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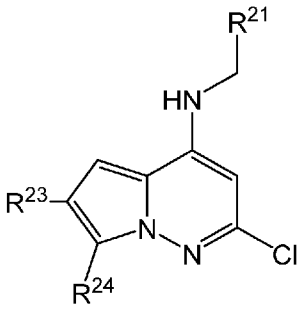
(54) Title: COMPOSITIONS USEFUL FOR MODULATING SPLICING

(57) Abstract: The present application discloses compounds of Formula (I) that modulate splicing of a pre-mRNA, encoded by genes, and methods of treating diseases and conditions associated with gene expression or activity of proteins encoded by genes, such as Spinocerebellar Ataxia 3 (SCA3 or Machado-Joseph Disease).



Formula (I)

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COMPOSITIONS USEFUL FOR MODULATING SPLICING

RELATED APPLICATIONS

[001] This application claims the benefit of U.S. provisional patent application no. 63/480,558 filed on January 19, 2023, which is incorporated by reference in its entirety.

SEQUENCE LISTING

[002] This instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on December 20, 2023, is named 51503-769_601_SL.xml and is 12,471 bytes in size.

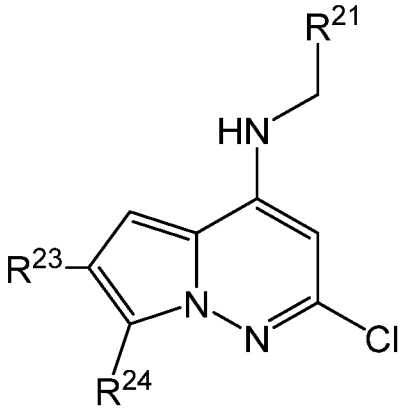
BACKGROUND

[003] Spinocerebellar Ataxia 3 (SCA3 or Machado-Joseph Disease) is a rare, inherited, neurodegenerative, autosomal dominant disease. It is characterized by progressive degeneration of the brainstem, cerebellum and spinal cord, however, neurons in other areas of the brain are also affected. Presenting features include gait problems, speech difficulties, clumsiness, and often visual blurring and diplopia; saccadic eye movements become slow and ophthalmoparesis develops, resulting initially in up-gaze restriction. Ambulation becomes increasingly difficult, leading to the need for assistive devices 10 to 15 years following onset. Late in the disease course, individuals are wheelchair bound and have severe dysarthria, dysphagia, facial and temporal atrophy. The disease progresses relentlessly until death occurs at any time from 6 to approximately 30 years after onset through pulmonary complications.

[004] SCA3 is caused by CAG tri-nucleotide repeats in exon 10 of the Ataxin 3 (ATXN3) gene. ATXN3 encodes for a deubiquinase with wide-ranging functions, but it does not appear to be an essential gene. Disease causing variants of the ATXN3 gene have approximately 40 to over 200 CAG tri-nucleotide repeats in exon 10. Expanded CAG repeats in the ATXN3 gene are translated into expanded polyglutamine repeats (polyQ) in the ataxin-3 protein and this toxic Ataxin 3 protein is associated with aggregates. The polyglutamine expanded ataxin-3 protein in these aggregates is ubiquitinated and the aggregates contain other proteins, including heat shock proteins and transcription factors. Aggregates are frequently observed in the brain tissue of SCA3 patients. There are currently no treatments for SCA3.

SUMMARY

[005] In one aspect, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof.



Formula (I)

wherein R^{21}, R^{23} and R^{24} are as defined herein.

[006] Also provided herein are pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

[007] In some aspects, described herein, is a method of modulating splicing of a Ataxin3 (ATXN3) pre-mRNA, comprising contacting a small molecule splicing modulator compound disclosed herein (SMSM) to the ATXN3 pre-mRNA with a splice site sequence or cells comprising the ATXN3 pre-mRNA, wherein the SMSM binds to the ATXN3 pre-mRNA and modulates splicing of the ATXN3 pre-mRNA in a cell of a subject to produce a spliced product of the ATXN3 pre-mRNA.

[008] In some aspects, described herein, is a method of treating, preventing, delaying of progress, or ameliorating symptoms of a disease or a condition associated with Ataxin 3 (ATXN3) expression level or activity level in a subject in need thereof, comprising administering a therapeutically effective amount of a small molecule splicing modulator compound disclosed herein (SMSM), wherein the SMSM binds to a pre-mRNA encoded by ATXN3 and modulates splicing of the ATXN3 pre-mRNA in a cell of the subject to produce a spliced product of the ATXN3 pre-mRNA, wherein the amount of full length ATXN3 is reduced.

INCORPORATION BY REFERENCE

[009] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION

[0010] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods, and materials are described below.

Definitions

[0011] The term "small molecule splicing modulator" or "SMSM" denotes a small molecule compound that binds to a cell component (*e.g.*, DNA, RNA, pre-mRNA, protein, RNP, snRNA, carbohydrates, lipids, co–factors, nutrients, and/or metabolites) and modulates splicing. For example, a SMSM can bind to a polynucleotide, *e.g.*, an RNA (*e.g.*, a pre-mRNA) with an aberrant splice site, resulting in steric modulation of the polynucleotide. For example, a SMSM can bind to a protein, *e.g.*, a spliceosome protein or a ribonuclear protein, resulting in steric modulation of the protein. For example, a SMSM can bind to a spliceosome component, *e.g.*, a spliceosome protein or snRNA resulting in steric modulation of the spliceosome protein or snRNA. For example, a SMSM is a compound of Formula (I). The term "small molecule splicing modulator" or "SMSM" specifically excludes compounds consisting of oligonucleotides.

[0012] "Steric alteration," "steric modification," or "steric modulation" herein refers to changes in the spatial orientation of chemical moieties with respect to each other. A person of ordinary skill in the art would recognize steric mechanisms include, but are not limited to, steric hindrance, steric shielding, steric attraction, chain crossing, steric repulsions, steric inhibition of resonance, and steric inhibition of protonation.

[0013] Any open valency appearing on a carbon, oxygen, sulfur or nitrogen atom in the structures herein indicates the presence of a hydrogen, unless indicated otherwise.

[0014] The definitions described herein apply irrespective of whether the terms in question appear alone or in combination. It is contemplated that the definitions described herein can be appended to form chemically relevant combinations, such as *e.g.*, "heterocycloalkylaryl," "haloalkylheteroaryl," "arylalkylheterocycloalkyl," or "alkoxyalkyl." The last member of the combination is the radical which is binding to the rest of the molecule. The other members of the combination are attached to the binding radical in reversed order in respect of the literal sequence, *e.g.*, the combination arylalkylheterocycloalkyl refers to a heterocycloalkyl–radical which is substituted by an alkyl which is substituted by an aryl.

[0015] When indicating the number of substituents, the term "one or more" refers to the range from one substituent to the highest possible number of substitutions, *i.e.*, replacement of one hydrogen up to replacement of all hydrogens by substituents.

[0016] The term "optional" or "optionally" denotes that a subsequently described event or circumstance can but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

[0017] The term "substituent" denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule.

[0018] The term "substituted" denotes that a specified group bears one or more substituents. Where any group can carry multiple substituents and a variety of possible substituents is provided, the substituents are independently selected and need not to be the same. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the

specified group is unsubstituted or substituted by one or more substituents, independently chosen from the group of possible substituents. When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitutions, *i.e.*, replacement of one hydrogen up to replacement of all hydrogens by substituents.

[0019] The terms "compound(s) of this disclosure," "compound(s) of the present disclosure," "small molecule steric modulator," "small molecule splicing modulator," "steric modulator," "splicing modulator," "compounds that modify splicing," and "compounds modifying splicing" are interchangeably used herein and refer to compounds as disclosed herein and stereoisomers, tautomers, solvates, and salts (*e.g.*, pharmaceutically acceptable salts) thereof.

[0020] The following abbreviations are used throughout the specification: acetic acid (AcOH); ethyl acetate (EtOAc); butyl alcohol (n–BuOH); 1,2–dichloroethane (DCE); dichloromethane (CH_2Cl_2, DCM); diisopropylethylamine (Diipea); dimethylformamide (DMF); hydrogen chloride (HCl); methanol (MeOH); methoxymethyl bromide (MOMBr); N–methyl–2–pyrrolidone (NMP); methyl Iodide (MeI); n–propanol (n–PrOH); p–methoxybenzyl (PMB); triethylamine (Et_3N); [1,1'–Bis(diphenylphosphino)ferrocene] dichloropalladium(II); ($Pd(dppf)Cl_2$); sodium ethane thiolate (EtSNa); sodium acetate (NaOAc); sodium hydride (NaH); sodium hydroxide (NaOH); tetrahydropyran (THP); tetrahydrofuran (THF).

[0021] As used herein, C_1–C_x includes C_1–C_2, C_1–C_3... C_1–C_x. By way of example only, a group designated as "C_1–C_4" indicates that there are one to four carbon atoms in the moiety, *i.e.* groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example only, "C_1–C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, *iso*–propyl, *n*–butyl, *iso*–butyl, *sec*–butyl, and *t*–butyl.

[0022] The term "oxo" refers to the =O substituent.

[0023] "Carboxyl" refers to -COOH.

[0024] "Cyano" refers to -CN.

[0025] The term "thioxo" refers to the =S substituent.

[0026] "Amidinyl" refers to a radical of the formula $-C(=NR^a)-N(R^a)_2$ wherein each R^a is independently a hydrogen, a C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6cycloalkyl, or 3-6 membered heterocycloalkyl. In some embodiments, an amidinyl is $C(=NH)NH_2$. In some embodiments, an amidinyl is $C(=NH)NH(C_1$-C_6 alkyl).

[0027] The term "halo," "halogen," and "halide" are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

[0028] The term "alkyl" refers to a straight or branched hydrocarbon chain radical, having from one to twenty carbon atoms, and which is attached to the rest of the molecule by a single bond. An alkyl comprising up to 10 carbon atoms is referred to as a C_1–C_{10} alkyl, likewise, for example, an alkyl comprising up to 6 carbon atoms is a C_1–C_6 alkyl. Alkyls (and other moieties defined herein)

comprising other numbers of carbon atoms are represented similarly. Alkyl groups include, but are not limited to, C_1–C_{10} alkyl, C_1–C_9 alkyl, C_1–C_8 alkyl, C_1–C_7 alkyl, C_1–C_6 alkyl, C_1–C_5 alkyl, C_1–C_4 alkyl, C_1–C_3 alkyl, C_1–C_2 alkyl, C_2–C_8 alkyl, C_3–C_8 alkyl and C_4–C_8 alkyl. Representative alkyl groups include, but are not limited to, methyl, ethyl, *n*–propyl, 1–methylethyl (*i*–propyl), *n*–butyl, *i*–butyl, *s*–butyl, *n*–pentyl, 1,1–dimethylethyl (*t*–butyl), 3–methylhexyl, 2–methylhexyl, 1–ethyl–propyl, and the like. In some embodiments, the alkyl is methyl or ethyl. In some embodiments, the alkyl is –$CH(CH_3)_2$ or –$C(CH_3)_3$. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted as described below. "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group. In some embodiments, the alkylene is –CH_2–, –CH_2CH_2–, or –$CH_2CH_2CH_2$–. In some embodiments, the alkylene is –CH_2–. In some embodiments, the alkylene is –CH_2CH_2–. In some embodiments, the alkylene is –$CH_2CH_2CH_2$–.

[0029] The term "alkoxy" refers to a radical of the formula –OR where R is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted as described below. Representative alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, pentoxy. In some embodiments, the alkoxy is methoxy. In some embodiments, the alkoxy is ethoxy.

[0030] The term "alkylamino" refers to a radical of the formula –NHR or –NRR where each R is, independently, an alkyl radical as defined above. Unless stated otherwise specifically in the specification, an alkylamino group may be optionally substituted as described below.

[0031] The term "alkenyl" refers to a type of alkyl group in which at least one carbon–carbon double bond is present. In one embodiment, an alkenyl group has the formula –$C(R)=CR_2$, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. In some embodiments, R is H or an alkyl. In some embodiments, an alkenyl is selected from ethenyl (*i.e.*, vinyl), propenyl (*i.e.*, allyl), butenyl, pentenyl, pentadienyl, and the like. Non–limiting examples of an alkenyl group include –$CH=CH_2$, –$C(CH_3)=CH_2$, –$CH=CHCH_3$, –$C(CH_3)=CHCH_3$, and –$CH_2CH=CH_2$.

[0032] The term "alkynyl" refers to a type of alkyl group in which at least one carbon–carbon triple bond is present. In one embodiment, an alkenyl group has the formula –C≡C–R, wherein R refers to the remaining portions of the alkynyl group. In some embodiments, R is H or an alkyl. In some embodiments, an alkynyl is selected from ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Non–limiting examples of an alkynyl group include –C≡CH, –C≡CCH_3 –C≡CCH_2CH_3, –CH_2C≡CH.

[0033] The term "aromatic" refers to a planar ring having a delocalized π–electron system containing 4n+2 π electrons, where n is an integer. Aromatics can be optionally substituted. The term "aromatic" includes both aryl groups (*e.g.*, phenyl, naphthalenyl) and heteroaryl groups (*e.g.*, pyridinyl, furanyl, quinolinyl).

[0034] The term "aryl" refers to a radical derived from a hydrocarbon ring system comprising at least one aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, and naphthyl. In some embodiments, the aryl is phenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (*i.e.*, an arylene group). Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar–"(such as in "aralkyl") is meant to include aryl radicals that are optionally substituted. In some embodiments, an aryl group is partially reduced to form a cycloalkyl group defined herein. In some embodiments, an aryl group is fully reduced to form a cycloalkyl group defined herein.

[0035] The term "haloalkyl" denotes an alkyl group wherein at least one of the hydrogen atoms of the alkyl group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkyl include monofluoro–, difluoro–or trifluoro–methyl, –ethyl or –propyl, for example, 3,3,3–trifluoropropyl, 2–fluoroethyl, 2,2,2–trifluoroethyl, fluoromethyl, or trifluoromethyl. The term "perhaloalkyl" denotes an alkyl group where all hydrogen atoms of the alkyl group have been replaced by the same or different halogen atoms. Exemplary haloalkyl groups further include trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2–trifluoroethyl, 1,2–difluoroethyl, 3–bromo–2–fluoropropyl, 1,2–dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group may be optionally substituted.

[0036] "Hydroxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[0037] "Aminoalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

[0038] "Cyanoalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more cyano groups. In some embodiments, the alkyl is substituted with one cyano group. In some embodiments, the alkyl is substituted with one, two, or three cyano groups. Aminoalkyl include, for example, cyanomethyl, cyanoethyl, cyanopropyl, cyanobutyl, or cyanopentyl.

[0039] The term "haloalkoxy" denotes an alkoxy group wherein at least one of the hydrogen atoms of the alkoxy group has been replaced by same or different halogen atoms, particularly fluoro atoms. Examples of haloalkoxyl include monofluoro–, difluoro–or trifluoro–methoxy, –ethoxy or –propoxy, for example, 3,3,3–trifluoropropoxy, 2–fluoroethoxy, 2,2,2–trifluoroethoxy, fluoromethoxy, or trifluoromethoxy. The term "perhaloalkoxy" denotes an alkoxy group where all hydrogen atoms of

the alkoxy group have been replaced by the same or different halogen atoms. Examples of haloalkoxyl further include trifluoromethoxy, difluoromethoxy, fluoromethoxy, trichloromethoxy, 2,2,2–trifluoroethoxy, 1,2–difluoroethoxy, 3–bromo–2–fluoropropoxy, 1,2–dibromoethoxy, and the like. Unless stated otherwise specifically in the specification, a haloalkoxy group may be optionally substituted.

[0040] The term "bicyclic ring system" denotes two rings which are fused to each other via a common single or double bond (annelated bicyclic ring system), via a sequence of three or more common atoms (bridged bicyclic ring system) or via a common single atom (spiro bicyclic ring system). Bicyclic ring systems can be saturated, partially unsaturated, unsaturated, or aromatic. Bicyclic ring systems can comprise heteroatoms selected from N, O, and S.

[0041] The terms "carbocyclic" or "carbocycle" refer to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from "heterocyclic" rings or "heterocycles" in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, at least one of the two rings of a bicyclic carbocycle is aromatic. In some embodiments, both rings of a bicyclic carbocycle are aromatic. Carbocycle includes cycloalkyl and aryl.

[0042] The term "cycloalkyl" refers to a monocyclic or polycyclic non–aromatic radical, wherein each of the atoms forming the ring (*i.e.*, skeletal atoms) is a carbon atom. In some embodiments, cycloalkyls are saturated or partially unsaturated. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are fused with an aromatic ring (in which case the cycloalkyl is bonded through a non–aromatic ring carbon atom). Cycloalkyl groups include groups having from 3 to 10 ring atoms. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to ten carbon atoms, from three to eight carbon atoms, from three to six carbon atoms, or from three to five carbon atoms. Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In some embodiments, the monocyclic cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In some embodiments, the monocyclic cycloalkyl is cyclopentenyl or cyclohexenyl. In some embodiments, the monocyclic cycloalkyl is cyclopentenyl. Polycyclic radicals include, for example, adamantyl, 1,2–dihydronaphthalenyl, 1,4–dihydronaphthalenyl, tetrainyl, decalinyl, 3,4–dihydronaphthalenyl–1(2H)–one, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl. Unless otherwise stated specifically in the specification, a cycloalkyl group may be optionally substituted.

[0043] The term "bridged" refers to any ring structure with two or more rings that contains a bridge connecting two bridgehead atoms. The bridgehead atoms are defined as atoms that are the part of the skeletal framework of the molecule and which are bonded to three or more other skeletal atoms. In some embodiments, the bridgehead atoms are C, N, or P. In some embodiments, the bridge is a single atom or a chain of atoms that connects two bridgehead atoms. In some embodiments, the bridge is a

valence bond that connects two bridgehead atoms. In some embodiments, the bridged ring system is cycloalkyl. In some embodiments, the bridged ring system is heterocycloalkyl.

[0044] The term "fused" refers to any ring structure described herein which is fused to an existing ring structure. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring may be replaced with one or more N, S, and O atoms. The non–limiting examples of fused heterocyclyl or heteroaryl ring structures include 6–5 fused heterocycle, 6–6 fused heterocycle, 5–6 fused heterocycle, 5–5 fused heterocycle, 7–5 fused heterocycle, and 5–7 fused heterocycle.

[0045] The term "fluoroalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoroalkyl is a C_1–C_6 fluoroalkyl. In some embodiments, a fluoroalkyl is selected from trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2–trifluoroethyl, 1–fluoromethyl–2–fluoroethyl, and the like.

[0046] The term "heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (*e.g.*, –NH–, –N(alkyl)–, or –N(aryl)–), sulfur (*e.g.*, –S–, –S(=O)–, or –$S(=O)_2$–), or combinations thereof. In some embodiments, a heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In some embodiments, a heteroalkyl is attached to the rest of the molecule at a heteroatom of the heteroalkyl. In some embodiments, a heteroalkyl is a C_1–C_6 heteroalkyl. Representative heteroalkyl groups include, but are not limited to –OCH_2OMe, –OCH_2CH_2OH, –OCH_2CH_2OMe, or –$OCH_2CH_2OCH_2CH_2NH_2$. In some embodiments, a heteroalkyl contains one skeletal heteroatom. In some embodiments, a heteroalkyl contains 1-3 skeletal heteroatoms.

[0047] The term "heteroalkylene" refers to an alkyl radical as described above where one or more carbon atoms of the alkyl is replaced with a O, N or S atom. "Heteroalkylene" or "heteroalkylene chain" refers to a straight or branched divalent heteroalkyl chain linking the rest of the molecule to a radical group. Unless stated otherwise specifically in the specification, the heteroalkyl or heteroalkylene group may be optionally substituted as described below. Representative heteroalkylene groups include, but are not limited to –OCH_2CH_2O–, –$OCH_2CH_2OCH_2CH_2O$–, or –$OCH_2CH_2OCH_2CH_2OCH_2CH_2O$–.

[0048] The term "heterocycloalkyl" refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen, and sulfur. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, or bicyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non–aromatic ring atom) or bridged ring systems. In some embodiments, a heterocycloalkyl is monocyclic. In some embodiments, a heterocycloalkyl is bicyclic. In some embodiments, a heterocycloalkyl is partially saturated. In some embodiments, a heterocycloalkyl is fully saturated. The nitrogen, carbon, or sulfur atoms in the heterocyclyl radical may be optionally oxidized. The nitrogen atom may be optionally quaternized. The heterocycloalkyl radical is partially or fully

saturated. Examples of heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2–oxopiperazinyl, 2–oxopiperidinyl, 2–oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4–piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1–oxo–thiomorpholinyl, 1,1–dioxo–thiomorpholinyl. The term heterocycloalkyl also includes all ring forms of carbohydrates, including but not limited to monosaccharides, disaccharides, and oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 12 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring and 1 or 2 N atoms. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring and 3 or 4 N atoms. In some embodiments, heterocycloalkyls have from 2 to 12 carbons, 0–2 N atoms, 0–2 O atoms, 0–2 P atoms, and 0–1 S atoms in the ring. In some embodiments, heterocycloalkyls have from 2 to 12 carbons, 1–3 N atoms, 0–1 O atoms, and 0–1 S atoms in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (*i.e.* skeletal atoms of the heterocycloalkyl ring). Unless stated otherwise specifically in the specification, a heterocycloalkyl group may be optionally substituted.

[0049] The term “heterocycle” or “heterocyclic” refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings (also known as heteroalicyclic groups) that includes at least one heteroatom selected from nitrogen, oxygen and sulfur, wherein each heterocyclic group has from 3 to 12 atoms in its ring system, and with the proviso that any ring does not contain two adjacent O or S atoms. In some embodiments, heterocycles are monocyclic, bicyclic, polycyclic, spirocyclic or bridged compounds. Non–aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 12 atoms in its ring system and aromatic heterocyclic groups include rings having 5 to 12 atoms in its ring system. The heterocyclic groups include benzo–fused ring systems. Examples of non–aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6–tetrahydropyridinyl, pyrrolin–2–yl, pyrrolin–3–yl, indolinyl, 2H–pyranyl, 4H–pyranyl, dioxanyl, 1,3–dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3–azabicyclo[3.1.0]hexanyl, 3–azabicyclo[4.1.0]heptanyl, $_3$h–indolyl, indolin–2–onyl, isoindolin–1–onyl, isoindoline–1,3–dionyl, 3,4–dihydroisoquinolin–1(2H)–onyl, 3,4–dihydroquinolin–2(1H)–onyl, isoindoline–1,3–dithionyl, benzo[d]oxazol–2(3H)–onyl, 1H–benzo[d]imidazol–2(3H)–onyl, benzo[d]thiazol–2(3H)–onyl, and quinolizinyl. Examples of

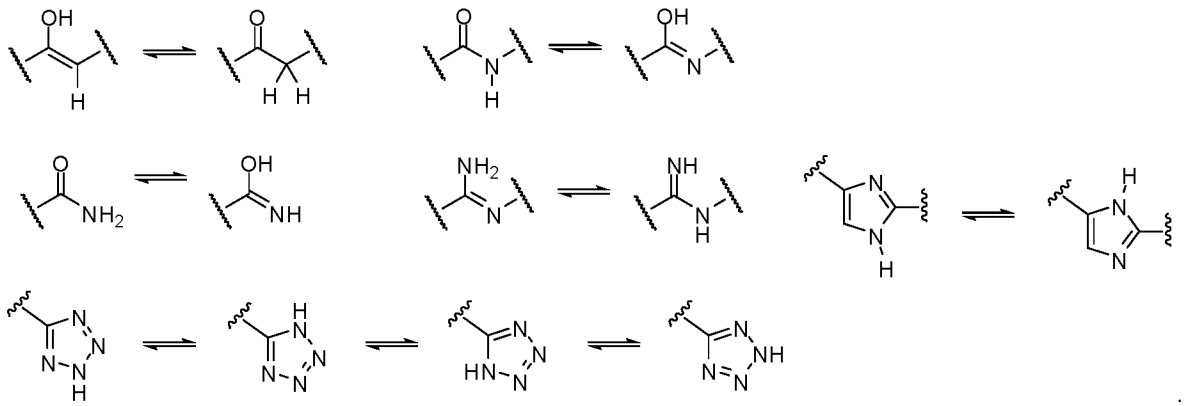
aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups are either C–attached (or C–linked) or *N*–attached where such is possible. For instance, a group derived from pyrrole includes both pyrrol–1–yl (*N*–attached) or pyrrol–3–yl (C–attached). Further, a group derived from imidazole includes imidazol–1–yl or imidazol–3–yl (both *N*–attached) or imidazol–2–yl, imidazol–4–yl or imidazol–5–yl (all C–attached). The heterocyclic groups include benzo–fused ring systems. Non–aromatic heterocycles are optionally substituted with one or two oxo (=O) moieties, such as pyrrolidin–2–one. In some embodiments, at least one of the two rings of a bicyclic heterocycle is aromatic. In some embodiments, both rings of a bicyclic heterocycle are aromatic.

[0050] The term "heteroaryl" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen, and sulfur. The heteroaryl can be monocyclic or bicyclic. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, furazanyl, indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8–naphthyridine, and pteridine. Illustrative examples of monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Illustrative examples of bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8–naphthyridine, and pteridine. In some embodiments, heteroaryl is pyridinyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, thiadiazolyl or furyl. In some embodiments, a heteroaryl contains 0–6 N atoms in the ring. In some embodiments, a heteroaryl contains 1–4 N atoms in the ring. In some embodiments, a heteroaryl contains 4–6 N atoms in the ring. In some embodiments, a heteroaryl contains 0–4 N atoms, 0–1 O atoms, 0–1 P atoms, and 0–1 S atoms in the ring. In some embodiments, a heteroaryl contains 1–4 N atoms, 0–1 O atoms, and 0–1 S atoms in the ring. In some embodiments, heteroaryl is a C_1–C_9 heteroaryl. In some embodiments, monocyclic heteroaryl is a C_1–C_5 heteroaryl. In some embodiments, monocyclic heteroaryl is a 5–membered or 6–membered heteroaryl. In some embodiments, a bicyclic heteroaryl is a C_6–C_9 heteroaryl. In some embodiments, a heteroaryl group is partially reduced to form a heterocycloalkyl group defined herein. In some embodiments, a heteroaryl group is fully reduced to form a heterocycloalkyl group defined herein.

[0051] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0052] The term "optionally substituted" or "substituted" means that the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from D, halogen, –CN, $–NH_2$, –NH(alkyl), $–N(alkyl)_2$, –OH, $–CO_2H$, $–CO_2$alkyl, $–C(=O)NH_2$, –C(=O)NH(alkyl), $–C(=O)N(alkyl)_2$, $–S(=O)_2NH_2$, $–S(=O)_2$NH(alkyl), $–S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from D, halogen, –CN, $–NH_2$, $–NH(CH_3)$, $–N(CH_3)_2$, –OH, $–CO_2H$, $–CO_2(C_1–C_4$ alkyl), $–C(=O)NH_2$, $–C(=O)NH(C_1–C_4$ alkyl), $–C(=O)N(C_1–C_4$ alkyl)$_2$, $–S(=O)_2NH_2$, $–S(=O)_2NH(C_1–C_4$ alkyl), $–S(=O)_2N(C_1–C_4$ alkyl)$_2$, $C_1–C_4$ alkyl, $C_3–C_6$ cycloalkyl, $C_1–C_4$ fluoroalkyl, $C_1–C_4$ heteroalkyl, $C_1–C_4$ alkoxy, $C_1–C_4$ fluoroalkoxy, $–SC_1–C_4$ alkyl, $–S(=O)C_1–C_4$ alkyl, and $–S(=O)_2(C_1–C_4$ alkyl). In some embodiments, optional substituents are independently selected from D, halogen, –CN, $–NH_2$, –OH, $–NH(CH_3)$, $–N(CH_3)_2$, –NH(cyclopropyl), $–CH_3$, $–CH_2CH_3$, $–CF_3$, $–OCH_3$, and $–OCF_3$. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O).

[0053] The term "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The compounds presented herein may exist as tautomers. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Some examples of tautomeric interconversions include:



[0054] The terms "administer," "administering," "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include but are not limited to oral routes (p.o.), intraduodenal routes (i.d.), parenteral injection (including intravenous (i.v.), subcutaneous (s.c.), intraperitoneal

(i.p.), intramuscular (i.m.), intravascular or infusion (inf.)), topical (top.) and rectal (p.r.) administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally.

[0055] The terms "co–administration" or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[0056] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the mammalian class: humans, non–human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human. The term "animal" as used herein comprises human beings and non–human animals. In one embodiment, a "non–human animal" is a mammal, for example a rodent such as rat or a mouse. In one embodiment, a non–human animal is a mouse.

[0057] The term "pharmaceutically acceptable" denotes an attribute of a material which is useful in preparing a pharmaceutical composition that is generally safe, non toxic, and neither biologically nor otherwise undesirable and is acceptable for veterinary as well as human pharmaceutical use. "Pharmaceutically acceptable" can refer a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, *i.e.*, the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[0058] The terms "pharmaceutically acceptable excipient", "pharmaceutically acceptable carrier" and "therapeutically inert excipient" can be used interchangeably and denote any pharmaceutically acceptable ingredient in a pharmaceutical composition having no therapeutic activity and being non–toxic to the subject administered, such as disintegrators, binders, fillers, solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants, carriers, diluents, excipients, preservatives or lubricants used in formulating pharmaceutical products.

[0059] The term "pharmaceutically acceptable salts" denotes salts which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts include both acid and base addition salts. A "pharmaceutically acceptable salt" can refer to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and/or does not abrogate the biological activity and properties of the compound. In some embodiments, pharmaceutically acceptable salts are obtained by reacting a SMSM compound of the present disclosure with acids. Pharmaceutically

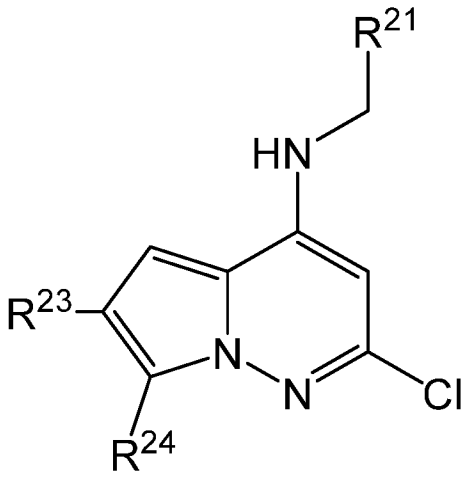
acceptable salts are also obtained by reacting a compound of the present disclosure with a base to form a salt.

[0060] As used herein, a "small molecular weight compound" can be used interchangeably with "small molecule" or "small organic molecule." Small molecules refer to compounds other than peptides or oligonucleotides; and typically have molecular weights of less than about 2000 Daltons, *e.g.*, less than about 900 Daltons.

Small Molecule Splicing Modulators (SMSMs)

[0061] It has now been found that compounds of this disclosure, and pharmaceutically acceptable compositions thereof, are effective as agents for use in treating, preventing, or ameliorating a disease or a condition associated with a target RNA. The present disclosure provides the unexpected discovery that certain small chemical molecules can modify splicing events in pre-mRNA molecules, herein referred to as small molecule splicing modulators (SMSMs). These SMSMs can modulate specific splicing events in specific pre-mRNA molecules. The small molecules of this disclosure are different from and are not related to antisense or antigene oligonucleotides.

[0062] In one aspect, a SMSM described herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein,

- R^{21} is thiophenyl, which is unsubstituted or substituted with 1, 2, or 3, independently selected R^{1A} groups; each R^{1A} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, -C(=O)OH, -C(=O)C_{1-6} alkyl, -C(=O)C_{1-6} haloalkyl, and -C(=O)C_{1-6} alkoxy;
- R^{23} is selected from the group consisting of H, azido, halo, CN, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, -(C_{1-6} alkylene)-C_{3-10} cycloalkyl, -(C_{1-6} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-6} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-6} heteroalkylene)-4-10 membered heterocycloalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4- 10 membered

heterocycloalkyl, OR^{a3}, SR^{a3}, $C(=O)R^{b3}$, $C(=O)OR^{b3}$, $NR^{c3}R^{d3}$, $C(=O)NR^{c3}R^{d3}$, $-OC(=O)NR^{c3}R^{d3}$, $NR^{c3}C(=O)R^{b3}$, $NR^{c3}C(=O)OR^{b3}$, $NR^{c3}C(=O)NR^{c3}R^{d3}$, $NR^{c3}S(=O)_2R^{b3}$, $NR^{c3}S(=O)_2NR^{c3}R^{d3}$, $S(O)NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

- R^{24} is selected from the group consisting of H, azido, halo, CN, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4- 10 membered heterocycloalkyl, OR^{a4}, $C(=O)R^{b4}$, $C(=O)OR^{b4}$, $NR^{c4}R^{d4}$, $C(=O)NR^{c4}R^{d4}$, $-OC(=O)NR^{c4}R^{d4}$, $NR^{c4}C(=O)R^{b4}$, $NR^{c4}C(=O)OR^{b4}$, $NR^{c4}C(=O)NR^{c4}R^{d4}$, $NR^{c4}S(=O)_2R^{b4}$, $NR^{c4}S(=O)_2NR^{c4}R^{d4}$, $S(O)NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$, wherein the C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;
- each R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a4}, R^{b4}, R^{c4}, and R^{d4}, is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $-(C_{1-6}$ alkylene$)$-C_{1-6} alkoxy, C_{3-10} cycloalkyl, $-(C_{1-6}$ alkylene$)$-C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, $-(C_{1-6}$ alkylene$)$-C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

  or R^{c3} and R^{d3} together with the N atom to which they are connected, come together to form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl ring, each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

  or R^{c4} and R^{d4} together with the N atom to which they are connected, come together to form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl ring, each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

  and
- each R^{20} is independently selected from the group consisting of OH, SH, CN, NO_2, halo, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, $-(C_{1-4}$ alkyl$)$-$(C_{1-4}$ alkoxy$)$, $-(C_{1-4}$ alkoxy$)$-$(C_{1-4}$ alkoxy$)$, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, amino, C_{1-4} alkylamino, di$(C_{1-4}$ alkyl$)$amino, carbamyl, C_{1-4} alkylcarbamyl, di$(C_{1-4}$ alkyl$)$carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di$(C_{1-4}$ alkyl$)$carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di$(C_{1-4}$ alkyl$)$aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di$(C_{1-4}$ alkyl$)$aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, di$(C_{1-4}$ alkyl$)$aminocarbonylamino, and amidinyl.

[0063] In some embodiments of a compound of Formula (I) or a pharmaceutically acceptable salt thereof,

- R^{21} is thiophenyl, which is unsubstituted or substituted with 1, 2, or 3, independently selected R^{1A} groups; wherein each R^{1A} is independently selected from halo, CN, NO_2, alkyl, alkenyl, C_{2-6} alkynyl, alkoxy, -C(=O)OH, an ether group, or an ester group, each of which is unsubstituted or substituted;
- R^{23} is selected from the group consisting of H, oxo, azido, halo, CN, NO_2, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, OR^{a3}, SR^{a3}, $C(=O)R^{b3}$, $C(=O)OR^{b3}$, $NR^{c3}R^{d3}$, $C(=O)NR^{c3}R^{d3}$, $-OC(=O)NR^{c3}R^{d3}$, $NR^{c3}C(=O)R^{b3}$, $NR^{c3}C(=O)OR^{b3}$, $NR^{c3}C(=O)NR^{c3}R^{d3}$, $NR^{c3}S(=O)_2R^{b3}$, $NR^{c3}S(=O)_2NR^{c3}R^{d3}$, $S(O)NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$, wherein the alkyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl are each unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups;
- R^{24} is selected from the group consisting of H, oxo, azido, halo, CN, NO_2, alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, OR^{a4}, $C(=O)R^{b4}$, $C(=O)OR^{b4}$, $NR^{c4}R^{d4}$, $C(=O)NR^{c4}R^{d4}$, - $OC(=O)NR^{c4}R^{d4}$, $NR^{c4}C(=O)R^{b4}$, $NR^{c4}C(=O)OR^{b4}$, $NR^{c4}C(=O)NR^{c4}R^{d4}$, $NR^{c4}S(=O)_2R^{b4}$, $NR^{c4}S(=O)_2NR^{c4}R^{d4}$, $S(O)NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$, wherein the alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl are each unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups;
- each R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a4}, R^{b4}, R^{c4}, and R^{d4}, is independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, aryl, heteroaryl, and heterocycloalkyl, each of which is unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups;

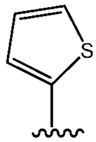
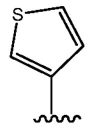
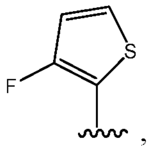
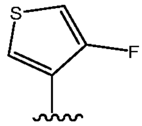
  each R^{c3} and R^{d3} together with the N atom to which they are connected, come together to form a heteroaryl or heterocycloalkyl ring, each of which is unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups;

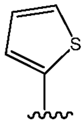
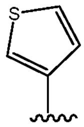
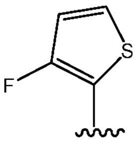
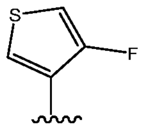
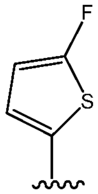
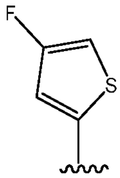
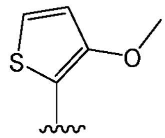
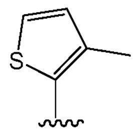
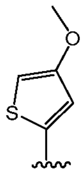
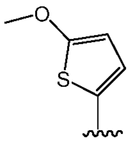
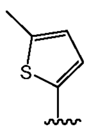
  or each R^{c4} and R^{d4} together with the N atom to which they are connected, come together to form a heteroaryl or heterocycloalkyl ring, each of which is unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups; and
- each R^{20} is independently selected from the group consisting of OH, SH, CN, NO_2, halo, oxo, alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, amino, carbamyl, or carbamoyl.

[0064] In some embodiments, R^{24} is selected from the group consisting of H, azido, halo, CN, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4- 10 membered heterocycloalkyl, OR^{a4}, $C(=O)R^{b4}$, $C(=O)OR^{b4}$, $NR^{c4}R^{d4}$, $C(=O)NR^{c4}R^{d4}$, - $OC(=O)NR^{c4}R^{d4}$, $NR^{c4}C(=O)R^{b4}$, $NR^{c4}C(=O)OR^{b4}$, $NR^{c4}C(=O)NR^{c4}R^{d4}$, $NR^{c4}S(=O)_2R^{b4}$, $NR^{c4}S(=O)_2NR^{c4}R^{d4}$, $S(O)NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$, wherein the C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{6-}

$_{10}$ aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^{24} is selected from the group consisting of H, halo, CN, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 4-10 membered heterocycloalkyl, OH, C_{1-6} alkoxyl, and C_{1-6} haloalkyl. In some embodiments, R^{24} is selected from the group consisting of H, halo, CN, C_{1-6} alkyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, OH, C_{1-6} alkoxyl, and C_{1-6} haloalkyl. In some embodiments, R^{24} is selected from the group consisting of hydrogen, OH, halo, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted C_{2-4} alkenyl, and substituted or unsubstituted C_{2-4} alkynyl. In some embodiments, R^{24} is hydrogen. In some embodiments, R^{24} is halogen. In some embodiments, R^{24} is -Br. In some embodiments, R^{24} is -F. In some embodiments, R^{24} is -Cl. In some embodiments, R^{24} is -CN. In some embodiments, R^{24} is OH. In some embodiments, R^{24} is C_{1-4} alkyl. In some embodiments, R^{24} is C_{1-4} haloalkyl. In some embodiments, R^{24} is C_{1-4} alkoxyl. In some embodiments, R^{24} is methyl. In some embodiments, R^{24} is ethyl. In some embodiments, R^{24} is cycloalkyl. In some embodiments, R^{24} is cyclopropyl. In some embodiments, R^{24} is C_{2-4} alkenyl. In some embodiments, R^{24} is C_{2-4} alkynyl. In some embodiments, R^{24} is ethynyl. In some embodiment, R^{24} is propynyl.

[0065] In some embodiments, R^{21} is unsubstituted or substituted thiophenyl. In some embodiments, R^{21} is unsubstituted thiophenyl. In some embodiments, R^{21} is substituted thiophenyl. In some embodiments, R^{21} is thiophenyl, which is substituted with 1, 2, or 3, independently selected R^{1A} groups; wherein each R^{1A} is independently selected from halo, CN, NO_2, alkyl, alkenyl, C_{2-6} alkynyl, alkoxy, -C(=O)OH, an ether group, or an ester group, each of which is unsubstituted or substituted. In some embodiments, R^{21} is thiophenyl, which is substituted with 1, 2, or 3 substituents independently selected R^{1A} groups; wherein each R^{1A} is independently selected from halo, C_{1-6}alkyl, C_{1-6}haloalkyl, and C_{1-6}alkoxy. In some embodiments, R^{21} is thiophenyl, which is substituted with 1, 2, or 3 substituents independently selected R^{1A} groups; wherein each R^{1A} is independently selected from halo, C_{1-3}alkyl, C_{1-3}haloalkyl, and C_{1-3}alkoxy. In some embodiments, each R^{1A} is independently selected from halo, CN, NO_2, C_{1-3}alkyl, C_{1-3}haloalkyl, and C_{1-3}alkoxy. In some embodiments, each R^{1A} is independently selected from halo, C_{1-3}alkyl, C_{1-3}haloalkyl, and C_{1-3}alkoxy. In some embodiments, each R^{1A} is independently selected from halo, C_{1-3}alkyl, and C_{1-3}haloalkyl. In some embodiments, R^{1A} is halo. In some embodiments, R^{1A} is fluoro, chloro, bromo, or iodo. In some embodiments, R^{1A} is fluoro. In some embodiments, R^{1A} is chloro. In some embodiments, R^{1A} is bromo. In some embodiments, R^{1A} is iodo.

[0066] In some embodiments, R^{21} is selected from the group consisting of  ,  ,  , and  .

In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  .

[0067] In some embodiments, R^{23} is H.

[0068] In some embodiments, R^{23} is substituted with 1, 2, or 3 independently selected R^{20} groups, wherein each R^{20} group is independently selected from the group consisting of OH, SH, CN, NO_2, halo, oxo, amino, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, carbamyl, and carbamoyl. In some embodiments, R^{23} is substituted with 1, 2, or 3 independently selected R^{20} groups, wherein each R^{20} group is independently selected from the group consisting of OH, halo, and $C_{1\text{-}3}$alkoxy. In some embodiments, R^{23} is substituted with 1, 2, or 3 independently selected R^{20} groups, wherein each R^{20} group is independently selected from the group consisting of OH, halo, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$haloalkyl, amino, and $C_{1\text{-}3}$alkoxy.In some embodiments, R^{23} is substituted with 1, 2, or 3 independently selected R^{20} groups, wherein each R^{20} group is independently selected from the group consisting of OH, halo, amino, and $C_{1\text{-}3}$alkoxy. In some embodiments, R^{20} group is OH. In some

embodiments, R^{20} group is halo. In some embodiments, R^{20} group is amino. In some embodiments, R^{20} group is C_{1-3}alkoxy.

[0069] In some embodiments, R^{23} is substituted or unsubstituted C_{1-6} alkyl. In some embodiments, R^{23} is C_{1-6} alkyl, wherein C_{1-6} alkyl is substituted with 1, 2, or 3 independently selected R^{20} groups. In some embodiments, R^{23} is C_{1-6} alkyl, wherein C_{1-6} alkyl is substituted with 1, 2, or 3 independently selected R^{20} groups, wherein each R^{20} group is independently selected from the group consisting of OH, SH, CN, NO_2, halo, oxo, amino, C_{1-3}alkyl, C_{1-3}alkoxy, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, carbamyl, and carbamoyl. In some embodiments, R^{23} is C_{1-6} alkyl, wherein C_{1-6} alkyl is substituted with 1, 2, or 3 independently selected R^{20} groups, wherein each R^{20} group is independently selected from the group consisting of OH, halo, and C_{1-3}alkoxy.

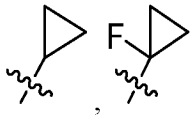
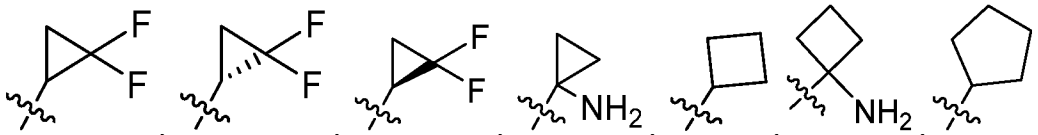
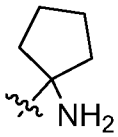
[0070] In some embodiments, R^{23} is substituted or unsubstituted C_{1-6} alkenyl. In some embodiments, R^{23} is C_{1-6} alkenyl, wherein C_{1-6} alkenyl is substituted with 1, 2, or 3 independently selected R^{20} groups.

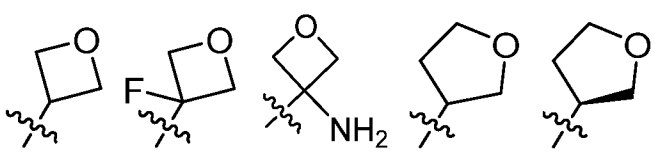
[0071] In some embodiments, R^{23} is substituted or unsubstituted C_{1-6} alkynyl. In some embodiments, R^{23} is C_{1-6} alkynyl, wherein C_{1-6} alkynyl is substituted with 1, 2, or 3 independently selected R^{20} groups.

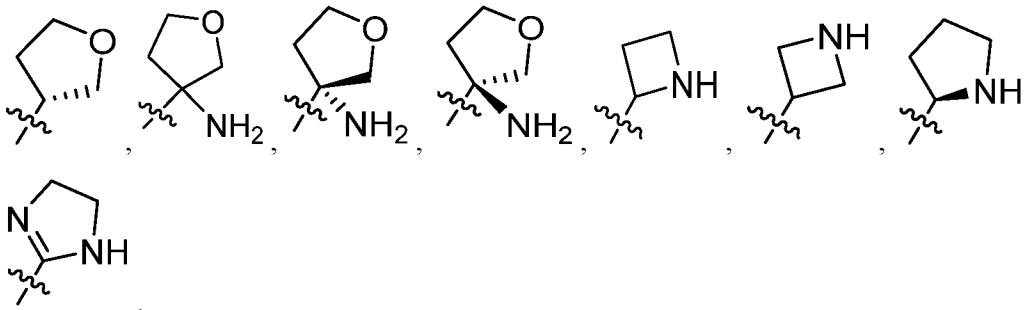
[0072] In some embodiments, R^{23} is substituted or unsubstituted C_{1-6} alkyl or substituted or unsubstituted C_{1-6} heteroalkyl. In some embodiments, R^{23} is substituted or unsubstituted C_{1-6} heteroalkyl. In some embodiments, the C_{1-6} heteroalkyl is $-CH_2CH(NH_2)CH_2-S(=O)_2-CH_3$ or $-CH_2CH(NH_2)CH_2-S(=O)-CH_3$. In some embodiments, R^{23} is $-CH_2CH(NH_2)CH_2-S(=O)_2-CH_3$. In some embodiments, R^{23} is $-CH_2CH(NH_2)CH_2-S(=O)-CH_3$. In some embodiments, R^{23} is $CH_2CHNH_2CH_3$. In some embodiments, R^{23} is $CH_2CHNH_2CH_2OH$. In some embodiments, R^{23} is $CH_2CHNH_2CH_2CH_3$. In some embodiments, R^{23} is $CH_2CHNH_2CH_2CH_2OH$. In some embodiments, R^{23} is $CH_2CHNH_2CH_2CH_2F$. In some embodiments, R^{23} is $CH_2CHNH_2CH_2CHF_2$. In some embodiments, R^{23} is $CH_2CHNH_2CH_2CH(CH_3)_2$. In some embodiments, R^{23} is $CH_2CHNH_2CHFCH_3$. In some embodiments, R^{23} is $CH_2CHNH_2CH_2F$. In some embodiments, R^{23} is $CH_2CHNH_2CH_2OCH_3$. In some embodiments, R^{23} is $CH_2CHNH_2CH_2OCD_3$.

[0073] In some embodiments, R^{23} is substituted or unsubstituted C_{1-6} heteroalkyl. In some embodiments, R^{23} is C_{1-6} heteroalkyl, wherein the C_{1-6} heteroalkyl is substituted with 1, 2, or 3 independently selected R^{20} groups. In some embodiments, R^{23} is C_{1-6} heteroalkyl, wherein the C_{1-6} heteroalkyl is substituted with 1, 2, or 3 independently selected R^{20} groups, wherein each R^{20} group is independently selected from the group consisting of OH, SH, CN, NO_2, halo, oxo, amino, C_{1-3}alkyl, C_{1-3}alkoxy, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, carbamyl, and carbamoyl. In some embodiments, R^{23} is C_{1-6} heteroalkyl, wherein the C_{1-6} heteroalkyl is substituted with 1, 2, or 3 independently selected R^{20} groups, wherein each R^{20} group is independently selected from the group consisting of OH, halo, and C_{1-3}alkoxy. In some embodiments, R^{23} is C_{1-6} alkyl, wherein C_{1-6} alkyl is

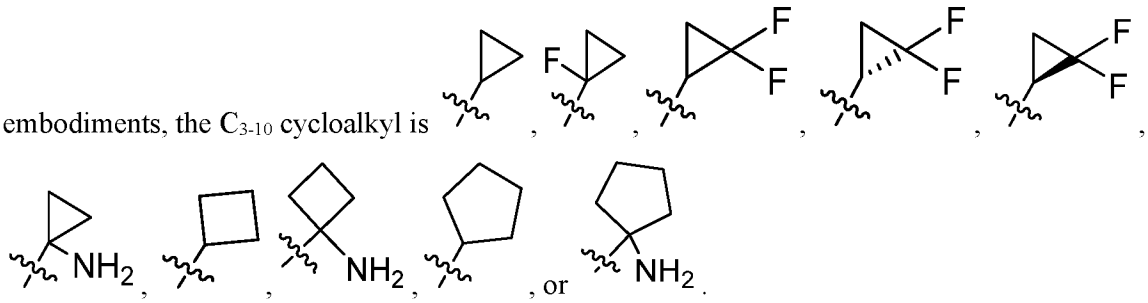
substituted with 1, 2, or 3 independently selected R^{20} groups, wherein each R^{20} group is independently selected from the group consisting of OH, halo, amino, and C_{1-3}alkoxy.

[0074] In some embodiments, R^{23} is substituted or unsubstituted -(C_{1-6} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{23} is -(C_{1-6} alkylene)-C_{3-10} cycloalkyl, wherein -(C_{1-6} alkylene)-C_{3-10} cycloalkyl is substituted with 1, 2, or 3 independently selected R^{20} groups. In some embodiments, the C_{1-6} alkylene is C_{1-3} alkylene. In some embodiments, the C_{1-6} alkylene is CH_2. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted 3-6 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted 3 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted 4 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted 5 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted 6 membered ring. In some embodiments, the C_{3-10} cycloalkyl is  ,  , or  .

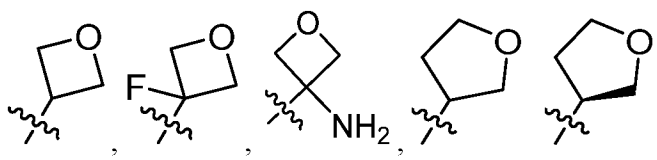
[0075] In some embodiments, R^{23} is substituted or unsubstituted -(C_{1-6} alkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{23} is -(C_{1-6} alkylene)-4-10 membered heterocycloalkyl, wherein -(C_{1-6} alkylene)-4-10 membered heterocycloalkyl is substituted with 1, 2, or 3 independently selected R^{20} groups. In some embodiments, the C_{1-6} alkylene is C_{1-3} alkylene. In some embodiments, the C_{1-6} alkylene is CH_2. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted 4-6 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted 4 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted 5 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted 6 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl contains 0-1 oxygen and 0-2 nitrogen atoms. In some embodiments, the 4-10 membered heterocycloalkyl is  .

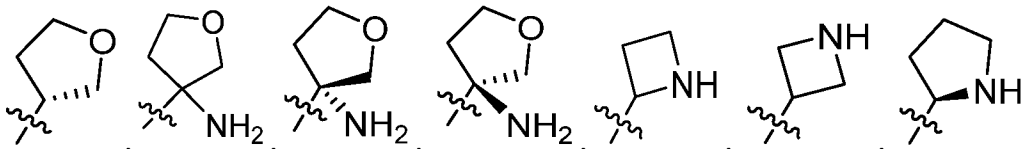


[0076] In some embodiments, R^{23} is substituted or unsubstituted -(C_{1-6} heteroalkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{23} is -(C_{1-6} heteroalkylene)-C_{3-10} cycloalkyl, wherein -(C_{1-6} heteroalkylene)-C_{3-10} cycloalkyl is substituted with 1, 2, or 3 independently selected R^{20} groups. In some embodiments, the heteroalkylene is C_{1-3} heteroalkylene. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted 3-6 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted 3 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted 4 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted 5 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted 6 membered ring. In some embodiments, the heteroalkylene is C_{1-3} heteroalkylene. In some embodiments, the C_{3-10} cycloalkyl is



[0077] In some embodiments, R^{23} is substituted or unsubstituted -(C_{1-6} heteroalkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{23} is -(C_{1-6} heteroalkylene)-4-10 membered heterocycloalkyl, wherein -(C_{1-6} heteroalkylene)-4-10 membered heterocycloalkyl is substituted with 1, 2, or 3 independently selected R^{20} groups. In some embodiments, the heteroalkylene is C_{1-3} heteroalkylene. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted 4-6 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted 4 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted 5 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted 6 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl contains 0-1 oxygen and 0-2 nitrogen atoms. In some embodiments, the 4-10 membered heterocycloalkyl is

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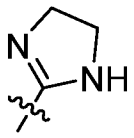
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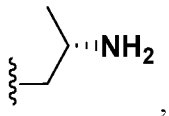
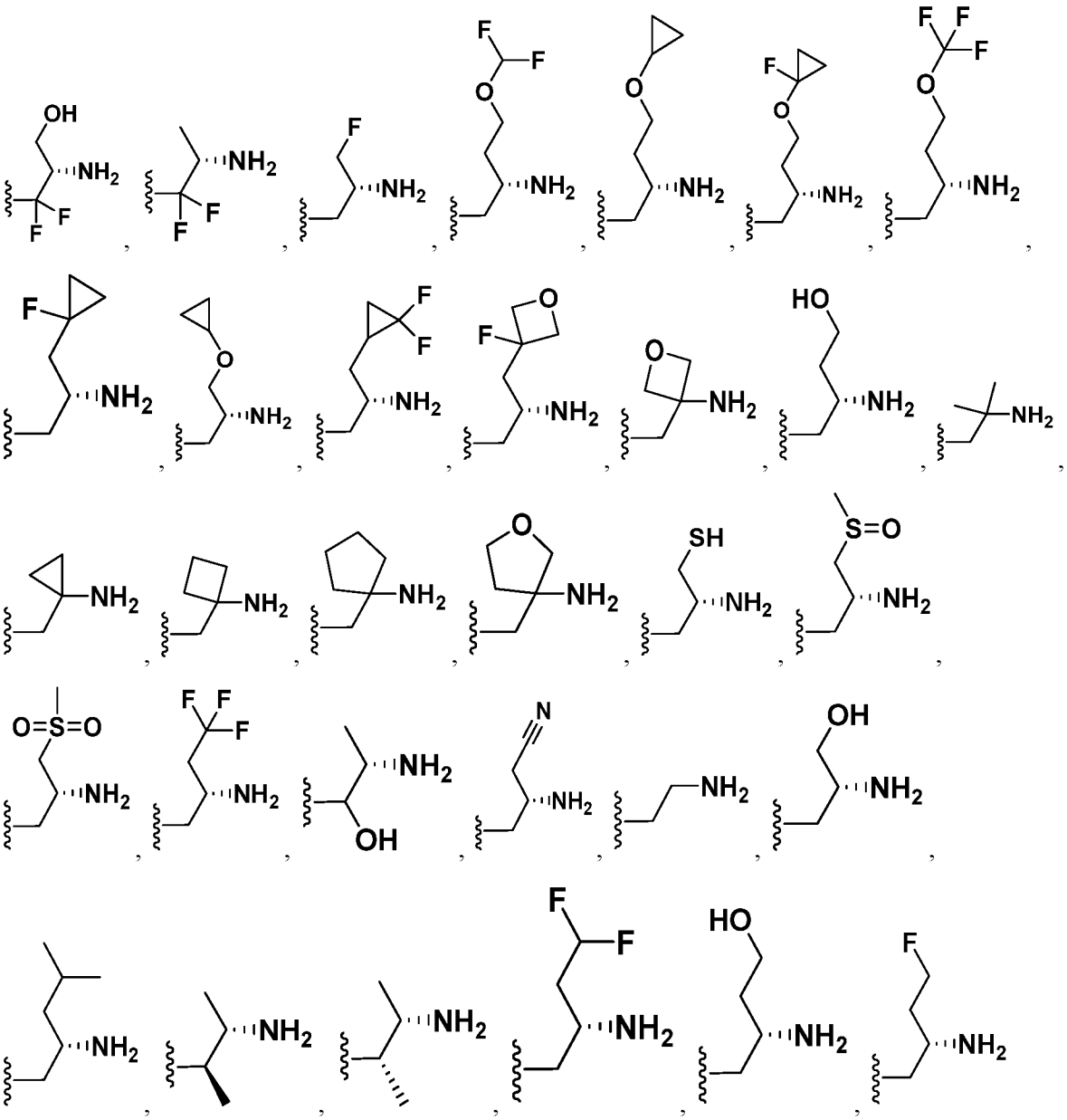
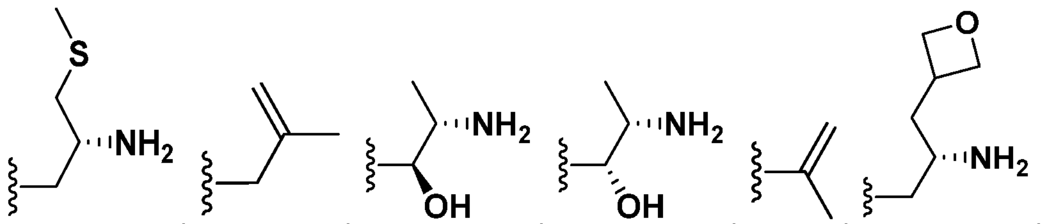
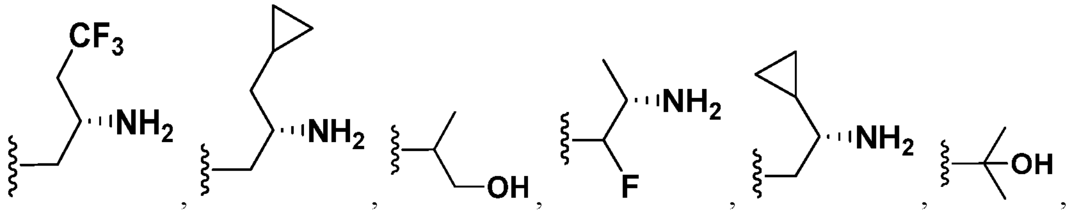
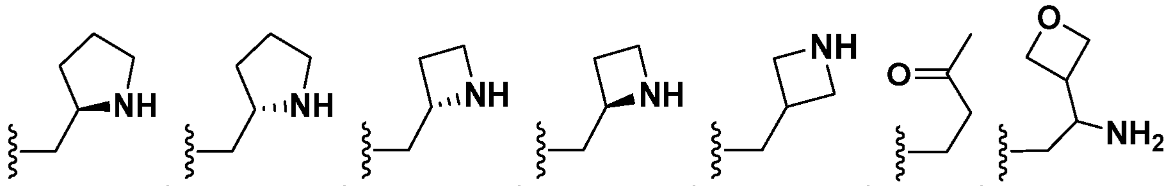
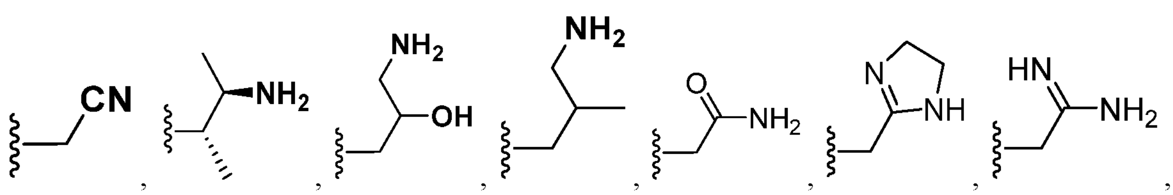
[0078] In some embodiments, R^{23} is any one selected from the group consisting of:  ,

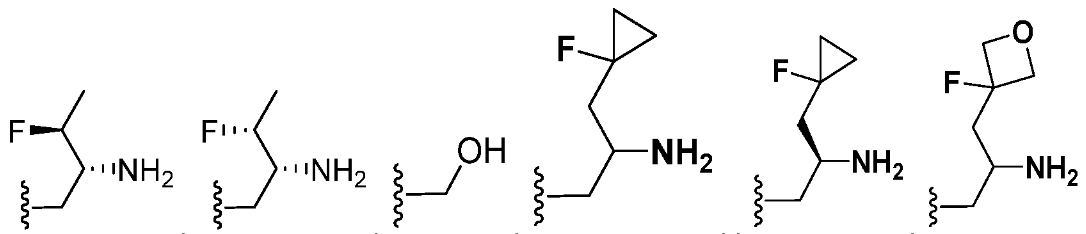


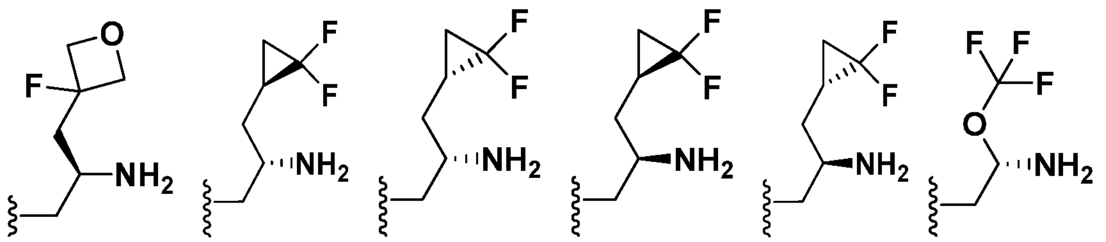


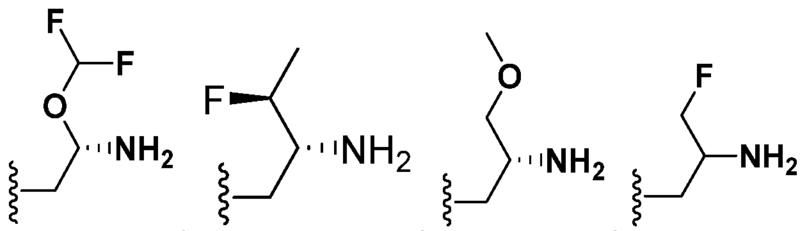
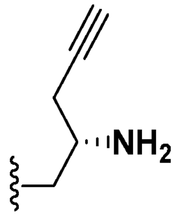
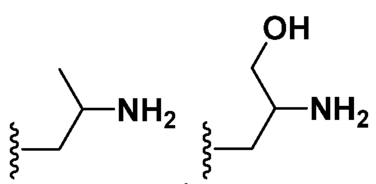


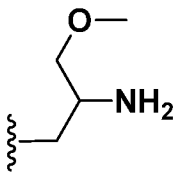
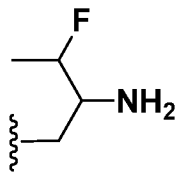
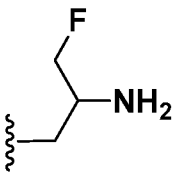
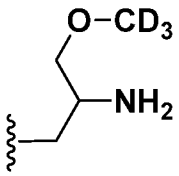
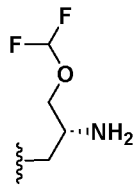
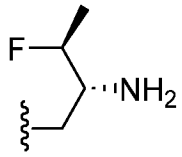








 , and  . In some embodiments, R^{23} is any one selected from the group consisting of: 

, , and . In some embodiments, R^{23} is . In some embodiments, R^{23} is . In some embodiments, R^{23} is .

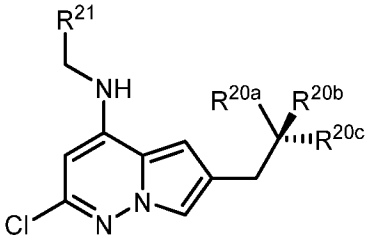
[0079] In some embodiments, each R^{20} is independently selected from the group consisting of OH, SH, CN, NO_2, halo, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, di(C_{1-4} alkyl)aminocarbonylamino, and amidinyl. In some embodiments, each R^{20} is independently selected from the group consisting of OH, SH, CN, NO_2, halo, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, and amidinyl. In some embodiments, each R^{20} is independently selected from the group consisting of OH, SH, CN, NO_2, halo, oxo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, 4-6 membered heterocycloalkyl, amino, carbamyl C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, and amidinyl. In some embodiments, R^{20} is OH. In some embodiments, R^{20} is NH_2. In some embodiments, R^{20} is SH. In some embodiments, R^{20} is CN. In some embodiments, R^{20} is F. In some embodiments, R^{20} is carbamyl.

[0080] In some embodiments, R^{24} is selected from the group consisting of halo, CN, and substituted or unsubstituted C_{1-6} alkyl. In some embodiments, R^{24} is selected from the group consisting of hydrogen, OH, halo, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxyl, substituted or unsubstituted C_{3-10} cycloalkyl, substituted or unsubstituted C_{2-4} alkenyl, and substituted or unsubstituted C_{2-4} alkynyl.

[0081] In some embodiments, each R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a4}, R^{b4}, R^{c4}, and R^{d4}, is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, and C_{1-6} haloalkyl. In some embodiments, each R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a4}, R^{b4}, R^{c4}, and R^{d4}, is independently selected from the group consisting of H and C_{1-6} alkyl. In some embodiments, each R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a4}, R^{b4}, R^{c4}, and R^{d4}, is

independently selected from the group consisting of H and C_{1-3} alkyl. In some embodiments, each R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a4}, R^{b4}, R^{c4}, and R^{d4}, is hydrogen.

[0082] In some embodiments, the compound is of the Formula (IIa):



Formula (IIa),

wherein

R^{21} has the meaning defined in Formula (I);

each R^{20a}, R^{20b}, and R^{20c} is independently selected from the group consisting of H, OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{1-4} heteroalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, -(C_{1-3} alkylene)-C_{3-10} cycloalkyl, -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl, amidinyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino, wherein:

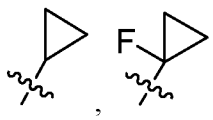
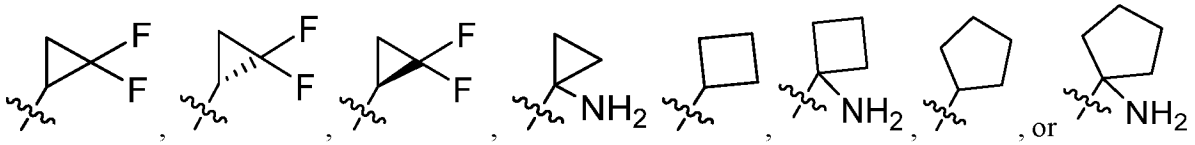
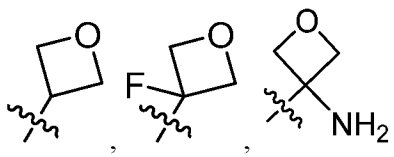
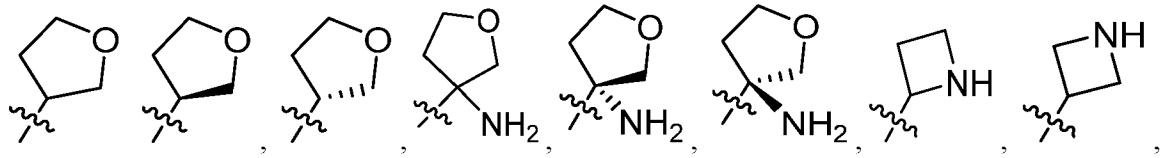
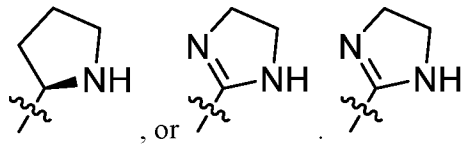
each of the cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, CN, SH, -CN, oxo, NO_2, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} aminoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, and amino,

or R^{20a} and R^{20b} are taken together to form a =NH or =N(C_{1-4} alkyl),

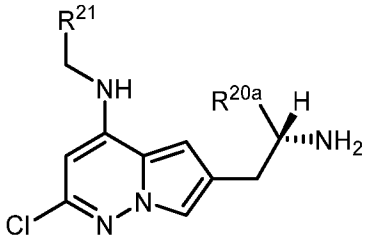
or a pharmaceutically acceptable salt thereof.

[0083] In some embodiments of the compound of the Formula (IIa) or a pharmaceutically acceptable salt thereof, each R^{20a}, R^{20b}, and R^{20c} is independently selected from the group consisting of H, OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4}

$_4$ alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino.

[0084] In some embodiments, R^{20a} is methyl. In some embodiments, R^{20a} is ethyl. In some embodiments, R^{20a} is CH_2OH. In some embodiments, R^{20a} is CH_2CH_2OH. In some embodiments, R^{20a} is CH_2CH_2F. In some embodiments, R^{20a} is CH_2CHF_2. In some embodiments, R^{20a} is $CH_2CH(CH_3)_2$. In some embodiments, R^{20c} is NH_2. In some embodiments, R^{20b} is hydrogen. In some embodiments, R^{20a} and R^{20b} are taken together to form a =NH or =N(C_{1-4} alkyl). In some embodiments, R^{20a} is 4-6 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl. In some embodiments, the C_{3-10} cycloalkyl is  ,  , or . In some embodiments, the C_{3-10} cycloalkyl is a 3-5 membered ring, which is optionally substituted. In some embodiments, the 4-10 membered heterocycloalkyl is  ,  , or  . In some embodiments, the 4-10 membered heterocycloalkyl is a 4-5 membered ring, which is optionally substituted. In some embodiments, R^{20a} is C_{1-4} heteroalkyl.

[0085] In some embodiments, the compound is of the Formula (IIb):



Formula (IIb),

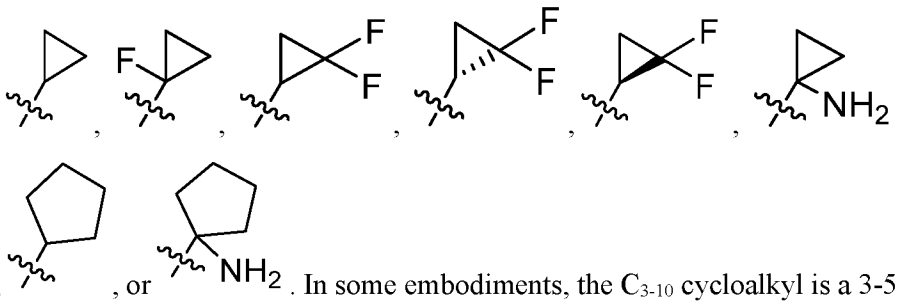
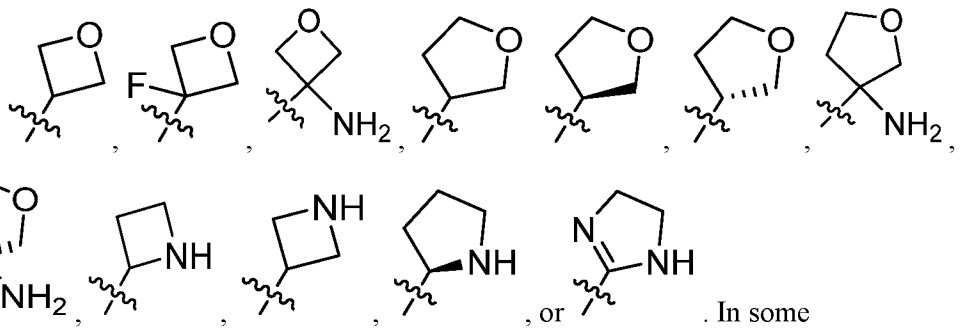
wherein

R^{21} has the meaning defined in Formula (I);

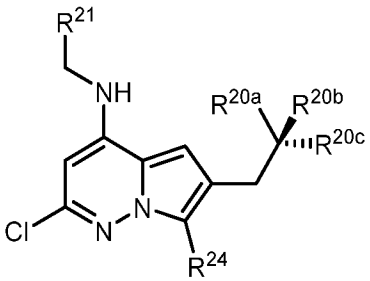
R^{20a} is selected from the group consisting of H, OH, SH, CN, NO_2, halo, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{1-4} heteroalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, -(C_{1-3} alkylene)-C_{3-10} cycloalkyl, -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl, amidinyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino, wherein each of the cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, CN, SH, -CN, oxo, NO_2, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} aminoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, and amino,
or a pharmaceutically acceptable salt thereof.

[0086] In some embodiments of the compound of the Formula (IIb) or a pharmaceutically acceptable salt thereof: R^{20a} is selected from the group consisting of OH, SH, CN, NO_2, halo, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino.

[0087] In some embodiments, R^{20a} is methyl. In some embodiments, R^{20a} is ethyl. In some embodiments, R^{20a} is CH_2OH. In some embodiments, R^{20a} is CH_2CH_2OH. In some embodiments, R^{20a} is CH_2CH_2F. In some embodiments, R^{20a} is CH_2CHF_2. In some embodiments, R^{20a} is $CH_2CH(CH_3)_2$. In some embodiments, R^{20a} is 4-6 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl. In some embodiments,

the C_{3-10} cycloalkyl is  . In some embodiments, the C_{3-10} cycloalkyl is a 3-5 membered ring, which is optionally substituted. In some embodiments, the 4-10 membered heterocycloalkyl is  . In some embodiments, the 4-10 membered heterocycloalkyl is a 4-5 membered ring, which is optionally substituted. In some embodiments, R^{20a} is C_{1-4} heteroalkyl. In some embodiments, R^{20a} is C_{1-4} alkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} heteroalkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} alkyl.

[0088] In some embodiments, the compound is of the Formula (IIIa):



Formula (IIIa),

wherein

R^{21} and R^{24} each has the meaning defined in Formula (I);

each R^{20a}, R^{20b}, and R^{20c} is independently selected from the group consisting of H, OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{1-4} heteroalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, -(C_{1-3} alkylene)-C_{3-10} cycloalkyl, -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl, amidinyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-}

$_4$ alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino, wherein:

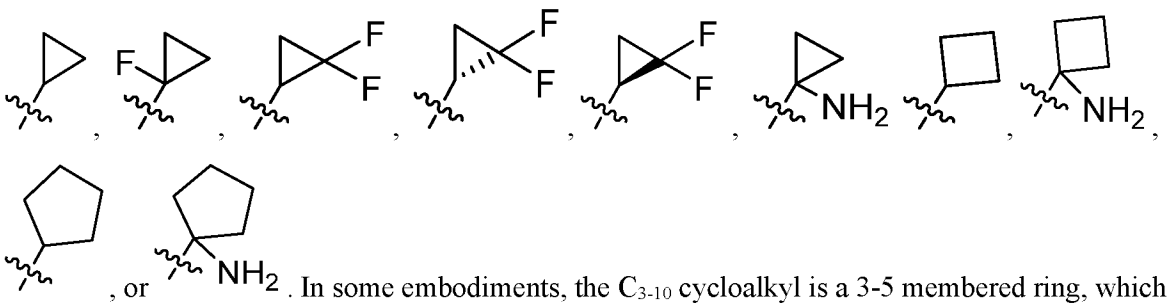
each of the cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, CN, SH, -CN, oxo, NO_2, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} aminoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, and amino,

or R^{20a} and R^{20b} are taken together to form a =NH or =N(C_{1-4} alkyl),

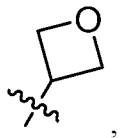
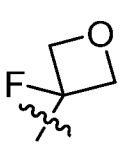
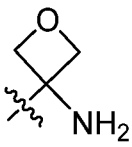
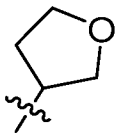
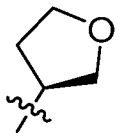
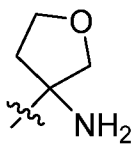
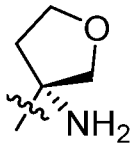
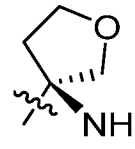
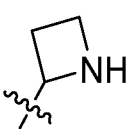
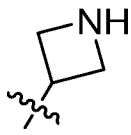
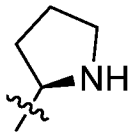
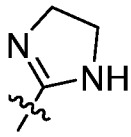
or a pharmaceutically acceptable salt thereof.

[0089] In some embodiments of the compound of the Formula (IIIa) or a pharmaceutically acceptable salt thereof, each R^{20a}, R^{20b}, and R^{20c} is independently selected from the group consisting of H, OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino.

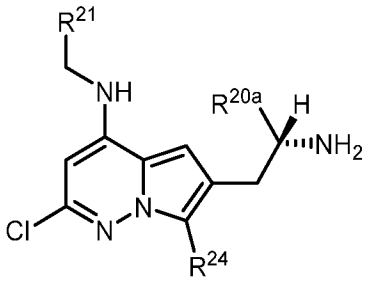
[0090] In some embodiments, R^{20a} is methyl. In some embodiments, R^{20a} is ethyl. In some embodiments, R^{20a} is CH_2OH. In some embodiments, R^{20a} is CH_2CH_2OH. In some embodiments, R^{20a} is CH_2CH_2F. In some embodiments, R^{20a} is CH_2CHF_2. In some embodiments, R^{20a} is $CH_2CH(CH_3)_2$. In some embodiments, R^{20c} is NH_2. In some embodiments, R^{20b} is hydrogen. In some embodiments, R^{20a} is 4-6 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl. In some embodiments, the C_{3-10} cycloalkyl is



. In some embodiments, the C_{3-10} cycloalkyl is a 3-5 membered ring, which is

optionally substituted. In some embodiments, the 4-10 membered heterocycloalkyl is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, the 4-10 membered heterocycloalkyl is a 4-5 membered ring, which is optionally substituted. In some embodiments, R^{20a} is C_{1-4} heteroalkyl. In some embodiments, R^{20a} is C_{1-4} alkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} heteroalkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} alkyl.

[0091] In some embodiments, the compound is of the Formula (IIIb):



Formula (IIIb),

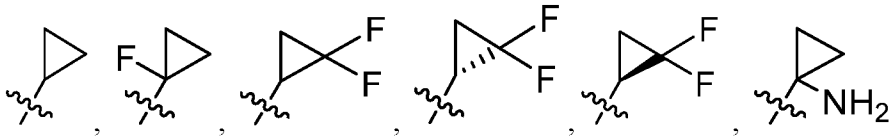
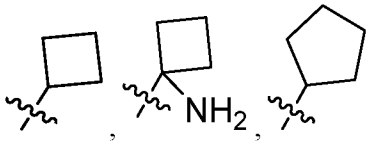
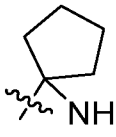
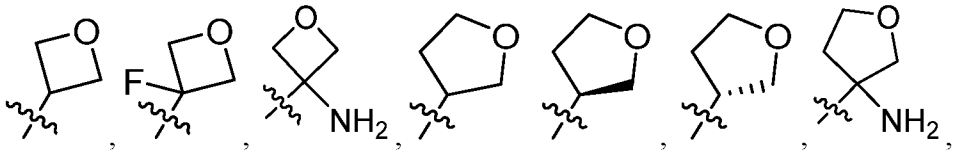
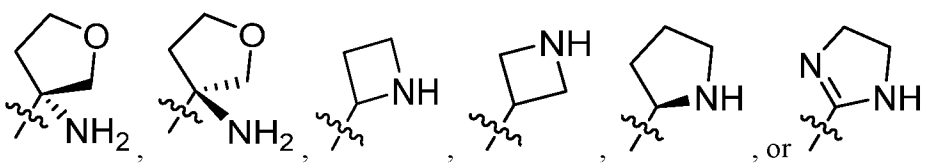
wherein

R^{21} and R^{24} each has the meaning defined in Formula (I);

R^{20a} is selected from the group consisting of H, OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{1-4} heteroalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, -(C_{1-3} alkylene)-C_{3-10} cycloalkyl, -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl, amidinyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino, wherein each of the cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, CN, SH, -CN, oxo, NO_2, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} aminoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, and amino,

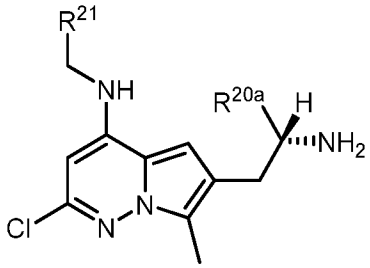
or a pharmaceutically acceptable salt thereof.

[0092] In some embodiments of the compound of the Formula (IIIb) or a pharmaceutically acceptable salt thereof, R^{20a} is selected from the group consisting of OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino.

[0093] In some embodiments, R^{20a} is methyl. In some embodiments, R^{20a} is ethyl. In some embodiments, R^{20a} is CH_2OH. In some embodiments, R^{20a} is CH_2CH_2OH. In some embodiments, R^{20a} is CH_2CH_2F. In some embodiments, R^{20a} is CH_2CHF_2. In some embodiments, R^{20a} is $CH_2CH(CH_3)_2$. In some embodiments, R^{20a} is 4-6 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl. In some embodiments, the C_{3-10} cycloalkyl is  ,  , or  . In some embodiments, the C_{3-10} cycloalkyl is a 3-5 membered ring, which is optionally substituted. In some embodiments, the 4-10 membered heterocycloalkyl is  ,  , or . In some embodiments, the 4-10 membered heterocycloalkyl is a 4-5 membered ring, which is optionally substituted. In some embodiments, R^{20a} is C_{1-4} heteroalkyl. In some embodiments, R^{20a} is C_{1-4} alkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} heteroalkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} alkyl.

[0094] In some embodiments, R^{24} is C_{1-6} alkyl. In some embodiments, R^{24} is methyl. In some embodiments, R^{24} is halo. In some embodiments, R^{24} is fluoro, bromo, or chloro. In some embodiments, R^{24} is hydrogen. In some embodiments, R^{24} is CN. In some embodiments, R^{24} is C_{3-10} cycloalkyl.

[0095] In some embodiments, the compound is of the Formula (IIIc):



Formula (IIIc),

wherein

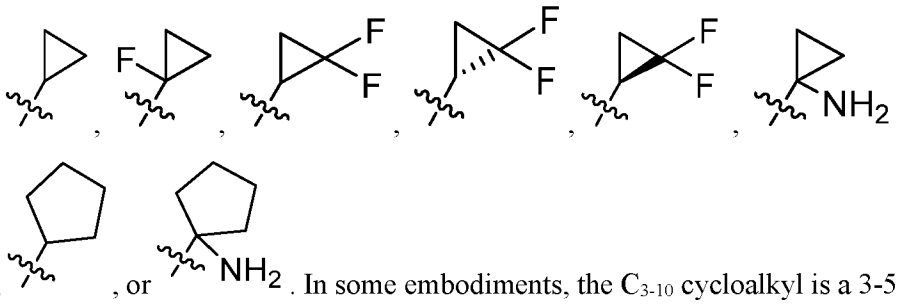
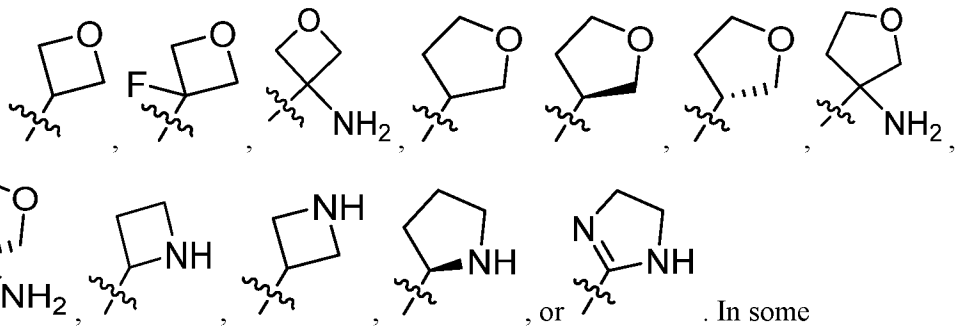
R^{21} has the meaning defined in Formula (I);

R^{20a} is selected from the group consisting of H, OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{1-4} heteroalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, -(C_{1-3} alkylene)-C_{3-10} cycloalkyl, -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl, amidinyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino, wherein each of the cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, CN, SH, -CN, oxo, NO_2, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} aminoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, and amino,

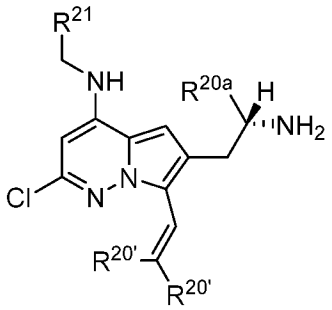
or a pharmaceutically acceptable salt thereof.

[0096] In some embodiments of the compound of the Formula (IIIc) or a pharmaceutically acceptable salt thereof, R^{20a} is selected from the group consisting of OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl,

aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino.

[0097] In some embodiments, R^{20a} is methyl. In some embodiments, R^{20a} is ethyl. In some embodiments, R^{20a} is CH_2OH. In some embodiments, R^{20a} is CH_2CH_2OH. In some embodiments, R^{20a} is CH_2CH_2F. In some embodiments, R^{20a} is CH_2CHF_2. In some embodiments, R^{20a} is $CH_2CH(CH_3)_2$. In some embodiments, R^{20a} is 4-6 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl. In some embodiments, the C_{3-10} cycloalkyl is  . In some embodiments, the C_{3-10} cycloalkyl is a 3-5 membered ring, which is optionally substituted. In some embodiments, the 4-10 membered heterocycloalkyl is  . In some embodiments, the 4-10 membered heterocycloalkyl is a 4-5 membered ring, which is optionally substituted. In some embodiments, R^{20a} is C_{1-4} heteroalkyl. In some embodiments, R^{20a} is C_{1-4} alkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} heteroalkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} alkyl.

[0098] In some embodiments, the compound is of the Formula (IIId):



Formula (IIId),

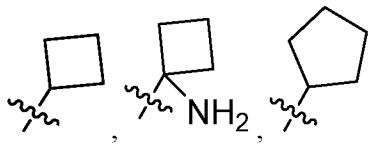
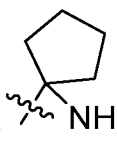
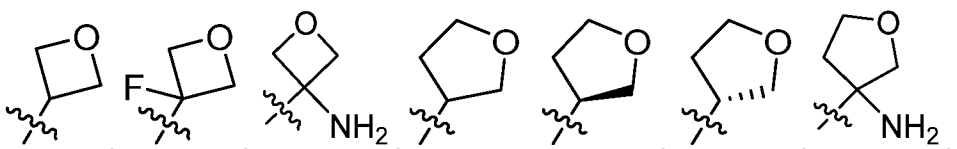
wherein

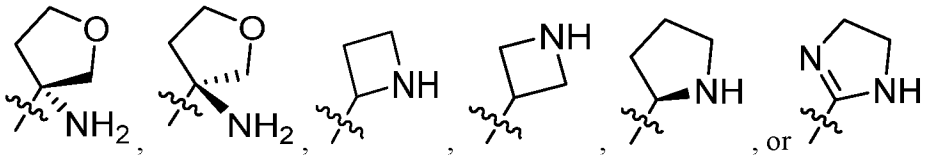
R^{21} has the meaning defined in Formula (I);

R^{20a} is selected from the group consisting of H, OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{1-4} heteroalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, -(C_{1-3} alkylene)-C_{3-10} cycloalkyl, -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl, amidinyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino, wherein each of the cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, CN, SH, -CN, oxo, NO_2, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} aminoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, and amino,

wherein each of $R^{20'}$ is independently H or R^{20} as disclosed herein,

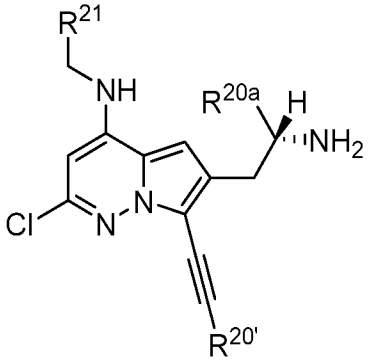
or a pharmaceutically acceptable salt thereof.

[0099] In some embodiments, R^{20a} is methyl. In some embodiments, R^{20a} is ethyl. In some embodiments, R^{20a} is CH_2OH. In some embodiments, R^{20a} is CH_2CH_2OH. In some embodiments, R^{20a} is CH_2CH_2F. In some embodiments, R^{20a} is CH_2CHF_2. In some embodiments, R^{20a} is $CH_2CH(CH_3)_2$. In some embodiments, R^{20a} is 4-6 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl. In some embodiments, the C_{3-10} cycloalkyl is  ,  , or  . In some embodiments, the C_{3-10} cycloalkyl is a 3-5 membered ring, which is optionally substituted. In some embodiments, the 4-10 membered heterocycloalkyl is  ,



. In some embodiments, the 4-10 membered heterocycloalkyl is a 4-5 membered ring, which is optionally substituted. In some embodiments, R^{20a} is C_{1-4} heteroalkyl. In some embodiments, R^{20a} is C_{1-4} alkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} heteroalkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} alkyl.

[00100] In some embodiments, the compound is of the Formula (IIIe):



Formula (IIIe),

wherein

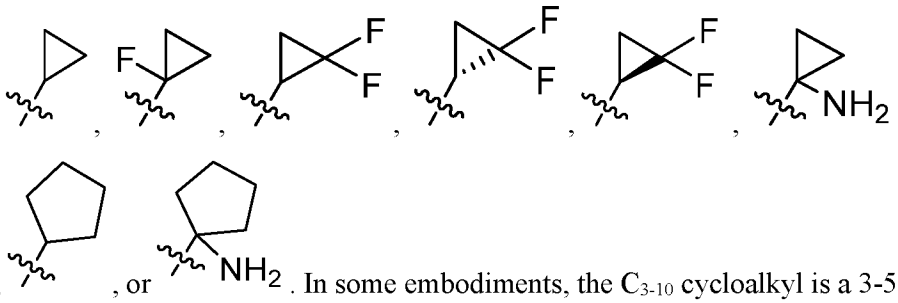
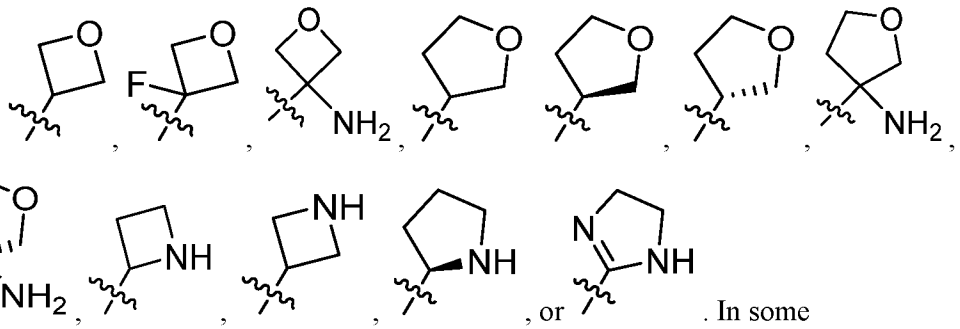
R^{21} has the meaning defined in Formula (I);

R^{20a} is selected from the group consisting of H, OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{1-4} heteroalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, -(C_{1-3} alkylene)-C_{3-10} cycloalkyl, -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl, amidinyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino, wherein each of the cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, CN, SH, -CN, oxo, NO_2, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} aminoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, and amino,

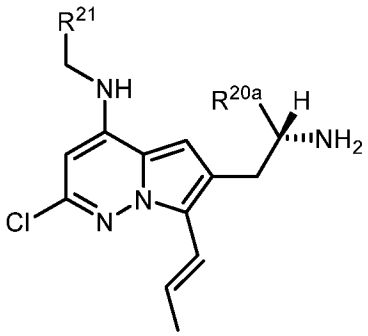
wherein $R^{20'}$ is H or R^{20} as disclosed herein,

or a pharmaceutically acceptable salt thereof.

[00101] In some embodiments, R^{20a} is methyl. In some embodiments, R^{20a} is ethyl. In some embodiments, R^{20a} is CH_2OH. In some embodiments, R^{20a} is CH_2CH_2OH. In some embodiments, R^{20a}

is CH_2CH_2F. In some embodiments, R^{20a} is CH_2CHF_2. In some embodiments, R^{20a} is $CH_2CH(CH_3)_2$. In some embodiments, R^{20a} is 4-6 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl. In some embodiments, the C_{3-10} cycloalkyl is  , or . In some embodiments, the C_{3-10} cycloalkyl is a 3-5 membered ring, which is optionally substituted. In some embodiments, the 4-10 membered heterocycloalkyl is  , or . In some embodiments, the 4-10 membered heterocycloalkyl is a 4-5 membered ring, which is optionally substituted. In some embodiments, R^{20a} is C_{1-4} heteroalkyl. In some embodiments, R^{20a} is C_{1-4} alkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} heteroalkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} alkyl.

[00102] In some embodiments, the compound is of the Formula (IIIf):



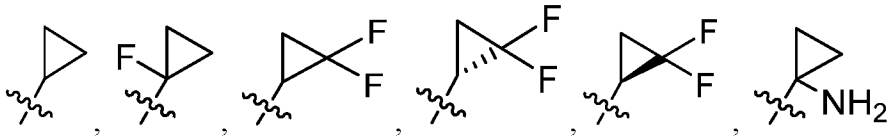
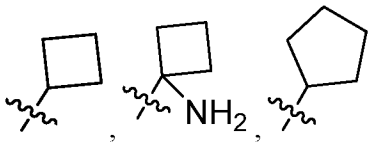
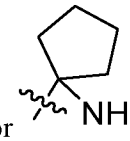
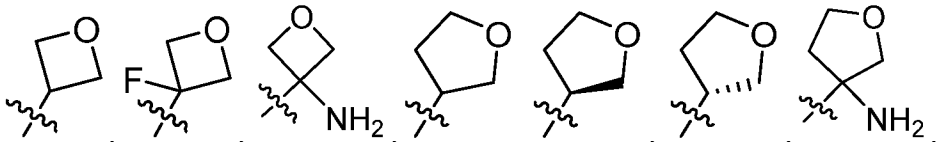
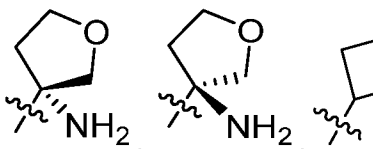
Formula (IIIf),

wherein

R^{21} has the meaning defined in Formula (I);

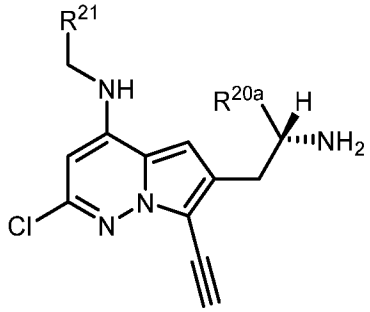
R^{20a} is selected from the group consisting of H, OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-

(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{1-4} heteroalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, -(C_{1-3} alkylene)-C_{3-10} cycloalkyl, -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl, amidinyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino, wherein each of the cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, CN, SH, -CN, oxo, NO_2, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} aminoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, and amino, or a pharmaceutically acceptable salt thereof.

[00103] In some embodiments, R^{20a} is methyl. In some embodiments, R^{20a} is ethyl. In some embodiments, R^{20a} is CH_2OH. In some embodiments, R^{20a} is CH_2CH_2OH. In some embodiments, R^{20a} is CH_2CH_2F. In some embodiments, R^{20a} is CH_2CHF_2. In some embodiments, R^{20a} is $CH_2CH(CH_3)_2$. In some embodiments, R^{20a} is 4-6 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl. In some embodiments, the C_{3-10} cycloalkyl is  ,  , or  . In some embodiments, the C_{3-10} cycloalkyl is a 3-5 membered ring, which is optionally substituted. In some embodiments, the 4-10 membered heterocycloalkyl is  ,  , or . In some embodiments, the 4-10 membered heterocycloalkyl is a 4-5 membered ring, which is optionally substituted. In some embodiments, R^{20a} is C_{1-4} heteroalkyl. In some embodiments, R^{20a} is C_{1-4} alkyl. In

some embodiments, R^{20a} is optionally substituted C_{1-4} heteroalkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} alkyl.

[00104] In some embodiments, the compound is of the Formula (IIIg):



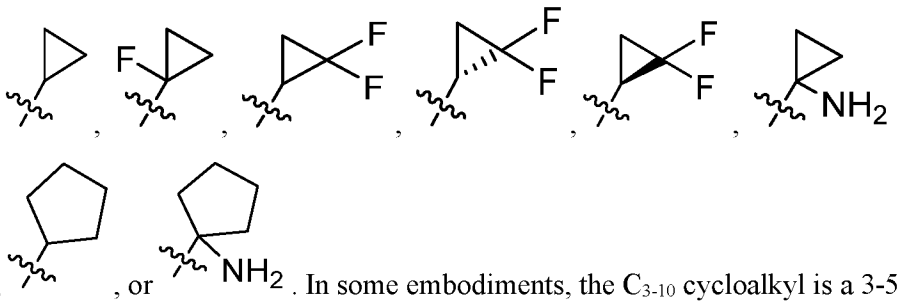
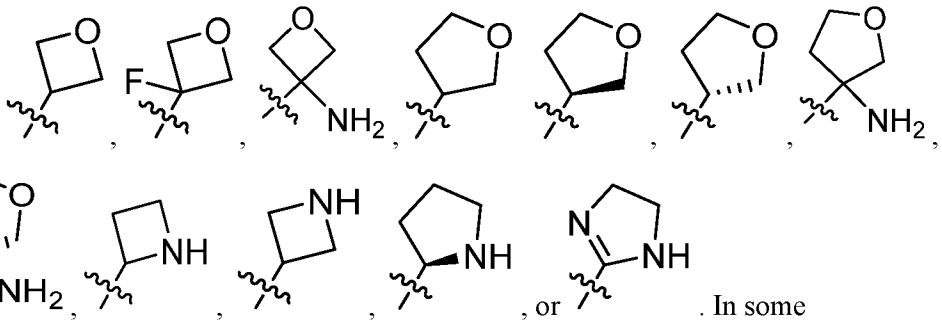
Formula (IIIg),

wherein

R^{21} has the meaning defined in Formula (I);

R^{20a} is selected from the group consisting of H, OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{1-4} heteroalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, -(C_{1-3} alkylene)-C_{3-10} cycloalkyl, -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl, amidinyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino, wherein each of the cycloalkyl and heterocycloalkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, CN, SH, -CN, oxo, NO_2, OH, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} aminoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, and amino,
or a pharmaceutically acceptable salt thereof.

[00105] In some embodiments, R^{20a} is methyl. In some embodiments, R^{20a} is ethyl. In some embodiments, R^{20a} is CH_2OH. In some embodiments, R^{20a} is CH_2CH_2OH. In some embodiments, R^{20a} is CH_2CH_2F. In some embodiments, R^{20a} is CH_2CHF_2. In some embodiments, R^{20a} is $CH_2CH(CH_3)_2$. In some embodiments, R^{20a} is 4-6 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} alkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{20a} is -(C_{1-3} heteroalkylene)-4-10 membered heterocycloalkyl. In some embodiments,

the C_{3-10} cycloalkyl is  . In some embodiments, the C_{3-10} cycloalkyl is a 3-5 membered ring, which is optionally substituted. In some embodiments, the 4-10 membered heterocycloalkyl is  . In some embodiments, the 4-10 membered heterocycloalkyl is a 4-5 membered ring, which is optionally substituted. In some embodiments, R^{20a} is C_{1-4} heteroalkyl. In some embodiments, R^{20a} is C_{1-4} alkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} heteroalkyl. In some embodiments, R^{20a} is optionally substituted C_{1-4} alkyl.

[00106] In some embodiments, the compound is selected from Table 1.

[00107] In some embodiments, a SMSM described herein, possesses one or more stereocenters and each stereocenter exists independently in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. In certain embodiments, compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof (See, for example, Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley and Sons, Inc., 1981.) In one aspect, stereoisomers are obtained by stereoselective synthesis.

[00108] In some embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in

some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, the design of a prodrug increases the effective water solubility. An example, without limitation, of a prodrug is a compound described herein, which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility, but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound.

[00109] In one aspect, prodrugs are designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacokinetic, pharmacodynamic processes and drug metabolism *in vivo*, once a pharmaceutically active compound is known, the design of prodrugs of the compound is possible. (see, for example, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392; Silverman (1992), The Organic Chemistry of Drug Design and Drug Action, Academic Press, Inc., San Diego, pages 352-401, Rooseboom *et al.*, *Pharmacological Reviews*, 56:53-102, 2004; Aesop Cho, "Recent Advances in Oral Prodrug Discovery", *Annual Reports in Medicinal Chemistry*, Vol. 41, 395-407, 2006; T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series).

[00110] In some cases, some of the herein-described compounds may be a prodrug for another derivative or active compound.

[00111] In some embodiments, sites on the aromatic ring portion of compounds described herein are susceptible to various metabolic reactions Therefore incorporation of appropriate substituents on the aromatic ring structures will reduce, minimize or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, or an alkyl group.

[00112] In another embodiment, the compounds described herein are labeled isotopically (*e.g.* with a radioisotope) or by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00113] Compounds described herein include isotopically labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present

compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine and chlorine, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, and ^{36}Cl. In one aspect, isotopically labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. In one aspect, substitution with isotopes such as deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements.

[00114] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

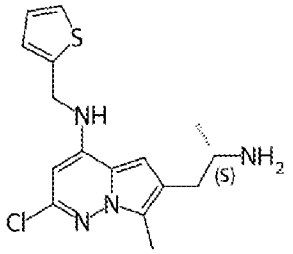
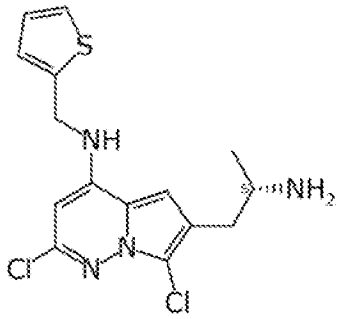
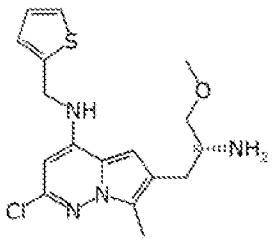
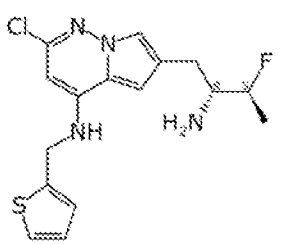
[00115] Compounds described herein may be formed as, and/or used as, pharmaceutically acceptable salts. The type of pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic acid, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, metaphosphoric acid, and the like; or with an organic acid, such as, for example, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, trifluoroacetic acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like; (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, *e.g.*, an alkali metal ion (*e.g.* lithium, sodium, potassium), an alkaline earth ion (*e.g.* magnesium, or calcium), or an aluminum ion. In some cases, compounds described herein may coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein may form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

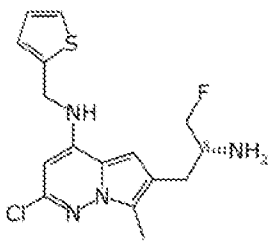
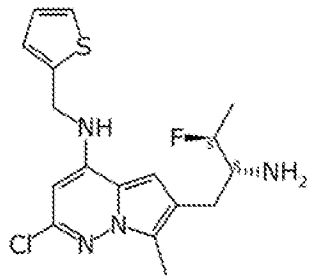
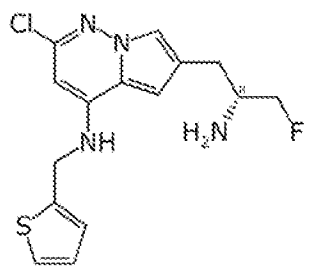
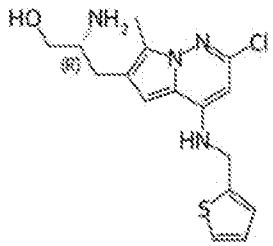
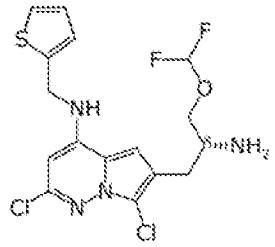
[00116] In some embodiments, the compounds provided herein can exist in unsolvated as well as solvated forms.

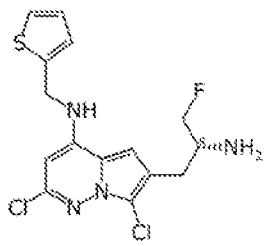
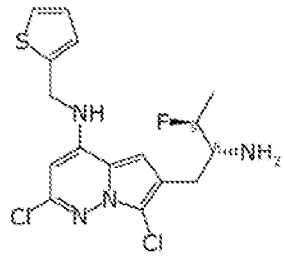
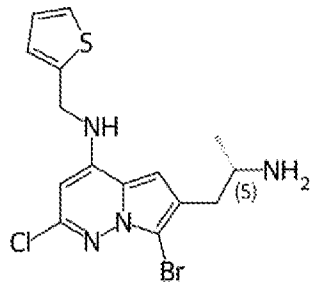
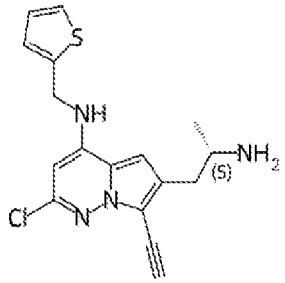
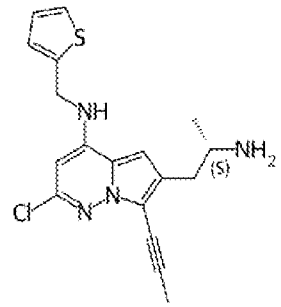
[00117] In some embodiments, a SMSM has a molecular weight of at most about 2000 Daltons, 1500 Daltons, 1000 Daltons or 900 Daltons. In some embodiments, a SMSM has a molecular weight of at least 100 Daltons, 200 Daltons, 300 Daltons, 400 Daltons or 500 Daltons. In some embodiments, a

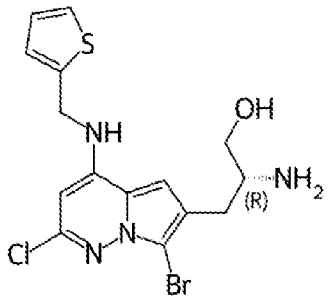
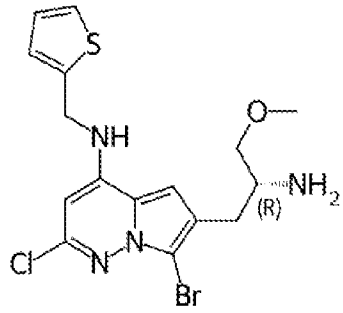
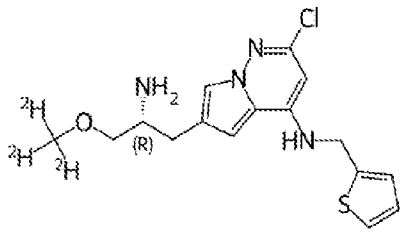
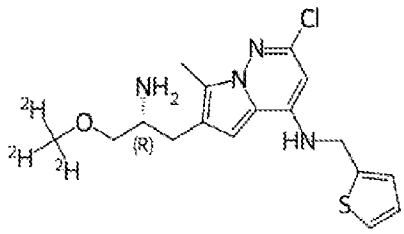
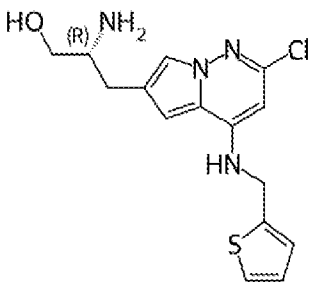
SMSM does not comprise a phosphodiester linkage. In some embodiments, a SMSM is a compound with a structure set forth in Table 1 below.

Table 1: Exemplary SMSM compounds

Compound	Structure	Molecular Weight (g/mol)
1		334.876
2		355.294
3		364.902
4		352.866

Compound	Structure	Molecular Weight (g/mol)
5		352.866
6		366.893
7		338.839
8		350.875
9		421.3

Compound	Structure	Molecular Weight (g/mol)
10		373.284
11		387.311
12		
13		
14		

Compound	Structure	Molecular Weight (g/mol)
15		
16		
17		
18		
19		

Pharmaceutical Compositions

[00118] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins, 1999), herein incorporated by reference for such disclosure.

[00119] A pharmaceutical composition can be a mixture of a SMSM described herein with one or more other chemical components (*i.e.*, pharmaceutically acceptable ingredients), such as carriers, excipients, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti–foaming agents, antioxidants, preservatives, or one or more combination thereof. The pharmaceutical composition facilitates administration of the compound to an organism.

[00120] The compositions described herein can be administered to the subject in a variety of ways, including parenterally, intravenously, intradermally, intramuscularly, colonically, rectally, or intraperitoneally. In some embodiments, the small molecule splicing modulator, or a pharmaceutically acceptable salt thereof is administered by intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection of the subject. In some embodiments, the pharmaceutical compositions can be administered parenterally, intravenously, intramuscularly or orally. The oral agents comprising a small molecule splicing modulator can be in any suitable form for oral administration, such as liquid, tablets, capsules, or the like. The oral formulations can be further coated or treated to prevent or reduce dissolution in stomach. The compositions of the present disclosure can be administered to a subject using any suitable methods known in the art. Suitable formulations for use in the present disclosure and methods of delivery are generally well known in the art. For example, the small molecule splicing modulators described herein can be formulated as pharmaceutical compositions with a pharmaceutically acceptable diluent, carrier, or excipient. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions including pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, such as, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.

[00121] In some embodiments, the pharmaceutical formulation is in the form of a tablet. In other embodiments, pharmaceutical formulations containing a SMSM described herein are in the form of a

capsule. In one aspect, liquid formulation dosage forms for oral administration are in the form of aqueous suspensions or solutions selected from the group including, but not limited to, aqueous oral dispersions, emulsions, solutions, elixirs, gels, and syrups.

[00122] For administration by inhalation, a SMSM described herein can be formulated for use as an aerosol, a mist, or a powder. For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in a conventional manner. In some embodiments, a SMSM described herein can be prepared as transdermal dosage forms. In some embodiments, a SMSM described herein can be formulated into a pharmaceutical composition suitable for intramuscular, subcutaneous, or intravenous injection. In some embodiments, a SMSM described herein can be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams, or ointments. In some embodiments, a SMSM described herein can be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas.

[00123] In some embodiments, disclosed herein is a pharmaceutical composition comprising a compound of the disclosure or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

Splicing Modulation of Target Gene Products

[00124] The present disclosure contemplates use of small molecules with favorable drug properties that modulate the activity of splicing of a target RNA. Provided herein are small molecule splicing modulators (SMSMs) that modulate splicing of a polynucleotide. In some embodiments, the SMSMs bind and modulate target RNA. In some embodiments, provided herein is a library of SMSMs that bind and modulate one or more target RNAs. In some embodiments, the target RNA is mRNA. In some embodiments, the target RNA is a noncoding RNA. In some embodiments, the target RNA is a pre-mRNA. In some embodiments, the target RNA is hnRNA. In some embodiments, the small molecules modulate splicing of the target RNA. In some embodiments, a small molecule provided herein modulates splicing at a sequence of the target RNA. In some embodiments, a small molecule provided herein modulates splicing at a cryptic splice site sequence of the target RNA. In some embodiments, a small molecule provided herein modulates splicing at an alternative splice site sequence of the target RNA. In some embodiments, a small molecule provided herein modulates splicing at a native splice site sequence of the target RNA. In some embodiments, a small molecule provided herein binds to a target RNA. In some embodiments, a small molecule provided herein binds to a splicing complex or a component thereof. In some embodiments, a small molecule provided herein binds to a target RNA and a splicing complex or a component thereof. In some embodiments, a small molecule provided herein modulates binding affinity of a splicing complex component to a target RNA such as a pre-mRNA. In some embodiments, a small molecule provided herein modulates

binding affinity of a splicing complex component to a target RNA such as a pre-mRNA at a splice site sequence. In some embodiments, a small molecule provided herein modulates binding affinity of a splicing complex component to a target RNA such as a pre-mRNA upstream of a splice site sequence or downstream of a splice site sequence.

[00125] Described herein are compounds modifying splicing of gene products, such as Ataxin 3 pre-mRNA for use in the treatment, prevention, and/or delay of progression of diseases or conditions.

[00126] In some embodiments, described herein, is a method of treating, preventing, delaying of progress, or ameliorating symptoms of a disease or a condition associated with Ataxin 3 (ATXN3) expression level or activity level in a subject in need thereof, comprising administering a therapeutically effective amount of a small molecule splicing modulator (SMSM), wherein the SMSM binds to a pre-mRNA encoded by ATXN3 and modulates splicing of the ATXN3 pre-mRNA in a cell of the subject to produce a spliced product of the ATXN3 pre-mRNA.

[00127] In some embodiments, described herein is a method of treating, preventing, delaying of progress, or ameliorating symptoms of a disease or a condition associated with Ataxin 3 (ATXN3) expression level or activity level in a subject in need thereof, comprising administering a therapeutically effective amount of a compound or salt of Formula (I). In some embodiments, described herein is a method of modulating splicing of a Ataxin3 (ATXN3) pre-mRNA, comprising contacting a compound or salt of Formula (I) to the ATXN3 pre-mRNA with a splice site sequence or cells comprising the ATXN3 pre-mRNA, wherein the compound binds to the ATXN3 pre-mRNA and modulates splicing of the ATXN3 pre-mRNA in a cell of a subject to produce a spliced product of the ATXN3 pre-mRNA. In some embodiments, described herein is use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition or disease associated with Ataxin 3 (ATXN3) expression level or activity level.

[00128] In some embodiments, the spliced product of the ATXN3 pre-mRNA undergoes non-sense mediated decay (NMD) and/or nuclear retention. In some embodiments, the nonsense-mediated decay (NMD) and/or nuclear retention of the spliced product of the ATXN3 pre-mRNA is promoted. In some embodiments, the nonsense-mediated decay (NMD) and/or nuclear retention of the spliced product of the ATXN3 pre-mRNA is increased compared to a spliced product of the ATXN3 pre-mRNA produced in the absence of the SMSM.

[00129] In some embodiments, described herein is a method of modulating splicing of a Ataxin3 (ATXN3) pre-mRNA, comprising contacting a small molecule splicing modulator (SMSM) to the ATXN3 pre-mRNA with a splice site sequence or cells comprising the ATXN3 pre-mRNA, wherein the SMSM binds to the ATXN3 pre-mRNA and modulates splicing of the ATXN3 pre-mRNA in a cell of a subject to produce a spliced product of the ATXN3 pre-mRNA.

[00130] In some embodiments, described herein, is a method of modulating splicing of Ataxin 3 (ATXN3) pre-mRNA, comprising contacting a small molecule splicing modulator (SMSM) to the ATXN3 pre-mRNA with a splice site sequence or cells comprising the ATXN3 pre-mRNA, wherein

the SMSM binds to the ATXN3 pre-mRNA and modulates splicing of the ATXN3 pre-mRNA in a cell of a subject to produce a spliced product of the ATXN3 pre-mRNA, wherein the splice site sequence comprises UCCUAU/guaagauucugu.

[00131] In some embodiments, described herein, is a method of treating, preventing, delaying of progress, or ameliorating symptoms of a disease or condition associated with Ataxin 3 (ATXN3) expression level or activity level in a subject in need thereof, comprising administering a therapeutically effective amount of a small molecule splicing modulator (SMSM) to the subject, wherein the SMSM binds to a ATXN3 pre-mRNA with a splice site sequence and modulates splicing of the ATXN3 pre-mRNA in a cell of the subject, wherein a spliced product of the ATXN3 pre-mRNA undergoes nonsense-mediated decay (NMD), and wherein the splice site sequence comprises UCCUAU/guaagauucugu.

[00132] In some embodiments, the modulating splicing comprises modulating alternative splicing. In some embodiments, the modulating splicing comprises promoting exon skipping. In some embodiments, the modulating splicing comprises promoting exon inclusion. In some embodiments, the modulating splicing comprises modulating nonsense-mediated mRNA decay (NMD). In some embodiments, the modulating NMD comprises promoting NMD. In some embodiments, the modulating splicing comprises modulating nuclear retention of the spliced product of the pre-mRNA. In some embodiments, the modulating intron retention comprises promoting nuclear retention of the spliced product of the pre-mRNA.

[00133] In some embodiments, the splice site sequence is a native splice site sequence. In some embodiments, the native splice site is a canonical splice site. In some embodiments, the native splice site is an alternative splice site. In some embodiments, the alternative splice site comprises a 5' splice site sequence. In some embodiments, the alternative splice site sequence comprises UCCUAU/guaagauucugu. In some embodiments, the SMSM induces splicing at the alternative splice site. In some embodiments, the splicing at the alternative splice site results in a frameshift in a downstream exon in the spliced product. In some embodiments, the downstream exon comprises an in-frame stop codon that is not in frame in the absence of splicing at the alternative splice site. In some embodiments, the in-frame stop codon in the downstream exon is at least 50 or at least 60 base pairs upstream of the 3' end of the downstream exon. In some embodiments, the in-frame stop codon in the downstream exon is at least 50 or at least 60 base pairs upstream of a final exon-exon junction.

[00134] In some embodiments, the splicing of the pre-mRNA at the alternative splice site promotes NMD of the spliced product of the ATXN3 pre-mRNA. In some embodiments, the spliced product comprises an alternative exon. In some embodiments, the SMSM promotes inclusion of the alternative exon in the spliced product. In some embodiments, the alternative exon comprises a poison exon. In some embodiments, the SMSM promotes inclusion of the poison exon in the spliced product. In some embodiments, the poison exon comprises an in-frame stop codon. In some embodiments, the in-frame stop codon is a premature termination codon. In some embodiments, the in-frame stop codon is at

least 50 or 60 base pairs upstream of the 3' end of the poison exon. In some embodiments, the in-frame stop codon is less than 60 base pairs upstream of the 3' end of the poison exon and wherein the exon immediately downstream of the poison exon is not the last exon in the pre-mRNA. In some embodiments, the sum of (a) the number of base pairs in the exon immediately downstream of the poison exon and (b) the number of base pairs between the premature termination codon in the poison exon and the 3' end of the poison exon is at least 50 or at least 60.

[00135] In some embodiments, the cells comprise primary cells. In some embodiments, the cells comprise disease cells. In some embodiments, the SMSM modulates proliferation or survival of the cells. In some embodiments, the SMSM modulates the expression level of a protein encoded by the spliced product of the pre-mRNA in the cells.

Table 2. Exemplary targets for exon inclusion

Gene	ATXN3
Exon Coordinates	Chr14:92093746-92093831
Splicing Event Region	chr14:92093319-92096092
Strand	-
Target site	Exon 4
Exon length	86
SEQ ID NO:	1
5' ss sequence (-6~+12)	UCCUAU/guaagauucugu
5' ss-U1 duplex structure	-1U-C loop
Disease	Spinocerebellar Ataxia Type 3

Methods of Treatment

[00136] The compositions and methods described herein can be used for treating a human disease or disorder associated with aberrant splicing, such as aberrant pre-mRNA splicing. The compositions and methods described herein can be used for treating a human disease or disorder by modulating mRNA, such as pre-mRNA. In some embodiments, the compositions and methods described herein can be used for treating a human disease or disorder by modulating splicing of a nucleic acid even when that nucleic acid is not aberrantly spliced in the pathogenesis of the disease or disorder being treated.

[00137] In some embodiments, an effective amount in the context of the administration of a SMSM or a pharmaceutically acceptable salt thereof, or composition or medicament thereof refers to an amount of a SMSM or a pharmaceutically acceptable salt thereof to a patient which has a therapeutic effect and/or beneficial effect. In certain specific embodiments, an effective amount in the context of the administration of a SMSM or a pharmaceutically acceptable salt thereof, or composition or medicament thereof to a patient results in one, two or more of the following effects: (i) reduces or ameliorates the severity of a disease; (ii) delays onset of a disease; (iii) inhibits the progression of a disease; (iv) reduces hospitalization of a subject; (v) reduces hospitalization length for a subject; (vi) increases the survival of a subject; (vii) improves the quality of life of a subject; (viii) reduces the number of symptoms associated with a disease; (ix) reduces or ameliorates the severity of a symptom associated with a disease; (x) reduces the duration of a symptom associated with a disease associated; (xi) prevents the recurrence of a symptom associated with a disease; (xii) inhibits the development or onset of a symptom of a disease; and/or (xiii) inhibits of the progression of a symptom associated with a disease. In some embodiments, an effective amount of a SMSM or a pharmaceutically acceptable salt thereof is an amount effective to restore the amount of an RNA transcript of a gene to the amount of the RNA transcript detectable in healthy patients or cells from healthy patients. In other embodiments, an effective amount of a SMSM or a pharmaceutically acceptable salt thereof is an amount effective to restore the amount an RNA isoform and/or protein isoform of a gene to the amount of the RNA isoform and/or protein isoform detectable in healthy patients or cells from healthy patients.

[00138] In some embodiments, an effective amount of a SMSM or a pharmaceutically acceptable salt thereof is an amount effective to decrease the aberrant amount of an RNA transcript of a gene which associated with a disease. In some embodiments, an effective amount of a SMSM or a pharmaceutically acceptable salt thereof is an amount effective to decrease the amount of the aberrant expression of an isoform of a gene. In some embodiments, an effective amount of a SMSM or a pharmaceutically acceptable salt thereof is an amount effective to result in a substantial change in the amount of an RNA transcript (*e.g.*, an mRNA transcript), alternative splice variant, or isoform.

[00139] In some embodiments, an effective amount of a SMSM or a pharmaceutically acceptable salt thereof is an amount effective to increase the amount of an RNA transcript (*e.g.*, an mRNA transcript)

of a gene that is beneficial for the prevention and/or treatment of a disease. In some embodiments, an effective amount of a SMSM or a pharmaceutically acceptable salt thereof is an amount effective to increase the amount of an alternative splice variant of an RNA transcript of a gene that is beneficial for the prevention and/or treatment of a disease. In some embodiments, an effective amount of a SMSM or a pharmaceutically acceptable salt thereof is an amount effective to increase the amount of an isoform of a gene that is beneficial for the prevention and/or treatment of a disease.

[00140] In some embodiments, an effective amount of a SMSM or a pharmaceutically acceptable salt thereof is an amount effective to decrease the amount of an RNA transcript (*e.g.*, an mRNA transcript) which causes or is related to the symptoms of the condition or disease. In particular embodiments, the SMSM decreases the amount of an RNA transcript that causes or relates to the symptoms of the condition or disease by modulating one or more splicing elements of the RNA transcript. In some embodiments, the SMSM promotes skipping of one or more exons. In some embodiments, the SMSM promotes inclusion of one or more exons. In some embodiments, the SMSM promotes inclusion of one or more exons and/or introns that relate to nonsense-mediated mRNA decay (NMD). In some embodiments, the one or more exons harbor a premature termination codon. In particular embodiments, the premature stop codon is an in-frame codon that does not cause frameshift of the downstream exon(s). In some embodiments, inclusion of the one or more exons causes a reading frameshift in a downstream exon, for example, in the immediately downstream exon, introducing a premature termination codon.

[00141] A method of treating a disease or a condition in a subject in need thereof can comprise administering to the subject a therapeutically effective amount of a compound described herein or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure relates to a method for the treatment, prevention and/or delay of progression of a disease or a condition associated with a gene listed in Table 2.

[00142] Non-limiting examples of effective amounts of a SMSM or a pharmaceutically acceptable salt thereof are described herein. For example, the effective amount may be the amount required to prevent and/or treat a disease associated with the aberrant amount of an mRNA transcript of gene in a human subject. In general, the effective amount will be in a range of from about 0.001 mg/kg/day to about 500 mg/kg/day for a patient having a weight in a range of between about 1 kg to about 200 kg. The typical adult subject is expected to have a median weight in a range of between about 70 and about 100 kg.

[00143] In one embodiment, a SMSM described herein can be used in the preparation of medicaments for the treatment of diseases or conditions described herein. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, can involve administration of pharmaceutical compositions that include at least one SMSM described herein or a pharmaceutically acceptable salt, thereof, in a therapeutically effective amount to a subject.

[00144] In certain embodiments, a SMSM described herein can be administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or a condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or the condition. Amounts effective for this use depend on the severity and course of the disease or the condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation clinical trial. In prophylactic applications, compositions containing a SMSM described herein can be administered to a patient susceptible to or otherwise at risk of a particular disease, disorder, or condition.

Methods of Administering

[00145] The compositions described herein can be administered to the subject in a variety of ways, including parenterally, intravenously, intradermally, intramuscularly, colonically, rectally or intraperitoneally. In some embodiments, the small molecule splicing modulator (SMSM) or a pharmaceutically acceptable salt thereof is administered by intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection of the subject. In some embodiments, the pharmaceutical compositions can be administered parenterally, intravenously, intramuscularly or orally. The oral agents comprising a small molecule splicing modulator can be in any suitable form for oral administration, such as liquid, tablets, capsules, or the like. The compositions of the present disclosure can be administered to a subject using any suitable methods known in the art. Suitable formulations for use in the present disclosure and methods of delivery are generally well known in the art. For example, the small molecule splicing modulators described herein can be formulated as pharmaceutical compositions with a pharmaceutically acceptable diluent, carrier, or excipient.

Dosing and Schedules

[00146] The SMSMs utilized in the methods of the disclosure can be, *e.g.*, administered at dosages that may be varied depending upon the requirements of the subject, the severity of the condition being treated and/or imaged, and/or the SMSM being employed. For example, dosages can be empirically determined considering the type and stage of disease diagnosed in a particular subject and/or the type of imaging modality being used in conjunction with the SMSMs. The dose administered to a subject, in the context of the present disclosure should be sufficient to affect a beneficial diagnostic or therapeutic response in the subject. The size of the dose also can be determined by the existence, nature, and extent of any adverse side–effects that accompany the administration of a SMSM in a particular subject.

[00147] Within the scope of the present description, the effective amount of a SMSM or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament, the preparation of a pharmaceutical kit or in a method for preventing and/or treating a disease in a human subject in need thereof, is intended to include an amount in a range of from about 1 μg to about 50 grams.

[00148] The compositions of the present disclosure can be administered as frequently as necessary.

Subjects

[00149] The subjects that can be treated with the SMSMs and methods described herein can be any subject that produces mRNA that is subject to alternative splicing, *e.g.*, the subject may be a eukaryotic subject, such as a plant or an animal. In some embodiments, the subject is a mammal, *e.g.*, human. In some embodiments, the subject is a human. In some embodiments, the subject is a non–human animal. In some embodiments, the subject is a fetus, an embryo, or a child. In some embodiments, the subject is a non–human primate such as chimpanzee, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like.

[00150] In some embodiments, the subject is prenatal (*e.g.*, a fetus), a child (*e.g.*, a neonate, an infant, a toddler, a preadolescent), an adolescent, a pubescent, or an adult (*e.g.*, an early adult, a middle-aged adult, a senior citizen).

Methods of Making Compounds

[00151] Compounds described herein can be synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology can be employed. Compounds can be prepared using standard organic chemistry techniques such as those described in, for example, March's Advanced Organic Chemistry, 6th Edition, John Wiley and Sons, Inc. Alternative reaction conditions for the synthetic transformations described herein may be employed such as variation of solvent, reaction temperature, reaction time, as well as different chemical reagents and other reaction conditions. The starting materials can be available from commercial sources or can be readily prepared. By way of example only, provided are schemes for preparing the SMSMs described herein.

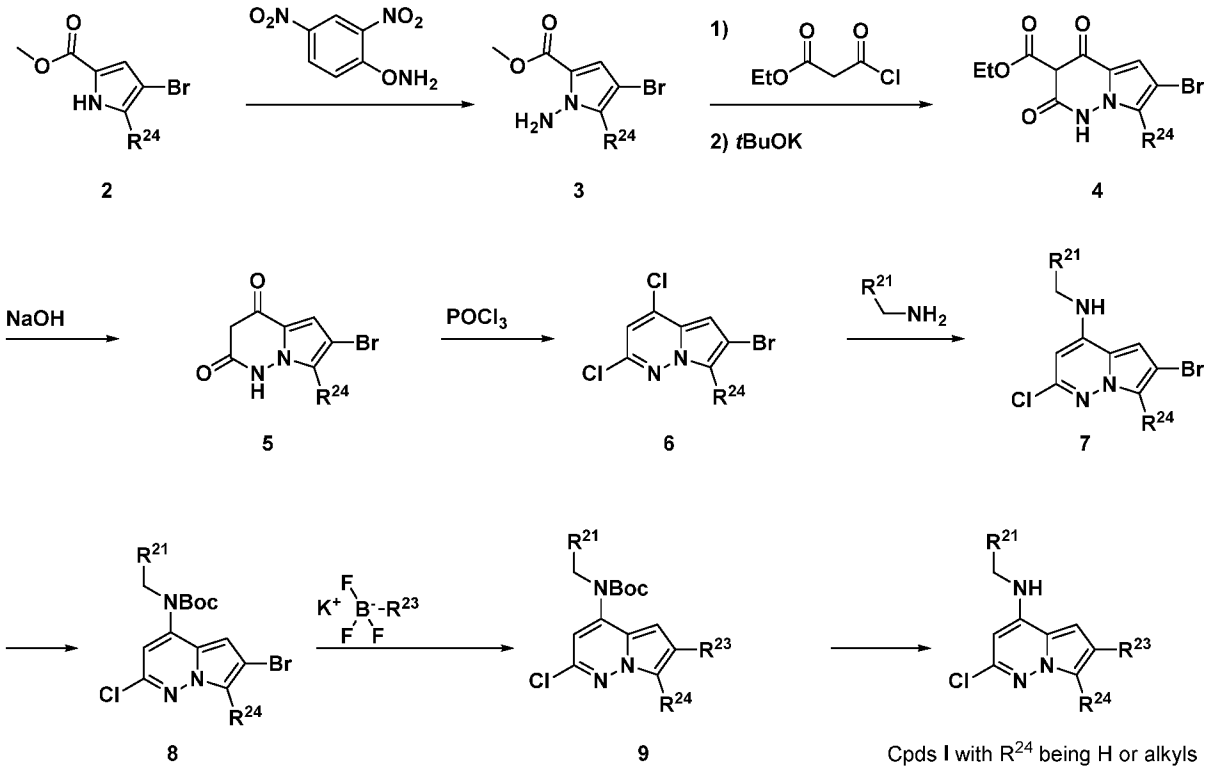
[00152] Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3 527–29074–5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0–19–509618–5; Larock, R. C. "Comprehensive

Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley–VCH, ISBN: 0–471–19031–4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0–471–60180–2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley–VCH, ISBN: 3–527–29871–1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0–471–93022–9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0–471–19095–0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley–Interscience, ISBN: 0–471–57456–2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3–527–29645–X, in 8 volumes; "Organic Reactions" (1942–2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

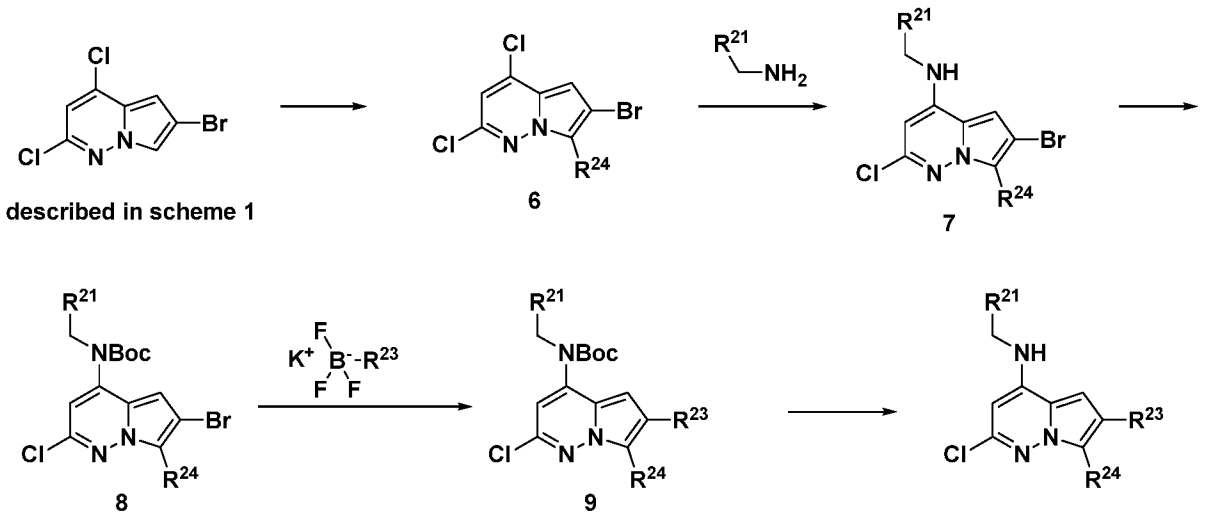
[00153] In the reactions described, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, in order to avoid their unwanted participation in reactions. A detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference for such disclosure).

[00154] SMSMs can be made using known techniques and further chemically modified, in some embodiments, to facilitate intranuclear transfer to, *e.g.*, a splicing complex component, a spliceosome or a pre-mRNA molecule. One of ordinary skill in the art will appreciate the standard medicinal chemistry approaches for chemical modifications for intranuclear transfer (*e.g.*, reducing charge, optimizing size, and/or modifying lipophilicity).

[00155] General Synthesis Scheme 1 (R^{24} being Hydrogen or alkyls).



[00156] General Synthesis Scheme 2:

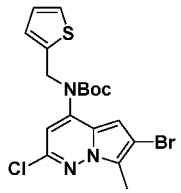


EXAMPLES

[00157] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein. The starting materials and reagents used for the synthesis of the compounds described herein may be synthesized or can be obtained from commercial sources, such as, but not limited to, Sigma–Aldrich, Acros Organics, Fluka, and Fisher Scientific.

[00158] Example A1. Synthesis of Intermediates of type 8

[00159] Intermediate **8-1**: *tert*-butyl (6-bromo-2-chloro-7-methylpyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate



[00160] **Step 1**: Into a 500-mL round bottom flask purged and maintained with an inert atmosphere of nitrogen were added ethyl 5-methyl-1H-pyrrole-2-carboxylate (20 g, 130.5 mmol, 1 eq.), NBS (23.2 g, 130.5 mmol, 1 eq.) and DCM (200 mL) at 0°C. The resulting solution was stirred for 2h at RT. The resulting mixture was extracted with DCM (3 x 300 mL). The combined organic layers were washed with water (3x300 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by trituration with MeOH (100 mL) to afford ethyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (20 g, 66%) as a white solid.

[00161] **Step 2**: A solution of ethyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (20 g, 86.2 mmol, 1 eq.) in THF (200 ml) was treated with sodium hydride (4.14 g, 172.4 mmol, 2 eq.) for 2 h at 0°C under nitrogen atmosphere followed by the addition of O-(2,4-dinitrophenyl)hydroxylamine (25.74 g, 129.3 mmol, 1.5 eq.) in portions at RT. The resulting mixture was stirred for 2h at RT. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford ethyl 1-amino-4-bromo-5-methylpyrrole-2-carboxylate (13.5 g, 63%) as a yellow semi-solid.

[00162] **Step 3**: A solution of ethyl 1-amino-4-bromo-5-methylpyrrole-2-carboxylate (13.5 g, 54.65 mmol, 1 eq.) and ethyl 3-chloro-3-oxopropanoate (9.87 g, 65.5 mmol, 1.2 eq.), pyridine (8.64 g, 109.3 mmol, 2 eq.) in DCM (200 ml) was stirred for 2h at RT. The aqueous layer was extracted with DCM (2x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford ethyl 4-bromo-1-(3-ethoxy-3-oxopropanamido)-5-methylpyrrole-2-carboxylate (7.5 g, 38%) as a light yellow semi-solid.

[00163] **Step 4**: A solution of ethyl 4-bromo-1-(3-ethoxy-3-oxopropanamido)-5-methylpyrrole-2-carboxylate (7.5 g, 20.7 mmol, 1 equiv) and t-BuOK (4.66 g, 41.5 mmol, 2 equiv) in THF (100mL) was stirred for 4h at room temperature. The resulting mixture was concentrated under vacuum. The resulting mixture containing ethyl 6-bromo-7-methyl-2,4-dioxo-1H,3H-pyrrolo[1,2-b]pyridazine-3-carboxylate was used in the next step directly without further purification.

[00164] **Step 5**: A solution of ethyl 6-bromo-7-methyl-2,4-dioxo-1H,3H-pyrrolo[1,2-b]pyridazine-3-carboxylate (5 g, 15.8 mmol, 1 eq.) and NaOH (3.173 g, 79 mmol, 5 eq.) in 1,4-dioxane : water (1:1) (100mL) was stirred for 16h at 80°C. The mixture was acidified to pH 7 with conc. HCl. The precipitated solids were collected by filtration. The residue was purified by reversed-phase flash chromatography (column, C18; mobile phase, MeCN in water (0.1% FA), 10% to 50% gradient in 10

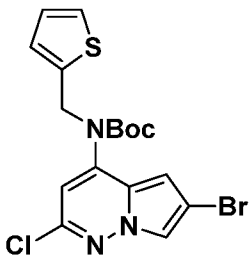
min; detector, UV 254 nm) to yield 6-bromo-7-methyl-1H,3H-pyrrolo[1,2-b]pyridazine-2,4-dione (2.8 g, 73%) as a brown solid.

[00165] **Step 6**: A solution of 6-bromo-7-methyl-1H,3H-pyrrolo[1,2-b]pyridazine-2,4-dione (2.8 g, 11.5 mmol, 1 eq.) and DIEA (2.9g, 23.0 mmol, 2 eq.) in $POCl_3$ (30mL) was stirred for 3 days at 125°C. The mixture was acidified to pH 7 with conc. HCl. The precipitated solids were collected by filtration. The residue was purified by reversed-phase flash chromatography (column, C18; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm) to yield 6-bromo-2,4-dichloro-7-methylpyrrolo[1,2-b]pyridazine (200 mg, 6.2%) as a light yellow solid.

[00166] **Step 7**: A solution of 6-bromo-2,4-dichloro-7-methylpyrrolo[1,2-b]pyridazine (200 mg, 0.714 mmol, 1 eq.) and 1-(thiophen-2-yl)methanamine (82.5 mg, 0.728 mmol, 1.02 eq.), DIEA (185 mg, 1.428 mmol, 2 eq.) in DMSO (3mL) was stirred for 8h at 100°C. The residue was purified by reversed-phase flash chromatography (column, C18; mobile phase, MeCN in water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm) to yield 6-bromo-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (160 mg, 63%) as an orange oil.

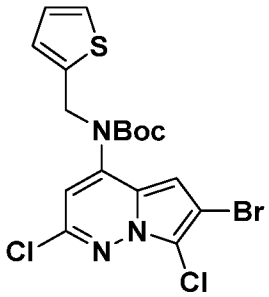
[00167] **Step 8**: A solution of 6-bromo-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (160 mg, 0.449 mmol, 1 eq.) and Boc_2O (196 mg, 0.898 mmol, 2 eq.), DMAP (109 mg, 0.898 mmol, 2 eq.), TEA (91 mg, 0.898 mmol, 2 eq.) in DCM (3ml) was stirred for 2h at RT. The resulting mixture was diluted with water (20mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 20mL). The combined organic layers were washed with NaCl (1x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (column, C18; mobile phase, MeCN in water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm) to yield *tert*-butyl (6-bromo-2-chloro-7-methylpyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate (180 mg, 88%) as an orange oil.

[00168] Intermediate **8-2**: *tert*-butyl (6-bromo-2-chloropyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate



[00169] In analogy to the preparation of the intermediate **8-1**, starting from methyl 4-bromo-1H-pyrrole-2-carboxylate in the second step, was prepared *tert*-butyl (6-bromo-2-chloropyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate as a light yellow solid.

[00170] Intermediate **8-3**: *tert*-butyl (6-bromo-2,7-dichloropyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate



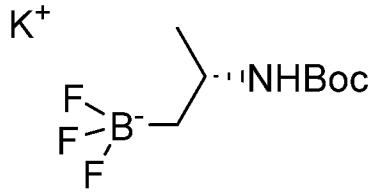
[00171] **Step 1**: To a stirred mixture of 6-bromo-2,4-dichloropyrrolo[1,2-b]pyridazine (compound obtained in the course of the preparation of the intermediate **8-2**) (200 mg, 0.752 mmol, 1 eq.) in TFA (5 mL) was added NCS (120 mg, 0.902 mmol, 1.2 eq.) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 10min at 0°C under nitrogen atmosphere. The resulting mixture was diluted with CH_2Cl_2 (10 mL). The reaction was quenched by the addition of water (20mL) at 0°C. The resulting mixture was extracted with CH_2Cl_2 (3 x 20mL). The combined organic layers were washed with brine (1x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography (column, C18; mobile phase, MeCN in water (10mmol/L NH_4HCO_3), 20% to 100% gradient in 25 min; detector, UV 254 nm) to yield 6-bromo-2,4,7-trichloropyrrolo[1,2-b]pyridazine (170 mg, 75%) as a yellow solid.

[00172] **Step 2**: To a stirred solution of 6-bromo-2,4,7-trichloropyrrolo[1,2-b]pyridazine (200 mg, 0.666 mmol, 1 eq.) and 1-(thiophen-2-yl)methanamine (90 mg, 0.799 mmol, 1.2 eq.) in DMSO (10 mL) was added DIEA (172 mg, 1.332 mmol, 2 eq.) dropwise at RT under air atmosphere. The resulting mixture was stirred for 5h at 100°C under air atmosphere. The mixture was allowed to cool down to RT. The residue was purified by reversed-phase flash chromatography (column, C18; mobile phase, MeCN in water (10mmol/L NH_4HCO_3), 20% to 100% gradient in 25 min; detector, UV 254 nm) to yield 6-bromo-2,7-dichloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (200 mg, 80%) as a white solid.

[00173] **Step 3**: To a stirred solution of 6-bromo-2,7-dichloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (400 mg, 1.061 mmol, 1 eq.) in DCM (10 mL, 157 mmol, 148 eq.) was added DMAP (12.9 mg, 0.106 mmol, 0.1 eq.) and di-tert-butyl dicarbonate (347 mg, 1.591 mmol, 1.5 eq.) in portions at RT under air atmosphere. The resulting mixture was stirred for 3h at RT under air atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford *tert*-butyl (6-bromo-2,7-dichloropyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate (400 mg, 79%) as a yellow solid.

[00174] Example A2. Synthesis of potassium trifluoroborate salts

[00175] Borate salt **1**: Potassium (*S*)-(2-((*tert*-butoxycarbonyl)amino)propyl)trifluoroborate

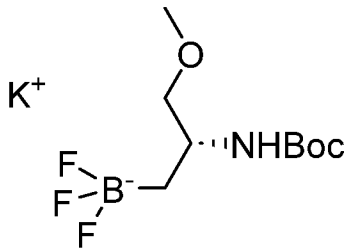


[00176] **Step 1**: To a stirred mixture of tert-butyl N-[(2S)-1-hydroxypropan-2-yl]carbamate (10 g, 57.07 mmol, 1 eq.) and triphenylphosphine (18.01 g, 64.48 mmol, 1.2 eq.) in THF (100 mL) and DCM (100 mL) was added NBS (12.19 g, 68.48 mmol, 1.2 eq.) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred overnight at RT under nitrogen atmosphere. The residue was diluted with DCM (200 mL) and washed with water (2x100 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford tert-butyl N-[(2S)-1-bromopropan-2-yl]carbamate (6 g, 44%) as a light yellow solid.

[00177] **Step 2**: A mixture of tert-butyl N-(1-bromopropan-2-yl)carbamate (4 g, 16.80 mmol, 1 eq.), copper(I) iodide (0.32 g, 1.68 mmol, 0.1 eq.), triphenylphosphine (0.44 g, 1.68 mmol, 0.13 eq.), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (5.55 g, 21.84 mmol, 1.3 eq.) and methoxylithium (0.83 g, 21.84 mmol, 1.3 eq.) in dimethylformamide (80 mL) was stirred for 16 h at RT under air atmosphere. The resulting mixture was diluted with water (200mL) and extracted with tert-Butyl methyl ether (3x100 mL). The organic phase was concentrated under vacuum. The crude product was used in the next step directly without further purification.

[00178] **Step 3**: To a stirred mixture of tert-butyl N-[1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-2-yl]carbamate (4 g, 14.03 mmol, 1 eq.) in with tert-Butyl methyl ether (40 mL) was added KHF_2 (2.19 g, 28.05 mmol, 2 eq.) and water (1 mL) at RT under air atmosphere. The resulting mixture was stirred overnight and the resulting mixture was concentrated under vacuum. The residue was diluted with tert-Butyl methyl ether (100 mL). The mixture was stirred for 30 min and filtered. The filter cake was diluted with acetone (300 mL) and stirred for another 30 min. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure to afford potassium (*S*)-(2-((*tert*-butoxycarbonyl)amino)propyl)trifluoroborate (2 g, 54%) as a light yellow solid. The crude product was used in the next step directly without further purification.

[00179] Borate salt **2**: Potassium (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-methoxypropyl)trifluoroborate



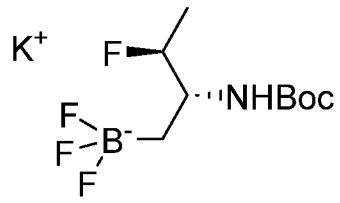
[00180] **Step 1**: To an ice-cooled solution of (2S)-2-[(tert-butoxycarbonyl)amino]-3-methoxypropanoic acid (5 g, 22.81 mmol, 1 eq.) and DIEA (3.54 g, 27.37 mmol, 1.2 eq.) in THF (40 mL) was added isopropyl chloroformate (3.07 g, 25.09 mmol, 1.1 eq.) dropwise. The cooling bath was removed and the mixture was stirred at 23 °C for 2 h. The mixture was filtered to remove the white precipitate, and the filtrate was treated with $NaBH_4$ (1.73 g, 45.61 mmol, 2 eq.) resulting in vigorous gas evolution. After the mixture was stirred at RT for 2 h, brine (25 mL) was added. The mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, then concentrated under vacuum. The residue was purified by silica gel flash chromatography to give tert-butyl N-[(2R)-1-hydroxy-3-methoxypropan-2-yl]carbamate (2.5 g, 53%) as a white solid.

[00181] **Step 2**: To a stirred solution of tert-butyl N-[(2R)-1-hydroxy-3-methoxypropan-2-yl]carbamate (2.5 g, 12.180 mmol, 1 eq.), triphenylphosphine (5.91 g, 22.53 mmol, 1.85 eq.) in THF (8 mL) and DCM (40 mL) were added NBS (4.01 g, 22.53 mmol, 1.85 eq.) in portions at -20°C under air atmosphere. The resulting mixture was stirred for additional overnight at RT. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford tert-butyl N-[(2S)-1-bromo-3-methoxypropan-2-yl]carbamate (1.2 g, 37%) as a white oil.

[00182] **Step 3**: A mixture of tert-butyl N-[(2S)-1-bromo-3-methoxypropan-2-yl]carbamate (1.2 g, 4.47 mmol, 1 eq.) copper(I) iodide (0.09 g, 0.448 mmol, 0.1 eq.) methoxylithium (0.34 g, 8.950 mmol, 2 eq.) triphenylphosphine (0.15 g, 0.582 mmol, 0.13 eq.) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.71 mL, 5.817 mmol, 1.3 equiv) in DMF (11 mL) was stirred for overnight at RT under air atmosphere. The resulting mixture was filtered, the filter cake was washed with water and tert-Butyl methyl ether (3x20 mL). The resulting mixture was extracted with MTBE (3 x 100 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

[00183] **Step 4**: A mixture of tert-butyl N-[(2R)-1-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-2-yl]carbamate (1.2 g, 3.807 mmol, 1 eq.) and KHF_2 (0.59 g, 7.614 mmol, 2 eq.) in 2-methoxy-2-methylpropane (100 mL) was stirred for overnight at RT under air atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by trituration with MTBE (300 mL). The mixture was stirred for 30 min and filtered. The filter cake was suspended with acetone (400 mL) and stirred for another 30 min. The resulting mixture was filtered, and the filter cake was washed with acetone (1x50 mL). The filtrate was concentrated under reduced pressure. This resulted in potassium (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-methoxypropyl)trifluoroborate (500 mg, 51%) as a white solid.

[00184] Borate salt **3**: Potassium ((2*R*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-fluorobutyl)trifluoroborate



[00185] Step 1: To a stirred solution of imidazole (144.76 g, 2126.348 mmol, 4 equiv) in DCM (3720 mL) were added $SOCl_2$ (57.84 mL, 797.38 mmol, 1.5 equiv) and DIEA (185.19 mL, 1063.17 mmol, 2 eq.) dropwise at 0°C. The resulting mixture was stirred for 0.5h at 0oC. To the above mixture was added methyl (2S,3R)-2-[(tert-butoxycarbonyl)amino]-3-hydroxybutanoate (124 g, 531.587 mmol, 1 eq.) in DCM (620ml) dropwise at 0°C. The resulting mixture was stirred for additional overnight at RT. The resulting mixture was washed with 3 x 800 mL of HCl (0.5M). The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

[00186] Step 2: A solution of 3-(tert-butyl) 4-methyl (4S,5R)-5-methyl-1,2,3-oxathiazolidine-3,4-dicarboxylate 2-oxide (144 g, 515.55 mmol, 1 eq.) in H_2O (1008 mL) and acetonitrile (1872 mL) was treated with $NaIO_4$ (132.33 g, 618.66 mmol, 1.2 eq.) and ruthenium(iv) oxide hydrate (1.56 g, 10.31 mmol, 0.02 eq.) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 0°C under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with EtOAc (5 x 1000 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to provide 3-(tert-butyl) 4-methyl (4S,5R)-5-methyl-1,2,3-oxathiazolidine-3,4-dicarboxylate 2,2-dioxide (145 g, 95%) as a light yellow oil.

[00187] Step 3: A solution of 3-(tert-butyl) 4-methyl (4S,5R)-5-methyl-1,2,3-oxathiazolidine-3,4-dicarboxylate 2,2-dioxide (144 g, 487.62 mmol, 1 eq.) in THF (975 mL) was treated with $Et_3N.3HF$ (430.11 mL, 3169.55 mmol, 6.5 eq.) at 60°C under nitrogen atmosphere. The resulting mixture was stirred for 3 days at 60°C under nitrogen atmosphere. The mixture was neutralized to pH 7 with NaOH (20%). The aqueous layer was extracted with EtOAc (3 x 800 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford methyl (2R,3S)-2-((tert-butoxycarbonyl)amino)-3-fluorobutanoate (55 g, 48%) as a light yellow oil.

[00188] Step 4: A solution of methyl (2R,3S)-2-((tert-butoxycarbonyl)amino)-3-fluorobutanoate (55 g, 233.79 mmol, 1 eq.) in EtOH (500 mL) was treated with $NaBH_4$ (22.11 g, 584.47 mmol, 2.5 eq.) at 0°C under nitrogen atmosphere. The resulting mixture was stirred overnight at 0°C under nitrogen atmosphere. The reaction was quenched by the addition of Water/Ice (500mL) at 0°C. The aqueous layer was extracted with EtOAc (3x400mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography,

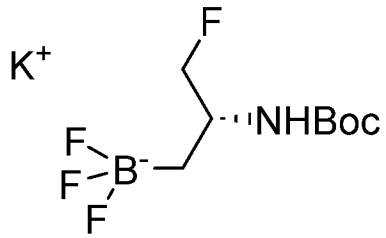
eluted with PE / EA (1:1) to afford tert-butyl N-[(2R,3S)-3-fluoro- 1-hydroxybutan-2-yl]carbamate (46 g, 95%) as a yellow solid.

[00189] **Step 5**: To a stirred mixture of tert-butyl N-[(2R,3S)-3-fluoro-1-hydroxybutan-2-yl]carbamate (44 g, 212.31 mmol, 1 eq.) and triphenylphosphine (103.02 g, 392.77 mmol, 1.85 eq.) in THF (170 mL) and DCM (880 mL) was added NBS (69.91 g, 392.77 mmol, 1.85 eq.) in portions at -20°C under air atmosphere. The resulting mixture was stirred overnight at RT under air atmosphere. The resulting mixture was washed with 1x500 mL of water, washed with brine (1x200 mL) and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford tert-butyl N-[(2S,3S)-1-bromo-3-fluorobutan-2-yl]carbamate (30 g, 52%) as a light yellow solid.

[00190] **Step 6**: A mixture of tert-butyl N-[(2S,3S)-1-bromo-3-fluorobutan-2-yl]carbamate (15.2 g, 56.27 mmol, 1 eq.), copper(I) iodide (1.07 g, 5.63 mmol, 0.1 eq.), triphenylphosphine (1.92 g, 7.31 mmol, 0.13 eq.), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (18.57 g, 73.15 mmol, 1.3 eq.) and methoxylithium (4.27 g, 112.53 mmol, 2 eq.) in DMF (150 mL) was stirred for 16h at RT under air atmosphere. The resulting mixture was diluted with water (500mL). The resulting mixture was filtered, the filter cake was washed with MTBE (1x100 mL). The resulting mixture was extracted with MTBE (3 x300 mL). The combined organic layers were washed with brine (2x100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture was used in the next step directly without further purification.

[00191] **Step 7**: A mixture of tert-butyl N-[(2R,3S)-3-fluoro-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-yl] carbamate (15.2 g, 47.92 mmol, 1 eq.) and KHF_2 (8.8 g, 112.67 mmol, 2.35 eq.) in MTBE (600 mL) and H_2O (4 mL) was stirred for 16h at RT under air atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by trituration with MTBE. The mixture was stirred for 30 min and filtered. The filter cake was diluted with acetone (800 mL) and stirred for another 30 min. The resulting mixture was filtered, and the filter cake was washed with acetone (1x50 mL). The filtrate was concentrated under reduced pressure. This resulted in potassium ((2*R*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-fluorobutyl)trifluoroborate (8 g, 56%) as a white solid.

[00192] Borate salt **4**: Potassium (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-fluoropropyl)trifluoroborate



[00193] Step 1: To a stirred solution of Imidazole (96.79 g, 1421.71 mmol, 4 eq.) in DCM (3000 mL) were added $SOCl_2$ (38.67 mL, 533.14 mmol, 1.5 eq.) and DIEA (123.82 mL, 710.85 mmol, 2 eq.) dropwise at 0°C. The resulting mixture was stirred for 0.5 h at 0°C. To the mixture was added tert-butyl N-[(2S)-1-(benzyloxy)-3-hydroxypropan-2-yl]carbamate (100 g, 355.43 mmol, 1 eq.) in DCM (500 mL) dropwise at 0°C. The resulting mixture was stirred overnight at RT. The resulting mixture was washed with 3x1000 mL of HCl (0.5 mol/L) and concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

[00194] Step 2: A solution of tert-butyl (4R)-4-[(benzyloxy)methyl]-2-oxo-1,2lambda4,3-oxathiazolidine-3-carboxylate (122 g, 372.63 mmol, 1 eq.) in H_2O (854 mL) and acetonitrile (1586 mL) was treated with $NaIO_4$ (95.64 g, 447.16 mmol, 1.2 eq.) and ruthenium(iv) oxide hydrate (1.13 g, 7.45 mmol, 0.02 eq.) at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1h at 0 °C. The resulting mixture was filtered, the filter cake was washed with EtOAc (4 x 1000 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford tert-butyl (4R)-4-[(benzyloxy)methyl]-2,2-dioxo-1,2lambda6,3-oxathiazolidine-3-carboxylate (117 g, 91%) as a light yellow solid.

[00195] Step 3: A solution of tert-butyl (4R)-4-[(benzyloxy)methyl]-2,2-dioxo-1,2lambda6,3-oxathiazolidine-3-carboxylate (117 g, 340.72 mmol, 1 eq.) in THF (1725 mL) was treated with TBAF (340.72 mL, 340.720 mmol, 1 equiv) at 0°C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The reaction was quenched by the addition of citric acid (10%) (1500 mL) at RT. The aqueous layer was extracted with EtOAc (3 x 1000 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford tert-butyl N-[(2R)-1-(benzyloxy)-3-fluoropropan-2-yl]carbamate (76 g, 79%) as a colorless oil.

[00196] Step 4: A solution of tert-butyl N-[(2R)-1-(benzyloxy)-3-fluoropropan-2-yl]carbamate (76 g, 268.226 mmol, 1 equiv) in EtOAc (760 mL) was treated with Pd/C (15.2 g, 20%) at room temperature. The resulting mixture was stirred overnight at 50°C under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with EtOAc (300 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:2) to afford tert-butyl N-[(2R)-1-fluoro-3-hydroxypropan-2-yl]carbamate (49.8 g, 96%) as a colorless oil.

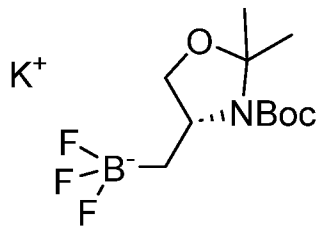
[00197] Step 5: To a stirred mixture of tert-butyl N-[(2R)-1-fluoro-3-hydroxypropan-2-yl]carbamate (10.5 g, 54.34 mmol, 1 eq.) and triphenylphosphine (17.15 g, 65.21 mmol, 1.2 eq.) in DCM (100 mL) and THF (100 mL) was added NBS (11.62 g, 65.28 mmol, 1.2 eq.) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 16 h at room temperature under nitrogen atmosphere. The residue was washed with water (2x50 mL) and brine (50 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column

chromatography, eluted with PE / EA (4:1) to afford tert-butyl N-[(2S)-1-bromo-3-fluoropropan-2-yl]carbamate (3.5 g, 25%) as a yellow solid.

[00198] **Step 6**: A mixture of tert-butyl N-[(2S)-1-bromo-3-fluoropropan-2-yl]carbamate (3.5 g, 13.66 mmol, 1 eq.), copper(I) iodide (0.26 g, 1.37 mmol, 0.1 eq.), triphenylphosphine (0.36 g, 1.37 mmol, 0.1 eq.), Bis(pinacolato) diboron (6.94 g, 27.33 mmol, 2 eq.) and methoxylithium (1.04 g, 27.33 mmol, 2 eq.) in DMF (60 mL) was stirred for 16 h at RT under air atmosphere. The resulting mixture was diluted with water (60 mL) and extracted with MTBE (3 x 100 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

[00199] **Step 7**: A mixture of tert-butyl N-[(2R)-1-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-2-yl]carbamate (5 g, 16.49 mmol, 1 eq.) and fluorine potassium hydride (2.57 g, 32.98 mmol, 2 eq.) in MTBE (200 mL) and H_2O (2 mL) was stirred for 16 h at room temperature under air atmosphere. The resulting mixture was concentrated under vacuum. The residue was diluted with MTBE (200 mL). The mixture was stirred for 30 min and filtered. The filter cake was diluted with acetone (300 mL) and stirred for another 30 min. The resulting mixture was filtered, and the filter cake was washed with acetone (1x50 mL). The filtrate was concentrated under reduced pressure to afford potassium (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-fluoropropyl)trifluoroborate (3 g, 64%) as an off-white solid. The crude product was used in the next step directly without further purification.

[00200] Borate salt **5**: Potassium (*R*)-((3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)methyl)trifluoroborate



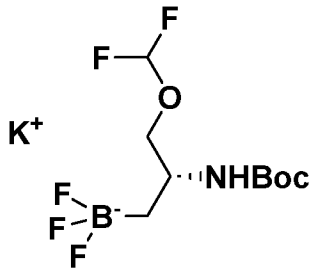
[00201] **Step 1**: To a stirred mixture of tert-butyl (4R)-4-(hydroxymethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (11 g, 47.6 mmol, 1 eq.) and triphenylphosphine (23.08 g, 87.98 mmol, 1.85 eq.) in THF (44 mL) and DCM (220 mL) was added NBS (15.66 g, 87.98 mmol, 1.85 eq.) in portions at -20°C under air atmosphere. The resulting mixture was stirred for 16h at RT under air atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford tert-butyl (4S)-4-(bromomethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (2.5 g, 18%) as a colorless oil.

[00202] **Step 2**: A mixture of tert-butyl (4S)-4-(bromomethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (2.5 g, 8.50 mmol, 1 eq.), methoxylithium (0.65 g, 17.0 mmol, 2 eq.), copper(I) iodide (0.16 g, 0.85 mmol, 0.1 eq.), triphenylphosphine (0.29 g, 1.105 mmol, 0.13 eq.) and 4,4,5,5-

tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.81 g, 11.05 mmol, 1.3 eq.) in DMF (25 mL) was stirred overnight at RT under air atmosphere. The resulting mixture was diluted with water (100 mL), filtered, and the filter cake was washed with MTBE (2x30 mL). The filtrate was extracted with MTBE (2 x 80 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

[00203] **Step 3**: A mixture of tert-butyl (4R)-2,2-dimethyl-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-1,3-oxazolidine-3-carboxylate (2.5 g, 7.32 mmol, 1 eq.) and potassium bifluoride (1.14 g, 14.65 mmol, 2 eq.) in MTBE (250 mL) was stirred for overnight at room temperature under air atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by trituration with MTBE (100 mL). The mixture was stirred for 30 min and filtered. The filter cake was suspended with acetone (100 mL) and stirred for another 30 min. The resulting mixture was filtered, and the filter cake was washed with acetone (1x50 mL). The filtrate was concentrated under reduced pressure. This resulted in potassium (*R*)-((3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)methyl)trifluoroborate (1 g, 42.5%) as a white solid.

[00204] Borate salt **6**: Potassium (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-(difluoromethoxy)propyl)trifluoroborate



[00205] **Step 1**: To a stirred solution of tert-butyl (4S)-4-(hydroxymethyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (20 g, 86.471 mmol, 1 equiv) in DCM (800 mL) and H_2O (800 mL) was added (bromodifluoromethyl) trimethylsilane (52.69 g, 259.41 mmol, 3 eq.) and potassium acetate (50.92 g, 518.83 mmol, 6 eq.) in portions at 10°C under nitrogen atmosphere. The resulting mixture was stirred for 24h at RT under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was extracted with CH_2Cl_2 (3 x 100mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1) to afford tert-butyl (4R)-4-[(difluoromethoxy)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (21 g, 86.33%) as a yellow oil.

[00206] **Step 2**: To a stirred solution of tert-butyl (4R)-4-[(difluoromethoxy)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (1 g, 3.55 mmol, 1 eq.) in MeCN (20 mL) and was added bismuth tribromide (1.28 g, 2.84 mmol, 0.2 eq.) in portions at 0°C under air atmosphere. The resulting mixture

was stirred for 2h at RT under air atmosphere. The resulting mixture was diluted with H_2O (5mL). The resulting mixture was filtered, the filter cake was washed with MeCN (20 mL) (2x30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1) to afford tert-butyl N-[(2R)-1-(difluoromethoxy)-3-hydroxypropan-2-yl]carbamate (2.4 g, 70%) as a yellow oil.

[00207] **Step 3**: To a stirred mixture of tert-butyl N-[(2R)-1-(difluoromethoxy)-3-hydroxypropan-2-yl]carbamate (1 g, 4.14 mmol, 1 eq.) and triphenylphosphine (2.01 g, 7.67 mmol, 1.85 eq.) in THF (4 mL) and DCM (20 mL) were added NBS (1.36 g, 7.67 mmol, 1.85 eq.) in portions at -20°C under air atmosphere. The resulting mixture was stirred for overnight at RT under air atmosphere. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford tert-butyl N-[(2S)-1-bromo-3-(difluoromethoxy)propan-2-yl]carbamate (380 mg, 30.14%) as a yellow oil.

[00208] **Step 4**: To a stirred mixture of tert-butyl N-[(2S)-1-bromo-3-(difluoromethoxy)propan-2-yl]carbamate (380 mg, 1.25 mmol, 1 eq.), methoxylithium (95 mg, 2.50 mmol, 2 eq.), copper(I) iodide (23.8 mg, 0.125 mmol, 0.1 eq.), triphenylphosphine (43 mg, 0.16 mmol, 0.13 eq.) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (412 mg, 1.62 mmol, 1.3 eq.) in DMF (4 mL) at room temperature under air atmosphere. The resulting mixture was stirred for overnight at RT under air atmosphere. The resulting mixture was diluted with water (100mL). The resulting mixture was filtered, the filter cake was washed with MTBE (3x10 mL). The resulting mixture was extracted with MTBE (3 x 20mL). The combined organic layers were washed with saturated salt solution (1x20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product was used in the next step directly without further purification.

[00209] **Step 5**: To a stirred mixture of tert-butyl N-[(2R)-1-(difluoromethoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-2-yl]carbamate (2 g, 5.69 mmol, 1 eq.) and KHF_2 (0.89 g, 11.39 mmol, 2 eq.) in H_2O (2 mL) and MTBE (200 mL) at RT under air atmosphere. The resulting mixture was stirred overnight at 25°C under air atmosphere. The resulting mixture was concentrated under vacuum. The residue was dissolved in MTBE (200mL). The precipitated solids were collected by filtration and washed with MTBE (3x10 mL). The residue was dissolved in acetone (200mL). The resulting mixture was filtered, the filter cake was washed with acetone (3x10 mL). The filtrate was concentrated under reduced pressure. This resulted in potassium (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-(difluoromethoxy)propyl)trifluoroborate (1.1 g, 58%) as a white solid.

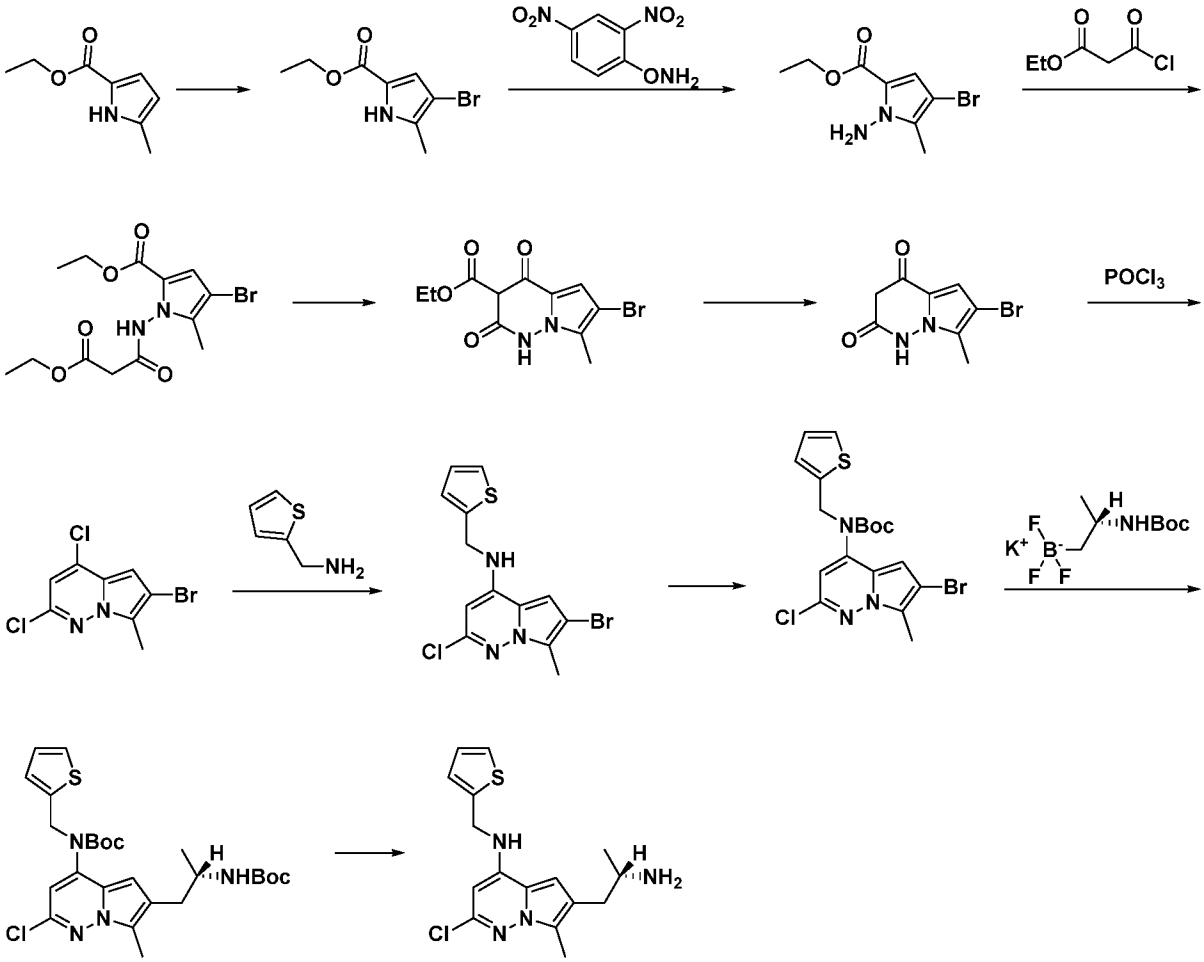
General procedures

[00210] Cross coupling reaction between an intermediate of type 4 with a trifluoroborate salt

[00211] A mixture of an intermediate **8** (1 eq.), a potassium trifluoroborate salt (1.5 eq.), $Pd_2(dba)_3$ or $Pd(Amphos)_2Cl_2$ (0.1 eq.) and Cs_2CO_3 (2 eq.) in Toluene / H_2O (25/1) was stirred at 100 °C under a

nitrogen atmosphere until completion of the reaction. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, to afford the desired compound.

[00212] Example 1. Synthesis of (S)-6-(2-aminopropyl)-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (Compound 1)



[00213] Step 1: Into a 500-mL round bottom flask purged and maintained with an inert atmosphere of nitrogen were added ethyl 5-methyl-1H-pyrrole-2-carboxylate (20 g, 130.5 mmol, 1 equiv), NBS (23.24 g, 130.5 mmol, 1 equiv) and DCM (200 mL) at 0°C. The resulting solution was stirred for 2h at room temperature. The resulting mixture was extracted with DCM (3 x 300 mL). The combined organic layers were washed with water (3x300 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by trituration with MeOH (100 mL) to afford ethyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (20 g, 66%) as a white solid.

[00214] Step 2: A solution of ethyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (20 g, 86.2 mmol, 1 equiv) in THF (200 ml) was treated with sodium hydride (4.14 g, 172.4 mmol, 2 equiv) for 2 h at 0°C under nitrogen atmosphere followed by the addition of O-(2,4-dinitrophenyl)hydroxylamine (25.74 g, 129.3 mmol, 1.5 equiv) in portions at room temperature. The resulting mixture was stirred for 2h at

room temperature. The aqueous layer was extracted with EtOAc (2x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford ethyl 1-amino-4-bromo-5-methylpyrrole-2-carboxylate (13.5 g, 63.4%) as a yellow semi-solid.

[00215] Step 3: A solution of ethyl 1-amino-4-bromo-5-methylpyrrole-2-carboxylate (13.5 g, 54.65 mmol, 1 equiv) and ethyl 3-chloro-3-oxopropanoate (9.87 g, 65.5 mmol, 1.2 equiv), Pyridine (8.64 g, 109.3 mmol, 2 equiv) in DCM (200 ml) was stirred for 2h at room temperature. The aqueous layer was extracted with DCM (2x100 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford ethyl 4-bromo-1-(3-ethoxy-3-oxopropanamido)-5-methylpyrrole-2-carboxylate (7.5 g, 38%) as a light yellow semi-solid.

[00216] Step 4: A solution of ethyl 4-bromo-1-(3-ethoxy-3-oxopropanamido)-5-methylpyrrole-2-carboxylate (7.5 g, 20.7 mmol, 1 equiv) and t-BuOK (4.66 g, 41.5 mmol, 2 equiv) in THF (100mL) was stirred for 4h at room temperature. The resulting mixture was concentrated under vacuum. The resulting mixture was used in the next step directly without further purification.

[00217] Step 5: A solution of ethyl 6-bromo-7-methyl-2,4-dioxo-1H,3H-pyrrolo[1,2-b]pyridazine-3-carboxylate (5 g, 15.8 mmol, 1 equiv) and NaOH (3173.13 mg, 79 mmol, 5 equiv) in 1,4-dioxane:water (1:1) (100mL) was stirred for 16h at 80°C. The mixture was acidified to pH 7 with conc. HCl. The precipitated solids were collected by filtration. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 6-bromo-7-methyl-1H,3H-pyrrolo[1,2-b]pyridazine-2,4-dione (2.8 g, 72.6%) as a brown solid.

[00218] Step 6: A solution of 6-bromo-7-methyl-1H,3H-pyrrolo[1,2-b]pyridazine-2,4-dione (2.8 g, 11.5 mmol, 1 equiv) and DIEA (2.9g, 23.0 mmol, 2 equiv) in $POCl_3$ (30mL) was stirred for 3 days at 125°C. The mixture was acidified to pH 7 with conc. HCl. The precipitated solids were collected by filtration. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 6-bromo-2,4-dichloro-7-methylpyrrolo[1,2-b]pyridazine (200 mg, 6.2%) as a light yellow solid.

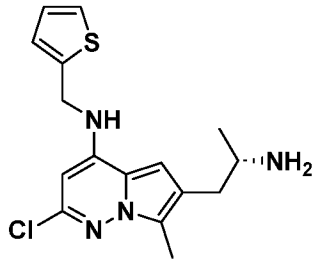
[00219] Step 7: A solution of 6-bromo-2,4-dichloro-7-methylpyrrolo[1,2-b]pyridazine (200 mg, 0.714 mmol, 1 equiv) and 1-(thiophen-2-yl)methanamine (82.5 mg, 0.728 mmol, 1.02 equiv), DIEA (185 mg, 1.428 mmol, 2 equiv) in DMSO (3mL) was stirred for 8h at 100°C. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 6-bromo-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (160 mg, 62.8%) as an orange oil.

[00220] Step 8: A solution of 6-bromo-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (160 mg, 0.449 mmol, 1 equiv) and Boc_2O (196 mg, 0.898 mmol, 2 equiv), DMAP (109 mg, 0.898 mmol, 2 equiv), TEA (91 mg, 0.898 mmol, 2 equiv) in DCM (3ml) was stirred for 2h at room temperature . The resulting mixture was diluted with water (20mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 20mL). The combined organic layers were washed with NaCl (1x10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C18; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in tert-butyl N-{6-bromo-2-chloro-7-methylpyrrolo[1,2-b]pyridazin-4-yl}-N-(thiophen-2-ylmethyl)carbamate (180 mg, 87.8%) as an orange oil.

[00221] Step 9: A solution of tert-butyl N-{6-bromo-2-chloro-7-methylpyrrolo[1,2-b]pyridazin-4-yl}-N-(thiophen-2-ylmethyl)carbamate (100 mg, 0.219 mmol, 1 equiv) and tert-butyl N-[(2S)-1-(trifluoroboranuidyl)propan-2-yl]carbamate (99 mg, 0.438 mmol, 2 equiv), potassium (S)-(2-((tert-butoxycarbonyl)amino)propyl)trifluoroborate (17 mg, 0.438 mmol, 2 equiv), butylbis[(3R,5S,7s)-adamantan-1-yl]phosphane (7.9 mg, 0.022 mmol, 0.1 equiv), $Pd_2(dba)_3$ (20.0 mg, 0.022 mmol, 0.1 equiv), Cs_2CO_3 (143 mg, 0.438 mmol, 2 equiv) in toluene:water (50:1) (5 mL) was stirred for 2h at 100°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in tert-butyl N-{6-[(2S)-2-[(tert-butoxycarbonyl)amino]propyl]-2-chloro-7-methylpyrrolo[1,2-b]pyridazin-4-yl}-N-(thiophen-2-ylmethyl)carbamate (60 mg, 51.2%) as an orange solid.

[00222] Step 10: A solution of tert-butyl N-(6-{2-[(tert-butoxycarbonyl)amino]propyl}-2-chloro-7-methylpyrrolo[1,2-b]pyridazin-4-yl)-N-(thiophen-2-ylmethyl)carbamate (80 mg, 0.150 mmol, 1 equiv) and TFA (0.1mL) in DCM (2mL) was stirred for 2h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm. This resulted in 6-(2-aminopropyl)-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (15.3 mg, 30.5%). LC-MS (ES, *m/z*): $[M+H]^+ = 334.95$.

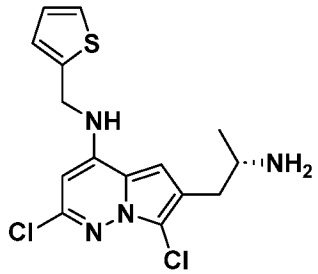
[00223] Example 2. Alternate Synthesis of (S)-6-(2-aminopropyl)-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (Compound 1)



[00224] **Step 1**: Using the general cross coupling reaction between the *tert*-butyl (6-bromo-2-chloro-7-methylpyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate (intermediate **8-1**) and potassium (*S*)-(2-((*tert*-butoxycarbonyl)amino)propyl)trifluoroborate (borate salt **1**) was obtained 60 mg of *tert*-butyl (*S*)-(6-(2-((*tert*-butoxycarbonyl)amino)propyl)-2-chloro-7-methylpyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate as an orange solid.

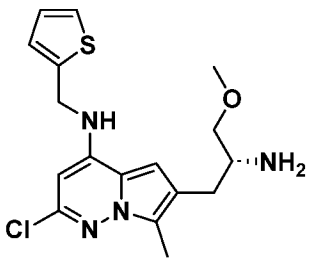
[00225] **Step 2**: A solution of *tert*-butyl (*S*)-(6-(2-((*tert*-butoxycarbonyl)amino)propyl)-2-chloro-7-methylpyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate (80 mg, 0.150 mmol, 1 eq.) and TFA (1 mL) in DCM (2mL) was stirred for 2h at RT. The residue was purified by reversed-phase flash chromatography (column, C18; mobile phase, MeCN in water (0.1% FA), 10% to 50% gradient in 10 min; detector, UV 254 nm) to yield (*S*)-6-(2-aminopropyl)-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (15 mg, 31%). LC-MS-(ES, m/z): $[M+H]^+ = 334.95$.

[00226] **Example 3.** Synthesis of (S)-6-(2-aminopropyl)-2,7-dichloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (Compound 2)



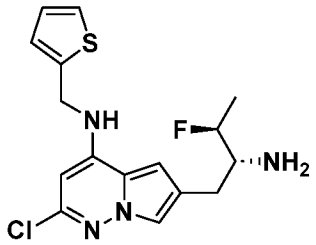
[00227] In analogy to the preparation of example 2, but using in the first step *tert*-butyl (6-bromo-2,7-dichloropyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate (intermediate **8-3**) was prepared 5 mg of (*S*)-6-(2-aminopropyl)-2,7-dichloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine. LC-MS-(ES, m/z): $[M+H]^+ = 354.90$.

[00228] **Example 4**. Synthesis of (R)-6-(2-amino-3-methoxypropyl)-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (Compound 3)



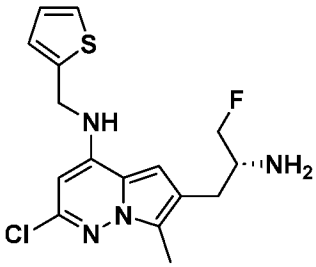
[00229] In analogy to the preparation of example 2, but using in the first step potassium (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-methoxypropyl)trifluoroborate (borate salt **2**) was prepared 7 mg of (*R*)-6-(2-amino-3-methoxypropyl)-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine. LC-MS-(ES, m/z): $[M+H]^+ = 364.95$.

[00230] **Example 5**. Synthesis of 6-((2R,3S)-2-amino-3-fluorobutyl)-2-chloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (Compound 4)



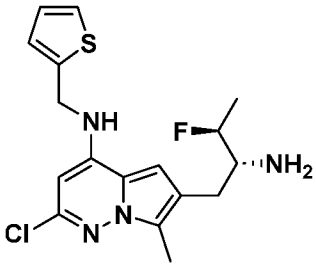
[00231] In analogy to the preparation of example 2, but using in the first step *tert*-butyl (6-bromo-2-chloropyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate (intermediate **8-2**) and potassium ((2*R*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-fluorobutyl)trifluoroborate (borate salt **3**) was prepared 12 mg of 6-((2*R*,3*S*)-2-amino-3-fluorobutyl)-2-chloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine. LC-MS-(ES, *m/z*): $[M+H]^+ = 353.00$.

[00232] **Example 6.** Synthesis of (R)-6-(2-amino-3-fluoropropyl)-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (Compound 5)



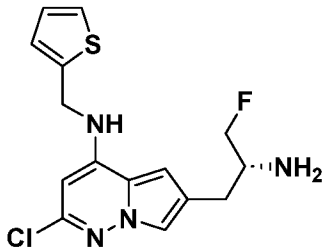
[00233] In analogy to the preparation of example 2, but using in the first step potassium (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-fluoropropyl)trifluoroborate (borate salt **4**) was prepared 6 mg of (*R*)-6-(2-amino-3-fluoropropyl)-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine. LC-MS-(ES, m/z): $[M+H]^+ = 352.95$.

[00234] **Example 7**. Synthesis of 6-((2R,3S)-2-amino-3-fluorobutyl)-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (Compound 6)



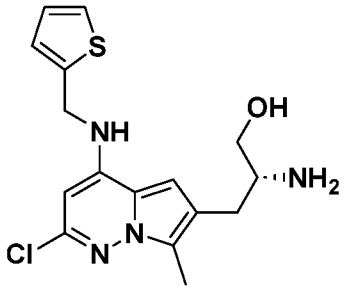
[00235] In analogy to the preparation of example 2, but using in the first step potassium ((2*R*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-fluorobutyl)trifluoroborate (borate salt **3**) was prepared 11 mg of 6-((2*R*,3*S*)-2-amino-3-fluorobutyl)-2-chloro-7-methyl-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine. LC-MS-(ES, m/z): $[M+H]^+ = 366.90$.

[00236] **Example 8.** Synthesis of (R)-6-(2-amino-3-fluoropropyl)-2-chloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (Compound 7)



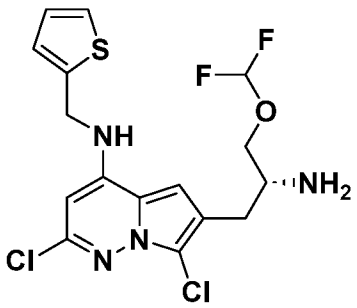
[00237] In analogy to the preparation of example 2, but using in the first step *tert*-butyl (6-bromo-2-chloropyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate (intermediate **8-2**) and potassium (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-fluoropropyl)trifluoroborate (borate salt **4**) was prepared 9 mg of (*R*)-6-(2-amino-3-fluoropropyl)-2-chloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine. LC-MS-(ES, *m/z*): $[M+H]^+ = 338.90$.

[00238] **Example 9.** Synthesis of (R)-2-amino-3-(2-chloro-7-methyl-4-((thiophen-2-ylmethyl)amino)pyrrolo[1,2-b]pyridazin-6-yl)propan-1-ol (Compound 8)



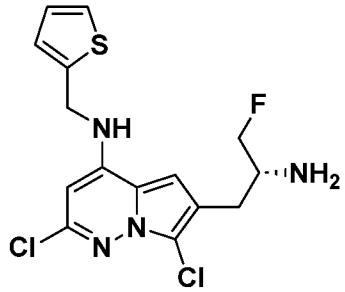
[00239] In analogy to the preparation of example 2, but using in the first step potassium (*R*)-((3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)methyl)trifluoroborate (borate salt **5**) was prepared 9 mg of (*R*)-2-amino-3-(2-chloro-7-methyl-4-((thiophen-2-ylmethyl)amino)pyrrolo[1,2-b]pyridazin-6-yl)propan-1-ol. LC-MS-(ES, m/z): $[M+H]^+ = 350.90$.

[00240] **Example 10.** Synthesis of (R)-6-(2-amino-3-(difluoromethoxy)propyl)-2,7-dichloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (Compound 9)



[00241] In analogy to the preparation of example 2, but using in the first step *tert*-butyl (6-bromo-2,7-dichloropyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate (intermediate **8-3**) and potassium (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-(difluoromethoxy)propyl)trifluoroborate (borate salt **6**) was prepared 4 mg of (*R*)-6-(2-amino-3-(difluoromethoxy)propyl)-2,7-dichloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine. LC-MS-(ES, m/z): $[M+H]^+ = 421.05$.

[00242] **Example 11**. Synthesis of (R)-6-(2-amino-3-fluoropropyl)-2,7-dichloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine (Compound 10)



[00243] In analogy to the preparation of example 2, but using in the first step *tert*-butyl (6-bromo-2,7-dichloropyrrolo[1,2-b]pyridazin-4-yl)(thiophen-2-ylmethyl)carbamate (intermediate **8-3**) and potassium (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-fluoropropyl)trifluoroborate (borate salt **4**) was prepared 5 mg of (*R*)-6-(2-amino-3-fluoropropyl)-2,7-dichloro-N-(thiophen-2-ylmethyl)pyrrolo[1,2-b]pyridazin-4-amine. LC-MS-(ES, m/z): $[M+H]^+ = 372.85$.

[00244] **Example 12**: ATXN3 Quantitative Splicing Assay.

[00245] Human neuroblastoma SK-N-MC cells were plated in 384-well plates at 20,000 cells/well. Twenty-four hours after plating, cells were treated with compounds for 24 h at appropriate concentrations ranging from 30 μM to 0.6 nM (0.3% DMSO). Treated cells were lysed in 15 μL of lysis buffer, and cDNA was synthesized using the Fast Advanced Cells-to-Ct kit. Two μL of each cDNA was used in qPCR reactions to confirm the exon 4 skipped transcripts of ATXN3. A second set of primers/probe E4E5 was used to detect the transcripts containing exon 4. The third set of primers/probe E8E9 was used to detect total gene level of ATXN3. The qPCR reactions were prepared in 384-well plates in 10 μL volume, using TaqMan™ Fast Advanced Master Mix with primers and probes shown in the table below. Reactions were run in a Quant Studio 6 qPCR instrument with default settings.

[00246] The primers and probes are listed below in **Table 3**.

Table 3.

Target Sequence	Forward Primer	Probe	Reverse Primer
ATXN3 E4skpping-FAM	SEQ ID NO: 2 5' GCAGCCTTCTGGAAATATGG 3'	SEQ ID NO: 3 5' TTCTCTATTCAGAAATGAAAGATCATT 3'	SEQ ID NO: 4 5' CTGGACCCGTCAAGAGAGAA 3'
ATXN3 E4E5-Cy5	SEQ ID NO: 5 5' TGTTCAACAGTCCAGAGTATCAG 3'	SEQ ID NO: 6 5' AGGCTCAGGATCGATCCTATAAATGAAAGA 3'	SEQ ID NO: 7 5' ACCCGTCAAGAGAGAATTCAAG 3'
ATXN3 E8E9-total-FAM	SEQ ID NO: 8 5' GATGAGGAGGATTTGCAGAGG 3'	SEQ ID NO: 9 5' ATGTTTCTGGAACTACCTTGCATACTTAGCTG 3'	SEQ ID NO: 10 5' CCTGATGTCTGTGTCATATCTTGA 3'
TBP-YAK (endogenous control)	SEQ ID NO: 11 5' TCGGAGAGTTCTGGGATT 3'	SEQ ID NO: 12 5' CCGCAGCTGCAAAATATTGTATCCACA 3'	SEQ ID NO: 13 5' AAGTGCAATGGTCTTTAGGT 3'

[00247] **Example 13**: ATXN3 total protein assay.

[00248] Human neuroblastoma SK-N-MC cells were seeded at 10,000 cells/well in 384 well plates one day prior to compound treatment. The concentrations of compounds were tested at appropriate doses ranging from 30 μM to 0.6 nM. After incubation for 48 hours, the cells were lysed with 25 μL of lysis buffer containing protease inhibitors, and total ATXN3 protein levels were assessed by Mesoscale Discovery (MSD) assay developed with one pair of anti-ATXN3 antibodies. The capture and detect antibodies were raised in mouse and rabbit respectively. Anti-rabbit MSD-ST antibody was used for secondary antibody.

[00249] ATXN3 recombinant protein was used for standards. The readouts were captured with 35 μL of MSD read buffer and multi-array 384-well high binding plates.

[00250] One plate replica was carried out for parallel viability testing by CellTiter Glo® 2.0 with a seeding density of 4,000 cells/well. Compounds were incubated for 48 hours. The viability readouts were carried out by Envision according to the manufacturer's instructions.

[00251] Compounds were tested as outlined in Examples 12 and 13 above and the results are shown below in **Table 4**.

Table 4

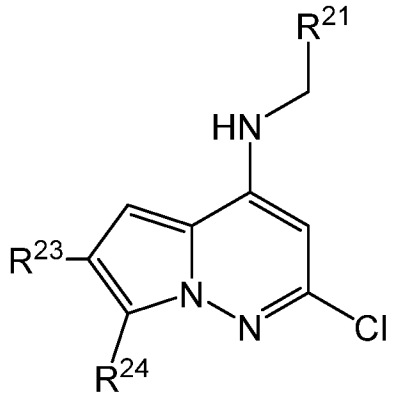
* IC_{50}/EC_{50} range (nM): $0.01 \leq A \leq 100$; $101 \leq B \leq 500$; $501 \leq C \leq 5000$; $5001 \leq D \leq 10000$; $10001 \leq E \leq 40{,}000$.

Compound	ATXN3 Potency - Protein IC50 (nM)	ATXN3 Potency - Splicing E4E5 IC50 Mean (nM)
1	B	B
2		A
3		C
4		B
5	B	C
6	B	B
7		B
8		A
9		A
10		A
11		A

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein,

- R^{21} is thiophenyl, which is unsubstituted or substituted with 1, 2, or 3, independently selected R^{1A} groups; each R^{1A} is independently selected from halo, CN, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, -C(=O)OH, -C(=O)C_{1-6} alkyl, -C(=O)C_{1-6} haloalkyl, and -C(=O)C_{1-6} alkoxy
- R^{23} is selected from the group consisting of H, azido, halo, CN, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, -(C_{1-6} alkylene)-C_{3-10} cycloalkyl, -(C_{1-6} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-6} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-6} heteroalkylene)-4-10 membered heterocycloalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4- 10 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $C(=O)R^{b3}$, $C(=O)OR^{b3}$, $NR^{c3}R^{d3}$, $C(=O)NR^{c3}R^{d3}$, $OC(=O)NR^{c3}R^{d3}$, $NR^{c3}C(=O)R^{b3}$, $NR^{c3}C(=O)OR^{b3}$, $NR^{c3}C(=O)NR^{c3}R^{d3}$, $NR^{c3}S(=O)_2R^{b3}$, $NR^{c3}S(=O)_2NR^{c3}R^{d3}$, $S(O)NR^{c3}R^{d3}$, and $S(O)_2NR^{c3}R^{d3}$, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;
- R^{24} is selected from the group consisting of H, azido, halo, CN, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4- 10 membered heterocycloalkyl, OR^{a4}, $C(=O)R^{b4}$, $C(=O)OR^{b4}$, $NR^{c4}R^{d4}$, $C(=O)NR^{c4}R^{d4}$, - $OC(=O)NR^{c4}R^{d4}$, $NR^{c4}C(=O)R^{b4}$, $NR^{c4}C(=O)OR^{b4}$, $NR^{c4}C(=O)NR^{c4}R^{d4}$, $NR^{c4}S(=O)_2R^{b4}$, $NR^{c4}S(=O)_2NR^{c4}R^{d4}$, $S(O)NR^{c4}R^{d4}$, and $S(O)_2NR^{c4}R^{d4}$, wherein the C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;
- each R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a4}, R^{b4}, R^{c4}, and R^{d4}, is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, C_{1-}

$_{6}$ alkoxy, - (C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, -(C_{1-6} alkylene)-C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, -(C_{1-6} alkylene)-C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

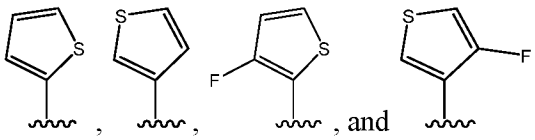
or R^{c3} and R^{d3} together with the N atom to which they are connected, come together to form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl ring, each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

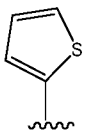
or R^{c4} and R^{d4} together with the N atom to which they are connected, come together to form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl ring, each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups; and

- each R^{20} is independently selected from the group consisting of OH, SH, CN, NO_2, halo, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carbamyl, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{1-4} alkylcarbonyl, C_{1-4} alkoxycarbonyl, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, aminosulfonyl, C_{1-4} alkylaminosulfonyl, di(C_{1-4} alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4} alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, di(C_{1-4} alkyl)aminocarbonylamino, and amidinyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein each R^{1A} is independently selected from C_{1-6} alkyl, C_{1-6} haloalkyl, and halo.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^{1A} is fluoro.

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^{21} is selected from the group consisting of,  .

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^{21} is  .

6. The compound of any of the preceding claims, wherein R^{23} is substituted or unsubstituted C_{1-6} alkyl or substituted or unsubstituted C_{1-6} heteroalkyl.

7. The compound of claim 6, or a pharmaceutically acceptable salt, wherein R^{23} is $CH_2CHNH_2CH_3$.

8. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein R^{23} is $CH_2CHNH_2CH_2OH$.

9. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein R^{23} is $CH_2CHNH_2CHFCH_3$.

10. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein R^{23} is $CH_2CHNH_2CH_2CH_2OH$.

11. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein R^{23} is $CH_2CHNH_2CH_2F$.

12. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein R^{23} is $CH_2CHNH_2CH_2OCH_3$.

13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^{23} is $CH_2CHNH_2CH_2OCD_3$.

14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein R^{24} is selected from the group consisting of hydrogen, OH, halo, CN, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxyl, substituted or unsubstituted C_{3-6} cycloalkyl, substituted or unsubstituted C_{2-4} alkenyl, and substituted or unsubstituted C_{2-4} alkynyl.

15. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein R^{24} is substituted or unsubstituted C_{1-6} alkyl.

16. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein R^{24} is selected from the group consisting of F, Cl, and Br.

17. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from Table 1.

18. A pharmaceutical composition comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

19. A method of treating, preventing, delaying of progress, or ameliorating symptoms of a disease or a condition associated with ATXN3 expression level or activity level in a subject in need thereof, comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1-17.

20. A method of modulating splicing of a ATXN3 pre-mRNA, comprising contacting a compound or salt of any one of claims 1-17 to the ATXN3 pre-mRNA with a splice site sequence or cells comprising the ATXN3 pre-mRNA, wherein the compound binds to the ATXN3 pre-mRNA and modulates splicing of the ATXN3 pre-mRNA in a cell of a subject to produce a spliced product of the ATXN3 pre-mRNA.

21. Use of a compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition or disease associated with ATXN3 expression level or activity level.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/012061

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P25/00 C07D487/04 A61K31/5025
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2022/169864 A1 (PTC THERAPEUTICS INC [US]) 11 August 2022 (2022-08-11) the whole document	1-21
A	WO 2022/169868 A1 (PTC THERAPEUTICS INC [US]) 11 August 2022 (2022-08-11) the whole document	1-21
A	WO 2014/143607 A1 (BRISTOL MYERS SQUIBB CO [US]) 18 September 2014 (2014-09-18) N-benzyl-2,5-dichloropyrrolo[1,2-b]pyridazine-4- amine; page 41	1-21

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2024	26/03/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sarakinos, Georgios

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/012061

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2024/012061

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022169864 A1	11-08-2022	EP 4288441 A1	13-12-2023
		WO 2022169864 A1	11-08-2022
WO 2022169868 A1	11-08-2022	EP 4288059 A1	13-12-2023
		US 2024043444 A1	08-02-2024
		WO 2022169868 A1	11-08-2022
WO 2014143607 A1	18-09-2014	CN 105008366 A	28-10-2015
		EP 2970295 A1	20-01-2016
		ES 2616026 T3	09-06-2017
		JP 6386527 B2	05-09-2018
		JP 2016512504 A	28-04-2016
		US 2016016961 A1	21-01-2016
		WO 2014143607 A1	18-09-2014