OR^O$, wherein R^O is unsubstituted C_{1-3} alkyl. In certain embodiments, R^1 is $-OMe$.

[204] In certain embodiments, R^1 is $-OR^O$, wherein R^O is C_{1-6} haloalkyl. In certain embodiments, R^1 is $-OR^O$, wherein R^O is C_{1-3} haloalkyl. In certain embodiments, R^1 is $-OR^O$, wherein R^O is C_1 haloalkyl. In certain embodiments, R^1 is $-OCF_3$.

[205] In certain embodiments, R^1 is $-CN$. In certain embodiments, R^1 is $-N(R^N)_2$. In certain embodiments, R^1 is optionally substituted C_{1-6} acyl.

[206] In certain embodiments, R^1 is $-SR^S$. In certain embodiments, R^1 is $-SMe$.

[207] In certain embodiments, R^1 is $-S(=O)_2R^{S1}$. In certain embodiments, R^1 is $-S(=O)_2Me$.

[208] In certain embodiments, R^1 is halogen, C_{1-6} haloalkyl, or $-OR^O$. In certain embodiments, R^1 is halogen, C_{1-6} haloalkyl, $-OR^O$, $-CN$, $-SR^S$, or $-S(=O)_2R^{S1}$.

[209] In certain embodiments, R^1 is F, Cl, $-CF_3$, or $-OMe$. In certain embodiments, R^1 is F, Cl, $-CF_3$, $-OMe$, $-OCF_3$, $-CN$, $-SMe$, or $-S(=O)_2Me$.

[210] As defined herein, R^2 is H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered

heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, -SR^S, -S(=O)₂R^{S1}, or C₁₋₆ acyl, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is optionally substituted.

[211] In certain embodiments, R² is H.

[212] In certain embodiments, R² is halogen. In certain embodiments, R² is F. In certain embodiments, R² is Cl. In certain embodiments, R² is F or Cl.

[213] In certain embodiments, R² is optionally substituted C₁₋₆ alkyl. In certain embodiments, R² is unsubstituted C₁₋₆ alkyl. In certain embodiments, R² is optionally substituted C₁₋₃ alkyl. In certain embodiments, R² is unsubstituted C₁₋₃ alkyl. In certain embodiments, R² is methyl.

[214] In certain embodiments, R² is C₁₋₆ haloalkyl. In certain embodiments, R² is optionally substituted C₃₋₇ cycloalkyl. In certain embodiments, R² is optionally substituted 3-7 membered heterocyclyl. In certain embodiments, R² is optionally substituted C₆₋₁₀ aryl. In certain embodiments, R² is optionally substituted 5-10 membered heteroaryl. In certain embodiments, R² is -CN.

[215] In certain embodiments, R² is -OR^O.

[216] In certain embodiments, R² is -OR^O, wherein R^O is optionally substituted C₁₋₆ alkyl. In certain embodiments, R² is -OR^O, wherein R^O is optionally substituted C₁₋₃ alkyl. In certain embodiments, R² is -OR^O, wherein R^O is unsubstituted C₁₋₃ alkyl. In certain embodiments, R² is -OMe.

[217] In certain embodiments, R² is -OR^O, wherein R^O is C₁₋₆ haloalkyl. In certain embodiments, R² is -OR^O, wherein R^O is C₁₋₃ haloalkyl. In certain embodiments, R² is -OR^O, wherein R^O is C₁ haloalkyl. In certain embodiments, R² is -OCF₃.

[218] In certain embodiments, R² is halogen or -OR^O. In certain embodiments, R² is F, Cl, or -OMe.

[219] In certain embodiments, R² is -N(R^N)₂. In certain embodiments, R² is optionally substituted C₁₋₆ acyl.

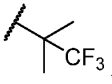
[220] In certain embodiments, R² is -SR^S. In certain embodiments, R² is -SMe.

[221] In certain embodiments, R² is -S(=O)₂R^{S1}. In certain embodiments, R² is -S(=O)₂Me.

[222] As defined herein, R³ is C₁₋₈ alkyl, C₃₋₁₀ cycloalkyl, 3-7 membered heterocyclyl, or -(CR'R'')_w-Ar¹, wherein the alkyl, cycloalkyl, or heterocyclyl is optionally substituted; w is 0, 1, or 2; and Ar¹ is C₆₋₁₀ aryl or 5-10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted.

[223] In certain embodiments, R³ is optionally substituted C₁₋₈ alkyl. In certain embodiments, R³ is unsubstituted C₁₋₈ alkyl. In certain embodiments, R³ is optionally substituted C₁₋₄ alkyl. In certain embodiments, R³ is unsubstituted C₁₋₄ alkyl. In certain embodiments, R³ is *tert*-butyl.

[224] In certain embodiments, R³ is C₁₋₆ alkyl substituted with one or more halogen. In certain embodiments, R³ is C₁₋₆ alkyl substituted with one or more F. In certain embodiments, R³ is C₁₋₃ alkyl

substituted with one or more F. In certain embodiments, R³ is -CF₃, -CH₂CF₃, or . In certain embodiments, R³ is -CH₂CF₃.

[225] In certain embodiments, R³ is optionally substituted C₃₋₁₀ cycloalkyl.

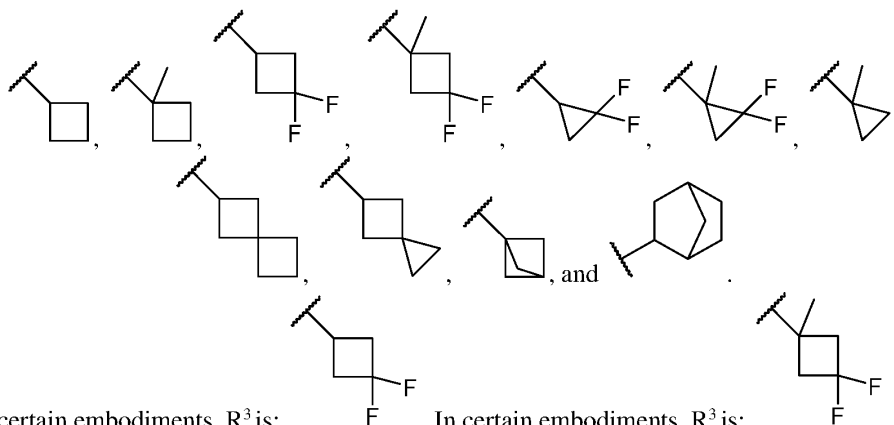
[226] In certain embodiments, R³ is optionally substituted C₃₋₈ cycloalkyl. In certain embodiments, R³ is C₃₋₈ cycloalkyl optionally substituted with one or more instances of halogen and/or unsubstituted C₁₋₆

alkyl. In certain embodiments, R^3 is C_{3-8} cycloalkyl optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-3} alkyl. In certain embodiments, R^3 is C_{3-8} cycloalkyl optionally substituted with one or more instances of F and/or methyl. In certain embodiments, R^3 is C_{3-8} cycloalkyl optionally substituted with one or more instances of F. In certain embodiments, R^3 is C_{3-8} cycloalkyl optionally substituted with one or more instances of halogen, C_{1-6} haloalkyl, and/or unsubstituted C_{1-6} alkyl. In certain embodiments, R^3 is C_{3-8} cycloalkyl optionally substituted with one or more instances of halogen, C_{1-3} haloalkyl, and/or unsubstituted C_{1-3} alkyl. In certain embodiments, R^3 is C_{3-8} cycloalkyl optionally substituted with one or more instances of F, $-CF_3$, and/or methyl.

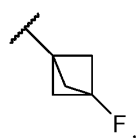
[227] In certain embodiments, R^3 is optionally substituted C_{3-5} cycloalkyl. In certain embodiments, R^3 is C_{3-5} cycloalkyl optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl. In certain embodiments, R^3 is C_{3-5} cycloalkyl optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-3} alkyl. In certain embodiments, R^3 is C_{3-5} cycloalkyl optionally substituted with one or more instances of F and/or methyl. In certain embodiments, R^3 is C_{3-5} cycloalkyl optionally substituted with one or more instances of halogen, C_{1-6} haloalkyl, and/or unsubstituted C_{1-6} alkyl. In certain embodiments, R^3 is C_{3-5} cycloalkyl optionally substituted with one or more instances of halogen, C_{1-3} haloalkyl, and/or unsubstituted C_{1-3} alkyl. In certain embodiments, R^3 is C_{3-5} cycloalkyl optionally substituted with one or more instances of F, $-CF_3$, and/or methyl.

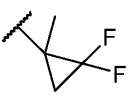
[228] In certain embodiments, R^3 is C_{3-5} cycloalkyl optionally substituted with one or more instances of F. In certain embodiments, R^3 is C_{3-5} cycloalkyl substituted with one or more instances of F. In certain embodiments, R^3 is C_4 cycloalkyl (cyclobutyl) substituted with one or more instances of F.

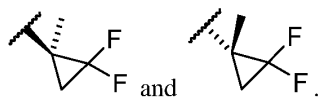
[229] In certain embodiments, R^3 is selected from:



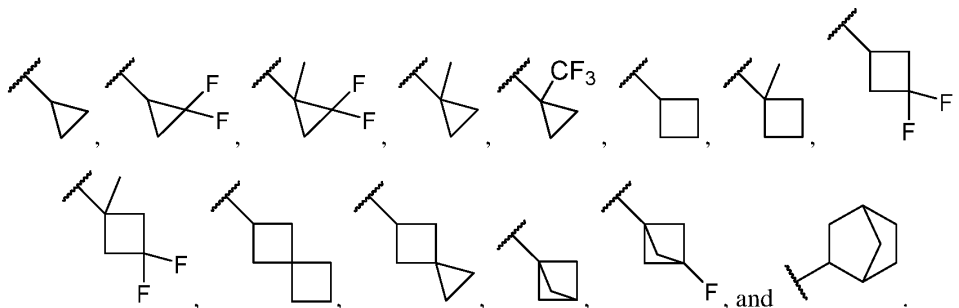
[230] In certain embodiments, R^3 is: . In certain embodiments, R^3 is: . In certain

embodiments, R^3 is: .

[231] In certain embodiments, R^3 is: . In certain embodiments, R^3 is selected from:

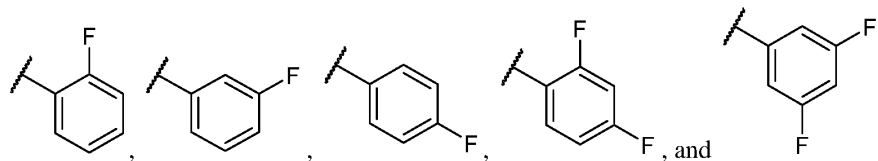


[232] In certain embodiments, R^3 is selected from:

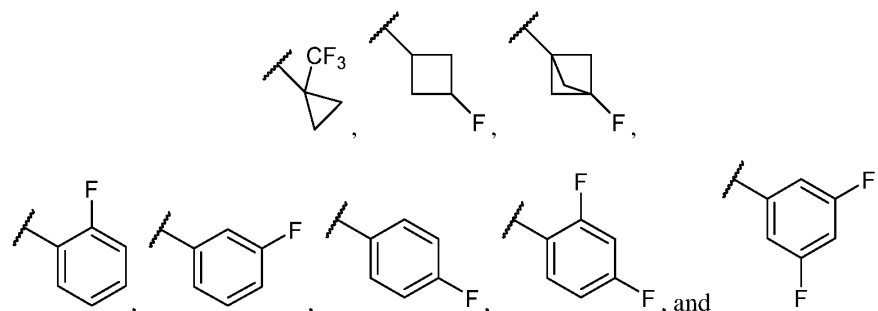


[233] In certain embodiments, R^3 is optionally substituted C_{6-10} aryl. In certain embodiments, R^3 is optionally substituted phenyl. In certain embodiments, R^3 is phenyl optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl. In certain embodiments, R^3 is phenyl optionally substituted with one or more instances of halogen. In certain embodiments, R^3 is phenyl optionally substituted with one or more instances of F.

[234] In certain embodiments, R^3 is selected from:

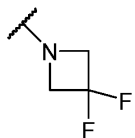


[235] In certain embodiments, R^3 is selected from:

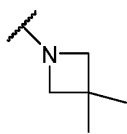


[236] In certain embodiments, R^3 is optionally substituted 3-7 membered heterocyclyl. In certain embodiments, R^3 is optionally substituted 3-6 membered heterocyclyl having 1 or 2 ring N atoms. In certain embodiments, R^3 is 3-6 membered heterocyclyl having 1 or 2 ring N atoms and optionally substituted with one or more halogen. In certain embodiments, R^3 is 3-6 membered heterocyclyl having 1 or 2 ring N atoms and optionally substituted with one or more F. In certain embodiments, R^3 is 3-6 membered heterocyclyl having 1 or 2 ring N atoms and substituted with one or more F. In certain embodiments, R^3 is azetidiny substituted with one or more F. In certain embodiments, R^3 is optionally substituted 3-6 membered heterocyclyl having 1 or 2 ring heteroatoms independently selected from N and O. In certain embodiment, R^3 is 3-6 membered heterocyclyl having 1 or 2 ring heteroatoms

independently selected from N and O, wherein the heterocyclyl is optionally substituted with one or more instances of halogen, unsubstituted C₁₋₆ alkyl, and/or C₁₋₆ haloalkyl. In certain embodiment, R³ is 3-6 membered heterocyclyl having 1 ring N atom, wherein the heterocyclyl is optionally substituted with one or more instances of halogen, unsubstituted C₁₋₆ alkyl, and/or C₁₋₆ haloalkyl. In certain embodiments, R³ is 3-6 membered heterocyclyl having 1 ring heteroatom selected from N and O, wherein the heterocyclyl is optionally substituted with one or more instances of F, Me, and/or -CF₃. In certain embodiments, R³ is 3-6 membered heterocyclyl having 1 ring N atom, wherein the heterocyclyl is optionally substituted with one or more instances of F, Me, and/or -CF₃.

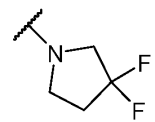


[237] In certain embodiments, R³ is:

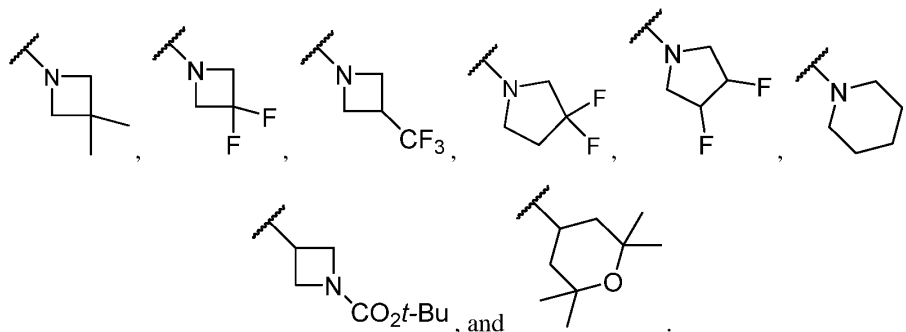


[238] In certain embodiments, R³ is:

. In certain embodiments, R³ is:



[239] In certain embodiments, R³ is selected from:



[240] In certain embodiments, R³ is or -(CR'R'')_w-Ar¹.

[241] As defined herein, w is 0, 1, or 2. In certain embodiments, w is 0. In certain embodiments, w is 1. In certain embodiments, w is 2.

[242] As defined herein, Ar¹ is C₆₋₁₀ aryl or 5-10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted. In certain embodiments, Ar¹ is optionally substituted C₆₋₁₀ aryl. In certain embodiments, Ar¹ is optionally substituted 5-10 membered heteroaryl.

[243] As defined herein, Z¹ is CR^Z or N. In certain embodiments, Z¹ is CR^Z. In certain embodiments, Z¹ is CH. In certain embodiments, Z¹ is CCl. In certain embodiments, Z¹ is CF. In certain embodiments, Z¹ is N. In certain embodiments, Z¹ is CH or N.

[244] As defined herein, Z² is CR^Z or N. In certain embodiments, Z² is CR^Z. In certain embodiments, Z² is CH. In certain embodiments, Z² is CCl. In certain embodiments, Z² is CF. In certain embodiments, Z² is N. In certain embodiments, Z² is CH or N.

[245] In certain embodiments, Z¹ is CR^Z and Z² is CR^Z. In certain embodiments, Z¹ is CH and Z² is CH. In certain embodiments, Z¹ is CR^Z and Z² is N. In certain embodiments, Z¹ is CH and Z² is N. In certain

embodiments, Z^1 is N and Z^2 is CR^Z . In certain embodiments, Z^1 is N and Z^2 is CH. In certain embodiments, Z^1 is N and Z^2 is N.

[246] As defined herein, each instance of R^Z is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted.

[247] In certain embodiments, at least one instance of R^Z is H. In certain embodiments, each instance of R^Z is H.

[248] In certain embodiments, at least one instance of R^Z is halogen. In certain embodiments, at least one instance of R^Z is F. In certain embodiments, at least one instance of R^Z is Cl.

[249] In certain embodiments, at least one instance of R^Z is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^Z is C_{1-6} haloalkyl. In certain embodiments, at least one instance of R^Z is optionally substituted C_{3-7} cycloalkyl. In certain embodiments, at least one instance of R^Z is optionally substituted 3-7 membered heterocyclyl. In certain embodiments, at least one instance of R^Z is optionally substituted C_{6-10} aryl. In certain embodiments, at least one instance of R^Z is optionally substituted 5-10 membered heteroaryl. In certain embodiments, at least one instance of R^Z is -CN. In certain embodiments, at least one instance of R^Z is -OR^O. In certain embodiments, at least one instance of R^Z is -N(R^N)₂. In certain embodiments, at least one instance of R^Z is optionally substituted C_{1-6} acyl.

[250] As defined herein, Y is a bond, -CR'R"-, -O-, or -NR^Y-.

[251] In certain embodiments, Y is a bond.

[252] In certain embodiments, Y is -CR'R"-. In certain embodiments, Y is -CH₂-. In certain embodiments, Y is -CH(Me)-.

[253] In certain embodiments, Y is -O-.

[254] In certain embodiments, Y is -NR^Y-. In certain embodiments, Y is -NH-.

[255] As defined herein, R^Y is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or a nitrogen protecting group, wherein the alkyl, or cycloalkyl is optionally substituted.

[256] In certain embodiments, R^Y is H.

[257] In certain embodiments, R^Y is optionally substituted C_{1-6} alkyl. In certain embodiments, R^Y is optionally substituted C_{3-7} cycloalkyl. In certain embodiments, R^Y is a nitrogen protecting group.

[258] In other embodiments, R^Y and R³ are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein the heterocyclyl is optionally substituted. In some embodiments, R^Y and R³ are joined together with the intervening atoms to form optionally substituted 4-6 membered heterocyclyl.

[259] In certain embodiments, Y is -CR'R"- and R³ is optionally substituted C_{1-8} alkyl. In certain embodiments, Y is -CR'R"- and R³ is optionally substituted C_{1-4} alkyl. In certain embodiments, Y is -CH₂- and R³ is unsubstituted C_{1-4} alkyl. In certain embodiments, Y is -CH₂- and R³ is *tert*-butyl.

[270] In certain embodiments, two R⁵ attached to the same carbon atom are taken together to form =O.

[271] As defined herein, each instance of R' is independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted.

[272] In certain embodiments, at least one instance of R' is H.

[273] In certain embodiments, at least one instance of R' is halogen. In certain embodiments, at least one instance of R' is optionally substituted C₁₋₆ alkyl. In certain embodiments, at least one instance of R' is C₁₋₆ haloalkyl. In certain embodiments, at least one instance of R' is optionally substituted C₃₋₇ cycloalkyl. In certain embodiments, at least one instance of R' is optionally substituted 3-7 membered heterocyclyl.

[274] As defined herein, each instance of R'' is independently H, halogen, C₁₋₆ alkyl, -OR^O, or -N(R^N)₂, wherein the each alkyl is independently optionally substituted.

[275] In certain embodiments, at least one instance of R'' is H.

[276] In certain embodiments, at least one instance of R'' is halogen. In certain embodiments, at least one instance of R'' is optionally substituted C₁₋₆ alkyl. In certain embodiments, at least one instance of R'' is -OR^O. In certain embodiments, at least one instance of R'' is -N(R^N)₂.

[277] In certain embodiments, R' and R'' attached to the same carbon atom are joined together with the intervening atoms to form C₃₋₇ cycloalkyl or 3-7 membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted. In certain embodiments, R' and R'' attached to the same carbon atom are joined together with the intervening atoms to form optionally substituted C₃₋₇ cycloalkyl. In certain embodiments, R' and R'' attached to the same carbon atom are joined together with the intervening atoms to form optionally substituted 3-7 membered heterocyclyl.

[278] In certain embodiments, R' and R'' attached to the same carbon atom are taken together to form =O.

[279] As defined herein, R^{NI} is H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ acyl, or a nitrogen protecting group, wherein the alkyl, cycloalkyl, or acyl is optionally substituted.

[280] In certain embodiments, R^{NI} is H.

[281] In certain embodiments, R^{NI} is optionally substituted C₁₋₆ alkyl. In certain embodiments, R^{NI} is optionally substituted C₃₋₇ cycloalkyl. In certain embodiments, R^{NI} is optionally substituted C₁₋₆ acyl. In certain embodiments, R^{NI} is a nitrogen protecting group.

[282] As defined herein, each R^N is independently H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ acyl, or a nitrogen protecting group, or two R^N attached to the same nitrogen atom are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, acyl, or heterocyclyl is independently optionally substituted.

[283] In certain embodiments, at least one instance of R^N is H. In certain embodiments, each instance of R^N is H.

[284] In certain embodiments, at least one instance of R^N is optionally substituted C₁₋₆ alkyl.

[285] In certain embodiments, at least one instance of R^N is optionally substituted C₃₋₇ cycloalkyl. In

certain embodiments, at least one instance of R^N is optionally substituted C_{1-6} acyl. In certain embodiments, at least one instance of R^N is a nitrogen protecting group.

[286] In certain embodiments, two R^N attached to the same nitrogen atom are joined together with the intervening atoms to form optionally substituted 3-7 membered heterocyclyl. In certain embodiments, two R^N attached to the same nitrogen atom are joined together with the intervening atoms to form optionally substituted 4-6 membered heterocyclyl.

[287] As defined herein, each instance of R^O is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{1-6} acyl, or an oxygen protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted.

[288] In certain embodiments, at least one instance of R^O is H. In certain embodiments, each instance of R^O is H.

[289] In certain embodiments, at least one instance of R^O is optionally substituted C_{1-6} alkyl.

[290] In certain embodiments, at least one instance of R^O is C_{1-6} haloalkyl. In certain embodiments, at least one instance of R^O is C_{1-3} haloalkyl. In certain embodiments, at least one instance of R^O is C_1 haloalkyl. In certain embodiments, at least one instance of R^O is $-CF_3$.

[291] In certain embodiments, at least one instance of R^O is optionally substituted C_{3-7} cycloalkyl. In certain embodiments, at least one instance of R^O is optionally substituted 3-7 membered heterocyclyl. In certain embodiments, at least one instance of R^O is optionally substituted C_{1-6} acyl. In certain embodiments, at least one instance of R^O is an oxygen protecting group.

[292] As defined herein, each instance of R^S is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{1-6} acyl, or a sulfur protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted.

[293] In certain embodiments, at least one instance of R^S is H.

[294] In certain embodiments, at least one instance of R^S is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^S is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^S is optionally substituted C_{1-3} alkyl. In certain embodiments, at least one instance of R^S is unsubstituted C_{1-3} alkyl. In certain embodiments, at least one instance of R^S is methyl.

[295] In certain embodiments, at least one instance of R^S is C_{1-6} haloalkyl. In certain embodiments, at least one instance of R^S is optionally substituted C_{3-7} cycloalkyl. In certain embodiments, at least one instance of R^S is optionally substituted 3-7 membered heterocyclyl. In certain embodiments, at least one instance of R^S is optionally substituted C_{1-6} acyl. In certain embodiments, at least one instance of R^S is a sulfur protecting group.

[296] As defined herein, each instance of R^{S1} is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted.

[297] In certain embodiments, at least one instance of R^{S1} is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S1} is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^{S1} is optionally substituted C_{1-3} alkyl. In certain embodiments, at least one instance of R^{S1} is

unsubstituted C₁₋₃ alkyl. In certain embodiments, at least one instance of R^{S1} is methyl.

[298] In certain embodiments, at least one instance of R^{S1} is C₁₋₆ haloalkyl. In certain embodiments, at least one instance of R^{S1} is optionally substituted C₃₋₇ cycloalkyl. In certain embodiments, at least one instance of R^{S1} is optionally substituted 3-7 membered heterocyclyl.

Pharmaceutical Compositions, Kits, and Administration

[299] The present disclosure provides pharmaceutical compositions comprising a compound provided herein (*e.g.*, a compound of Formula (I), or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof) and one or more pharmaceutically acceptable carriers and/or excipients. In certain embodiments, a compound described herein 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.

[300] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include bringing the compound described herein (*i.e.*, the “active ingredient”) into association with a carrier or excipient, 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.

[301] 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. 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 one-half or one-third of such a dosage.

[302] Relative amounts of the active ingredient, the pharmaceutically acceptable carrier or excipient, and/or any additional ingredients in a pharmaceutical composition described herein 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.

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

[304] The compounds and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, intradermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, buccal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (*e.g.*, systemic

intravenous injection), regional administration *via* blood and/or lymph supply, and/or direct administration to an affected site. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (*e.g.*, its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration).

[305] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[306] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions described herein will be decided by a physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex, and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[307] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound, mode of administration, and the like. An effective amount may be included in a single dose (*e.g.*, single oral dose) or multiple doses (*e.g.*, multiple oral doses). In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, any two doses of the multiple doses include different or substantially the same amounts of a compound described herein.

[308] 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, 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.

[309] 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 a single unit dosage form. 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 and/or preventing a disease, disorder, or condition in a subject in need thereof.

[310] 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 provide instructions for treating a disease (*e.g.*, cancer) in a subject in need thereof. In certain embodiments, the kits provide instructions for preventing a disease in a subject in need thereof. A kit described herein may include one or more additional pharmaceutical agents described herein as a separate composition.

Methods of Treatment and Uses

[311] As described in some aspects, compounds provided herein can act as voltage-gated potassium channel potentiators (*e.g.*, Kv7.2/Kv7.3 potentiators) and are therefore useful, *e.g.*, for the treatment of diseases, disorders, and conditions.

[312] In one aspect, provided herein are methods of potentiating a Kv7 potassium channel in a subject comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof. In certain embodiments, the Kv7 potassium channel is Kv7.2, Kv7.3, Kv7.4, and/or Kv7.5. In certain embodiments, the Kv7 potassium channel is Kv7.2. In certain embodiments, the Kv7 potassium channel is Kv7.3. In certain embodiments, the Kv7 potassium channel is Kv7.2/Kc7.3. In certain embodiments, the compound or composition is selective for one or more of Kv7.2-Kv7.5 over Kv7.1. In certain embodiments, the compound or composition is selective for one or more of Kv7.2/Kv7.3 over Kv7.1.

[313] Also provided herein are compounds disclosed herein, and a pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof, and pharmaceutical compositions thereof, for use in potentiating a Kv7 potassium channel in a subject.

[314] In another aspect, provided herein are methods of treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject in need thereof comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition

thereof. In certain embodiments, the disease, disorder, or condition is associated with Kv7.2, Kv7.3, Kv7.4, and/or Kv7.5 dysfunction. In certain embodiments, the disease, disorder, or condition is associated with Kv7.2 dysfunction. In certain embodiments, the disease, disorder, or condition is associated with Kv7.3 dysfunction. In certain embodiments, the disease, disorder, or condition is associated with Kv7.2/Kc7.3 dysfunction.

[315] Also provided herein are compounds disclosed herein, and a pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof, and pharmaceutical compositions thereof, for use in treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject.

[316] In another aspect, provided herein are methods of treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject in need thereof comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

[317] Also provided herein are compounds disclosed herein, and a pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof, and pharmaceutical compositions thereof, for use in treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject in need thereof.

[318] In certain embodiments, the disease, disorder, or condition is a seizure disorder. “Seizure disorders” refers to seizures and disorders associated with seizures such as partial onset seizures (also known as focal onset seizures), photosensitive epilepsy, self-induced syncope, intractable epilepsy, Angelman syndrome, benign rolandic epilepsy, CDKL5 disorder, childhood and juvenile absence epilepsy, Dravet syndrome, frontal lobe epilepsy, Glut1 deficiency syndrome, hypothalamic hamartoma, infantile spasms/West’s syndrome, juvenile myoclonic epilepsy, Landau-Kleffner syndrome, Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic-absences, Ohtahara syndrome, Panayiotopoulos syndrome, PCDH19 epilepsy, progressive myoclonic epilepsies, Rasmussen’s syndrome, ring chromosome 20 syndrome, reflex epilepsies, temporal lobe epilepsy, Lafora progressive myoclonus epilepsy, neurocutaneous syndromes, tuberous sclerosis complex, early infantile epileptic encephalopathy, early onset epileptic encephalopathy, generalized epilepsy with febrile seizures +, Rett syndrome, multiple sclerosis, Alzheimer’s disease, autism, ataxia, hypotonia, paroxysmal dyskinesia, generalized onset seizures, or primary generalized tonic-clonic seizures, or a combination thereof. In certain embodiments, the seizure disorder refers to generalized onset seizures. In some embodiments, the generalized onset seizures are primary generalized tonic-clonic seizures. In some embodiments, the seizure disorder is primary generalized tonic-clonic seizures.

[319] In certain embodiments, the term “seizure disorder” refers to focal onset epilepsy, also known as partial onset epilepsy. In some embodiments, the seizure disorder is photosensitive epilepsy. In some embodiments, the seizure disorder is self-induced syncope. In some embodiments, the seizure disorder is intractable epilepsy. In some embodiments, the seizure disorder is Angelman syndrome. In some embodiments, the seizure disorder is benign rolandic epilepsy. In some embodiments, the seizure disorder

is CDKL5 disorder. In some embodiments, the seizure disorder is childhood and juvenile absence epilepsy. In some embodiments, the seizure disorder is Dravet syndrome. In some embodiments, the seizure disorder is frontal lobe epilepsy. In some embodiments, the seizure disorder is Glut1 deficiency syndrome. In some embodiments, the seizure disorder is hypothalamic hamartoma. In some embodiments, the seizure disorder is infantile spasms/West's syndrome. In some embodiments, the seizure disorder is juvenile myoclonic epilepsy. In some embodiments, the seizure disorder is Landau-Kleffner syndrome. In some embodiments, the seizure disorder is Lennox-Gastaut syndrome (LGS). In some embodiments, the seizure disorder is epilepsy with myoclonic-absences. In some embodiments, the seizure disorder is Ohtahara syndrome. In some embodiments, the seizure disorder is Panayiotopoulos syndrome. In some embodiments, the seizure disorder is PCDH19 epilepsy. In some embodiments, the seizure disorder is progressive myoclonic epilepsies. In some embodiments, the seizure disorder is Rasmussen's syndrome. In some embodiments, the seizure disorder is ring chromosome 20 syndrome. In some embodiments, the seizure disorder is reflex epilepsies. In some embodiments, the seizure disorder is temporal lobe epilepsy. In some embodiments, the seizure disorder is Lafora progressive myoclonus epilepsy. In some embodiments, the seizure disorder is neurocutaneous syndromes. In some embodiments, the seizure disorder is tuberous sclerosis complex. In some embodiments, the seizure disorder is early infantile epileptic encephalopathy. In some embodiments, the seizure disorder is early onset epileptic encephalopathy. In some embodiments, the seizure disorder is generalized epilepsy. In some embodiments, the seizure disorder is generalized epilepsy with febrile seizures +. In some embodiments, the seizure disorder is Rett syndrome. In some embodiments, the seizure disorder is multiple sclerosis. In some embodiments, the seizure disorder is Alzheimer's disease. In some embodiments, the seizure disorder is autism. In some embodiments, the seizure disorder is ataxia. In some embodiments, the seizure disorder is hypotonia. In some embodiments, the seizure disorder is paroxysmal dyskinesia. In some embodiments, the seizure disorder is generalized onset seizures. In some embodiments, the seizure disorder is focal onset seizures (also known as partial onset seizures).

[320] In certain embodiments, the disease, disorder, or condition is a depressive disorder. "Depressive disorders" are mood disorders characterized by depressed mood. In certain embodiments, the depressive disorder is major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder, bipolar spectrum disorder, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated with agitation or anxiety, adjustment disorder with depressed mood, prolonged depressive reaction, or a combination thereof.

[321] In some embodiments, the depressive disorder is major depressive disorder (MDD). In some embodiments, the depressive disorder is disruptive mood dysregulation disorder. In some embodiments, the depressive disorder is persistent depressive disorder. In some embodiments, the depressive disorder is bipolar spectrum disorder. In some embodiments, the depressive disorder is postpartum depression. In some embodiments, the depressive disorder is premenstrual dysphoric disorder (PMDD). In some embodiments, the depressive disorder is seasonal affective disorder (SAD). In some embodiments, the

depressive disorder is atypical depression. In some embodiments, the depressive disorder is treatment-resistant depression (TRD). In some embodiments, the depressive disorder is depression associated with agitation or anxiety. In some embodiments, the depressive disorder is adjustment disorder with depressed mood. In some embodiments, the depressive disorder is prolonged depressive reaction.

[322] Also contemplated by the disclosure is treatment of obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder, social phobia, agoraphobia, agoraphobia with panic disorder, hypochondriasis, post-traumatic stress disorder (PTSD), treatment-resistant bipolar disorder, generalized anxiety disorder, attention-deficit/hyperactivity disorder (ADHD), bipolar I disorder, bipolar II disorder, manic disorder, cyclothymic disorder and bipolar disorder not otherwise specified, dysthymic disorder, depressive disorder not otherwise specified, minor depression, recurrent brief depressive disorder, depressive-type psychosis, impulse-control disorders, schizophrenia, schizophreniform disorder, schizoaffective disorder, Parkinson's disease, dementia, Alzheimer's disease, Huntington's disease, Tourette's syndrome, aggression, and substance use and/or abuse, or a combination thereof.

[323] In certain embodiments, the disease, disorder, or condition is pain. "Pain" as used herein refers to all categories of pain and includes, but is not limited to, neuropathic pain, inflammatory pain, nociceptive pain, idiopathic pain, neuralgic pain, orofacial pain, burn pain, burning mouth syndrome, somatic pain, visceral pain, myofascial pain, dental pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, reflex sympathetic dystrophy, brachial plexus avulsion, neurogenic bladder, acute pain (*e.g.*, musculoskeletal and post-operative pain), chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, familial hemiplegic migraine, conditions associated with cephalic pain, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, pain following stroke, thalamic lesions, radiculopathy, HIV pain, post-herpetic pain, non-cardiac chest pain, irritable bowel syndrome and pain associated with bowel disorders and dyspepsia, and combinations thereof.

[324] In certain embodiments, the disease, disorder, or condition is anhedonia. "Anhedonia" as used herein refers to markedly diminished interest or pleasure in all, or almost all activities. Anhedonia of mild degree is sometimes referred to as hypohedonia. Social anhedonia is a type of anhedonia. "Social anhedonia" as used herein refers to a disinterest in social contact and a lack of pleasure in social situations. Social anhedonia is characterized by social withdrawal and typically manifests as an indifference to social interactions with other people. This trait is considered to be a central characteristic, as well as a predictor, of schizophrenia spectrum disorders.

[325] In another aspect, provided herein are compounds disclosed herein, and a pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof, and pharmaceutical compositions thereof, for use as medicaments. In certain embodiments, the medicament is for treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject (*e.g.*, Kv7.2, Kv7.3, Kv7.4, and/or Kv7.5 dysfunction, *e.g.*, Kv7.2/Kc7.3 dysfunction). In certain embodiments, the medicament is for treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject.

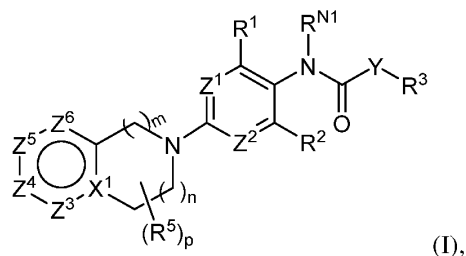
[326] Also provided herein are methods of potentiating a Kv7 potassium channel in a cell *in vitro* comprising contacting the cell with a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof. In certain embodiments, the Kv7 potassium channel is Kv7.2, Kv7.3, Kv7.4, and/or Kv7.5. In certain embodiments, the Kv7 potassium channel is Kv7.2. In certain embodiments, the Kv7 potassium channel is Kv7.3. In certain embodiments, the Kv7 potassium channel is Kv7.2/Kc7.3. In certain embodiments, the compound or composition is selective for one or more of Kv7.2-Kv7.5 over Kv7.1. In certain embodiments, the compound or composition is selective for one or more of Kv7.2/Kv7.3 over Kv7.1.

[327] Provided herein are methods of potentiating a Kv7 potassium channel (*e.g.*, Kv7.2/Kv7.3) in a subject or in a cell *in vitro*. In certain embodiments, the activity of the Kv7 potassium channel (*e.g.*, Kv7.2/Kv7.3) is increased by 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%, or at least 100%, relative to control. In certain embodiments, the activity of the Kv7 potassium channel (*e.g.*, Kv7.2/Kv7.3) is increased by at least 1-fold, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, at least 100-fold, at least 200-fold, at least 300-fold, at least 400-fold, at least 500-fold, or at least 1000-fold, relative to control.

Additional Embodiments

[328] Additional embodiments are provided according to the following numbered embodiments:

Embodiment 1. A compound of Formula (I):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein:

X^1 is C or N;

Z^3 , Z^4 , and Z^6 are each independently CR^4 , N, NR^N , S, or O;

Z^5 is a bond, CR^4 , N, NR^N , S, or O;

provided that least one of Z^3 , Z^4 , Z^5 , and Z^6 is N, NR^N , S, or O, and no more than one of Z^3 , Z^4 , Z^5 , and Z^6 is S or O;

R^1 and R^2 are each independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, -SR^S, -S(=O)₂R^{S1}, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

R^3 is C_{1-8} alkyl, C_{3-10} cycloalkyl, 3-7 membered heterocyclyl, or $-(CR'R'')_w-Ar^1$, wherein the alkyl, cycloalkyl, or heterocyclyl is optionally substituted; w is 0, 1, or 2; Ar^1 is C_{6-10} aryl or 5-10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted;

Y is a bond, $-CR'R''$ -, $-O$ -, or $-NR^Y$ -;

R^Y is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or a nitrogen protecting group, or R^Y and R^3 are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein the alkyl, cycloalkyl, acyl, or heterocyclyl is optionally substituted;

Z^1 and Z^2 are each independently CR^Z or N;

each instance of R^Z is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, $-CN$, $-OR^O$, $-N(R^N)_2$, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R^4 is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, $-CN$, $-OR^O$, $-N(R^N)_2$, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R^5 is independently halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, $-CN$, $-OR^O$, $-N(R^N)_2$, or C_{1-6} acyl, or two R^5 attached to the same carbon atom are joined together with the intervening atoms to form C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, or two R^5 attached to the same carbon atom are taken together to form $=O$, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl, is independently optionally substituted;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

m is 1 or 2;

n is 0, 1, or 2;

each instance of R' is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, or 3-7 membered heterocyclyl, each instance of R'' is independently H, halogen, C_{1-6} alkyl, $-OR^O$, or $-N(R^N)_2$, or R' and R'' attached to the same carbon atom are joined together with the intervening atoms to form C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted, or R' and R'' attached to the same carbon atom are taken together to form $=O$;

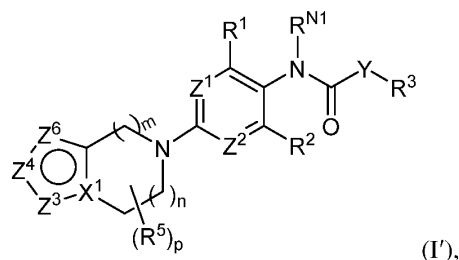
each instance of R^N and R^N is independently H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} acyl, or a nitrogen protecting group, or two R^N attached to the same nitrogen atom are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, acyl, or heterocyclyl is independently optionally substituted;

each instance of R^O is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{1-6} acyl, or an oxygen protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted;

each instance of R^S is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{1-6} acyl, or a sulfur protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted; and

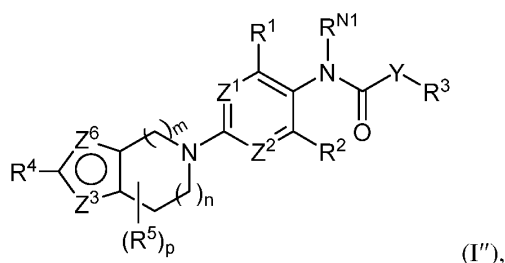
each instance of R^{S1} is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted.

Embodiment 2. The compound of Embodiment 1, wherein the compound is of Formula (I'):



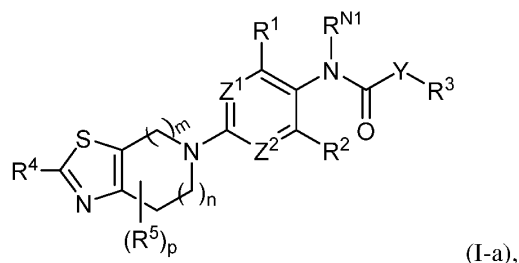
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 3. The compound of Embodiment 1, wherein the compound is of Formula (I''):



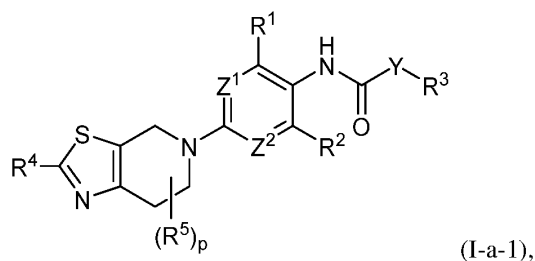
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 4. The compound of Embodiment 1, wherein the compound is of Formula (I-a):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

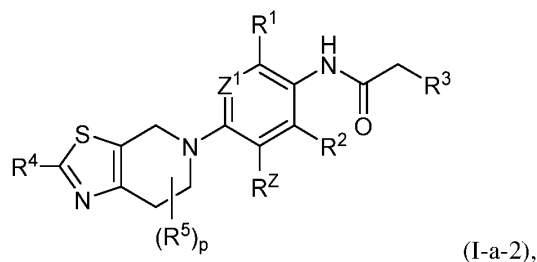
Embodiment 5. The compound of Embodiment 1, wherein the compound is of Formula (I-a-1):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or

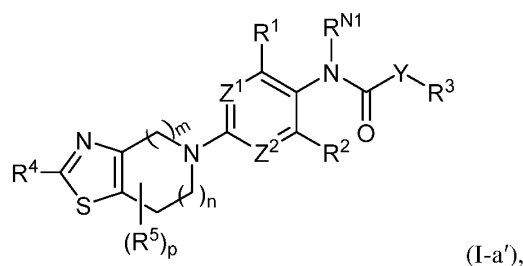
prodrug thereof.

Embodiment 6. The compound of Embodiment 1, wherein the compound is of Formula (I-a-2):



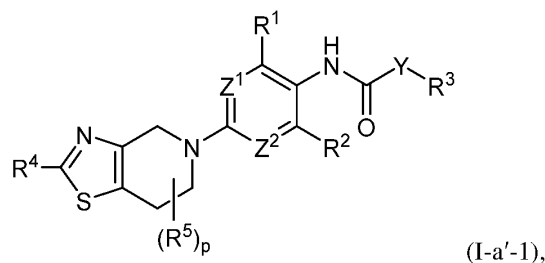
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 7. The compound of Embodiment 1, wherein the compound is of Formula (I-a'):



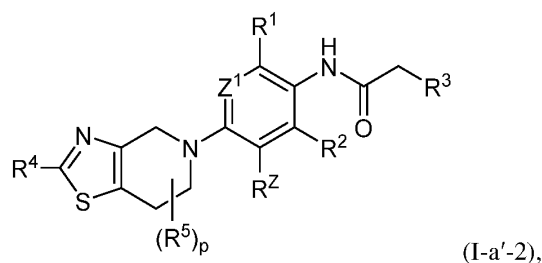
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 8. The compound of Embodiment 1, wherein the compound is of Formula (I-a'-1):



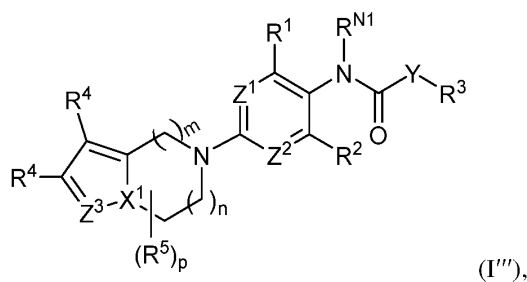
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 9. The compound of Embodiment 1, wherein the compound is of Formula (I-a'-2):



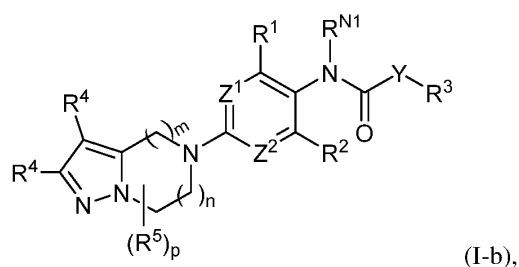
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 10. The compound of Embodiment 1, wherein the compound is of Formula (I'''):



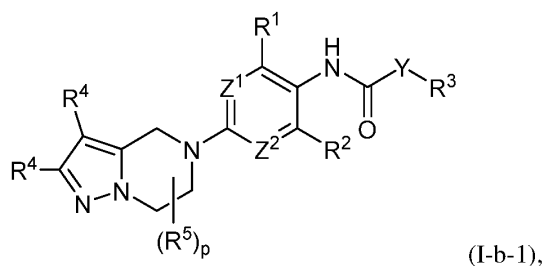
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 11. The compound of Embodiment 1, wherein the compound is of Formula (I-b):



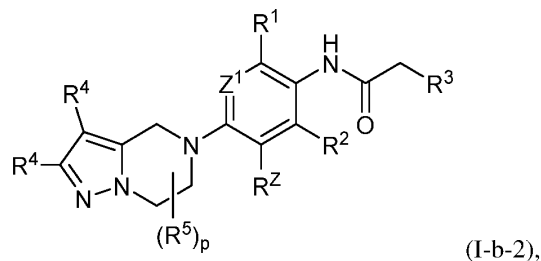
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 12. The compound of Embodiment 1, wherein the compound is of Formula (I-b-1):



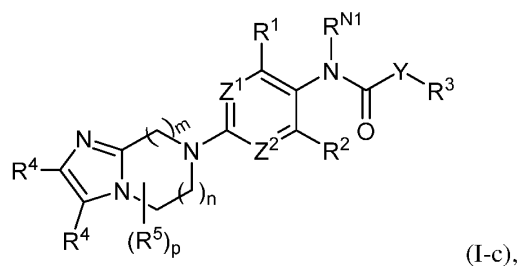
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 13. The compound of Embodiment 1, wherein the compound is of Formula (I-b-2):



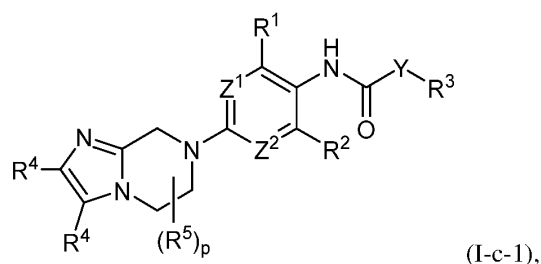
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 14. The compound of Embodiment 1, wherein the compound is of Formula (I-c):



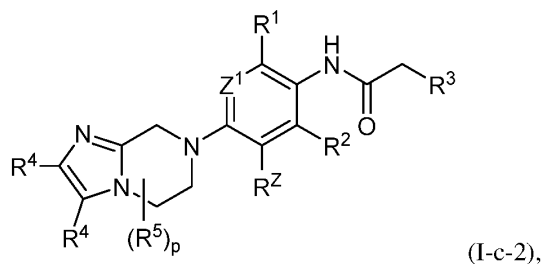
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 15. The compound of Embodiment 1, wherein the compound is of Formula (I-c-1):



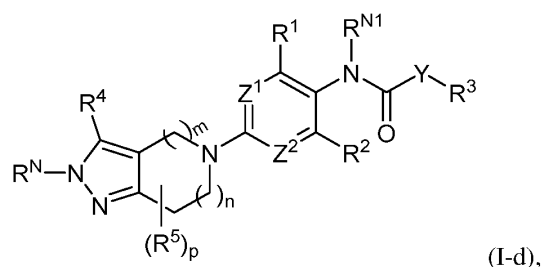
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 16. The compound of Embodiment 1, wherein the compound is of Formula (I-c-2):



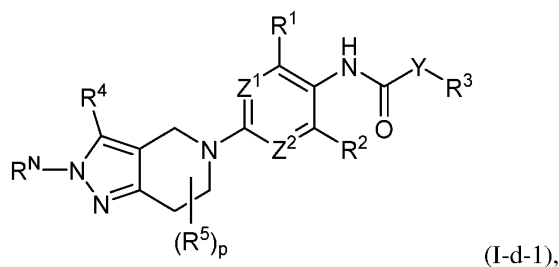
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 17. The compound of Embodiment 1, wherein the compound is of Formula (I-d):



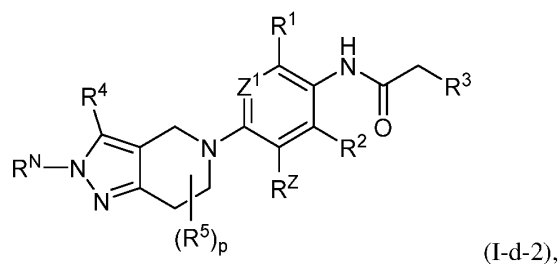
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 18. The compound of Embodiment 1, wherein the compound is of Formula (I-d-1):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 19. The compound of Embodiment 1, wherein the compound is of Formula (I-d-2):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 20. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1.

Embodiment 21. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein n is 1.

Embodiment 22. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein n is 2.

Embodiment 23. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^{N1} is H.

Embodiment 24. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R¹ is optionally substituted C₁₋₆ alkyl.

Embodiment 25. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R¹ unsubstituted C₁₋₃ alkyl.

Embodiment 26. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R¹ is methyl.

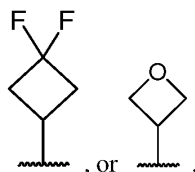
Embodiment 27. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is halogen, C_{1-6} haloalkyl, or $-OR^O$.

Embodiment 28. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is F, Cl, $-CF_3$, or $-OMe$.

Embodiment 29. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted.

Embodiment 30. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is C_{3-5} cycloalkyl or 3-5 membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl.

Embodiment 31. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is:



Embodiment 32. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is H.

Embodiment 33. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is optionally substituted C_{1-6} alkyl.

Embodiment 34. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is unsubstituted C_{1-3} alkyl.

Embodiment 35. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is methyl.

Embodiment 36. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is halogen.

Embodiment 37. The compound of any one of the preceding Embodiments, or a

pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is F or Cl.

Embodiment 38. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is $-CR'R''-$.

Embodiment 39. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is $-CH_2-$.

Embodiment 40. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is $-CH(Me)-$.

Embodiment 41. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C_{1-8} alkyl.

Embodiment 42. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is unsubstituted C_{1-4} alkyl.

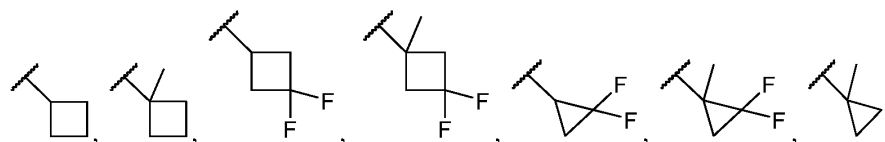
Embodiment 43. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is *tert*-butyl.

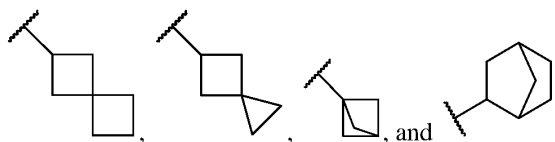
Embodiment 44. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C_{3-10} cycloalkyl.

Embodiment 45. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C_{3-8} cycloalkyl.

Embodiment 46. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is C_{3-8} cycloalkyl optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl.

Embodiment 47. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is selected from:



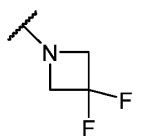


Embodiment 48. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted 3-7 membered heterocyclyl.

Embodiment 49. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted 3-6 membered heterocyclyl having 1 or 2 ring N atoms.

Embodiment 50. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is 3-6 membered heterocyclyl having 1 or 2 ring N atoms and optionally substituted with one or more halogen and/or unsubstituted C_{1-6} alkyl.

Embodiment 51. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is:



Embodiment 52. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is CR^Z .

Embodiment 53. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is CH.

Embodiment 54. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is N.

Embodiment 55. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is CR^Z .

Embodiment 56. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is CH.

Embodiment 57. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or

prodrug thereof, wherein Z^2 is CF.

Embodiment 58. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is N.

Embodiment 59. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_{1-6} haloalkyl.

Embodiment 60. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_{1-3} haloalkyl.

Embodiment 61. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_1 haloalkyl.

Embodiment 62. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is $-CF_3$.

Embodiment 63. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, or optionally substituted phenyl.

Embodiment 64. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is halogen, unsubstituted C_{1-6} alkyl, halogen, unsubstituted C_{3-7} cycloalkyl, or unsubstituted phenyl.

Embodiment 65. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is methyl, *tert*-butyl, Cl, cyclopropyl, or phenyl.

Embodiment 66. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein p is 0.

Embodiment 67. The compound of Embodiment 1, wherein the compound is selected from those in **Tables 1A-1C**, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof.

Embodiment 68. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt thereof.

Embodiment 69. A pharmaceutical composition comprising a compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 70. A method of potentiating a Kv7 potassium channel in a subject comprising administering to the subject a compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

Embodiment 71. A method of treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject in need thereof comprising administering to the subject a compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

Embodiment 72. The method of Embodiment 70 or 71, wherein the method enhances opening of a Kv7 potassium channel.

Embodiment 73. The method of any one of Embodiments 70-72, wherein the Kv7 potassium channel is selected from one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5.

Embodiment 74. The method of any one of Embodiments 70-73, wherein the Kv7 potassium channel is Kv7.2/Kv7.3.

Embodiment 75. A method of treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject in need thereof comprising administering to the subject a compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

Embodiment 76. The method of any one of Embodiments 70-75, wherein the subject is a human.

Embodiment 77. A compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in potentiating a Kv7 potassium channel in a subject.

Embodiment 78. A compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject.

Embodiment 79. The compound for use of Embodiment 77 or 78, wherein the compound enhances opening of a Kv7 potassium channel.

Embodiment 80. The compound for use of any one of Embodiments 77-79, wherein the Kv7 potassium channel is selected from one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5.

Embodiment 81. The compound for use of any one of Embodiments 77-80, wherein the Kv7 potassium channel is Kv7.2/Kv7.3.

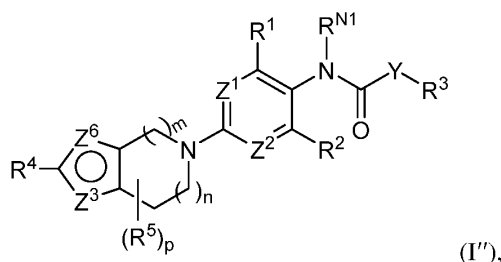
Embodiment 82. A compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject.

Embodiment 83. The compound for use of any one of Embodiments 77-82, wherein the subject is a human.

Embodiment 84. A compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use as a medicament.

[329] Further additional embodiments are provided according to the following numbered Embodiments:

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



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein:

Z^3 is N and Z^6 is S, or Z^3 is S and Z^6 is N;

R^1 and R^2 are each independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, -SR^S, -S(=O)₂R^{S1}, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

R^3 is C_{1-8} alkyl, C_{3-10} cycloalkyl, 3-7 membered heterocyclyl, or -(CR'R'')_w-Ar¹, wherein the alkyl, cycloalkyl, or heterocyclyl is optionally substituted; w is 0, 1, or 2; Ar¹ is C_{6-10} aryl or 5-10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted;

Y is a bond, -CR'R''-, -O-, or -NR^Y-;

R^Y is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or a nitrogen protecting group, or R^Y and R³ are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein the alkyl, cycloalkyl, acyl, or heterocyclyl is optionally substituted;

Z^1 and Z^2 are each independently CR^Z or N;

each instance of R^Z is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

R^4 is H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R⁵ is independently halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, or two R⁵ attached to the same carbon atom are joined together with the intervening atoms to form C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, or two R⁵ attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl,

heterocyclyl, or acyl, is independently optionally substituted;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

m is 1 or 2;

n is 0, 1, or 2;

each instance of R' is independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3-7 membered heterocyclyl, each instance of R'' is independently H, halogen, C₁₋₆ alkyl, -OR^O, or -N(R^N)₂, or R' and R'' attached to the same carbon atom are joined together with the intervening atoms to form C₃₋₇ cycloalkyl or 3-7 membered heterocyclyl, or R' and R'' attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted;

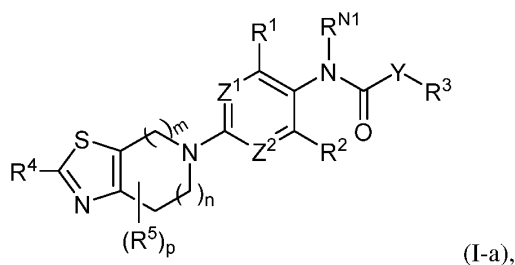
each instance of R^{N1} and R^N is independently H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ acyl, or a nitrogen protecting group, or two R^N attached to the same nitrogen atom are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, acyl, or heterocyclyl is independently optionally substituted;

each instance of R^O is independently H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₁₋₆ acyl, or an oxygen protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted;

each instance of R^S is independently H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₁₋₆ acyl, or a sulfur protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted; and

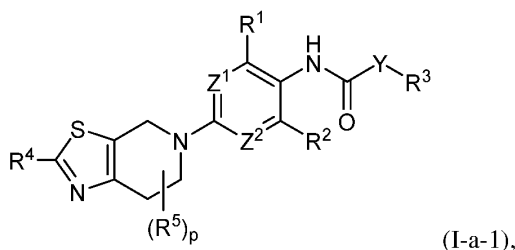
each instance of R^{S1} is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted.

Embodiment 2. The compound of Embodiment 1, wherein the compound is of Formula (I-a):



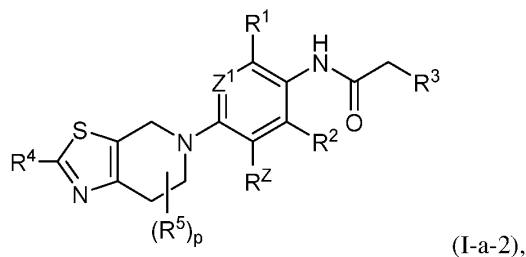
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 3. The compound of Embodiment 1, wherein the compound is of Formula (I-a-1):



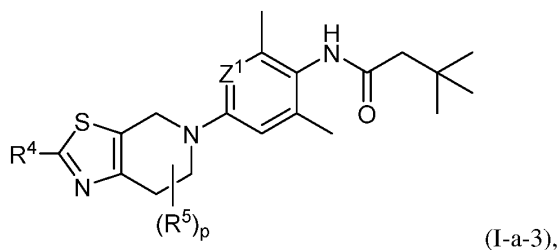
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 4. The compound of Embodiment 1, wherein the compound is of Formula (I-a-2):



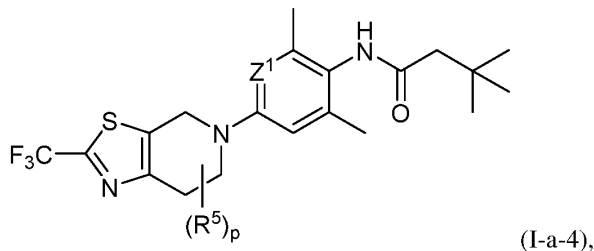
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 5. The compound of Embodiment 1, wherein the compound is of Formula (I-a-3):



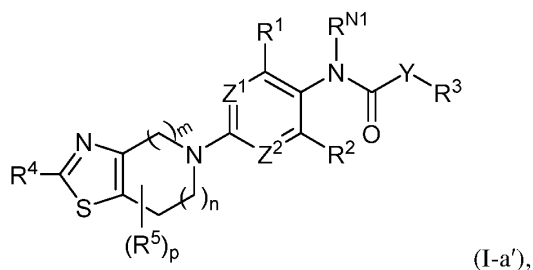
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 6. The compound of Embodiment 1, wherein the compound is of Formula (I-a-4):



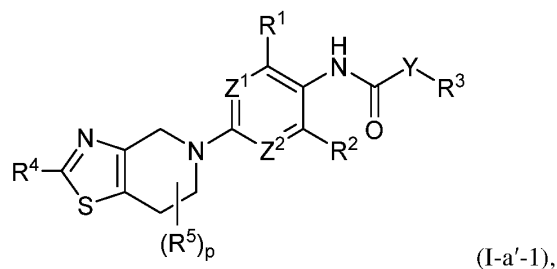
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 7. The compound of Embodiment 1, wherein the compound is of Formula (I-a'):



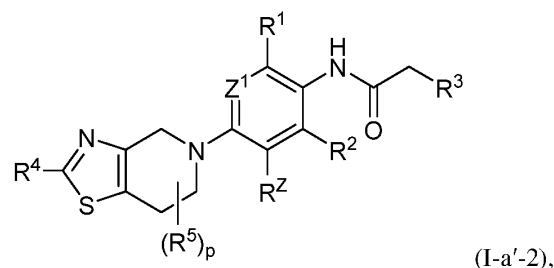
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 8. The compound of Embodiment 1, wherein the compound is of Formula (I-a'-1):



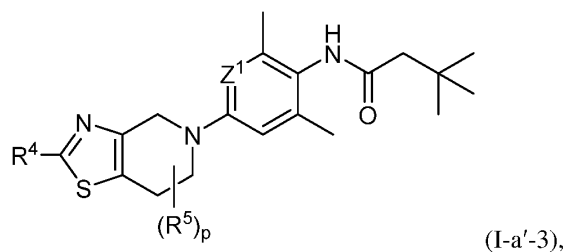
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 9. The compound of Embodiment 1, wherein the compound is of Formula (I-a'-2):



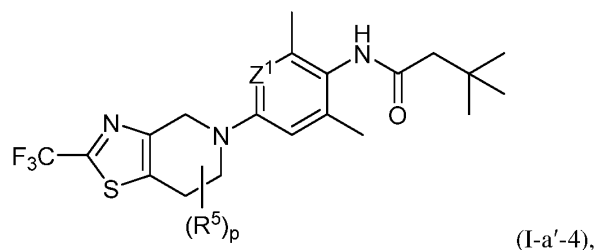
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 10. The compound of Embodiment 1, wherein the compound is of Formula (I-a'-3):



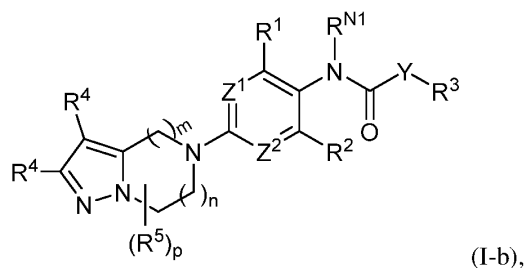
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 11. The compound of Embodiment 1, wherein the compound is of Formula (I-a'-4):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 12. A compound of Formula (I-b):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein:

R^1 and R^2 are each independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, -SR^S, -S(=O)₂R^{S1}, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

R^3 is C_{1-8} alkyl, C_{3-10} cycloalkyl, 3-7 membered heterocyclyl, or -(CR'R'')_w-Ar¹, wherein the alkyl, cycloalkyl, or heterocyclyl is optionally substituted; w is 0, 1, or 2; Ar¹ is C_{6-10} aryl or 5-10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted;

Y is a bond, -CR'R''-, -O-, or -NR^Y-;

R^Y is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or a nitrogen protecting group, or R^Y and R^3 are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein the alkyl, cycloalkyl, acyl, or heterocyclyl is optionally substituted;

Z^1 and Z^2 are each independently CR^Z or N;

each instance of R^Z is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R^4 is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R^5 is independently halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, or two R^5 attached to the same carbon atom are joined together with the intervening atoms to form C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, or two R^5 attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl, is independently optionally substituted;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

m is 1 or 2;

n is 0, 1, or 2;

each instance of R' is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, or 3-7 membered heterocyclyl, each instance of R'' is independently H, halogen, C_{1-6} alkyl, -OR^O, or -N(R^N)₂, or R' and R'' attached to the same carbon atom are joined together with the intervening atoms to form C_{3-7}

cycloalkyl or 3-7 membered heterocyclyl, or R' and R'' attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted;

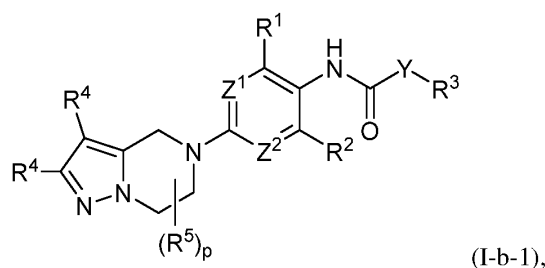
each instance of R^{N1} and R^N is independently H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ acyl, or a nitrogen protecting group, or two R^N attached to the same nitrogen atom are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, acyl, or heterocyclyl is independently optionally substituted;

each instance of R^O is independently H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₁₋₆ acyl, or an oxygen protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted;

each instance of R^S is independently H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₁₋₆ acyl, or a sulfur protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted; and

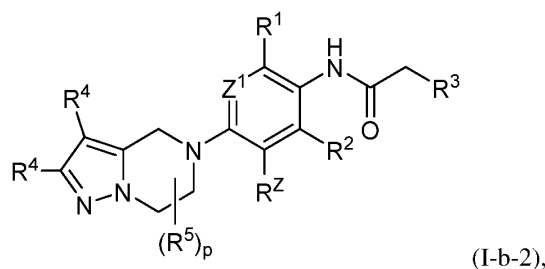
each instance of R^{S1} is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted.

Embodiment 13. The compound of Embodiment 12, wherein the compound is of Formula (I-b-1):



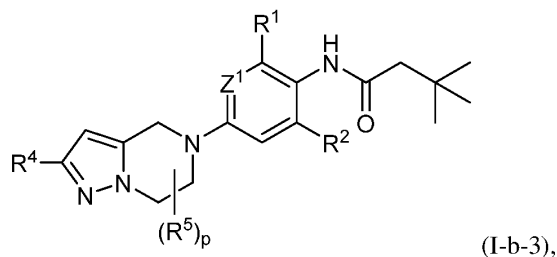
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 14. The compound of Embodiment 12, wherein the compound is of Formula (I-b-2):



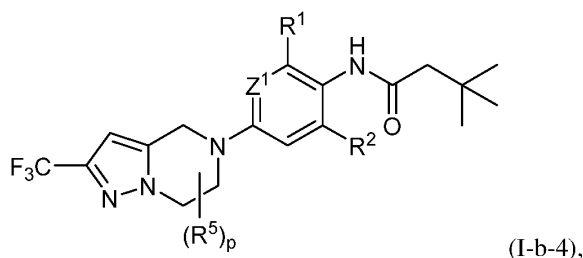
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 15. The compound of Embodiment 12, wherein the compound is of Formula (I-b-3):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 16. The compound of Embodiment 12, wherein the compound is of Formula (I-b-4):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 17. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1.

Embodiment 18. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein n is 1.

Embodiment 19. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1 and n is 1.

Embodiment 20. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein n is 2.

Embodiment 21. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1 and n is 2.

Embodiment 22. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^{N1} is H.

Embodiment 23. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1, n is 1, and R^{N1} is H.

Embodiment 24. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is optionally substituted C_{1-6} alkyl.

Embodiment 25. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 unsubstituted C_{1-3} alkyl.

Embodiment 26. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is methyl.

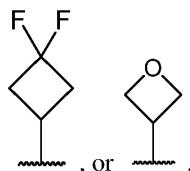
Embodiment 27. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is halogen, C_{1-6} haloalkyl, or $-OR^O$.

Embodiment 28. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is F, Cl, $-CF_3$, or $-OMe$.

Embodiment 29. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted.

Embodiment 30. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is C_{3-5} cycloalkyl or 3-5 membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl.

Embodiment 31. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is:



Embodiment 32. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is H.

Embodiment 33. The compound of any one of the preceding Embodiments, or a

pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is optionally substituted C_{1-6} alkyl.

Embodiment 34. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is unsubstituted C_{1-3} alkyl.

Embodiment 35. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is methyl.

Embodiment 36. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is halogen.

Embodiment 37. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is F or Cl.

Embodiment 38. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is $-CR'R''-$.

Embodiment 39. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is $-CH_2-$.

Embodiment 40. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is $-CH(Me)-$.

Embodiment 41. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C_{1-8} alkyl.

Embodiment 42. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is unsubstituted C_{1-4} alkyl.

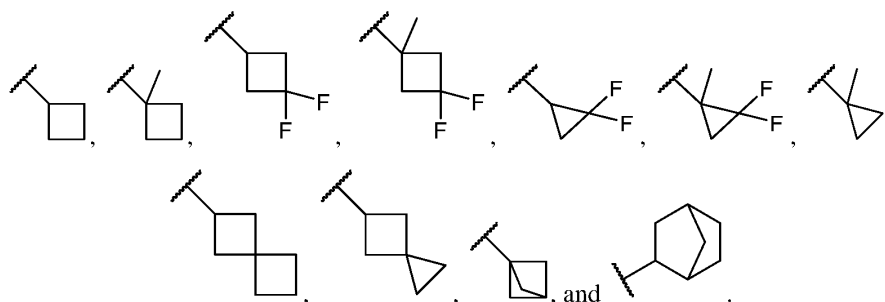
Embodiment 43. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is *tert*-butyl.

Embodiment 44. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C_{3-10} cycloalkyl.

Embodiment 45. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C_{3-8} cycloalkyl.

Embodiment 46. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is C_{3-8} cycloalkyl optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl.

Embodiment 47. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is selected from:

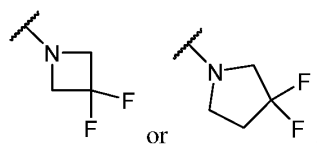


Embodiment 48. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted 3-7 membered heterocyclyl.

Embodiment 49. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted 3-6 membered heterocyclyl having 1 or 2 ring N atoms.

Embodiment 50. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is 3-6 membered heterocyclyl having 1 or 2 ring N atoms and optionally substituted with one or more halogen and/or unsubstituted C_{1-6} alkyl.

Embodiment 51. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is:



Embodiment 52. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is CR^Z .

Embodiment 53. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is CH.

Embodiment 54. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is N.

Embodiment 55. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is CR^Z .

Embodiment 56. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is CH.

Embodiment 57. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is CF.

Embodiment 58. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is N.

Embodiment 59. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_{1-6} haloalkyl.

Embodiment 60. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_{1-3} haloalkyl.

Embodiment 61. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_1 haloalkyl.

Embodiment 62. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is $-CF_3$.

Embodiment 63. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, or optionally substituted phenyl.

Embodiment 64. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is halogen, unsubstituted C_{1-6} alkyl, halogen, unsubstituted C_{3-7} cycloalkyl, or unsubstituted phenyl.

Embodiment 65. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is methyl, *tert*-butyl, Cl, cyclopropyl, or phenyl.

Embodiment 66. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein p is 0.

Embodiment 67. A compound selected from those in **Tables 1A-1C**, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof.

Embodiment 68. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt thereof.

Embodiment 69. A pharmaceutical composition comprising a compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 70. A method of potentiating a Kv7 potassium channel in a subject comprising administering to the subject a compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

Embodiment 71. A method of treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject in need thereof comprising administering to the subject a compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

Embodiment 72. The method of Embodiment 70 or 71, wherein the method enhances opening of a Kv7 potassium channel.

Embodiment 73. The method of any one of Embodiments 70-72, wherein the Kv7 potassium channel is selected from one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5.

Embodiment 74. The method of any one of Embodiments 70-73, wherein the Kv7 potassium channel is Kv7.2/Kv7.3.

Embodiment 75. A method of treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject in need thereof comprising administering to the subject a compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

Embodiment 76. The method of any one of Embodiments 70-75, wherein the subject is a human.

Embodiment 77. A compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in potentiating a Kv7 potassium channel in a subject.

Embodiment 78. A compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject.

Embodiment 79. The compound for use of Embodiment 77 or 78, wherein the compound enhances opening of a Kv7 potassium channel.

Embodiment 80. The compound for use of any one of Embodiments 77-79, wherein the Kv7 potassium channel is selected from one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5.

Embodiment 81. The compound for use of any one of Embodiments 77-80, wherein the Kv7 potassium channel is Kv7.2/Kv7.3.

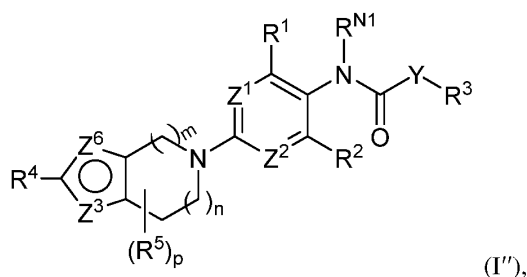
Embodiment 82. A compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject.

Embodiment 83. The compound for use of any one of Embodiments 77-82, wherein the subject is a human.

Embodiment 84. A compound of any one of Embodiments 1-68, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use as a medicament.

[330] Further additional embodiments are provided according to the following numbered Embodiments:

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



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein:

Z^3 is N and Z^6 is S,

Z^3 is S and Z^6 is N,

Z^3 is N and Z^6 is O, or

Z^3 is O and Z^6 is N;

R^1 and R^2 are each independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, -SR^S, -S(=O)₂R^{S1}, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

R^3 is C_{1-8} alkyl, C_{3-10} cycloalkyl, 3-7 membered heterocyclyl, or -(CR'R'')_w-Ar¹, wherein the alkyl, cycloalkyl, or heterocyclyl is optionally substituted; w is 0, 1, or 2; Ar¹ is C_{6-10} aryl or 5-10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted;

Y is a bond, -CR'R''), -O-, or -NR^Y-;

R^Y is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or a nitrogen protecting group, or R^Y and R^3 are joined

together with the intervening atoms to form 3-7 membered heterocyclyl, wherein the alkyl, cycloalkyl, acyl, or heterocyclyl is optionally substituted;

Z^1 and Z^2 are each independently CR^Z or N;

each instance of R^Z is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

R^4 is H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R^5 is independently halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, or two R^5 attached to the same carbon atom are joined together with the intervening atoms to form C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, or two R^5 attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl, is independently optionally substituted;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

m is 1 or 2;

n is 0, 1, or 2;

each instance of R' is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, or 3-7 membered heterocyclyl, each instance of R'' is independently H, halogen, C_{1-6} alkyl, -OR^O, or -N(R^N)₂, or R' and R'' attached to the same carbon atom are joined together with the intervening atoms to form C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, or R' and R'' attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted;

each instance of R^{N1} and R^N is independently H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} acyl, or a nitrogen protecting group, or two R^N attached to the same nitrogen atom are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, acyl, or heterocyclyl is independently optionally substituted;

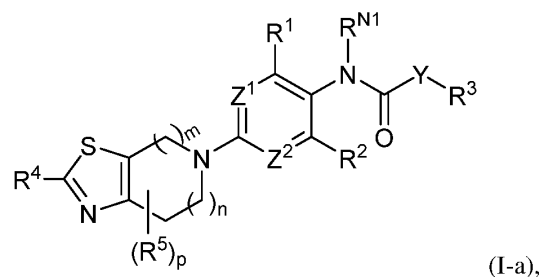
each instance of R^O is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{1-6} acyl, or an oxygen protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted;

each instance of R^S is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{1-6} acyl, or a sulfur protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted; and

each instance of R^{S1} is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted.

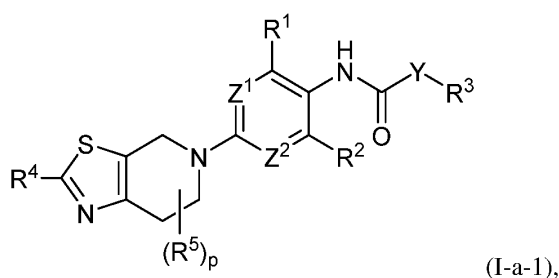
Embodiment 2. The compound of Embodiment 1, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^3 is N and Z^6 is S, or Z^3 is S and Z^6 is N.

Embodiment 3. The compound of Embodiment 1, wherein the compound is of Formula (I-a):



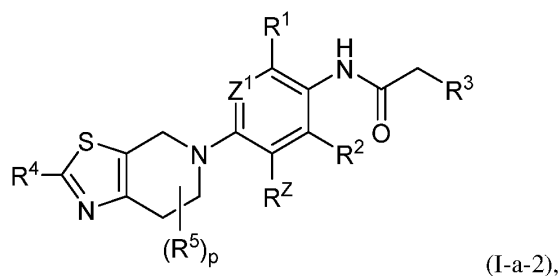
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 4. The compound of Embodiment 1, wherein the compound is of Formula (I-a-1):



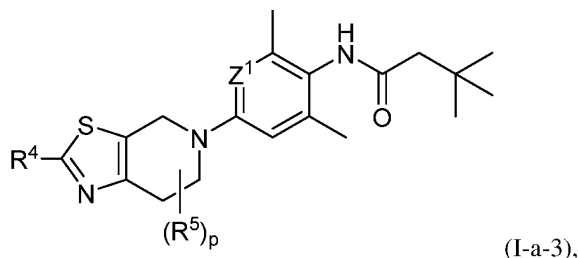
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 5. The compound of Embodiment 1, wherein the compound is of Formula (I-a-2):



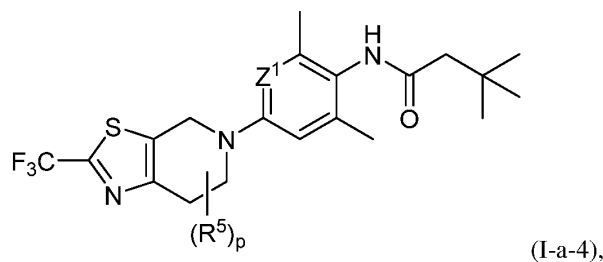
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 6. The compound of Embodiment 1, wherein the compound is of Formula (I-a-3):



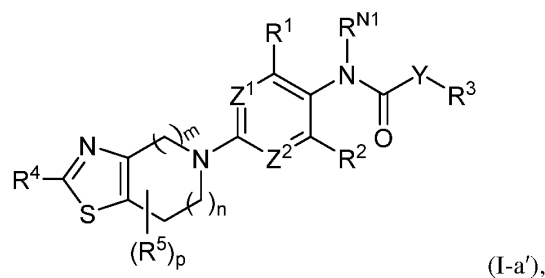
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 7. The compound of Embodiment 1, wherein the compound is of Formula (I-a-4):



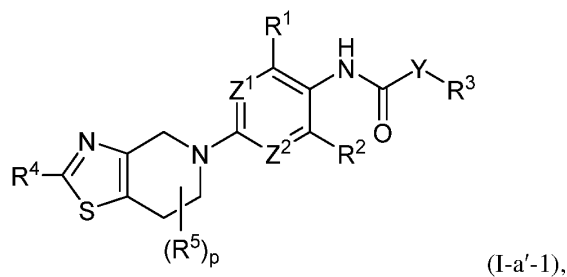
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 8. The compound of Embodiment 1, wherein the compound is of Formula (I-a'):



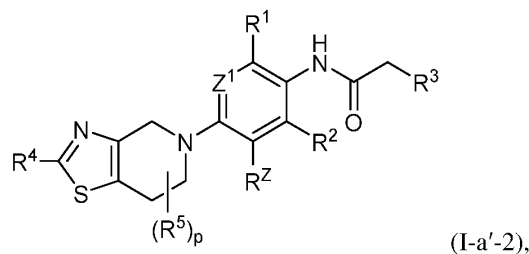
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 9. The compound of Embodiment 1, wherein the compound is of Formula (I-a'-1):



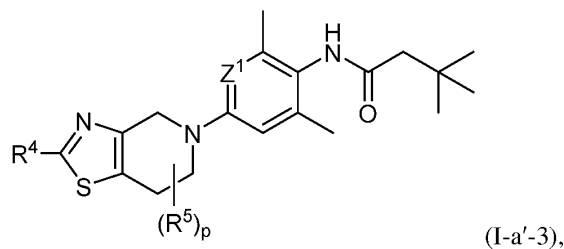
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 10. The compound of Embodiment 1, wherein the compound is of Formula (I-a'-2):



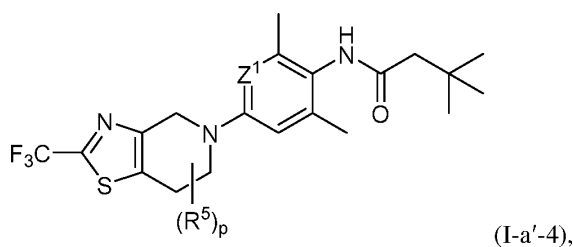
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 11. The compound of Embodiment 1, wherein the compound is of Formula (I-a'-3):



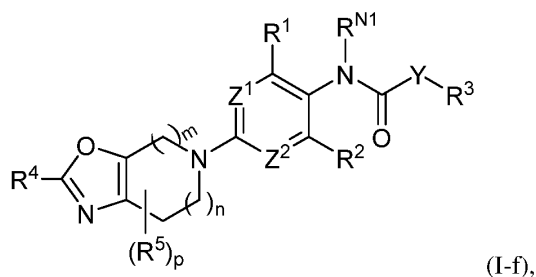
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 12. The compound of Embodiment 1, wherein the compound is of Formula (I-a'-4):



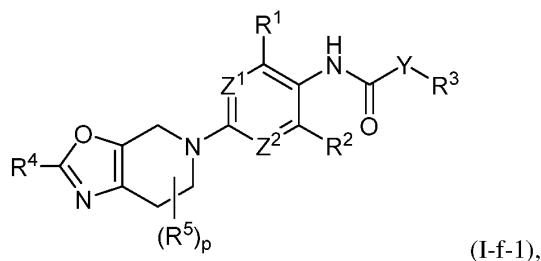
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 13. The compound of Embodiment 1, wherein the compound is of Formula (I-f):



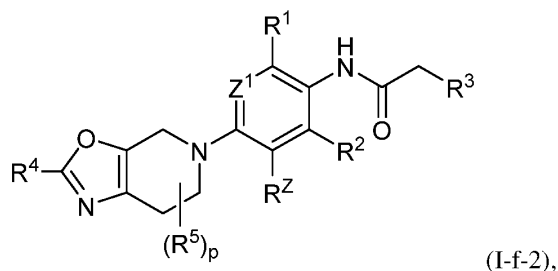
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 14. The compound of Embodiment 1, wherein the compound is of Formula (I-f-1):



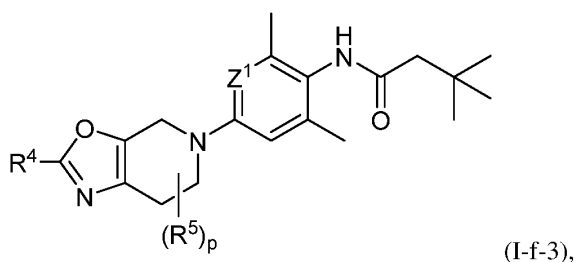
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 15. The compound of Embodiment 1, wherein the compound is of Formula (I-f-2):



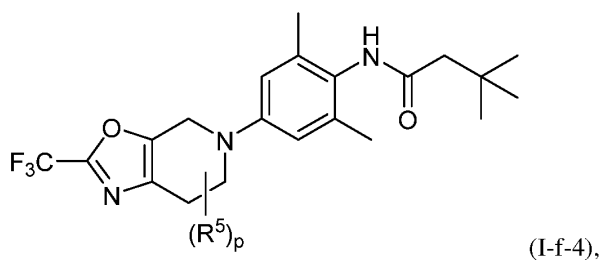
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 16. The compound of Embodiment 1, wherein the compound is of Formula (I-f-3):



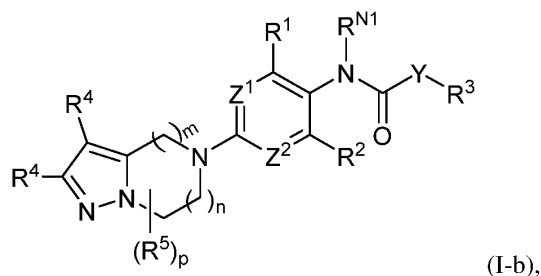
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 17. The compound of Embodiment 1, wherein the compound is of Formula (I-f-4):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 18. A compound of Formula (I-b):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein:

R^1 and R^2 are each independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7

membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, -SR^S, -S(=O)₂R^{S1}, or C₁₋₆ acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

R³ is C₁₋₈ alkyl, C₃₋₁₀ cycloalkyl, 3-7 membered heterocyclyl, or -(CR'R'')_w-Ar^l, wherein the alkyl, cycloalkyl, or heterocyclyl is optionally substituted; w is 0, 1, or 2; Ar^l is C₆₋₁₀ aryl or 5-10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted;

Y is a bond, -CR'R''-, -O-, or -NR^Y-;

R^Y is H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or a nitrogen protecting group, or R^Y and R³ are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein the alkyl, cycloalkyl, acyl, or heterocyclyl is optionally substituted;

Z¹ and Z² are each independently CR^Z or N;

each instance of R^Z is independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C₁₋₆ acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R⁴ is independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C₁₋₆ acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R⁵ is independently halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, -CN, -OR^O, -N(R^N)₂, or C₁₋₆ acyl, or two R⁵ attached to the same carbon atom are joined together with the intervening atoms to form C₃₋₇ cycloalkyl or 3-7 membered heterocyclyl, or two R⁵ attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl, is independently optionally substituted;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

m is 1 or 2;

n is 0, 1, or 2;

each instance of R' is independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3-7 membered heterocyclyl, each instance of R'' is independently H, halogen, C₁₋₆ alkyl, -OR^O, or -N(R^N)₂, or R' and R'' attached to the same carbon atom are joined together with the intervening atoms to form C₃₋₇ cycloalkyl or 3-7 membered heterocyclyl, or R' and R'' attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted;

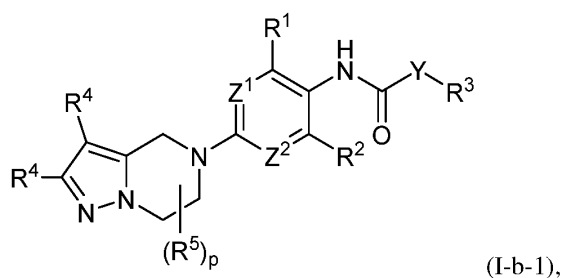
each instance of R^{N1} and R^N is independently H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ acyl, or a nitrogen protecting group, or two R^N attached to the same nitrogen atom are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, acyl, or heterocyclyl is independently optionally substituted;

each instance of R^O is independently H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₁₋₆ acyl, or an oxygen protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted;

each instance of R^S is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{1-6} acyl, or a sulfur protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted; and

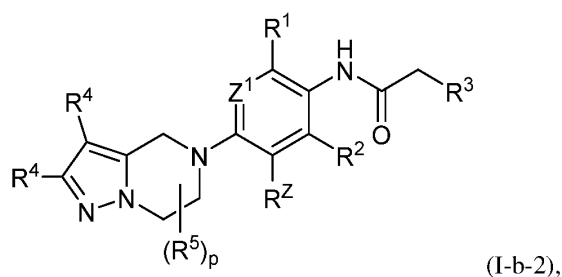
each instance of R^{S1} is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted.

Embodiment 19. The compound of Embodiment 18, wherein the compound is of Formula (I-b-1):



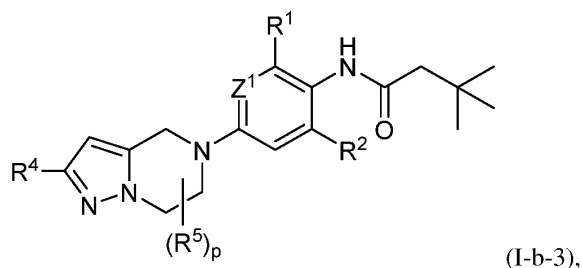
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 20. The compound of Embodiment 18, wherein the compound is of Formula (I-b-2):



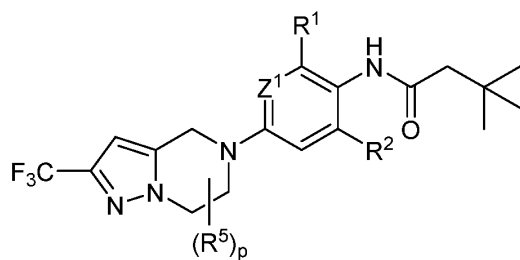
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 21. The compound of Embodiment 18, wherein the compound is of Formula (I-b-3):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 22. The compound of Embodiment 18, wherein the compound is of Formula (I-b-4):



(I-b-4),

or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 23. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1.

Embodiment 24. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein n is 1.

Embodiment 25. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1 and n is 1.

Embodiment 26. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein n is 2.

Embodiment 27. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1 and n is 2.

Embodiment 28. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^{N1} is H.

Embodiment 29. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1, n is 1, and R^{N1} is H.

Embodiment 30. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is optionally substituted C_{1-6} alkyl.

Embodiment 31. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 unsubstituted C_{1-3} alkyl.

Embodiment 32. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is methyl.

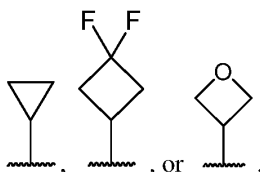
Embodiment 33. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is halogen, C_{1-6} haloalkyl, $-OR^O$, $-CN$, $-SR^S$, or $-S(=O)_2R^{S1}$.

Embodiment 34. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is F, Cl, $-CF_3$, $-OMe$, $-OCF_3$, $-CN$, $-SMe$, or $-S(=O)_2Me$.

Embodiment 35. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted.

Embodiment 36. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is C_{3-5} cycloalkyl or 3-5 membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl.

Embodiment 37. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is:



Embodiment 38. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is H.

Embodiment 39. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is optionally substituted C_{1-6} alkyl.

Embodiment 40. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is unsubstituted C_{1-3} alkyl.

Embodiment 41. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is methyl.

Embodiment 42. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is halogen or $-OR^O$.

Embodiment 43. The compound of any one of the preceding Embodiments, or a

pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is F, Cl, or -OMe.

Embodiment 44. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is -CR'R"-.

Embodiment 45. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is -CH₂-.

Embodiment 46. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is -CH(Me)-.

Embodiment 47. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C₁₋₈ alkyl.

Embodiment 48. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is unsubstituted C₁₋₄ alkyl.

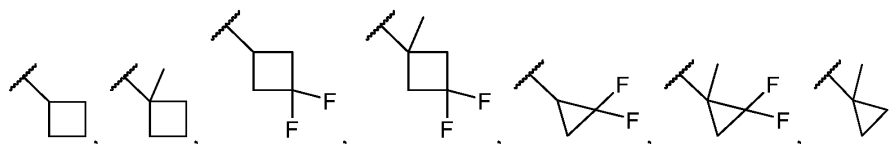
Embodiment 49. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is *tert*-butyl.

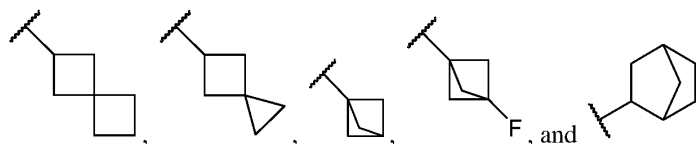
Embodiment 50. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C₃₋₁₀ cycloalkyl.

Embodiment 51. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C₃₋₈ cycloalkyl.

Embodiment 52. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is C₃₋₈ cycloalkyl optionally substituted with one or more instances of halogen and/or unsubstituted C₁₋₆ alkyl.

Embodiment 53. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is selected from:



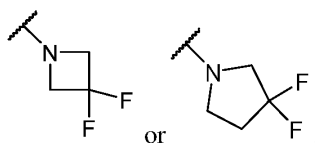


Embodiment 54. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted 3-7 membered heterocyclyl.

Embodiment 55. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted 3-6 membered heterocyclyl having 1 or 2 ring N atoms.

Embodiment 56. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is 3-6 membered heterocyclyl having 1 or 2 ring N atoms and optionally substituted with one or more halogen and/or unsubstituted C_{1-6} alkyl.

Embodiment 57. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is:

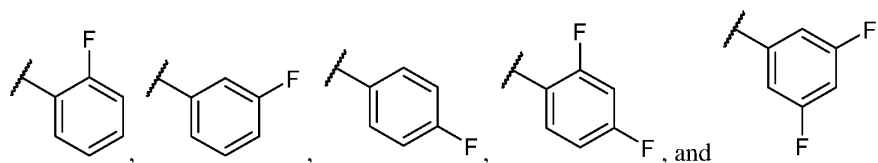


Embodiment 58. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C_{6-10} aryl.

Embodiment 59. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted phenyl.

Embodiment 60. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is phenyl optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl.

Embodiment 61. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is selected from:



Embodiment 62. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is CR^Z .

Embodiment 63. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is CH.

Embodiment 64. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is CCl.

Embodiment 65. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is N.

Embodiment 66. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is CR^Z .

Embodiment 67. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is CH.

Embodiment 68. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is CF.

Embodiment 69. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is N.

Embodiment 70. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_{1-6} haloalkyl.

Embodiment 71. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_{1-3} haloalkyl.

Embodiment 72. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_1 haloalkyl.

Embodiment 73. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is $-CF_3$.

Embodiment 74. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or

prodrug thereof, wherein at least one instance of R⁴ is -CF₂H.

Embodiment 75. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R⁴ is halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₃₋₇ cycloalkyl, or optionally substituted phenyl.

Embodiment 76. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R⁴ is halogen, unsubstituted C₁₋₆ alkyl, halogen, unsubstituted C₃₋₇ cycloalkyl, or unsubstituted phenyl.

Embodiment 77. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R⁴ is methyl, *tert*-butyl, Cl, cyclopropyl, or phenyl.

Embodiment 78. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R⁴ is H.

Embodiment 79. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein p is 0.

Embodiment 80. A compound selected from those in **Table 1**, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof.

Embodiment 81. The compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt thereof.

Embodiment 82. A pharmaceutical composition comprising a compound of any one of the preceding Embodiments, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

Embodiment 83. A method of potentiating a Kv7 potassium channel in a subject comprising administering to the subject a compound of any one of Embodiments 1-81, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

Embodiment 84. A method of treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject in need thereof comprising administering to the subject a compound of any one of Embodiments 1-81, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

Embodiment 85. The method of Embodiment 83 or 84, wherein the method enhances opening of a Kv7 potassium channel.

Embodiment 86. The method of any one of Embodiments 83-85, wherein the Kv7 potassium channel is selected from one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5.

Embodiment 87. The method of any one of Embodiments 83-86, wherein the Kv7 potassium channel is Kv7.2/Kv7.3.

Embodiment 88. A method of treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject in need thereof comprising administering to the subject a compound of any one of Embodiments 1-81, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

Embodiment 89. The method of any one of Embodiments 83-88, wherein the subject is a human.

Embodiment 90. A compound of any one of Embodiments 1-81, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in potentiating a Kv7 potassium channel in a subject.

Embodiment 91. A compound of any one of Embodiments 1-81, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject.

Embodiment 92. The compound for use of Embodiment 90 or 91, wherein the compound enhances opening of a Kv7 potassium channel.

Embodiment 93. The compound for use of any one of Embodiments 90-92, wherein the Kv7 potassium channel is selected from one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5.

Embodiment 94. The compound for use of any one of Embodiments 90-93, wherein the Kv7 potassium channel is Kv7.2/Kv7.3.

Embodiment 95. A compound of any one of Embodiments 1-81, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject.

Embodiment 96. The compound for use of any one of Embodiments 90-95, wherein the subject is a human.

Embodiment 97. A compound of any one of Embodiments 1-81, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use as a medicament.

EXAMPLES

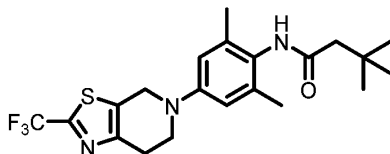
[331] In order that the present disclosure may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed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

[332] The examples provided below include procedures, intermediates, and characterization data useful, *e.g.*, for the preparation of compounds provided herein. All synthetic steps, procedures, compounds (*e.g.*,

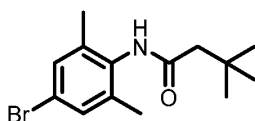
synthetic intermediates), reaction conditions, reaction mixtures, reagents, *etc.* are included herein as aspects of the present disclosure.

Synthesis of Compounds

Example 1. *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide

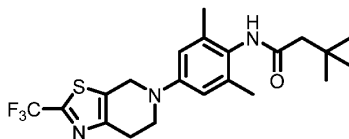


Step 1. Preparation of N-(4-bromo-2,6-dimethylphenyl)-3,3-dimethylbutanamide



[333] *N*-(4-bromo-2,6-dimethylphenyl)-3,3-dimethylbutanamide was prepared according to the procedure described in page 52 of WO 2008/024398.

Step 2. Preparation of tert-butyl 3-(4-(3,3-dimethylbutanamido)-3,5-dimethylphenyl)azetidine-1-carboxylate



[334] To a solution of *N*-(4-bromo-2,6-dimethylphenyl)-3,3-dimethylbutanamide (0.050 g, 0.168 mmol) and 2-(trifluoromethyl)-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (0.049 g, 0.201 mmol, hydrochloride) in dioxane (1 mL) was added potassium *tert*-butoxide (0.075 g, 0.671 mmol), 2-(2-ditert-butylphosphanylphenyl)-*N,N*-dimethylaniline (0.026 g, 0.067 mmol) and tris(dibenzylideneacetone) dipalladium(0) (0.031 g, 0.034 mmol) under nitrogen. The mixture was stirred at 100 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 mm × 25 mm × 10 μm; mobile phase: [water(formic acid)-acetonitrile]; gradient: 55%-85% B over 10 min). The desired fraction was collected and lyophilized to afford 0.014 g of *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)phenyl)-3,3-dimethyl butanamide (18% yield) as a light yellow solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.88 (s, 1H), 6.75 (s, 2H), 4.61 (s, 2H), 3.68 (t, *J* = 5.6 Hz, 2H), 2.92 (t, *J* = 5.2 Hz, 2H), 2.16 (s, 2H), 2.09 (s, 6H), 1.04 (s, 9H); MS (ES+) *m/z* 462.2 (M+1).

[335] The following further Examples were prepared analogously to Example 1 (as described above), substituting appropriate starting materials where necessary and making appropriate changes to experimental conditions informed by common general knowledge. Purification was performed either by silica gel chromatography, reverse-phase preparative HPLC, or supercritical fluid chromatography (SFC).

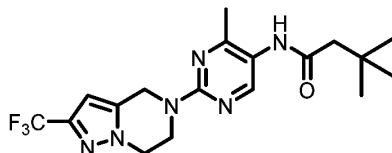
EXAMPLE	Analytical Data
2	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.90 (s, 1H), 6.75 (s, 2H), 5.88 (s, 1H), 4.34 (s, 2H), 4.06 (t, <i>J</i> = 5.6 Hz, 2H), 3.68 (t, <i>J</i> = 5.6 Hz, 2H), 2.17 (s, 2H), 2.12 (s, 3H), 2.10 (s, 6H), 1.05 (s, 9H); MS (ES+) <i>m/z</i> 355.2 (M + 1).
3	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.91 (s, 1H), 6.77–6.73 (m, 3H), 4.26 (s, 2H), 3.97 (t, <i>J</i> = 5.2 Hz, 2H), 3.62 (t, <i>J</i> = 5.2 Hz, 2H), 2.17 (s, 2H), 2.10 (s, 6H), 2.06 (s, 3H), 1.05 (s, 9H); MS (ES+) <i>m/z</i> 348.1 (M + 1), 355.2 (M + 1).
4	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.88 (s, 1H), 6.73 (s, 2H), 4.39 (s, 2H), 3.60 (t, <i>J</i> = 5.6 Hz, 2H), 2.78 (t, <i>J</i> = 5.6 Hz, 2H), 2.60 (s, 3H), 2.17 (s, 2H), 2.09 (s, 6H), 1.05 (s, 9H); MS (ES+) <i>m/z</i> 372.1 (M + 1).
5	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.91 (s, 1H), 7.23 (s, 1H), 6.79 (s, 2H), 4.29 (s, 2H), 4.12 (t, <i>J</i> = 5.2 Hz, 2H), 3.66 (t, <i>J</i> = 5.2 Hz, 2H), 2.18 (s, 2H), 2.11 (s, 6H), 1.99 (s, 3H), 1.05 (s, 9H); MS (ES+) <i>m/z</i> 355.2 (M + 1).
6	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.90 (s, 1H), 6.75 (s, 2H), 5.96 (s, 1H), 4.35 (s, 2H), 4.09 (t, <i>J</i> = 5.6 Hz, 2H), 3.68 (t, <i>J</i> = 5.6 Hz, 2H), 2.17 (s, 2H), 2.10 (s, 6H), 1.22 (s, 9H), 1.05 (s, 9H); MS (ES+) <i>m/z</i> 397.2 (M + 1).
7	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.92 (s, 1H), 6.77 (s, 2H), 6.59 (s, 1H), 4.46 (s, 2H), 4.25 (t, <i>J</i> = 5.2 Hz, 2H), 3.76 (t, <i>J</i> = 5.2 Hz, 2H), 2.17 (s, 2H), 2.11 (s, 6H), 1.05 (s, 9H); MS (ES+) 409.1 (M + 1).
8	¹ H NMR (400 MHz, CDCl ₃) δ 7.15 (s, 1H), 6.71 (s, 2H), 6.52 (s, 1H), 4.23 (m, 2H), 3.87–3.86 (m, 3H), 3.58 (t, <i>J</i> = 5.6 Hz, 2H), 2.88 (t, <i>J</i> = 5.6 Hz, 2H), 2.28 (s, 2H), 2.22 (s, 6H), 1.15 (s, 9H); MS (ES+) <i>m/z</i> 355.1 (M + 1).
9	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.80 (s, 2H), 4.57 (s, 2H), 3.73 (t, <i>J</i> = 5.6 Hz, 2H), 2.97 (t, <i>J</i> = 5.6 Hz, 2H), 2.83–2.69 (m, 2H), 2.65–54 (m, 3H), 2.45–2.28 (m, 2H), 2.15 (s, 6H); MS (ES+) <i>m/z</i> 460.2 (M+1).
10	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.82 (s, 2H), 6.50 (s, 1H), 4.47 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.80 (t, <i>J</i> = 5.6 Hz, 2H), 2.84–2.69 (m, 2H), 2.61 (s, 3H), 2.45–2.30 (m, 2H), 2.17 (s, 6H); MS (ES+) <i>m/z</i> 443.2 (M+1).
11	¹ H NMR (400 MHz, CDCl ₃) δ 7.24 (d, <i>J</i> = 0.8 Hz, 1H), 6.71 (s, 2H), 6.59 (s, 1H), 4.45 (s, 2H), 4.15 (t, <i>J</i> = 5.2 Hz, 2H), 3.70 (t, <i>J</i> = 5.2 Hz, 2H), 2.33–2.29 (m, 2H), 2.28–2.23 (m, 6H), 1.22–1.13 (m, 9H); MS (ES+) <i>m/z</i> 409.3 (M + 1).
12	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 9.18 (s, 1H), 7.47 (s, 1H), 6.82 (s, 2H), 4.35 (s, 2H), 4.21 (t, <i>J</i> = 5.2 Hz, 2H), 3.75 (t, <i>J</i> = 5.2 Hz, 2H), 2.30 (s, 2H), 2.21 (s, 6H), 1.13 (s, 9H); MS (ES+) <i>m/z</i> 375.2, 377.2 (M+1).
13	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 1H), 7.85–7.71 (m, 2H), 7.40 (t, <i>J</i> = 7.6 Hz, 2H), 7.34–7.25 (m, 1H), 6.80 (s, 2H), 6.58 (s, 1H), 4.46 (s, 2H), 4.23 (t, <i>J</i> = 5.6 Hz, 2H), 3.77 (t, <i>J</i> = 5.6 Hz, 2H), 2.19 (s, 2H), 2.12 (s, 6H), 1.06 (s, 9H); MS (ES+) <i>m/z</i> 417.3 (M + 1).
14	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.91 (s, 1H), 6.74 (s, 2H), 5.81 (s, 1H), 4.32 (s, 2H), 4.07–3.99 (m, 2H), 3.99–3.99 (m, 1H), 3.66 (t, <i>J</i> = 5.2 Hz, 2H), 2.17 (s, 2H), 2.10 (s, 6H), 1.86–1.78 (m, 1H), 1.05 (s, 9H), 0.85–0.76 (m, 2H), 0.65–0.56 (m, 2H); MS (ES+) <i>m/z</i> 381.3 (M+1).
15	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.83–6.72 (m, 2H), 6.51 (s, 1H), 4.52 (s, 2H), 4.29 (t, <i>J</i> = 5.6 Hz, 2H), 3.84 (t, <i>J</i> = 5.6 Hz, 2H), 2.83–2.67 (m, 2H), 2.64–2.55 (m, 3H), 2.46–2.29 (m, 2H), 2.21 (s, 3H); MS (ES+) <i>m/z</i> 447.2 (M+1).
16	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.70 (s, 1H), 6.50 (s, 1H), 4.80 (s, 2H), 4.31–4.24 (m, 2H), 4.18–4.11 (m, 2H), 2.84–2.69 (m, 2H), 2.58–2.66 (m, 3H), 2.44–2.31 (m, 2H), 2.28 (s, 3H), 2.16 (s, 3H); MS (ES+) <i>m/z</i> 444.2 (M + 1).
17	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.71 (s, 1H), 4.94 (s, 2H), 3.99 (t, <i>J</i> = 5.6 Hz, 2H), 2.98 (t, <i>J</i> = 5.6 Hz, 2H), 2.84–2.68 (m, 2H), 2.64–2.59 (m, 3H), 2.45–2.30 (m, 2H), 2.26 (s, 3H), 2.15 (s, 3H); MS (ES+) <i>m/z</i> 461.1 (M + 1).

EXAMPLE	Analytical Data
18	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.09 (s, 1H), 6.79 (s, 2H), 6.60 (s, 1H), 4.48 (s, 2H), 4.27 (t, <i>J</i> = 5.2 Hz, 2H), 3.78 (t, <i>J</i> = 5.2 Hz, 2H), 2.49–2.47 (m, 2H), 2.11 (s, 6H), 1.98 (qdd, <i>J</i> = 7.2, 11.6, 14.4 Hz, 1H), 1.71–1.57 (m, 1H), 1.27 (tdd, <i>J</i> = 3.6, 7.6, 17.2 Hz, 1H); MS (ES+) <i>m/z</i> 429.1 (M+1).
18a ^a	Peak 1 from SFC chiral separation: ¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.84 (s, 2H), 6.52 (s, 1H), 4.49 (s, 2H), 4.30 (t, <i>J</i> = 5.6 Hz, 2H), 3.82 (t, <i>J</i> = 5.6 Hz, 2H), 2.68–2.52 (m, 2H), 2.21 (s, 6H), 2.11–1.92 (m, 1H), 1.72–1.51 (m, 1H), 1.29–1.16 (m, 1H); MS (ES+) <i>m/z</i> 429.1 (M + 1).
18b ^a	Peak 2 from SFC chiral separation: ¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.84 (s, 2H), 6.52 (s, 1H), 4.49 (s, 2H), 4.29 (t, <i>J</i> = 5.6 Hz, 2H), 3.82 (t, <i>J</i> = 5.6 Hz, 2H), 2.68–2.51 (m, 2H), 2.21 (s, 6H), 2.09–1.94 (m, 1H), 1.61 (ddt, <i>J</i> = 4.8, 7.6, 12.0 Hz, 1H), 1.30–1.15 (m, 1H); MS (ES+) <i>m/z</i> 429.1 (M + 1).
19	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.83 (s, 2H), 6.50 (s, 1H), 4.48 (s, 2H), 4.28 (t, <i>J</i> = 5.6 Hz, 2H), 3.80 (t, <i>J</i> = 5.6 Hz, 2H), 2.57 (s, 2H), 2.20 (s, 6H), 1.46–1.38 (m, 1H), 1.36 (s, 3H), 1.20 (ddd, <i>J</i> = 4.4, 8.0, 12.8 Hz, 1H); MS (ES+) <i>m/z</i> 443.2 (M+1).
19a ^b	Peak 1 from SFC chiral separation: ¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.82 (s, 2H), 6.50 (s, 1H), 4.47 (s, 2H), 4.28 (t, <i>J</i> = 5.6 Hz, 2H), 3.80 (t, <i>J</i> = 5.6 Hz, 2H), 2.64–2.50 (m, 2H), 2.20 (s, 6H), 1.41 (dt, <i>J</i> = 4.0, 8.4 Hz, 1H), 1.35 (s, 3H), 1.20 (ddd, <i>J</i> = 4.4, 8.0, 12.4 Hz, 1H); MS (ES+) <i>m/z</i> 443.2 (M + 1).
19b ^b	Peak 2 from SFC chiral separation: ¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.82 (s, 2H), 6.49 (s, 1H), 4.47 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.80 (t, <i>J</i> = 5.6 Hz, 2H), 2.60–2.52 (m, 2H), 2.19 (s, 6H), 1.41 (dt, <i>J</i> = 4.0, 8.4 Hz, 1H), 1.35 (s, 3H), 1.19 (ddd, <i>J</i> = 4.4, 8.0, 12.4 Hz, 1H); MS (ES+) <i>m/z</i> 443.3 (M + 1).
20	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.82 (s, 2H), 6.50 (s, 1H), 4.47 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.80 (t, <i>J</i> = 5.6 Hz, 2H), 2.72 (q, <i>J</i> = 13.6 Hz, 2H), 2.60 (s, 2H), 2.43–2.32 (m, 2H), 2.19 (s, 6H), 1.39 (s, 3H); MS (ES+) <i>m/z</i> 457.2 (M+1).
21	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.82 (s, 2H), 6.50 (s, 1H), 4.47 (s, 2H), 4.28 (t, <i>J</i> = 5.6 Hz, 2H), 3.80 (t, <i>J</i> = 5.6 Hz, 2H), 2.54 (s, 2H), 2.50 (s, 1H), 2.20 (s, 6H), 1.88 (s, 6H); MS (ES+) <i>m/z</i> 419.3 (M+1).
22	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.81 (s, 2H), 6.49 (s, 1H), 4.46 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.79 (t, <i>J</i> = 5.6 Hz, 2H), 2.61 (quin, <i>J</i> = 8.0 Hz, 1H), 2.44 (d, <i>J</i> = 8.0 Hz, 2H), 2.23 (ddd, <i>J</i> = 2.4, 7.6, 9.6 Hz, 2H), 2.17 (s, 6H), 2.06 (t, <i>J</i> = 7.2 Hz, 2H), 1.97–1.91 (m, 2H), 1.85–1.76 (m, 4H); MS (ES+) <i>m/z</i> 447.3 (M+1).
23	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.81 (s, 2H), 6.49 (s, 1H), 4.47 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.79 (t, <i>J</i> = 5.6 Hz, 2H), 3.00–2.82 (m, 1H), 2.61 (d, <i>J</i> = 7.6 Hz, 2H), 2.29–2.21 (m, 2H), 2.17 (s, 6H), 2.07–1.99 (m, 2H), 0.52–0.35 (m, 4H); MS (ES+) <i>m/z</i> 433.2 (M+1).

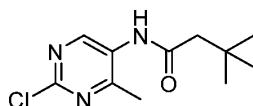
^a Examples 18a and 18b are individual enantiomers of unknown absolute stereochemistry. The absolute stereochemistry of each has been arbitrarily defined.

^b Examples 19a and 19b are individual enantiomers of unknown absolute stereochemistry. The absolute stereochemistry of each has been arbitrarily defined.

Example 24. 3,3-dimethyl-*N*-(4-methyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)pyrimidin-5-yl)butanamide

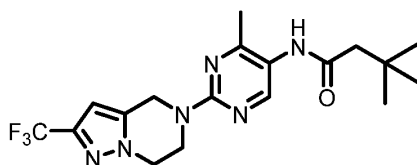


Step 1. Preparation of N-(2-chloro-4-methylpyrimidin-5-yl)-3,3-dimethylbutanamide



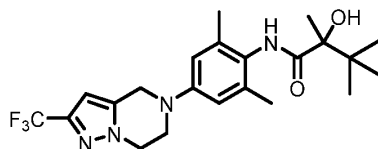
[336] To a cold (0 °C) solution of 2-chloro-4-methylpyrimidin-5-amine (4.50 g, 31.30 mmol) in dichloromethane (50.0 mL) was added pyridine (7.44 g, 94.00 mmol) and 3,3-dimethylbutanoyl chloride (4.22 g, 31.30 mmol). The mixture was stirred at 15 °C for 2 h. Water (100 mL) was added to the mixture, then the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed with aqueous saturated sodium bicarbonate (100 mL), 1M hydrochloric (100 mL) and brine (3 × 100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (80 g SepaFlash® Silica Flash Column, eluent of 0–55% ethyl acetate/petroleum ether gradient at 150 mL/min). The desired fraction was collected and concentrated *in vacuo* to afford 4.0 g of *N*-(2-chloro-4-methylpyrimidin-5-yl)-3,3-dimethylbutanamide as a crude white solid that was used without further purification: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 1H), 8.76 (s, 1H), 2.43 (s, 3H), 2.29 (s, 2H), 1.04 (s, 9H).

Step 2. Preparation of 3,3-dimethyl-N-(4-methyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)pyrimidin-5-yl)butanamide

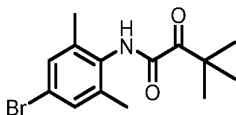


[337] A mixture of *N*-(2-chloro-4-methylpyrimidin-5-yl)-3,3-dimethylbutanamide (0.030 g, 0.124 mmol), 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (0.028 g, 0.124 mmol, hydrochloride), *N,N*-diisopropylethylamine (0.080 g, 0.621 mmol) in dimethylsulfoxide (1.0 mL) was stirred at 120 °C for 12 h. The reaction mixture was cooled to room temperature. The mixture was purified by prep-HPLC (column: Phenomenex luna C18 150 mm × 25 mm × 10 μm; mobile phase: [water (formic acid)-acetonitrile]; B%: 45%–75%, B over 10 min). The desired fraction was collected and lyophilized to afford 0.016 g of 3,3-dimethyl-*N*-(4-methyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)pyrimidin-5-yl)butanamide (32% yield) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 8.26 (s, 1H), 6.57 (s, 1H), 6.31 (s, 1H), 4.95 (s, 2H), 4.41–4.07 (m, 4H), 2.28 (s, 3H), 2.19 (s, 2H), 1.05 (s, 9H); MS (ES+) *m/z* 397.2 (M + 1).

Example 25. *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)-2-hydroxy-2,3,3-trimethylbutanamide

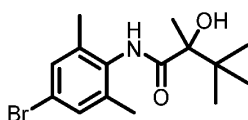


Step 1. Preparation of N-(4-bromo-2,6-dimethylphenyl)-3,3-dimethyl-2-oxobutanamide



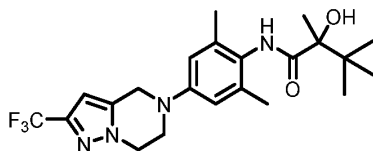
[338] To a solution of 3,3-dimethyl-2-oxobutanoic acid (5.0 g, 38.4 mmol) in tetrahydrofuran (50 mL) was added *N,N*-diisopropylethylamine (12.4 g, 96.1 mmol) and 2-chloro-1-methylpyridinium iodide (12.3 g, 48.0 mmol). The mixture was stirred at 25 °C for 1 h. 4-bromo-2,6-dimethylaniline (6.41 g, 32.0 mmol) was added and the mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 5/1). The desired fraction was collected under reduced pressure to afford 5.7 g of *N*-(4-bromo-2,6-dimethylphenyl)-3,3-dimethyl-2-oxobutanamide (57% yield) as a yellow solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.03 (s, 1H), 7.34 (s, 2H), 2.14 (s, 6H), 1.28 (s, 9H).

Step 2. Preparation of (+/-) N-(4-bromo-2,6-dimethylphenyl)-2-hydroxy-2,3,3-trimethyl-butanamide



[339] To a solution of *N*-(4-bromo-2,6-dimethylphenyl)-3,3-dimethyl-2-oxobutanamide (3.00 g, 9.61 mmol) in tetrahydrofuran (30 mL) was added thiophen-2-yl magnesium bromide (3 M in diethyl ether, 16 mL) at 0 °C under nitrogen. The mixture was stirred at 25 °C for 1 h. The reaction was quenched with saturated ammonium chloride (20 mL). Water (30 mL) was added to the mixture, then the mixture was extracted with ethyl acetate (3 $\times$ 30 mL). The combined organic phases were washed with brine (3 $\times$ 30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (40 g SepaFlash® Silica Flash Column, eluent of 0-40% ethyl acetate/petroleum ether gradient at 100 mL/min) to afford 1.70 g of racemic *N*-(4-bromo-2,6-dimethylphenyl)-2-hydroxy-2,3,3-trimethylbutanamide (43% yield) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 7.22 (s, 2H), 2.20 (s, 6H), 1.51 (s, 3H), 1.12 (s, 9H).

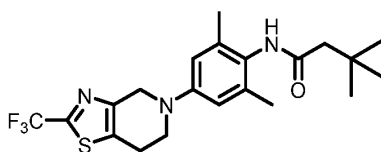
Step 2. Preparation of (+/-) N-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)-2-hydroxy-2,3,3-trimethylbutanamide



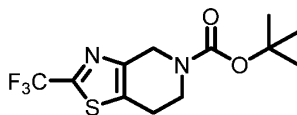
[340] To a solution of racemic *N*-(4-bromo-2,6-dimethylphenyl)-2-hydroxy-2,3,3-trimethylbutanamide (0.050 g, 0.152 mmol) and 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (0.045 g, 0.198 mmol hydrochloride) in dioxane (1 mL) was added potassium *tert*-butoxide (0.051 g, 0.457 mmol), 2-(2-ditert-butylphosphanylphenyl)-*N,N*-dimethylaniline (0.012 g, 0.031 mmol) and tris(dibenzylideneacetone) dipalladium(0) (0.056 g, 0.061 mmol) under nitrogen. The mixture was

stirred at 100 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 mm × 25 mm × 10 μm; mobile phase: [water (formic acid) - acetonitrile]; gradient: 48%-78% B over 10 min). The desired fraction was collected and lyophilized to afford 0.015 g of racemic *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl) phenyl)-2-hydroxy-2,3,3-trimethylbutanamide (49% yield) as an off-white solid: ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 1H), 6.71 (s, 2H), 6.37 (s, 1H), 4.41 (s, 2H), 4.37–4.30 (m, 2H), 3.72 (t, *J* = 5.4 Hz, 2H), 2.24 (s, 6H), 1.54 (s, 3H), 1.15 (s, 9H); MS (ES+) *m/z* 439.2 (M+1).

Example 26. *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[4,5-*c*]pyridin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide

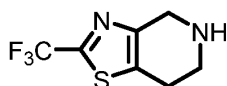


*Step 1. Preparation of tert-butyl 2-(trifluoromethyl)-6,7-dihydrothiazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate*



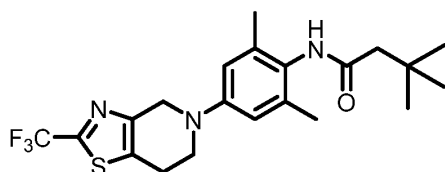
[341] A mixture of *tert*-butyl 2-bromo-6,7-dihydrothiazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate (0.200 g, 0.627 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.241 g, 1.25 mmol) and copper(I) iodide (0.240 g, 1.26 mmol) in dimethyl formamide (6.0 mL) was stirred at 80 °C for 16 h under nitrogen. The reaction mixture was cooled to room temperature. Water (10 mL) was added to the mixture, then the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine (3 × 10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 mm × 25 mm × 10 μm; mobile phase: [water (formic acid)–acetonitrile]; gradient: 54%–84% B over 10 min). The desired fraction was collected and concentrated under reduced pressure to remove the acetonitrile. The mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with brine (3 × 10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 0.086 g of *tert*-butyl 2-(trifluoromethyl)-6,7-dihydrothiazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate (45% yield) as yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 4.75–4.65 (m, 2H), 3.85–3.75 (m, 2H), 3.00–2.90 (m, 2H), 1.50 (s, 9H).

*Step 2. Preparation of 2-(trifluoromethyl)-4,5,6,7-tetrahydrothiazolo[4,5-*c*]pyridine*



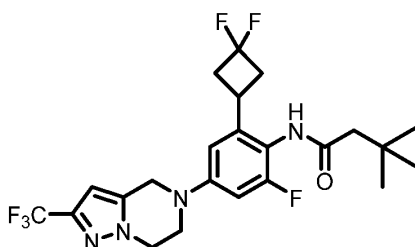
[342] To a solution of *tert*-butyl 2-(trifluoromethyl)-6,7-dihydrothiazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate (0.086 g, 0.279 mmol) in methanol (2.0 mL) was added acetyl chloride (0.109 g, 1.390 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure to afford 0.065 g of 2-(trifluoromethyl)-4,5,6,7-tetrahydrothiazolo[4,5-*c*]pyridine (95% yield, hydrochloride) as a yellow solid: ¹H NMR (400 MHz, MeOD-*d*₄) δ 4.50–4.46 (m, 2H), 3.64 (t, *J* = 6.0 Hz, 2H), 3.30–3.29 (m, 2H).

Step 3. Preparation of N-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[4,5-*c*]pyridin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide

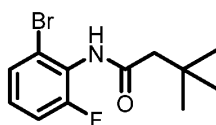


[343] To a solution of *N*-(4-bromo-2,6-dimethylphenyl)-3,3-dimethylbutanamide (0.066 g, 0.221 mol) and 2-(trifluoromethyl)-4,5,6,7-tetrahydrothiazolo[4,5-*c*]pyridine (0.065 g, 0.266 mmol, hydrochloride) in dioxane (4.0 mL) was added potassium *tert*-butoxide (0.100 g, 0.891 mmol), 2-(2-ditert-butylphosphanylphenyl)-*N,N*-dimethylaniline (0.018 g, 0.046 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.021 g, 0.023 mmol) under nitrogen. The mixture was stirred at 100 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 mm × 25 mm × 10 μm; mobile phase: [water(formic acid)–acetonitrile]; gradient: 56%–76% B over 10 min). The desired fraction was collected and lyophilized to afford 0.024 g of *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[4,5-*c*]pyridin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide (25% yield) as a light yellow solid: ¹H NMR (400 MHz, MeOD-*d*₄) δ 6.80 (s, 2H), 4.41 (s, 2H), 3.66 (t, *J* = 5.6 Hz, 2H), 3.08 (t, *J* = 5.2 Hz, 2H), 2.30 (s, 2H), 2.20 (s, 6H), 1.13 (s, 9H); MS (ES+) *m/z* 426.2 (M+1).

Example 27. *N*-(2-(3,3-difluorocyclobutyl)-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide

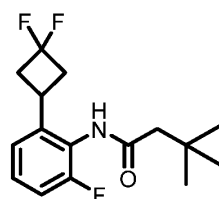


Step 1. Preparation of N-(2-bromo-6-fluorophenyl)-3,3-dimethylbutanamide



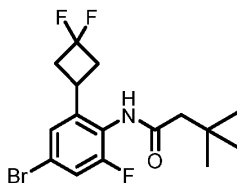
[344] To a cold (0 °C) solution of 2-bromo-6-fluoroaniline (10.0 g, 52.6 mmol) in dichloromethane (100.0 mL) was added pyridine (8.3 g, 105.0 mmol) and 3,3-dimethylbutanoyl chloride (7.8 g, 57.9 mmol). The mixture was stirred at 15 °C for 1 h. Water (100 mL) was added to the mixture and the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed with saturated sodium bicarbonate (100 mL), 1M hydrochloric acid (100 mL) and brine (3 × 100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (80 g SepaFlash® Silica Flash Column, eluent of 0–22% ethyl acetate/petroleum ether gradient at 100 mL/min). The desired fraction was collected and concentrated *in vacuo* to afford 13.0 g of *N*-(2-bromo-6-fluorophenyl)-3,3-dimethylbutanamide (86% yield) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.56 (s, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.43–7.20 (m, 2H), 2.23 (s, 2H), 1.06 (s, 9H).

Step 2. Preparation of N-(2-(3,3-difluorocyclobutyl)-6-fluorophenyl)-3,3-dimethylbutanamide



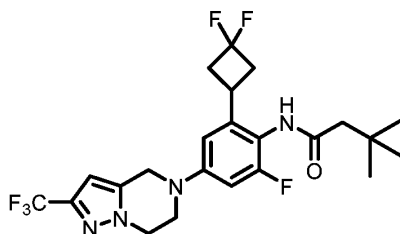
[345] The reaction was carried out in 3 batches on 0.300 g scale each. To a vial equipped with a stir bar was added *N*-(2-bromo-6-fluorophenyl)-3,3-dimethylbutanamide (0.300 g, 1.040 mmol), 3-bromo-1,1-difluorocyclobutane (0.267 g, 1.560 mmol), bis[2-(2,4-difluorophenyl)-5-trifluoromethylpyridine][2-2-bipyridyl]iridiumhexafluorophosphate (0.012 g, 0.011 mmol), tris(trimethylsilyl)silane (0.259 g, 1.040 mmol), [4-4-bis(1,1-dimethylethyl)-2,2-bipyridine] nickel(II)dichloride (0.013 g, 0.033 mmol), sodium carbonate (0.221 g, 0.209 mmol) and acetonitrile (12.0 mL). The vial was sealed and placed under nitrogen. The reaction was stirred and irradiated with a 34 W blue LED lamp (7 cm away), with cooling fan to keep the reaction temperature at 25 °C for 14 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (40 g SepaFlash® Silica Flash Column, Eluent of 0~12% Ethyl acetate/Petroleum ethergradient @ 100 mL/min). The desired fraction was collected and concentrated *in vacuo* to afford 0.410 g of *N*-(2-(3,3-difluorocyclobutyl)-6-fluorophenyl)-3,3-dimethylbutanamide (44% yield) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.18 (s, 1H), 7.28–7.18 (m, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 8.8 Hz, 1H), 3.45–3.31 (m, 1H), 2.91–2.76 (m, 2H), 2.63–2.46 (m, 2H), 2.14 (s, 2H), 0.96 (s, 9H).

Step 3. Preparation of N-(4-bromo-2-(3,3-difluorocyclobutyl)-6-fluorophenyl)-3,3-dimethylbutanamide



[346] To a cold (0 °C) solution of *N*-(2-(3,3-difluorocyclobutyl)-6-fluorophenyl)-3,3-dimethylbutanamide (0.500 g, 1.67 mmol) in acetonitrile (5.0 mL) was added 1-bromopyrrolidine-2,5-dione (2.38 g, 13.4 mmol). The mixture was then stirred at 50 °C for 72 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by prep-HPLC (column: Phenomenex luna 150 mm × 25 mm × 10 μm; mobile phase: [water (ammonium bicarbonate)–acetonitrile]; B%: 54%–74%, B over 2 min). The desired fraction was collected and lyophilized to afford 0.28 g of *N*-(4-bromo-2-(3,3-difluorocyclobutyl)-6-fluorophenyl)-3,3-dimethylbutanamide (44% yield) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.33 (s, 1H), 7.52 (*J* = 2.0, 9.2 Hz, 1H), 7.43 (s, 1H), 3.52–3.39 (m, 1H), 3.01–2.83 (m, 2H), 2.80–2.61 (m, 2H), 2.23 (s, 2H), 1.04 (s, 9H).

Step 4. Preparation of N-(2-(3,3-difluorocyclobutyl)-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide

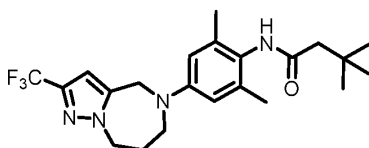


[347] To a solution of *N*-(4-bromo-2-(3,3-difluorocyclobutyl)-6-fluorophenyl)-3,3-dimethylbutanamide (0.050 g, 0.132 mmol), 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (0.030 g, 0.132 mmol, hydrochloride), potassium *tert*-butoxide (0.059 g, 0.526 mmol) in dioxane (1.0 mL) was added tris(dibenzylideneacetone)dipalladium(0) (0.024 g, 0.026 mmol) and 2-(2-dicyclohexylphosphanylphenyl)-*N,N*-dimethyl-aniline (0.021 g, 0.053 mmol) under nitrogen atmosphere. The mixture was stirred at 100 °C for 12 h under nitrogen. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by prep-HPLC (column: Waters xbridge 150 mm × 25 mm × 10 μm; mobile phase: [water (ammonium bicarbonate)-acetonitrile]; B%: 45%–75%). The desired fraction was collected and lyophilized to afford 0.010 g of *N*-(2-(3,3-difluorocyclobutyl)-6-fluoro-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo [1,5-*a*]pyrazin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide (16% yield) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 6.69 (s, 1H), 6.65 (dd, *J* = 2.4, 12.0 Hz, 1H), 6.55 (s, 1H), 6.43 (s, 1H), 4.48 (s, 2H), 4.40 (t, *J* = 5.6 Hz, 2H), 3.80 (t, *J* = 5.6 Hz, 2H), 3.66–3.63 (m, 1H), 3.62–3.48 (m, 1H), 3.12–2.92 (m, 2H), 2.77–2.53 (m, 2H), 2.31 (s, 2H), 1.16 (s, 9H); MS (ES+) *m/z* 489.3 (*M* + 1).

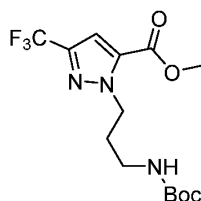
[348] The following further Examples were prepared analogously to Example 27 (as described above), substituting appropriate starting materials where necessary and making appropriate changes to experimental conditions informed by common general knowledge. Purification was performed either by silica gel chromatography, reverse-phase preparative HPLC, or supercritical fluid chromatography (SFC).

EXAMPLE	Analytical Data
28	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.10 (s, 1H), 6.85 (dd, <i>J</i> = 2.4, 10.0 Hz, 2H), 6.60 (s, 1H), 4.53 (s, 2H), 4.29 (t, <i>J</i> = 5.2 Hz, 2H), 3.83 (t, <i>J</i> = 5.6 Hz, 2H), 3.41–3.35 (m, 1H), 2.94–2.78 (m, 2H), 2.78–2.61 (m, 4H), 2.54 (s, 3H), 2.44–2.30 (m, 2H), 2.08 (s, 3H); MS (ES+) <i>m/z</i> 519.3 (<i>M</i> + 1).
29	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 7.10 (d, <i>J</i> = 2.4 Hz, 1H), 6.93 (d, <i>J</i> = 2.4 Hz, 1H), 6.52 (s, 1H), 4.98 (d, <i>J</i> = 2.4 Hz, 2H), 4.76 (t, <i>J</i> = 6.8 Hz, 2H), 4.55 (s, 2H), 4.43–4.38 (m, 1H), 4.31 (t, <i>J</i> = 5.4 Hz, 2H), 3.87 (t, <i>J</i> = 5.4 Hz, 2H), 2.28 (s, 2H), 2.22 (s, 3H), 1.13 (s, 9H); MS (ES+) <i>m/z</i> 451.2 (<i>M</i> + 1).

Example 30. *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,4]diazepin-5(6*H*)-yl)phenyl)-3,3-dimethylbutanamide

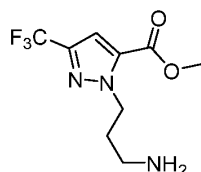


*Step 1. Preparation of methyl 1-(3-((tert-butoxycarbonyl)amino) propyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate*



[349] A mixture of methyl 3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (2.00 g, 10.30 mmol), *tert*-butyl *N*-(3-bromopropyl)carbamate (3.68 g, 15.50 mmol) and potassium carbonate (4.27 g, 30.90 mmol) in dimethyl formamide (30.0 mL) was stirred at 30 °C for 12 h. Water (30 mL) was added to the mixture, then the mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic layer were washed with brine (3 × 50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (40 g SepaFlash® Silica Flash Column, eluent of 0–25% ethyl acetate/petroleum ether gradient at 100 mL/min) to afford 3.00 g of methyl 1-(3-((*tert*-butoxycarbonyl)amino) propyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (83% yield) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 7.10 (s, 1H), 4.95–4.78 (m, 1H), 4.70 (t, *J* = 6.8 Hz, 2H), 3.94 (s, 3H), 3.24–3.02 (m, 2H), 2.09 (quin, *J* = 6.4 Hz, 2H), 1.47 (s, 9H).

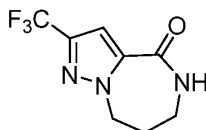
*Step 2. Preparation of methyl 1-(3-aminopropyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate*



[350] A mixture of methyl 1-(3-((*tert*-butoxycarbonyl)amino) propyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (3.00 g, 8.54 mmol) in hydrogen chloride/dioxane (4 M, 10 mL) was stirred at 25 °C for 12 h.

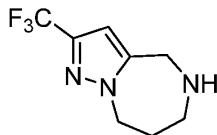
The reaction mixture was concentrated under reduced pressure to afford 2.50 g of crude methyl 1-(3-aminopropyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate as a white solid that was used without further purification: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.10 (s, 3H), 7.40 (s, 1H), 4.80–4.55 (m, 2H), 3.88 (s, 3H), 2.99–2.70 (m, 2H), 2.22–2.03 (m, 2H).

*Step 3. Preparation of 2-(trifluoromethyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,4]diazepin-4-one*



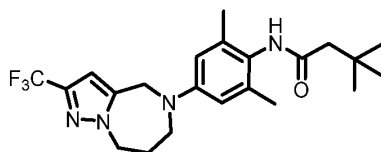
[351] A mixture of methyl 1-(3-aminopropyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylate (2.50 g, 8.69 mmol, hydrochloride) in ammonium hydroxide (250 mL, 25% purity) and methanol (125 mL) was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure to remove methanol. Water (200 mL) was added to the mixture, then the mixture was extracted with ethyl acetate (3 × 200 mL). The combined organic layer was washed with brine (500 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 1.6 g of crude 2-(trifluoromethyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,4]diazepin-4-one as a white solid that was used without further purification: ¹H NMR (400 MHz, CDCl₃) δ 7.14 (s, 1H), 7.11 (s, 1H), 4.59 (t, *J* = 6.8 Hz, 2H), 3.51–3.35 (m, 2H), 2.35 (quin, *J* = 6.4 Hz, 2H).

*Step 4. Preparation of 2-(trifluoromethyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,4]diazepine*



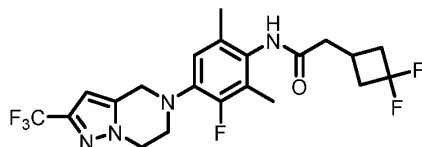
[352] To a solution of 2-(trifluoromethyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,4]diazepin-4-one (0.50 g, 2.28 mmol) in tetrahydrofuran (10.0 mL) was added borane dimethyl sulfide complex (10 M, 1.10 mL) at 25 °C, then the mixture was stirred at 70 °C for 12 h. The reaction mixture was cooled to room temperature and quenched by the addition of methanol (5 mL) at 25 °C. Hydrogen chloride/methanol (4 M, 10 mL) was added to the mixture, then the mixture was stirred at 70 °C for 2 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was triturated with ethyl acetate (5 mL) at 25 °C for 2 h. The mixture was filtered and filter cake concentrated under reduced pressure to afford 0.40 g of 2-(trifluoromethyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,4]diazepine (73% yield, hydrochloride) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.68 (s, 2H), 6.89 (s, 1H), 4.64–4.50 (m, 2H), 4.47 (s, 2H), 3.46–3.37 (m, 2H), 2.12–2.00 (m, 2H).

*Step 4. Preparation of N-(2,6-dimethyl-4-(2-(trifluoromethyl)-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,4]diazepin-5(6*H*)-yl)phenyl)-3,3-dimethylbutanamide*

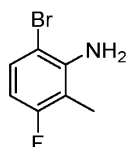


[353] A mixture of *N*-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide (0.120 g, 0.402 mmol), 2-(trifluoromethyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*][1,4]diazepine (0.100 g, 0.413 mmol, hydrochloride), methanesulfonato(2-dicyclohexylphosphino-2',6'-di-*i*-propoxy-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (0.033 g, 0.041 mmol) and cesium carbonate (0.403 g, 1.240 mmol) in dioxane (5.0 mL) was stirred at 90 °C for 12 h under nitrogen. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 mm × 25 mm × 10 μm; mobile phase: [water (formic acid)-acetonitrile]; gradient: 54%–4% B over 10 min) and (column: Waters xbridge 150 mm × 25 mm × 10 μm; mobile phase: [water (ammonium bicarbonate)-acetonitrile]; gradient: 42%–72% B over 10 min). The desired fraction was collected and lyophilized to afford 0.011 g of *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-7,8-dihydro-4*H*-pyrazolo[1,5-*a*][1,4]diazepin-5(6*H*)-yl)phenyl)-3,3-dimethylbutanamide (7% yield) as a white solid: ¹H NMR (400 MHz, MeOD-*d*₄) δ 6.66 (s, 1H), 6.64 (s, 2H), 4.71 (s, 2H), 4.55–4.47 (m, 2H), 3.97–3.88 (m, 2H), 2.28 (s, 2H), 2.16 (s, 6H), 2.01–1.93(m, 2H), 1.13 (s, 9H); MS (ES+) *m/z* 423.2 (M + 1).

Example 31. 2-(3,3-difluorocyclobutyl)-*N*-(3-fluoro-2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)phenyl)acetamide

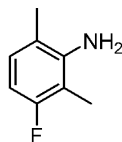


Step 1. Preparation of 6-bromo-3-fluoro-2-methylaniline



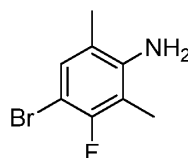
[354] To a solution of 1-bromo-4-fluoro-3-methyl-2-nitrobenzene (5.00 g, 21.40 mmol) in water (10.0 mL) and ethanol (100.0 mL) were added iron powder (5.97 g, 107.0 mmol) and acetic acid (26.2 g, 437.0 mmol). The mixture was stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature and filtered. The filter was concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate =10/1). The desired fraction was collected and concentrated under reduced pressure to afford 3.73 g of 6-bromo-3-fluoro-2-methylaniline (86% yield) as yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.23 (dd, *J* = 5.6, 8.8 Hz, 1H), 6.40 (t, *J* = 8.8 Hz, 1H), 4.48–3.59 (m, 2H), 2.13 (d, *J* = 1.6 Hz, 3H).

Step 2. Preparation of 3-fluoro-2,6-dimethylaniline



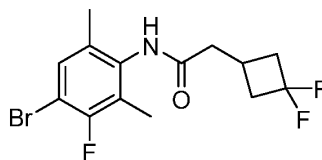
[355] To a solution of 6-bromo-3-fluoro-2-methylaniline (1.00 g, 4.90 mmol) in dioxane (15.0 mL) and water (1.5 mL) were added methylboronic acid (2.93 g, 49.00 mmol), potassium phosphate (3.12 g, 14.70 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.36 g, 0.49 mmol) under nitrogen. The mixture was stirred at 100 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate =5/1). The desired fraction was collected and concentrated under reduced pressure to afford 0.291 g of 3-fluoro-2,6-dimethylaniline (43% yield) as yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 6.91–6.82 (m, 1H), 6.49–6.40 (m, 1H), 4.01–3.60 (m, 2H), 2.15 (s, 3H), 2.10 (s, 3H).

Step 3. Preparation of 4-bromo-3-fluoro-2,6-dimethylaniline



[356] To a solution of 3-fluoro-2,6-dimethylaniline (0.29 g, 2.09 mmol) in acetic acid (3.0 mL) was added *N*-bromosuccinimide (0.41 g, 2.31 mmol) at 5 °C. The mixture was stirred at 25 °C for 1 h. Sodium bicarbonate (10 mL) was added to the mixture, then the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=5/1). The desired fraction was collected and concentrated under reduced pressure to afford 0.289 g of 4-bromo-3-fluoro-2,6-dimethylaniline (63% yield) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 7.08 (d, *J* = 7.6 Hz, 1H), 4.09–3.46 (m, 2H), 2.13 (s, 6H).

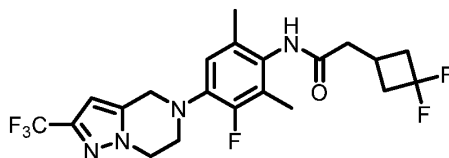
Step 4. Preparation of N-(4-bromo-3-fluoro-2,6-dimethylphenyl)-2-(3,3-difluorocyclobutyl)acetamide



[357] To a solution of 2-(3,3-difluorocyclobutyl)acetic acid (0.15 g, 1.01 mmol) in tetrahydrofuran (3.0 mL) were added *N,N*-diisopropylethylamine (0.36 g, 2.75 mmol) and 2-chloro-1-methylpyridinium iodide (0.35 g, 1.38 mmol). The mixture was stirred at 25 °C for 1 h. 4-bromo-3-fluoro-2,6-dimethylaniline (0.20 g, 0.92 mmol) was added and the mixture was stirred at 70 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate =3/1). The desired fraction was

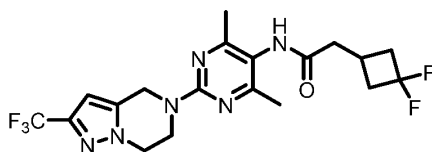
collected and concentrated under reduced pressure to afford 0.20 g of *N*-(4-bromo-3-fluoro-2,6-dimethylphenyl)-2-(3,3-difluorocyclobutyl)acetamide (62% yield) as a yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 7.29–7.27 (m, 1H), 6.74 (s, 1H), 2.92–2.76 (m, 2H), 2.73–2.60 (m, 3H), 2.46–2.27 (m, 2H), 2.15 (s, 6H).

Step 5. Preparation of 2-(3,3-difluorocyclobutyl)-N-(3-fluoro-2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)acetamide

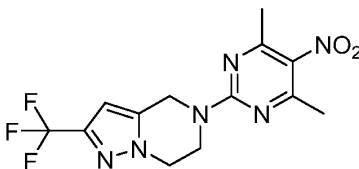


[358] To a solution of *N*-(4-bromo-3-fluoro-2,6-dimethylphenyl)-2-(3,3-difluorocyclobutyl)acetamide (0.100 g, 0.286 mmol) and 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (0.078 g, 0.343 mmol, hydrochloride) in dioxane (3.0 mL) were added cesium carbonate (0.280 g, 0.859 mmol) and methanesulfonato(2-dicyclohexylphosphino)-2,6-bis(dimethylamino)-1,1-biphenyl(2-amino-1,1-biphenyl-2 (0.023 g, 0.029 mmol) under nitrogen. The mixture was stirred at 90 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=2/1). The desired fraction was collected and concentrate dunder reduced pressure to afford 0.025 g of 2-(3,3-difluorocyclobutyl)-*N*-(3-fluoro-2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)acetamide (19% yield) as a white solid: ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ 6.85 (d, $J = 9.2$ Hz, 1H), 6.48 (s, 1H), 4.38 (s, 2H), 4.29 (t, $J = 5.6$ Hz, 2H), 3.66 (t, $J = 5.6$ Hz, 2H), 2.84–2.70 (m, 2H), 2.68–2.55 (m, 3H), 2.45–2.30 (m, 2H), 2.15 (s, 3H), 2.11 (d, $J = 2.4$ Hz, 3H); MS (ES+) m/z 461.2 (M+1).

Example 32. 2-(3,3-difluorocyclobutyl)-*N*-(4,6-dimethyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)pyrimidin-5-yl)acetamide



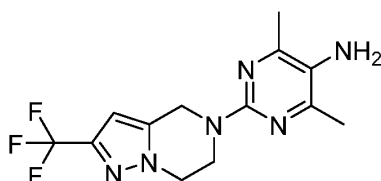
Step 1. Preparation of 5-(4,6-dimethyl-5-nitropyrimidin-2-yl)-2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine



[359] A mixture of 2-chloro-4,6-dimethyl-5-nitro-pyrimidine (0.20 g, 1.07 mmol), 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (0.27 g, 1.18 mmol, hydrochloride) and *N*-

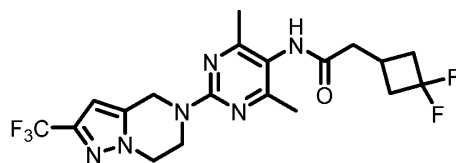
diisopropylethylamine (0.41 g, 3.19 mmol) in dimethylsulfoxide (3.0 mL) was stirred at 25 °C for 12 h. Water (10 mL) was added to the mixture, then the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 0.36 g of 5-(4,6-dimethyl-5-nitropyrimidin-2-yl)-2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine as a crude yellow solid that was used without further purification: ¹H NMR (400 MHz, CDCl₃) δ 6.42 (s, 1H), 5.13 (s, 2H), 4.48–4.42 (m, 2H), 4.36–4.32 (m, 2H), 2.53 (s, 6H).

*Step 2. Preparation of 4,6-dimethyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4H)-yl)pyrimidin-5-amine*



[360] A mixture of 5-(4,6-dimethyl-5-nitropyrimidin-2-yl)-2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (0.36 g, 1.05 mmol), iron powder (0.33 g, 5.83 mmol) and acetic acid (1.20 g, 20.00 mmol) in ethanol (10.0 mL)/water (1.0 mL) was stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20 g SepaFlash® Silica Flash Column, eluent of 0–45% ethyl acetate/petroleum ether gradient at 80 mL/min) to afford 0.26 g of 4,6-dimethyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4H)-yl)pyrimidin-5-amine (79% yield) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 6.37 (s, 1H), 4.94 (s, 2H), 4.35–4.17 (m, 4H), 3.53–2.78 (m, 2H), 2.34 (s, 6H).

*Step 3. Preparation of 2-(3,3-difluorocyclobutyl)-N-(4,6-dimethyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4H)-yl)pyrimidin-5-yl)acetamide*



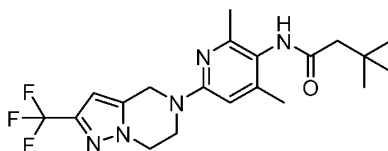
[361] A mixture of 2-(3,3-difluorocyclobutyl)acetic acid (0.028 g, 0.187 mmol), 4,6-dimethyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4H)-yl)pyrimidin-5-amine (0.050 g, 0.160 mmol), 2-chloro-1-methyl-pyridin-1-ium iodide (0.061 g, 0.240 mmol) and *N,N*-diisopropylethylamine (0.062 g, 0.480 mmol) in tetrahydrofuran (1.0 mL) was stirred at 70 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 mm × 25 mm × 10 μm; mobile phase: [water (formic acid)-acetonitrile]; gradient: 48%–78% B over 10 min) and (column: Waters xbridge 150 mm × 25 mm × 10 μm; mobile phase: [water (ammonium bicarbonate)-acetonitrile]; gradient: 42%–2% B over 10 min). The desired fraction was collected and lyophilized to afford 0.014 g of 2-(3,3-difluorocyclobutyl)-*N*-(4,6-

dimethyl-2-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)pyrimidin-5-yl)acetamide (20% yield) as a white solid: ^1H NMR (400 MHz, $\text{MeOD-}d_4$) δ 6.50 (s, 1H), 5.05 (s, 2H), 4.40–4.34 (m, 2H), 4.29–4.20 (m, 2H), 2.85–2.71 (m, 2H), 2.66–2.54 (m, 3H), 2.46–2.30 (m, 2H), 2.26 (s, 6H); MS (ES+) m/z 445.2 ($M + 1$).

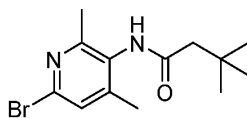
[362] The following further Examples were prepared analogously to Example 32 (as described above), substituting appropriate starting materials where necessary and making appropriate changes to experimental conditions informed by common general knowledge. Purification was performed either by silica gel chromatography, reverse-phase preparative HPLC, or supercritical fluid chromatography (SFC).

EXAMPLE	Analytical Data
33	^1H NMR (400 MHz, $\text{MeOD-}d_4$) δ 6.50 (s, 1H), 5.05 (s, 2H), 4.41–4.33 (m, 2H), 4.30–4.21 (m, 2H), 2.30 (s, 2H), 2.29 (s, 6H), 1.13 (s, 9H); MS (ES+) m/z 411.2 ($M + 1$).

Example 34. *N*-(2,4-dimethyl-6-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)pyridin-3-yl)-3,3-dimethylbutanamide

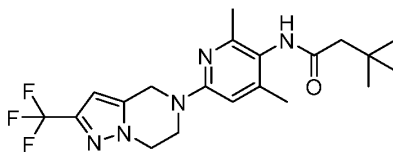


Step 1. Preparation of N-(6-bromo-2,4-dimethylpyridin-3-yl)-3,3-dimethylbutanamide



[363] To a solution of 6-bromo-2,4-dimethyl-pyridin-3-amine (5.0 g, 24.9 mmol) in dichloromethane (50.0 mL) was added pyridine (5.9 g, 74.6 mmol), then 3,3-dimethylbutanoyl chloride (3.7 g, 27.3 mmol) was added at 0 °C. The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure. Water (20 mL) was added to the mixture, then the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (2 × 10 mL), 1M hydrochloric acid (2 × 10 mL) and sodium bicarbonate (2 × 20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (80 g SepaFlash® Silica Flash Column, eluent of 0–25% ethyl acetate/petroleum ether gradient at 80 mL/min) to afford 5.4 g of *N*-(6-bromo-2,4-dimethylpyridin-3-yl)-3,3-dimethylbutanamide (69% yield) as a white solid: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.41 (s, 1H), 7.41 (s, 1H), 2.31 (s, 3H), 2.24 (s, 2H), 2.14 (s, 3H), 1.05 (s, 9H).

Step 2. Preparation of N-(2,4-dimethyl-6-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)pyridin-3-yl)-3,3-dimethylbutanamide

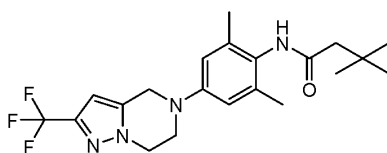


[364] To a solution of *N*-(6-bromo-2,4-dimethyl-3-pyridyl)-3,3-dimethylbutanamide (0.250 g, 0.794 mmol) in dioxane (5.0 mL) was added 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (0.180 g, 0.791 mmol, hydrochloride) and cesium carbonate (0.776 g, 2.380 mmol) then methanesulfonato(2-dicyclohexylphosphino-2,6-bis(dimethylamino)-1,1-biphenyl)(2-amino-1,1-biphenyl-2-yl)palladium(II) (0.064 g, 0.079 mmol) was added under a nitrogen atmosphere. The mixture was stirred at 90 °C for 12 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (40 g SepaFlash® Silica Flash Column, eluent of 0–45% ethyl acetate/petroleum ether gradient at 80 mL/min) to afford *N*-(2,4-dimethyl-6-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4H)-yl)pyridin-3-yl)-3,3-dimethylbutanamide (64% yield) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.06 (s, 1H), 6.75 (s, 1H), 6.63 (s, 1H), 4.78 (s, 2H), 4.29–4.21 (m, 2H), 4.07 (t, *J* = 5.2 Hz, 2H), 2.22 (s, 3H), 2.18 (s, 2H), 2.10 (s, 3H), 1.05 (s, 9H); MS (ES+) *m/z* 410.2 (*M* + 1).

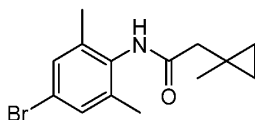
[365] The following further Examples were prepared analogously to Example 34 (as described above), substituting appropriate starting materials where necessary and making appropriate changes to experimental conditions informed by common general knowledge. Purification was performed either by silica gel chromatography, reverse-phase preparative HPLC, or supercritical fluid chromatography (SFC).

EXAMPLE	Analytical Data
35	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.02 (s, 1H), 6.74 (s, 1H), 4.93–4.92 (m, 2H), 3.93 (t, <i>J</i> = 5.6 Hz, 2H), 2.93 (t, <i>J</i> = 5.6 Hz, 2H), 2.19 (s, 3H), 2.17 (s, 2H), 2.08 (s, 3H), 1.04 (s, 9H); MS (ES+) <i>m/z</i> 427.2 (<i>M</i> +1).

Example 36. *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4H)-yl)phenyl)-2-(1-methylcyclopropyl)acetamide



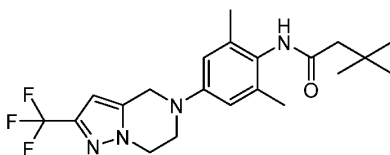
Step 1. Preparation of N-(4-bromo-2,6-dimethylphenyl)-2-(1-methylcyclopropyl)acetamide



[366] A solution of 2-(1-methylcyclopropyl)acetic acid (0.13 g, 1.10 mmol), 2-chloro-1-methylpyridinium iodide (0.38 g, 1.50 mmol) and *N,N*-diisopropylethylamine (0.39 g, 3.00 mmol) in tetrahydrofuran (2.0 mL) was stirred at 25 °C for 0.5 h. 4-bromo-2,6-dimethylaniline (0.20 g, 1.00 mmol) was added. The final mixture was stirred at 70 °C for 12 h. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 × 5 mL). The combined organic layers were

washed with brine (5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (12 g SepaFlash® Silica Flash Column, eluent of 40–70% ethyl acetate/petroleum ether gradient at 70 mL/min) to afford 0.17 g of *N*-(4-bromo-2,6-dimethylphenyl)-2-(1-methylcyclopropyl)acetamide (52% yield) as white oil: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.08 (s, 1H), 7.29 (s, 2H), 2.21 (s, 2H), 2.13 (s, 6H), 1.14 (s, 3H), 0.55–0.51 (m, 2H), 0.34–0.30 (m, 2H).

Step 2. Preparation of N-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)phenyl)-2-(1-methylcyclopropyl)acetamide



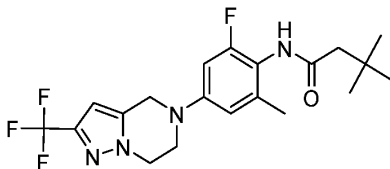
[367] Methanesulfonato(2-dicyclohexylphosphino)-2,6-bis(dimethylamino)-1,1-biphenyl)(2-amino-1,1-biphenyl-2-yl)palladium(II) (0.025 g, 0.030 mmol) was added to a solution of *N*-(4-bromo-2,6-dimethylphenyl)-2-(1-methylcyclopropyl)acetamide (0.100 g, 0.303 mmol), 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (0.069 g, 0.303 mmol, hydrochloride) and cesium carbonate (0.297 g, 0.911 mmol) in dioxane (3.0 mL) under nitrogen. The mixture was stirred at 90 °C for 12 h. The mixture was cooled to 25 °C and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (20 g SepaFlash® Silica Flash Column, eluent of 50–80% ethyl acetate/petroleum ether gradient at 70 mL/min). The desired product was dissolved with methanol (5 mL) and water (15 mL), then lyophilized to afford *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)phenyl)-2-(1-methylcyclopropyl)acetamide (65% yield) as a yellow solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.87 (s, 1H), 6.78 (s, 2H), 6.59 (s, 1H), 4.47 (s, 2H), 4.26 (t, *J* = 5.2 Hz, 2H), 3.77 (t, *J* = 5.2 Hz, 2H), 2.17 (s, 2H), 2.11 (s, 6H), 1.14 (s, 3H), 0.57–0.50 (m, 2H), 0.33–0.28 (m, 2H); MS (ES+) *m/z* 407.3 (M+1).

[368] The following further Examples were prepared analogously to Example 36 (as described above), substituting appropriate starting materials where necessary and making appropriate changes to experimental conditions informed by common general knowledge. Purification was performed either by silica gel chromatography, reverse-phase preparative HPLC, or supercritical fluid chromatography (SFC).

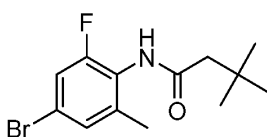
EXAMPLE	Analytical Data
37	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.83 (s, 2H), 6.51 (s, 1H), 4.48 (s, 2H), 4.29 (t, <i>J</i> = 5.4 Hz, 2H), 3.81 (t, <i>J</i> = 5.6 Hz, 2H), 3.02–2.90 (m, 1H), 2.75–2.48 (m, 1H), 2.35–2.25 (m, 1H), 2.24–2.15 (m, 6H), 1.74–1.20 (m, 8H); MS (ES+) <i>m/z</i> 433.2 (M+1).
46	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.81 (s, 2H), 6.49 (s, 1H), 4.46 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.79 (t, <i>J</i> = 5.6 Hz, 2H), 2.48 (s, 2H), 2.19 (s, 6H), 2.19–2.12 (m, 2H), 2.06–1.88 (m, 2H), 1.87–1.75 (m, 2H), 1.33 (s, 3H); MS (ES+) <i>m/z</i> 421.2 (M+1).
47	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.81 (s, 2H), 6.49 (s, 1H), 4.47 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.79 (t, <i>J</i> = 5.6 Hz, 2H), 2.62–2.45 (m, 2H), 2.17 (s, 6H), 2.16–2.06 (m, 2H), 1.96–1.73 (m, 4H), 1.14 (d, <i>J</i> = 6.4 Hz, 3H); MS (ES+) <i>m/z</i> 421.3 (M+1).

EXAMPLE	Analytical Data
48	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.79 (s, 2H), 5.95 (s, 1H), 4.36 (s, 2H), 4.12 (t, <i>J</i> = 5.6 Hz, 2H), 3.72 (t, <i>J</i> = 5.6 Hz, 2H), 2.83–2.69 (m, 2H), 2.60 (s, 3H), 2.44–2.31 (m, 2H), 2.21 (s, 3H), 2.16 (s, 6H); MS (ES+) <i>m/z</i> 389.3 (M+1).

Example 38. *N*-(2-fluoro-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide

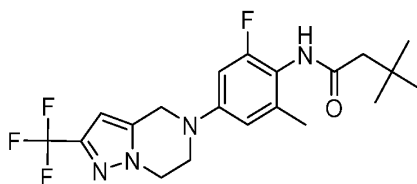


Step 1: Preparation of N-(4-bromo-2-fluoro-6-methylphenyl)-3,3-dimethylbutanamide



[369] To a solution of 4-bromo-2-fluoro-6-methyl-aniline (0.50 g, 2.45 mmol) in MeCN (10 mL) was added triethylamine (0.74 g, 7.35 mmol, 1.02 mL) and 3,3-dimethylbutanoyl chloride (0.40 g, 2.93 mmol, 0.41 mL). The mixture was stirred at 25 °C for 5 hours. Ethyl acetate (40 mL) and water (40 mL) were added and layers were separated. The aqueous phase was extracted with ethyl acetate (2 × 40 mL). Combined organic phases were washed with brine (40 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1 / 1) to afford 0.39 g of *N*-(4-bromo-2-fluoro-6-methyl-phenyl)-3,3-dimethyl-butnamide (47% yield) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 7.28 (s, 1H), 7.13 (m, 1H), 6.7 (s, 1H), 2.28 (m, 1H), 2.28 (m, 2H), 2.25 (m, 3H), 1.12 (s, 9H) ppm. MS (ES+) *m/z* 303.9, (M + 1).

Step 2: Preparation of N-(2-fluoro-6-methyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide



[370] A mixture of *N*-(4-bromo-2-fluoro-6-methyl-phenyl)-3,3-dimethyl-butnamide (0.30 g, 0.94 mmol), 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine;hydrochloride (0.25 g, 1.10 mmol), [2-(2-aminophenyl)phenyl]palladium(1+);2-(2-dicyclohexylphosphanylphenyl)-N1,N1,N3,N3-tetramethyl-benzene-1,3-diamine;methanesulfonate (0.076 g, 0.094 mmol), and cesium carbonate (0.92 g, 2.82 mmol) in dioxane (10 mL) was degassed and purged with nitrogen 3 times, and then the mixture was stirred at 90 °C for 16 hours under a nitrogen atmosphere. The resulting mixture was filtered over

Celite and the filtrate was extracted with ethyl acetate (3 ×30 mL). The combined organic phases were washed with brine (30 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(FA)-ACN]; gradient: 49%-79% B over 10 min).

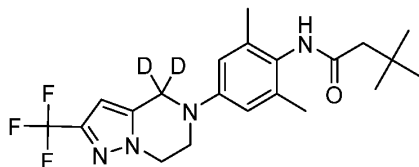
Concentration of the desired fractions afforded 0.151 g of *N*-[2-fluoro-6-methyl-4-[2-(trifluoromethyl)-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazin-5-yl]phenyl]-3,3-dimethyl-butanamide (37% yield) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 6.62–6.55 (m, 3H), 6.39 (m, 1H), 4.43 (s, 2H), 4.35 (m, 2H), 3.75 (m, 2H), 2.28 (m, 5H), 1.16 (s, 9H); MS (ES⁺) *m/z* 413.1, (M + 1).

[371] The following further Examples were prepared analogously to Example 38 (as described above), substituting appropriate starting materials where necessary and making appropriate changes to experimental conditions informed by common general knowledge. Purification was performed either by silica gel chromatography, reverse-phase preparative HPLC, or supercritical fluid chromatography (SFC).

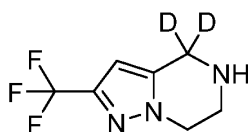
EXAMPLE	Analytical Data
39	¹ H NMR (400 MHz, CDCl ₃) δ (6.82, m, 1H) 6.62–6.55 (m, 2H), 6.39 (m, 1H), 4.47 (s, 2H), 4.35 (t, 2H, <i>J</i> = 5.3 Hz), 3.78 (t, 2H, <i>J</i> = 5.3 Hz), 2.28 (s, 2H), 1.16 (s, 9H); MS (ES ⁺) <i>m/z</i> 433.1 (M + 1).
49	¹ H-NMR (400 MHz; CD ₃ OD): δ 6.58-6.54 (m, 2H), 6.50 (s, 1H), 4.50 (s, 2H), 4.31-4.28 (m, 2H), 3.83 (t, <i>J</i> = 5.5 Hz, 2H), 3.80 (s, 3H), 2.26 (s, 2H), 2.19 (s, 3H), 1.12 (s, 9H); MS (ES ⁺) <i>m/z</i> 425.2 (M+1).
50	¹ H-NMR (400 MHz; CD ₃ OD): δ 7.36-7.30 (m, 3H), 6.53 (s, 1H), 4.58 (s, 2H), 4.33 (t, <i>J</i> = 5.4 Hz, 2H), 3.90 (t, <i>J</i> = 5.5 Hz, 2H), 2.28 (s, 2H), 1.10 (s, 9H); MS (ES ⁺) <i>m/z</i> 449.2 (M+1).
51	¹ H NMR (400 MHz, CDCl ₃) δ = 7.00 (d, <i>J</i> = 1.6 Hz, 1H), 6.93–6.82 (m, 1H), 6.61 (s, 1H), 6.43 (s, 1H), 4.52 (s, 2H), 4.40 (t, <i>J</i> = 5.6 Hz, 2H), 3.83 (t, <i>J</i> = 5.6 Hz, 2H), 2.29 (s, 2H), 1.13 (s, 9H); MS ES ⁺ <i>m/z</i> 467.2 (M + 1).
52	¹ H NMR (400 MHz, CDCl ₃) δ 7.08 (d, <i>J</i> = 2.8 Hz, 1H), 7.02 (d, <i>J</i> = 2.8 Hz, 1H), 6.81 (s, 1H), 6.40 (s, 1H), 4.48 (s, 2H), 4.38 (t, <i>J</i> = 5.6 Hz, 2H), 3.83–3.76 (m, 2H), 2.30 (d, <i>J</i> = 2.8 Hz, 5H), 1.16 (s, 1H), 1.14 (s, 9H); MS (ES ⁺) <i>m/z</i> 463.1 (M + 1).
53	¹ H NMR (400 MHz, CDCl ₃) δ 6.81 (d, <i>J</i> = 1.6 Hz, 1H), 6.65 (dd, <i>J</i> = 2.8, 12.4 Hz, 1H), 6.58 (s, 1H), 4.53 (s, 2H), 3.71 (t, <i>J</i> = 5.7 Hz, 2H), 3.08 (t, <i>J</i> = 5.6 Hz, 2H), 2.29 (s, 2H), 1.14 (s, 9H); MS (ES ⁺) <i>m/z</i> 450.1, 452.1 (M + 1).
54	¹ H NMR (400 MHz, CDCl ₃) δ 6.61 (s, 1H), 6.59–6.53 (m, 2H), 4.51 (s, 2H), 3.68 (t, <i>J</i> = 5.6 Hz, 2H), 3.06 (t, <i>J</i> = 5.6 Hz, 2H), 2.28 (s, 2H), 2.25 (s, 3H), 1.14 (s, 9H); MS (ES ⁺) <i>m/z</i> 430.1 (M + 1).
55	¹ H NMR (400 MHz, CDCl ₃) δ = 6.99 (s, 1H), 6.90–6.85 (m, 1H), 6.58 (s, 1H), 4.57 (s, 2H), 3.76 (t, <i>J</i> = 5.6 Hz, 2H), 3.11 (t, <i>J</i> = 5.6 Hz, 2H), 2.28 (s, 2H), 1.13 (s, 9H); MS (ES ⁺) <i>m/z</i> 484.1 (M + 1).
56	¹ H NMR (400 MHz, CDCl ₃) δ 8.01 (d, <i>J</i> = 8.8 Hz, 1H), 7.23–7.16 (m, 2H), 7.16–7.11 (m, 1H), 4.54 (s, 2H), 3.72 (t, <i>J</i> = 5.6 Hz, 2H), 3.09 (t, <i>J</i> = 5.6 Hz, 2H), 2.25 (s, 2H), 1.11 (s, 9H); MS (ES ⁺) <i>m/z</i> 466.1 (M + 1).
57	¹ H NMR (400 MHz, CD ₃ OD, 298 K) δ 7.19 (d, <i>J</i> = 5.2 Hz, 1H), 6.79 (d, <i>J</i> = 5.2 Hz, 1H), 6.78 (s, 2H), 4.58 (s, 1H), 4.40 (s, 2H), 3.57 (t, <i>J</i> = 5.6 Hz, 2H), 2.78 (t, <i>J</i> = 5.6 Hz, 2H), 2.29 (s, 2H), 2.19 (s, 6H), 1.13 (s, 9H); MS (ES ⁺) <i>m/z</i> 357.3 (M + 1).
58	¹ H NMR (400 MHz, CDCl ₃) δ 6.63 (s, 1H), 6.60 (s, 1H), 6.43 (s, 1H), 6.37 (s, 1H), 4.30 (s, 2H), 3.79 (s, 3H), 3.55 (t, <i>J</i> = 5.2 Hz, 2H), 2.72 (s, 2H), 2.27 (s, 2H), 2.22 (s, 3H), 1.14 (s, 9H); MS (ES ⁺) <i>m/z</i> 407.1, 409.1 (M + 1).
124	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.00 (s, 1H), 6.75 (d, <i>J</i> = 2.8 Hz, 1H), 6.58 (s, 1H), 6.38 (d, <i>J</i> = 2.8 Hz, 1H), 4.45 (s, 2H), 4.25 (t, <i>J</i> = 5.2 Hz, 2H), 3.75 (t, <i>J</i> = 5.2 Hz, 2H), 2.21 (s, 2H), 2.11 (s, 3H), 1.91 (t, <i>J</i> = 5.2, 8.4 Hz, 1H), 1.05 (s, 9H), 0.85–0.78 (m, 2H), 0.64–0.57 (m, 2H); MS (ES ⁺) <i>m/z</i> 435.2 (M + 1).

EXAMPLE	Analytical Data
135	¹ H NMR: (400 MHz, DMSO- <i>d</i> ₆) δ 9.32 (s, 1H), 7.04-6.98 (m, 2H), 6.59 (s, 1H), 4.63 (s, 2H), 4.43 (t, <i>J</i> = 4.8 Hz, 2H), 3.92 (t, <i>J</i> = 4.8 Hz, 2H), 3.82 (s, 3H), 2.17 (s, 2H), 1.04 (s, 9H); MS (ES ⁺) <i>m/z</i> 436.2 (M+1).

Example 40. *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl-4,4-*d*₂)phenyl)-3,3-dimethylbutanamide

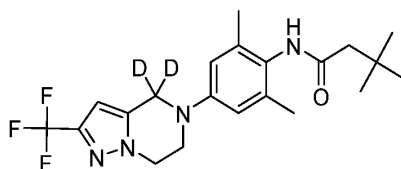


*Step 1: Preparation of 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-4,4-*d*₂*



[372] To a solution of 2-(trifluoromethyl)-6,7-dihydro-5*H*-pyrazolo[1,5-*a*]pyrazin-4-one (0.50 g, 2.44 mmol) in tetrahydrofuran (10.0 mL) was added lithium tetradeuterioaluminum (0.34 g, 7.31 mmol) at 0 °C under nitrogen. The mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched by addition of sodium sulfate decahydrate (1.00 g) at 25 °C under nitrogen. The mixture was filtered and concentrated under reduced pressure to afford 0.43 g of crude 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-4,4-*d*₂ as a yellow solid that was used without further purification: ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.43 (s, 1H), 4.03 (t, *J* = 5.6 Hz, 2H), 3.12 (t, *J* = 5.6 Hz, 2H).

*Step 2: Preparation of N-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl-4,4-*d*₂)phenyl)-3,3-dimethylbutanamide*



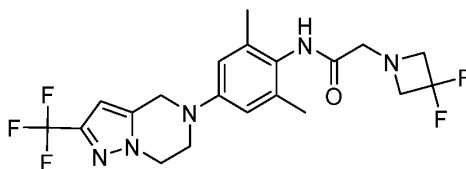
[373] A mixture of 4,4-dideuterio-2-(trifluoromethyl)-6,7-dihydro-5*H*-pyrazolo[1,5-*a*]pyrazine (0.200 g, 1.040 mmol), *N*-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butylamine (0.300 g, 1.010 mmol), methanesulfonato (2-dicyclohexylphosphino-2,6-bis(dimethylamino)-1,1-biphenyl)(2-amino-1,1-biphenyl-2-yl)palladium(II) (0.085 g, 0.105 mmol) and cesium carbonate (0.840 g, 2.580 mmol) in dioxane (10.0 mL) was stirred at 90 °C for 12 h under nitrogen. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (40 g SepaFlash® Silica Flash Column, eluent of 0–45% ethyl acetate/petroleum ether gradient at 80 mL/min) to afford 0.296 g of *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl-4,4-*d*₂)phenyl)-3,3-dimethyl butanamide (66% yield) as a white

solid: ^1H NMR (400 MHz, $\text{MeOD-}d_4$) δ 6.81 (s, 2H), 6.50 (s, 1H), 4.27 (t, $J = 5.6$ Hz, 2H), 3.83–3.76 (m, 2H), 2.30 (s, 2H), 2.20 (s, 6H), 1.13 (s, 9H); MS (ES+) m/z 411.3 ($M + 1$).

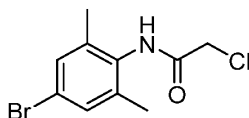
[374] The following further Examples were prepared analogously to Example 40 (as described above), substituting appropriate starting materials where necessary and making appropriate changes to experimental conditions informed by common general knowledge. Purification was performed either by silica gel chromatography, reverse-phase preparative HPLC, or supercritical fluid chromatography (SFC).

EXAMPLE	Analytical Data
59	^1H NMR (400 MHz, $\text{MeOD-}d_4$) δ 6.79 (s, 2H), 3.73 (t, $J = 5.6$ Hz, 2H), 2.97 (t, $J = 5.6$ Hz, 2H), 2.29 (s, 2H), 2.19 (s, 6H), 1.13 (s, 9H); MS (ES+) m/z 428.2 ($M + 1$).

Example 41. 2-(3,3-difluoroazetidin-1-yl)-N-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)acetamide

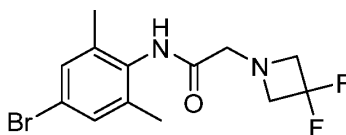


Step 1: Preparation of N-(4-bromo-2,6-dimethylphenyl)-2-(3,3-difluoroazetidin-1-yl)acetamide



[375] To a solution of 4-bromo-2,6-dimethyl-aniline (1.00 g, 5.00 mmol) and triethylamine (1.52 g, 14.90 mmol) in dichloromethane (10.0 mL) was added 2-chloroacetyl chloride (0.62 g, 5.49 mmol) at 25 °C and the mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (20 g SepaFlash® Silica Flash Column, eluent of 0–15% ethyl acetate/petroleum ether gradient at 80 mL/min) to afford 0.70 g of *N*-(4-bromo-2,6-dimethyl-phenyl)-2-chloro-acetamide (51% yield) as a white solid: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 9.67 (s, 1H), 7.31 (s, 2H), 4.28 (s, 2H), 2.13 (s, 6H).

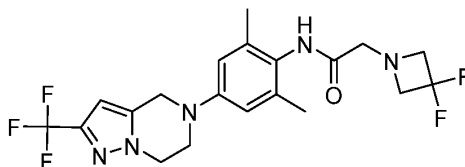
Step 2: Preparation of N-(4-bromo-2,6-dimethyl-phenyl)-2-chloro-acetamide



[376] A mixture of 3,3-difluoroazetidine (0.299 g, 2.310 mmol, hydrochloride), *N*-(4-bromo-2,6-dimethyl-phenyl)-2-chloro-acetamide (0.400 g, 1.450 mmol), sodium iodide (0.022 g, 0.144 mmol) and potassium carbonate (0.600 g, 4.340 mmol) in acetonitrile (6.0 mL) was stirred at 80 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (40 g SepaFlash® Silica Flash Column, eluent of 0–45% ethyl

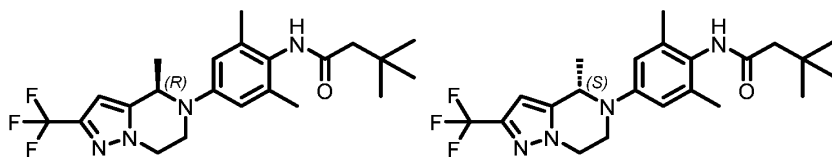
acetate/petroleum ether gradient at 100 mL/min) to afford 0.36 g of *N*-(4-bromo-2,6-dimethyl-phenyl)-2-(3,3-difluoroazetidin-1-yl)acetamide (75% yield) as a yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 8.20 (s, 1H), 7.28 (s, 2H), 3.90 (t, $J = 12.0$ Hz, 4H), 3.51 (s, 2H), 2.20 (s, 6H).

Step 3: Preparation of 2-(3,3-difluoroazetidin-1-yl)-N-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)acetamide

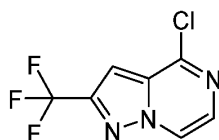


[377] A mixture of *N*-(4-bromo-2,6-dimethyl-phenyl)-2-(3,3-difluoroazetidin-1-yl)acetamide (0.150 g, 0.450 mmol), 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (0.123 g, 0.540 mmol, hydrochloride), cesium carbonate (0.440 g, 1.350 mmol) and methanesulfonato(2-dicyclohexylphosphino-2,4,6-tri-*i*-propyl-1,1-biphenyl)(2-methylamino-1,1-biphenyl-2-yl)palladium(II) (0.039 g, 0.045 mmol) in dioxane (5.0 mL) was stirred at 90 °C for 12 h under nitrogen. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters xbridge 150 mm $\times$ 25 mm $\times$ 10 μm ; mobile phase: [water (ammonium bicarbonate)-acetonitrile]; gradient: 46%–66%). The desired fraction was collected and lyophilized to afford 0.087 g of 2-(3,3-difluoroazetidin-1-yl)-*N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4H)-yl)phenyl)acetamide (42% yield) as an off-white solid: ^1H NMR (400 MHz, $\text{MeOD}-d_4$) δ 6.82 (s, 2H), 6.50 (s, 1H), 4.48 (s, 2H), 4.27 (t, $J = 5.2$ Hz, 2H), 3.85 (t, $J = 12.4$ Hz, 4H), 3.82–3.78 (m, 2H), 3.51 (s, 2H), 2.18 (s, 6H); MS (ES+) m/z 444.2 ($M + 1$).

Examples 42 and 43. (*R*) and (*S*)-*N*-(2,6-dimethyl-4-(4-methyl-2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4H)-yl)phenyl)-3,3-dimethylbutanamide



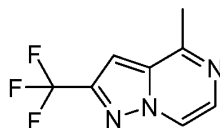
*Step 1. Preparation of 4-chloro-2-(trifluoromethyl)pyrazolo[1,5-*a*]pyrazine*



[378] To a solution of 2-(trifluoromethyl)pyrazolo[1,5-*a*]pyrazin-4-ol (10.00 g, 49.20 mmol) in phosphorus oxychloride (50 mL) was added dimethyl formamide (0.18 g, 2.46 mmol). The mixture was stirred at 100 °C for 8 hrs. The excess phosphorus oxychloride was removed by distillation at reduced pressure, the residue was mixed with ice (100 g) and sodium carbonate (10.0 g), the mixture was then extracted with dichloromethane (3 $\times$ 100 mL). The combined organic phases were dried over anhydrous

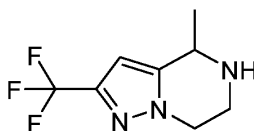
sodium sulfate, filtered and concentrated under reduced pressure to afford 10.0 g of crude 4-chloro-2-(trifluoromethyl)pyrazolo[1,5-a]pyrazine (10.0 g, crude) as a white solid that was used without further purification.

Step 2. Preparation of 4-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrazine



[379] To a solution of 4-chloro-2-(trifluoromethyl)pyrazolo[1,5-a]pyrazine (8.00 g, 36.10 mmol) in dimethyl formamide (100 mL) was added methylboronic acid (6.48 g, 0.11 mol), Bis(triphenylphosphine)palladium(II) dichloride (1.27 g, 1.81 mmol) and potassium carbonate (25.00 g, 0.18 mol) under nitrogen. The mixture was stirred at 90 °C for 12 hrs until LCMS showed reaction was complete. The reaction mixture was diluted with water 100 mL and extracted with ethyl acetate 300 mL (3 x 100 mL). The combined organic phases were washed with brine 200 mL (2 x 100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Petroleum ether : Ethyl acetate = 2 : 1, P1 R_f = 0.75 Petroleum ether : Ethyl acetate = 500 : 1 to 1 : 1) to afford 2.0 g of 4-methyl-2-(trifluoromethyl) pyrazolo[1,5-a]pyrazine (27.5% yield) as a yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 8.29 (d, J = 4.8 Hz, 1H), 7.92 (d, J = 4.8 Hz, 1H), 7.05 (s, 1H), 2.81 (s, 3H); LCMS (ES-): m/z 202.0 ($M + 1$).

Step 3. Preparation of 4-methyl-2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine



[380] To a solution of 4-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrazine (2.00 g, 9.94 mmol) in propan-2-ol (20 mL) was added 10% Pd/C (1.06 g, 0.99 mmol). The mixture was stirred at 50 °C for 12 hrs. TLC (Petroleum ether : Ethyl acetate = 3 : 1, P1 R_f = 0.28, R1 R_f = 0.75). The reaction mixture was filtered and the filter cake was washed with ethyl alcohol (200 mL) and the filtrate was concentrated under reduced pressure to afford 2.20 g of crude 4-methyl-2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine as a colorless oil that was used without further purification: ^1H NMR (400 MHz, CDCl_3) δ 6.28 (s, 1H), 4.17-4.24 (m, 1H), 4.07-4.16 (m, 2H), 3.43-3.49 (m, 1H), 3.20-3.32 (m, 1H), 1.47 (d, J = 6.8 Hz, 3H).

Step 4. Preparation of N-(2,6-dimethyl-4-(4-methyl-2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)phenyl)-3,3-dimethylbutanamide and chiral separation of enantiomers (Peak 1 and Peak 2)

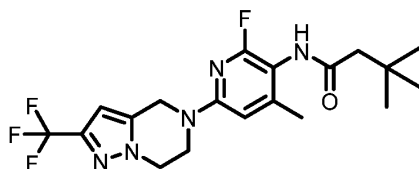
[381] To a solution of *N*-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide (1.74 g, 5.85 mmol) in dioxane (10 mL) was added cesium carbonate (3.81 g, 11.70 mmol), 4-methyl-2-(trifluoromethyl)-

4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (0.80 g, 3.90 mmol) 2-dicyclohexylphosphino-2,6-di-*i*-propoxy-1,1-biphenyl (0.73 g, 1.56 mmol) and tris(dibenzylideneacetone)dipalladium (0.36 g, 0.39 mmol). The mixture was stirred at 100 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-TLC (silica gel, P1 R_f = 0.35, Petroleum ether : Ethyl acetate = 1 : 1). The crude product was purified by SFC (column: DAICEL CHIRALPAK IC (250 mm * 30 mm, 5 μ m); mobile phase: [carbon dioxide- methanol (0.1% ammonium hydroxide)]; B%:40%, isocratic elution mode). SFC of P1: RT = 1.316 min. SFC of P2: RT = 2.291 min. The individual enantiomers were isolated and stereochemistry listed below arbitrarily assigned.

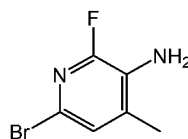
[382] Peak 1: *N*-(2,6-dimethyl-4-(4-methyl-2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide (210 mg, 12.6% yield, 98.9% purity) was obtained as a white solid: HPLC (RT = 3.370 min) showed the purity (210 mg, 497.06 μ mol, 12.75% yield) was 98.923%: ^1H NMR (400 MHz, DMSO- d_6) δ 8.92 (s, 1H), 6.75 (s, 2H), 6.63 (s, 1H), 5.16 (q, J = 6.4 Hz, 1H), 4.08-4.33 (m, 2H), 3.84-3.98 (m, 1H), 3.56 (ddd, J = 14.0, 10.0, 4.0 Hz, 1H), 2.17 (s, 2H), 2.10 (s, 6H), 1.33 (d, J = 6.8 Hz, 3H), 1.05 (s, 9H); MS (ES+) m/z 423.3 ($M + 1$).

[383] Peak 2: *N*-(2,6-dimethyl-4-(4-methyl-2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide (250 mg, 14.8% yield) was obtained as a white solid: HPLC (RT = 3.375 min) showed the purity of (250 mg, 591.74 μ mol, 15.18% yield) was 97.8%. ^1H NMR and ^{13}C NMR of P2 (400 MHz, DMSO. SFC of P1: EC16504-40-P1A1, P1: RT = 1.316 min: ^1H NMR (400 MHz, DMSO- d_6) δ 8.91 (s, 1H), 6.76 (s, 2H), 6.63 (s, 1H), 5.12-5.23 (m, 1H), 4.10-4.30 (m, 2H), 3.87-3.98 (m, 1H), 3.50-3.63 (m, 1H), 2.18 (s, 2H), 2.11 (s, 6H), 1.33 (d, J = 6.8 Hz, 3H), 1.06 (s, 9H).

Example 44. *N*-(2-fluoro-4-methyl-6-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4*H*)-yl)pyridin-3-yl)-3,3-dimethylbutanamide



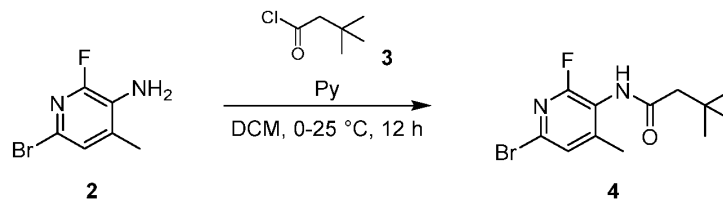
Step 1. Preparation of 6-bromo-2-fluoro-4-methylpyridin-3-amine



[384] To a solution of 2-fluoro-4-methylpyridin-3-amine (0.50 g, 3.96 mmol) in dichloromethane (5.0 mL) was added 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (0.56 g, 1.98 mmol) at 0 °C under nitrogen. The mixture was stirred at 25 °C for 1 h. The reaction was quenched with water (5 mL). Water (10 mL) was added to the mixture, then the mixture was extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic phases were washed with brine (3 $\times$ 10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 0.79 g of 6-bromo-2-fluoro-4-methylpyridin-3-amine (88%

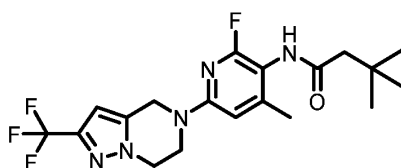
yield) as a yellow solid that was used without further purification: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.18 (s, 1H), 5.37 (s, 2H), 2.14 (s, 3H).

Step 2. Preparation of N-(6-bromo-2-fluoro-4-methylpyridin-3-yl)-3,3-dimethylbutanamide



[385] To a solution of 6-bromo-2-fluoro-4-methylpyridin-3-amine (0.79 g, 3.48 mmol) in dichloromethane (7.0 mL) was added pyridine (0.55 g, 6.94 mmol) and 3,3-dimethylbutanoyl chloride (0.52 g, 3.84 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 h. Water (10 mL) was added to the mixture, then the mixture was extracted with ethyl acetate (3 $\times$ 5 mL). The combined organic phases were washed with saturated sodium bicarbonate (3 $\times$ 5 mL) and brine (3 $\times$ 5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=3/1) and then prep-HPLC (column: Phenomenex luna C18 150 mm $\times$ 25 mm $\times$ 10 μm ; mobile phase: [water (formic acid)-acetonitrile]; gradient: 44%–64% B over 10 min). The desired fraction was collected under reduced pressure to remove acetonitrile. Water (10 mL) was added to the mixture, then the mixture was extracted with ethyl acetate (3 $\times$ 5 mL). The combined organic phases were washed with brine (3 $\times$ 5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 0.33 g of *N*-(6-bromo-2-fluoro-4-methylpyridin-3-yl)-3,3-dimethylbutanamide (31% yield) as a white solid: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.57 (s, 1H), 7.60 (s, 1H), 2.24 (s, 3H), 2.22 (s, 2H), 1.03 (s, 9H).

Step 3. Preparation of N-(2-fluoro-4-methyl-6-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)pyridin-3-yl)-3,3-dimethylbutanamide



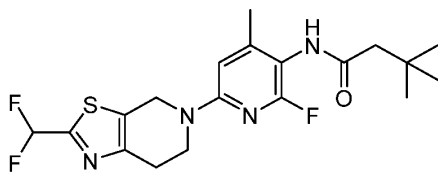
[386] To a solution of *N*-(6-bromo-2-fluoro-4-methylpyridin-3-yl)-3,3-dimethylbutanamide (0.083 g, 0.268 mmol) and 2-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (0.074 g, 0.325 mmol, hydrochloride) in dioxane (3.0 mL) were added cesium carbonate (0.262 g, 0.804 mmol) and methanesulfonato(2-dicyclohexyl phosphino)-2,6-bis(dimethylamino)-1,1-biphenyl(2-amino-1,1-biphenyl-2-yl)palladium(II) (0.025 g, 0.031 mmol) under nitrogen. The mixture was stirred at 90 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 mm $\times$ 25 mm $\times$ 10 μm ; mobile phase: [water (formic acid)-acetonitrile]; gradient: 50%–70% B over 10 min). The desired

fraction was collected and lyophilized to afford 0.037 g of *N*-(2-fluoro-4-methyl-6-(2-(trifluoromethyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)pyridin-3-yl)-3,3-dimethylbutanamide (31% yield) as a white solid: ¹H NMR (400 MHz, MeOD-*d*₄) δ 6.70 (s, 1H), 6.52 (s, 1H), 4.80 (s, 2H), 4.32–4.26 (m, 2H), 4.17–4.10 (m, 2H), 2.27 (s, 2H), 2.25 (s, 3H), 1.11 (s, 9H); MS (ES+) *m/z* 414.3 (M+1).

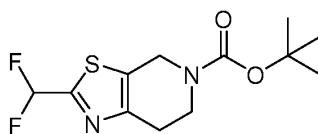
[387] The following further Examples were prepared analogously to Example 44 (as described above), substituting appropriate starting materials where necessary and making appropriate changes to experimental conditions informed by common general knowledge. Purification was performed either by silica gel chromatography, reverse-phase preparative HPLC, or supercritical fluid chromatography (SFC).

EXAMPLE	Analytical Data
45	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.71 (s, 1H), 4.91 (s, 2H), 4.01–3.98 (m, 2H), 3.04–2.95 (m, 2H), 2.26 (s, 2H), 2.24 (s, 3H), 1.10 (s, 9H); MS (ES+) <i>m/z</i> 431.2 (M+1)

Example 91: *N*-(6-(2-(difluoromethyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-fluoro-4-methylpyridin-3-yl)-3,3-dimethylbutanamide

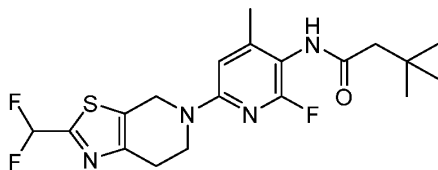


*Step 1. Preparation of tert-butyl 2-(difluoromethyl)-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate*



[388] To a solution of *tert*-butyl 2-formyl-4*H*,5*H*,6*H*,7*H*-[1,3]thiazolo[5,4-*c*]pyridine-5-carboxylate (1.00 g, 3.73 mmol) in dichloromethane (20 mL) was added diethylaminosulfur trifluoride (2.40 g, 40.91 mmol) at 0 °C and the mixture was stirred at ambient temperature for 16 h. The reaction mixture was quenched with cold (0 °C) water (100 mL) and stirred for 15 minutes. The mixture was then diluted with dichloromethane (50 mL) and two layers were separated. The aqueous layer was extracted with dichloromethane (100 mL $\times$ 2). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting with a gradient of 0% to 50% of ethyl acetate in heptane afforded 1.06 g of the title compound as a colorless syrup (97% yield): MS (ES+) *m/z*: 291.6 (M+1).

Step 2. Preparation of N-(6-(2-(difluoromethyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)-2-fluoro-4-methylpyridin-3-yl)-3,3-dimethylbutanamide



[389] To a solution of *tert*-butyl 2-(difluoromethyl)-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridine-5-carboxylate (1.06 g, 3.67 mmol) in dichloromethane (30 mL) was added trifluoroacetic acid (1.40 mL, 18.35 mmol) and the reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was diluted with dichloromethane (100 mL) and aqueous sodium bicarbonate solution (100 mL) and stirred for 20 minutes. Two layers separated and the organic layer was washed with aqueous sodium bicarbonate solution (100 mL × 2). Two layers were separated, and organic layer was dried with anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to afford 0.61 g of crude 2-(difluoromethyl)-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine as a brown oil (87% yield) that was used in the next step without further purification: MS (ES+) *m/z*: 191.0 (M+1).

[390] To a solution of 2-(difluoromethyl)-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (0.20 g, 1.05 mmol) and *N*-(6-bromo-2-fluoro-4-methyl-3-pyridyl)-3,3-dimethyl-butanamide (0.48 g, 1.58 mmol) in toluene (45 mL) was added potassium *tert*-butoxide (0.30 g, 2.63 mmol), 2-(dicyclohexylphosphino)-2'-(*N,N*-dimethylamino) biphenyl (0.12 g, 0.31 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.10 g, 0.10 mmol) under nitrogen atmosphere. The mixture was stirred at 100 °C for 18 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluting with a gradient of 0% to 40% ethyl acetate in heptane, afforded 0.04 g of the title compound as a pale yellow solid (9% yield): ¹H-NMR (400 MHz; CD₃OD): δ 6.98 (t, *J* = 54.7 Hz, 1H), 6.72 (s, 1H), 4.00 (t, *J* = 5.8 Hz, 2H), 2.99-2.97 (m, 2H), 2.28 (s, 2H), 2.25 (s, 3H), 1.12 (s, 9H); MS (ES+) *m/z* 413.2 (M+1).

[391] The following further Examples were prepared analogously to the foregoing Examples (as described above), substituting appropriate starting materials where necessary and making appropriate changes to experimental conditions informed by common general knowledge. Purification was performed either by silica gel chromatography, reverse-phase preparative HPLC, or supercritical fluid chromatography (SFC).

EXAMPLE	Analytical Data
60	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.96 (s, 1H), 6.49 (s, 1H), 4.39 (s, 2H), 4.34 (t, <i>J</i> = 5.2 Hz, 2H), 3.64 (t, <i>J</i> = 5.2 Hz, 2H), 2.31 (s, 2H), 2.25 (s, 3H), 1.13 (s, 9H); MS (ES+) <i>m/z</i> 447.2, 449.2 (M + 1).
61	¹ H NMR (400 MHz, CDCl ₃) δ 6.96 (s, 2H), 6.72 (s, 1H), 6.40 (s, 1H), 4.47 (s, 2H), 4.37 (t, <i>J</i> = 5.6 Hz, 2H), 3.78 (t, <i>J</i> = 5.6 Hz, 2H), 2.31 (s, 2H), 1.16 (s, 9H); MS (ES+) <i>m/z</i> 449.0, 450.0, 452.0 (M + 1).
62	¹ H-NMR (400 MHz; MeOD- <i>d</i> ₄): δ 6.78-6.73 (m, 2H), 6.17 (s, 1H), 4.45 (s, 2H), 4.18 (t, <i>J</i> = 5.5 Hz, 2H), 3.82 (t, <i>J</i> = 5.5 Hz, 2H), 2.30 (s, 2H), 2.25 (s, 3H), 1.13 (s, 9H); MS (ES+) <i>m/z</i> 379.2, 381.2 (M+1).
63	¹ H-NMR (400 MHz; MeOD- <i>d</i> ₄): δ 6.84 (d, <i>J</i> = 0.6 Hz, 1H), 6.54 (s, 1H), 4.84 (s, 2H), 4.31 (t, <i>J</i> = 5.4 Hz, 2H), 4.18 (t, <i>J</i> = 5.4 Hz, 2H), 2.31 (s, 2H), 2.26 (d, <i>J</i> = 0.6 Hz, 3H), 1.15 (s, 9H); MS (ES+) <i>m/z</i> 430.0 (M+1).

EXAMPLE	Analytical Data
64	¹ H NMR (400 MHz; DMSO- <i>d</i> ₆): δ 9.12 (s, 1H), 6.95 (t, <i>J</i> = 54.8 Hz, 1H), 6.80 (s, 1H), 6.44 (s, 1H), 4.75 (s, 2H), 4.26-4.17 (m, 2H), 4.08-4.01 (m, 2H), 2.25-2.04 (m, 5H), 1.03 (s, 9H); MS (ES+) <i>m/z</i> 396.0 (M + 1).
65	¹ H NMR (400 MHz, CDCl ₃) δ = 6.79 (d, <i>J</i> = 2.4 Hz, 1H), 6.73 (s, 1H), 6.64 (s, 1H), 6.40 (s, 1H), 4.45 (s, 2H), 4.37 (t, <i>J</i> = 5.6 Hz, 2H), 3.76 (t, <i>J</i> = 5.6 Hz, 2H), 2.29 (s, 5H), 1.14 (s, 9H); MS (ES+) <i>m/z</i> 479.1 (M + 1).
66	¹ H-NMR (400 MHz; MeOD- <i>d</i> ₄): δ 7.06 (d, <i>J</i> = 2.7 Hz, 1H), 6.96 (d, <i>J</i> = 2.4 Hz, 1H), 6.53 (s, 1H), 4.54 (s, 2H), 4.31 (t, <i>J</i> = 5.5 Hz, 2H), 3.86 (t, <i>J</i> = 5.5 Hz, 2H), 2.32 (s, 2H), 2.26 (s, 3H), 1.16 (s, 9H); MS (ES+) <i>m/z</i> 429.2, 431.2 (M+1).
67	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 7.49 (d, <i>J</i> = 2.8 Hz, 1H), 7.30 (d, <i>J</i> = 2.8 Hz, 1H), 4.70 (s, 2H), 3.84 (t, <i>J</i> = 5.6 Hz, 2H), 3.08 (s, 3H), 3.03 (t, <i>J</i> = 5.6 Hz, 2H), 2.35 (s, 2H), 2.27 (s, 3H), 1.14 (s, 9H); MS (ES+) <i>m/z</i> 490.1 (M + 1).
68	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.78–6.72 (m, 2H), 4.62 (s, 2H), 3.76 (t, <i>J</i> = 5.6 Hz, 2H), 2.99 (t, <i>J</i> = 5.6 Hz, 2H), 2.40 (s, 3H), 2.28 (s, 2H), 2.17 (s, 3H), 1.14 (s, 9H); MS (ES+) <i>m/z</i> 458.1 (M + 1).
69	¹ H NMR (400 MHz, CDCl ₃) δ 8.26 (d, <i>J</i> = 9.2 Hz, 1H), 7.16 (s, 1H), 6.92 (dd, <i>J</i> = 2.8 Hz, 9.2 Hz, 1H), 6.86 (s, 1H), 6.40 (s, 1H), 4.42 (s, 2H), 4.37 (t, <i>J</i> = 5.6 Hz, 2H), 3.78–3.69 (m, 2H), 2.27 (s, 2H), 1.11 (s, 9H); MS (ES+) <i>m/z</i> 465.2 (M + 1).
70	¹ H NMR (400 MHz; DMSO- <i>d</i> ₆): δ 8.93 (s, 1H), 6.77 (s, 2H), 6.57 (s, 1H), 4.57-4.32 (m, 3H), 3.96-3.87 (m, 1H), 3.40-3.36 (m, 1H), 2.18 (s, 2H), 2.11 (s, 6H), 1.52 (d, <i>J</i> = 6.4 Hz, 3H), 1.05 (s, 9H); MS (ES +) <i>m/z</i> 423.2 (M + 1).
71	¹ H NMR (400 MHz; DMSO- <i>d</i> ₆): δ 8.94 (s, 1H), 6.81 (s, 2H), 4.41 (s, 2H), 4.32-4.25 (m, 2H), 3.81-3.74 (m, 2H), 2.18 (s, 2H), 2.12 (s, 6H), 1.05 (s, 9H); MS (ES +) <i>m/z</i> 243.0, 245.0 (M + 1).
72	¹ H-NMR (400 MHz; MeOD- <i>d</i> ₄): δ 6.53 (s, 1H), 6.37 (s, 2H), 4.56 (s, 2H), 4.34-4.32 (m, 2H), 3.89-3.86 (m, 2H), 3.82 (s, 6H), 2.24 (s, 2H), 1.13 (s, 9H); MS (ES +) <i>m/z</i> 441.2 (M+1).
73	¹ H NMR (400 MHz, CDCl ₃) δ 6.64 (s, 1H), 6.60 (d, <i>J</i> = 7.6 Hz, 1H), 6.37 (s, 1H), 4.38 (s, 2H), 4.35 (t, <i>J</i> = 5.6 Hz, 2H), 3.66 (t, <i>J</i> = 5.6 Hz, 2H), 2.31 (s, 2H), 2.23 (s, 3H), 1.15 (s, 9H); MS (ES+) <i>m/z</i> 431.1 (M + 1).
74	¹ H NMR (400 MHz, CDCl ₃) δ = 6.82 (<i>J</i> = 2.0, 7.6 Hz, 1H), 6.67 (s, 1H), 4.49 (s, 2H), 3.62 (t, <i>J</i> = 5.6 Hz, 2H), 3.11 (t, <i>J</i> = 5.6 Hz, 2H), 2.33 (s, 2H), 1.21–1.12 (m, 9H); MS (ES+) <i>m/z</i> 468.1, 470.1 (M + 1).
75	¹ H NMR (400 MHz, CDCl ₃) δ 7.00 (s, 1H), 6.96–6.80 (m, 1H), 6.60 (s, 1H), 6.42 (s, 1H), 4.51 (s, 2H), 4.40 (t, <i>J</i> = 5.6 Hz, 2H), 3.82 (t, <i>J</i> = 5.6 Hz, 2H), 2.49 (s, 2H), 2.19–2.05 (m, 2H), 2.05–1.88 (m, 2H), 1.88–1.80 (m, 2H), 1.32 (s, 3H); MS (ES+) <i>m/z</i> 479.1 (M + 1).
76	¹ H NMR (400 MHz, CDCl ₃) δ 7.62 (d, <i>J</i> = 9.2 Hz, 1H), 6.86–6.82 (m, 2H), 6.77 (s, 1H), 6.37 (s, 1H), 4.41 (s, 2H), 4.34 (t, <i>J</i> = 5.6 Hz, 2H), 3.72 (t, <i>J</i> = 5.6 Hz, 2H), 2.28–2.24 (m, 5H), 1.13 (s, 9H); MS (ES+) <i>m/z</i> 395.2 (M + 1).
77	¹ H NMR (400 MHz, CDCl ₃) δ = 8.26 (d, <i>J</i> = 9.2 Hz, 1H), 7.36 (s, 1H), 6.99 (d, <i>J</i> = 2.8 Hz, 1H), 6.95–6.87 (m, 1H), 6.39 (s, 1H), 4.42 (s, 2H), 4.35 (t, <i>J</i> = 5.6 Hz, 2H), 3.73 (t, <i>J</i> = 5.6 Hz, 2H), 2.28 (s, 2H), 1.13 (s, 9H); MS (ES+) <i>m/z</i> 415.1, 417.1 (M + 1).
78	¹ H NMR (400 MHz, CDCl ₃) δ = 6.87–6.80 (m, 1H), 6.70 (s, 1H), 6.39 (s, 1H), 4.41–4.35 (m, 4H), 3.71–3.67 (m, 2H), 2.32 (s, 2H), 1.14 (s, 9H); MS (ES+) <i>m/z</i> 451.1, 453.1 (M + 1).
79	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.73 (d, <i>J</i> = 11.2 Hz, 2H), 4.64 (s, 2H), 3.79 (t, <i>J</i> = 5.6 Hz, 2H), 3.01 (t, <i>J</i> = 5.6 Hz, 2H), 2.26 (s, 2H), 1.09 (s, 9H); MS (ES+) <i>m/z</i> 434.1 (M+1).
80	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 7.31–7.15 (m, 2H), 4.69 (s, 2H), 3.84 (t, <i>J</i> = 5.2 Hz, 2H), 3.08–2.98 (m, 2H), 2.30 (s, 2H), 1.12 (s, 9H); MS (ES+) <i>m/z</i> 441.2 (M+1).
81	¹ H NMR (400 MHz, CDCl ₃) δ = 6.78 (d, <i>J</i> = 2.8 Hz, 1H), 6.72 (s, 1H), 6.62 (s, 1H), 4.52 (s, 2H), 3.70 (t, <i>J</i> = 5.6 Hz, 2H), 3.08 (t, <i>J</i> = 5.6 Hz, 2H), 2.27 (d, <i>J</i> = 2.8 Hz, 5H), 1.14 (s, 9H); MS (ES+) <i>m/z</i> 496.1 (M + 1).

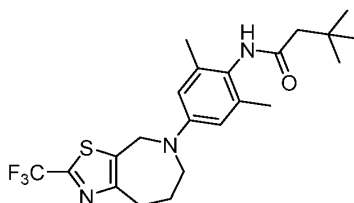
EXAMPLE	Analytical Data
82	¹ H NMR (400 MHz, CDCl ₃) δ 8.21 (d, J = 9.2 Hz, 1H), 7.13 (s, 1H), 6.90 (dd, J = 2.8, 9.2 Hz, 1H), 6.87–6.84 (m, 1H), 4.50 (s, 2H), 3.68 (t, J = 5.6 Hz, 2H), 3.10–3.05 (m, 2H), 2.26 (s, 2H), 1.11 (s, 9H); MS (ES+) m/z 482.5 (M + 1).
83	¹ H NMR (400 MHz, CDCl ₃) δ 6.61 (s, 1H), 6.48–6.37 (m, 2H), 4.49 (s, 2H), 3.80 (s, 3H), 3.67 (t, J = 5.6 Hz, 2H), 3.08 (t, J = 5.6 Hz, 2H), 2.28 (s, 2H), 2.23 (s, 3H), 1.14 (s, 9H); MS (ES+) m/z 442.2 (M + 1).
84	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.77 (s, 2H), 4.17 (s, 2H), 3.70 (s, 3H), 3.66 (t, J = 5.6 Hz, 2H), 2.84–2.73 (m, 2H), 2.29 (s, 2H), 2.19 (s, 6H), 1.16 (s, 9H); MS (ES+) m/z 423.2 (M + 1).
85	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 7.13 (s, 1H), 5.00 (s, 2H), 4.07 (t, J = 5.6 Hz, 2H), 3.01 (t, J = 5.6 Hz, 2H), 2.29 (s, 2H), 2.24 (s, 3H), 1.11 (s, 9H); MS (ES+) m/z 481.1 (M+1).
86	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.88 (s, 1H), 6.75 (s, 2H), 4.63 (s, 2H), 3.70 (t, J = 5.6 Hz, 2H), 3.41 (s, 3H), 2.93 (t, J = 5.2 Hz, 2H), 2.16 (s, 2H), 2.08 (s, 6H), 1.04 (s, 9H); MS (ES+) m/z 436.2 (M + 1).
87	¹ H NMR (400 MHz, CDCl ₃) δ 7.60–7.54 (m, 1H), 6.83 (d, J = 2.8 Hz, 2H), 6.76 (s, 1H), 4.49 (s, 2H), 3.66 (t, J = 5.6 Hz, 2H), 3.05 (t, J = 5.6 Hz, 2H), 2.25 (s, 5H), 1.13 (s, 9H); MS (ES+) m/z 412.2 (M + 1).
88	¹ H NMR (400 MHz, CDCl ₃) δ = 8.21 (d, J = 9.2 Hz, 1H), 7.33 (s, 1H), 6.98 (d, J = 2.8 Hz, 1H), 6.92–6.88 (m, 1H), 4.49 (s, 2H), 3.67 (t, J = 5.6 Hz, 2H), 3.06 (t, J = 5.6 Hz, 2H), 2.27 (s, 2H), 1.12 (s, 9H); MS (ES+) m/z 432.1/434.1 (M + 1).
89	¹ H-NMR (400 MHz; MeOD- <i>d</i> ₄): δ 7.03 (d, J = 54.7 Hz, 1H), 6.81 (s, 2H), 4.56-4.54 (m, 2H), 3.72 (t, J = 5.8 Hz, 2H), 2.97-2.95 (m, 2H), 2.31 (s, 2H), 2.21 (s, 6H), 1.15 (s, 9H); MS (ES +) m/z 408.0 (M+1).
90	¹ H NMR (400 MHz, CDCl ₃) δ 6.63 (s, 1H), 6.58 (d, J = 8.4 Hz, 1H), 4.45 (s, 2H), 3.58 (t, J = 5.6 Hz, 2H), 3.08 (t, J = 5.6 Hz, 2H), 2.30 (s, 2H), 2.20 (s, 3H), 1.14 (s, 9H); MS (ES+) m/z 448.2 (M + 1).
122	¹ H NMR (400 MHz, CDCl ₃) δ 8.28 (d, J = 9.2 Hz, 1H), 7.18 (s, 1H), 6.96 (d, J = 9.2 Hz, 1H), 4.94 (s, 2H), 3.98 (t, J = 6.0 Hz, 2H), 3.08 (t, J = 6.0 Hz, 2H), 2.25 (s, 2H), 1.11 (s, 9H). MS (ES+) m/z 467.1 (M + 1)
91	¹ H-NMR (400 MHz; MeOD- <i>d</i> ₄): δ 6.98 (t, J = 54.7 Hz, 1H), 6.72 (s, 1H), 4.00 (t, J = 5.8 Hz, 2H), 2.99-2.97 (m, 2H), 2.28 (s, 2H), 2.25 (s, 3H), 1.12 (s, 9H); MS (ES +) m/z 413.2 (M+1).
92	¹ H NMR (400 MHz, CDCl ₃) δ 6.88 (d, J = 2.8 Hz, 1H), 6.75 (d, J = 2.8 Hz, 1H), 6.69 (s, 1H), 4.46 (s, 2H), 3.66 (t, J = 5.6 Hz, 2H), 3.06 (s, 2H), 2.50 (s, 2H), 2.26 (s, 3H), 2.18–2.10 (m, 2H), 2.05–1.81 (m, 4H), 1.36 (s, 3H); MS (ES+) m/z 458.1/460.1 (M + 1).
93	¹ H-NMR (400 MHz; MeOD- <i>d</i> ₄): δ 7.00 (d, J = 0.9 Hz, 1H), 6.82 (s, 2H), 4.48 (s, 2H), 4.28 (t, J = 5.4 Hz, 2H), 3.74 (t, J = 5.5 Hz, 2H), 2.30 (s, 2H), 2.21 (s, 6H), 1.13 (s, 9H); MS (ES+) m/z 409 (M+1).
94	¹ H-NMR (400 MHz; MeOD- <i>d</i> ₄): δ 6.82 (s, 2H), 6.16 (s, 1H), 4.41 (s, 2H), 4.16 (t, J = 5.5 Hz, 2H), 3.78 (t, J = 5.5 Hz, 2H), 2.31 (s, 2H), 2.22 (s, 6H), 1.15 (s, 9H); MS (ES+) m/z 375, 377.2 (M+1).
95	¹ H-NMR (400 MHz; MeOD- <i>d</i> ₄): δ 7.16 (d, J = 2.7 Hz, 1H), 7.08-6.80 (m, 3H), 4.26-4.24 (m, 2H), 3.62 (t, J = 5.7 Hz, 2H), 3.00-2.97 (m, 2H), 2.31 (s, 2H), 2.22 (s, 6H), 1.15 (s, 9H); MS (ES+) m/z 407.2 (M+1).
96	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.77 (s, 2H), 4.17 (s, 2H), 3.70 (s, 3H), 3.66 (t, J = 5.6 Hz, 2H), 2.84–2.73 (m, 2H), 2.29 (s, 2H), 2.19 (s, 6H), 1.16 (s, 9H); MS (ES+) m/z 423.2 (M + 1).
97	¹ H NMR (400 MHz, CDCl ₃) δ 8.53 (s, 1H), 7.49 (s, 1H), 6.72 (s, 2H), 6.52 (s, 1H), 4.43 (s, 2H), 3.56 (t, J = 5.6 Hz, 2H), 3.05 (t, J = 5.6 Hz, 2H), 2.29 (s, 2H), 2.25 (s, 6H), 1.16 (s, 9H); MS (ES+) m/z 420.2 (M + 1).
98	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.44 (s, 2H), 4.71 (s, 2H), 4.58–4.56 (m, 2H), 2.30 (s, 2H), 2.22 (s, 6H), 1.14 (s, 9H); MS (ES+) m/z 412.2 (M + 1).

EXAMPLE	Analytical Data
99	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 9.09 (s, 1H), 6.40 (s, 1H), 4.81 (s, 2H), 4.73–4.64 (m, 2H), 2.19 (s, 3H), 2.18 (s, 2H), 1.05 (s, 9H); MS (ES+) <i>m/z</i> 417.2 (M+1).
100	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.64 (s, 1H), 6.51 (dd, <i>J</i> = 2.4, 12.0 Hz, 1H), 4.74 (s, 2H), 4.63–4.59 (m, 2H), 2.29 (s, 2H), 1.13 (s, 9H); MS (ES+) <i>m/z</i> 436.1, 438.1 (M + 1).264
101	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 8.44 (s, 1H), 6.80 (s, 2H), 4.25 (s, 2H), 3.64 (s, 3H), 3.60 (t, <i>J</i> = 5.6 Hz, 2H), 2.73 (t, <i>J</i> = 5.6 Hz, 2H), 2.50 (s, 3H), 2.30 (s, 2H), 2.20 (s, 6H), 1.13 (s, 9H); MS (ES+) <i>m/z</i> 369.3 (M + 1)
102	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 7.42 (s, 1H), 6.41 (s, 2H), 4.37 (s, 4H), 3.92 (s, 3H), 2.31 (s, 2H), 2.22 (s, 6H), 1.16 (s, 9H); MS (ES+) <i>m/z</i> 341.3 (M + 1).
103 ^d	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.82 (s, 2H), 6.49 (s, 1H), 4.47 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.80 (t, <i>J</i> = 5.6 Hz, 2H), 2.60–2.52 (m, 2H), 2.19 (s, 6H), 1.41 (dt, <i>J</i> = 4.0, 8.4 Hz, 1H), 1.35 (s, 3H), 1.19 (ddd, <i>J</i> = 4.4, 8.0, 12.4 Hz, 1H); MS (ES+) <i>m/z</i> 443.3 (M + 1).
104	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.81 (s, 2H), 6.49 (s, 1H), 4.46 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.79 (t, <i>J</i> = 5.6 Hz, 2H), 2.48 (s, 2H), 2.19 (s, 6H), 2.19–2.12 (m, 2H), 2.06–1.88 (m, 2H), 1.87–1.75 (m, 2H), 1.33 (s, 3H); MS (ES+) <i>m/z</i> 421.2 (M+1).
105 ^d	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.82 (s, 2H), 6.50 (s, 1H), 4.47 (s, 2H), 4.28 (t, <i>J</i> = 5.6 Hz, 2H), 3.80 (t, <i>J</i> = 5.6 Hz, 2H), 2.64–2.50 (m, 2H), 2.20 (s, 6H), 1.41 (dt, <i>J</i> = 4.0, 8.4 Hz, 1H), 1.35 (s, 3H), 1.20 (ddd, <i>J</i> = 4.4, 8.0, 12.4 Hz, 1H); MS (ES+) <i>m/z</i> 443.2 (M + 1).
106	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 7.45 (dt, <i>J</i> = 6.8, 8.8 Hz, 1H), 7.05–6.93 (m, 2H), 6.82 (s, 2H), 6.51 (s, 1H), 4.48 (s, 2H), 4.29 (t, <i>J</i> = 5.6 Hz, 2H), 3.85–3.73 (m, 4H), 2.19 (s, 6H); MS (ES+) <i>m/z</i> 465.1 (M + 1).
107	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.82 (s, 2H), 6.50 (s, 1H), 4.47 (s, 2H), 4.28 (t, <i>J</i> = 5.6 Hz, 2H), 3.80 (t, <i>J</i> = 5.6 Hz, 2H), 2.36 (d, <i>J</i> = 7.2 Hz, 2H), 2.19 (s, 6H), 2.11–1.96 (m, 3H), 1.95–1.88 (m, 2H), 1.87–1.68 (m, 2H), 1.49–1.33 (m, 2H); MS (ES+) <i>m/z</i> 471.2 (M + 1).
108	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ = 7.48–7.39 (m, 2H), 7.13–7.03 (m, 2H), 6.80 (s, 2H), 6.49 (s, 1H), 4.46 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.79 (t, <i>J</i> = 5.6 Hz, 2H), 3.68 (s, 2H), 2.11 (s, 6H); MS (ES+) <i>m/z</i> 447.1 (M + 1).
109	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 7.36 (dt, <i>J</i> = 6.0, 8.0 Hz, 1H), 7.23 (d, <i>J</i> = 8.0 Hz, 1H), 7.18 (d, <i>J</i> = 10.0 Hz, 1H), 7.01 (dt, <i>J</i> = 2.8, 8.4 Hz, 1H), 6.80 (s, 2H), 6.49 (s, 1H), 4.46 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.79 (t, <i>J</i> = 5.6 Hz, 2H), 3.72 (s, 2H), 2.11 (s, 6H) MS (ES+) <i>m/z</i> 447.1 (M + 1).
110	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 7.03 (dd, <i>J</i> = 2.0, 8.4 Hz, 2H), 6.94–6.84 (m, 1H), 6.80 (s, 2H), 6.49 (s, 1H), 4.46 (s, 2H), 4.27 (t, <i>J</i> = 5.2 Hz, 2H), 3.79 (t, <i>J</i> = 5.6 Hz, 2H), 3.72 (s, 2H), 2.12 (s, 6H); MS (ES+) <i>m/z</i> 465.1 (M + 1).
111	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ = 7.47–7.38 (m, 1H), 7.35–7.28 (m, 1H), 7.19–7.08 (m, 2H), 6.81 (s, 2H), 6.50 (s, 1H), 4.47 (s, 2H), 4.27 (t, <i>J</i> = 5.2 Hz, 2H), 3.87–3.75 (m, 4H), 2.18 (s, 6H); MS (ES+) <i>m/z</i> 447.1 (M + 1).
112	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.80 (s, 2H), 4.58 (br s, 2H), 3.73 (t, <i>J</i> = 5.6 Hz, 2H), 3.02–2.94 (m, 2H), 2.73 (s, 2H), 2.17 (s, 6H), 2.07 (d, <i>J</i> = 2.4 Hz, 6H); MS (ES+) <i>m/z</i> 454.1 (M + 1).
113	¹ H NMR (400 MHz, CDCl ₃) δ = 6.81 (s, 1H), 6.68–6.62 (m, 1H), 6.56 (s, 1H), 4.48 (s, 2H), 3.68 (t, <i>J</i> = 5.6 Hz, 2H), 3.08 (s, 2H), 2.49 (s, 2H), 2.18–2.09 (m, 2H), 2.01–1.78 (m, 4H), 1.34 (s, 3H); MS (ES+) <i>m/z</i> 462.1, 464.1 (M + 1).
114	¹ H NMR (400 MHz, CDCl ₃) δ 6.80 (s, 1H), 6.64 (dd, <i>J</i> = 2.8, 12.0 Hz, 1H), 6.57 (s, 1H), 4.52 (s, 2H), 3.70 (t, <i>J</i> = 5.6 Hz, 2H), 3.08 (t, <i>J</i> = 5.6 Hz, 2H), 2.49 (s, 2H), 2.23–2.05 (m, 2H), 2.05–1.78 (m, 4H), 1.34 (s, 3H); MS (ES+) <i>m/z</i> 462.0, 464.0 (M + 1).
115	¹ H NMR (400 MHz, CD ₃ OD) δ 6.70 (s, 1H), 6.50 (s, 1H), 4.58 (s, 2H), 4.30–4.25 (m, 2H), 4.17–4.10 (m, 2H), 2.48 (s, 2H), 2.30 (s, 3H), 2.18 (s, 3H), 2.16–2.12 (m, 1H), 2.11–1.71 (m, 5H), 1.32 (s, 3H); MS (ES+) <i>m/z</i> 422.2 (M + 1).

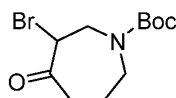
EXAMPLE	Analytical Data
116	¹ H NMR (400 MHz, CDCl ₃) δ 6.81 (s, 1H), 6.66 (dd, <i>J</i> = 2.8, 12.0 Hz, 1H), 6.59 (s, 1H), 6.40 (s, 1H), 4.46 (s, 2H), 4.37 (t, <i>J</i> = 5.6 Hz, 2H), 3.77 (t, <i>J</i> = 5.2 Hz, 2H), 2.50 (s, 2H), 2.24–2.09 (m, 2H), 2.06–1.90 (m, 2H), 1.88–1.78 (m, 2H), 1.34 (s, 3H); MS (ES+) <i>m/z</i> 445.1 (<i>M</i> + 1).
117	¹ H NMR (400 MHz, MeOD- <i>d</i> ₄) δ 6.82 (s, 2H), 6.50 (s, 1H), 4.47 (s, 2H), 4.27 (t, <i>J</i> = 5.6 Hz, 2H), 3.80 (t, <i>J</i> = 5.6 Hz, 2H), 2.74 (s, 2H), 2.19 (s, 6H), 2.08 (d, <i>J</i> = 2.4 Hz, 6H); MS (ES+) <i>m/z</i> 437.2 (<i>M</i> + 1).
123	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.97 (s, 1H), 6.73 (d, <i>J</i> = 2.4 Hz, 1H), 6.34 (d, <i>J</i> = 2.4 Hz, 1H), 4.59 (s, 2H), 3.66 (t, <i>J</i> = 5.6 Hz, 2H), 2.91 (t, <i>J</i> = 5.6 Hz, 2H), 2.19 (s, 2H), 2.09 (s, 3H), 1.94–1.84 (m, 1H), 1.04 (s, 9H), 0.83–0.76 (m, 2H), 0.62–0.54 (m, 2H); MS (ES+) <i>m/z</i> 452.1 (<i>M</i> + 1).

^a The absolute stereochemistry of Examples 103 and 105 have been arbitrarily defined.

Example 118: *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-4,6,7,8-tetrahydro-5*H*-thiazolo[5,4-*c*]azepin-5-yl)phenyl)-3,3-dimethylbutanamide

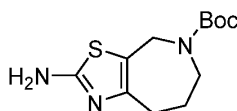


Step 1. Preparation of tert-butyl 3-bromo-4-oxo-azepane-1-carboxylate

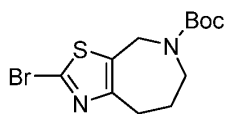


[392] To a solution of *tert*-butyl 4-oxoazepane-1-carboxylate (25.00 g, 0.12 mol) in dichloromethane (200 mL) and tetrahydrofuran (200 mL) was added *p*-toluene sulfonic acid (2.02 g, 11.70 mmol) and *N*-bromosuccinimide (25.00 g, 0.14 mol). The mixture was stirred at 25 °C for 8 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (Petroleum ether: Ethyl acetate = 3: 1, P1: *R*_f = 0.61 Petroleum ether/ Ethyl acetate = 400/ 1 to 1/ 1) to afford 34.0 g of *tert*-butyl 3-bromo-4-oxo-azepane-1-carboxylate (crude) as a yellow oil: MS (ES) *m/z* 235.9 (*M* + H).

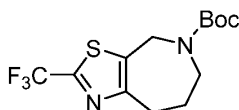
*Step 2. Preparation of tert-butyl 2-amino-4,6,7,8-tetrahydrothiazolo[5,4-*c*]azepine-5-carboxylate*



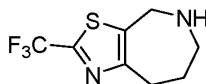
[393] To a solution of thiourea (8.86 g, 0.12 mol) in ethyl alcohol (300 mL) was added *tert*-butyl 3-bromo-4-oxo-azepane-1-carboxylate (34.00 g, 0.12 mol). The mixture was stirred at 75 °C for 8 hrs. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by reverse-phase HPLC (H₂O condition) to afford 7.5 g of *tert*-butyl 2-amino-4,6,7,8-tetrahydrothiazolo[5,4-*c*]azepine-5-carboxylate (24% yield) as a yellow oil: MS (ES-) *m/z* 270.1 (*M* + H).

Step 3. Preparation of *tert*-butyl 2-bromo-4,6,7,8-tetrahydrothiazolo[5,4-*c*]azepine-5-carboxylate

[394] To a solution of *tert*-butyl 2-amino-4,6,7,8-tetrahydrothiazolo[5,4-*c*]azepine-5-carboxylate (7.50 g, 27.80 mmol) in acetonitrile (150 mL) was added *tert*-butyl nitrite (4.59 g, 44.60 mmol) and cuprous bromide (4.79 g, 33.40 mmol). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by reverse-phase HPLC (column: Daisogel C18 250*70mm*10um; mobile phase: [water(NH₄HCO₃)-ACN];gradient:45%-65% B over 22 min) to afford 0.50 g of *tert*-butyl 2-bromo-4,6,7,8-tetrahydrothiazolo[5,4-*c*] azepine-5-carboxylate (5% yield) was obtained as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ ppm 4.35 - 4.51 (m, 2H), 3.68 (dd, *J* = 11.2, 4.8 Hz, 2H), 2.95 - 3.09 (m, 2H), 1.87 (s, 2H), 1.42 (d, *J* = 9.6 Hz, 9H); MS (ES-) *m/z* 332.9 (M + H).

Step 4. Preparation of *tert*-butyl 2-(trifluoromethyl)-4,6,7,8-tetrahydrothiazolo[5,4-*c*]azepine-5-carboxylate

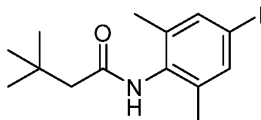
[395] To a solution of *tert*-butyl 2-bromo-4,6,7,8-tetrahydrothiazolo[5,4-*c*]azepine-5-carboxylate (0.50 g, 1.50 mmol) in dimethyl formamide (10 mL) was added cuprous iodide (0.57 g, 3.00 mmol), *N*-[bis(dimethylamino)phosphoryl]-*N*-methylmethanamine (0.27 g, 1.50 mmol) and methyl 2,2-difluoro-2-fluorosulfonyl-acetate (0.58 g, 3.00 mmol) under nitrogen. The mixture was stirred at 90 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by reverse-phase HPLC (H₂O condition) to afford 0.40 g of *tert*-butyl 2-(trifluoromethyl)-4,6,7,8-tetrahydrothiazolo[5,4-*c*] azepine-5-carboxylate (83% yield) was obtained as a white solid: ¹H NMR (400 MHz, CDCl₃) δ ppm 4.48 - 4.66 (m, 2H), 3.74 (dd, *J* = 10.0, 5.2 Hz, 2H), 3.10 - 3.24 (m, 2H), 1.90 (d, *J* = 4.0 Hz, 2H), 1.43 (d, *J* = 12.0 Hz, 9H); LCMS: *m/z* = 323.1 (M+H).

Step 5. Preparation of 2-(trifluoromethyl)-5,6,7,8-tetrahydro-4H-thiazolo[5,4-*c*]azepine

[396] To a solution of *tert*-butyl 2-(trifluoromethyl)-4,6,7,8-tetrahydrothiazolo[5,4-*c*]azepine-5-carboxylate (0.40 g, 1.24 mmol) was added HCl / ethyl acetate (2 M, 4 mL). The mixture was stirred at 25 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Dichloromethane: Methanol = 10: 1, P1: R_f = 0.63, Dichloromethane/ Methanol = 500/ 1 to 5/ 1) to afford 0.30 g of crude 2-(trifluoromethyl)-5,6,7,8-

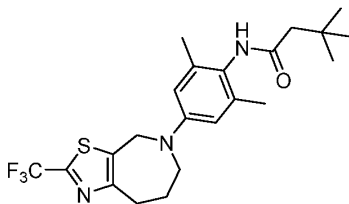
tetrahydro-4*H*-thiazolo[5,4-*c*] azepine as a yellow oil that was used without further purification: MS (ES⁻) m/z 222.9 (M+H)

Step 6. Preparation of N-(4-iodo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide



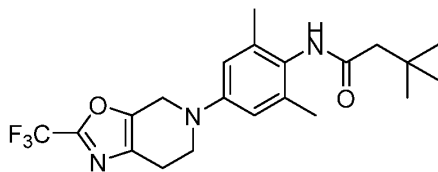
[397] To a solution of 4-iodo-2,6-dimethyl-aniline (1.00 g, 4.05 mmol) in acetonitrile (20 mL) was added triethylamine (0.82 g, 8.09 mmol) and 3,3-dimethylbutanoyl chloride (0.82 g, 6.07 mmol). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Petroleum ether: Ethyl acetate = 3: 1, P1: R_f = 3: 1, Petroleum ether/ Ethyl acetate = 500/ 1 to 1/ 1) to afford 1.0 g of *N*-(4-iodo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide (72% yield) was obtained as a white solid: MS (ES⁻) m/z 345.9 (M+H).

*Step 7. Preparation of N-[2,6-dimethyl-4-[2-(trifluoromethyl)-4,6,7,8-tetrahydrothiazolo[5,4-*c*]azepin-5-yl]phenyl]-3,3-dimethyl-butanamide*

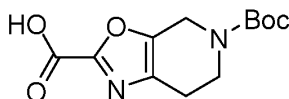


[398] To a solution of *N*-(4-iodo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide (0.58 g, 1.67 mmol) in 2-methylbutan-2-ol (5 mL) was added cesium carbonate (0.21 g, 0.66 mmol) and dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (0.08 g, 0.10 mmol) and 2-(trifluoromethyl)-5,6,7,8-tetrahydro-4*H*-thiazolo[5,4-*c*]azepine (0.17 g, 0.66 mmol). The mixture was stirred at 90 °C for 2 hrs under nitrogen. The reaction mixture was filtered and the filter was washed by 50 mL ethyl acetate and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Petroleum ether: Ethyl acetate = 3: 1, P1: R_f = 0.56, Petroleum ether/ Ethyl acetate = 500/ 1 to 1/ 1) to afford 39 mg of *N*-[2,6-dimethyl-4-[2-(trifluoromethyl)-4,6,7,8-tetrahydrothiazolo[5,4-*c*]azepin-5-yl]phenyl]-3,3-dimethyl-butanamide (13% yield) as a white solid: ¹H NMR: EC16504-461-p1C1 (400 MHz, MeOD) δ 6.60 (s, 2H), 4.82 (s, 2H), 3.85 - 3.98 (m, 2H), 3.07 - 3.18 (m, 2H), 2.26 (s, 2H), 2.14 (s, 6H), 1.88 (t, *J* = 4.0 Hz, 2H), 1.11 (s, 9H); MS (ES⁻) m/z 440.1 (M+H).

Example 119: *N*-[2,6-dimethyl-4-[2-(trifluoromethyl)-6,7-dihydro-4*H*-oxazolo[5,4-*c*]pyridin-5-yl]phenyl]-3,3-dimethyl-butanamide

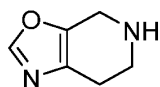


Step 1. Preparation of 5-tert-butoxycarbonyl-6,7-dihydro-4H-oxazolo[5,4-c]pyridine-2-carboxylic acid



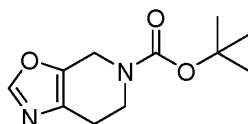
[399] To a solution of O5-tert-butyl O2-ethyl 6,7-dihydro-4H-oxazolo[5,4-c]pyridine-2,5-dicarboxylate (2.00 g, 6.75 mmol) in methanol (20 mL) and water (20 mL) was added sodium hydroxide (0.81 g, 20.20 mmol). The mixture was stirred at 80 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove solvent and then adjust pH to 2.0 by 1M hydrochloric acid, then extracted with ethyl acetate 60 mL (3 x 20 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 1.5 g of crude 5-tert-butoxycarbonyl-6,7-dihydro-4H-oxazolo[5,4-c]pyridine-2-carboxylic acid (82% yield) as a colorless oil: MS (ES) m/z 269.1 (M + H).

Step 2. Preparation of 4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine



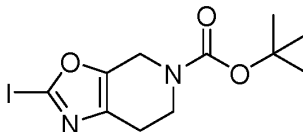
[400] To a solution of 5-tert-butoxycarbonyl-6,7-dihydro-4H-oxazolo[5,4-c]pyridine-2-carboxylic acid (1.00 g, 3.73 mmol) was added hydrochloric acid/ dioxane (2 M, 20 mL, 10.73 eq). The mixture was stirred at 25 °C for 2hr. The reaction mixture was concentrated under reduced pressure to remove solvent to afford 462 mg of crude 4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine (99% yield) as a white solid.

Step 3. Preparation of tert-butyl 6,7-dihydro-4H-oxazolo[5,4-c]pyridine-5-carboxylate



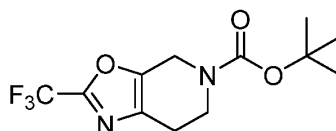
[401] To a solution of 4,5,6,7-tetrahydrooxazolo[5,4-c]pyridine (0.46 g, 3.72 mmol) in water (10 mL) and tetrahydrofuran (10 mL) was added di-tert-butyl dicarbonate (1.62 g, 7.44 mmol, 1.71 mL) and sodium bicarbonate (0.94 g, 11.10 mmol). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was extracted with ethyl acetate 90 mL (3 x 30 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (Petroleum ether: Ethyl acetate = 4: 1, P1: R_f = 0.65 Petroleum ether/ Ethyl acetate = 100/ 1 to 1/ 1) to afford 1.0 g of tert-butyl 6,7-dihydro-4H-oxazolo[5,4-c]pyridine-5-carboxylate was obtained as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.78 (s, 1H), 4.52 (s, 2H), 3.72 (s, 2H), 2.67 (s, 2H), 1.50 (s, 9H); MS (ES-) m/z 225.2 (M + H).

Step 4. Preparation of *tert*-butyl 2-iodo-6,7-dihydro-4*H*-oxazolo[5,4-*c*]pyridine-5-carboxylate



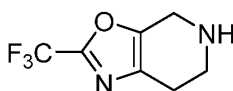
[402] Lithium bis(trimethylsilyl)amide (1M, 6.69 mL) was added at -78 °C to a solution of *tert*-butyl 6,7-dihydro-4*H*-oxazolo[5,4-*c*]pyridine-5-carboxylate (1.00 g, 4.46 mmol) in tetrahydrofuran (20 mL) under nitrogen. The reaction mixture was stirred at -78 °C for 1 hr and zinc chloride (0.97 g, 7.13 mmol) was added dropwise. The reaction mixture was warmed to 20 °C and stirred for 30 min under nitrogen. A solution of iodine (2.26 g, 8.92 mmol) in tetrahydrofuran (20 mL) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 15 mins and at 20 °C for 1 hr. The reaction mixture was quenched by the addition of saturated sodium thiosulfate solution (40 mL) at 25 °C and then extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (Petroleum ether: Ethyl acetate = 3: 1, P1: R_f = 0.38 Petroleum ether/ Ethyl acetate = 500/ 1 to 1/ 1) to afford 1.4 g of *tert*-butyl 2-iodo-6,7-dihydro-4*H*-oxazolo[5,4-*c*]pyridine-5-carboxylate (89% yield) as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ ppm 4.53 (s, 2H), 3.68 (s, 2H), 2.65 (s, 2H), 1.40 - 1.57 (m, 9H); LCMS: m/z = 351.0 (M+H).

Step 5. Preparation of *tert*-butyl 2-(trifluoromethyl)-6,7-dihydro-4*H*-oxazolo[5,4-*c*]pyridine-5-carboxylate



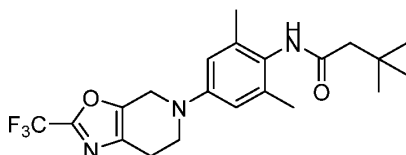
[403] To a solution of *tert*-butyl 2-iodo-6,7-dihydro-4*H*-oxazolo[5,4-*c*]pyridine-5-carboxylate (1.40 g, 4.00 mmol) in dimethyl formamide (20 mL) was added copper iodide (1.52 g, 8.00 mmol), *N*-[bis(dimethylamino)phosphoryl]-*N*-methylmethanamine (0.72 g, 4.00 mmol, 0.70 mL) and methyl 2,2-difluoro-2-fluorosulfonyl-acetate (1.54 g, 8.00 mmol, 1.02 mL) under nitrogen. The mixture was stirred at 90 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by silica gel chromatography (Petroleum ether: Ethyl acetate = 3: 1, P1: R_f = 0.41 Petroleum ether/ Ethyl acetate = 500/ 1 to 1/ 1) to afford 0.50 g of *tert*-butyl 2-(trifluoromethyl)-6,7-dihydro-4*H*-oxazolo[5,4-*c*]pyridine-5-carboxylate (43% yield) as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ ppm 4.58 (s, 2H), 3.75 (s, 2H), 2.72 (s, 2H), 1.50 (s, 9H); MS (ES-) m/z 293.1 (M+H).

Step 6. Preparation of 2-(trifluoromethyl)-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine



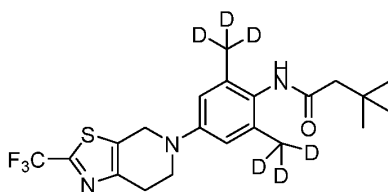
[404] To a solution of *tert*-butyl 2-(trifluoromethyl)-6,7-dihydro-4*H*-oxazolo[5,4-*c*]pyridine-5-carboxylate (0.50 g, 1.71 mmol) was added hydrochloric acid/ dioxane (2 M, 9.18 mL). The mixture was stirred at 25 °C for 2 hrs. The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove solvent to afford 0.328 g of crude 2-(trifluoromethyl)-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine as a yellow oil.

Step 7. Preparation of N-[2,6-dimethyl-4-[2-(trifluoromethyl)-6,7-dihydro-4H-oxazolo[5,4-c]pyridin-5-yl]phenyl]-3,3-dimethyl-butanamide

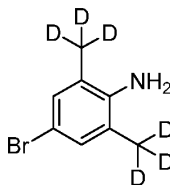


[405] To a solution of 2-(trifluoromethyl)-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine (0.17 g, 0.74 mmol) in tetrahydrofuran (10 mL) was added cesium carbonate (1.20 g, 3.69 mmol) and dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane;methanesulfonate;[2-[2-(methylamino)phenyl]phenyl]palladium(1+) (0.06 g, 0.07 mmol) and 2-(trifluoromethyl)-5,6,7,8-tetrahydro-4*H*-thiazolo[5,4-*c*]azepine (0.22 g, 0.74 mmol). The mixture was stirred at 90 °C for 2 hrs under nitrogen. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by silica gel chromatography (Petroleum ether: Ethyl acetate = 3: 1, P1: R_f = 0.34, Petroleum ether/ Ethyl acetate = 500/ 1 to 1/ 1) to afford 0.17 g of *N*-[2,6-dimethyl-4-[2-(trifluoromethyl)-6,7-dihydro-4*H*-oxazolo[5,4-*c*]pyridin-5-yl]phenyl]-3,3-dimethyl-butanamide (55% yield) as a white solid: ¹H NMR (400 MHz, MeOD) δ 6.78 (s, 2H), 4.38 (s, 2H), 3.65 (t, *J* = 5.6 Hz, 2H), 2.68 - 2.87 (m, 2H), 2.29 (s, 2H), 2.20 (s, 6H), 1.13 (s, 9H); LCMS *m/z* = 410.4 (M+H)⁺.

Example 120: *N*-(2,6-bis(methyl-*d*3)-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide



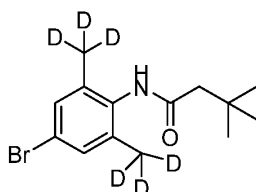
*Step 1. Preparation of 4-bromo-2,6-bis(methyl-*d*3)aniline*



[406] To a solution of 2,6-dimethylaniline[*d*6] (2.5 g, 19.7 mmol) in acetic acid (4 mL) was added a solution of bromine (1.0 mL, 19.7 mmol) in acetic acid (6 mL). The reaction mixture was stirred at

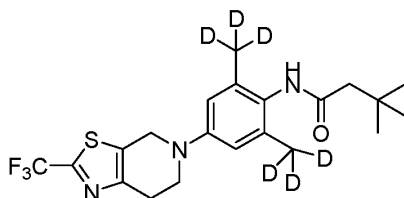
ambient temperature for 1 hour. The resulting brown suspension was diluted with heptane, filtered and the solid washed with heptane. The solid was neutralized with aqueous saturated NaHCO_3 solution and extracted with ethyl acetate. The organic phase was separated and concentrated in vacuo to afford 3.6 g of 4-bromo-2,6-bis(methyl- d_3)aniline (88% yield) as a purple liquid that was used without further purification: ^1H NMR (400 MHz, CDCl_3) δ 7.08 (sm 2H); MS (ES+) m/z 206 and 208 (M+H).

Step 2. Preparation of N-(4-bromo-2,6-bis(methyl- d_3)phenyl)-3,3-dimethylbutanamide



[407] To a solution of 4-bromo-2,6-bis(trideuteriomethyl)aniline (3.6 g, 17.5 mmol) in acetonitrile (25 mL) at 0-5 °C was added 3,3-dimethylbutanoyl chloride (2.5 mL, 18.3 mmol) followed by *N,N*-diisopropylethylamine (3.8 mL, 21.0 mmol). The mixture was stirred vigorously at ambient temperature for 6 hours. To the reaction mixture was added ice-cold water (35 mL, 10 vol) and the resulting suspension was filtered and washed with water and then *n*-heptane. The resulting solid was dried in a vacuum oven at 50 °C for 4 hours to afford 5.1 g of *N*-(4-bromo-2,6-bis(methyl- d_3)phenyl)-3,3-dimethylbutanamide (96 % yield) as a beige colored powder: ^1H -NMR (400 MHz; CDCl_3): δ 7.22 (s, 2H), 2.28 (s, 2H), 1.14 (s, 9H); MS (ES+) m/z 306.1 (M+H).

*Step 3. Preparation of N-(2,6-bis(methyl- d_3)-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide*



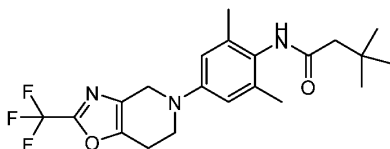
[408] To a flask were added 2-(trifluoromethyl)-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine;hydrochloride (2.00 g, 8.17 mmol), *N*-[4-bromo-2,6-bis(trideuteriomethyl)phenyl]-3,3-dimethyl-butnamide (2.49 g, 8.17 mmol), cesium carbonate (6.66 g, 20.40 mmol) and 1,4-dioxane (20mL) (10 vol) at ambient temperature. The suspension was degassed by purging nitrogen for 30 min. Then, 2-dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane;[2-[2-(methylamino)phenyl]phenyl]-methylsulfonyloxy-palladium (0.21 g, 0.25 mmol) was added and the mixture was stirred at 100 °C for 16 hours. The mixture was cooled to ambient temperature and concentrated in vacuo. The residue was diluted with water (20 mL, 10 vol) and 2-MeTHF (20 mL, 10 vol). The bilayer was filtered through celite. The layers were separated and the organic phase was concentrated in vacuo. The resulting residue was purified by silica gel chromatography (ethyl acetate/heptane (1:9 to 1:1)). Fractions containing the product were combined and concentrated in vacuo. The resulting solid was dissolved in dichloromethane and the

product was precipitated by addition of excess heptane. The suspension was filtered and the filtered solid was dried in vacuum at 50 °C overnight to afford 2.7 g of *N*-(2,6-bis(methyl-*d*3)-4-(2-(trifluoromethyl)-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide (76 % yield) as a white powder: ¹H-NMR (400 MHz; DMSO-*d*₆): δ 8.89 (s, 1H), 6.75 (s, 2H), 4.61 (s, 2H), 3.68 (t, *J* = 5.8 Hz, 2H), 2.92 (t, *J* = 5.6 Hz, 2H), 2.16 (s, 2H), 1.04 (s, 9H); MS (ES+) *m/z* : 432.2 (*M* + *H*).

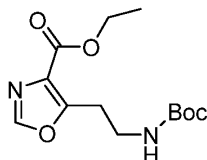
[409] The following further Examples were prepared analogously to the foregoing Example 120 (as described above), substituting appropriate starting materials where necessary and making appropriate changes to experimental conditions informed by common general knowledge. Purification was performed either by silica gel chromatography, reverse-phase preparative HPLC, or supercritical fluid chromatography (SFC).

EXAMPLE	Analytical Data
121	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.93 (s, 1H), 6.77 (s, 2H), 6.59 (s, 1H), 4.46 (s, 2H), 4.26 (t, <i>J</i> = 5.3 Hz, 2H), 3.77 (t, <i>J</i> = 5.4 Hz, 2H), 2.17 (s, 2H), 1.05 (s, 9H); MS (ES+) <i>m/z</i> 415.2 (<i>M</i> + 1).

Example 136: *N*-(2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrooxazolo[4,5-*c*]pyridin-5(4*H*)-yl)phenyl)-3,3-dimethylbutanamide

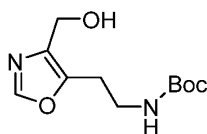


Step 1. Preparation of ethyl 5-(2-((tert-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylate



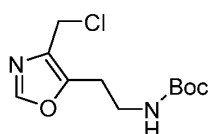
[410] 3-(*tert*-butoxycarbonylamino)propanoic acid (20.00 g, 105.70 mmol, 1 *eq*) was dissolved in THF (330 mL) and carbonyl diimidazole (20.57 g, 126.84 mmol) was added in portions to the solution. The resulting mixture was heated at 55 °C for 1 hr and then cooled to 0 °C. Ethyl 2-(methyleamino)acetate (14.35 g, 126.84 mmol) was added in one portion, followed by DBU (19.31 g, 126.84 mmol, 19.12 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 3 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 100/1 to 2/1) to afford 30 g of ethyl 5-(2-((*tert*-butoxycarbonyl)amino)ethyl)oxazole-4-carboxylate: MS (ES) *m/z* 229.0 (*M* + 1 - 56).

Step 2. Preparation of tert-butyl (2-(4-(hydroxymethyl)oxazol-5-yl)ethyl)carbamate



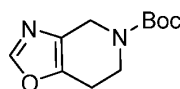
[411] To a solution of ethyl 5-[2-(tert-butoxycarbonylamino)ethyl]oxazole-4-carboxylate (27.0 g, 94.7 mmol) in THF (270 mL) was added LiBH₄ (2 M, 118.35 mL, 2.50 eq) in small portions at 0 °C under N₂. The mixture was warmed to 55 °C and stirred 3 hrs. The reaction mixture was quenched by the addition of aqueous saturated NH₄Cl solution (300 mL) at 0 °C under nitrogen atmosphere, and then extracted with ethyl acetate (3 x 200 mL). The combined organic phases were washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 100/1 to 0/1) to afford 6 g of *tert*-butyl *N*-[2-[4-(hydroxymethyl)oxazol-5-yl]ethyl]carbamate: MS (ES+) *m/z* 265.0 (M+23).

Step 3 Preparation of tert-butyl (2-(4-(chloromethyl)oxazol-5-yl)ethyl)carbamate



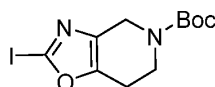
[412] To a solution of *tert*-butyl *N*-[2-[4-(hydroxymethyl)oxazol-5-yl]ethyl]carbamate (2 g, 8.26 mmol) in CH₂Cl₂ (20 mL) was added triethylamine (5.01 g, 49.53 mmol). The mixture was cooled to 0 °C and then MsCl (4.73 g, 41.28 mmol) was added dropwise. The mixture was stirred at 0-25 °C for 12hr. The mixture was poured into ice water (50 mL) and extracted with CH₂Cl₂ (3 x 40 mL), washed by brine, dried over Na₂SO₄, filtrated and concentrated under reduced pressure. The crude product used directly in the next step without further purification to afford 2.4 g of *tert*-butyl *N*-[2-[4-(chloromethyl)oxazol-5-yl]ethyl]carbamate (2.4 g, crude) as a yellow oil.

Step 4. Preparation of tert-butyl 6,7-dihydrooxazolo[4,5-c]pyridine-5(4H)-carboxylate



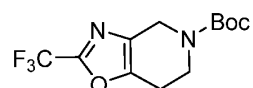
[413] To a solution of *tert*-butyl *N*-[2-[4-(chloromethyl)oxazol-5-yl]ethyl]carbamate (2.40 g, 9.21 mmol) in DMF (240 mL) was added sodium *tert*-butoxide (1.06 g, 11.05 mmol) at 0°C. The reaction mixture was stirred at 25 °C for 2 hrs. The reaction mixture was partitioned between EtOAc (20 mL) and water (20 mL). The organic phase was separated and the water phase was extracted with EtOAc (2 x 20 mL), the combined organic layers were washed with brine (2 x 20 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (petroleum ether/Ethyl acetate=1/0 to 1/1) to afford 1.0 g of *tert*-butyl 6,7-dihydro-4*H*-oxazolo[4,5-*c*]pyridine-5-carboxylate as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ = 7.77 (s, 1H), 4.42 (s, 2H), 3.76 (s, 2H), 2.74 (s, 2H), 1.47 (s, 9H); MS (ES+) *m/z* 225.1 (M+H-Boc).

Step 5 Preparation of tert-butyl 2-iodo-6,7-dihydrooxazolo[4,5-c]pyridine-5(4H)-carboxylate



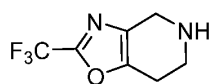
[414] To a solution of *tert*-butyl 6,7-dihydro-4*H*-oxazolo[4,5-*c*]pyridine-5-carboxylate (0.45 g, 2.01 mmol) in THF (4.5 mL) was added LiHMDS (1 M, 3.01 mL) at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred at -78 °C for 1 hr and ZnCl₂ (0.44 g, 3.21 mmol) was added dropwise. The reaction mixture was warmed to 20 °C and stirred for 30 min under a nitrogen atmosphere. A solution of iodine (1.02 g, 4.01 mmol) in THF (4.5 mL) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 15 mins and at 20 °C for 1 hr. The reaction mixture was quenched by the addition of aqueous saturated sodium thiosulfate solution (10 mL) at 25 °C and then extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure and combined with a second batch of crude material. The combined residues were purified by silica gel chromatography (petroleum ether/ethyl acetate = 100/1 to 9/1) to afford 780 mg of *tert*-butyl 2-iodo-6,7-dihydro-4*H*-oxazolo[4,5-*c*]pyridine-5-carboxylate as a pale yellow gum: MS (ES+) *m/z* 351.0 (M+1).

*Step 6. Preparation of tert-butyl 2-(trifluoromethyl)-6,7-dihydrooxazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate*



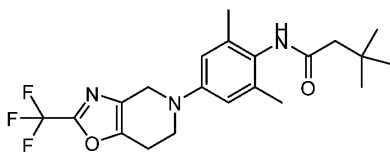
[415] To a solution of *tert*-butyl 2-iodo-6,7-dihydro-4*H*-oxazolo[4,5-*c*]pyridine-5-carboxylate (0.73 g, 2.08 mmol) and CuI (0.79 g, 4.17 mmol) in HMPA (7.00 mL) was added methyl 2,2-difluoro-2-fluorosulfonylacetate (0.80 g, 4.17 mmol). The mixture was stirred at 110 °C for 16 hrs. The reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by reversed-phase HPLC (FA condition) to afford 210 mg of *tert*-butyl 2-(trifluoromethyl)-6,7-dihydro-4*H*-oxazolo[4,5-*c*]pyridine-5-carboxylate as a yellow solid: MS (ES+) *m/z* 237.0 (M+1).

*Step 7. Preparation of 2-(trifluoromethyl)-4,5,6,7-tetrahydrooxazolo[4,5-*c*]pyridine*



[416] To a solution of *tert*-butyl 2-(trifluoromethyl)-6,7-dihydro-4*H*-oxazolo[4,5-*c*]pyridine-5-carboxylate (0.21 g, 0.72 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (2 M, 8 mL). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure. The resulting residue was used directly without further purification. 2-(Trifluoromethyl)-4,5,6,7-tetrahydrooxazolo[4,5-*c*]pyridine (145 mg, HCl) was obtained as a yellow solid: ¹H NMR (400 MHz, d₆-DMSO) δ 9.84 (s, 2H), 4.24 (s, 2H), 3.51 (t, *J* = 5.6 Hz, 2H), 3.11 (t, *J* = 5.6 Hz, 2H).

Step 8. Preparation of *N*-[2,6-dimethyl-4-(2-(trifluoromethyl)-6,7-dihydrooxazolo[4,5-*c*]pyridin-5(4*H*)-yl)phenyl]-3,3-dimethylbutanamide



[417] To a solution of 2-(trifluoromethyl)-4,5,6,7-tetrahydrooxazolo[4,5-*c*]pyridine (0.115 g, 0.598 mmol) and *N*-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide (0.178 g, 0.598 mmol) in dioxane (3.50 mL) was added Cs₂CO₃ (0.585 g, 1.800 mmol) and RuPhos Pd G3 (0.051 g, 0.059 mmol). The mixture was stirred at 100 °C for 3hr under a nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (petroleum ether/3thyl acetate = 1/0 to 3/1) to afford 90 mg of *N*-[2,6-dimethyl-4-[2-(trifluoromethyl)-6,7-dihydro-4*H*-oxazolo[4,5-*c*]pyridin-5-yl]phenyl]-3,3-dimethylbutanamide as a yellow solid: ¹H NMR: δ 8.89 (s, 1H), 6.76 (s, 2H), 4.23 (s, 2H), 3.66 (t, *J* = 5.6 Hz, 2H), 2.93 (t, *J* = 5.6 Hz, 2H), 2.17 (s, 2H), 2.09 (s, 6H), 1.05 (s, 9H); MS (ES+) *m/z* 410.2 (*M*+1).

Biological Activity

Kv7.2/Kv7.3 Potassium Channel Assay

[418] This potassium flux assay employs the cell-permeable, potassium-sensitive dye, IPG-2 AM, to quantify potassium ion flux through potassium channels. In general, TREX HEK 293 or HEK 293 cells were stably transfected with either an inducible or non-inducible expression vector containing the full-length cDNA coding for the desired human Kv7.2/Kv7.3 or in combination with another full-length cDNA for a second desired human Kv7 potassium channel. Potassium channel-expressing cell lines were induced with tetracycline (1 µg/mL), if required, and plated on 384-well poly-D-lysine (PDL)-coated plates in culture media (DMEM, containing 10% FBS and 1% L-glutamine). After overnight incubation, culture media was removed and cells were loaded with 5 µM IPG-2 AM dye for 1 hour in Assay buffer (140 mM NaCl, 20 mM RbCl, 2 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid buffer), 10 mM glucose, adjusted with Tris to pH 7.4). Excess dye was removed, and cells incubated at room temperature for 20 minutes with or without test compound. A Hamamatsu FDSS µCell was used to perform a 1:1 addition of K challenge buffer (150 mM NaCl, 10 mM HEPES, 2 mM CaCl₂, 10 mM KCl, 1 mM MgCl₂, 10 mM glucose, adjusted with Tris to pH 7.4 for human Kv7.2/Kv7.3, and simultaneously read plates at excitation wavelength of 530 nm and emission wavelength of 558 nm. Non-potassium channel-mediated potassium influx was determined in the presence of DMSO, and maximal influx was determined in the presence of a known Kv7.x channel modulator. For each test compound, a concentration response curve was generated with 16 concentrations points, 2-fold serial dilution starting at 30 µM and an EC₅₀ value was determined.

[419] Compounds provided herein are potentiators of Kv7.2/Kv7.3 potassium channels as shown in

Table 2.

Table 2

EXAMPLE	K _V 7.2/ K _V 7.3 EC ₅₀ (μM)	EXAMPLE	K _V 7.2/ K _V 7.3 EC ₅₀ (μM)
1	++++	65	++++
2	+++	66	++++
3	+	67	++++
4	+++	68	++++
5	+++	69	++++
6	+++	70	+
7	++++	71	++++
8	++	72	++++
9	++++	73	++++
10	++++	74	++++
11	+++	75	++++
12	++++	76	++++
13	++++	77	++++
14	++++	78	++++
15	++++	79	++++
16	++++	80	++++
17	++++	81	++++
18	++++	82	++++
18a	++++	83	++++
18b	++++	84	++++
19	++++	85	++++
19a	+	86	+++
19b	++++	87	++++
20	++++	88	++++
21	++++	89	++++
22	++++	90	++++
23	++++	91	++++
24	+++	92	++++
25	++	93	++++
26	++++	94	++++
27	++++	95	++++
28	++++	96	+++
29	++++	97	++++
30	++++	98	++
31	++++	99	+
32	++++	100	+++
33	++++	101	+
34	++++	102	+
35	++++	103	++++
36	++++	104	++++
37	++++	105	++++
38	++++	106	++++
39	++++	107	++++
40	++++	108	++++
41	++++	109	++++
42	++++	110	++++
43	++++	111	++++
44	++++	112	++++

EXAMPLE	K _V 7.2/ K _V 7.3 EC ₅₀ (μM)	EXAMPLE	K _V 7.2/ K _V 7.3 EC ₅₀ (μM)
45	++++	113	++++
46	++++	114	++++
47	++++	115	++++
48	+++	116	++++
49	++++	117	++++
50	++++	118	++++
51	++++	119	++++
52	++++	122	++++
53	++++	123	++++
54	++++	124	++++
55	++++	125	++++
56	++++	126	++++
57	++++	127	++++
58	++++	128	++++
59	++++	129	++++
60	+++	130	++++
61	++++	131	++++
62	++++	132	++
63	++++	133	++++
64	++++	135	++++

For EC₅₀ values:

++++ indicates a value less than 1 μM

+++ indicates a value from 1 up to 10 μM

++ indicates a value from 10 up to 30 μM

+ indicates a value of 30 μM or more

EQUIVALENTS AND SCOPE

[420] 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 present disclosure 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 present disclosure 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.

[421] Furthermore, the present disclosure 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 be understood that, in general, where the present disclosure, or aspects of the present disclosure, is/are referred to as comprising particular elements and/or features, certain embodiments of the present disclosure or aspects of the present disclosure 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 present disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

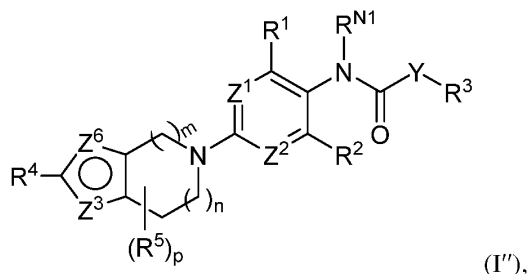
[422] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present disclosure 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 present disclosure can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[423] 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 disclosure, as defined in the following claims.

CLAIMS

What is claimed is:

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



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein:

Z^3 is N and Z^6 is S,

Z^3 is S and Z^6 is N,

Z^3 is N and Z^6 is O, or

Z^3 is O and Z^6 is N;

R^1 and R^2 are each independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, -SR^S, -S(=O)₂R^{S1}, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

R^3 is C_{1-8} alkyl, C_{3-10} cycloalkyl, 3-7 membered heterocyclyl, or -(CR'R'')_w-Ar¹, wherein the alkyl, cycloalkyl, or heterocyclyl is optionally substituted; w is 0, 1, or 2; Ar¹ is C_{6-10} aryl or 5-10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted;

Y is a bond, -CR'R''-, -O-, or -NR^Y-;

R^Y is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, or a nitrogen protecting group, or R^Y and R^3 are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein the alkyl, cycloalkyl, acyl, or heterocyclyl is optionally substituted;

Z^1 and Z^2 are each independently CR^Z or N;

each instance of R^Z is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

R^4 is H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R^5 is independently halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, or two R^5 attached to the same carbon atom are joined together with the intervening atoms to form C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, or

two R^S attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl, is independently optionally substituted;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

m is 1 or 2;

n is 0, 1, or 2;

each instance of R' is independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3-7 membered heterocyclyl, each instance of R'' is independently H, halogen, C₁₋₆ alkyl, -OR^O, or -N(R^N)₂, or R' and R'' attached to the same carbon atom are joined together with the intervening atoms to form C₃₋₇ cycloalkyl or 3-7 membered heterocyclyl, or R' and R'' attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted;

each instance of R^{N1} and R^N is independently H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ acyl, or a nitrogen protecting group, or two R^N attached to the same nitrogen atom are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, acyl, or heterocyclyl is independently optionally substituted;

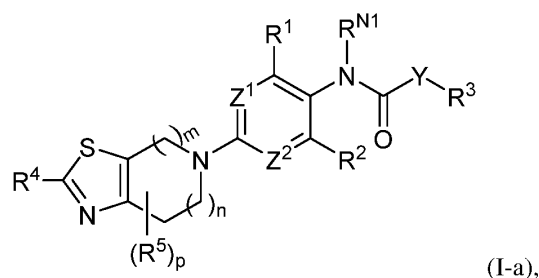
each instance of R^O is independently H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₁₋₆ acyl, or an oxygen protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted;

each instance of R^S is independently H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₁₋₆ acyl, or a sulfur protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted; and

each instance of R^{S1} is independently C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted.

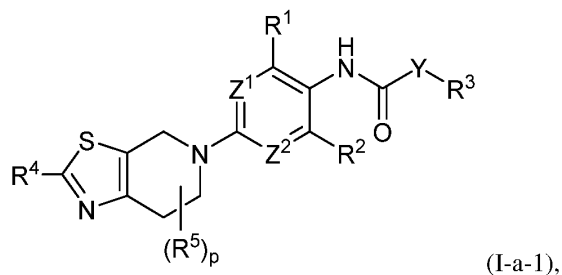
2. The compound of claim 1, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z³ is N and Z⁶ is S, or Z³ is S and Z⁶ is N.

3. The compound of claim 1, wherein the compound is of Formula (I-a):



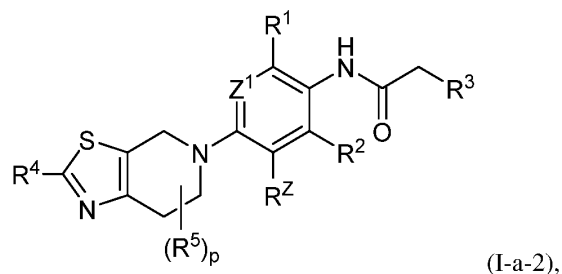
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

4. The compound of claim 1, wherein the compound is of Formula (I-a-1):



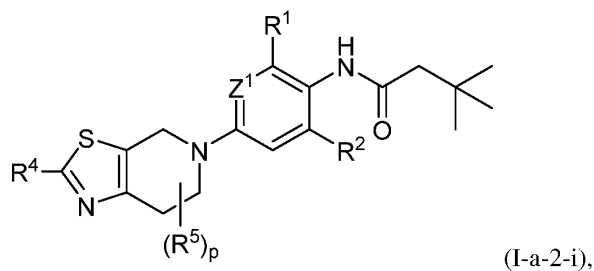
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

5. The compound of claim 1, wherein the compound is of Formula (I-a-2):



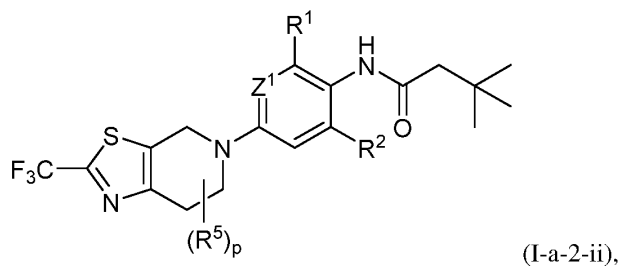
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

6. The compound of claim 1, wherein the compound is of Formula (I-a-2-i):



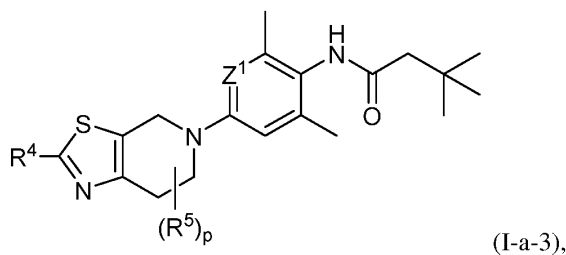
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

7. The compound of claim 1, wherein the compound is of Formula (I-a-2-ii):



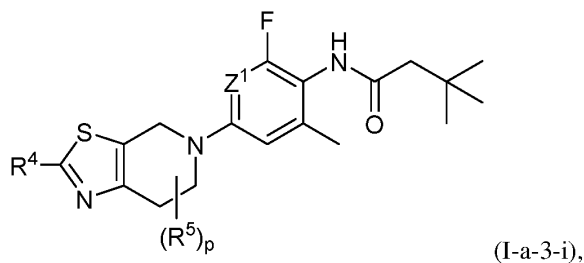
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

8. The compound of claim 1, wherein the compound is of Formula (I-a-3):



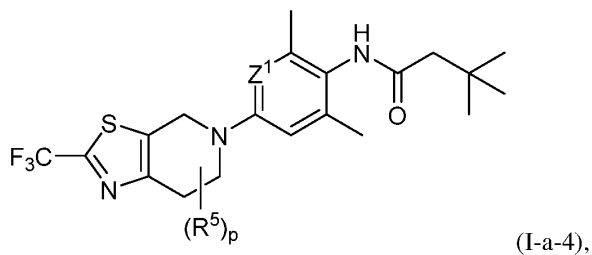
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

9. The compound of claim 1, wherein the compound is of Formula (I-a-3-i):



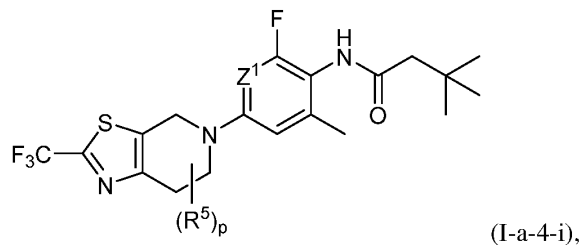
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

10. The compound of claim 1, wherein the compound is of Formula (I-a-4):



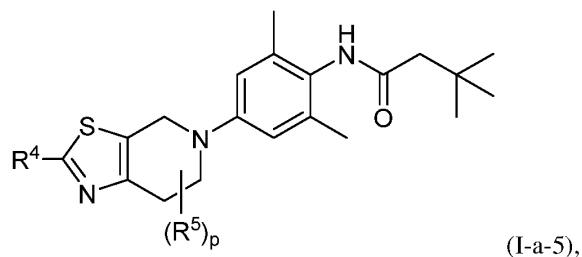
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

11. The compound of claim 1, wherein the compound is of Formula (I-a-4-i):



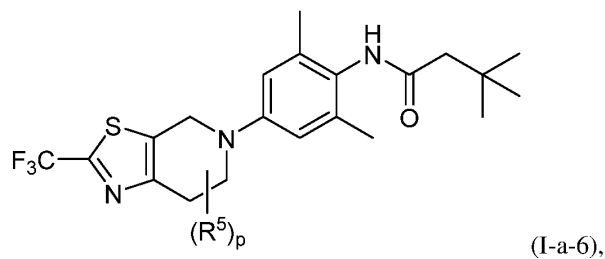
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

12. The compound of claim 1, wherein the compound is of Formula (I-a-5):



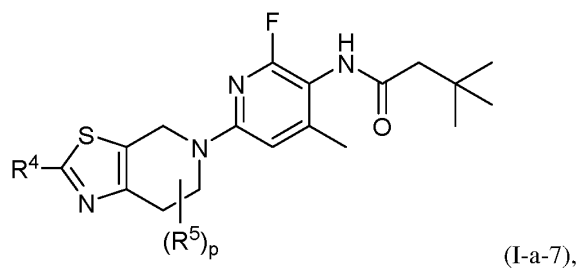
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

13. The compound of claim 1, wherein the compound is of Formula (I-a-6):



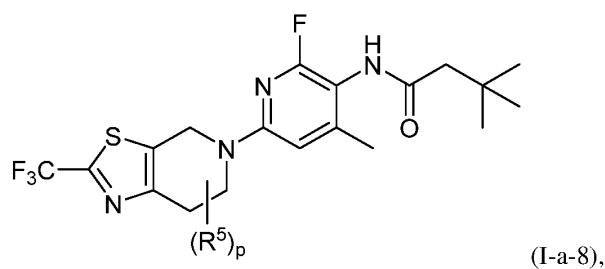
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

14. The compound of claim 1, wherein the compound is of Formula (I-a-7):



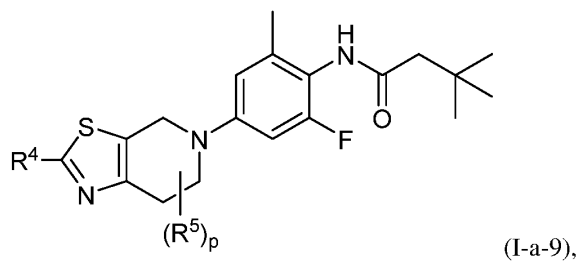
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

15. The compound of claim 1, wherein the compound is of Formula (I-a-8):



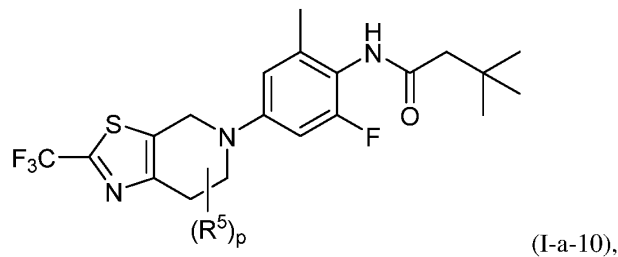
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

16. The compound of claim 1, wherein the compound is of Formula (I-a-9):



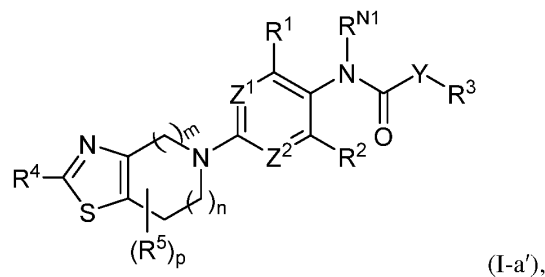
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

17. The compound of claim 1, wherein the compound is of Formula (I-a-10):



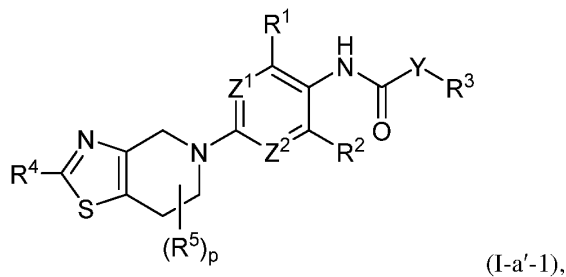
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

18. The compound of claim 1, wherein the compound is of Formula (I-a'):



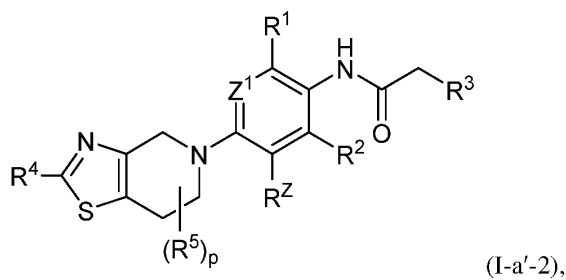
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

19. The compound of claim 1, wherein the compound is of Formula (I-a'-1):



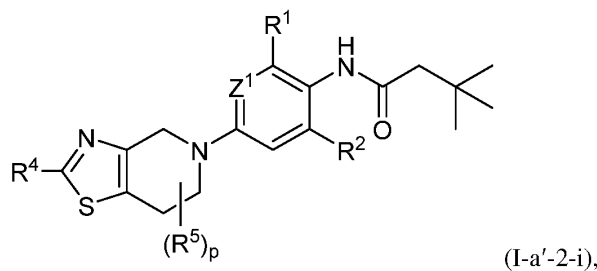
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

20. The compound of claim 1, wherein the compound is of Formula (I-a'-2):



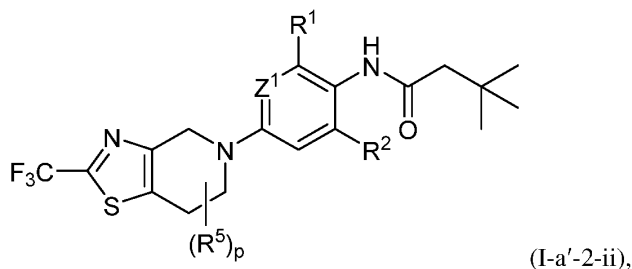
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

21. The compound of claim 1, wherein the compound is of Formula (I-a'-2-i):



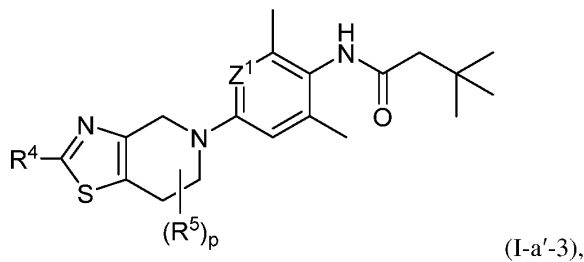
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

22. The compound of claim 1, wherein the compound is of Formula (I-a'-2-ii):



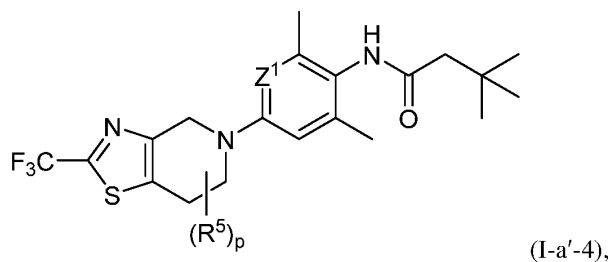
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

23. The compound of claim 1, wherein the compound is of Formula (I-a'-3):



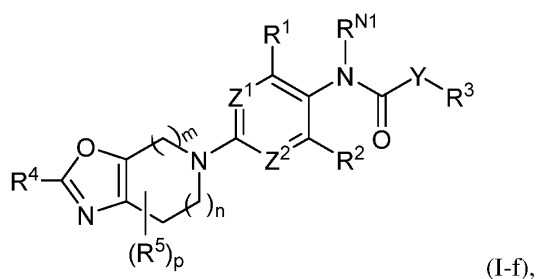
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

24. The compound of claim 1, wherein the compound is of Formula (I-a'-4):



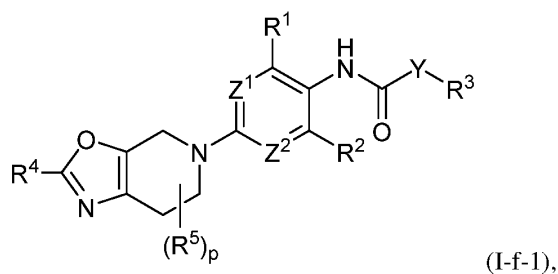
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

25. The compound of claim 1, wherein the compound is of Formula (I-f):



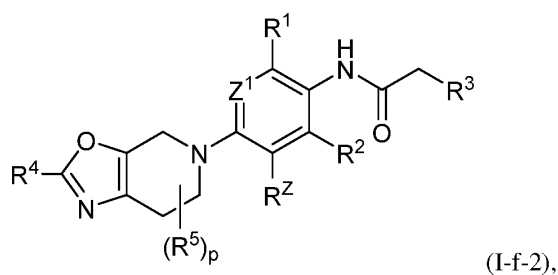
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

26. The compound of claim 1, wherein the compound is of Formula (I-f-1):



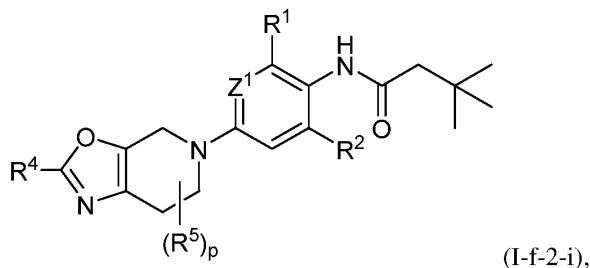
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

27. The compound of claim 1, wherein the compound is of Formula (I-f-2):



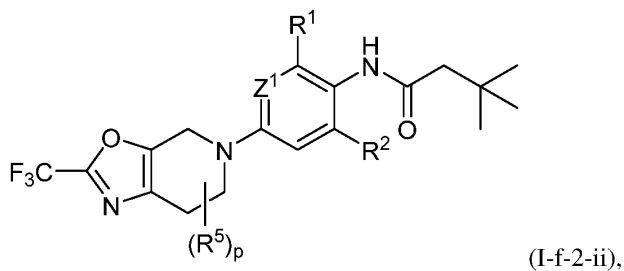
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

28. The compound of claim 1, wherein the compound is of Formula (I-f-2-i):



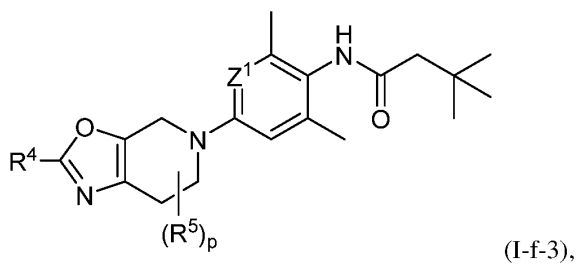
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

29. The compound of claim 1, wherein the compound is of Formula (I-f-2-ii):



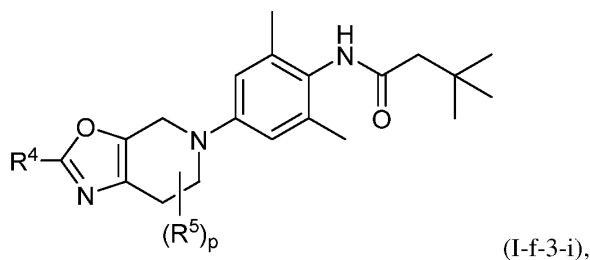
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

30. The compound of claim 1, wherein the compound is of Formula (I-f-3):



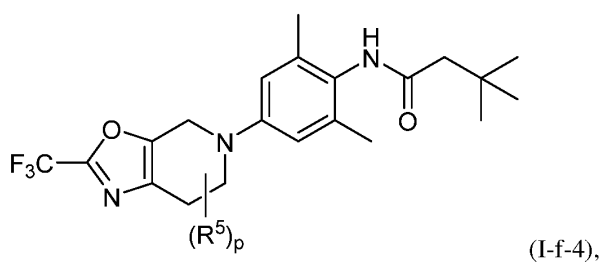
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

31. The compound of claim 1, wherein the compound is of Formula (I-f-3-i):



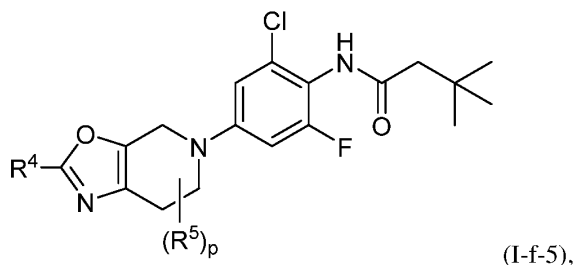
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

32. The compound of claim 1, wherein the compound is of Formula (I-f-4):



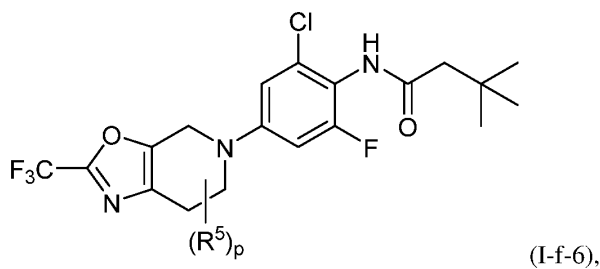
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

33. The compound of claim 1, wherein the compound is of Formula (I-f-5):



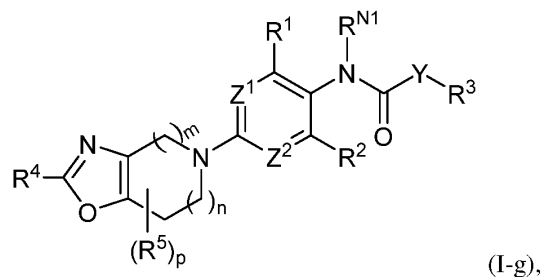
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

34. The compound of claim 1, wherein the compound is of Formula (I-f-6):



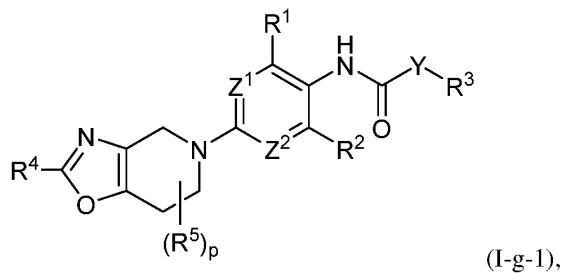
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

35. The compound of claim 1, wherein the compound is of Formula (I-g):



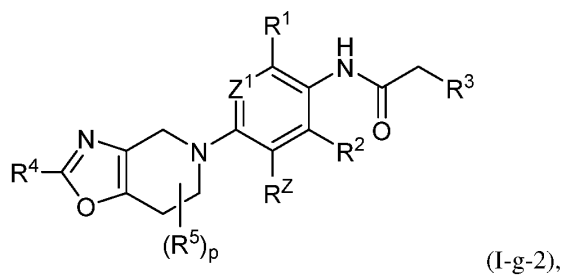
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

36. The compound of claim 1, wherein the compound is of Formula (I-g-1):



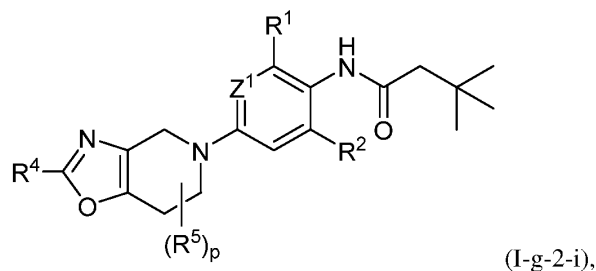
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

37. The compound of claim 1, wherein the compound is of Formula (I-g-2):



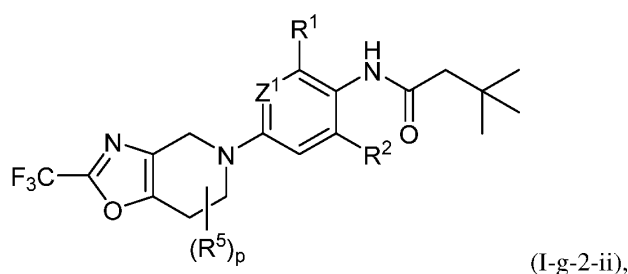
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

38. The compound of claim 1, wherein the compound is of Formula (I-g-2-i):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

39. The compound of claim 1, wherein the compound is of Formula (I-g-2-ii):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

40. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1.

41. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein n is 1.

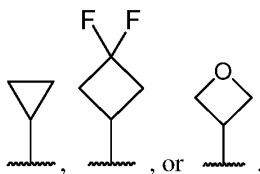
42. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1 and n is 1.

43. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein n is 2.

44. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1 and n is 2.

45. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^{N1} is H.
46. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein m is 1, n is 1, and R^{N1} is H.
47. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is optionally substituted C_{1-6} alkyl.
48. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 unsubstituted C_{1-3} alkyl.
49. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is methyl.
50. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is halogen, C_{1-6} haloalkyl, $-OR^O$, $-CN$, $-SR^S$, or $-S(=O)_2R^{S1}$.
51. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is F, Cl, $-CF_3$, $-OMe$, $-OCF_3$, $-CN$, $-SMe$, or $-S(=O)_2Me$.
52. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted.
53. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is C_{3-5} cycloalkyl or 3-5 membered heterocyclyl, wherein the cycloalkyl or heterocyclyl is optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl.

54. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^1 is:



55. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is H.

56. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is optionally substituted C_{1-6} alkyl.

57. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is unsubstituted C_{1-3} alkyl.

58. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is methyl.

59. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is halogen or $-OR^O$.

60. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^2 is F, Cl, or $-OMe$.

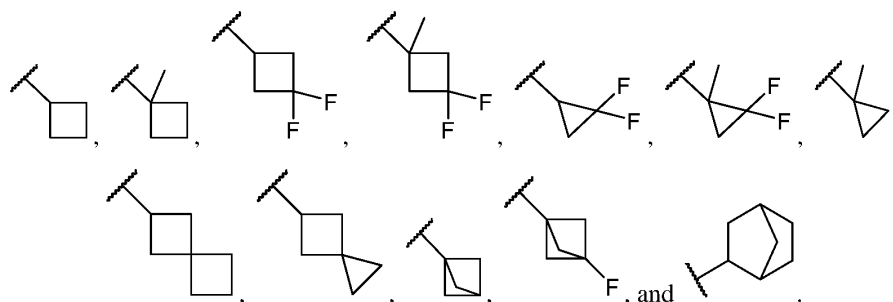
61. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is $-CR'R''$.

62. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is $-CH_2-$.

63. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Y is $-CH(Me)-$.

64. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C_{1-8} alkyl.
65. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is unsubstituted C_{1-4} alkyl.
66. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is *tert*-butyl.
67. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is C_{1-4} alkyl optionally substituted with one or more F.
68. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is $-CH_2CF_3$.
69. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C_{3-10} cycloalkyl.
70. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C_{3-8} cycloalkyl.
71. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is C_{3-8} cycloalkyl optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl.

72. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is selected from:

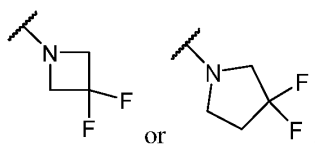


73. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted 3-7 membered heterocyclyl.

74. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted 3-6 membered heterocyclyl having 1 or 2 ring N atoms.

75. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is 3-6 membered heterocyclyl having 1 or 2 ring N atoms and optionally substituted with one or more halogen and/or unsubstituted C_{1-6} alkyl.

76. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is:

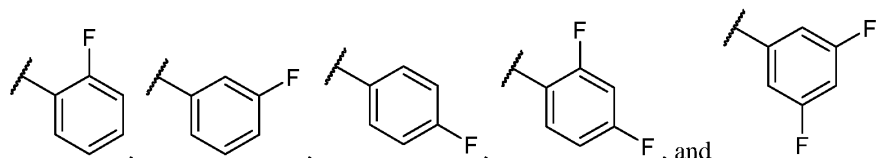


77. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted C_{6-10} aryl.

78. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is optionally substituted phenyl.

79. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is phenyl optionally substituted with one or more instances of halogen and/or unsubstituted C_{1-6} alkyl.

80. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein R^3 is selected from:



81. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is CR^Z .

82. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is CH.

83. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is CCl.

84. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^1 is N.

85. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is CR^Z .

86. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is CH.

87. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is CF.

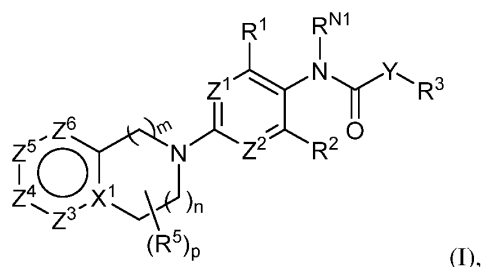
88. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein Z^2 is N.

89. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_{1-6} haloalkyl.
90. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_{1-3} haloalkyl.
91. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is C_1 haloalkyl.
92. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is $-CF_3$.
93. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is $-CF_2H$.
94. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{3-7} cycloalkyl, or optionally substituted phenyl.
95. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is halogen, unsubstituted C_{1-6} alkyl, halogen, unsubstituted C_{3-7} cycloalkyl, or unsubstituted phenyl.
96. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is methyl, *tert*-butyl, Cl, cyclopropyl, or phenyl.
97. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein at least one instance of R^4 is H.

98. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein p is 0.

99. A compound selected from those in **Table 1B**, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof.

100. A compound of Formula (I):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, wherein:

X¹ is C or N;

Z³, Z⁴, and Z⁶ are each independently CR⁴, N, NR^N, S, or O;

Z⁵ is a bond, CR⁴, N, NR^N, S, or O;

provided that least one of Z³, Z⁴, Z⁵, and Z⁶ is N, NR^N, S, or O, and no more than one of Z³, Z⁴, Z⁵, and Z⁶ is S or O;

R¹ and R² are each independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, -SR^S, -S(=O)₂R^{S1}, or C₁₋₆ acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

R³ is C₁₋₈ alkyl, C₃₋₁₀ cycloalkyl, 3-7 membered heterocyclyl, or -(CR'R'')_w-Ar¹, wherein the alkyl, cycloalkyl, or heterocyclyl is optionally substituted; w is 0, 1, or 2; Ar¹ is C₆₋₁₀ aryl or 5-10 membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted;

Y is a bond, -CR'R''-, -O-, or -NR^Y-;

R^Y is H, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, or a nitrogen protecting group, or R^Y and R³ are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein the alkyl, cycloalkyl, acyl, or heterocyclyl is optionally substituted;

Z¹ and Z² are each independently CR^Z or N;

each instance of R^Z is independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C₁₋₆ acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R⁴ is independently H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, 3-7 membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, -CN, -OR^O, -N(R^N)₂, or C₁₋₆ acyl, wherein each alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, or acyl is independently optionally substituted;

each instance of R^5 is independently halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, -CN, -OR^O, -N(R^N)₂, or C_{1-6} acyl, or two R^5 attached to the same carbon atom are joined together with the intervening atoms to form C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, or two R^5 attached to the same carbon atom are taken together to form =O, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl, is independently optionally substituted;

p is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

m is 1 or 2;

n is 0, 1, or 2;

each instance of R' is independently H, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, or 3-7 membered heterocyclyl, each instance of R'' is independently H, halogen, C_{1-6} alkyl, -OR^O, or -N(R^N)₂, or R' and R'' attached to the same carbon atom are joined together with the intervening atoms to form C_{3-7} cycloalkyl or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted, or R' and R'' attached to the same carbon atom are taken together to form =O;

each instance of R^{N1} and R^N is independently H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} acyl, or a nitrogen protecting group, or two R^N attached to the same nitrogen atom are joined together with the intervening atoms to form 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, acyl, or heterocyclyl is independently optionally substituted;

each instance of R^O is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{1-6} acyl, or an oxygen protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted;

each instance of R^S is independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, C_{1-6} acyl, or a sulfur protecting group, wherein each alkyl, cycloalkyl, heterocyclyl, or acyl is independently optionally substituted; and

each instance of R^{S1} is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-7} cycloalkyl, or 3-7 membered heterocyclyl, wherein each alkyl, cycloalkyl, or heterocyclyl is independently optionally substituted.

101. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof.

102. A pharmaceutical composition comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof.

103. A method of potentiating a Kv7 potassium channel in a subject comprising administering to the subject a compound of any one of claims 1-101, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

104. A method of treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject in need thereof comprising administering to the subject a compound of any one of claims 1-101, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.
105. The method of claim 103 or 104, wherein the method enhances opening of a Kv7 potassium channel.
106. The method of any one of claims 103-105, wherein the Kv7 potassium channel is selected from one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5.
107. The method of any one of claims 103-106, wherein the Kv7 potassium channel is Kv7.2/Kv7.3.
108. A method of treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject in need thereof comprising administering to the subject a compound of any one of claims 1-101, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.
109. The method of any one of claims 103-108, wherein the subject is a human.
110. A compound of any one of claims 1-101, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in potentiating a Kv7 potassium channel in a subject.
111. A compound of any one of claims 1-101, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject.
112. The compound for use of claim 110 or 111, wherein the compound enhances opening of a Kv7 potassium channel.
113. The compound for use of any one of claims 110-112, wherein the Kv7 potassium channel is selected from one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5.
114. The compound for use of any one of claims 110-113, wherein the Kv7 potassium channel is Kv7.2/Kv7.3.

115. A compound of any one of claims 1-101, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use in treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject.

116. The compound for use of any one of claims 110-115, wherein the subject is a human.

117. A compound of any one of claims 1-101, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof, for use as a medicament.