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(54) Title: COMPOSITIONS USEFUL FOR MODULATING SPLICING

(57) Abstract: Described herein are compounds 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.

WO 2023/220433 A1

COMPOSITIONS USEFUL FOR MODULATING SPLICING

CROSS REFERENCE

[001] This application claims the benefit of priority to U.S. Provisional Application No. 63/341,358, filed May 12, 2022, which is incorporated herein by reference in its entirety.

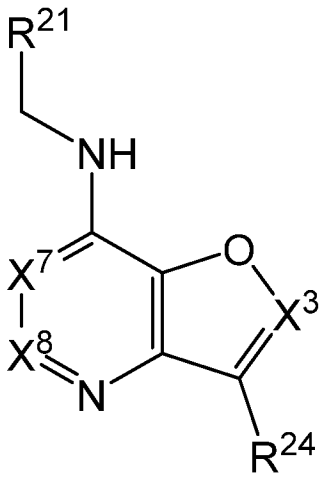
BACKGROUND

[002] 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.

[003] SCA3 is caused by CAG tri-nucleotide repeats in exon 10 of the Ataxin 3 (ATXN3) gene. ATXN3 encodes for a deubiquitinase 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

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



Formula (I)

wherein X^3, X^7, X^8, R^{21}, and R^{24} are as defined herein.

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

[006] 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.

[007] 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

[008] 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

[009] 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

[0010] 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.

[0011] "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.

[0012] 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.

[0013] 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.

[0014] 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.

[0015] 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.

[0016] The term "substituent" denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule.

[0017] 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.

[0018] 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.

[0019] 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).

[0020] 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.

[0021] The term "oxo" refers to the =O substituent.

[0022] "Carboxyl" refers to -COOH.

[0023] "Cyano" refers to -CN.

[0024] The term "thioxo" refers to the =S substituent.

[0025] The term "halo," "halogen," and "halide" are used interchangeably herein and denote fluoro, chloro, bromo, or iodo.

[0026] 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 –$CH_2CH_2CH_2$–.

[0027] 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.

[0028] 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.

[0029] 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 –$CH_2CH=CH_2$.

[0030] 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, –$C≡CCH_3$ –$C≡CCH_2CH_3$, –$CH_2C≡CH$.

[0031] 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).

[0032] 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.

[0033] 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.

[0034] "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.

[0035] "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.

[0036] "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.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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.

[0043] The term "haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, 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.

[0044] The term "haloalkoxy" refers to an alkoxy radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, 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.

[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 –$OCH_2CH_2OCH_2CH_2NH_2$.

[0047] "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. 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 is 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

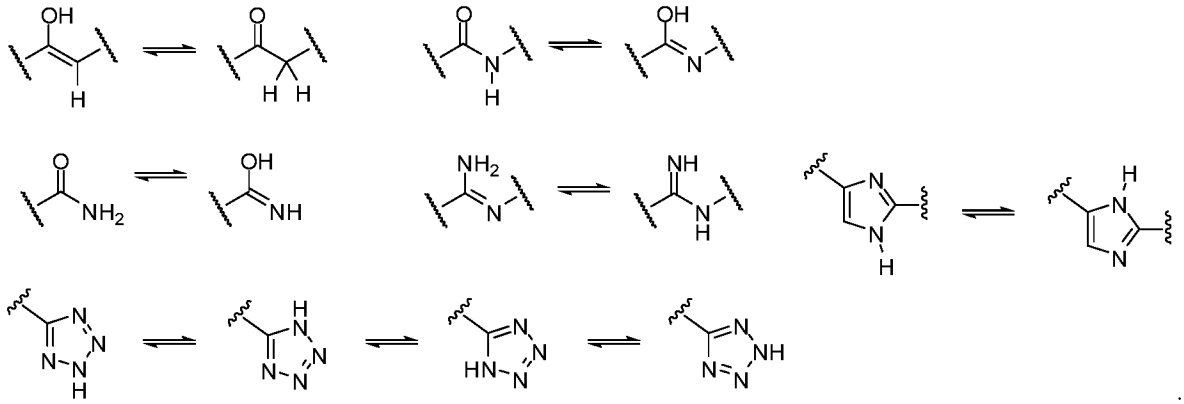
embodiments, heteroaryl is pyridinyl, pyrazinyl, pyrimidinyl, thiazolyl, thienyl, thiadiazolyl or furyl. In some embodiments, a heteroaryl contains 0–6 N atoms in the ring. In some embodiments, a heteroaryl contains 1–4 N atoms in the ring. In some embodiments, a heteroaryl contains 4–6 N atoms in the 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, oxo, –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, oxo, –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.

[0061] A ribonucleoprotein (RNP) refers to a nucleoprotein that contains RNA. An RNP can be a complex of a ribonucleic acid and an RNA–binding protein. Such a combination can also be referred to as a protein–RNA complex. These complexes can function in a number of biological functions that include, but are not limited to, DNA replication, gene expression, metabolism of RNA, and pre-mRNA splicing. Examples of RNPs include the ribosome, the

enzyme telomerase, vault ribonucleoproteins, RNase P, heterogeneous nuclear RNPs (hnRNPs) and small nuclear RNPs (snRNPs).

[0062] Nascent RNA transcripts from protein–coding genes and mRNA processing intermediates, collectively referred to as pre-mRNA, are generally bound by proteins in the nuclei of eukaryotic cells. From the time nascent transcripts first emerge from RNA polymerase (*e.g.*, RNA polymerase II) until mature mRNAs are transported into the cytoplasm, the RNA molecules are associated with an abundant set of splicing complex components (*e.g.*, nuclear proteins and snRNAs). These proteins can be components of hnRNPs, which can contain heterogeneous nuclear RNA (hnRNA) (*e.g.*, pre-mRNA and nuclear RNA complexes) of various sizes.

[0063] Splicing complex components function in splicing and/or splicing regulation. Splicing complex components can include, but are not limited to, ribonuclear proteins (RNPs), splicing proteins, small nuclear RNAs (snRNAs), small nuclear ribonucleoproteins (snRNPs), and heterogeneous nuclear ribonucleoproteins (hnRNPs). Splicing complex components include, but are not limited to, those that may be required for splicing, such as constitutive splicing, alternative splicing, regulated splicing, and splicing of specific messages or groups of messages. A group of related proteins, the serine/arginine–rich (SR) proteins, can function in constitutive pre-mRNA splicing and may also regulate alternative splice–site selection in a concentration–dependent manner. SR proteins typically have a modular structure that consists of one or two RNA–recognition motifs (RRMs) and a C–terminal rich in arginine and serine residues (RS domain). Their activity in alternative splicing may be antagonized by members of the hnRNP A/B family of proteins. Splicing complex components can also include proteins that are associated with one or more snRNAs. snRNAs in human include, but are not limited to, U1 snRNA, U2 snRNA, U4 snRNA, U5 snRNA, U6 snRNA, U11 snRNA, U12 snRNA, U4atac snRNA, U5 snRNA, and U6atac snRNA. SR proteins in human include, but are not limited to, SC35, SRp55, SRp40, SRm300, SFRS10, TASR–1, TASR–2, SF2/ASF, 9G8, SRp75, SRp30c, SRp20, and P54/SFRS11. Other splicing complex components in human that can be involved in splice site selection include, but are not limited to, U2 snRNA auxiliary factors (*e.g.* U2AF65, U2AF35), Urp/U2AF1–RS2, SF1/BBP, CBP80, CBP 20, SF1 and PTB/hnRNP1. hnRNP proteins in humans include, but are not limited to, A1, A2/B1, L, M, K, U, F, H, G, R, I and C1/C2. Human genes encoding hnRNPs include *HNRNPA0*, *HNRNPA1*, *HNRNPA1L1*, *HNRNPA1L2*, *HNRNPA3*, *HNRNPA2B1*, *HNRNPAB*, *HNRNPB1*, *HNRNPC*, *HNRNPCL1*, *HNRNPD*, *HNRPDL*, *HNRNPF*, *HNRNPH1*, *HNRNPH2*, *HNRNPH3*, *HNRNPK*, *HNRNPL*,

HNRPLL, *HNRNPM*, *HNRNPR*, *HNRNPU*, *HNRNPUL1*, *HNRNPUL2*, *HNRNPUL3*, and *FMR1*.

[0064] In some embodiments, the splicing complex component comprises a nucleic acid, a protein, a carbohydrate, a lipid, a co–factor, a nutrient, a metabolite, or an auxiliary splicing factor. In some embodiments, the splicing complex component comprises an auxiliary splicing factor such as a ribonucleoprotein (RNP) which can be a heterogeneous nuclear ribonucleoprotein (hnRNP) or a small nuclear ribonucleoprotein (snRNP). In some embodiments, the auxiliary splicing factor includes, but are not limited to, 9G8, A1 hnRNP, A2 hnRNP, ASD–1, ASD–2b, ASF, B1 hnRNP, C1 hnRNP, C2 hnRNP, CBP20, CBP80, CELF, F hnRNP, FBP11, Fox–1, Fox–2, G hnRNP, H hnRNP, hnRNP C, hnRNP G, hnRNP K, hnRNP M, hnRNP U, Hu, HUR, K hnRNP, KH–type splicing regulatory protein (KSRP), L hnRNP, M hnRNP, mBBP, muscle–blind like (MBNL), NF45, NFAR, Nova–1, Nova–2, P54/SFRS11, polypyrimidine tract binding protein (PTBP) 1, PTBP2, PRP19 complex proteins, R hnRNP, RNPC1, SAM68, SC35, SF, SF1/BBP, SF2, SF3 a, SF3B, SFRS10, Sm proteins, SR proteins, SRm300, SRp20, SRp30c, SRP35C, SRP36, SRP38, SRp40, SRp55, SRp75, SRSF, STAR, GSG, SUP–12, TASR–1, TASR–2, TIA, TIAR, TRA2, TRA2a/b, U hnRNP, U1 snRNP, U11 snRNP, U12 snRNP, U1-70K, U1-A, U1–C, U2 snRNP, U2AF1–RS2, U2AF35, U2AF65, U4 snRNP, U5 snRNP, U6 snRNP, Urp, and YB1.

[0065] Splicing complex components may be stably or transiently associated with a snRNP or with a transcript (*e.g.*, pre-mRNA). In some embodiments, the pre-mRNA binds to a splicing complex or a component thereof.

[0066] The term “intron” refers to both the DNA sequence within a gene and the corresponding sequence in the unprocessed RNA transcript. As part of the RNA processing pathway, introns can be removed by RNA splicing either shortly after or concurrent with transcription. Introns are found in the genes of most organisms and many viruses. They can be located in a wide range of genes, including those that generate proteins, ribosomal RNA (rRNA), and transfer RNA (tRNA).

[0067] An “exon” can be any part of a gene that encodes a part of the final mature RNA produced by that gene after introns have been removed by RNA splicing. The term “exon” refers to both the DNA sequence within a gene and to the corresponding sequence in RNA transcripts.

[0068] A “spliceosome” can be assembled from snRNAs and protein complexes. The spliceosome can remove introns from a transcribed pre-mRNA.

[0069] The term "cryptic exon" can refer to an intronic sequence that may be flanked by apparent consensus splice sites (*e.g.*, cryptic splice site) but are generally not spliced into the mature mRNA or the product of splicing. The term "poison exon" can refer to a cryptic exon that contains a premature termination codon in the reading frame of the exon when included in an RNA transcript. "Poison exon" can also refer to a cryptic exon inclusion of which in an RNA transcript causes a reading frameshift in downstream exons resulting in a premature stop codon, which was not in frame prior to the frameshift caused by inclusion of the cryptic exon. In some embodiments, the poison exon is a variant of an existing exon. In some embodiments, the poison exon is an extended form of an existing exon. In some embodiments, the poison exon is a truncated form of an existing exon. The terms "poison exon" and "toxic exon" are used interchangeably in the present disclosure. The terms "stop codon" and "termination codon" are used interchangeably in the present disclosure.

[0070] A splicing event that promotes inclusion of a poison exon can further promote inclusion of an intron immediately following the poison exon in an RNA transcript. Inclusion of the poison exon and the intron immediately following the poison exon can result in "nuclear retention" of the RNA transcript, *e.g.*, mRNA, wherein the RNA transcript is retained in the nucleus and not transported or exported to the cytoplasm and thus, not translated into a protein.

Small Molecule Splicing Modulators (SMSMs)

[0071] It has now been found that compounds of this disclosuredisclosure, 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 disclosuredisclosure 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. These SMSMs can operate by a variety of mechanisms to modify splicing events. For example, the SMSMs of this disclosuredisclosure can: 1) interfere with the formation and/or function and/or other properties of splicing complexes, spliceosomes, and/or their components such as hnRNPs, snRNPs, SR–proteins and other splicing factors or elements, resulting in the prevention or induction of a splicing event in a pre-mRNA molecule. As another example, the SMSMs of this disclosuredisclosure can: 2) prevent and/or modify post–transcriptional regulation (*e.g.*, splicing) of gene products, such as hnRNPs, snRNPs, SR–proteins and other splicing factors, which can subsequently be involved in the formation and/or function of a spliceosome or splicing

complex component; 3) prevent and/or modify phosphorylation, glycosylation and/or other modifications of gene products including, but not limited to, hnRNPs, snRNPs, SR–proteins and other splicing factors, which can subsequently be involved in the formation and/or function of a spliceosome or splicing complex component; or 4) bind to and/or otherwise affect specific pre-mRNA so that a specific splicing event is prevented or induced, *e.g.*, via a mechanism that does not involve base-pairing with RNA in a sequence–specific manner. The small molecules of this disclosuredisclosure are different from and are not related to antisense or antigene oligonucleotides.

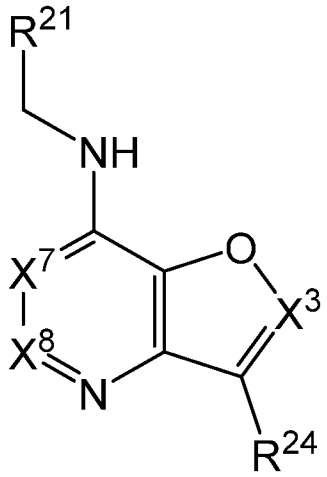
[0072] Described herein are compounds modifying splicing of gene products for use in the treatment, prevention, and/or delay of progression of diseases or conditions. Described herein are compounds modifying splicing of gene products wherein the compounds induce a transcriptionally inactive variant or transcript of a gene product. Described herein are compounds modifying splicing of gene products wherein the compounds induce a transcriptionally active variant or transcript of a gene product. Described herein are compounds modifying splicing of gene products wherein the compounds repress a transcriptionally active variant or transcript of a gene product. Described herein are compounds modifying splicing of gene products wherein the compounds repress a transcriptionally inactive variant or transcript of a gene product.

[0073] Described herein are compounds modifying splicing of gene products wherein the compounds induce a specific variant or isoform of a mature mRNA. Described herein are compounds modifying splicing of gene products wherein the compounds cause increased expression of a protein encoded by a variant or an isoform of an mRNA derived from a pre-mRNA that the compounds bind. Described herein are compounds modifying splicing of gene products wherein the compounds cause increased expression of a variant or an isoform of an mRNA derived from a pre-mRNA that the compounds bind, leading to increased expression of the protein encoded by the variant or the isoform of the mRNA. Described herein are compounds modifying splicing of gene products wherein the compounds cause increased expression of a variant or an isoform of an mRNA containing a specific exon by inducing exon inclusion in a pre-mRNA that compounds bind, leading to increased expression of the protein encoded by the variant or the isoform of the mRNA. Described herein are compounds modifying splicing of gene products wherein the compounds cause exon inclusion in a pre-mRNA that compounds bind, leading to increased expression of the protein encoded by the specific variant or the isoform of the mRNA.

[0074] Described herein are compounds modifying splicing of gene products wherein the compounds repress a specific variant or isoform of a mature mRNA. Described herein are compounds modifying splicing of gene products wherein the compounds cause decreased expression of a protein encoded by a variant or an isoform of an mRNA derived from a pre-mRNA that the compounds bind. Described herein are compounds modifying splicing of gene products wherein the compounds cause decreased expression of a variant or an isoform of an mRNA derived from a pre-mRNA that the compounds bind, leading to decreased expression of the protein encoded by the variant or the isoform of the mRNA. Described herein are compounds modifying splicing of gene products wherein the compounds cause decreased expression of a variant or an isoform of an mRNA containing a specific exon by inducing exon inclusion in a pre-mRNA that compounds bind, leading to decreased expression of the protein encoded by the variant or the isoform of the mRNA. Described herein are compounds modifying splicing of gene products wherein the compounds cause exon inclusion in a pre-mRNA that compounds bind, leading to decreased expression of the protein encoded by the specific variant or the isoform of the mRNA.

[0075] Described herein are compounds modifying splicing of gene products wherein the compounds induce a post-transcriptionally inactive variant or transcript of a gene product. Described herein are compounds modifying splicing of gene products wherein the compounds repress a post-transcriptionally active variant or transcript of a gene product. Described herein are compounds modifying splicing of gene products wherein the compounds induce a post-transcriptionally destabilized variant or transcript of a gene product. Described herein are compounds modifying splicing of gene products wherein the compounds cause less expression of a protein encoded by an mRNA derived from a pre-mRNA that the compounds bind. Described herein are compounds modifying splicing of gene products wherein the compounds cause less expression of an mRNA derived from a pre-mRNA that the compounds bind, leading to decreased expression of the protein encoded by the mRNA. Described herein are compounds modifying splicing of gene products wherein the compounds cause increased expression of an mRNA containing a poison exon derived from a pre-mRNA that compounds bind, leading to decreased expression of the protein encoded by the mRNA. Described herein are compounds modifying splicing of gene products wherein the compounds cause nonsense-mediated decay (NMD) of an mRNA derived from a pre-mRNA that compounds bind, leading to decreased expression of the protein encoded by the mRNA.

[0076] In one aspect, a SMSM described herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

- X^3 is selected from the group consisting of N, and CR^{23};
- X^7 is CR^{27} or N;
- X^8 is CR^{28} or N;
- R^{21} is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 5-6 membered heterocycloalkyl, each of which is unsubstituted or substituted with 1, 2, 3 or 4, 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_{1-4} haloalkoxy, 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_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4- 10 membered heterocycloalkyl, -(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_{1-6} alkylene)-C_{6-10} aryl, -(C_{1-6} alkylene)-5-10 membered heteroaryl, -(C_{1-6} heteroalkylene)-C_{6-10} aryl, -(C_{1-6} heteroalkylene)-5-10 membered heteroaryl, -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_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl,

and 4- 10 membered heterocycloalkyl, are each unsubstituted or substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{20} groups;

- R^{24} is -C≡C-R^{20d} or C_{3-6} alkynyl, wherein the C_{3-6} alkynyl is optionally substituted with 1, 2, 3, or 4 independently selected R^{20d} groups;

R^{27} is selected from the group consisting of H, azido, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, -CN, -NO_2, -OR^{a7}, -C(=O)R^{b7}, -C(=O)OR^{b7}, -$NR^{c7}R^{d7}$, -C(=O)$NR^{c7}R^{d7}$, -OC(=O)$NR^{c7}R^{d7}$, -NR^{c7}C(=O)R^{b7}, -NR^{c7}C(=O)OR^{b7}, -NR^{c7}C(=O)$NR^{c7}R^{d7}$, -NR^{c7}S(=O)$_2R^{b7}$, and -NR^{c7}S(=O)$_2NR^{c7}R^{d7}$, wherein the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups;

R^{28} is selected from the group consisting of H, azido, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, -CN, -NO_2, -OR^{a8}, -C(=O)R^{b8}, -C(=O)OR^{b8}, -$NR^{c8}R^{d8}$, -C(=O)$NR^{c8}R^{d8}$, -OC(=O)$NR^{c8}R^{d8}$, -NR^{c8}C(=O)R^{b8}, -NR^{c8}C(=O)OR^{b8}, -NR^{c8}C(=O)$NR^{c8}R^{d8}$, -NR^{c8}S(=O)$_2R^{b8}$, and -NR^{c8}S(=O)$_2NR^{c8}R^{d8}$, wherein the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl 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^{a7}, R^{b7}, R^{c7}, R^{d7}, R^{a8}, R^{b8}, R^{c8}, and R^{d8} 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 each of which is unsubstituted or substituted with 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 a 4-10 membered heterocycloalkyl ring, each of which is unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups;

each R^{20} is independently selected from the group consisting of -OH, -SH, -CN, -NO_2, halo, oxo, amino, carbamyl, carbamoyl, 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_{6-10} aryl, 4-6 membered heteroaryl, 5-6 membered heterocycloalkyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, 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; and

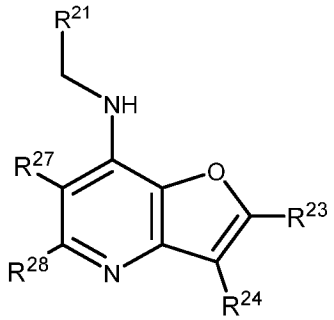
each R^{20d} is independently selected from the group consisting of -OH, -SH, -CN, -NO_2, halogen, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} heteroalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} 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, and di(C_{1-4} alkyl)aminocarbonylamino.

[0077] In some embodiments of a compound of Formula (I), (Ia) or (Ib), R^{23} is substituted with 1, 2, 3, or 4 independently selected R^{20} groups.

[0078] In some embodiment, R^{24} is propynyl.

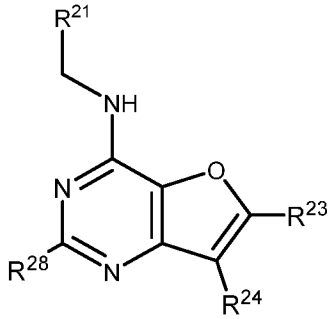
[0079] In some embodiments, X^8 is CR^{28}. In some embodiments, X^8 is CR^{28}, wherein R^{28} is hydrogen. In some embodiments, X^8 is N. In some embodiments, X^7 is CR^{27}. In some embodiments, X^7 is N.

[0080] In some embodiments, the compound is of the Formula (Ia).

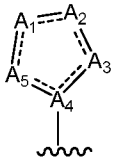
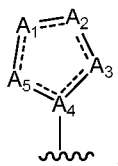


Formula (Ia).

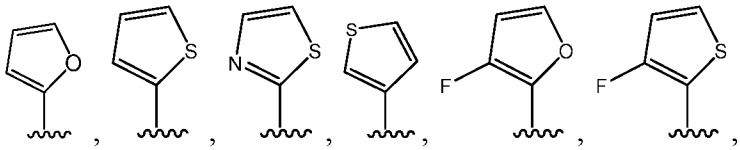
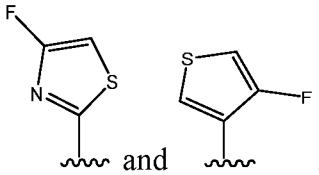
[0081] In some embodiments, the compound is of the Formula (Ib).



Formula (Ib).

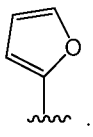
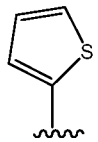
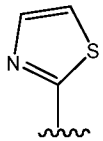
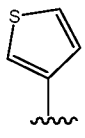
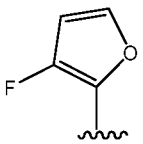
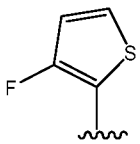
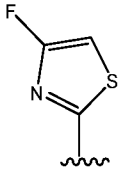
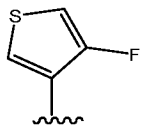
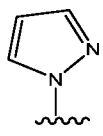
[0082] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{21} is selected from the group consisting of phenyl and 5-6 membered heteroaryl, each of which is unsubstituted or substituted with 1, 2, 3 or 4, 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. In some embodiments, R^{21} is unsubstituted or substituted 5 membered heteroaryl. In some embodiments, R^{21} is unsubstituted or substituted 5 membered heterocycloalkyl. In some embodiments, R^{21} is unsubstituted. In some embodiments, R^{21} 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 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 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, R^{21} is  wherein ====== represents a single or a double bond; each of A_1, A_2, A_3, and A_5 is independently selected from the group consisting of O, S, N, NH, NR^{1A}, CH, CR^{1A}, CH_2, and CHR^{1A}; and A_4 is selected from the group consisting of N, C, CH and CR^{1A}. In some embodiments, R^{21} is  , wherein ====== represents a single or a double bond; each of A_1, A_2, A_3, and A_5 is independently selected from the group consisting

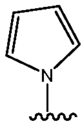
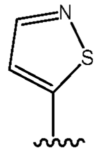
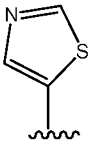
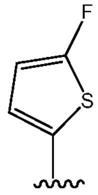
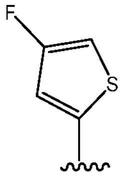
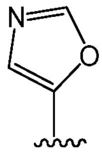
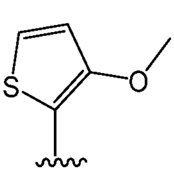
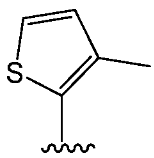
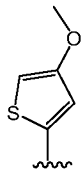
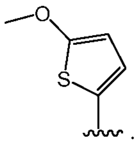
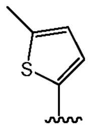
of O, S, N, NH, NR^{1A}, C, CH, CR^{1A}, CH_2, and CHR^{1A}; and A4 is selected from the group consisting of N, C, CH and CR^{1A} .

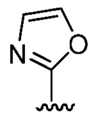
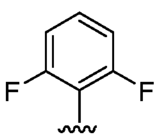
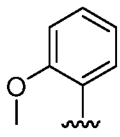
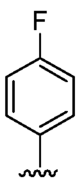
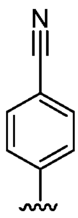
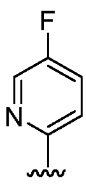
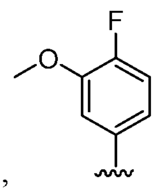
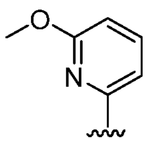
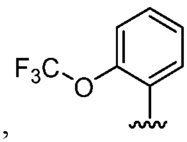
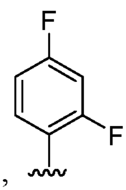
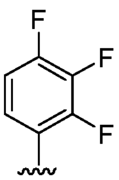
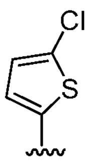
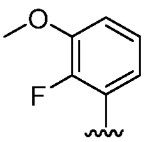
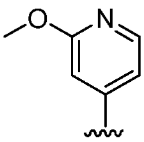
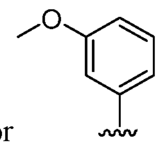
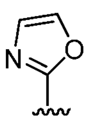
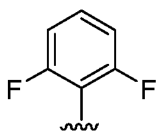
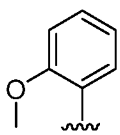
[0083] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{21} is selected from the group consisting of  and  .

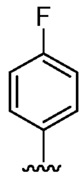
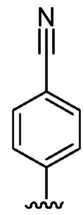
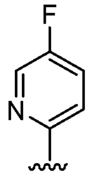
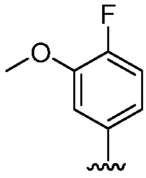
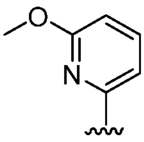
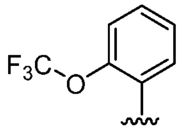
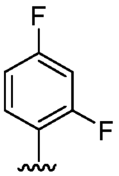
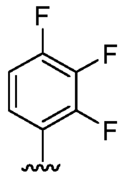
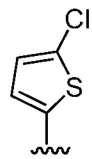
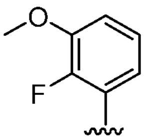
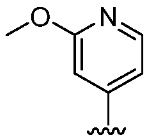
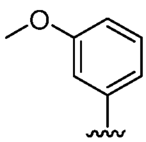
[0084] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{21} is 5 membered heteroaryl. In some embodiments, R^{21} is furanyl, or thiazolyl each of which is substituted or unsubstituted.

[0085] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{21} is unsubstituted furanyl. In some embodiments, R^{21} is substituted furanyl. In some embodiments, R^{21} is unsubstituted thiazolyl. In some embodiments, R^{21} is substituted thiazolyl.

[0086] 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

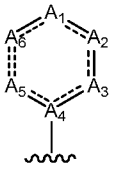
some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is 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

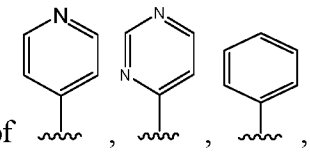
[0087] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{21} is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In

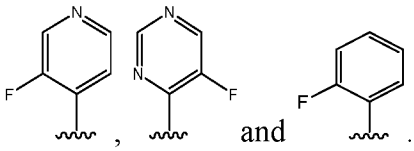
some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is  . In some embodiments, R^{21} is 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

[0088] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{21} is unsubstituted or substituted phenyl. In some embodiments, R^{21} is unsubstituted or substituted 6 membered heteroaryl. In some embodiments, R^{21} is unsubstituted or substituted 6 membered heterocycloalkyl. In some embodiments, R^{21} is unsubstituted. In some embodiments, R^{21} is substituted with 1, 2, 3, or 4 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 substituted with 1, 2, 3, or 4 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 substituted with 1, 2, 3, or 4 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, R^{21} is  wherein ------ represents a single or a double bond; each of A_1, A_2, A_3, A_5 and A_6 is independently selected from the group consisting of O, S, N, NH, NR^{1A}, CH, CR^{1A}, CH_2, and CHR^{1A}; and A_4 is selected from the group consisting of N, C, CH and CR^{1A}. In some embodiments, R^{21} is

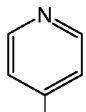
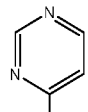
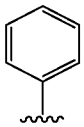
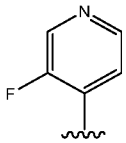
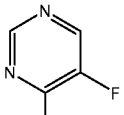
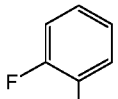


, wherein ------ represents a single or a double bond; each of A_1, A_2, A_3, A_5 and A_6 is independently selected from the group consisting of O, S, N, NH, NR^{1A}, C, CH, CR^{1A}, CH_2, and CHR^{1A}; and A_4 is selected from the group consisting of N, C, CH, and CR^{1A} . In some embodiments, R^{21} is selected from the group consisting of 

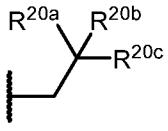
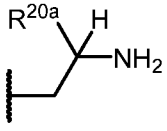


[0089] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{21} is substituted or unsubstituted phenyl. In some embodiments, R^{21} is 6 membered heteroaryl. In some embodiments, R^{21} is pyridinyl, thiophenyl, pyrimidinyl, each of which is substituted or unsubstituted.

[0090] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{21} is unsubstituted pyridinyl. In some embodiments, R^{21} is substituted pyridinyl. In some embodiments, R^{21} is unsubstituted thiophenyl. In some embodiments, R^{21} is substituted thiophenyl. In some embodiments, R^{21} is unsubstituted pyrimidinyl. In some embodiments, R^{21} is substituted pyrimidinyl.

[0091] 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  .

[0092] In some embodiments of a compound of Formula (I) or (Ia), X^3 is CH. In some embodiments, X^3 is CR^{23}. In some embodiments, X^3 is CR^{23}, wherein R^{23} is C_{1-6} alkyl or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl and C_{1-6} heteroalkyl are unsubstituted or substituted independently with 1, 2, 3, or 4 R^{20} groups. In some embodiments, X^3 is $CCH_2CHNH_2CH_3$. In some embodiments, X^3 is $CCH_2CHNH_2CH_2OH$. In some embodiments, X^3 is $CCH_2CHNH_2CH_2CH_3$. In some embodiments, X^3 is $CCH_2CHNH_2CH_2CH_2OH$. In some embodiments, X^3 is $CCH_2CHNH_2CH_2CH_2F$. In some embodiments, X^3 is $CCH_2CHNH_2CH_2CHF_2$. In some embodiments, X^3 is $CCH_2CHNH_2CH_2CH(CH_3)_2$. In some embodiments, R^{24} is selected from $-C{\equiv}C-R^{20d}$ and C_{3-6} alkynyl, wherein the C_{3-6} alkynyl is optionally substituted by 1, 2, 3, or 4 independently selected R^{20d} groups. In some embodiments, R^{24} is propyne. In some embodiments, X^8 is N. In some embodiments, X^8 is CR^{28}.

[0093] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{23} (or,  or ) is selected from the group consisting of 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_{1-6} alkylene)-C_{6-10} aryl, -(C_{1-6} alkylene)-5-10 membered heteroaryl, -(C_{1-6} heteroalkylene)-C_{6-10} aryl, and -(C_{1-6} heteroalkylene)-5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4- 10 membered heterocycloalkyl are each unsubstituted or substituted with 1, 2, 3, 4, 5, 6, 7, or 8 independently selected R^{20} groups. 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 $CH_2CHNH_2CH_2OCD_3$. In some embodiments, R^{23} is $CF_2CH(NH_2)CH_3$. In some embodiments, R^{23} is $CH_2CH(NH_2)CH_2OCH_3$. In some embodiments, R^{23} is $CF_2CH(NH_2)CH_3$. In some embodiments, R^{23} is $CH_2CH(NH_2)CHF_2$.

[0094] In some embodiments of a compound of Formula (I) or (Ia), R^{23} is H.

[0095] In some embodiments of a compound of Formula (I) or (Ia), 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_{1-3}alkyl, C_{1-3}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_{1-3}alkoxy.

[0096] In some embodiments of a compound of Formula (I) or (Ia), 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.

[0097] In some embodiments of a compound of Formula (I) or (Ia), 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.

[0098] In some embodiments of a compound of Formula (I) or (Ia), R^{23} is substituted or unsubstituted C_{2-6} alkynyl. In some embodiments, R^{23} is C_{2-6} alkynyl, wherein C_{2-6} alkynyl is substituted with 1, 2, or 3 independently selected R^{20} groups.

[0099] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), each R^{20} is independently selected from the group consisting of -OH, -SH, -CN, $-NO_2$, halogen, 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, and di(C_{1-4} alkyl)aminocarbonylamino, and wherein each of the alkyl, alkenyl, phenyl, cycloalkyl, alkenyl, heteroaryl, and heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 groups independently selected from OH, -SH, -CN, $-NO_2$, halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, amino, oxo, C_{1-4} alkylamino, and di(C_{1-4} alkyl)amino.

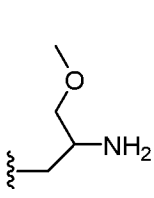
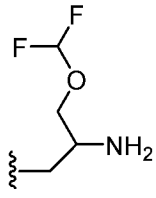
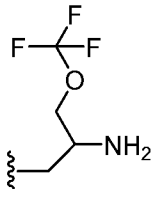
[00100] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), each R^{20} is independently selected from the group consisting of -OH, -SH, -CN, $-NO_2$, halogen, oxo, C_{1-4} 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, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, amino, C_{1-4} alkylamino, and di(C_{1-4} alkyl)amino, and wherein each of the alkyl, alkenyl, phenyl, cycloalkyl, alkenyl, heteroaryl, and heterocycloalkyl is optionally substituted with 1, 2, 3, or 4 groups independently selected from OH, -SH, -CN, $-NO_2$, halogen, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, amino, C_{1-4} alkylamino, and di(C_{1-4} alkyl)amino.

[00101] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), each R^{20} is independently selected from the group consisting of -OH, -SH, -CN, $-NO_2$, halogen,

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} heteroalkyl, 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, and di(C_{1-4} alkyl)aminocarbonylamino, wherein alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, phenyl, heteroaryl and heterocycloalkyl are each optionally substituted with 1, 2, 3 or 4 R^{31} groups, wherein each R^{31} is independently -OH, -SH, -CN, -NO_2, halogen, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy. In some embodiments, R^{31} is -OH. In some embodiments, R^{31} is -SH. In some embodiments, R^{31} is -CN. In some embodiments, R^{31} is -NO_2. In some embodiments, R^{31} is halogen. In some embodiments, R^{31} is oxo. In some embodiments, R^{31} is C_{1-4} alkyl. In some embodiments, R^{31} is C_{2-4} alkenyl. In some embodiments, R^{31} is C_{1-4} haloalkyl. In some embodiments, R^{31} is C_{1-4} cyanoalkyl. In some embodiments, R^{31} is C_{1-4} hydroxyalkyl. In some embodiments, R^{31} is C_{1-4} alkoxy.

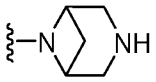
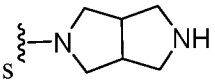
[00102] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), each R^{20} is independently selected from the group consisting of -OH, -SH, -CN, -NO_2, halogen, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} heteroalkyl, 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, and di(C_{1-4} alkyl)aminocarbonylamino, wherein alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, phenyl, heteroaryl and heterocycloalkyl are each optionally substituted with 1, 2, 3 or 4 R^{31} groups, wherein each R^{31} is independently oxo, halogen, methyl, ethyl, -CN, -CF_3, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, R^{31} is oxo. In some embodiments, R^{31} halogen. In some embodiments, R^{31} methyl, ethyl. In some

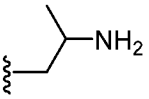
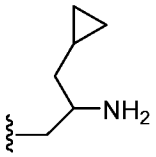
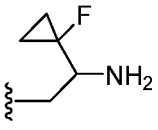
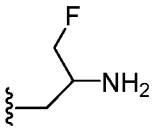
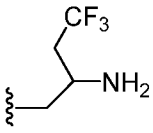
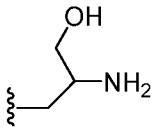
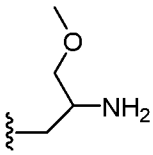
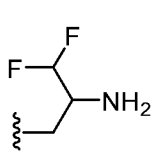
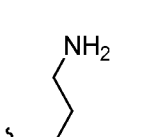
embodiments, R^{31} -CN. In some embodiments, R^{31} $-CF_3$. In some embodiments, R^{31} -OH. In some embodiments, R^{31} -OMe. In some embodiments, R^{31} $-NH_2$. In some embodiments, R^{31} $-NO_2$.

[00103] In some embodiments of a compound of Formula (I), (Ia) or (Ib), R^{23} is C_{1-6} alkyl or C_{1-6} heteroalkyl, and wherein the C_{1-6} alkyl and C_{1-6} heteroalkyl are substituted independently with 1, 2, or 3 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. In some embodiments, the C_{1-6} heteroalkyl is  ,  , or  . In some embodiments, C_{1-6} alkyl is substituted with 1 R^{20} group. In some embodiments, C_{1-6} alkyl is substituted with 2 independently selected R^{20} groups. In some embodiments, C_{1-6} alkyl is substituted with 3 independently selected R^{20} groups. In some embodiments, C_{1-6} heteroalkyl is substituted with 1 R^{20} group. In some embodiments, C_{1-6} heteroalkyl is substituted with 2 independently selected R^{20} groups. In some embodiments, C_{1-6} heteroalkyl is substituted with 3 independently selected R^{20} groups.

[00104] In some embodiments of a compound of Formula (I), (Ia) or (Ib), R^{23} is selected from the group consisting of hydrogen, oxo, azido, halogen, -CN, $-NO_2$, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, 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_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are unsubstituted or substituted independently with 1, 2, 3, or 4 R^{20} groups. In some embodiments, R^{23} is selected from the group consisting of hydrogen, oxo, azido, halogen, -CN, $-NO_2$, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $-OR^{a3}$, and $-NR^{c3}R^{d3}$, wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are unsubstituted or substituted. In some embodiments, R^{23} is hydrogen.

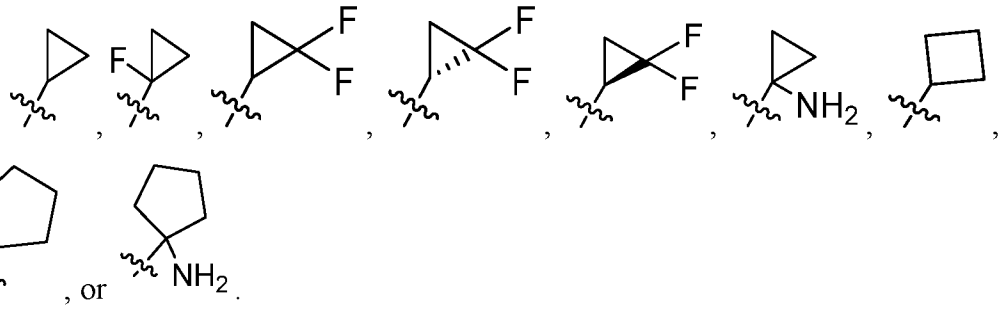
[00105] In some embodiments of a compound of Formula (I), (Ia) or (Ib), R^{23} is $-NR^{c3}R^{d3}$. In some embodiments, R^{c3} and R^{d3} together with the N atom to which they are connected, come

together to form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, wherein the 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl are unsubstituted or substituted independently with 1, 2, 3, or 4 R^{20} groups. In some embodiments, R^{23} is  . In some embodiments, R^{23} is  .

[00106] In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  .

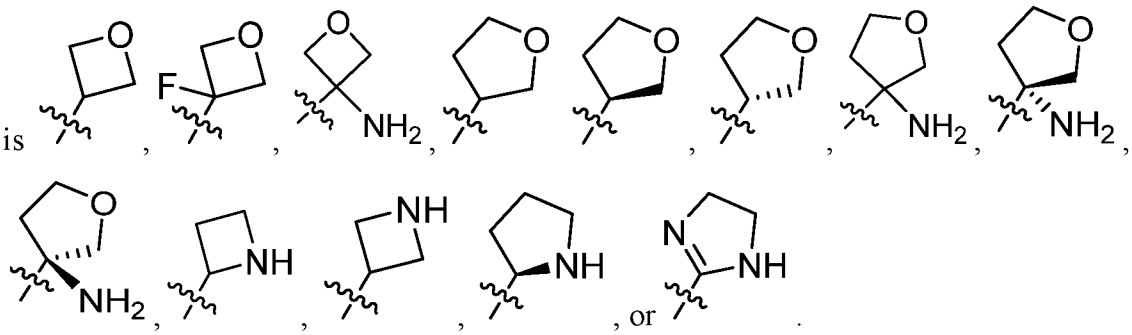
[00107] In some embodiments of a compound of Formula (I), (Ib) or (Ia), R^{23} is -(C_{1-6} alkylene)-C_{3-10} cycloalkyl, -(C_{1-6} alkylene)-4-10 membered heterocycloalkyl, -(C_{1-6} heteroalkylene)-C_{3-10} cycloalkyl, -(C_{1-6} heteroalkylene)-4-10 membered heterocycloalkyl, -(C_{1-6} alkylene)-C_{6-10} aryl, -(C_{1-6} alkylene)-5-10 membered heteroaryl, -(C_{1-6} heteroalkylene)-C_{6-10} aryl, -(C_{1-6} heteroalkylene)-5-10 membered heteroaryl. In some embodiments, R^{23} is -(C_{1-6} alkylene)-C_{3-10} cycloalkyl, optionally substituted with one or more R^{20}. In some embodiments, R^{23} is -(C_{1-6} alkylene)-4-10 membered heterocycloalkyl, optionally substituted with one or more R^{20}. In some embodiments, R^{23} is -(C_{1-6} heteroalkylene)-4-10 membered heterocycloalkyl, optionally substituted with one or more R^{20}. In some embodiments, R^{23} is -(C_{1-6} heteroalkylene)-C_{3-10} cycloalkyl, optionally substituted with one or more R^{20}. In some embodiments, R^{23} is -(C_{1-6} alkylene)-C_{6-10} aryl, optionally substituted with one or more R^{20}. In some embodiments, R^{23} is -(C_{1-6} alkylene)-5-10 membered heteroaryl, optionally substituted with one or more R^{20}. In some embodiments, R^{23} is -(C_{1-6} heteroalkylene)-C_{6-}

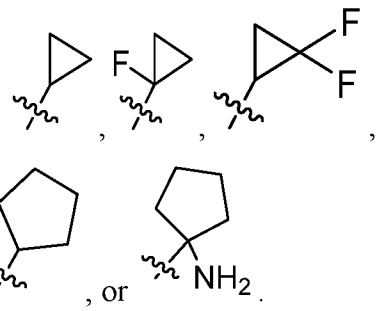
$_{10}$ aryl, optionally substituted with one or more R^{20}. In some embodiments, R^{23} is -(C_{1-6} heteroalkylene)-5-10 membered heteroaryl, optionally substituted with one or more R^{20}.

[00108] In some embodiments of a compound of Formula (I), (Ib) or (Ia), 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 a 3-6 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted a 3 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted a 4 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted a 5 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted a 6 membered ring. In some embodiments, the -C_{3-10} cycloalkyl is 

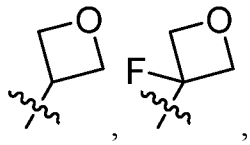
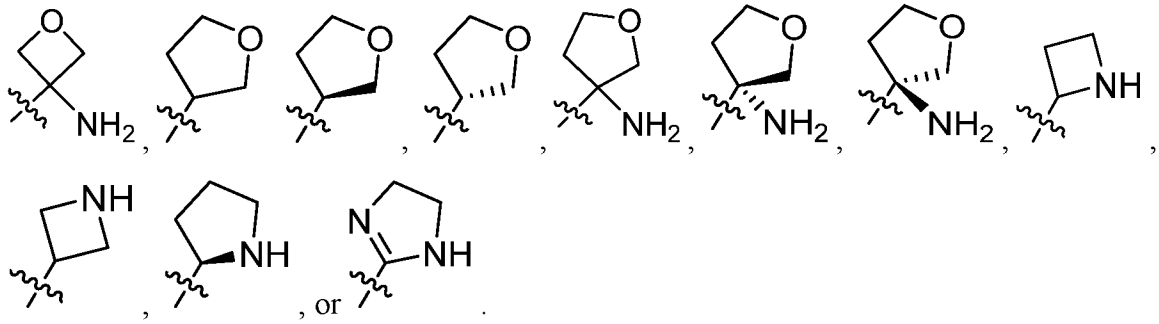
, or .

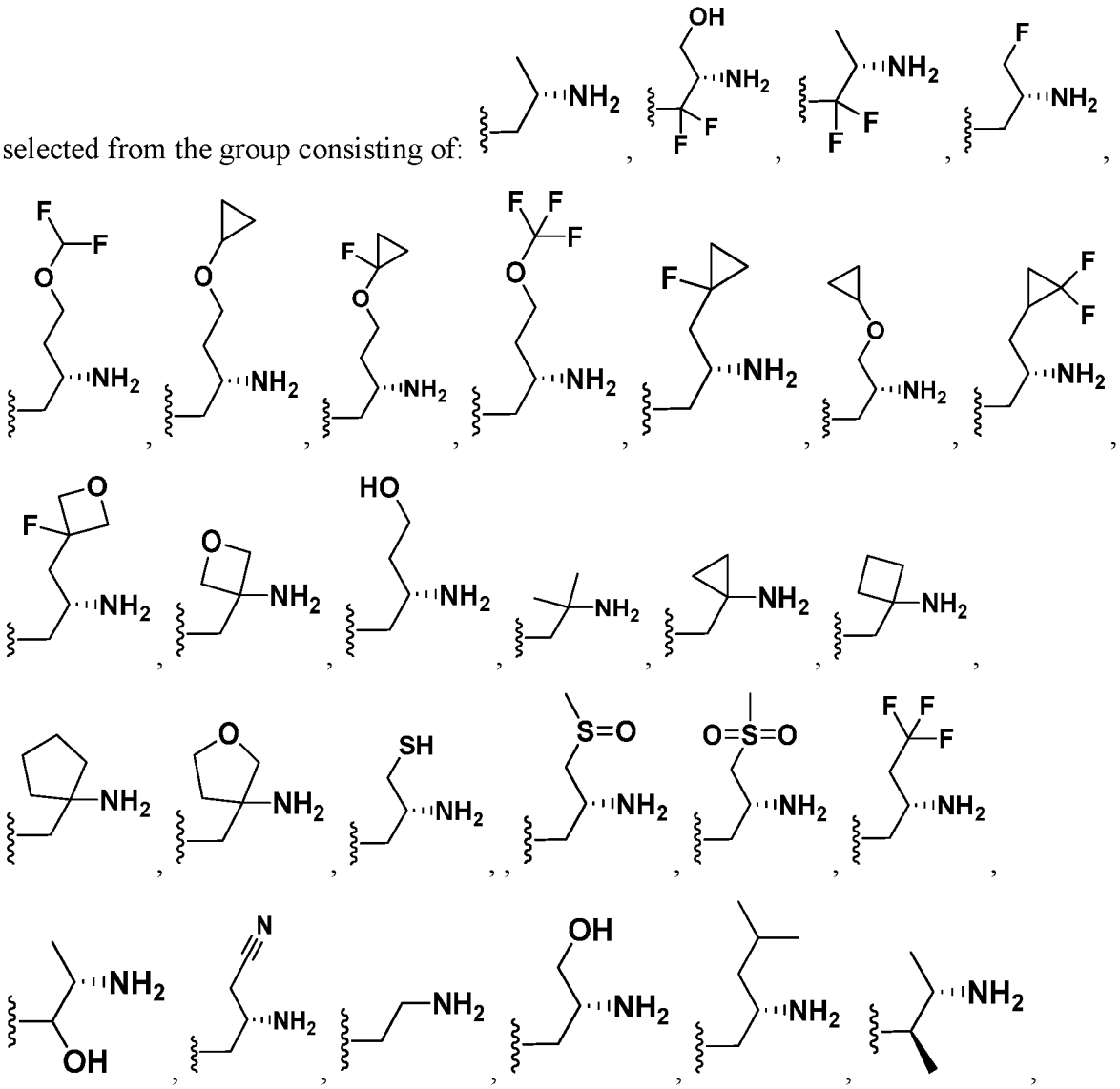
[00109] In some embodiments of a compound of Formula (I), (Ib) or (Ia), R^{23} is substituted or unsubstituted -(C_{1-6} alkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{23} is -(C_{1-6} alkylene)-4-10 membered heterocycloalkyl, wherein -(C_{1-6} alkylene)-4-10 membered heterocycloalkyl 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 a 4-6 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted a 4 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted a 5 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted a 6 membered ring. n some embodiments, the 4-10 membered heterocycloalkyl contains 0-1 oxygen and 0-2 nitrogen atoms. In some embodiments, the -4-10 membered heterocycloalkyl

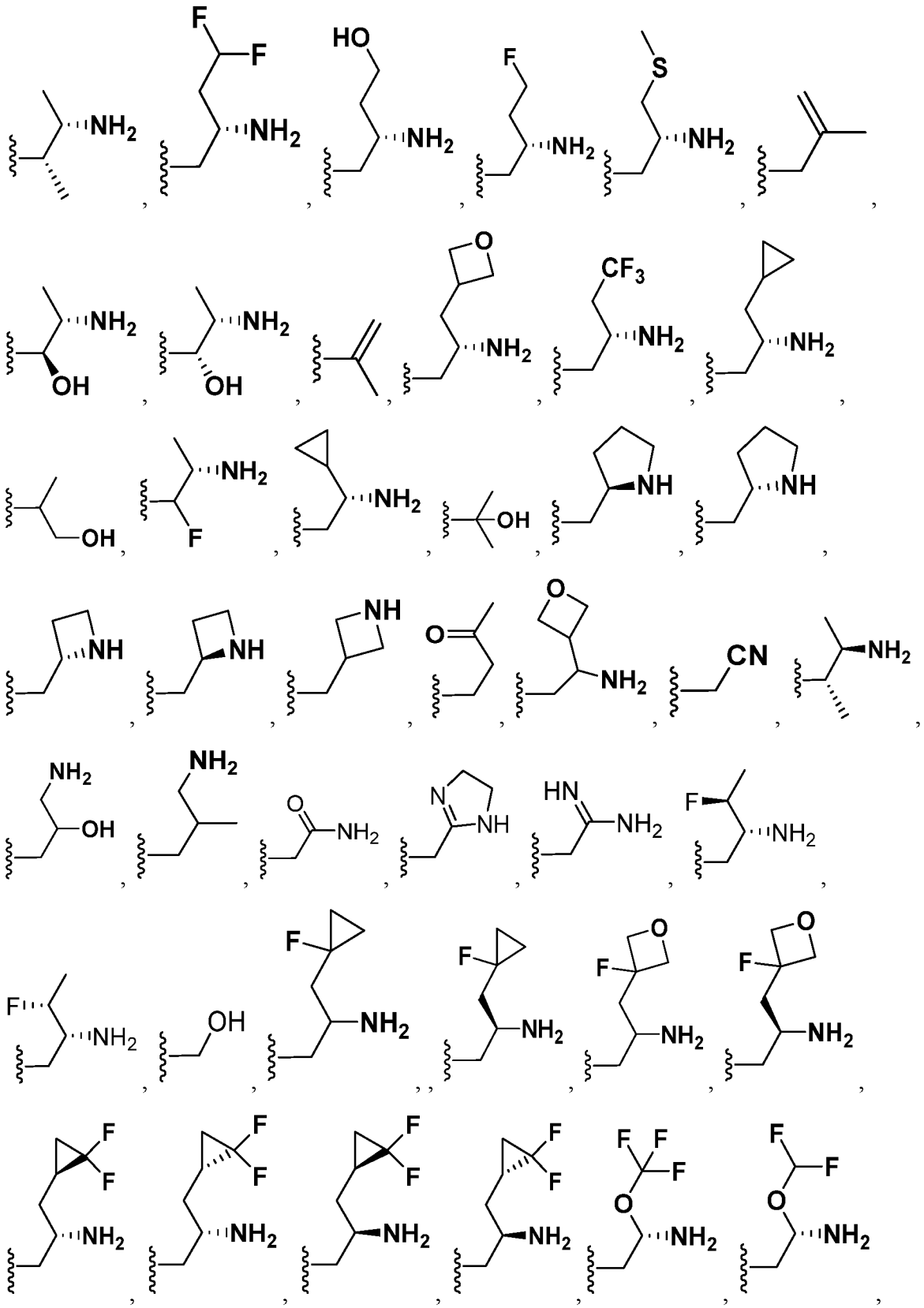
is 

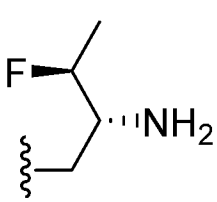
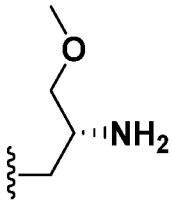
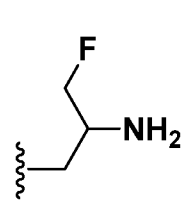
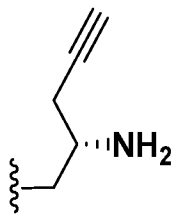
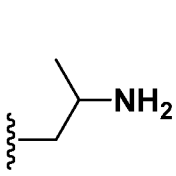
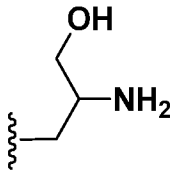
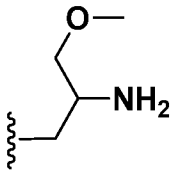
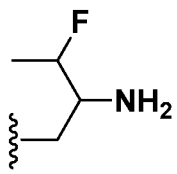
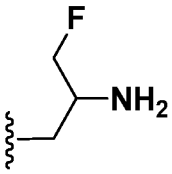
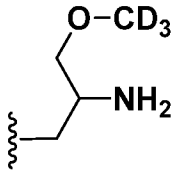
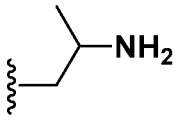
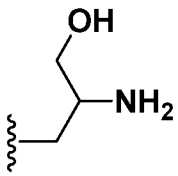
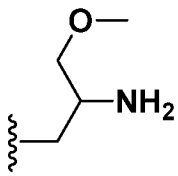
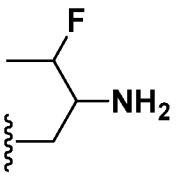
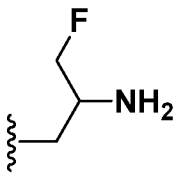
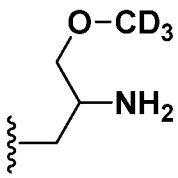
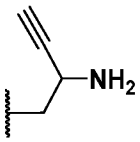
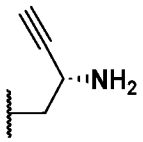
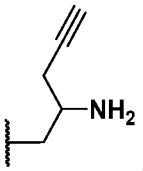
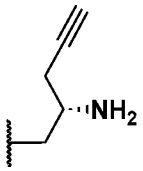
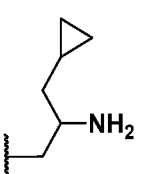
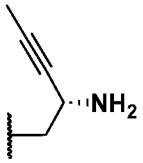
[00110] In some embodiments of a compound of Formula (I), (Ib) or (Ia), R^{23} is substituted or unsubstituted -(C_{1-6} heteroalkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{23} is -(C_{1-6} heteroalkylene)-C_{3-10} cycloalkyl, wherein -(C_{1-6} heteroalkylene)-C_{3-10} cycloalkyl is substituted 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 a 3-6 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted a 3 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted a 4 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted a 5 membered ring. In some embodiments, the C_{3-10} cycloalkyl is an optionally substituted a 6 membered ring.In some embodiments, the heteroalkylene is C_{1-3} heteroalkylene. In some embodiments, the -C_{3-10} cycloalkyl is 

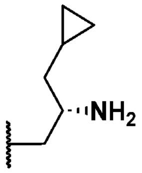
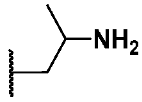
[00111] In some embodiments of a compound of Formula (I), (Ib) or (Ia), R^{23} is substituted or unsubstituted -(C_{1-6} heteroalkylene)-4-10 membered heterocycloalkyl. In some embodiments, R^{23} is -(C_{1-6} heteroalkylene)-4-10 membered heterocycloalkyl, wherein -(C_{1-6} heteroalkylene)-4-10 membered 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 a 4-6 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted a 4 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted a 5 membered ring. In some embodiments, the 4-10 membered heterocycloalkyl is an optionally substituted a 6 membered ring. n some embodiments, the 4-10 membered heterocycloalkyl contains 0-1 oxygen and 0-2 nitrogen

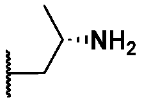
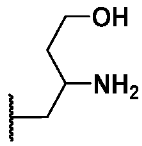
atoms. In some embodiments, the -4-10 membered heterocycloalkyl is  ,  , or .

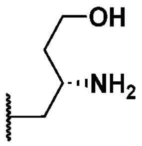
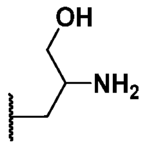
[00112] In some embodiments of a compound of Formula (I), (Ib) or (Ia), R^{23} is any one selected from the group consisting of: 

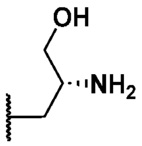
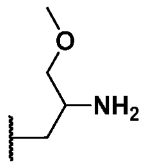


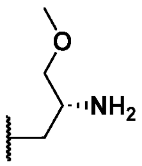
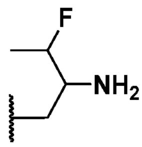



, and  . In some embodiments, R^{23} is any one selected from the group consisting of:  ,  ,  ,  , and  In some embodiments, R^{23} is  . In some embodiments, R^{23} is any one selected from the group consisting of:  ,  ,  ,  , and  In some embodiments, R^{23} is  . In some embodiments, R^{23} is  .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

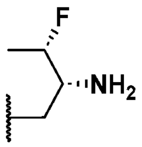
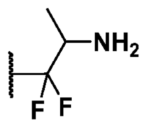
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

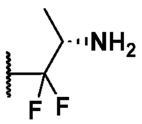
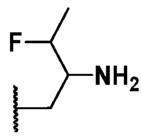
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

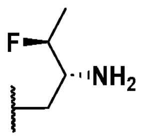
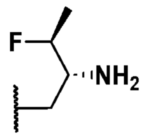
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

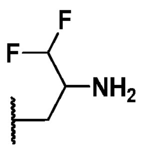
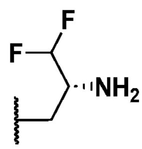
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

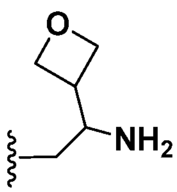
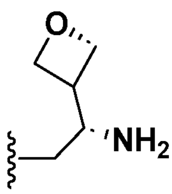
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

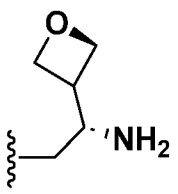
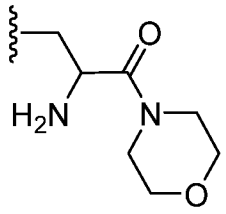
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

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

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

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

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


. In some embodiments, R^{23} is 
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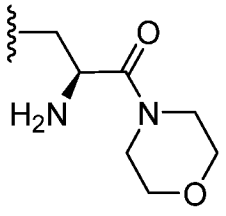
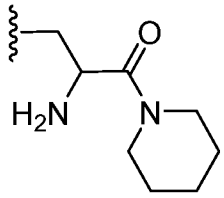

. In some embodiments, R^{23} is 
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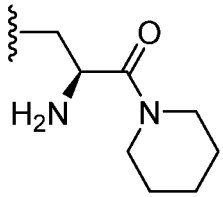
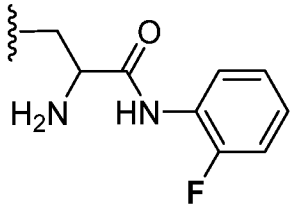

. In some embodiments, R^{23} is 
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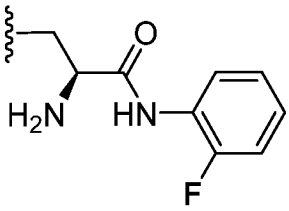
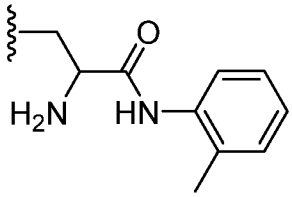
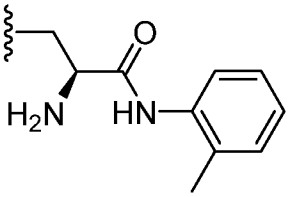

. In some embodiments, R^{23} is


. In some embodiments, R^{23} is 
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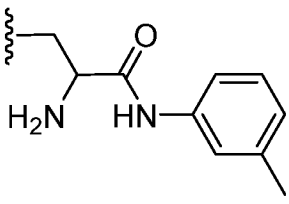
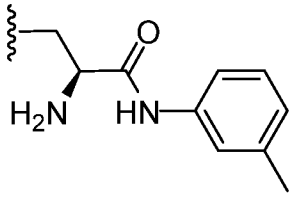
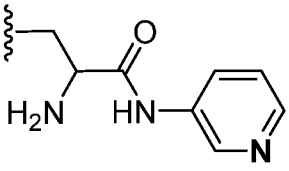

. In some embodiments, R^{23} is


. In some embodiments, R^{23} is 
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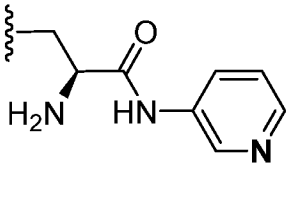
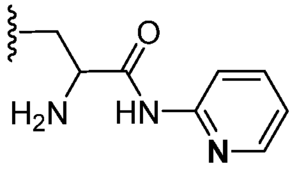
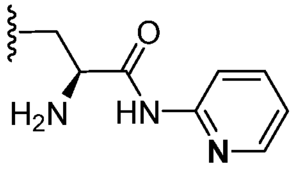
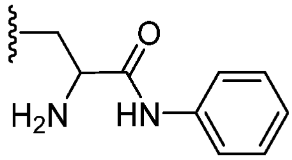
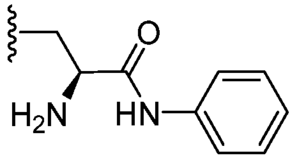
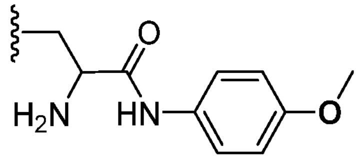
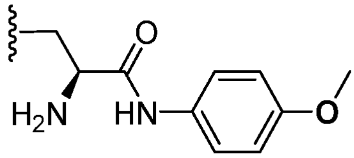
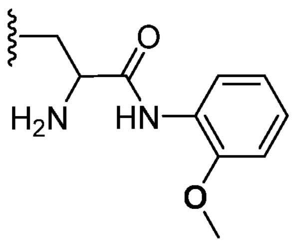
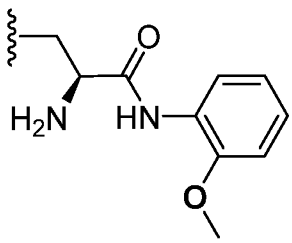
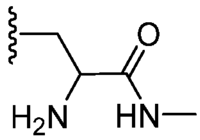
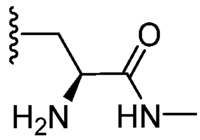
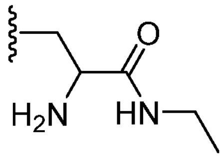
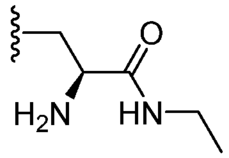
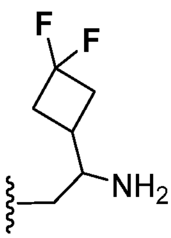
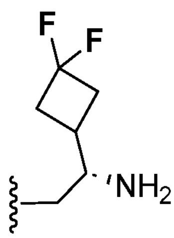
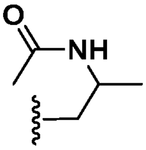
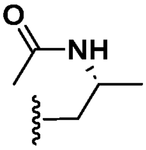
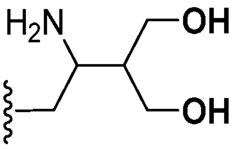
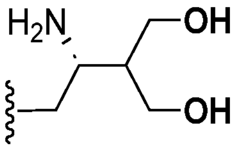
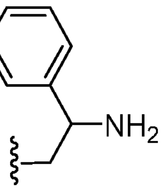
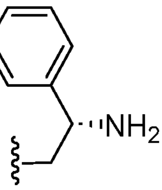
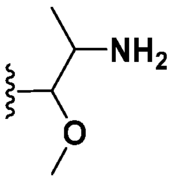
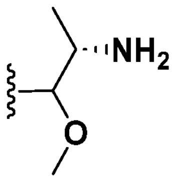
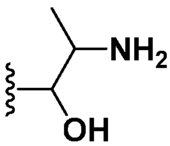
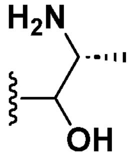
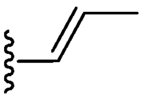
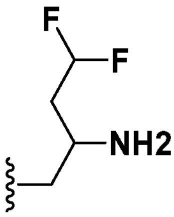
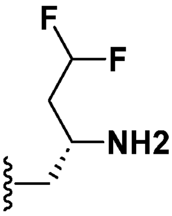
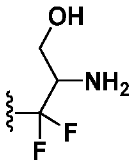
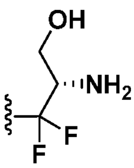
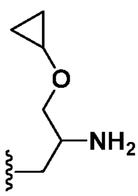
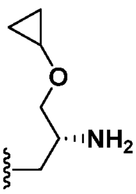
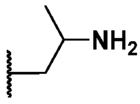
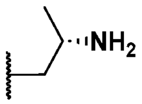
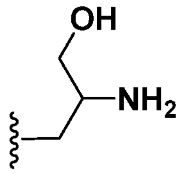
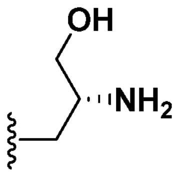
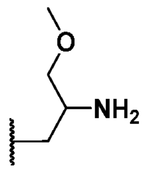
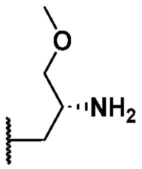
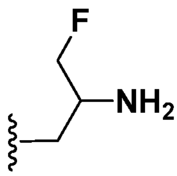
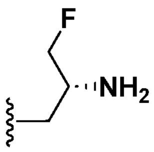
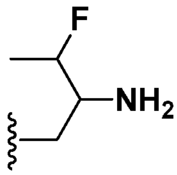
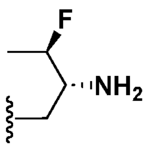
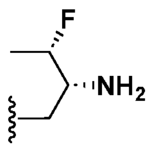
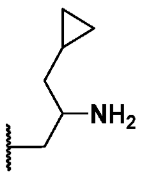
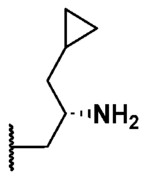
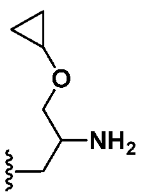
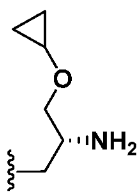
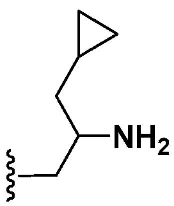
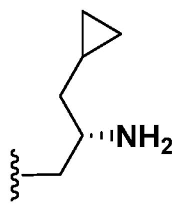
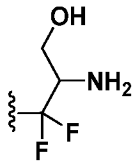
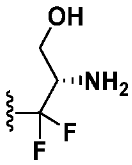
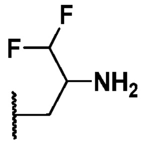
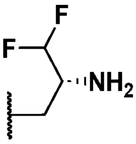

. In some embodiments, R^{23} is

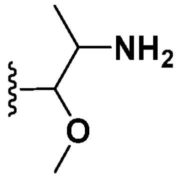
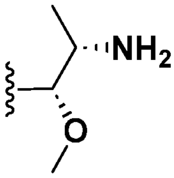
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23}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

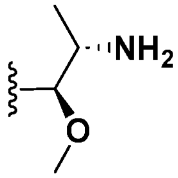
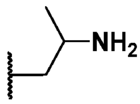
embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In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

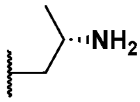
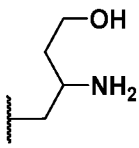
[00113] In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  .In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

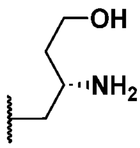
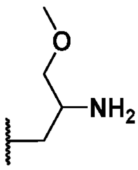
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

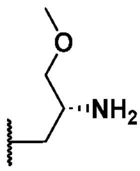
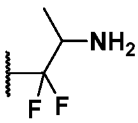
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

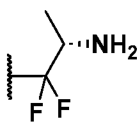
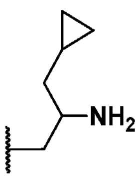
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

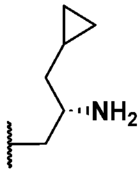
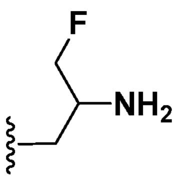
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

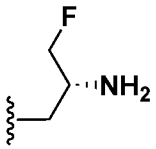
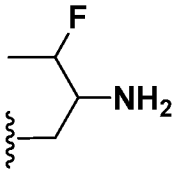
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is

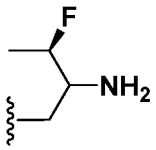
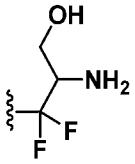
 .In some embodiments, R^{23} is  . In some embodiments, R^{23} is

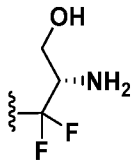
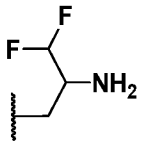
 .In some embodiments, R^{23} is  . In some embodiments, R^{23} is

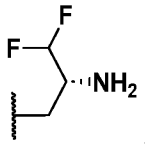
 .In some embodiments, R^{23} is  . In some embodiments, R^{23} is

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


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


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


. In some embodiments, R^{23} is 
. In some embodiments, R^{23} is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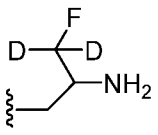
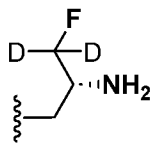
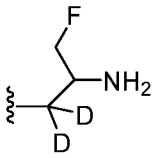
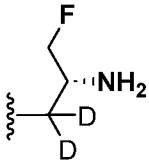
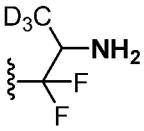
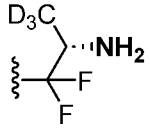
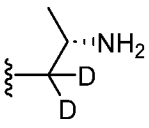
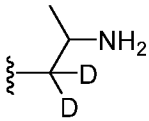
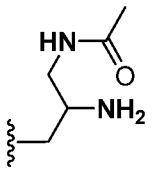
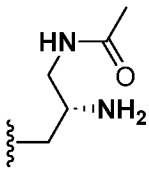
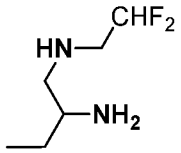
[00114] In some embodiments, R^{23} is 
. In some embodiments, R^{23} is

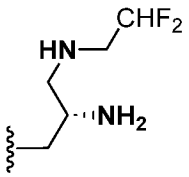

. In some embodiments, R^{23} is 
In some embodiments, R^{23} is

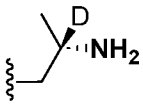

. In some embodiments, R^{23} is 
. In some embodiments, R^{23} is

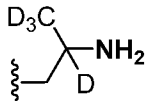

. In some embodiments, R^{23} is 
. In some embodiments, R^{23} is

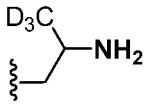

. In some embodiments, R^{23} is 
. In some embodiments, R^{23} is

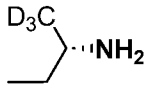

. In some embodiments, R^{23} is 
In some embodiments, R^{23} is

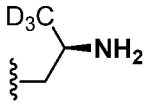


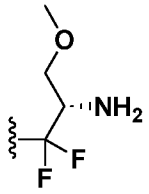
In some embodiments, R^{23} is 

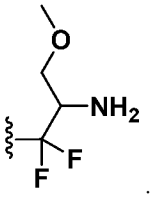
. In some embodiments, R^{23} is 

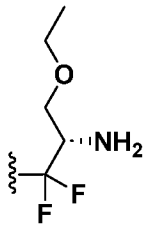
. In some embodiments, R^{23} is 

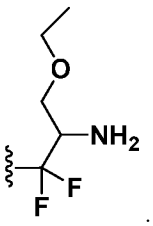
. In some embodiments, R^{23} is 

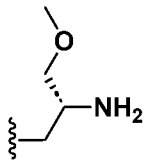
. In some embodiments, R^{23} is 

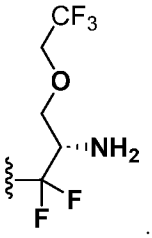
. In some embodiments, R^{23} is 

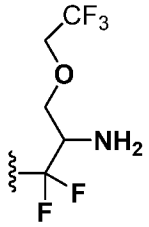
. In some embodiments, R^{23} is 

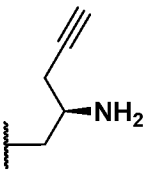
. In some embodiments, R^{23} is 

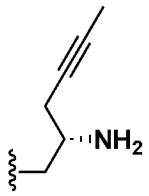
. In some embodiments, R^{23} is 

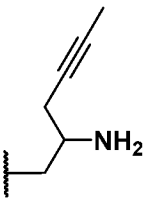
. In some embodiments, R^{23} is 

. In some embodiments, R^{23} is 

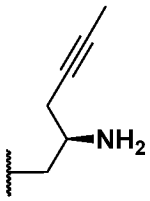
. In some embodiments, R^{23} is 

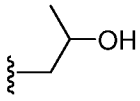
. In some embodiments, R^{23} is 

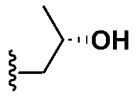
. In some embodiments, R^{23} is 

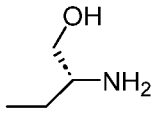
. In some embodiments, R^{23} is 

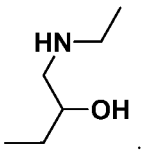
. In some embodiments, R^{23} is

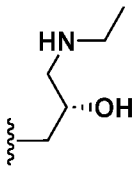


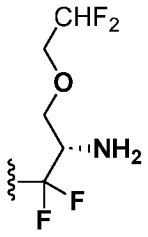
. In some embodiments, R^{23} is 

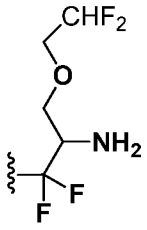
. In some embodiments, R^{23} is 

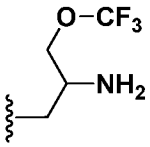
. In some embodiments, R^{23} is 

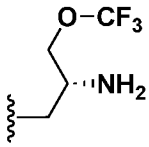
. In some embodiments, R^{23} is 

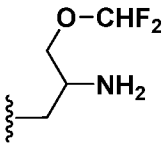
. In some embodiments, R^{23} is 

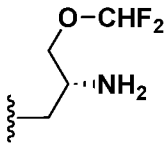
. In some embodiments, R^{23} is 

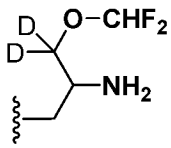
. In some embodiments, R^{23} is 

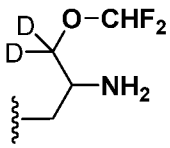
. In some embodiments, R^{23} is 

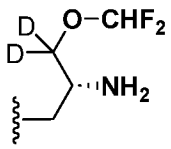
. In some embodiments, R^{23} is 

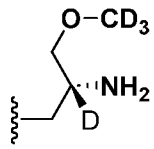
. In some embodiments, R^{23} is 

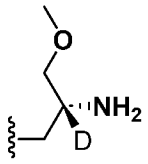
. In some embodiments, R^{23} is 

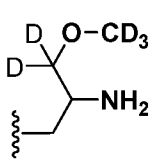
. In some embodiments, R^{23} is 

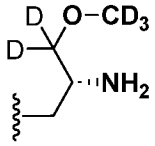
. In some embodiments, R^{23} is 

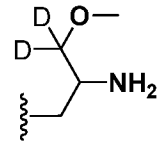
. In some embodiments, R^{23} is 

. In some embodiments, R^{23} is 

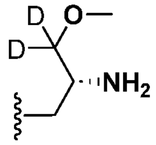
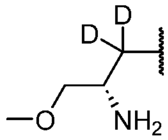
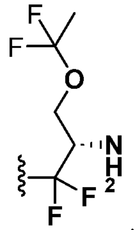
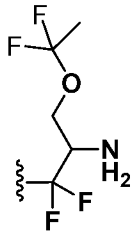
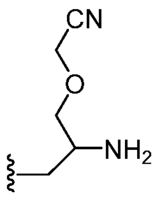
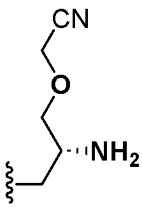
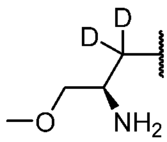
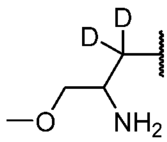
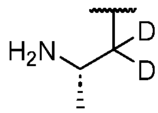
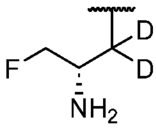
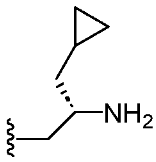
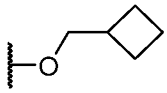
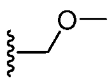
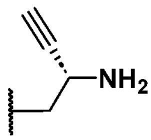
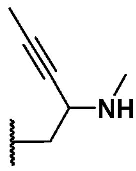
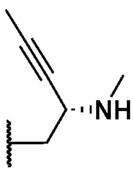
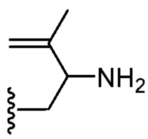
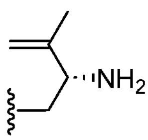
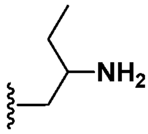
. In some embodiments, R^{23} is 

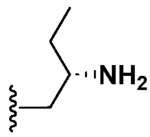
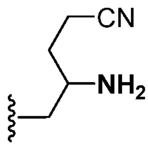
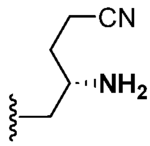
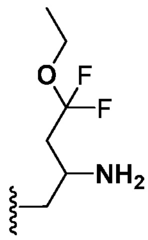
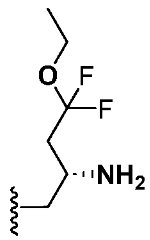
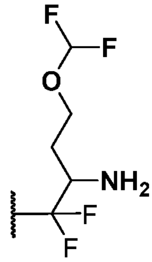
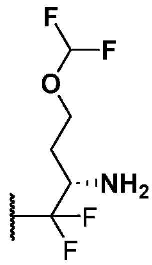
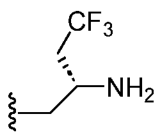
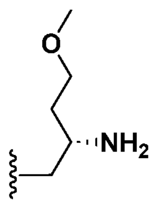
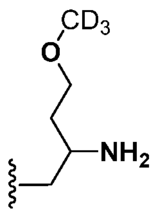
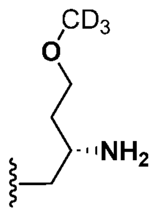
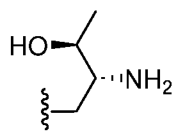
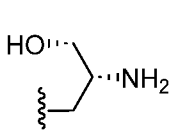
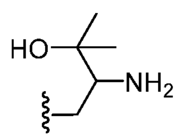
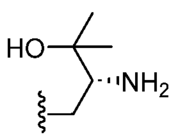
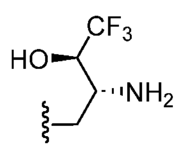
. In some embodiments, R^{23} is 

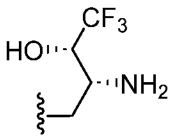
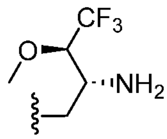
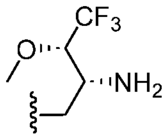
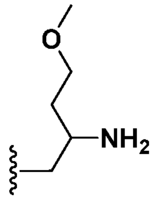
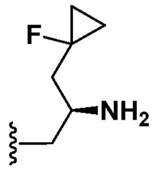
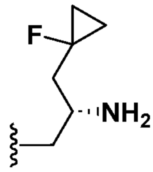
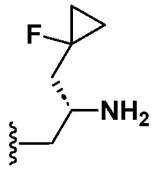
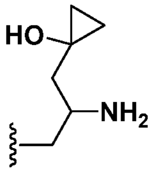
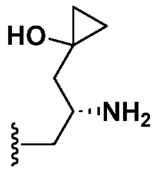
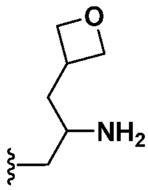
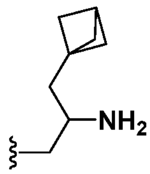
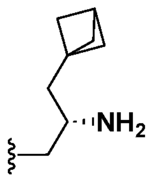
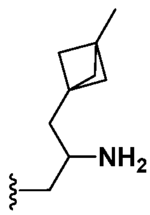
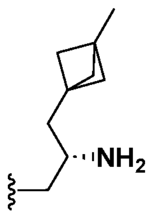
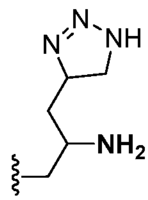
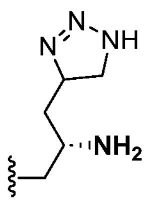
. In some embodiments, R^{23} is 

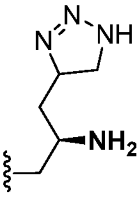
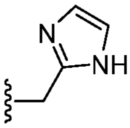
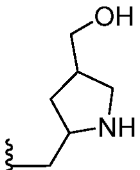
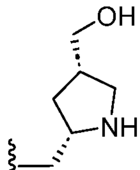
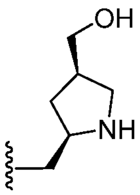
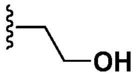
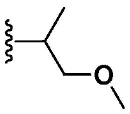
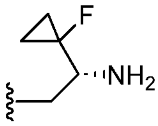
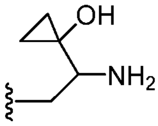
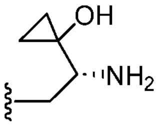
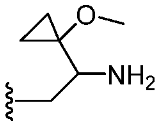
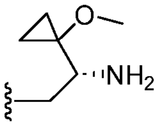
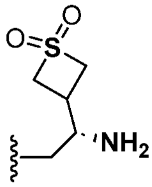
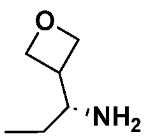
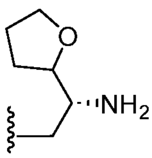
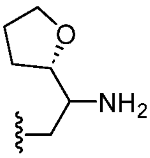
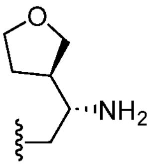
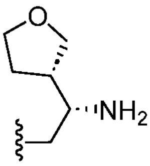
. In some embodiments, R^{23} is 

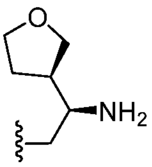
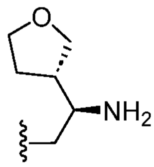
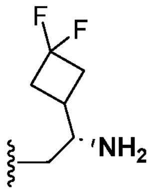
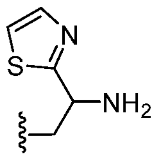
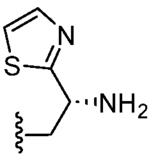
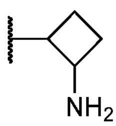
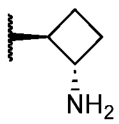
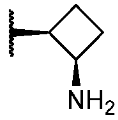
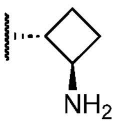
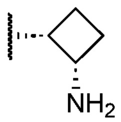
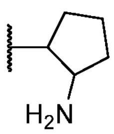
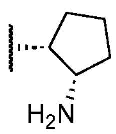
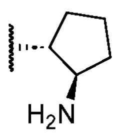
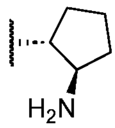
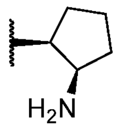
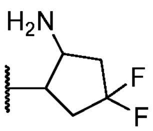
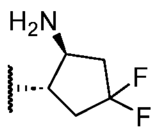
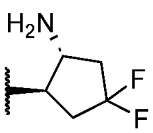
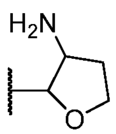
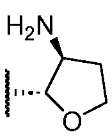
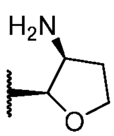
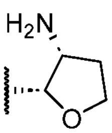
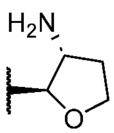
. In some embodiments, R^{23} is

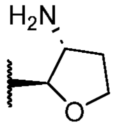
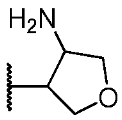
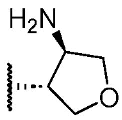
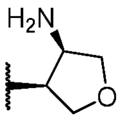
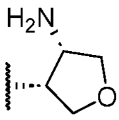
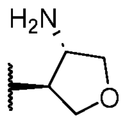
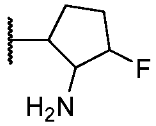
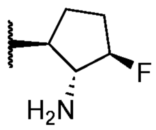
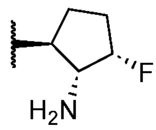
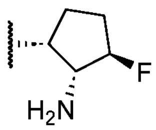
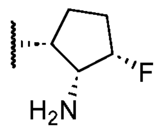
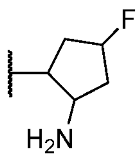
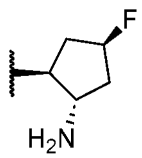
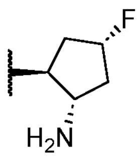
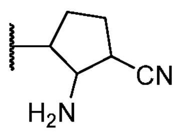
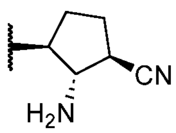
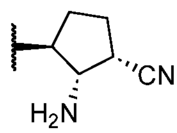
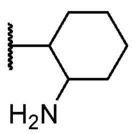
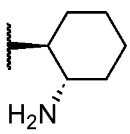
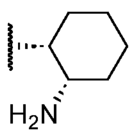
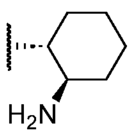
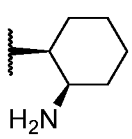
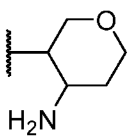
 . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is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

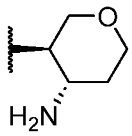
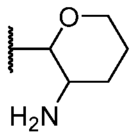
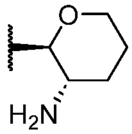
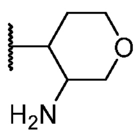
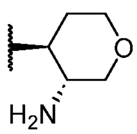
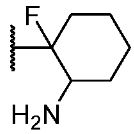
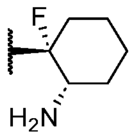
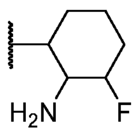
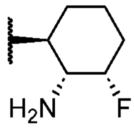
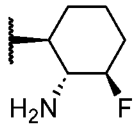
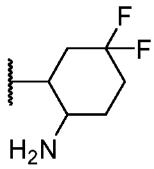
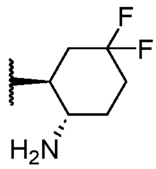
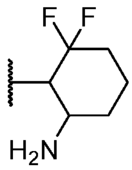
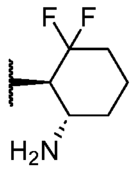
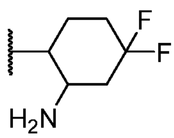
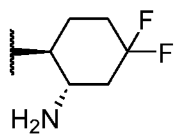
embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In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

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

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

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

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

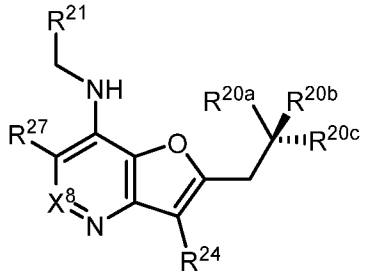
embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In some embodiments, R^{23} is  . In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

[00115] In some embodiments of a compound of Formula (I), (Ib) or (Ia), R^{23} is methylene substituted with 1, 2, or 3 independently selected R^{20} groups. In some embodiments, R^{20} is methyl, ethyl, NH_2, CH_2OH, CH_2CH_2OH, CH_2CH_2F, CH_2CHF_2, or $CH_2CH(CH_3)_2$. In some embodiments, R^{20} is NH_2 and methyl. In some embodiments, R^{20} is NH_2 and CH_2OH. In some embodiments, R^{20} is NH_2 and $CH_2CH(CH_3)_2$. In some embodiments, R^{20} is NH_2 and CH_2CHF_2. In some embodiments, R^{20} is NH_2 and CH_2CH_2F. In some embodiments, R^{20} is NH_2 and CH_2CH_2OH. In some embodiments, R^{20} is NH_2 and ethyl.

[00116] In some embodiments of a compound of Formula (I), (Ia), (IIa), (IIb), (IIc), (IId), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{20} is NH_2. In some embodiments, R^{20}

is OH. In some embodiments, R^{20} is F. In some embodiments, R^{20} is OCH_3. In some embodiments, R^{20} is  . In some embodiments, R^{20} is CH_2F. In some embodiments, R^{20} is CHF_2. In some embodiments, R^{20} is CF_3.

[00117] In some embodiments, the compound is of the Formula (IIa):

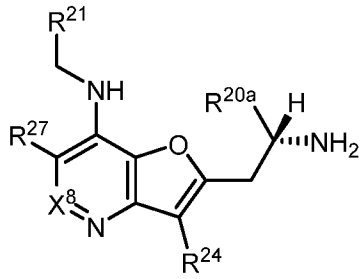


Formula (IIa),

wherein 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_{6-10} aryl, 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, or a pharmaceutically acceptable salt thereof.

[00118] 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.

[00119] In some embodiments, the compound is of the Formula (IIb):



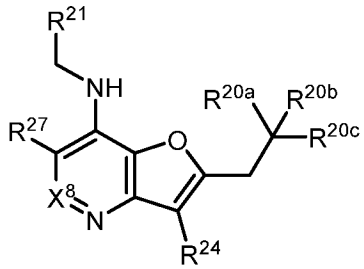
Formula (IIb),

wherein 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, C_{6-10} aryl, 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,

or a pharmaceutically acceptable salt thereof.

[00120] 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 $CH_2CH(CH_3)_2$.

[00121] In some embodiments, the compound is of Formula (IIc):

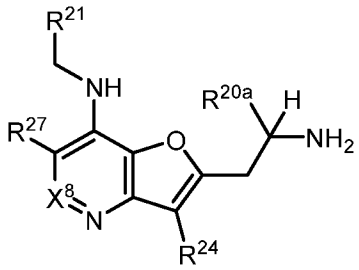


Formula (IIc),

wherein 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_{6-10} aryl, 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, or a pharmaceutically acceptable salt thereof.

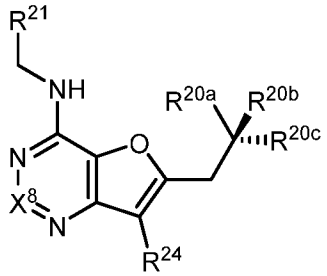
[00122] In some embodiments, the compound is of Formula (IId):



Formula (IId),

wherein 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, C_{6-10} aryl, 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,
or a pharmaceutically acceptable salt thereof.

[00123] In some embodiments, the compound is of the Formula (IIe):



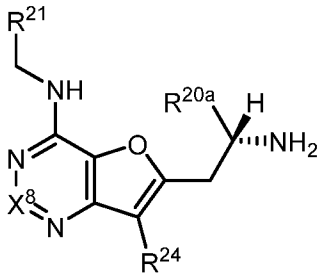
Formula (IIe),

wherein 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}

$_{4}$ 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_{6-10} aryl, 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, or a pharmaceutically acceptable salt thereof.

[00124] 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.

[00125] In some embodiments, the compound is of the Formula (IIf):

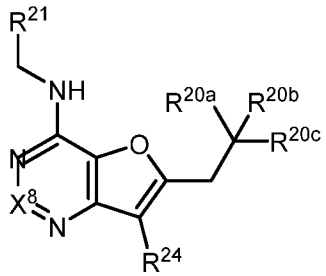


Formula (IIf),

wherein 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, C_{6-10} aryl, 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,
or a pharmaceutically acceptable salt thereof.

[00126] 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 $CH_2CH(CH_3)_2$.

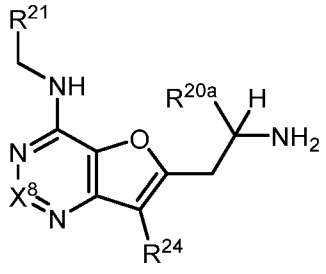
[00127] In some embodiments, the compound is of Formula (IIg):



Formula (IIg),

wherein 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_{6-10} aryl, 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, or a pharmaceutically acceptable salt thereof.

[00128] In some embodiments, the compound is of Formula (IIh):

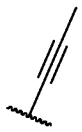
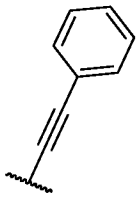
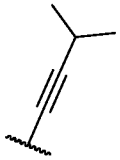


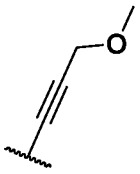
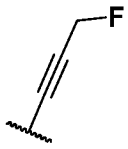
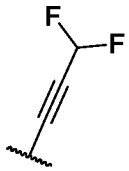
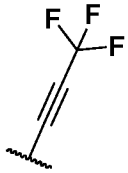
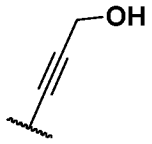
Formula (IIh),

wherein 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, C_{6-10} aryl, 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,

or a pharmaceutically acceptable salt thereof.

[00129] In some embodiments, of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^{24} is selected from -C≡C-C_{3-6} cycloalkyl, -C≡C-phenyl, -C≡C-5-6 membered heteroaryl, and -C≡C-4-6 membered heterocycloalkyl. In some embodiments, R^{24} is selected from -C≡C-C_{3-6} cycloalkyl and -C≡C-phenyl. In some embodiments, R^{24} is selected from -C≡C-C_{3-6} cycloalkyl and -C≡C-phenyl. In some embodiments, R^{24} is -C≡C-R^{20d}. In some embodiments, R^{24} is C_{3-6} alkynyl. In some embodiments, R^{24} is C_{3-6} alkynyl substituted by 1, 2, 3, or 4 independently selected R^{20d} groups. In some embodiments, R^{24} is C_{3-6} alkynyl substituted by 1 R^{20d} group. In some embodiments, R^{24} is C_{3-6} alkynyl substituted by 2 independently selected R^{20d} groups. In some embodiments, R^{24} is C_{3-6} alkynyl substituted by 3independently selected R^{20d} groups. In some embodiments, R^{24} is C_{3-6} alkynyl substituted by 4 independently selected R^{20d} groups. In some embodiments, R^{24} is -C≡C-C_{3-6} cycloalkyl, wherein the cycloalkyl is substituted by 1, 2, 3, or 4 independently selected R^{20d} groups. In some embodiments, R^{24} is -C≡C-phenyl, wherein the phenyl is substituted by 1, 2, 3, or 4 independently selected R^{20d} groups. In some embodiments, R^{24} is -C≡C-5-6 membered heteroaryl, wherein the heteroaryl is substituted by 1, 2, 3, or 4 independently selected R^{20d} groups. In some embodiments, R^{24} is -C≡C-4-6 membered heterocycloalkyl, wherein the heterocycloalkyl is substituted by 1, 2, 3, or 4 independently selected R^{20d} groups. In some embodiments, R^{24} is  . In some embodiments, R^{24} is  . In some embodiments, R^{24} is  . In some embodiments, R^{24} is  . In some embodiments, R^{24} is


. In some embodiments, R^{24} is 
. In some embodiments, R^{24} is 
. In some embodiments, R^{24} is 
. In some embodiments, R^{24} is 
. In some embodiments, R^{24} is 
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[00130] In some embodiments of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), each R^{20d} is independently selected from the group consisting of -OH, -SH, -CN, $-NO_2$, halogen, 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, 4-10 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. In some embodiments of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), each R^{20d} is independently selected from the group consisting of -OH, -SH, -CN, $-NO_2$, halogen, 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, and di(C_{1-4} alkyl)aminocarbonylamino. In some embodiments of

Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), each R^{20d} is independently selected from the group consisting of -OH, -SH, -CN, $-NO_2$, halogen, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} heteroalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(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, and di(C_{1-4} alkyl)amino. In some embodiments of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), each R^{20d} is independently selected from the group consisting of -OH, -SH, -CN, $-NO_2$, halogen, oxo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} heteroalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(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, and di(C_{1-4} alkyl)amino.

[00131] In some embodiments of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{20d} is -CN. In some embodiments, R^{20d} is $-NO_2$. In some embodiments, R^{20d} is halogen. In some embodiments, R^{20d} is oxo. In some embodiments, R^{20d} is C_{1-4} alkyl, C_{2-4} alkenyl. In some embodiments, R^{20d} is C_{2-4} alkynyl. In some embodiments, R^{20d} is C_{1-4} haloalkyl. In some embodiments, R^{20d} is C_{1-4} cyanoalkyl. In some embodiments, R^{20d} is C_{1-4} hydroxyalkyl. In some embodiments, R^{20d} is C_{1-4} alkoxy. In some embodiments, R^{20d} is -(C_{1-4} alkyl)-(C_{1-4} alkoxy). In some embodiments, R^{20d} is -(C_{1-4} alkoxy)-(C_{1-4} alkoxy). In some embodiments, R^{20d} is C_{1-4} haloalkoxy. In some embodiments, R^{20d} is C_{3-6} cycloalkyl. In some embodiments, R^{20d} is phenyl. In some embodiments, R^{20d} is 5-6 membered heteroaryl. In some embodiments, R^{20d} is 4-6 membered heterocycloalkyl. In some embodiments, R^{20d} is amino. In some embodiments, R^{20d} is C_{1-4} alkylamino. In some embodiments, R^{20d} is di(C_{1-4} alkyl)amino. In some embodiments, R^{20d} is carbamyl. In some embodiments, R^{20d} is C_{1-4} alkylcarbamyl. In some embodiments, R^{20d} is di(C_{1-4} alkyl)carbamyl. In some embodiments, R^{20d} is carbamoyl. In some embodiments, R^{20d} is C_{1-4} alkylcarbamoyl. In some embodiments, R^{20d} is di(C_{1-4} alkyl)carbamoyl. In some embodiments, R^{20d} is C_{1-4} alkylcarbonyl. In some embodiments, R^{20d} is C_{1-4} alkoxycarbonyl. In some embodiments, R^{20d} is C_{1-4} alkylcarbonylamino. In some embodiments, R^{20d} is C_{1-4} alkylsulfonylamino. In some embodiments, R^{20d} is aminosulfonyl. In some embodiments, R^{20d} is C_{1-4} alkylaminosulfonyl. In some embodiments, R^{20d} is di(C_{1-4} alkyl)aminosulfonyl. In some embodiments, R^{20d} is aminosulfonylamino. In some embodiments, R^{20d} is C_{1-4} alkylaminosulfonylamino. In some embodiments, R^{20d} is di(C_{1-4} alkyl)aminosulfonylamino. In some embodiments, R^{20d} is aminocarbonylamino. In some

embodiments, R^{20d} is C_{1-4} alkylaminocarbonylamino. In some embodiments, R^{20d} is di(C_{1-4} alkyl)aminocarbonylamino.

[00132] In some embodiments of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{20d} is CH_3. In some embodiments, R^{20d} is CH_2CH_3. In some embodiments, R^{20d} is F. In some embodiments, R^{20d} is CH_2F. In some embodiments, R^{20d} is CHF_2. In some embodiments, R^{20d} is CF_3. In some embodiments, R^{20d} is CH_3OH. In some embodiments, R^{20d} is CH_3OCH_3. In some embodiments, R^{20d} is OCH_3. In some embodiments, R^{20d} is CHF_2. In some embodiments, R^{20d} is  . In some embodiments, R^{20d} is  . In some embodiments, R^{20d} is substituted with 1, 2, 3, or 4 R^{32}.

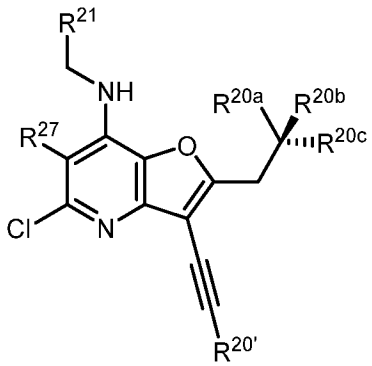
[00133] In some embodiments of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), each R^{20d} is independently selected from the group consisting of -OH, -SH, -CN, $-NO_2$, halogen, oxo, C_{1-4} alkyl, C_{2-4} 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, and di(C_{1-4} alkyl)aminocarbonylamino, wherein alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, phenyl, heteroaryl and heterocycloalkyl are each optionally substituted with 1, 2, 3 or 4 R^{32} groups.

[00134] In some embodiments of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), each R^{32} is independently -OH, -SH, -CN, $-NO_2$, halogen, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy. In some embodiments, R^{32} is -OH. In some embodiments, R^{32} is -SH. In some embodiments, R^{32} is -CN. In some embodiments, R^{32} is $-NO_2$. In some embodiments, R^{32} is halogen. In some embodiments, R^{32} is oxo. In some embodiments, R^{32} is C_{1-4} alkyl. In some embodiments, R^{32} is C_{2-4} alkenyl. In some embodiments, R^{32} is C_{1-4} haloalkyl. In some embodiments, R^{32} is C_{1-4} cyanoalkyl. In some embodiments, R^{32} is C_{1-4} hydroxyalkyl. In some embodiments, R^{32} is C_{1-4} alkoxy.

[00135] In some embodiments of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), each R^{20d} is independently selected from the group consisting of -OH, -SH, -CN, -NO_2, halogen, 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, and di(C_{1-4} alkyl)aminocarbonylamino, wherein alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, phenyl, heteroaryl and heterocycloalkyl are each optionally substituted with 1, 2, 3 or 4 R^{32} groups, wherein each R^{32} is independently oxo, halogen, methyl, ethyl, -CN, -CF_3, -OH, -OMe, -NH_2, or -NO_2. In some embodiments, R^{32} is oxo. In some embodiments, R^{32} halogen. In some embodiments, R^{32} methyl, ethyl. In some embodiments, R^{32} -CN. In some embodiments, R^{32} -CF_3. In some embodiments, R^{32} -OH. In some embodiments, R^{32} -OMe. In some embodiments, R^{32} -NH_2. In some embodiments, R^{32} -NO_2.

[00136] In some embodiments of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), (IIh), (IIIa), (IIIb), (IIIc), (IIId), (IIIe), (IIIf), (IIIg), or (IIIh), R^{24} is selected from -C≡C-C_{3-6} cycloalkyl, -C≡C-phenyl, -C≡C-5-6 membered heteroaryl, and -C≡C-4-6 membered heterocycloalkyl, wherein cycloalkyl, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl are each optionally substituted with 1, 2, 3 or 4 R^{32} groups. In some embodiments, R^{24} is selected from -C≡C-C_{3-6} cycloalkyl and -C≡C-phenyl, wherein cycloalkyl or phenyl are each optionally substituted with 1, 2, 3 or 4 R^{32} groups.

[00137] In some embodiments, the compound is of the Formula (IIIa):



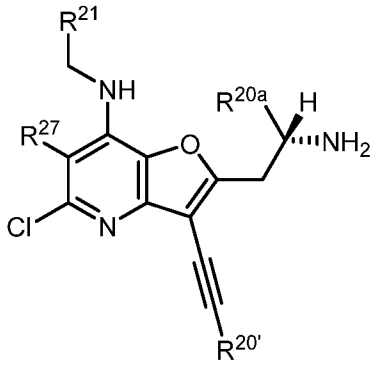
Formula (IIIa),

wherein 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_{6-10} aryl, 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, wherein $R^{20'}$ is R^{20d} as disclosed herein,

or a pharmaceutically acceptable salt thereof.

[00138] 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.

[00139] In some embodiments, the compound is of the Formula (IIIb):



Formula (IIIb),

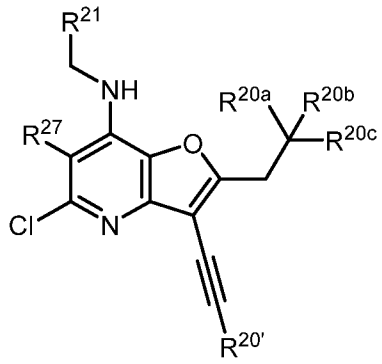
wherein R^{20a} is selected from the group consisting of OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{6-10} aryl, 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}

4 alkylaminosulfonylamino, di(C_{1-4} alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4} alkylaminocarbonylamino, and di(C_{1-4} alkyl)aminocarbonylamino, wherein $R^{20'}$ is R^{20d} as disclosed herein,

or a pharmaceutically acceptable salt thereof.

[00140] 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 $CH_2CH(CH_3)_2$.

[00141] In some embodiments, the compound is of Formula (IIIc):

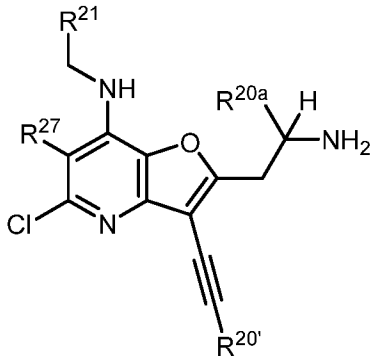


Formula (IIIc),

wherein 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_{6-10} aryl, 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, wherein $R^{20'}$ is R^{20d} as disclosed herein,

or a pharmaceutically acceptable salt thereof.

[00142] In some embodiments, the compound is of Formula (IIId):

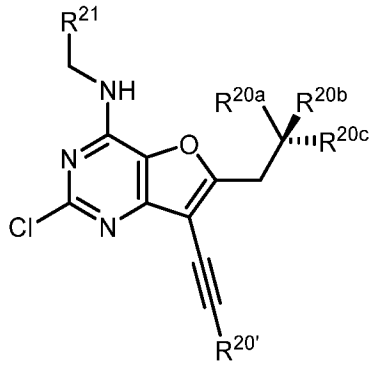


Formula (IIId),

wherein 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_{6-10} aryl, 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, wherein $R^{20'}$ is R^{20d} as disclosed herein,

or a pharmaceutically acceptable salt thereof.

[00143] In some embodiments, the compound is of the Formula (IIIe):



Formula (IIIe),

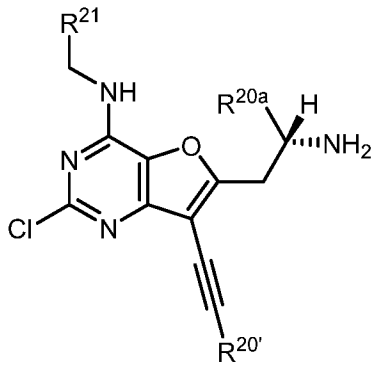
wherein each R^{20a}, R^{20b}, and R^{20c} is independently selected from the group consisting of H, OH, SH, CN, NO_2, halo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxy, -(C_{1-4} alkyl)-(C_{1-4} alkoxy), -(C_{1-4} alkoxy)-(C_{1-4} alkoxy), C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, C_{6-10} aryl, 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, wherein $R^{20'}$ is R^{20d} as disclosed herein,

or a pharmaceutically acceptable salt thereof.

[00144] 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.

[00145] In some embodiments, the compound is of the Formula (IIIf):



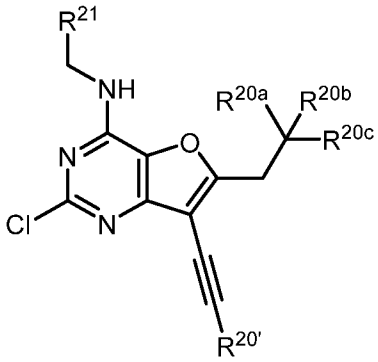
Formula (IIIf),

wherein 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, C_{6-10} aryl, 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, wherein $R^{20'}$ is R^{20d} as disclosed herein,

or a pharmaceutically acceptable salt thereof.

[00146] 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 $CH_2CH(CH_3)_2$.

[00147] In some embodiments, the compound is of Formula (IIIg):

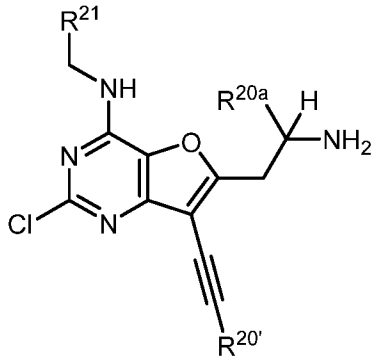


Formula (IIIg),

wherein 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_{6-10} aryl, 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, wherein $R^{20'}$ is R^{20d} as disclosed herein,

or a pharmaceutically acceptable salt thereof.

[00148] In some embodiments, the compound is of Formula (IIIh):



Formula (IIIh),

wherein 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_{6-10} aryl, 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, wherein $R^{20'}$ is R^{20d} as disclosed herein, or a pharmaceutically acceptable salt thereof.

[00149] In some embodiments of a compound of Formula (I), (Ia), (IIa), (IIb), (IIc), (IId), (IIIa), (IIIb), (IIIc), or (IIId), R^{27} is selected from the group consisting of H, azido, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, -CN, -NO_2, -OR^{a7}, -$C(=O)R^{b7}$, -$C(=O)OR^{b7}$, -$NR^{c7}R^{d7}$, -$C(=O)NR^{c7}R^{d7}$, -$OC(=O)NR^{c7}R^{d7}$, -$NR^{c7}C(=O)R^{b7}$, -$NR^{c7}C(=O)OR^{b7}$, -$NR^{c7}C(=O)NR^{c7}R^{d7}$, -$NR^{c7}S(=O)_2R^{b7}$, and -$NR^{c7}S(=O)_2NR^{c7}R^{d7}$, wherein the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^{27} is C_{1-6} alkyl substituted with 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^{27} is C_{1-6} heteroalkyl substituted with 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^{27} is C_{2-6} alkenyl substituted with 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^{27} is C_{2-6} alkynyl substituted with 1, 2, 3, or 4 independently selected R^{20} groups.

[00150] In some embodiments of a compound of Formula (I), (Ia), (IIa), (IIb), (IIc), (IId), (IIIa), (IIIb), (IIIc), or (IIId), R^{27} is selected from the group consisting of H, azido, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, -CN, -NO_2, -OR^{a7}, -$C(=O)R^{b7}$, -$C(=O)OR^{b7}$, -$NR^{c7}R^{d7}$, -$C(=O)NR^{c7}R^{d7}$, -$OC(=O)NR^{c7}R^{d7}$, -$NR^{c7}C(=O)R^{b7}$, -$NR^{c7}C(=O)OR^{b7}$, -$NR^{c7}C(=O)NR^{c7}R^{d7}$, -$NR^{c7}S(=O)_2R^{b7}$, and -$NR^{c7}S(=O)_2NR^{c7}R^{d7}$. In some embodiments, R^{27} is H. In some embodiments, R^{27} is azido. In some embodiments, R^{27} is halo. In some embodiments, R^{27} is C_{1-6} alkyl. In some embodiments, R^{27} is C_{2-6} alkenyl. In some embodiments, R^{27} is C_{2-6} alkynyl. In some embodiments, R^{27} is C_{1-6} heteroalkyl. In some embodiments, R^{27} is -CN. In some embodiments, R^{27} is -NO_2. In some embodiments, R^{27} is -OR^{a7}. In some embodiments, R^{27} is -$C(=O)R^{b7}$. In some embodiments, R^{27} is -$C(=O)OR^{b7}$. In some embodiments, R^{27} is -$NR^{c7}R^{d7}$. In some embodiments, R^{27} is -

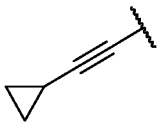
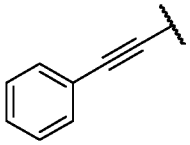
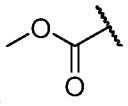
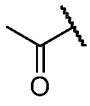
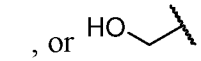
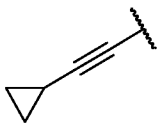
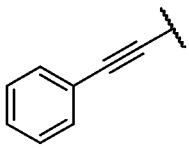
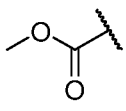
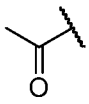
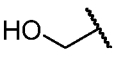
$C(=O)NR^{c7}R^{d7}$. In some embodiments, R^{27} is $-OC(=O)NR^{c7}R^{d7}$. In some embodiments, R^{27} is $-NR^{c7}C(=O)R^{b7}$. In some embodiments, R^{27} is $-NR^{c7}C(=O)OR^{b7}$. In some embodiments, R^{27} is $-NR^{c7}C(=O)NR^{c7}R^{d7}$. In some embodiments, R^{27} is $-NR^{c7}S(=O)_2R^{b7}$. In some embodiments, R^{27} is $-NR^{c7}S(=O)_2NR^{c7}R^{d7}$.

[00151] In some embodiments of a compound of Formula (I), (Ia), (IIa), (IIb), (IIc), (IId), (IIIa), (IIIb), (IIIc), or (IIId), R^{27} is H or F. In some embodiments, R^{27} is F.

[00152] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^{28} is selected from the group consisting of H, azido, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, -CN, $-NO_2$, $-OR^{a7}$, $-C(=O)R^{b7}$, $-C(=O)OR^{b7}$, $-NR^{c7}R^{d7}$, $-C(=O)NR^{c7}R^{d7}$, $-OC(=O)NR^{c7}R^{d7}$, $-NR^{c7}C(=O)R^{b7}$, $-NR^{c7}C(=O)OR^{b7}$, $-NR^{c7}C(=O)NR^{c7}R^{d7}$, $-NR^{c7}S(=O)_2R^{b7}$, and $-NR^{c7}S(=O)_2NR^{c7}R^{d7}$, wherein the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^{28} is C_{1-6} alkyl substituted with 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^{28} is C_{1-6} heteroalkyl substituted with 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^{28} is C_{2-6} alkenyl substituted with 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^{28} is C_{2-6} alkynyl substituted with 1, 2, 3, or 4 independently selected R^{20} groups.

[00153] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^{28} is selected from the group consisting of H, azido, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, -CN, $-NO_2$, $-OR^{a7}$, $-C(=O)R^{b7}$, $-C(=O)OR^{b7}$, $-NR^{c7}R^{d7}$, $-C(=O)NR^{c7}R^{d7}$, $-OC(=O)NR^{c7}R^{d7}$, $-NR^{c7}C(=O)R^{b7}$, $-NR^{c7}C(=O)OR^{b7}$, $-NR^{c7}C(=O)NR^{c7}R^{d7}$, $-NR^{c7}S(=O)_2R^{b7}$, and $-NR^{c7}S(=O)_2NR^{c7}R^{d7}$. In some embodiments, R^{28} is H. In some embodiments, R^{28} is azido. In some embodiments, R^{28} is halo. In some embodiments, R^{28} is Cl. In some embodiments, R^{28} is F. In some embodiments, R^{28} is C_{1-6} alkyl. In some embodiments, R^{28} is C_{2-6} alkenyl. In some embodiments, R^{28} is C_{2-6} alkynyl. In some embodiments, R^{28} is C_{1-6} heteroalkyl. In some embodiments, R^{28} is -CN. In some embodiments, R^{28} is $-NO_2$. In some embodiments, R^{28} is $-OR^{a7}$. In some embodiments, R^{28} is $-C(=O)R^{b7}$. In some embodiments, R^{28} is $-C(=O)OR^{b7}$. In some embodiments, R^{28} is $-NR^{c7}R^{d7}$. In some embodiments, R^{28} is $-C(=O)NR^{c7}R^{d7}$. In some embodiments, R^{28} is $-OC(=O)NR^{c7}R^{d7}$. In some embodiments, R^{28} is $-NR^{c7}C(=O)R^{b7}$. In some embodiments, R^{28} is $-NR^{c7}C(=O)OR^{b7}$. In some embodiments, R^{28} is $-NR^{c7}C(=O)NR^{c7}R^{d7}$. In some embodiments, R^{28} is $-NR^{c7}S(=O)_2R^{b7}$. In some embodiments, R^{28} is $-NR^{c7}S(=O)_2NR^{c7}R^{d7}$.

[00154] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), X^8 is CR^{28} and R^{28} is not H.

[00155] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^{28} is F, Cl, -CN, $-CH_3$, -C≡CH,  ,  ,  ,  ,  ,  , or  . In some embodiments, R^{28} is F. In some embodiments, R^{28} is Cl. In some embodiments, R^{28} is -CN. In some embodiments, R^{28} is $-CH_3$. In some embodiments, R^{28} is -C≡CH. In some embodiments, R^{28} is  . In some embodiments, R^{28} is  . In some embodiments, R^{28} is  . In some embodiments, R^{28} is  . In some embodiments, R^{28} is  . In some embodiments, R^{28} is  . In some embodiments, R^{28} is  .

[00156] In some embodiments, each R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a7}, R^{b7}, R^{c7}, R^{d7}, R^{a8}, R^{b8}, R^{c8}, and R^{d8} is independently selected from the group consisting of hydrogen, 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 unsubstituted or substituted independently with 1, 2, 3, or 4 R^{20} groups.

[00157] In some embodiments of a compound of Formula (I), (Ib) or (Ia), R^{a3} is hydrogen, 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, or 4-10 membered heterocycloalkyl. In some embodiments, R^{a3} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy. In some embodiments, R^{a3} is -(C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, or -(C_{1-}

$_{6}$ alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{a3} is C_{6-10} aryl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl. In some embodiments, R^{a3} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl. In some embodiments, R^{a3} is hydrogen. In some embodiments, R^{a3} is C_{1-6} alkyl. In some embodiments, R^{a3} is methyl. In some embodiments, R^{a3} is ethyl. In some embodiments, R^{a3} is propyl. In some embodiments, R^{a3} is C_{1-6} haloalkyl.

[00158] In some embodiments of a compound of Formula (I), (Ib) or (Ia), R^{b3} is hydrogen, 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, or 4-10 membered heterocycloalkyl. In some embodiments, R^{b3} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy. In some embodiments, R^{b3} is -(C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, or -(C_{1-6} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{b3} is C_{6-10} aryl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl. In some embodiments, R^{b3} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl. In some embodiments, R^{b3} is hydrogen. In some embodiments, R^{b3} is C_{1-6} alkyl. In some embodiments, R^{b3} is methyl. In some embodiments, R^{b3} is ethyl. In some embodiments, R^{b3} is propyl. In some embodiments, R^{b3} is C_{1-6} haloalkyl.

[00159] In some embodiments of a compound of Formula (I), (Ib) or (Ia), R^{c3} is hydrogen, 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, or 4-10 membered heterocycloalkyl. In some embodiments, R^{c3} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy. In some embodiments, R^{c3} is -(C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, or -(C_{1-6} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{c3} is C_{6-10} aryl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl. In some embodiments, R^{c3} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl. In some embodiments, R^{c3} is hydrogen. In some embodiments, R^{c3} is C_{1-6} alkyl. In some embodiments, R^{c3} is methyl. In some embodiments, R^{c3} is ethyl. In some embodiments, R^{c3} is propyl. In some embodiments, R^{c3} is C_{1-6} haloalkyl.

[00160] In some embodiments of a compound of Formula (I), (Ib) or (Ia), R^{d3} is hydrogen, 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, or 4-10 membered heterocycloalkyl. In some embodiments, R^{d3} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy. In some embodiments, R^{d3} is -(C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, or -(C_{1-6} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{d3} is C_{6-10} aryl, 5-10 membered

heteroaryl, or 4-10 membered heterocycloalkyl. In some embodiments, R^{d3} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl. In some embodiments, R^{d3} is hydrogen. In some embodiments, R^{d3} is C_{1-6} alkyl. In some embodiments, R^{d3} is methyl. In some embodiments, R^{d3} is ethyl. In some embodiments, R^{d3} is propyl. In some embodiments, R^{d3} is C_{1-6} haloalkyl.

[00161] In some embodiments of a compound of Formula (I), (Ib), or (Ia), 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, wherein the 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl are unsubstituted or substituted independently with 1, 2, 3, or 4 R^{20} groups. In some embodiments, 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.

[00162] In some embodiments of a compound of Formula (I), (Ia), (IIa), (IIb), (IIc), (IId), (IIIa), (IIIb), (IIIc), or (IIId), R^{a7} is hydrogen, 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, or 4-10 membered heterocycloalkyl. In some embodiments, R^{a7} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy. In some embodiments, R^{a7} is -(C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, or -(C_{1-6} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{a7} is C_{6-10} aryl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl. In some embodiments, R^{a7} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl. In some embodiments, R^{a7} is hydrogen. In some embodiments, R^{a7} is C_{1-6} alkyl. In some embodiments, R^{a7} is methyl. In some embodiments, R^{a7} is ethyl. In some embodiments, R^{a7} is propyl. In some embodiments, R^{a7} is C_{1-6} haloalkyl.

[00163] In some embodiments of a compound of Formula (I), (Ia), (IIa), (IIb), (IIc), (IId), (IIIa), (IIIb), (IIIc), or (IIId), R^{b7} is hydrogen, 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, or 4-10 membered heterocycloalkyl. In some embodiments, R^{b7} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy. In some embodiments, R^{b7} is -(C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, or -(C_{1-6} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{b7} is C_{6-10} aryl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl. In some embodiments, R^{b7} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl. In some embodiments, R^{b7} is hydrogen. In some embodiments, R^{b7} is C_{1-6} alkyl. In some

embodiments, R^{b7} is methyl. In some embodiments, R^{b7} is ethyl. In some embodiments, R^{b7} is propyl. In some embodiments, R^{b7} is C_{1-6} haloalkyl.

[00164] In some embodiments of a compound of Formula (I), (Ia), (IIa), (IIb), (IIc), (IId), (IIIa), (IIIb), (IIIc), or (IIId), R^{c7} is hydrogen, 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, or 4-10 membered heterocycloalkyl. In some embodiments, R^{c7} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy. In some embodiments, R^{c7} is -(C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, or -(C_{1-6} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{c7} is C_{6-10} aryl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl. In some embodiments, R^{c7} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl. In some embodiments, R^{c7} is hydrogen. In some embodiments, R^{c7} is C_{1-6} alkyl. In some embodiments, R^{c7} is methyl. In some embodiments, R^{c7} is ethyl. In some embodiments, R^{c7} is propyl. In some embodiments, R^{c7} is C_{1-6} haloalkyl.

[00165] In some embodiments of a compound of Formula (I), (Ia), (IIa), (IIb), (IIc), (IId), (IIIa), (IIIb), (IIIc), or (IIId), R^{d7} is hydrogen, 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, or 4-10 membered heterocycloalkyl. In some embodiments, R^{d7} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy. In some embodiments, R^{d7} is -(C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, or -(C_{1-6} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{d7} is C_{6-10} aryl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl. In some embodiments, R^{d7} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl. In some embodiments, R^{d7} is hydrogen. In some embodiments, R^{d7} is C_{1-6} alkyl. In some embodiments, R^{d7} is methyl. In some embodiments, R^{d7} is ethyl. In some embodiments, R^{d7} is propyl. In some embodiments, R^{d7} is C_{1-6} haloalkyl.

[00166] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^{a8} is hydrogen, 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, or 4-10 membered heterocycloalkyl. In some embodiments, R^{a8} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy. In some embodiments, R^{a8} is -(C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, or -(C_{1-6} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{a8} is C_{6-10} aryl, 5-10 membered heteroaryl, or 4-10 membered

heterocycloalkyl. In some embodiments, R^{a8} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl. In some embodiments, R^{a8} is hydrogen. In some embodiments, R^{a8} is C_{1-6} alkyl. In some embodiments, R^{a8} is methyl. In some embodiments, R^{a8} is ethyl. In some embodiments, R^{a8} is propyl. In some embodiments, R^{a8} is C_{1-6} haloalkyl.

[00167] In some embodiments of a compound of (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^{b8} is hydrogen, 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, or 4-10 membered heterocycloalkyl. In some embodiments, R^{b8} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy. In some embodiments, R^{b8} is - (C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, or -(C_{1-6} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{b8} is C_{6-10} aryl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl. In some embodiments, R^{b8} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl. In some embodiments, R^{b8} is hydrogen. In some embodiments, R^{b8} is C_{1-6} alkyl. In some embodiments, R^{b8} is methyl. In some embodiments, R^{b8} is ethyl. In some embodiments, R^{b8} is propyl. In some embodiments, R^{b8} is C_{1-6} haloalkyl.

[00168] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^{c8} is hydrogen, 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, or 4-10 membered heterocycloalkyl. In some embodiments, R^{c8} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} hydroxyalkyl, C_{1-6} haloalkyl, or C_{1-6} alkoxy. In some embodiments, R^{c8} is -(C_{1-6} alkylene)-C_{1-6} alkoxy, C_{3-10} cycloalkyl, or -(C_{1-6} alkylene)-C_{3-10} cycloalkyl. In some embodiments, R^{c8} is C_{6-10} aryl, 5-10 membered heteroaryl, or 4-10 membered heterocycloalkyl. In some embodiments, R^{c8} is hydrogen, C_{1-6} alkyl, or C_{1-6} haloalkyl. In some embodiments, R^{c8} is hydrogen. In some embodiments, R^{c8} is C_{1-6} alkyl. In some embodiments, R^{c8} is methyl. In some embodiments, R^{c8} is ethyl. In some embodiments, R^{c8} is propyl. In some embodiments, R^{c8} is C_{1-6} haloalkyl.

[00169] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh), R^{c7} and R^{d7} together with the N atom to which they are connected, come together to form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, wherein the 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl are unsubstituted or substituted independently with 1, 2, 3, or 4 R^{20} groups. In some embodiments, R^{c7} and R^{d7} together with the N atom to which they are connected, come together to form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl.

[00170] In some embodiments of a compound of Formula (I), (Ia), (Ib), (IIa), (IIb), (IIc), (IId), (IIe), (IIf), (IIg), or (IIh),R^{c8} and R^{d8} together with the N atom to which they are connected, come together to form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl, wherein the 5-10 membered heteroaryl and 4-10 membered heterocycloalkyl are unsubstituted or substituted independently with 1, 2, 3, or 4 R^{20} groups. In some embodiments, R^{c8} and R^{d8} together with the N atom to which they are connected, come together to form a 5-10 membered heteroaryl or 4-10 membered heterocycloalkyl.

[00171] In some embodiments, the compound is selected from Table 1.

[00172] 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. 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.

[00173] 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.

[00174] 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).

[00175] In some cases, some of the herein-described compounds may be a prodrug for another derivative or active compound.

[00176] 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.

[00177] In another embodiment, the compounds described herein are labeled isotopically (*e.g.* with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00178] 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, ^{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.

[00179] In some embodiments of a compound disclosed herein, one or more of R^{20}, R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{21}, R^{23}, R^{24}, R^{27}, R^{28}, R^{31}, R^{32}, R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a7}, R^{b7}, R^{c7}, R^{d7}, R^{a8}, R^{b8}, R^{c8}, and R^{d8} groups comprise deuterium at a percentage higher than the natural abundance of deuterium.

[00180] In some embodiments of a compound disclosed herein, one or more ^{1}H are replaced with one or more deuteriums in one or more of the following groups R^{20}, R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{21}, R^{23}, R^{24}, R^{27}, R^{28}, R^{31}, R^{32}, R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a7}, R^{b7}, R^{c7}, R^{d7}, R^{a8}, R^{b8}, R^{c8}, and R^{d8}.

[00181] In some embodiments of a compound disclosed herein, the abundance of deuterium in each of R^{20}, R^{20a}, R^{20b}, R^{20c}, R^{20d}, R^{21}, R^{23}, R^{24}, R^{27}, R^{28}, R^{31}, R^{32}, R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a7}, R^{b7}, R^{c7}, R^{d7}, R^{a8}, R^{b8}, R^{c8}, and R^{d8} is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar.

[00182] 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.

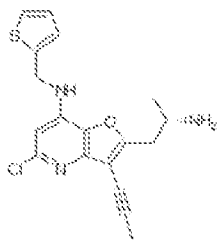
[00183] Compounds described herein may be formed as, and/or used as, pharmaceutically acceptable salts. The type of pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic 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,

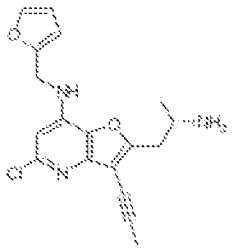
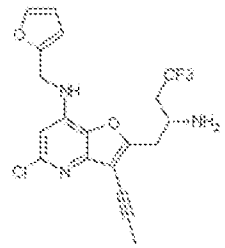
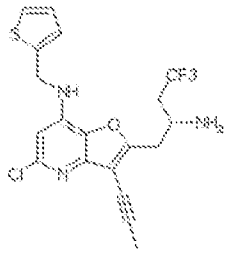
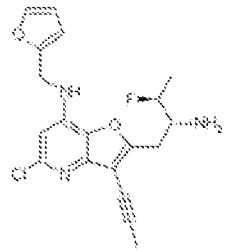
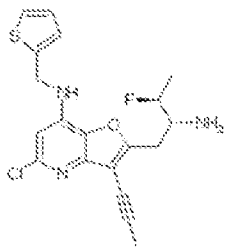
butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like; (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, *e.g.*, an alkali metal ion (*e.g.* lithium, sodium, potassium), an alkaline earth ion (*e.g.* magnesium, or calcium), or 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.

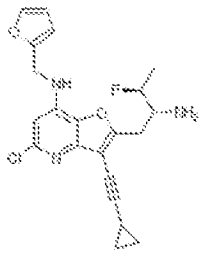
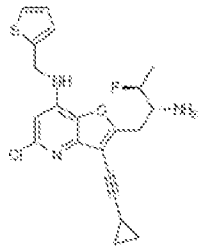
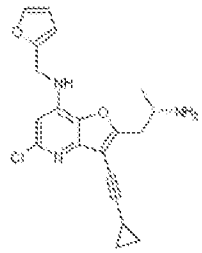
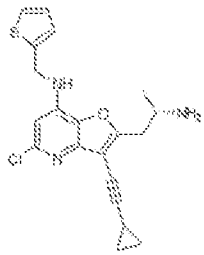
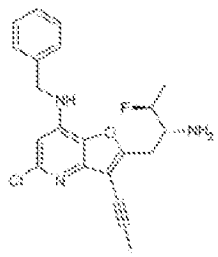
[00184] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms, particularly solvates. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In some embodiments, solvates of compounds described herein are conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

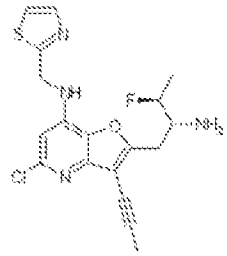
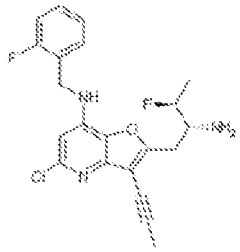
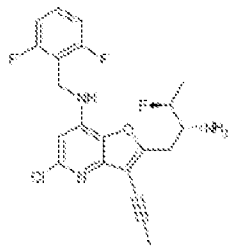
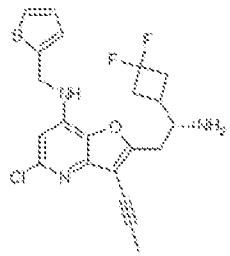
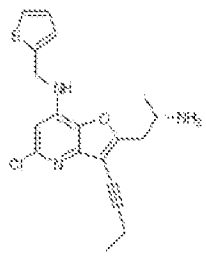
[00185] In some embodiments, a SMSM has a molecular weight of at most about 2000 Daltons, 1500 Daltons, 1000 Daltons or 900 Daltons. In some embodiments, a SMSM has a molecular weight of at least 100 Daltons, 200 Daltons, 300 Daltons, 400 Daltons or 500 Daltons. In some embodiments, a SMSM does not comprise a phosphodiester linkage. In some embodiments, a SMSM is a compound with a structure set forth in Table 1 below.

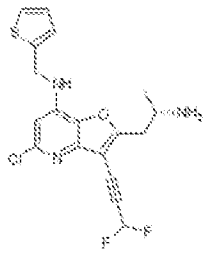
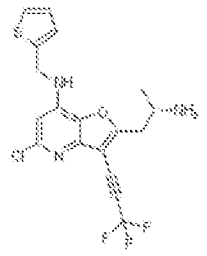
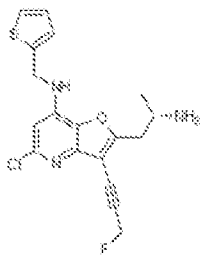
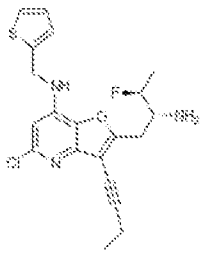
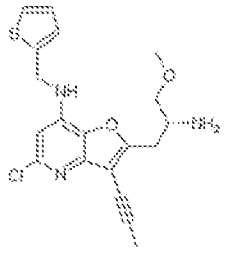
Table 1: Exemplary SMSM compounds

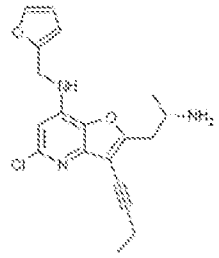
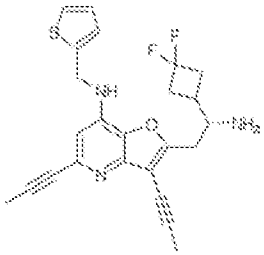
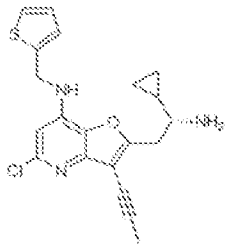
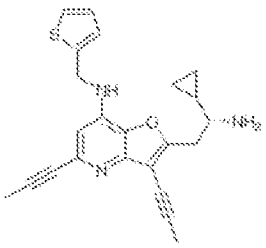
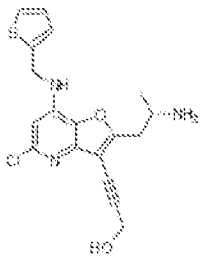
Compound #	Structure	IUPAC Name
1		2-[(S)-2-aminopropyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene

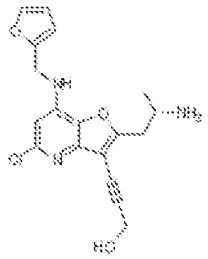
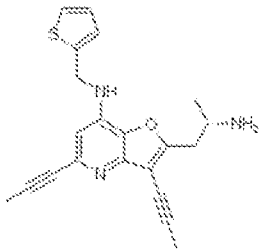
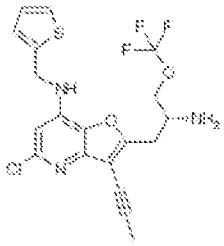
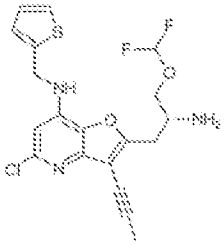
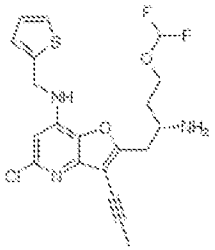
Compound #	Structure	IUPAC Name
2		2-[(S)-2-aminopropyl]-5-chloro-7-(furfurylamino)-3-(1-propynyl)-1-oxa-4-azaindene
3		2-[(R)-2-amino-4,4,4-trifluorobutyl]-5-chloro-7-(furfurylamino)-3-(1-propynyl)-1-oxa-4-azaindene
4		2-[(R)-2-amino-4,4,4-trifluorobutyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
5		2-[(2R,3S)-2-amino-3-fluorobutyl]-5-chloro-7-(furfurylamino)-3-(1-propynyl)-1-oxa-4-azaindene
6		2-[(2R,3S)-2-amino-3-fluorobutyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene

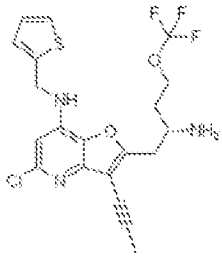
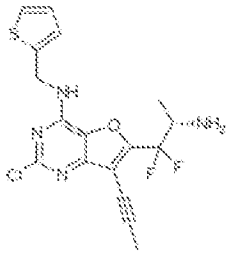
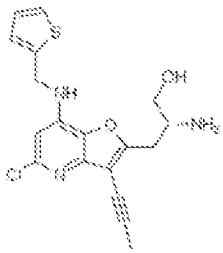
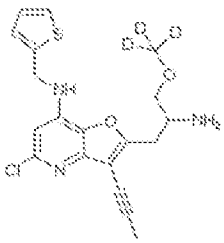
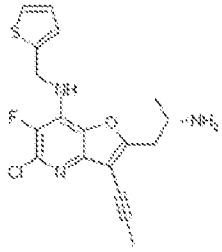
Compound #	Structure	IUPAC Name
7		2-[(2R,3S)-2-amino-3-fluorobutyl]-5-chloro-3-(2-cyclopropylethynyl)-7-(furfurylamino)-1-oxa-4-azaindene
8		2-[(2R,3S)-2-amino-3-fluorobutyl]-5-chloro-3-(2-cyclopropylethynyl)-7-thenylamino-1-oxa-4-azaindene
9		2-[(S)-2-aminopropyl]-5-chloro-3-(2-cyclopropylethynyl)-7-(furfurylamino)-1-oxa-4-azaindene
10		2-[(S)-2-aminopropyl]-5-chloro-3-(2-cyclopropylethynyl)-7-thenylamino-1-oxa-4-azaindene
11		2-[(2R,3S)-2-amino-3-fluorobutyl]-7-benzylamino-5-chloro-3-(1-propynyl)-1-oxa-4-azaindene

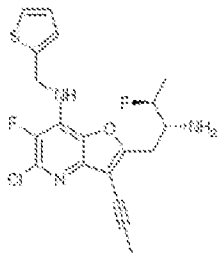
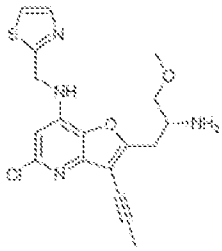
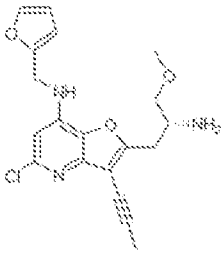
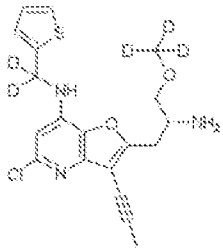
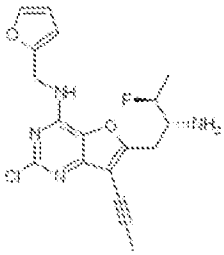
Compound #	Structure	IUPAC Name
12		2-[(2R,3S)-2-amino-3-fluorobutyl]-5-chloro-3-(1-propynyl)-7-{[(1,3-thiazol-2-yl)methyl]amino}-1-oxa-4-azaindene
13		2-[(2R,3S)-2-amino-3-fluorobutyl]-5-chloro-7-{[(o-fluorophenyl)methyl]amino}-3-(1-propynyl)-1-oxa-4-azaindene
14		2-[(2R,3S)-2-amino-3-fluorobutyl]-5-chloro-7-{[(2,6-difluorophenyl)methyl]amino}-3-(1-propynyl)-1-oxa-4-azaindene
15		2-[(R)-2-amino-2-(3,3-difluorocyclobutyl)ethyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
16		2-[(S)-2-aminopropyl]-3-(1-butynyl)-5-chloro-7-thenylamino-1-oxa-4-azaindene

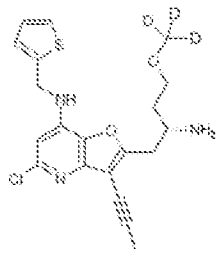
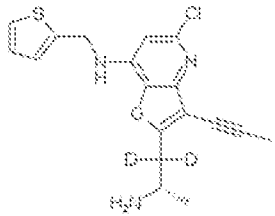
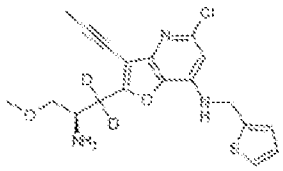
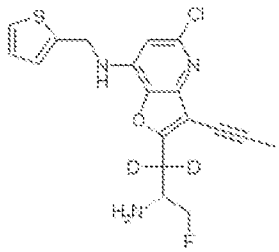
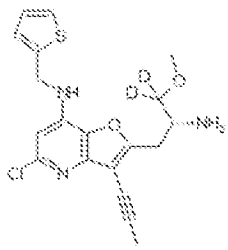
Compound #	Structure	IUPAC Name
17		2-[(S)-2-aminopropyl]-5-chloro-3-(3,3-difluoro-1-propynyl)-7-thenylamino-1-oxa-4-azaindene
18		2-[(S)-2-aminopropyl]-5-chloro-7-thenylamino-3-(3,3,3-trifluoro-1-propynyl)-1-oxa-4-azaindene
19		2-[(S)-2-aminopropyl]-5-chloro-3-(3-fluoro-1-propynyl)-7-thenylamino-1-oxa-4-azaindene
20		2-[(2R,3S)-2-amino-3-fluorobutyl]-3-(1-butynyl)-5-chloro-7-thenylamino-1-oxa-4-azaindene
21		2-[(R)-2-amino-3-methoxypropyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene

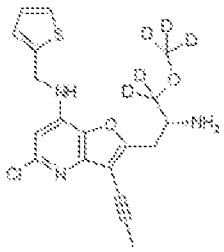
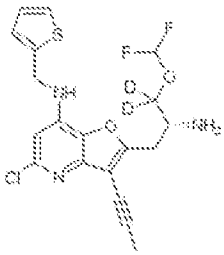
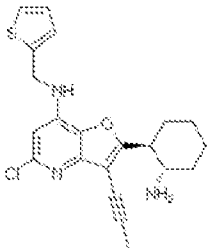
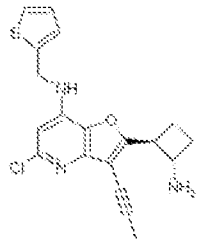
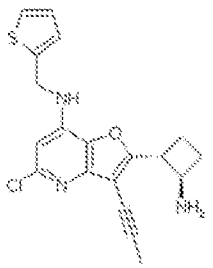
Compound #	Structure	IUPAC Name
22		2-[(S)-2-aminopropyl]-3-(1-butynyl)-5-chloro-7-(furfurylamino)-1-oxa-4-azaindene
23		2-[(R)-2-amino-2-(3,3-difluorocyclobutyl)ethyl]-3,5-bis(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
24		2-[(R)-2-amino-2-cyclopropylethyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
25		2-[(R)-2-amino-2-cyclopropylethyl]-3,5-bis(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
26		3-{2-[(S)-2-aminopropyl]-5-chloro-7-thenylamino-1-oxa-4-aza-3-indenyl}-2-propyn-1-ol

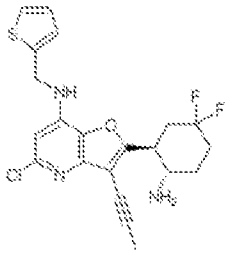
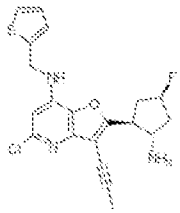
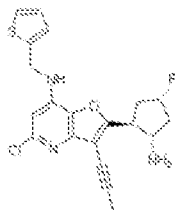
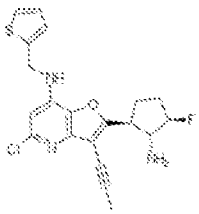
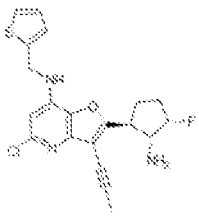
Compound #	Structure	IUPAC Name
27		3-{2-[(S)-2-aminopropyl]-5-chloro-7-(furfurylamino)-1-oxa-4-aza-3-indenyl}-2-propyn-1-ol
28		2-[(S)-2-aminopropyl]-3,5-bis(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
29		2-[(R)-2-amino-3-trifluoromethoxypropyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
30		2-[(R)-2-amino-3-difluoromethoxypropyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
31		2-[(S)-2-amino-4-difluoromethoxybutyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene

Compound #	Structure	IUPAC Name
32		2-[(S)-2-amino-4-trifluoromethoxybutyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
33		2-[(S)-2-amino-1,1-difluoropropyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4,6-diazaindene
34		(R)-2-amino-3-[5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-aza-2-indenyl]-1-propanol
35		2-[2-amino-3-($^{2}H_3$)methoxypropyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
36		2-[(S)-2-aminopropyl]-5-chloro-6-fluoro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene

Compound #	Structure	IUPAC Name
37		2-[(2R,3S)-2-amino-3-fluorobutyl]-5-chloro-6-fluoro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
38		2-[(R)-2-amino-3-methoxypropyl]-5-chloro-3-(1-propynyl)-7-{[(1,3-thiazol-2-yl)methyl]amino}-1-oxa-4-azaindene
39		2-[(R)-2-amino-3-methoxypropyl]-5-chloro-7-(furfurylamino)-3-(1-propynyl)-1-oxa-4-azaindene
40		2-[(R)-2-amino-3-($^2H_3$)methoxypropyl]-5-chloro-3-(1-propynyl)-7-{[(2-thienyl)($^2H_2$)methyl]amino}-1-oxa-4-azaindene
41		2-[(2R,3S)-2-amino-3-fluorobutyl]-5-chloro-7-(furfurylamino)-3-(1-propynyl)-1-oxa-4,6-diazaindene

Compound #	Structure	IUPAC Name
42		2-[(S)-2-amino-4-($^2H_3$)methoxybutyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
43		2-[(S)-2-amino(1,1-$^2H_2$)propyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
44		2-[(R)-2-amino-3-methoxy(1,1-$^2H_2$)propyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
45		2-[(R)-2-amino-3-fluoro(1,1-$^2H_2$)propyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
46		2-[(R)-2-amino-3-methoxy(3,3-$^2H_2$)propyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene

Compound #	Structure	IUPAC Name
47		2-[(R)-2-amino-3-($^2H_3$)methoxy(3,3-$^2H_2$)propyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
48		2-[(R)-2-amino-3-difluoromethoxy(3,3-$^2H_2$)propyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
49		2-[(1S,2S)-2-aminocyclohexyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
50 and 51	 	2-[(1S,2S)-2-aminocyclobutyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene 2-[(1R,2R)-2-aminocyclobutyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene

Compound #	Structure	IUPAC Name
52		2-[(1S,2S)-2-amino-5,5-difluorocyclohexyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
53		2-[(1S,2S,4R)-2-amino-4-fluorocyclopentyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
54		2-[(1S,2S,4S)-2-amino-4-fluorocyclopentyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
55		2-[(1S,2R,3R)-2-amino-3-fluorocyclopentyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene
56		2-[(1S,2R,3S)-2-amino-3-fluorocyclopentyl]-5-chloro-3-(1-propynyl)-7-thenylamino-1-oxa-4-azaindene

Pharmaceutical Compositions

[00186] 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 & Wilkins1999), herein incorporated by reference for such disclosure.

[00187] 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.

[00188] 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.

[00189] 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.

[00190] 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.

[00191] 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

[00192] 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.

[00193] 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.

[00194] 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.

[00195] 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.

[00196] 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.

[00197] 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.

[00198] 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.

[00199] 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.

[00200] 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.

[00201] 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.

[00202] 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.

[00203] 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 skipping

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

[00204] 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.

[00205] 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.

[00206] 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.

[00207] 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.

[00208] 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.

[00209] 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.

[00210] 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.

[00211] 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.

[00212] 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

[00213] 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

[00214] 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.

[00215] 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.

[00216] The compositions of the present disclosure can be administered as frequently as necessary.

Subjects

[00217] 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.

[00218] 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

[00219] 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.

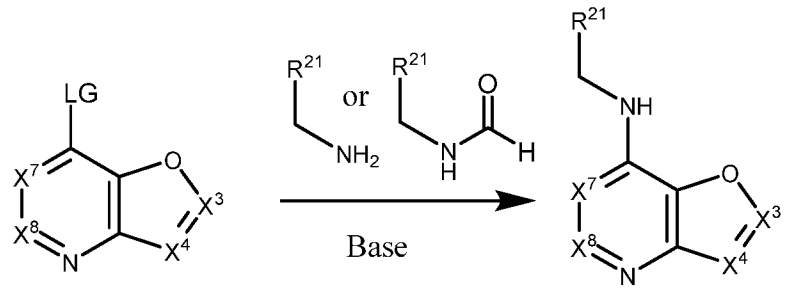
[00220] Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler 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.

[00221] 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).

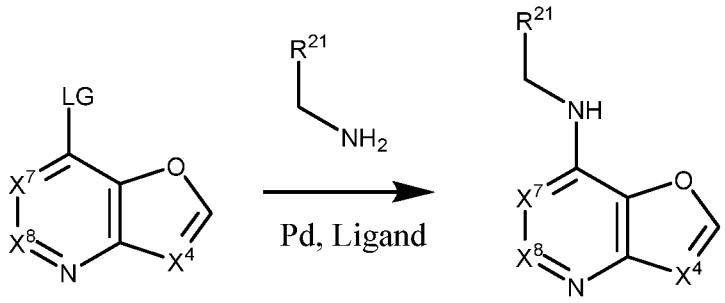
SMSMs can be made using known techniques and further chemically modified, in some embodiments, to facilitate intranuclear transfer to, *e.g.*, a splicing complex component, a spliceosome or a pre-mRNA molecule. One of ordinary skill in the art will appreciate the standard medicinal chemistry approaches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

[00222] General Synthesis Scheme 1



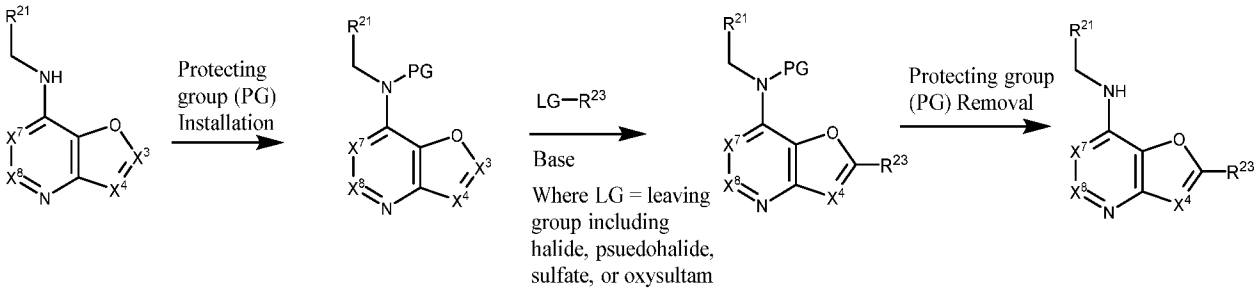
LG = Leaving group including halide, pseudohalide, or sulfone

[00223] General Synthesis Scheme 2:

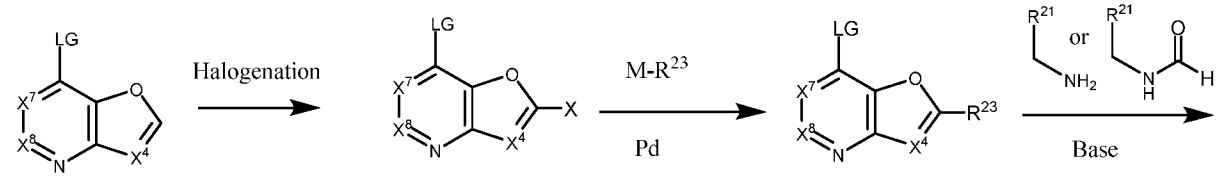


LG = Leaving group including halide, pseudohalide, or sulfone

[00224] General Synthesis Scheme 3



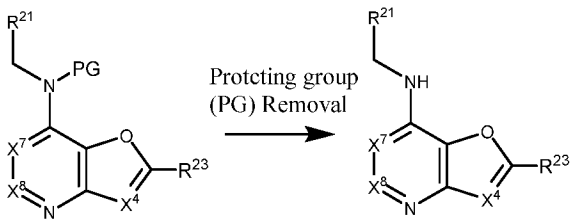
[00225] General Synthesis Scheme 4



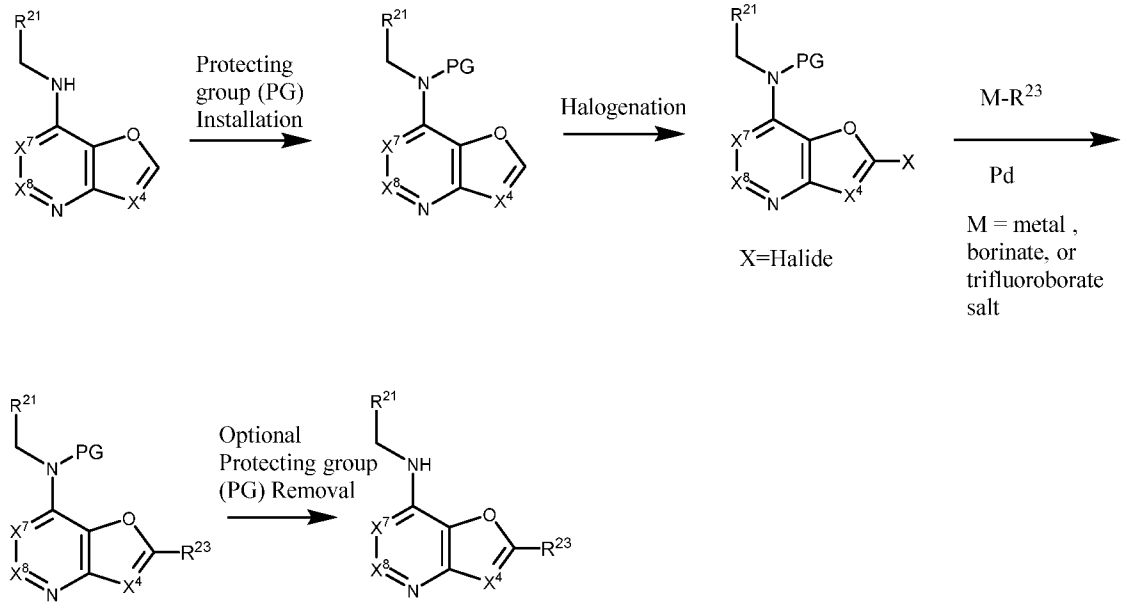
LG = Leaving group including halide, pseudohalide, or sulfone

X=Halide

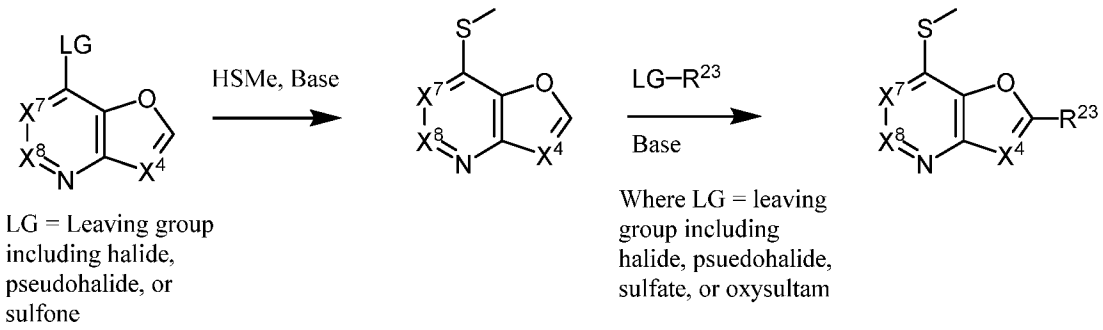
M = metal , borinate, or trifluoroborate salt

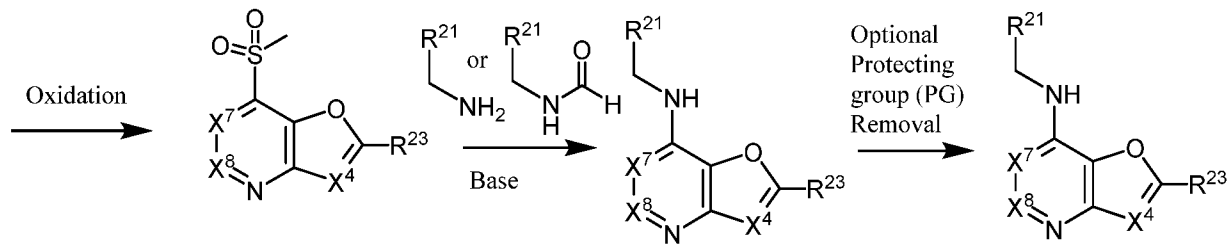


[00226] General Synthesis Scheme 5:

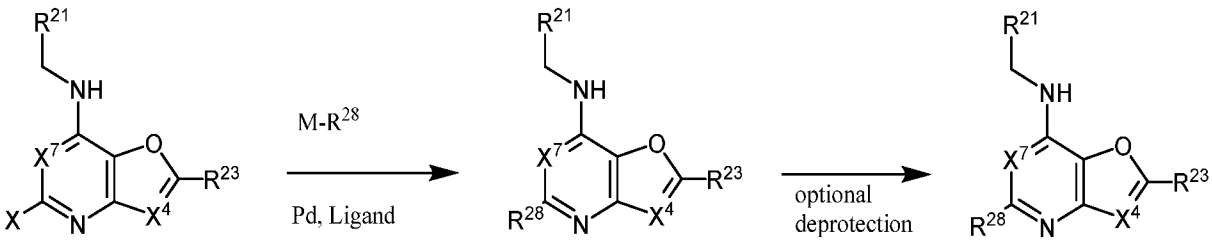


[00227] General Synthesis Scheme 6:

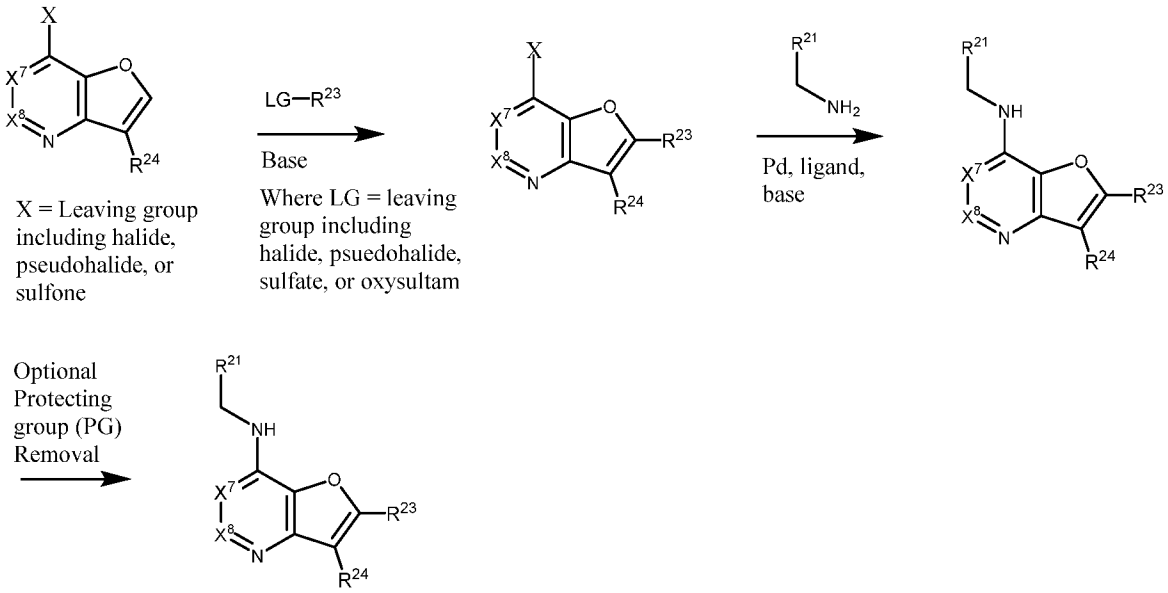




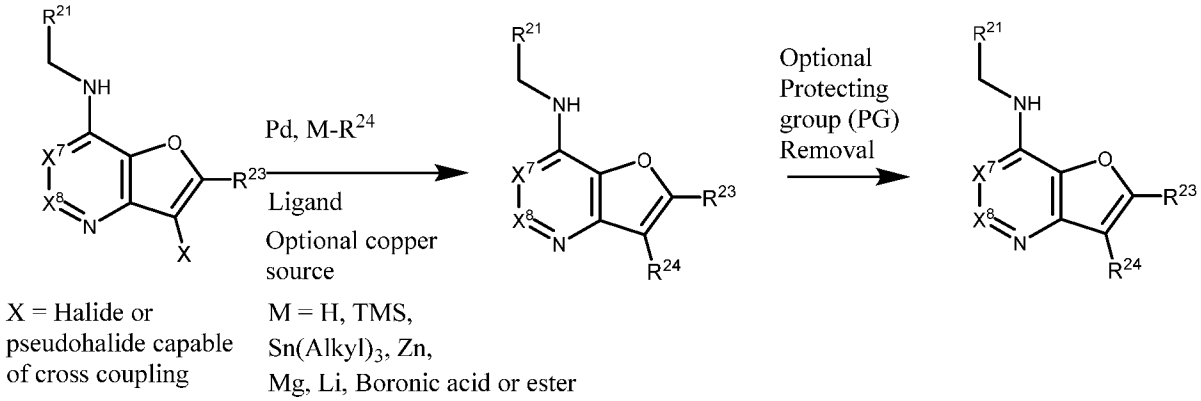
[00228] General Synthesis Scheme 7:



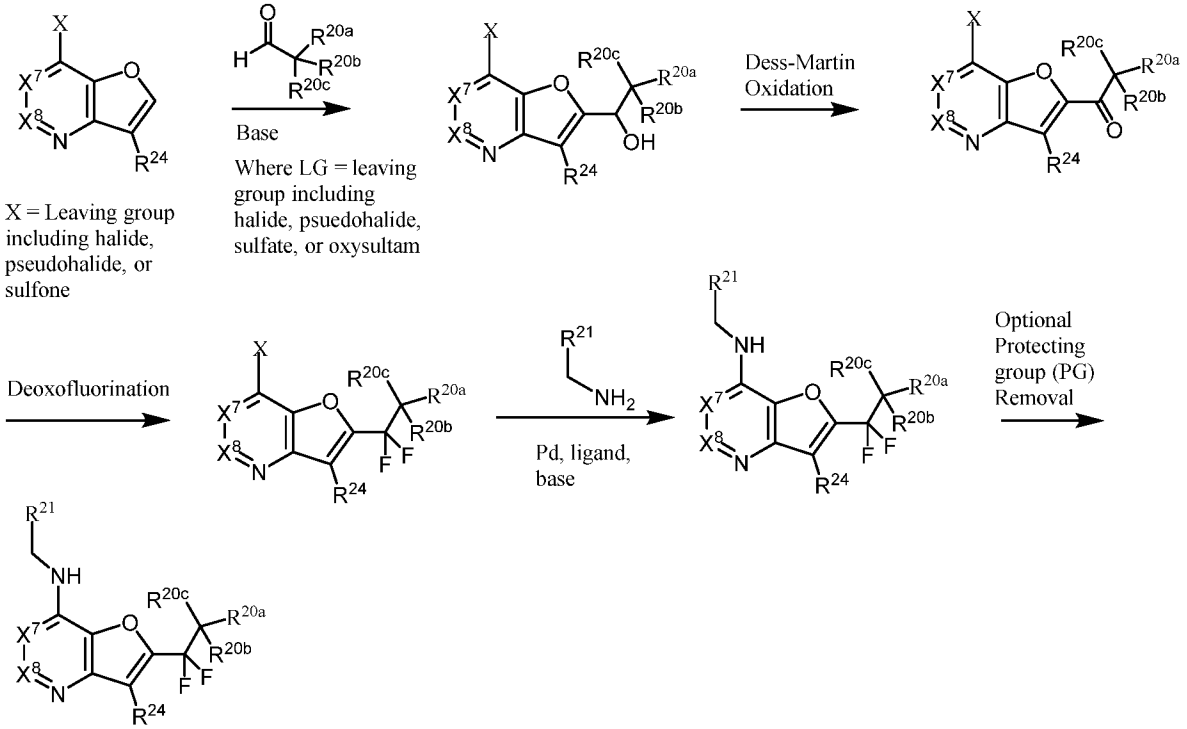
[00229] General Synthesis Scheme 8



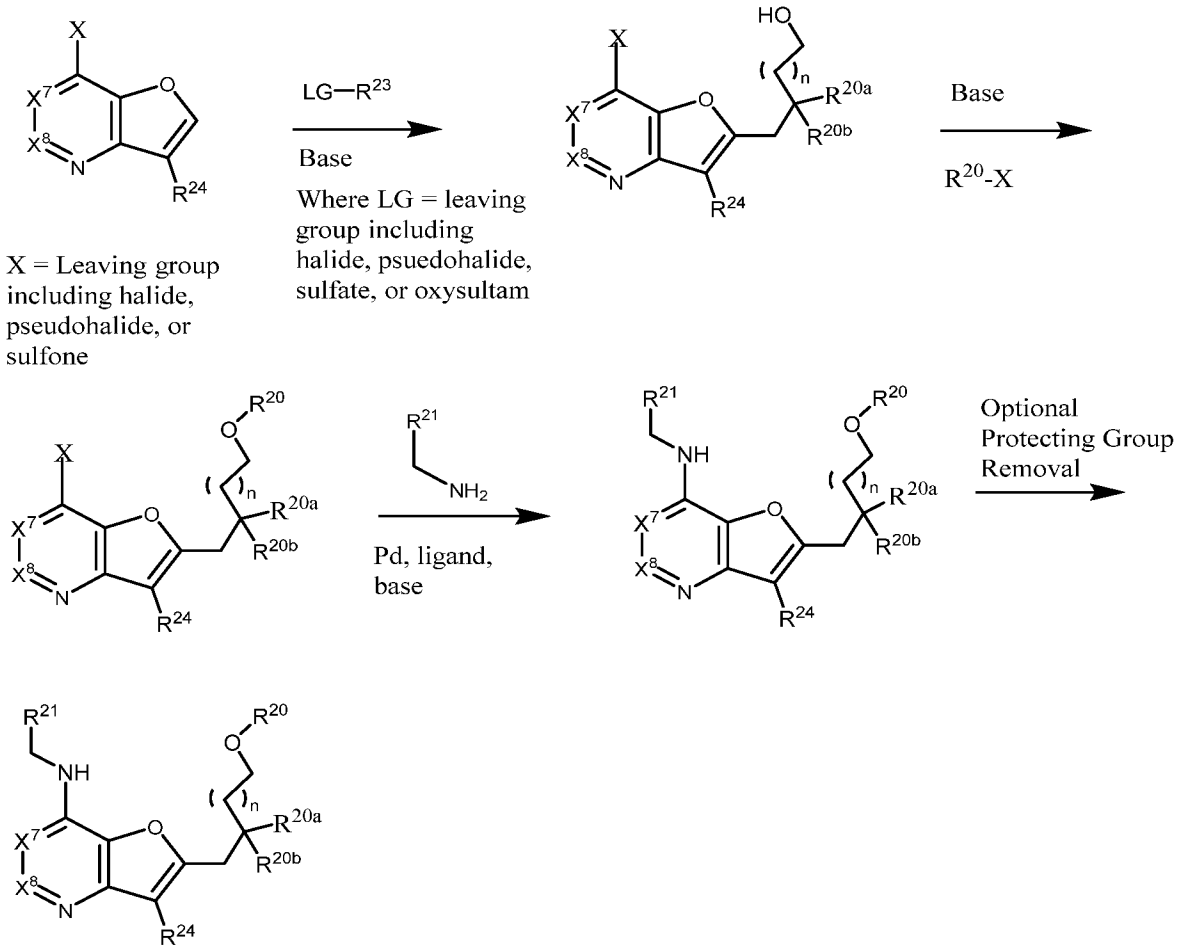
[00230] General Synthesis Scheme 9



[00231] General Synthesis Scheme 11

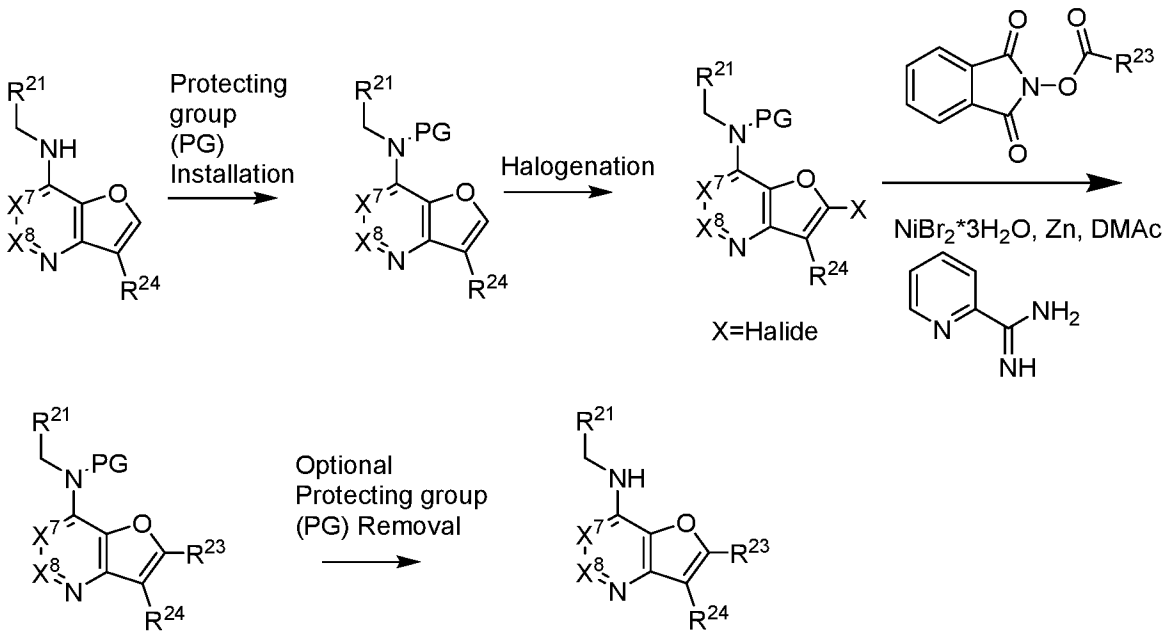


[00232] General Synthesis Scheme 12

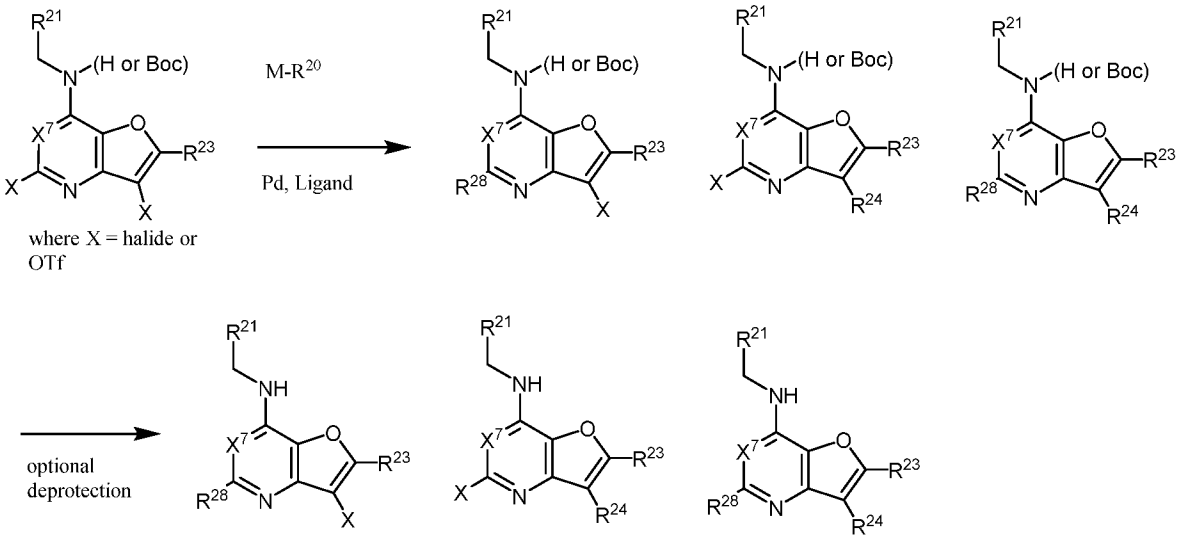


n is e.g., 0, 1, or 2.

[00233] General Synthesis Scheme 13



[00234] General Synthesis Scheme 17



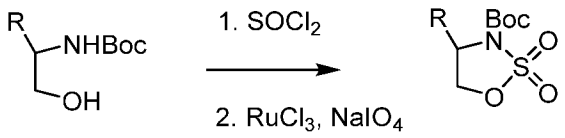
EXAMPLES

[00235] 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.

Example 1. References and syntheses of common building blocks and starting materials

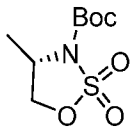
[00236] General Procedure for the Synthesis of Cyclic Sulfamidates AA:

Cyclic Sulfamidates can be synthesized by the following general method starting from the appropriate amino alcohol.



Building Block type AA

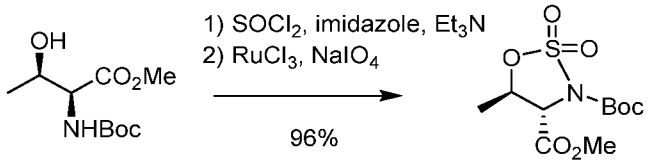
[00237] Additional synthetic procedures and/or literature references for known cyclic sulfamidates are provided below.Reference for tert-butyl (S)-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-1) Bower, J.F., Szetzo, P.; Gallagher, T. *Org. Lett.* **2007**, 9, 3283-3286.



AA-1

[00238] Synthesis of Tert-butyl (R)-4-((S)-1-fluoroethyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-2)

[00239] Step 1: Synthesis of 3-(tert-butyl) 4-methyl (4S,5R)-5-methyl-1,2,3-oxathiazolidine-3,4-dicarboxylate2,2-dioxide

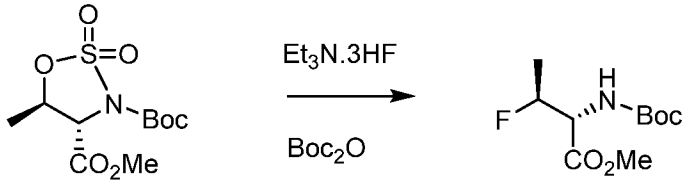


[00240] To a solution of imidazole (3.62 g, 4 Eq, 53.2 mmol), triethylamine (3.36 g, 4.63 mL, 2.5 Eq, 33.2 mmol) in DCM (60 mL) at -60°C was added dropwise thionyl chloride (1.74 g, 1.07 mL, 1.10 Eq, 14.6 mmol) followed by methyl (tert-butoxycarbonyl)-L-threoninate (3.10 g, 1 Eq, 13.3 mmol) in DCM (30.00 mL) keeping the reaction mixture below -55°C. The turbid mixture was allowed to warm to rt slowly and stirred 30 minutes. The reaction was quenched with 0.5N HCl (150 mL) and the water layer was extracted with DCM (2 x 75 mL). The combined organic layers were washed with half brine and half water, dried over sodium sulfate, filtered, and concentrated in vacuo.

[00241] The crude mixture was redissolved in MeCN (50 mL), cooled to 0°C, and treated with sodium periodate (3.27 g, 1.15 Eq, 15.3 mmol) followed by ruthenium trichloride (276 mg, 88.6 µL, 0.1 Eq, 1.33 mmol) and water (50 mL). The reaction was stirred for 1h at 0°C and diluted with water and TBME and filtered through a pad of celite. The water layer was extracted with TBME two times. The combined organic layers were washed with brine, dried

over sodium sulfate, filtered and concentrated in vacuo to afford 3-(tert-butyl) 4-methyl (4S,5R)-5-methyl-1,2,3-oxathiazolidine-3,4-dicarboxylate 2,2-dioxide (3.770 g, 12.77 mmol, 96.1 %).1H NMR (299 MHz, $CDCl_3$) δ 5.06 – 4.72 (m, 1H), 4.51 (dd, J = 5.8, 1.4 Hz, 1H), 3.87 (s, 3H), 1.73 (d, J = 6.4 Hz, 3H), 1.57 (s, 9H).

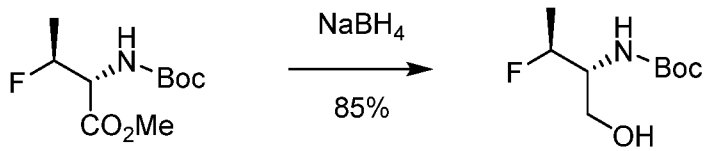
[00242] Step 2: Synthesis of methyl (2R,3S)-2-((tert-butoxycarbonyl)amino)-3-fluorobutanoate



[00243] To a solution of 3-(tert-butyl) 4-methyl (4S,5R)-5-methyl-1,2,3-oxathiazolidine-3,4-dicarboxylate 2,2-dioxide (5.770 g, 1 Eq, 19.54 mmol) in THF (100.00 mL) was added triethylamine trihydrofluoride (20.47 g, 20.7 mL, 6.50 Eq, 127.0 mmol) and the reaction mixture was refluxed for 16h. The reaction was neutralized with a saturated solution of sodium bicarbonate until the pH tested basic. Next, boc anhydride (4.264 g, 1 eq, 19.54 mmol) was added in one portion. The reaction mixture was stirred for 30 minutes at room temperature and extracted with EtOAc twice. The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified by column chromatography (Heptanes/EtOAc 90/10) to afford methyl (2R,3S)-2-((tert-butoxycarbonyl)amino)-3-fluorobutanoate (3.150 g, 13.39 mmol, 68.53 %).

[00244] ^1H NMR (299 MHz, $CDCl_3$) δ 5.38 (s, 1H), 4.88 (ddd, J = 47.2, 6.4, 3.7 Hz, 1H), 4.47 (dd, J = 22.2, 9.0 Hz, 1H), 3.82 (s, 3H), 1.51 – 1.36 (m, 12H).

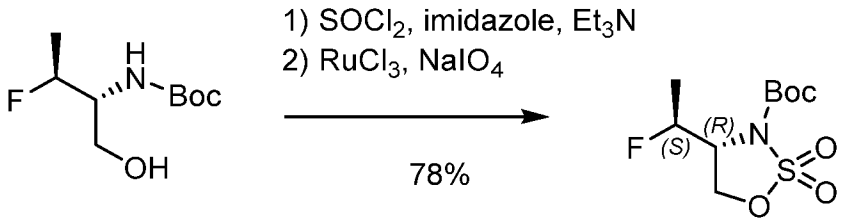
[00245] Step 3: Synthesis of Tert-butyl ((2R,3S)-3-fluoro-1-hydroxybutan-2-yl)carbamate



[00246] To a solution of methyl (2R,3S)-2-((tert-butoxycarbonyl)amino)-3-fluorobutanoate (3.08 g, 1 Eq, 13.1 mmol) in EtOH (65.00 mL) at 0°C was added $NaBH_4$ (1.24 g, 2.5 Eq, 32.7 mmol). The mixture was stirred at 0°C for 8h. The mixture was poured into 100 mL of water. The water layer was extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified by column chromatography (500 mL silica, Heptanes/EA, 65/35 to afford tert-butyl ((2R,3S)-3-fluoro-1-hydroxybutan-2-yl)carbamate (2.30 g, 11.1 mmol, 84.8 %).

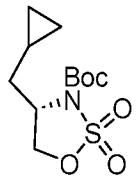
[00247] ^{1}H NMR (299 MHz, CDCl3) δ 5.12 (s, 1H), 4.80 (dt, J = 48.0, 6.1 Hz, 1H), 4.04 – 3.88 (m, 1H), 3.85 – 3.59 (m, 2H), 1.97 (s, 1H), 1.56 – 1.33 (m, 12H).

[00248] Step 4: Tert-butyl (R)-4-((S)-1-fluoroethyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide



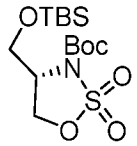
[00249] To a solution of imidazole (3.02 g, 4 Eq, 44.4 mmol), triethylamine (2.81 g, 3.87 mL, 2.5 Eq, 27.7 mmol) in DCM (60.00 mL) at -60°C was added dropwise thionyl chloride (1.45 g, 891 µL, 1.1 Eq, 12.2 mmol) followed by tert-butyl ((2R,3S)-3-fluoro-1-hydroxybutan-2-yl)carbamate (2.30 g, 1 Eq, 11.1 mmol) in DCM (30.00 mL) while keeping the temperature of the reaction mixture below -55°C. The turbid mixture was allowed to warm to rt slowly and stirred for 30 minutes. The reaction was quenched with 0.5N HCl (150 mL) and the phases were separated. The water layer was extracted with DCM (2 x 75 mL). The combined organic layers washed brine (100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. To a solution of the crude material in MeCN (40.00 mL) at 0°C was added sodium periodate (2.73 g, 1.15 Eq, 12.8 mmol) followed by ruthenium trichloride (230 mg, 74.0 µL, 0.1 Eq, 1.11 mmol) and water (40.00 mL). The reaction was stirred 1h at 0°C and diluted with water (50 mL) and TBME (150 mL) and filtered through a pad of celite. The celite cake was washed with 50 mL of TBME. The water layer was extracted with TBME twice (2 x 75 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified by column chromatography (500 mL silica, Hept/EtOAc, 80/20 to 75/25) to afford tert-butyl (R)-4-((S)-1-fluoroethyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (2.32 g, 8.62 mmol, 77.6 %) as a white solid. ^{1}H NMR (299 MHz, $CDCl_3$) δ 4.95 (d of quintets, J = 47.5, 6.3 Hz, 1H), 4.79 – 4.56 (m, 2H), 4.33 (dtd, J = 13.7, 5.5, 2.5 Hz, 1H), 1.58 (s, 9H), 1.43 (d, J = 24.1, 6.4, 1.1 Hz, 3H).

[00250] Reference for tert-butyl (S)-4-(cyclopropylmethyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-3) (WO2022/042657).



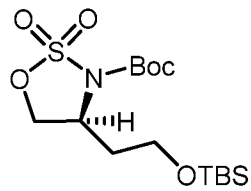
AA-3

[00251] Reference for tert-butyl (S)-4-(((tert-butyldimethylsilyl)oxy)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-4) Hebeisen, P.; Weiss, U.l Alker, A.l Ataempfli, A. *Tetrahedron Lett.* , **2011**, 52, 5229-5233.



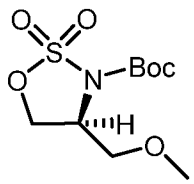
AA-4

[00252] Reference for tert-butyl (S)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-6): Zhang, N.; Arnold, M.A.; Dakka, A.; Karp, G.M.; Luong, T.T.; Narasimhan, J.; Naryshkin, N.A.; Wang, J.; Zhang, X. (WO2020167628).



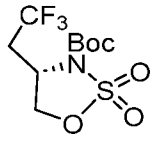
AA-6

[00253] Reference for tert-butyl (S)-4-(methoxymethyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-7) (WO2017/080979A1).

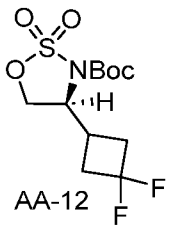


AA-7

[00254] Tert-butyl (S)-4-(2,2,2-trifluoroethyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-9) was synthesized from tert-butyl (S)-(4,4,4-trifluoro-1-hydroxybutan-2-yl)carbamate (WO2012/116279) according to the general method

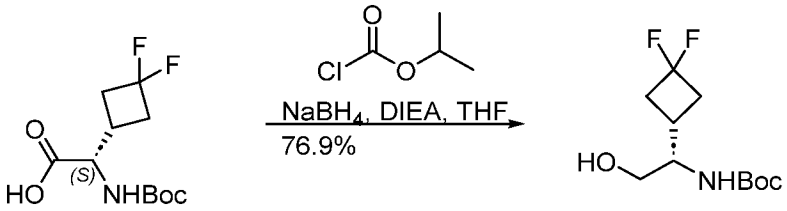


AA-9



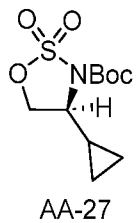
AA-12

[00255] Synthesis of tert-butyl N-[(1S)-1-(3,3-difluorocyclobutyl)-2-hydroxyethyl]carbamate



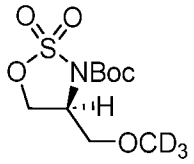
[00256] A solution of (S)-[(tert-butoxycarbonyl)amino](3,3-difluorocyclobutyl)acetic acid (4.8 g, 18.096 mmol, 1 equiv) in THF (50 mL) was treated with DIEA (4.68 g, 36.192 mmol, 2 equiv) and isopropyl chloroformate (2.88 g, 23.525 mmol, 1.3 equiv) at 0 °C for 30 min under nitrogen atmosphere followed by the addition of $NaBH_4$ (2.74 g, 72.384 mmol, 4 equiv) in portions at 0 °C. The resulting mixture was stirred for 2h at room temperature. The reaction was quenched with water at 0°C. The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 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 (5:1) to afford tert-butyl N-[(1S)-1-(3,3-difluorocyclobutyl)-2-hydroxyethyl]carbamate (3.5 g, 76.97%) as a colorless oil.

[00257] Synthesis of tert-butyl (S)-4-cyclopropyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-27) was performed according to the general method starting from (S)-tert-butyl (1-cyclopropyl-2-hydroxyethyl)carbamate (Parker, W.L.; Hanson, R.L.; Goldberg, S. L.; Tully, T.P.; Animesh, G.; *Organic Process Research and Development*, **2012**, *16*, 464-469.)



AA-27

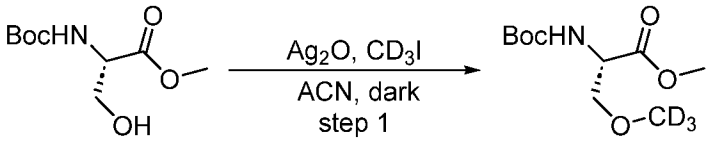
[00258] Synthesis of tert-butyl (S)-4-((methoxy-d3)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-32) was performed according to the general method starting from tert-butyl (4S)-4-[(2H3)methoxymethyl]-2-oxo-1,2lambda4,3-oxathiazolidine-3-carboxylate.



AA-32

[00259] Synthesis of tert-butyl (4S)-4-[(2H3)methoxymethyl]-2-oxo-1,2lambda4,3-oxathiazolidine-3-carboxylate

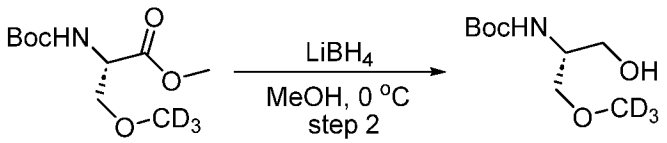
[00260] Step 1. Synthesis of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(2H3)methoxypropanoate



[00261] A mixture of methyl (2S)-2-[(tert-butoxycarbonyl) amino]-3-hydroxypropanoate (5 g, 22.806 mmol, 1 equiv), CD_3I (33.72 g, 232.621 mmol, 10.2 equiv) and Ag_2O (26.95 g, 116.311 mmol, 5.1 equiv) in ACN (100 mL) was stirred for 3 days at room temperature under nitrogen atmosphere in dark. The resulting mixture was filtered and the filter cake was washed with EtOAc (3x100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(2H3)methoxypropanoate (5 g, 92.79%) as a colorless oil.

[00262] ^1H NMR (300 MHz, Chloroform-d) δ 5.39 (d, J = 8.8 Hz, 1H) 4.43 (dd, J = 8.7, 3.5 Hz, 1H), 3.78 (s, 3H), 3.60 (dd, J = 9.4, 3.4 Hz, 1H) ,3.31 – 3.21 (m, 2H), 1.38 (s, 9H).

[00263] Step 2. Synthesis of afford tert-butyl N-[(2R)-1-hydroxy-3-(2H3) methoxypropan-2-yl] carbamate

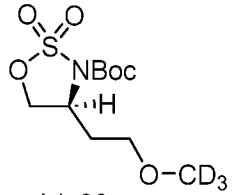


[00264] To a stirred solution of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(2H3)methoxypropanoate (5.4 g, 22.854 mmol, 1 equiv) in MeOH (30 mL) and THF (30 mL) was added 2M $LiBH_4$ (1.00 g, 45.708 mmol, 2 equiv) dropwise at 5 min at 0 °C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature. The

resulting mixture was filtered and the filter cake was washed with THF (2x50 mL). The filtrate 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)-1-hydroxy-3-(2H3) methoxypropan-2-yl] carbamate (4.3 g, 90.34%) as a light yellow oil.

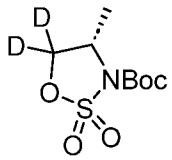
[00265] ^{1}H NMR (300 MHz, DMSO-d6) δ 6.48 (d, J = 8.4 Hz, 1H), 4.60 (t, J = 5.7 Hz, 1H), 3.54 (q, J = 7.5, 6.6 Hz, 1H), 3.34 (d, J = 1.6 Hz, 1H), 3.31 – 3.21 (m, 2H), 1.38 (s, 9H).

[00266] Tert-butyl (S)-4-(2-(methoxy-d3)ethyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-39) was made in an analogous fashion to AA-32 described above.



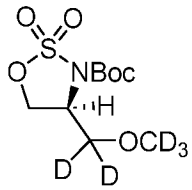
AA-39

[00267] Synthesis of tert-butyl (S)-4-methyl-1,2,3-oxathiazolidine-3-carboxylate-5,5-d2 2,2-dioxide (AA-42) was performed according to the general method starting from tert-butyl (S)-(1-hydroxyprop-2-yl-1,1-d2)carbamate (Guaragna, A.; Pedatella, S.; Pinto, V. *Synthesis*, **2006**, *23*, 4013-4016.



AA-42

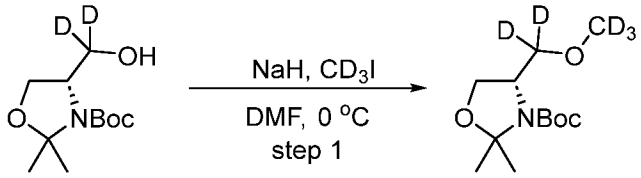
[00268] Synthesis of tert-butyl (S)-4-(methoxymethyl-d2)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-43) was performed according to the general method starting from tert-butyl N-[(2R)-1-hydroxy-3-(2H3)methoxy(3,3-2H2)propan-2-yl]carbamate.



AA-43

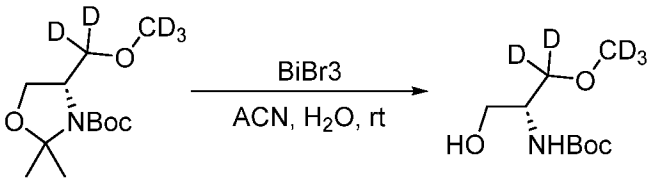
[00269] Synthesis of tert-butyl N-[(2R)-1-hydroxy-3-(2H3)methoxy(3,3-2H2)propan-2-yl]carbamate

[00270] Step 1. Synthesis of tert-butyl (4R)-4-[(2H3)methoxy(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate



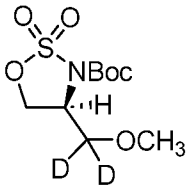
[00271] To a stirred mixture of tert-butyl (4R)-4-[hydroxy(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (5 g, 21.431 mmol, 1 equiv) and CD_3I (4.04 g, 27.860 mmol, 1.3 equiv) in DMF (100 mL) was added NaH (0.77 g, 32.147 mmol, 1.5 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature under nitrogen atmosphere. The reaction was quenched with water at 0°C.The mixture was acidified to pH 6 with HCl (aq.). The resulting mixture was extracted with EtOAc (600 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford tert-butyl (4R)-4-[(2H3)methoxy(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (4.8 g, 89.46%) as a colour-less oil.

[00272] Step 2. Synthesis of tert-butyl N-[(2R)-1-hydroxy-3-(2H3)methoxy(3,3-2H2)propan-2-yl]carbamate



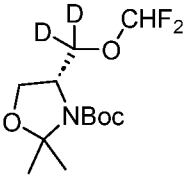
[00273] A mixture of tert-butyl (4R)-4-[(2H3)methoxy(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (4 g, 15.978 mmol, 1 equiv) and bismuth tribromide (1.43 g, 3.196 mmol, 0.2 equiv) in MeCN (80 mL) and H_2O (0.8 mL) was stirred for 1h at room temperature under nitrogen atmosphere. The resulting mixture was extracted with EtOAc (300 mL). The combined organic layers were washed with brine (100 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 (8:1) to afford tert-butyl N-[(2R)-1-hydroxy-3-(2H3)methoxy(3,3-2H2)propan-2-yl]carbamate (2.5 g, 74.41%) as a light yellow oil.

[00274] Synthesis of tert-butyl (S)-4-(methoxymethyl-d2)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-44) was performed analogously to tert-butyl (S)-4-(methoxymethyl-d2)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-43).



AA-44

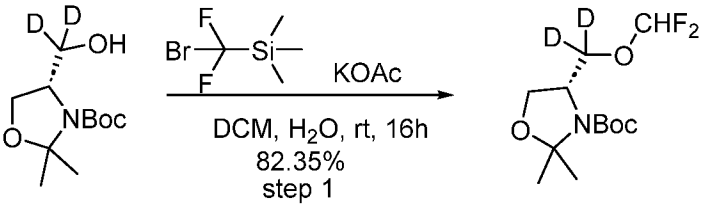
[00275] Synthesis of tert-butyl (R)-4-((difluoromethoxy)methyl-d2)-2,2-dimethyloxazolidine-3-carboxylate (AA-45) was performed according to the general method starting from tert-butyl N-[(2R)-1-(difluoromethoxy)-3-hydroxy(1,1-2H2)propan-2-yl]carbamate.



AA-45

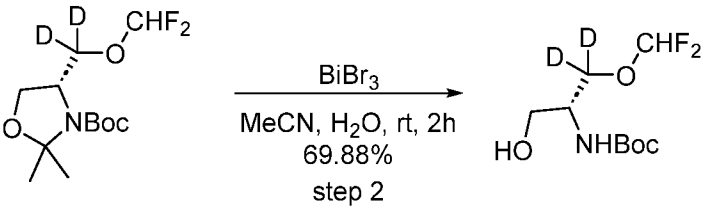
[00276] Synthesis of tert-butyl N-[(2R)-1-(difluoromethoxy)-3-hydroxy(1,1-2H2)propan-2-yl]carbamate

[00277] Step 1. Synthesis of tert-butyl (4R)-4-[(difluoromethoxy)(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate



[00278] To a stirred solution of tert-butyl (4R)-4-[hydroxy(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (20 g, 85.837mmol, 1 equiv) and (bromodifluoromethyl)trimethylsilane (52.232 g, 257.175 mmol, 3 equiv) in DCM (800.00 mL) and H_2O (800.00 mL) was added potassium acetate (50.479 g, 514.350 mmol, 6 equiv) in portions at 10°C under air atmosphere. The resulting mixture was stirred for 16h at room temperature under air atmosphere. The resulting mixture was concentrated under reduced pressure. The resulting mixture was extracted with CH_2Cl_2 (3 x 10mL). The combined organic layers were washed with brine (1x5 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)(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (20 g, 82.35%) as a yellow oil.

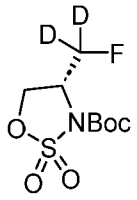
[00279] Step 2. Synthesis of tert-butyl N-[(2R)-1-(difluoromethoxy)-3-hydroxy(1,1-2H2)propan-2-yl]carbamate



[00280] To a stirred solution of tert-butyl (4R)-4-[(difluoromethoxy)(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (4 g, 14.119 mmol, 1 equiv) in MeCN (80 mL) was added bismuth

tribromide (1.27 g, 2.824 mmol, 0.2 equiv) dropwise at 0°C under air atmosphere. The resulting mixture was stirred for 2h at room temperature under air atmosphere. The reaction was quenched with Water (20 mL) at room temperature. The resulting mixture was filtered, the filter cake was washed with MeCN (1x20 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-hydroxy(1,1-2H2)propan-2-yl]carbamate (2.4 g, 69.88%) as a yellow oil.

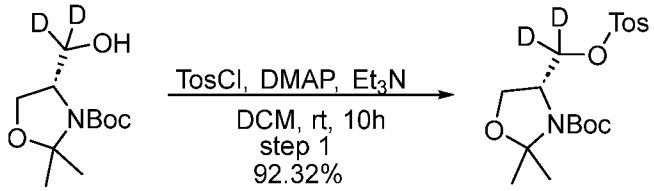
[00281] Synthesis of tert-butyl (R)-4-(fluoromethyl-d2)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (AA-46) was performed according to the general method starting from tert-butyl N-[(2R)-1-fluoro-3-hydroxy(1,1-2H2)propan-2-yl]carbamate.



AA-46

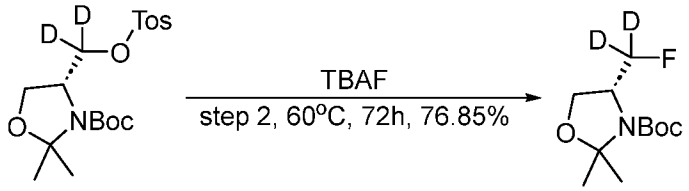
[00282] Synthesis of tert-butyl N-[(2R)-1-fluoro-3-hydroxy(1,1-2H2)propan-2-yl]carbamate

[00283] Step 1 tert-butyl (4R)-2,2-dimethyl-4-{[(4-methylbenzenesulfonyl)oxy](2H2)methyl}-1,3-oxazolidine-3-carboxylate



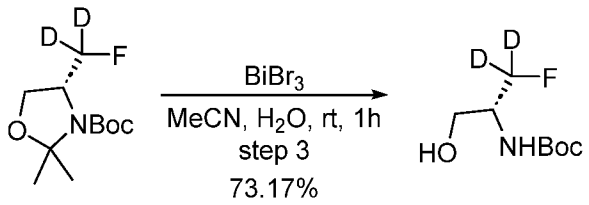
[00284] To a stirred solution of tert-butyl (4R)-4-[hydroxy(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (3 g, 12.859 mmol, 1 equiv) in DCM (40 mL) were added 4-methylbenzene-1-sulfonyl chloride (3.68 g, 19.288 mmol, 1.5 equiv) and Et_3N (2.60 g, 25.718 mmol, 2 equiv) in portions at 0°C under nitrogen atmosphere. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (10mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 50mL). 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 silica gel column chromatography, eluted with PE / EA (4:1) to afford tert-butyl (4R)-2,2-dimethyl-4-{[(4-methylbenzenesulfonyl)oxy](2H2)methyl}-1,3-oxazolidine-3-carboxylate (4.6 g, 92.32%) as a white solid.

[00285] Step 2. Synthesis of tert-butyl (4R)-4-[fluoro(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate



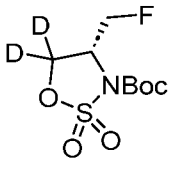
[00286] Into a 100mL 3-necked round-bottom flask were added tert-butyl (4R)-2,2-dimethyl-4-{[(4-methylbenzenesulfonyl)oxy](2H2)methyl}-1,3-oxazolidine-3-carboxylate (3 g, 7.742 mmol, 1 equiv) and TBAF (4.45 g, 17.032 mmol, 2.2 equiv) at room temperature. The resulting mixture was stirred for 3 days at 60°C under air atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was diluted with EtOAc (60mL). The resulting mixture was extracted with EtOAc (3 x 50mL). 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 silica gel column chromatography, eluted with PE / EA (9:1) to afford tert-butyl (4R)-4-[fluoro(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (1.4 g, 76.85%) as a yellow oil.

[00287] Step 3. Synthesis of tert-butyl N-[(2R)-1-fluoro-3-hydroxy(1,1-2H2)propan-2-yl]carbamate



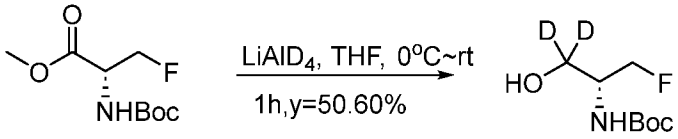
[00288] To a stirred solution of tert-butyl (4R)-4-[fluoro(2H2)methyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (1.4 g, 5.950 mmol, 1 equiv) in MeCN (20 mL) was added bismuth tribromide (0.53 g, 1.190 mmol, 0.2 equiv) and H_2O (0.2 mL) dropwise at 0°C under air atmosphere. The resulting mixture was stirred for 1h at room temperature under air atmosphere. The resulting mixture was extracted with CH_2Cl_2 (3 x 30mL). 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 silica gel column chromatography, eluted with PE / EA (4:1) to afford tert-butyl N-[(2R)-1-fluoro-3-hydroxy(1,1-2H2)propan-2-yl]carbamate (850 mg, 73.17%).

[00289] Synthesis of tert-butyl (R)-4-(fluoromethyl)-1,2,3-oxathiazolidine-3-carboxylate-5,5-d2 2,2-dioxide (AA-47) was performed according to the general method starting from tert-butyl N-[(2R)-1-fluoro-3-hydroxy(3,3-2H2)propan-2-yl]carbamate.



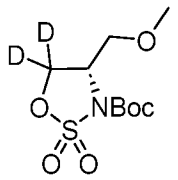
AA-47

[00290] Synthesis of tert-butyl N-[(2R)-1-fluoro-3-hydroxy(3,3-2H2)propan-2-yl]carbamate



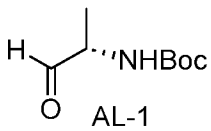
[00291] Into a 500-mL 3-necked round-bottom flask were added methyl (2R)-2-[(tert-butoxycarbonyl)amino]-3-fluoropropanoate (21.5 g, 97.185 mmol, 1.00 equiv) and THF (200 mL) at 0°C. To the above mixture was added $LiAlD_4$ (4.90 g, 116.722 mmol, 1.20 equiv) in portions over 30min at room temperature. The resulting mixture was stirred for additional 1h at room temperature. The resulting mixture was diluted with THF (200 mL). The mixture was allowed to cool down to 0°C. The reaction was quenched by the addition of Water (86 mL) and 15% NaOH(21.5mL) at 0°C. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1) to afford tert-butyl N-[(2R)-1-fluoro-3-hydroxy(3,3-2H2)propan-2-yl]carbamate (9.6 g, 50.60%) as a colorless oil.

[00292] Reference for tert-butyl (S)-4-(methoxymethyl)-1,2,3-oxathiazolidine-3-carboxylate-5,5-d2 2,2-dioxide (AA-48): (WO2022/89454)



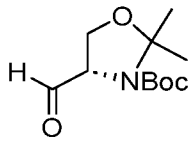
AA-48

[00293] Aldehydes Used: AL-1: (*S*)-N-Boc-2-aminopropanal



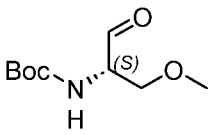
AL-1

[00294] AL-2: Tert-butyl (S)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate



AL-2

[00295] AL-3: Tert-butyl (S)-(1-methoxy-3-oxopropan-2-yl)carbamate

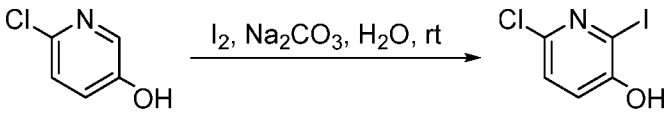


AL-3

[00296] Additional Building blocks:

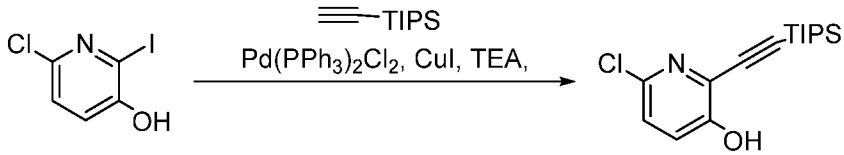
[00297] Synthesis of 3-bromo-5-chloro-7-iodofuro[3,2-b]pyridine:

[00298] Step 1. Synthesis of 6-chloro-2-iodopyridin-3-ol



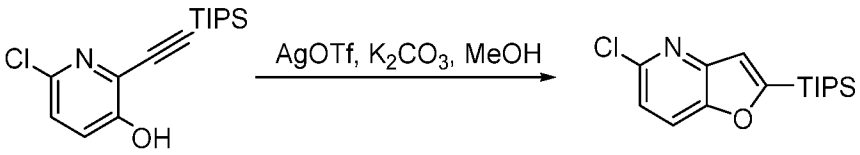
[00299] To a stirred solution of 6-chloropyridin-3-ol (100 g, 1 equiv, 770 mmol) in water (1400 mL) was added iodide (196 g, 1 equiv, 770 mmol) and sodium carbonate (164 g, 2 equiv, 1500 mmol). This mixture was stirred at 25°C for 3 h. The pH value of the solution was adjusted to 6~7 with hydrochloric acid (1 mol/L, 900 mL). The resulting solution was extracted with ethyl acetate (3x1500 mL). The combined organic layers were washed with sat. sodium chloride aqueous (3x1500 mL), dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure to afford 6-chloro-2-iodopyridin-3-ol (183 g, 92%) as a yellow solid.

[00300] Step 2. Synthesis of 6-chloro-2-((triisopropylsilyl)ethynyl)pyridin-3-ol



[00301] To a stirred solution of 6-chloro-2-iodopyridin-3-ol (180 g, 1 equiv, 700 mmol) in 1,4-dioxane (1200 mL) and triethylamine (1200 mL) was added ethynyltriisopropylsilane (167 g, 1.3 equiv, 910 mmol), cuprous iodide (6.71 g, 0.05 equiv, 35 mmol) and bis-(triphenylphosphino)-palladous chloride (9.89 g, 0.02 equiv, 14 mmol). This mixture was stirred at 45°C for 2.5 h under nitrogen atmosphere. After the reaction was cooled to room temperature, the residue was diluted with water (2000 mL) and extracted with ethyl acetate (3x1500 mL). The combined organic layers were dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with petroleum ether / ethyl acetate (5:1) to afford 6-chloro-2-((triisopropylsilyl)ethynyl)pyridin-3-ol (162 g, 73%) as a yellow solid.

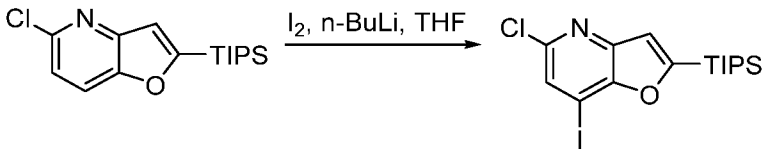
[00302] Step 3. Synthesis of 5-chloro-2-(triisopropylsilyl)furo[3,2-b]pyridine



[00303] To a stirred solution of 6-chloro-2-((triisopropylsilyl)ethynyl)pyridin-3-ol (160 g, 1 equiv, 510 mmol) in methanol (1600 mL) was added potassium carbonate (107 g, 1.5 equiv, 770 mmol) and silver(I)trifluoromethanesulfonate (13.3 g, 0.1 equiv, 51 mmol). This mixture was stirred at 50°C for 12 h. After the reaction was cooled to room temperature, the

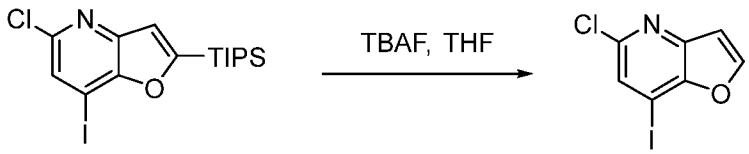
reaction was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with petroleum ether / ethyl acetate (10:1) to afford 5-chloro-2-(triisopropylsilyl)furo[3,2-b]pyridine (150 g, 93%) as a yellow solid.

[00304] Step 4. Synthesis of 5-chloro-7-iodo-2-(triisopropylsilyl)furo[3,2-b]pyridine



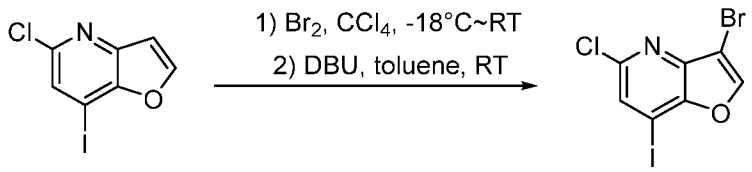
[00305] To a solution of 5-chloro-2-(triisopropylsilyl)furo[3,2-b]pyridine (70 g, 1 equiv, 0.22 mol) in tetrahydrofuran (500 mL) was added n-butyllithium (136 mL, 2 mol/L, 1.2 equiv, 0.28 mol) dropwise and the resulting mixture was stirred at -70°C for 40 minutes. A solution of iodide (86 g, 1.5 equiv, 0.34 mol) in tetrahydrofuran (240 mL) was added dropwise and the resulting mixture was allowed to warm up to 0°C over 3 h. The saturated ammonium chloride aqueous (600 mL) and saturated sodium thiosulfate aqueous solution (400 mL) were added at 0°C. The mixture was extracted with dichloromethane (3x700 mL) and the combined organic layers were dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with petroleum ether / ethyl acetate (10:1) to afford 5-chloro-7-iodo-2-(triisopropylsilyl)furo[3,2-b]pyridine (74 g, 75%) as a yellow solid.

[00306] Step 5. Synthesis of 5-chloro-7-iodofuro[3,2-b]pyridine

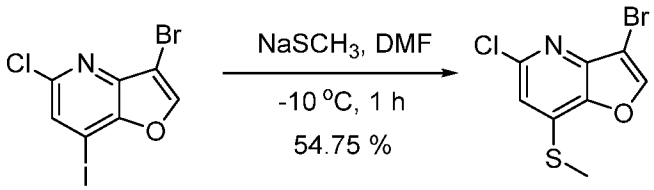


[00307] To a solution of 5-chloro-7-iodo-2-(triisopropylsilyl)furo[3,2-b]pyridine (74 g, 1 equiv, 170 mmol) in tetrahydrofuran (400 mL) was added tetrabutylammonium fluoride (204 mL, 1 mol/L in THF, 1.2 equiv, 0.20 mol) dropwise at -45°C and the resulting mixture was allowed to warm to 0°C over 60 minutes. The saturated ammonium chloride (120 mL) aqueous was added at 0°C. The mixture was extracted with ethyl acetate (3x700 mL) and the combined organic layers were dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was triturated by isopropyl alcohol and filtered to afford 5-chloro-7-iodofuro[3,2-b]pyridine (46 g, 97%) as a white solid.

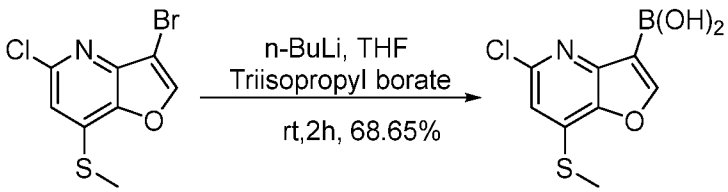
[00308] Step 6. Synthesis of 3-bromo-5-chloro-7-iodofuro[3,2-b]pyridine.



[00309] To a solution of 5-chloro-7-iodofuro[3,2-b]pyridine (44 g, 1 equiv, 158 mmol) in CCl_4 (480 mL) was added bromine (0.38 kg, 122 mL, 15 equiv, 2.4 mol) dropwise at -18°C and the resulting mixture was allowed to warm to 25°C over 1.5 h. Then the mixture was poured into saturated sodium thiosulfate aqueous (1000 mL) at 0°C and filtered through a Celite pad. The resulting mixture was extracted with dichloromethane (2x2000 mL). The organic layers were washed with brine (2000 mL) and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. Toluene (500 mL) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (80 mL) were added to the residue and the mixture was stirred at 25°C for 45 minutes. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography, eluted with petroleum ether / ethyl acetate (7:1) to afford 3-bromo-5-chloro-7-iodofuro[3,2-b]pyridine (24 g, 43%) as a white solid. Synthesis of 3-bromo-5-chloro-7-(methylsulfanyl)furo[3,2-b]pyridine



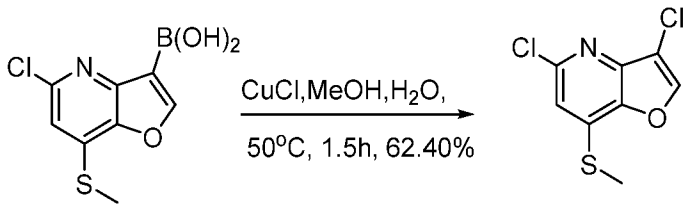
[00310] To a stirred mixture of 3-bromo-5,7-dichlorofuro[3,2-b]pyridine (2.1 g, 7.868 mmol, 1 equiv) in DMF (20 mL) was added (methylsulfanyl)sodium (551.40 mg, 7.868 mmol, 1 equiv) in portions at -10 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at -10 °C under nitrogen atmosphere. The residue was purified by reverse flash chromatography with the following conditions: column, C_{18} silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 60% gradient in 15 min; detector, UV 254 nm. This resulted in 3-bromo-5-chloro-7-(methylsulfanyl)furo[3,2-b]pyridine (1.2 g, 54.75%) as a white solid.Synthesis of 5-chloro-7-(methylsulfanyl)furo[3,2-b]pyridin-3-ylboronic acid



[00311] A solution of 3-bromo-5-chloro-7-(methylsulfanyl)furo[3,2-b]pyridine (500 mg, 1.795 mmol, 1 equiv) in THF (10 mL) was treated with n-BuLi (0.93 mL, 2.333 mmol, 1.3

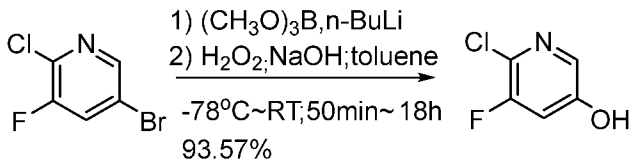
equiv) for 5min at -78°C under nitrogen atmosphere followed by the addition of triisopropyl borate (506.39 mg, 2.692 mmol, 1.5 equiv) dropwise at -78°C. The resulting mixture was stirred for additional 2h at room temperature. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 5-chloro-7-(methylsulfanyl)furo[3,2-b]pyridin-3-ylboronic acid (300 mg, 68.65%) as a white solid.

[00312] Synthesis of 3,5-dichloro-7-(methylsulfanyl)furo[3,2-b]pyridine



[00313] To a stirred solution of 5-chloro-7-(methylsulfanyl)furo[3,2-b]pyridin-3-ylboronic acid (500 mg, 2.054 mmol, 1 equiv) and CuCl (609.93 mg, 6.162 mmol, 3 equiv) in MeOH (6 mL) and H_2O (2 mL) under nitrogen atmosphere. The resulting mixture was stirred for additional 1.5h at 50°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 100% gradient in 10 min; detector, UV 254 nm.) to afford 3,5-dichloro-7-(methylsulfanyl)furo[3,2-b]pyridine (300 mg, 62.40%) as a light yellow solid.Synthesis of 3-bromo-5-chloro-6-fluoro-7-iodofuro[3,2-b]pyridine

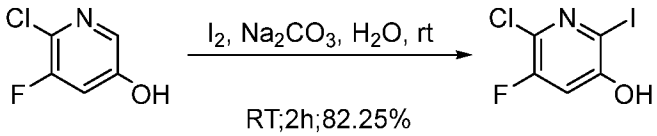
[00314] Step 1. Synthesis of 6-chloro-5-fluoropyridin-3-ol



[00315] To a stirred solution of 5-bromo-2-chloro-3-fluoropyridine (50 g, 237.609 mmol, 1 equiv) in toluene (500 mL) was added n-BuLi (2.5 M in hexane, 104.5 mL, 1631.283 mmol, 1.1 equiv) dropwise at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 10 min at -78°C under nitrogen atmosphere. To the above mixture was added trimethyl borate (29.63 g, 285.131 mmol, 1.2 equiv) dropwise over 20 min at -78 °C. The resulting mixture was stirred for additional 20min at -78°C. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. Into the 2L 4-necked round-bottom flask were added 8N sat. NaOH (aq.) (337 mL, 2696.000 mmol, 11.35 equiv) and

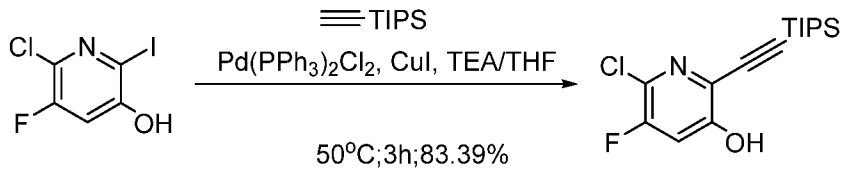
H_2O_2 (30%) (225 mL, 9657.788 mmol, 40.65 equiv) at 0°C. The resulting mixture was stirred for 2h at room temperature under air atmosphere. The reaction was quenched with sat. $Na_2S_2O_3$ (aq.) (500 mL) at 0°C.The aqueous layer was extracted with EtOAc (3x1000 mL). The combined organic layers were washed with water/NaCl (1x1000 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 6-chloro-5-fluoropyridin-3-ol (32.8 g, 93.57%) as a yellow solid.

[00316] Step 2. Synthesis of 6-chloro-5-fluoro-2-iodopyridin-3-ol



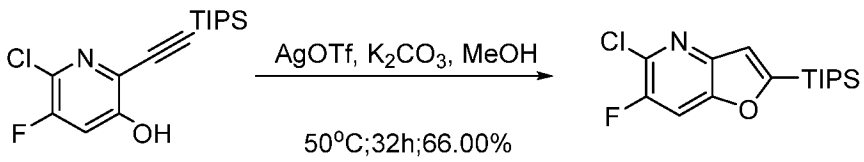
[00317] To a stirred solution of 6-chloro-5-fluoropyridin-3-ol (32.8 g, 222.328 mmol, 1 equiv) and Na_2CO_3 (47.13 g, 444.656 mmol, 2 equiv) in water (400mL) was added I_2 (59.25 g, 233.444 mmol, 1.05 equiv) in portions at room temperature under air atmosphere. The resulting mixture was stirred for 2h at room temperature under air atmosphere. The reaction was quenched with sat. $Na_2S_2O_3$ (aq.) (100 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x500 mL). The resulting mixture was concentrated under vacuum. This resulted in 6-chloro-5-fluoro-2-iodopyridin-3-ol (50 g, 82.25%) as a yellow solid.

[00318] Step 3. Synthesis of 6-chloro-5-fluoro-2-[2-(triisopropylsilyl)ethynyl]pyridin-3-ol



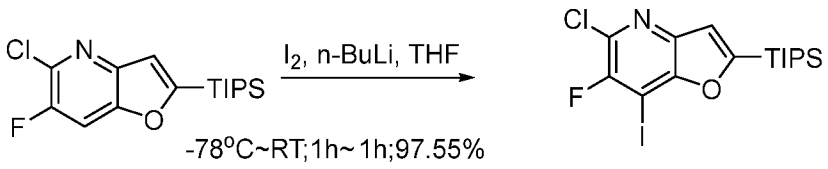
[00319] To a stirred solution of 6-chloro-5-fluoro-2-iodopyridin-3-ol (50 g, 182.862 mmol, 1 equiv) and ethynyltriisopropylsilane (41.69 g, 228.577 mmol, 1.25 equiv) in THF (150 mL) and TEA (150 mL) were added CuI (1.39 g, 7.314 mmol, 0.04 equiv) and $Pd(PPh_3)_2Cl_2$ (2.57 g, 3.657 mmol, 0.02 equiv) under nitrogen atmosphere. The resulting mixture was stirred for 3h at 50°C under nitrogen atmosphere. The reaction was quenched by the addition of Water (200mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 200mL). dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 6-chloro-5-fluoro-2-[2-(triisopropylsilyl)ethynyl]pyridin-3-ol (50 g, 83.39%) as a black solid.

[00320] Step 4. Synthesis of 5-chloro-6-fluoro-2-(triisopropylsilyl)furo[3,2-b]pyridine



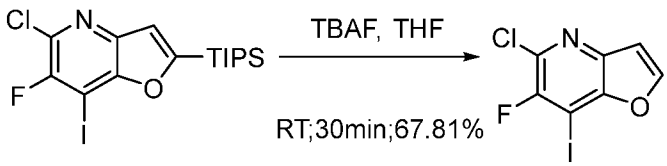
[00321] To a stirred solution of 6-chloro-5-fluoro-2-[2-(triisopropylsilyl)ethynyl]pyridin-3-ol (50 g, 152.486 mmol, 1 equiv) and K2CO3 (94.83 g, 686.187 mmol, 4.5 equiv) in MeOH (250 mL) was added silver(1+) trifluoromethanesulfonate (15.67 g, 60.994 mmol, 0.4 equiv) at 50 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 days at 50°C under nitrogen atmosphere. The reaction was quenched with Water at room temperature. The resulting mixture was concentrated under vacuum. The resulting mixture was extracted with EtOAc (3 x200 mL). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (12:1) to afford 5-chloro-6-fluoro-2-(triisopropylsilyl)furo[3,2-b]pyridine (33 g, 66.00%) as a brown solid.

[00322] Step 5. Synthesis of 5-chloro-6-fluoro-7-iodo-2-(triisopropylsilyl)furo[3,2-b]pyridine



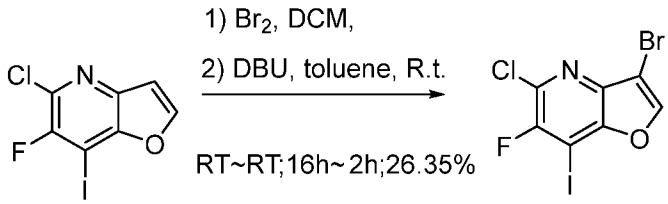
[00323] A solution of 5-chloro-6-fluoro-2-(triisopropylsilyl)furo[3,2-b]pyridine (5 g, 15.249 mmol, 1 equiv) in THF (30 mL) was treated with n-BuLi 2.5M in hexanes (9.75 mL, 1.6 equiv) for 60 min dropwise at -78°C under nitrogen atmosphere followed by the addition of I_2 (5.03 g, 19.824 mmol, 1.3 equiv) in THF (30 mL) dropwise at -78°C. The resulting mixture was stirred for 1h at -50°C under nitrogen atmosphere. The reaction was quenched with sat. $Na_2S_2O_3$ (aq.) (30 mL) at room temperature. The aqueous layer was extracted with EtOAc (4x30 mL). The resulting mixture was concentrated under vacuum. This resulted in 5-chloro-6-fluoro-7-iodo-2-(triisopropylsilyl)furo[3,2-b]pyridine (6.75 g, 97.55%) as a yellow solid.

[00324] Step 6. Synthesis of 5-chloro-6-fluoro-7-iodofuro[3,2-b]pyridine



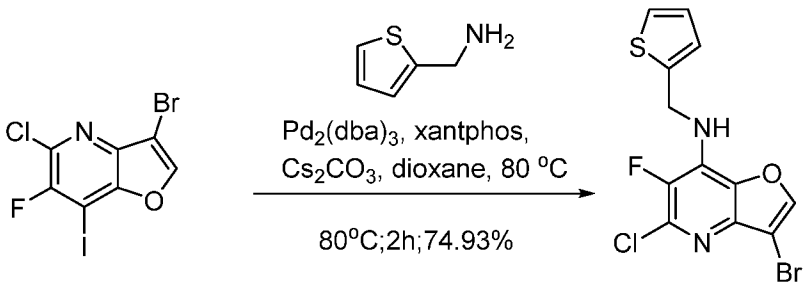
To a stirred solution of 5-chloro-6-fluoro-7-iodo-2-(triisopropylsilyl)furo[3,2-b]pyridine (6.75 g, 14.874 mmol, 1 equiv) in THF (50 mL) was added TBAF 1M in THF (4.45 mL, 0.3 equiv) dropwise at 0°C under air atmosphere. The resulting mixture was stirred for 0.5h at room temperature under air atmosphere. The reaction was quenched with Water at room temperature. The aqueous layer was extracted with EtOAc (3x50 mL). The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE / EA (20:1) to afford 5-chloro-6-fluoro-7-iodofuro[3,2-b]pyridine (3 g, 67.81%) as a yellow solid.

[00325] Step 7. Synthesis of 3-bromo-5-chloro-6-fluoro-7-iodofuro[3,2-b]pyridine



[00326] Into a 40 mL vial were added 5-chloro-6-fluoro-7-iodofuro[3,2-b]pyridine (3 g, 10.086 mmol, 1 equiv) and DCM (30.00 mL). Then Br_2 (8058.90 mg, 50.430 mmol, 5 equiv) were added at 0 °C. The resulting mixture was stirred for overnight at room temperature under nitrogen atmosphere. The reaction was quenched with sat. $Na_2S_2O_3$ (aq.) (10 mL) at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The resulting mixture was concentrated under reduced pressure. Then the crude product was dissolved in THF (30.00 mL) and DBU (3.0 g, 20.172 mmol, 2 equiv) was added. After stirring for 2 h at room temperature, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (9:1) to afford 3-bromo-5-chloro-6-fluoro-7-iodofuro[3,2-b]pyridine (1 g, 26.35%) as a white solid.

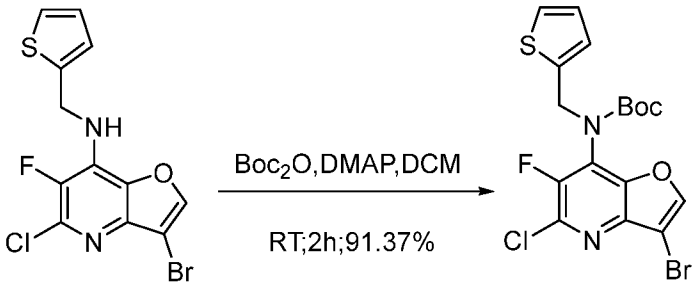
Example 2: Specific Example of General Scheme 2, synthesis of 3-bromo-5-chloro-6-fluoro-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine



[00327] To a stirred solution of 3-bromo-5-chloro-6-fluoro-7-iodofuro[3,2-b]pyridine (250 mg, 0.664 mmol, 1 equiv) and 1-(thiophen-2-yl)methanamine (90.22 mg, 0.797 mmol, 1.2 equiv) in dioxane (5 ml) were added $Pd_2(dba)_3$ (121.66 mg, 0.133 mmol, 0.2 equiv), xantphos (38.44 mg, 0.066 mmol, 0.1 equiv) and Cs_2CO_3 (432.87 mg, 1.328 mmol, 2 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2h at 80°C under nitrogen 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 3-bromo-5-chloro-6-fluoro-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine (180 mg, 74.93%).

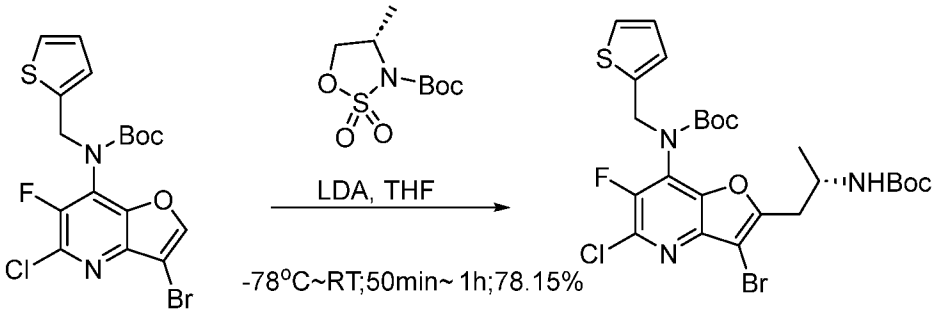
Example 3: Specific Example of General Scheme 3, synthesis of in tert-butyl N-{3-bromo-2-[(2S)-2-[(tert-butoxycarbonyl)amino]propyl] -5-chloro-6-fluorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate

[00328] Step 1. Synthesis of Synthesis of tert-butyl N-{3-bromo-5-chloro-6-fluorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl) carbamate



[00329] To a stirred solution of 3-bromo-5-chloro-6-fluoro-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine (180 mg, 0.498 mmol, 1 equiv) and DMAP (12.16 mg, 0.100 mmol, 0.2 equiv) in DCM (2 ml) was added Boc_2O (217.28 mg, 0.996 mmol, 2 equiv) dropwise at room temperature under air atmosphere. The resulting mixture was stirred for 2h at room temperature under air atmosphere. The reaction was quenched with Water at room temperature. 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 (5:1) to afford tert-butyl N-{3-bromo-5-chloro-6-fluorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl) carbamate (210 mg, 91.37%) as a yellow oil.

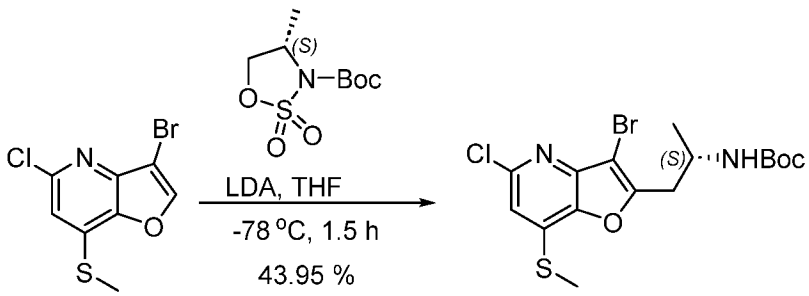
[00330] Step 2. Synthesis of tert-butyl N-{3-bromo-2-[(2S)-2-[(tert-butoxycarbonyl)amino]propyl] -5-chloro-6-fluorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate (200 mg, 78.15%) as a yellow solid.



[00331] In a 50-mL round bottom flask, to a solution of tert-butyl N-{3-bromo-5-chloro-6-fluorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate (200 mg, 0.433 mmol, 1 equiv) in THF (5 mL) was added dropwise LDA (in 2M THF) (0.32 mL, 0.649 mmol, 1.5 equiv) at -78 °C under N_2 atmosphere. The reaction mixture was stirred at -78 °C for 30 mins. Then a solution of tert-butyl (4S)-4-methyl-2,2-dioxo-1,2lambda6,3-oxathiazolidine-3-carboxylate (AA-1) (154.16 mg, 0.649 mmol, 1.5 equiv) in 3 mL THF was added dropwise and the mixture was stirred for another 30 mins. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl N-{3-bromo-2-[(2S)-2-[(tert-butoxycarbonyl)amino]propyl] -5-chloro-6-fluorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate (200 mg, 78.15%) as a yellow solid.

Example 4: Specific Example of General Scheme 6, Synthesis of tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-[(thiophen-2-ylmethyl)amino]furo[3,2-b]pyridin-2-yl}propan-2-yl]carbamate

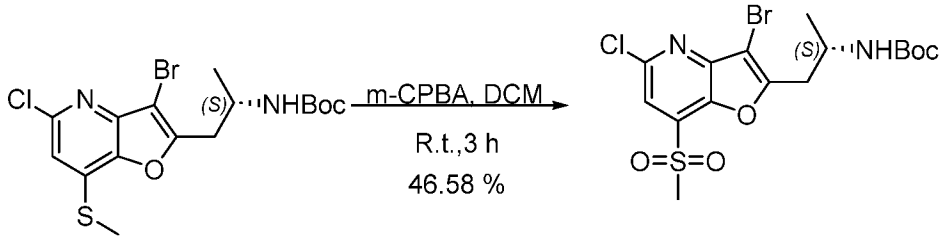
[00332] Step 1. Synthesis of tert-butyl N-[(2S)-1-[3-bromo-5-chloro-7-(methylsulfanyl) furo[3,2-b]pyridin-2-yl]propan-2-yl]carbamate



[00333] In a 25-mL round bottom flask, to a solution of 3-bromo-5-chloro-7-(methylsulfanyl)furo[3,2-b]pyridine (800 mg, 2.872 mmol, 1 equiv) in THF (10 mL) was

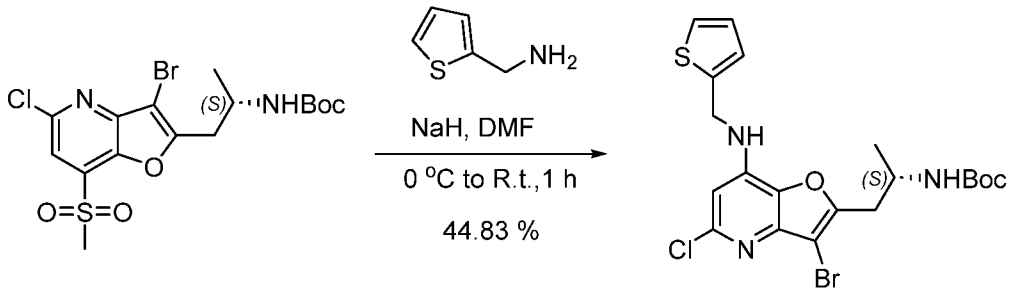
added dropwise LDA (2.87 mL, 5.744 mmol, 2 equiv) (2 M in THF, 2.87 mL, 5.744 mmol) at -78 degrees C under N_2 atmosphere. The reaction mixture was stirred at -78 degrees C for 30 mins. Then a solution of tert-butyl (4S)-4-methyl-2,2-dioxo-1,2lambda6,3-oxathiazolidine-3-carboxylate (255.54 mg, 1.077 mmol, 1.5 equiv) in 4 mL THF was added dropwise and the mixture was stirred for another 60 mins. The reaction was quenched with sat. NH_4Cl (0.2 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C_{18} silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 70% gradient in 15 min; detector, UV 254 nm. This resulted in tert-butyl N-[(2S)-1-[3-bromo-5-chloro-7-(methylsulfanyl) furo[3,2-b]pyridin-2-yl]propan-2-yl]carbamate (550 mg, 43.95%) as a white solid.

[00334] Step 2. Synthesis of tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-methanesulfonylfuro[3,2-b]pyridin-2-yl}propan-2-yl]carbamate



[00335] To a stirred mixture of tert-butyl N-[(2S)-1-[3-bromo-5-chloro-7-(methylsulfanyl)furo[3,2-b] pyridin-2-yl]propan-2-yl]carbamate (600 mg, 1.377 mmol, 1 equiv) in DCM (10 mL) was added m-CPBA (838.58 mg, 4.131 mmol, 3 equiv, 85%) in portions at 0 °C. The resulting mixture was stirred for 3 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C_{18} silica gel; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 20% to 100% gradient in 18 min; detector, UV 254 nm. This resulted in tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-methanesulfonylfuro[3,2-b]pyridin-2-yl}propan-2-yl]carbamate (300 mg, 46.58%) as a white solid.

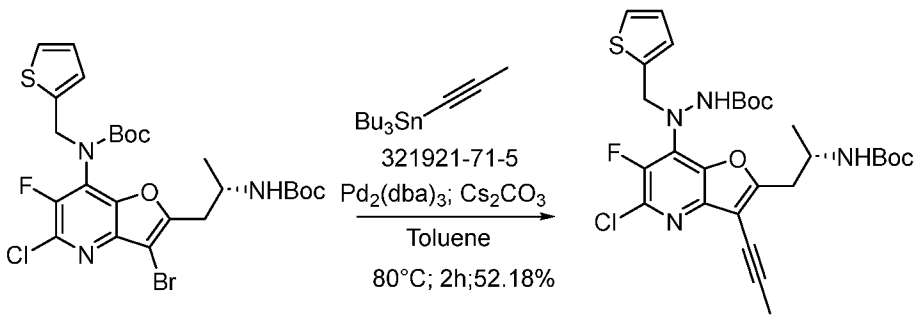
[00336] Step 3. Synthesis of tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-[(thiophen-2-ylmethyl)amino]furo[3,2-b]pyridin-2-yl}propan-2-yl]carbamate



[00337] To a solution of N-(thiophen-2-ylmethyl)formamide (150.92 mg, 1.068 mmol, 2 equiv) in DMF (1.5 mL) was added sodium hydride (60% in oil, 5.13 mg) at 0 degrees C. The mixture was stirred for 15 min. tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-methanesulfonylfuro[3,2-b]pyridin-2-yl}propan-2-yl]carbamate (250 mg, 0.534 mmol, 1 equiv) was added and the mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with Water (0.1 mL) at 0 °C. The residue was purified by reverse flash chromatography with the following conditions: column, C_{18} silica gel; mobile phase, MeCN in Water (0.1% FA), 30% to 100% gradient in 15 min; detector, UV 254 nm. This resulted in tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-[(thiophen-2-ylmethyl)amino]furo[3,2-b]pyridin-2-yl}propan-2-yl]carbamate (120 mg, 44.83%).

Example 5: Specific Example of General Method 9, Synthesis of 2-[(2S)-2-aminopropyl]-5-chloro-3-ethynyl-6-fluoro-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine (Compound 36)

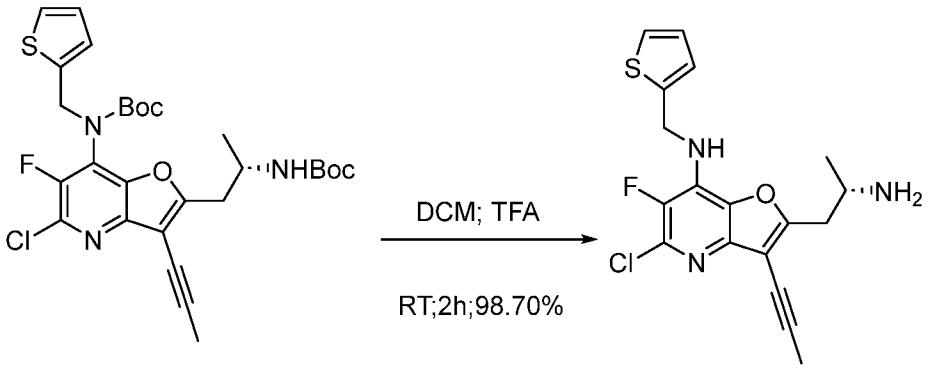
[00338] Step 1. Synthesis of tert-butyl N-[(2S)-1-(7-{[(tert-butoxycarbonyl)amino](thiophen-2-ylmethyl)amino}-5-chloro-6-fluoro-3-(prop-1-yn-1-yl)furo[3,2-b]pyridin-2-yl)propan-2-yl]carbamate



[00339] Into a 40 mL vial were added tert-butyl N-{3-bromo-2-[(2S)-2-[(tert-butoxycarbonyl)amino]propyl]-5-chloro-6-fluorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate (200 mg, 0.323 mmol, 1 equiv), $Pd_2(dba)_3$ (29.59 mg, 0.032 mmol, 0.1 equiv), Cs_2CO_3 (210.57 mg, 0.646 mmol, 2 equiv), butyldi-1-adamantylphosphine (23.17 mg, 0.065 mmol, 0.2 equiv) and toluene (10 mL) was treated with tributyl(prop-1-yn-1-

yl)stannane (212.70 mg, 0.646 mmol, 2 equiv) for 2h at 80°C under nitrogen atmosphere. The reaction was quenched by the addition of Water (5 mL) at room temperature. The aqueous layer was extracted with EtOAc (3x5 mL). 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 N-[(2S)-1-(7-{[(tert-butoxycarbonyl)amino](thiophen-2-ylmethyl)amino}-5-chloro-6-fluoro-3-(prop-1-yn-1-yl)furo[3,2-b]pyridin-2-yl)propan-2-yl]carbamate (100 mg, 52.18%) as a yellow solid.

[00340] Step 2. Synthesis of 2-[(2S)-2-aminopropyl]-5-chloro-3-ethynyl-6-fluoro-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine



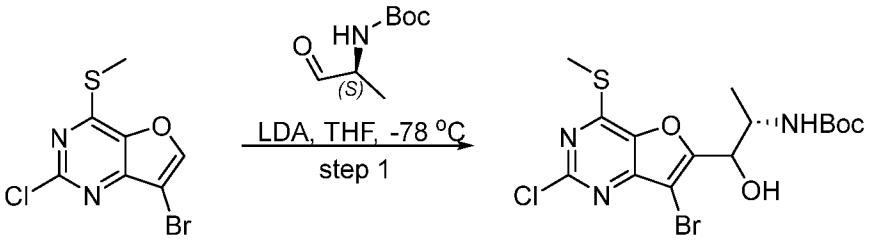
[00341] Into a 40 mL vial were tert-butyl N-{2-[(2S)-2-[(tert-butoxycarbonyl)amino]propyl]-5-chloro-6-fluoro-3-(prop-1-yn-1-yl)furo[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate (100 mg, 0.173 mmol, 1 equiv) in DCM (2 mL) was treated with TFA (1 mL) at 0°C. The mixture was stirred for 2h at room temperature. The resulting mixture was concentrated under reduced pressure. The mixtureneutralized to pH 7 with DIEA (0.5 mL). The crude product (80 mg) was purified by Prep-HPLC with the following conditions (Column: XBridge Shield RP18 OBD Column 30*150 mm, 5m; Mobile Phase A: Water (10mmol/L NH4HCO3+0.05%NH3.H2O), Mobile Phase B: ACN; Flow rate: 50 mL/min mL/min; Gradient: 35% B to 70% B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.661) to afford 2-[(2S)-2-aminopropyl]-5-chloro-3-ethynyl-6-fluoro-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine (25 mg, 39.72%).

[00342] LC-MS (ES, *m/z*): $[M+H]^+ = 378$.

[00343] ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.26 (dd, J = 5.1, 1.2 Hz, 1H), 7.01 (dq, J = 3.3, 1.0 Hz, 1H), 6.93 (dd, J = 5.1, 3.5 Hz, 1H), 5.02 (d, J = 33.6 Hz, 2H), 3.40 (dq, J = 12.3, 6.3 Hz, 1H), 2.96 (qdt, J = 10.1, 6.9, 3.4 Hz, 2H), 2.11 (s, 3H), 1.13 (dd, J = 6.5, 2.3 Hz, 3H).

Example 6: Specific Example of General Scheme 11, tert-butyl N-[(2S,3S)-1-{7-bromo-2-chloro -4-[(thiophen-2-ylmethyl)amino]furo[3,2-d]pyrimidin-6-yl}-1,1,3-trifluorobutan-2-yl]carbamate (synthesis intermediate)

[00344] Step 1. Synthesis of tert-butyl N-[(2S)-1-[7-bromo-2-chloro-4-(methylsulfanyl)furo[3,2-d]pyrimidin-6-yl]-1-hydroxypropan-2-yl]carbamate



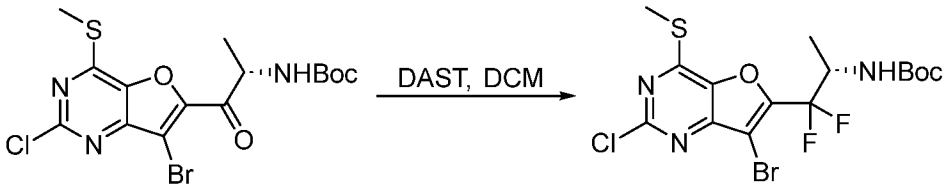
[00345] In a 100-mL round bottom flask, to a solution of 7-bromo-2-chloro-4-(methylsulfanyl)furo[3,2-d] pyrimidine (4 g, 14.309 mmol, 1 equiv) in THF (40 mL) was added dropwise LDA (2 M in hexane, 10.7 mL, 21.4 mmol) at -78 degrees C under N_2 atmosphere. The reaction mixture was stirred at -78 degrees C for 20 mins. Then a solution of tert-butyl N-[(2S)-1-oxopropan-2-yl]carbamate (3.22 g, 18.602 mmol, 1.3 equiv) in 5 mL THF was added dropwise and the mixture was stirred for another 50 mins. The reaction was quenched with water (2 mL). The residue was purified by reversed-phase flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (0.1% FA), 20% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl N-[(2S)-1-[7-bromo-2-chloro-4- (methylsulfanyl)furo[3,2-d]pyrimidin-6-yl]-1-hydroxypropan-2-yl]carbamate (3.6 g, 55.57%) as a white solid.

[00346] Step 2. Synthesis of tert-butyl N-[(2S)-1-[7-bromo-2-chloro-4-(methylsulfanyl)furo [3,2-d]pyrimidin-6-yl]-1- oxopropan-2-yl]carbamate

[00347] Into a 100mL 3-necked round-bottom flask were added tert-butyl N-[(2S)-1-[7-bromo-2-chloro-4- (methylsulfanyl)furo[3,2-d]pyrimidin-6-yl]-1-hydroxypropan-2-yl]carbamate (3.6 g, 7.951 mmol, 1 equiv), DCM (30 mL) and DMP (6.75 g, 15.902 mmol, 2 equiv) at room temperature. The resulting mixture was stirred for 2h at room temperature. The resulting mixture was diluted with water (50mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 50mL). The combined organic layers were washed with brine (2x50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under

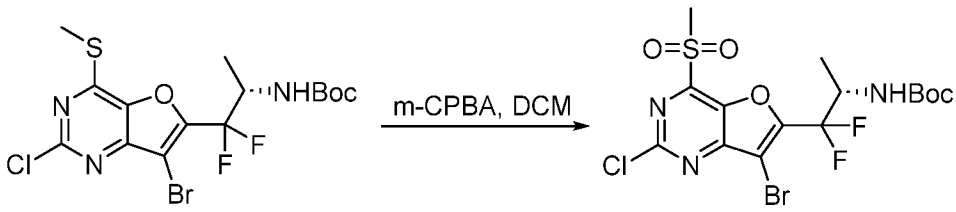
reduced pressure. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (0.1% FA), 20% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl N-[(2S)-1-[7-bromo-2-chloro-4-(methylsulfanyl)furo [3,2-d]pyrimidin-6-yl]-1- oxopropan-2-yl]carbamate (2 g, 55.80%) as a white solid.

[00348] Step 3. Synthesis of tert-butyl N-[(2S)-1-[7-bromo-2-chloro-4-(methylsulfanyl)furo[3,2-d]pyrimidin-6-yl]-1,1-difluoropropan-2-yl]carbamate



[00349] Into a 100mL round-bottom flask were added tert-butyl N-[(2S)-1-[7-bromo-2-chloro-4-(methyl sulfanyl)furo[3,2-d]pyrimidin-6-yl]-1-oxopropan-2-yl]carbamate (2 g, 4.437 mmol, 1 equiv), DCM (20 mL) and DAST (14.30 g, 88.740 mmol, 20 equiv) at room temperature. The resulting mixture was stirred for 3h at room temperature . The reaction was quenched by the addition of sat. Na_2CO_3 (aq.) (50mL) at room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 x 50mL). The combined organic layers were washed with brine (2x50 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, C_{18}; mobile phase, MeCN in Water (0.1% FA), 20% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl N-[(2S)-1-[7-bromo-2-chloro-4-(methylsulfanyl)furo[3,2-d]pyrimidin-6-yl]-1,1-difluoropropan-2-yl]carbamate (400 mg, 19.07%) as a yellow solid.

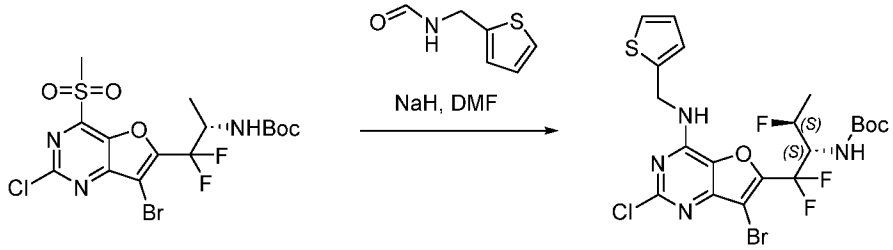
[00350] Step 4. Synthesis of tert-butyl N-[(2S)-1-{7- bromo-2-chloro-4-methanesulfonylfuro[3,2-d]pyrimidin-6-yl}-1,1-difluoropropan-2-yl]carbamate



[00351] Into a 25mL round-bottom flask were added tert-butyl N-[(2S)-1-[7-bromo-2-chloro-4-(methylsulfanyl) furo[3,2-d]pyrimidin-6-yl]-1,1-difluoropropan-2-yl]carbamate (400 mg, 0.846 mmol, 1 equiv), DCM (5 mL) and m-CPBA (438.03 mg, 2.538 mmol, 3 equiv 85%) at room temperature. The resulting mixture was stirred for 3h at room temperature. The resulting mixture was diluted with DMF (5mL). The resulting mixture was

concentrated under vacuum. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (0.1% FA), 20% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl N-[(2S)-1-{7- bromo-2-chloro-4-methanesulfonylfuro[3,2-d]pyrimidin-6-yl}-1,1-difluoropropan-2-yl]carbamate (300 mg, 70.24%) as a white solid.

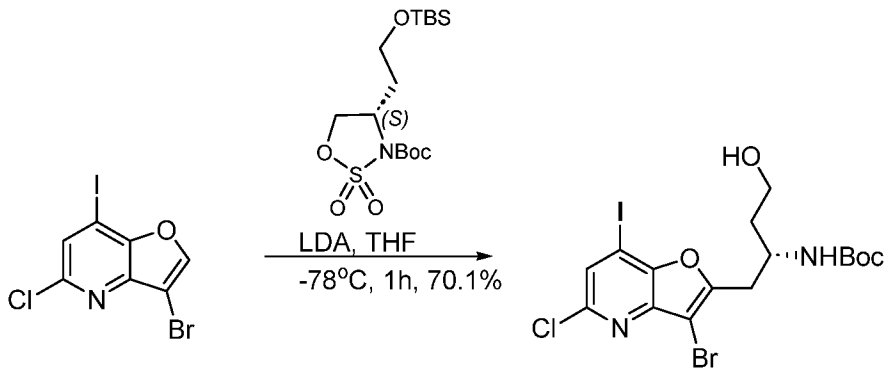
[00352] Step 5. Synthesis of tert-butyl N-[(2S,3S)-1-{7-bromo-2-chloro -4-[(thiophen-2-ylmethyl)amino]furo[3,2-d]pyrimidin-6-yl}-1,1,3-trifluorobutan-2-yl]carbamate



[00353] To a solution of N-(thiophen-2-ylmethyl)formamide (125.88 mg, 0.891 mmol, 1.5 equiv) in DMF was added sodium hydride (60% in oil, 47.55 mg) at 0 degrees C. The mixture was stirred for 15 min. tert-butyl N-[(2S)-1-{7-bromo-2-chloro-4-methanesulfonylfuro[3,2-d]pyrimidin-6-yl}-1,1-difluoropropan-2-yl]carbamate (300 mg, 0.594 mmol, 1 equiv) was added and the mixture was allowed to warm to RT and stirred for 1 h. The reaction mixture was quenched by water and extracted with DCM (3*25 mL). 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), 20% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl N-[(2S,3S)-1-{7-bromo-2-chloro -4-[(thiophen-2-ylmethyl)amino]furo[3,2-d]pyrimidin-6-yl}-1,1,3-trifluorobutan-2-yl]carbamate (150 mg, 44.29%) as a yellow oil.

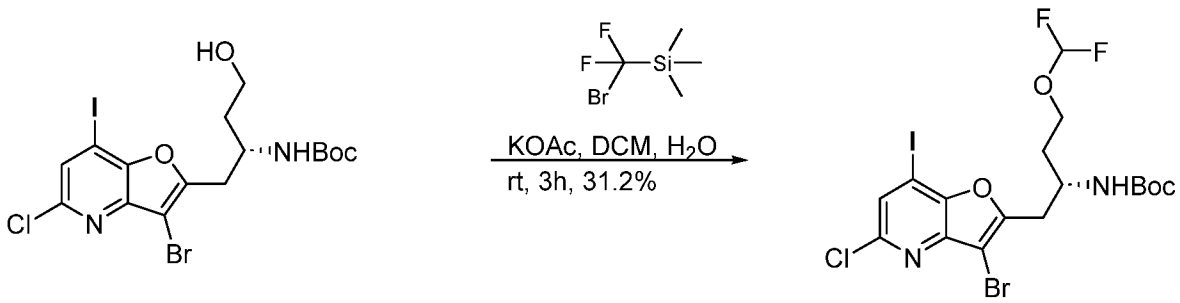
Example 7: Specific Example of General Synthesis Scheme 12, synthesis of tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-[(thiophen-2-ylmethyl)amino]furo[3,2-b]pyridin-2-yl}-4-(difluoromethoxy)butan-2-yl]carbamate

[00354] Step 1. Synthesis of tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-iodofuro[3,2-b]pyridin-2-yl}-4-hydroxybutan-2-yl]carbamate



[00355] Into a 50-mL three-necked bottle, to a solution of 3-bromo-5-chloro-7-iodofuro[3,2-b]pyridine (2.5 g, 6.976 mmol, 1 equiv) in THF (20 mL) was added LDA (5.23 mL, 10.464 mmol, 1.5 equiv) dropwise at -78 degrees C under N_2 atmosphere. The reaction mixture was stirred at -78 degrees C for 30 mins. Then a solution of tert-butyl (4S)-4-{2-[(tert-butyldimethylsilyl)oxy]ethyl}-2,2-dioxo-1,2lambda6,3- oxathiazolidine-3-carboxylate (3.99 g, 10.464 mmol, 1.5 equiv) in 10 mL THF was added dropwise and the mixture was stirred for another 1h -78 degrees C. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 20% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-iodofuro[3,2-b]pyridin-2-yl}-4-hydroxybutan-2-yl]carbamate (2.67 g, 70.15%) as a yellow solid.

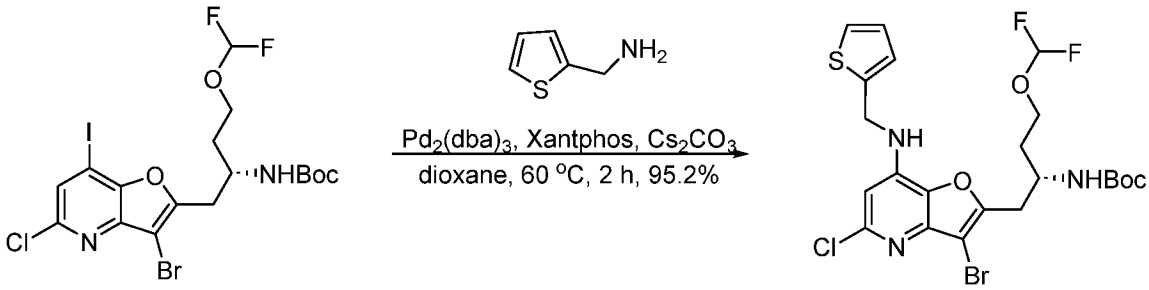
[00356] Step 2. Synthesis of tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-iodofuro[3,2-b]pyridin-2-yl}-4-(difluoromethoxy)butan-2-yl]carbamate



[00357] To a stirred mixture of tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-iodofuro[3,2-b]pyridin-2-yl}-4- hydroxybutan-2-yl]carbamate (410 mg, 0.751 mmol, 1 equiv) and (bromodifluoromethyl)trimethylsilane (457.87 mg, 2.253 mmol, 3 equiv) in DCM (4 mL) and H_2O (4 mL) was added KOAc (442.50 mg, 4.506 mmol, 6 equiv). The resulting mixture was stirred for 3h at room temperature. The resulting mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase

flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 20% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-iodofuro[3,2-b]pyridin-2-yl}-4-(difluoromethoxy)butan-2-yl]carbamate (140 mg, 31.28%) as a white solid.

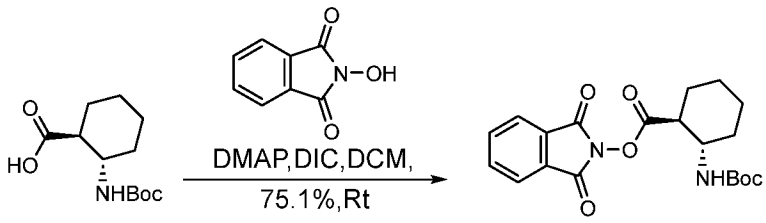
[00358] Step 3. Synthesis tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-[(thiophen-2-ylmethyl)amino]furo[3,2-b]pyridin-2-yl}-4-(difluoromethoxy)butan-2-yl]carbamate



[00359] Into a 8-mL vial purged and maintained with an inert atmosphere of nitrogen, were added tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-iodofuro[3,2-b]pyridin-2-yl}-4-(difluoromethoxy)butan-2-yl]carbamate (140 mg, 0.235 mmol, 1 equiv), 1-(thiophen-2-yl)methanamine (24.12 uL, 0.235 mmol, 1 equiv), $Pd_2(dba)_3$ (21.52 mg, 0.024 mmol, 0.1 equiv), Xantphos (27.20 mg, 0.047 mmol, 0.2 equiv) and Cs_2CO_3 (153.17 mg, 0.470 mmol, 2 equiv) in Dioxane (2 mL) at room temperature. The resulting mixture was stirred for 2h at 60°C under nitrogen atmosphere. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (10mmol/L NH_4HCO_3), 10% to 100% gradient in 20 min; detector, UV 254 nm. This resulted in tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-[(thiophen-2-ylmethyl)amino]furo[3,2-b]pyridin-2-yl}-4-(difluoromethoxy)butan-2-yl]carbamate (130 mg, 95.21%).

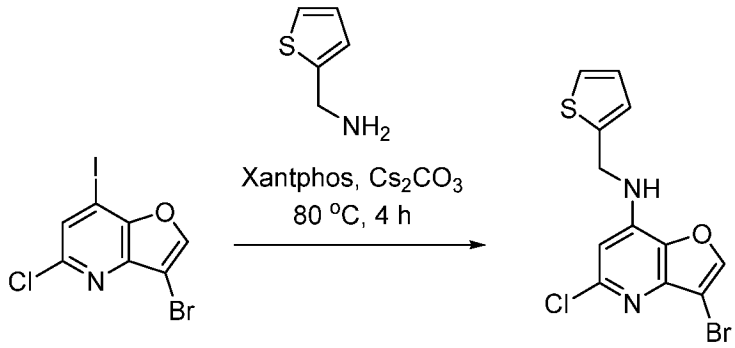
[00360] Example 8: Specific Example of General Scheme 13, Synthesis of tert-butyl N-{3-bromo-2-[(1S,2S)-2-[(tert-butoxycarbonyl)amino]cyclohexyl]-5-chlorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate

[00361] Step 1. Synthesis of 1,3-dioxoisoindol-2-yl (1S,2S)-2-[(tert-butoxycarbonyl)amino]cyclohexane-1-carboxylate



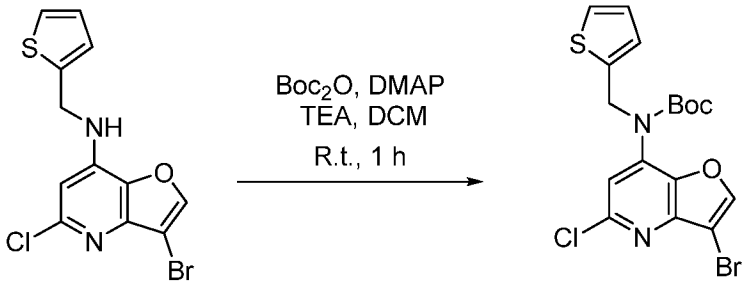
[00362] To a stirred solution of (1S,2S)-2-[(tert-butoxycarbonyl)amino]cyclohexane-1-carboxylic acid (1 g, 4.110 mmol, 1 equiv), DMAP (50.21 mg, 0.411 mmol, 0.1 equiv) and N-hydroxyphthalimide (670.49 mg, 4.110 mmol, 1 equiv) in DCM (15 mL, 235.959 mmol, 57.41 equiv) was added DIC (570.58 mg, 4.521 mmol, 1.1 equiv) dropwise at room temperature under nitrogen atmosphere. The residue was purified by silica gel column chromatography, eluted with PE / EA (6:1) to afford 1,3-dioxoisoindol-2-yl (1S,2S)-2-[(tert-butoxycarbonyl)amino]cyclohexane-1-carboxylate (1.2 g, 75.17%) as a light yellow solid.

[00363] Step 2. Synthesis of 3-bromo-5-chloro-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine



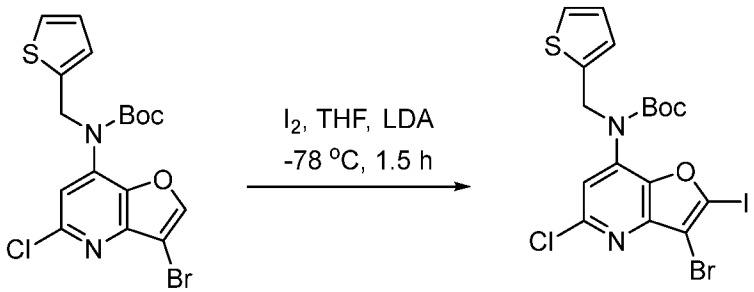
[00364] To a stirred mixture of 3-bromo-5-chloro-7-iodofuro[3,2-b]pyridine (10 g, 27.905 mmol, 1 equiv) and $Pd_2(dba)_3$ (2.5 g, 2.730 mmol, 0.10 equiv) in Dioxane (130 mL) were added Xantphos (3.2 g, 5.530 mmol, 0.20 equiv), Cs_2CO_3 (18.2 g, 55.687 mmol, 2.00 equiv) and 1-(thiophen-2-yl)methanamine (3.2 g, 28.274 mmol, 1.01 equiv) in portions at room temperature. The resulting mixture was stirred for 4 h at 80°C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford 3-bromo-5-chloro-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine (8.4 g, 87.60%) as a yellow solid.

[00365] Step 3. Synthesis of tert-butyl N-{3-bromo-5-chlorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate



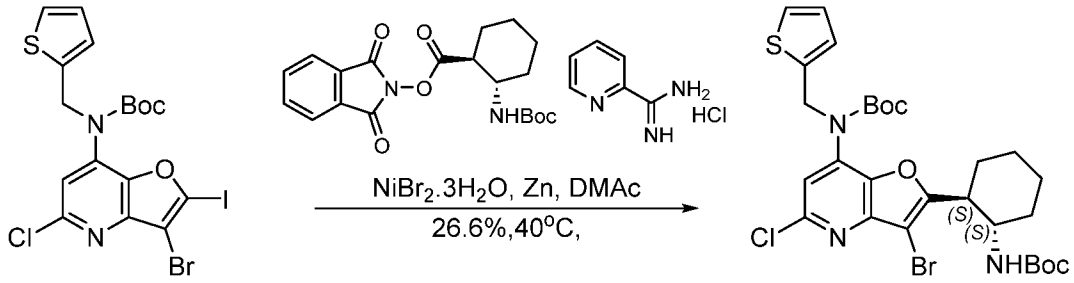
[00366] To a stirred mixture of 3-bromo-5-chloro-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine (8.4 g, 24.446 mmol, 1 equiv) and DMAP (149 mg, 1.220 mmol, 0.05 equiv) in DCM (100 mL) was added TEA (4.9 g, 48.422 mmol, 1.98 equiv) in portions at room temperature was added di-tert-butyl dicarbonate (7.5 g, 34.364 mmol, 1.41 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of Water (1mL) at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / PE (2:1) to afford tert-butyl N-{3-bromo-5-chlorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate (8.3 g, 76.52%) as a yellow solid.

[00367] Step 4. Synthesis of tert-butyl N-{3-bromo-5-chloro-2-iodofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl) carbamate

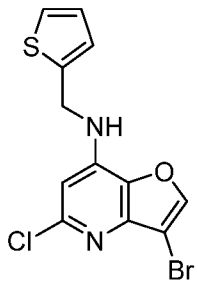
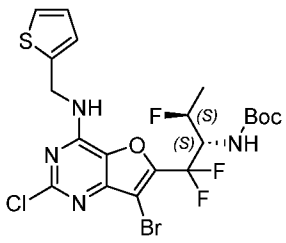
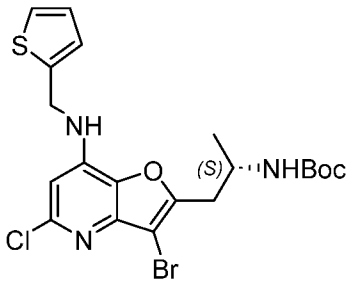
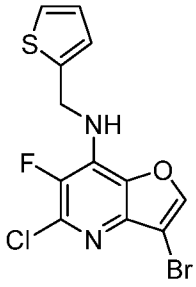


[00368] To a stirred mixture of tert-butyl N-{3-bromo-5-chlorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl) carbamate (8.3 g, 18.705 mmol, 1 equiv) in tetrahydrofuran (85 mL) in portions at room temperature was added LDA (2M in THF, 15.9 mL, 31.800 mmol, 1.70 equiv, 2 M in THF) in portions at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 20 min at -78°C under nitrogen atmosphere. To a stirred mixture of iodine (6.2 g, 24.428 mmol, 1.31 equiv) in tetrahydrofuran (15 mL) in portions at -78°C under nitrogen atmosphere. The resulting mixture was stirred for 1.5 h at -78°C under nitrogen atmosphere. 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-{3-bromo-5-chloro-2-iodofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl) carbamate (5.8 g, 54.43%) as a yellow solid.

[00369] Step 5. Synthesis of tert-butyl N-{3-bromo-2-[(1S,2S)-2-[(tert-butoxycarbonyl)amino]cyclohexyl]-5-chlorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate

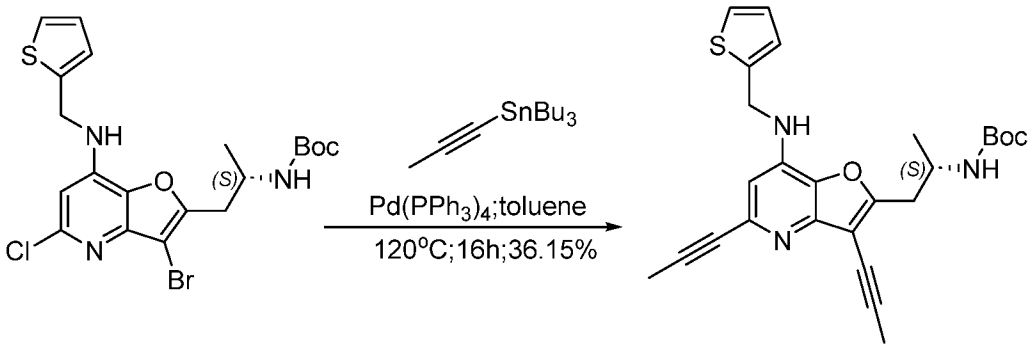


[00370] To a stirred solution of tert-butyl N-{3-bromo-5-chloro-2-iodofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate (1 g, 1.755 mmol, 1 equiv),Zn (918.19 mg, 14.040 mmol, 8 equiv) and 1,3-dioxoisoindol-2-yl (1S,2S)-2-[(tert-butoxycarbonyl)amino]cyclohexane-1-carboxylate (886.43 mg, 2.281 mmol, 1.3 equiv) in DMAc (15 mL) was added (A mixture of pyridine-2-carboximidamide (85.07 mg, 0.702 mmol, 0.4 equiv) and $NiBr_2.3H_2O$ (238.75 mg, 0.877 mmol, 0.5 equiv) in DMAc (5ml) was stirred for 10min at room temperature under nitrogen atmosphere.) dropwise at 40°C under nitrogen atmosphere. The resulting mixture was stirred for additional 1h at 40°C. The residue was purified by reversed-phase flash chromatography with the following conditions: column, C_{18}; mobile phase, MeCN in Water (0.1% TFA), 10% to 100% gradient in 10 min; detector, UV 254 nm. This resulted in tert-butyl N-{3-bromo-2-[(1S,2S)-2-[(tert-butoxycarbonyl)amino]cyclohexyl]-5-chlorofuro[3,2-b]pyridin-7-yl}-N-(thiophen-2-ylmethyl)carbamate (300 mg, 26.66%).

[00371] For the avoidance of doubt, compounds of the instant disclosure do not encompass the synthesis intermediates disclosed in Examples 2-4 and 6-8, e.g.,  ,  ,  , and  , which are provided for the purpose of illustrating the synthesis process.

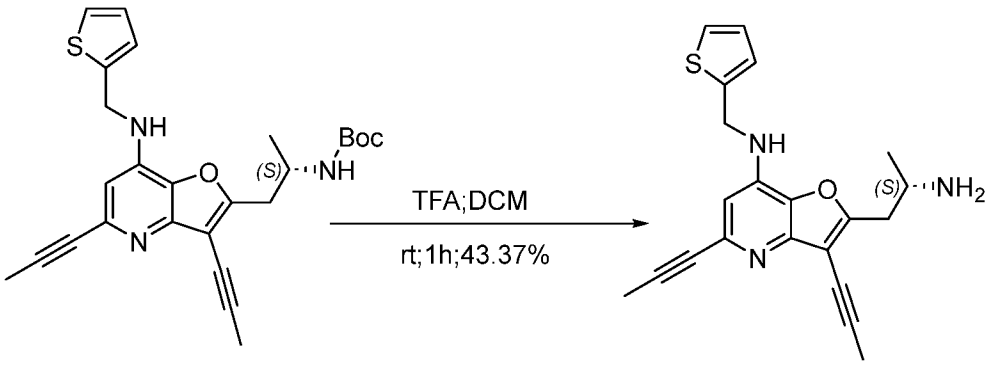
Example 9: Specific Example of General Synthesis Scheme 17, Synthesis of 2-[(2S)-2-aminopropyl]-3,5-bis(prop-1-yn-1-yl)-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine (Compound 28)

[00372] Step 1. Synthesis of (S)-(1-(3,5-di(prop-1-yn-1-yl)-7-((thiophen-2-ylmethyl)amino)furo[3,2-b]pyridin-2-yl)propan-2-yl)carbamate



[00373] To a solution of tert-butyl N-[(2S)-1-{3-bromo-5-chloro-7-[(thiophen-2-ylmethyl)amino]furo[3,2-b] pyridin-2-yl}propan-2-yl]carbamate (300 mg, 0.599 mmol, 1 equiv) and tributyl(prop-1-yn-1-yl)stannane (236.57 mg, 0.719 mmol, 1.2 equiv) in toluene (10 mL) were added tetrakis(triphenylphosphine)palladium(0) (69.22 mg, 0.060 mmol, 0.1 equiv). After stirring for overnight at 120°C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC, eluted with PE / EA (9:1) to afford tert-butyl (S)-(1-(3,5-di(prop-1-yn-1-yl)-7-((thiophen-2-ylmethyl)amino)furo[3,2-b]pyridin-2-yl)propan-2-yl)carbamate (100 mg, 36.15%) as a yellow solid.

[00374] Step 2. Synthesis of 2-[(2S)-2-aminopropyl]-3,5-bis(prop-1-yn-1-yl)-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine



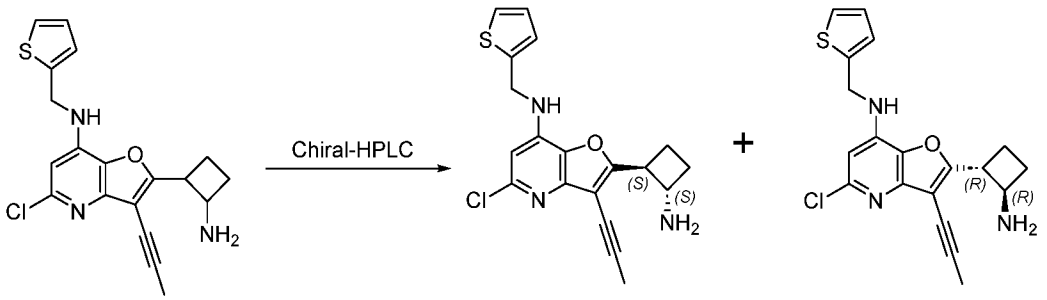
[00375] Into a 8 mL vial were added tert-butyl N-[(2S)-1-[3,5-bis(prop-1-yn-1-yl)-7-[(thiophen-2-ylmethyl)amino]furo[3,2-b]pyridin-2-yl]propan-2-yl]carbamate (100 mg, 0.216 mmol, 1 equiv), DCM (3 mL) and TFA (1 mL) at 0°C. The resulting mixture was stirred for 1

h at room temperature. The resulting mixture was concentrated under reduced pressure. The crude was purified by Prep-HPLC with the following conditions (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3+0.1%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 58% B in 9 min, 58% B; Wave Length: 254/220 nm; RT1(min): 8.25) to afford 2-[(2S)-2-aminopropyl]-3,5-bis(prop-1-yn-1-yl)-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine (34 mg, 43.37%).

[00376] LC-MS (ES, *m/z*): $[M+H]^+ = 364$.

[00377] ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.05 (dt, J = 3.3, 1.1 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.64 (s, 1H), 4.74 (d, J = 1.0 Hz, 2H), 3.60 (h, J = 6.6 Hz, 1H), 3.15 – 3.01 (m, 2H), 2.07 (d, J = 33.9 Hz, 6H), 1.26 (d, J = 6.5 Hz, 3H).

[00378] Example 10: Chiral Separation of Compounds 50 and 51.



Racemic, trans

Compounds 50 and 51

[00379] Racemic, (trans) 2-(2-aminocyclobutyl)-5-chloro-3-(prop-1-yn-1-yl)-N-(thiophen-2-ylmethyl)furo[3,2-b]pyridin-7-amine was made by general schemes 13 and 9 in sequence. The mixture was separated as follows: Column: Column: CHIRALPAK IC, 3*25 cm, 5 μm; Mobile Phase A: Hex (0.1% 2M NH_3-MeOH)--HPLC, Mobile Phase B: IPA; Flow rate: 40 mL/min; Gradient: isocratic 50; Wave Length: 200/220 nm; RT1(min): 7.5; RT2(min): 11; Sample Solvent: MEOH; Injection Volume: 4 mL; Number Of Runs: 10.

[00380] The first eluting peak was collected and concentrated to afford 20 mg of **compound 50**. The second eluting peak was collected and concentrated to afford 20 mg of **compound 51.** The absolute configuration was not determined.

[00381] Analytical Data of **Compound 50**: see table 3 below

[00382] Analytical Data of **Compound 51**: see table 3 below

[00383] The following compounds were made using the above synthesis schemes and have the physical criteria set forth in Table 3.

Compound #	General Synthesis Scheme	^{1}H-NMR data	LC/MS Ion
1	6,9	(400 MHz, Methanol-d4) δ 7.30 (dd, J = 5.0, 1.2 Hz, 1H), 7.06 (dd, J = 3.5, 1.2 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.55 (s, 1H), 4.75 (s, 2H), 3.46 (h, J = 6.5 Hz, 1H), 3.09 – 2.92 (m, 2H), 2.11 (s, 3H), 1.19 (d, J = 6.4 Hz, 3H).	360.0
2	6,9	(400 MHz, Methanol-d4) δ 7.45 (dd, J = 2.0, 0.8 Hz, 1H), 6.65 (s, 1H), 6.46 – 6.25 (m, 2H), 4.55 (s, 2H), 3.75 (h, J = 6.7 Hz, 1H), 3.26 – 3.01 (m, 2H), 2.12 (s, 3H), 1.35 (d, J = 6.6 Hz, 3H).	344.0
3	6,9	(400 MHz, Methanol-d4) δ 7.47 – 7.42 (m, 1H), 6.60 (s, 1H), 6.38 – 6.29 (m, 2H), 4.53 (s, 2H), 3.63 (s, 1H), 3.11 (dd, J = 14.9, 5.5 Hz, 1H), 3.02 (dd, J = 14.8, 7.5 Hz, 1H), 2.50 – 2.25 (m, 1H), 2.11 (s, 3H).	412.0
4	6,9	(400 MHz, Methanol-d4) δ 7.30 (dd, J = 5.1, 1.2 Hz, 1H), 7.10 – 7.04 (m, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.55 (s, 1H), 4.91 (s, 2H), 4.74 (s, 2H), 3.69 – 3.58 (m, 1H), 3.11 (dd, J = 14.9, 5.5 Hz, 1H), 3.03 (dd, J = 14.9, 7.5 Hz, 1H), 2.50 – 2.25 (m, 1H), 2.11 (s, 2H).	428.0
5	6,9	(400 MHz, Methanol-d4) δ 7.44 (dd, J = 1.9, 0.8 Hz, 1H), 6.62 (s, 1H), 6.34 (ddd, J = 14.3, 3.3, 1.4 Hz, 2H), 4.74 – 4.64 (m, 1H), 4.54 (s, 2H), 3.58 (ddt, J = 17.5, 8.9, 4.6 Hz, 1H), 3.26 (dd, J = 15.3, 5.0 Hz, 1H), 3.05 (dd, J = 15.3, 8.6 Hz, 1H), 2.12 (s, 3H), 1.42 (dd, J = 24.3, 6.4 Hz, 3H).	376.0

Compound #	General Synthesis Scheme	^{1}H-NMR data	LC/MS Ion
6	6,9	(400 MHz, Methanol-d4) δ 7.31 (dd, J = 5.1, 1.2 Hz, 1H), 7.08 (dd, J = 3.5, 1.2 Hz, 1H), 6.98 (dd, J = 5.1, 3.4 Hz, 1H), 6.58 (s, 1H), 4.75 (s, 2H), 3.72 (dddd, J = 18.7, 8.7, 5.2, 3.6 Hz, 1H), 3.11 (dd, J = 15.5, 8.6 Hz, 1H), 2.12 (s, 3H), 1.44 (dd, J = 24.3, 6.4 Hz, 3H).	392.0
7	6,9	(400 MHz, Methanol-d4) δ 7.44 (d, J = 1.9 Hz, 1H), 6.62 – 6.57 (m, 1H), 6.39 – 6.29 (m, 2H), 4.73- 4.53 (m, 1H), 4.53 (s, 2H), 3.44 (ddt, J = 15.8, 9.0, 4.7 Hz, 1H), 3.19 (dd, J = 15.2, 5.0 Hz, 1H), 2.96 (dd, J = 15.1, 8.4 Hz,1H), 1.54 (tt, J = 8.2, 5.0 Hz, 1H), 1.43- (d, J = 6.4 Hz, 3H), 0.95 – 0.80 (m, 4H).	402.0
8	6,9	(400 MHz, Methanol-d4) δ7.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.06 (dd, J = 3.6, 1.1 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.54 (s, 1H), 4.73 (s, 2H), 4.68 – 4.57 (m, 1H), 4.57 – 4.45 (m, 1H), 3.36 (dt, J = 8.4, 4.9 Hz, 1H), 3.15 (dd, J = 15.0, 4.9 Hz, 1H), 2.92 (dd, J = 15.0, 8.4 Hz, 1H), 1.53 (tt, J = 8.2, 5.0 Hz, 1H), 1.41-1.35 (d, J = 6.3 Hz, 3H), 0.95 – 0.78 (m, 4H).	418.0
9	6,9	(400 MHz, Methanol-d4) δ 7.44 (dd, J = 1.9, 0.9 Hz, 1H), 6.62 (s, 1H), 6.34 (ddd, J = 15.7, 3.3, 1.4 Hz, 2H), 4.54 (s, 2H), 3.59 (q, J = 6.5 Hz, 1H), 3.16 – 2.98 (m, 2H), 1.62 – 1.46 (m, 1H), 1.25 (d, J = 6.5 Hz, 3H), 0.98 – 0.75 (m, 4H).	370.0
10	6,9	(400 MHz, Methanol-d4) δ 7.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.06 (dt, J = 3.4, 1.1 Hz, 1H), 6.97 (dd, J = 5.1, 3.4 Hz, 1H), 6.53 (s, 1H), 4.74 (d, J = 1.0 Hz, 2H), 3.42 (h, J = 6.5 Hz, 1H), 3.02 – 2.90 (m, 2H), 1.58 – 1.45 (m, 1H), 1.15 (d, J = 6.4 Hz, 3H), 0.97 – 0.78 (m, 4H).	386.0

Compound #	General Synthesis Scheme	^{1}H-NMR data	LC/MS Ion
11	6,9	(400 MHz, Methanol-d4) δ 8.48 (d, J = 4.1 Hz, 0H), 7.41 – 7.30 (m, 4H), 7.30 – 7.22 (m, 1H), 6.44 (dd, J = 3.7, 1.7 Hz, 1H), 4.55 (d, J = 2.1 Hz, 2H), 3.70 – 3.56 (m, 1H), 3.31 – 3.23 (m, 1H), 3.07 (ddd, J = 15.6, 8.5, 2.2 Hz, 1H), 2.12 (s, 3H), 1.42 (dd, J = 24.2, 6.4 Hz, 3H).	386.0
12	8,9	(300 MHz, Methanol-d4) δ 8.42 (d, J = 1.8 Hz, 1H), 7.79 (d, J = 3.3 Hz, 1H), 7.57 (d, J = 3.3 Hz, 1H), 6.61 (s, 1H), 3.44 – 3.33 (m, 1H), 3.20 (dd, J = 15.7, 8.5 Hz, 1H), 2.15 (s, 3H), 1.48 (dd, J = 24.2, 6.5 Hz, 3H).	393.2
13	8,9	(400 MHz, Methanol-d4) δ 7.38 (td, J = 7.8, 1.9 Hz, 1H), 7.35 – 7.25 (m, 1H), 7.20 – 7.09 (m, 2H), 6.46 (s, 1H), 4.66 – 4.45 (m, 3H), 3.34 (t, J = 4.3 Hz, 1H), 3.28 (t, J = 4.3 Hz, 1H), 3.15 (dd, J = 15.0, 4.8 Hz, 1H), 2.91 (dd, J = 14.9, 8.5 Hz, 1H), 1.37 (dd, J = 24.3, 6.3 Hz, 3H).	404.0
14	6,9	(400 MHz, Methanol-d4) δ 7.37 (tt, J = 8.4, 6.5 Hz, 1H), 7.08 – 6.93 (m, 2H), 6.63 (s, 1H), 4.69 – 4.44 (m, 3H), 3.38 – 3.31 (m, 1H), 3.15 (dd, J = 15.0, 4.7 Hz, 1H), 2.90 (dd, J = 14.9, 8.7 Hz, 1H), 2.10 (s, 3H), 1.37 (dd, J = 24.3, 6.3 Hz, 3H).	422.0
15	8,9	(400 MHz, Methanol-d4) δ 7.30 (dd, J = 5.1, 1.2 Hz, 1H), 7.07 (dt, J = 3.4, 1.1 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.57 (s, 1H), 4.79 – 4.73 (m, 2H), 3.31 (p, J = 1.7 Hz, 8H), 3.10 – 2.98 (m, 2H), 2.61 (ddq, J = 18.6, 9.8, 5.2 Hz, 1H), 2.43 (dt, J = 25.4, 10.4 Hz, 1H), 2.27 (dd, J = 8.9, 4.3 Hz, 0H), 2.12 (s, 4H).	436.0

Compound #	General Synthesis Scheme	^{1}H-NMR data	LC/MS Ion
16	6,9	(400 MHz, Methanol-d4) δ 7.30 (dd, J = 5.1, 1.3 Hz, 1H), 7.07 (s, 1H), 6.97 (dd, J = 5.1, 3.4 Hz, 1H), 6.57 (s, 1H), 4.76 (s, 2H), 3.59 (q, J = 6.6 Hz, 1H), 3.08 (t, J = 6.2 Hz, 2H), 2.50 (q, J = 7.5 Hz, 2H), 1.34 – 1.21 (m, 6H).	374.2
19	6,9	(300 MHz, Methanol-d4) δ 7.34 (dd, J = 5.1, 1.3 Hz, 1H), 7.14 – 7.07 (m, 1H), 7.00 (dd, J = 5.1, 3.5 Hz, 1H), 6.64 (s, 1H), 5.38 (s, 1H), 5.23 (s, 1H), 4.79 (s, 2H), 3.69 (q, J = 6.7 Hz, 1H), 3.30 – 3.15 (m, 2H), 1.33 (d, J = 6.6 Hz, 3H).	378.0
21	6,9	(400 MHz, Methanol-d4) δ 7.31 (dd, J = 5.1, 1.2 Hz, 1H), 7.08 (dq, J = 3.3, 1.0 Hz, 1H), 6.98 (dd, J = 5.1, 3.5 Hz, 1H), 6.59 (s, 1H), 4.80 – 4.69 (m, 2H), 3.76 (dt, J = 10.7, 6.8 Hz, 1H), 3.58 (dd, J = 10.3, 3.7 Hz, 1H), 3.49 – 3.37 (m, 4H), 3.29 – 3.12 (m, 2H), 2.12 (s, 3H).	390.0
22	8,9	(400 MHz, Methanol-d4) δ 7.45 (dd, J = 2.0, 0.8 Hz, 1H), 6.64 (s, 1H), 6.39 – 6.30 (m, 2H), 4.55 (s, 2H), 3.67 (p, J = 6.5 Hz, 1H), 3.22 – 3.07 (m, 3H), 2.51 (q, J = 7.5 Hz, 2H), 1.33 – 1.23 (m, 6H).	358.2
23	8,17	(400 MHz, Methanol-d4) δ 7.30 (dd, J = 5.1, 1.3 Hz, 1H), 7.11 – 7.08 (m, 1H), 6.98 (dd, J = 5.1, 3.5 Hz, 1H), 6.69 (s, 1H), 4.76 (s, 2H), 3.61 (dt, J = 10.8, 5.9 Hz, 1H), 3.24 – 3.18 (m, 2H), 2.71 (dq, J = 10.7, 6.9, 5.8 Hz, 2H), 2.61 – 2.46 (m, 1H), 2.44 – 2.27 (m, 2H), 2.20 (s, 0H), 2.04 (s, 3H), 1.28 (s, 0H).	440.0

Compound #	General Synthesis Scheme	^{1}H-NMR data	LC/MS Ion
24	8,9	(400 MHz, Methanol-d4) δ 7.29 (dd, J = 5.1, 1.3 Hz, 1H), 7.06 (dt, J = 3.5, 1.1 Hz, 1H), 6.96 (dd, J = 5.1, 3.5 Hz, 1H), 6.54 (s, 1H), 4.74 (s, 2H), 3.20 – 3.03 (m, 2H), 2.46 (dt, J = 9.3, 6.7 Hz, 1H), 2.10 (s, 3H), 0.85 (dtt, J = 9.6, 8.0, 4.9 Hz, 1H), 0.57 – 0.47 (m, 1H), 0.46 – 0.36 (m, 1H), 0.26 (dq, J = 9.7, 4.9 Hz, 1H), 0.13 – -0.06 (m, 2H).	386.0
25	8,17	(400 MHz, Methanol-d4) δ 7.70 – 7.53 (m, 1H), 7.28 (dd, J = 5.1, 1.2 Hz, 3H), 7.07 – 7.03 (m, 3H), 6.97 (s, 1H), 6.63 (s, 3H), 4.74 (s, 6H), 3.22 – 3.10 (m, 6H), 2.53 (dt, J = 9.5, 6.7 Hz, 3H), 2.10 (s, 9H), 2.02 (s, 8H), 1.29 (d, J = 7.9 Hz, 1H), 0.88 (ddt, J = 13.2, 9.5, 4.6 Hz, 3H), 0.54 (dt, J = 9.1, 4.7 Hz, 2H), 0.44 (tt, J = 8.6, 4.8 Hz, 3H), 0.30 (dt, J = 9.6, 4.8 Hz, 3H), 0.00 (s, 18H).	390.0
26	8,9	(300 MHz, Methanol-d4) δ 7.45 (dd, J = 1.8, 0.9 Hz, 1H), 6.66 (s, 1H), 6.41 – 6.30 (m, 2H), 4.56 (s, 2H), 4.47 (s, 2H), 3.80 (p, J = 6.6 Hz, 1H), 3.28 – 3.18 (m, 2H), 1.38 (d, J = 6.6 Hz, 3H).	376.0
27	8,9	(300 MHz, Methanol-d4) δ 7.45 (dd, J = 1.8, 0.9 Hz, 1H), 6.66 (s, 1H), 6.41 – 6.30 (m, 2H), 4.56 (s, 2H), 4.47 (s, 2H), 3.80 (p, J = 6.6 Hz, 1H), 3.26 (t, J = 6.5 Hz, 2H), 1.38 (d, J = 6.6 Hz, 3H).	360.1
28	8,17	(400 MHz, Methanol-d4) δ 7.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.05 (dt, J = 3.3, 1.1 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.64 (s, 1H), 4.74 (d, J = 1.0 Hz, 2H), 3.60 (h, J = 6.6 Hz, 1H), 3.15 – 3.01 (m, 2H), 2.07 (d, J = 33.9 Hz, 6H), 1.26 (d, J = 6.5 Hz, 3H).	364.0

Compound #	General Synthesis Scheme	^{1}H-NMR data	LC/MS Ion
31	12,9	400 MHz, Methanol-d4) δ 7.34 – 7.24 (m, 1H), 7.11 – 7.01 (m, 1H), 7.01 – 6.91 (m, 1H), 6.56 – 6.13 (m, 2H), 4.74 (s, 2H), 3.99 (t, J = 6.3 Hz, 2H), 3.46 – 3.36 (m, 1H), 3.06 – 2.96 (m, 2H), 2.10 (s, 3H), 1.95 – 1.61 (m, 2H).	440.0
33	11,9	(300 MHz, Methanol-d4) δ 7.31 (dd, J = 5.1, 1.2 Hz, 1H), 7.12 (d, J = 3.5 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 3.69 (tt, J = 13.1, 6.6 Hz, 1H), 2.15 (s, 3H), 1.23 (d, J = 6.7 Hz, 3H).	396.8
34	6,9	(400 MHz, DMSO-d6) δ 7.95 (t, J = 6.2 Hz, 1H), 7.49 (d, J = 5.1 Hz, 1H), 7.18 (d, J = 3.5 Hz, 1H), 7.06 (dd, J = 5.0, 3.5 Hz, 1H), 6.63 (s, 1H), 4.78 (d, J = 6.2 Hz, 3H), 3.38 (t, J = 8.3 Hz, 2H), 3.25 (dq, J = 11.0, 5.7 Hz, 1H), 3.05 (dd, J = 14.7, 5.2 Hz, 1H), 2.82 (dd, J = 14.7, 8.2 Hz, 1H), 2.18 (s, 3H), 1.98 (d, J = 25.0 Hz, 2H).	376.2
35	8,9	(400 MHz, Methanol-d4) δ 7.30 (dd, J = 5.1, 1.2 Hz, 1H), 7.07 (dd, J = 3.5, 1.2 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.56 (s, 1H), 4.75 (s, 2H), 3.48 – 3.34 (m, 2H), 3.28 (s, 1H), 3.12 (dd, J = 14.8, 5.8 Hz, 1H), 2.98 (dd, J = 14.8, 7.2 Hz, 1H), 2.10 (s, 3H).	393.0
36	2,3,9	1 H NMR (400 MHz, Methanol-d4) δ 7.26 (dd, J = 5.1, 1.2 Hz, 1H), 7.01 (dq, J = 3.3, 1.0 Hz, 1H), 6.93 (dd, J = 5.1, 3.5 Hz, 1H), 5.02 (d, J = 33.6 Hz, 2H), 3.40 (dq, J = 12.3, 6.3 Hz, 1H), 2.96 (qdt, J = 10.1, 6.9, 3.4 Hz, 2H), 2.11 (s, 3H), 1.13 (dd, J = 6.5, 2.3 Hz, 3H).	378.0

Compound #	General Synthesis Scheme	^{1}H-NMR data	LC/MS Ion
37	2,3,9	(400 MHz, Methanol-d4) δ 7.26 (dd, J = 5.1, 1.3 Hz, 1H), 7.01 (dt, J = 3.3, 1.1 Hz, 1H), 6.94 (dd, J = 5.1, 3.5 Hz, 1H), 5.02 (s, 2H), 4.52 (ddt, J = 47.3, 11.2, 6.2 Hz, 1H), 3.31 (p, J = 1.6 Hz, 15H), 3.16 – 3.10 (m, 1H), 2.91 (dd, J = 14.9, 8.3 Hz, 1H), 2.11 (s, 3H), 1.34 (dd, J = 24.3, 6.4 Hz, 3H).	410.0
38	8,9	(400 MHz, Chloroform-d) δ 7.78 (d, J = 3.3 Hz, 1H), 7.32 (d, J = 3.3 Hz, 1H), 6.48 (s, 1H), 5.82 (s, 1H), 4.83 (d, J = 5.5 Hz, 2H), 3.51 (dq, J = 12.0, 6.4, 6.0 Hz, 1H), 3.44 (dd, J = 9.3, 4.2 Hz, 1H), 3.38 (s, 3H), 3.35 – 3.30 (m, 1H), 3.09 (dd, J = 14.8, 5.4 Hz, 1H), 2.97 (dd, J = 14.8, 7.8 Hz, 1H), 2.10 (s, 3H).	390.9
39	8,9	(400 MHz, Methanol-d4) δ 7.44 (d, J = 1.9 Hz, 1H), 6.57 (d, J = 2.2 Hz, 1H), 6.38 – 6.28 (m, 2H), 4.52 (d, J = 2.1 Hz, 2H), 3.44 – 3.36 (m, 3H), 3.33 – 3.26 (m, 3H), 3.06 (ddd, J = 15.0, 5.7, 2.2 Hz, 1H), 2.93 (ddd, J = 14.9, 7.3, 2.2 Hz, 1H), 2.10 (d, J = 2.0 Hz, 3H).	374.0
40	8,9	(400 MHz, Methanol-d4) δ 7.30 (dd, J = 5.1, 1.2 Hz, 1H), 7.07 (dd, J = 3.5, 1.2 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.56 (s, 1H), 3.59 (qd, J = 6.6, 4.1 Hz, 1H), 3.49 (dd, J = 9.8, 4.1 Hz, 1H), 3.37 (dd, J = 9.8, 6.1 Hz, 1H), 3.18 (dd, J = 15.0, 6.6 Hz, 1H), 3.07 (dd, J = 15.0, 7.1 Hz, 1H), 2.11 (s, 3H).	395.0
41	6,9	(300 MHz, Methanol-d4) δ 7.45 (dd, J = 1.8, 0.9 Hz, 2H), 6.36 (qd, J = 3.2, 1.3 Hz, 4H), 4.74 (s, 4H), 4.74 – 4.62 (m, 1H), 4.60 – 4.46 (m, 1H), 3.45 – 3.28 (m, 1H), 3.20 (dd, J = 15.0, 4.6 Hz, 2H), 2.96 (dd, J = 15.1, 8.7 Hz, 2H), 2.13 (s, 6H), 1.45 (d, J = 6.3 Hz, 3H), 1.36 (d, J = 6.3 Hz, 3H).	376.9

Compound #	General Synthesis Scheme	^{1}H-NMR data	LC/MS Ion
42	8,9	(400 MHz, Methanol-d4) δ 7.34 – 7.24 (m, 1H), 7.09 – 7.03 (m, 1H), 7.02 – 6.92 (m, 1H), 6.53 (d, J = 1.5 Hz, 1H), 4.74 (s, 2H), 3.59 – 3.36 (m, 3H), 2.99 (qm, 2H), 2.10 (s, 3H), 1.82 – 1.55 (m, 2H).	407.0
43	8,9	(400 MHz, Methanol-d4) δ 7.34 – 7.24 (m, 1H), 7.11 – 7.01 (m, 1H), 7.02 – 6.92 (m, 1H), 6.53 (s, 1H), 4.77 – 4.72 (m, 2H), 3.43 – 3.33 (m, 1H), 2.10 (s, 3H), 1.14 (d, J = 6.4 Hz, 3H).	362.0
44	8,9	(300 MHz, Methanol -d4) δ 7.29 (dd, J = 5.1, 1.2 Hz, 1H), 7.06 (dd, J = 3.5, 1.2 Hz, 1H), 6.96 (dd, J = 5.1, 3.5 Hz, 1H), 6.52 (s, 1H), 4.73 (s, 2H), 3.41 – 3.34 (m, 5H), 3.30 – 3.24 (m, 1H), 2.10 (s, 3H).	392.0
45	8,9	(400 MHz, Methanol-d4) δ 7.30 (dd, J = 5.1, 1.2 Hz, 1H), 7.07 (dq, J = 3.4, 1.1 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.54 (s, 1H), 4.74 (s, 2H), 4.50 – 4.23 (m, 2H), 3.47 (dt, J = 18.7, 5.0 Hz, 1H), 2.10 (s, 3H).	380.0
46	8,9	(300 MHz, Methanol-d4) δ 7.32 (dd, J = 5.1, 1.2 Hz, 1H), 7.09 (dq, J = 3.3, 1.1 Hz, 1H), 6.99 (dd, J = 5.1, 3.5 Hz, 1H), 6.56 (s, 1H), 4.77 (d, J = 0.9 Hz, 2H), 3.43 (dd, J = 7.4, 6.1 Hz, 1H), 3.38 (s, 3H), 3.16 – 2.86 (m, 2H), 2.13 (s, 3H).	392.0

Compound #	General Synthesis Scheme	^{1}H-NMR data	LC/MS Ion
47	8,9	(300 MHz, Methanol-d4) δ 7.32 (dd, J = 5.1, 1.2 Hz, 1H), 7.13 – 7.05 (m, 1H), 6.99 (dd, J = 5.1, 3.5 Hz, 1H), 6.57 (s, 1H), 4.77 (d, J = 0.9 Hz, 2H), 4.62 (s, 1H), 3.44 (dd, J =7.3, 6.2 Hz, 1H), 3.11 (dd, J = 14.8, 6.2 Hz, 1H), 2.98 (dd, J = 14.8, 7.3 Hz, 1H), 2.13 (s, 3H)	395.0
48	8,9	(400 MHz, Methanol-d4) δ 7.21 (dd, J = 5.1, 1.3 Hz, 1H), 7.02 – 6.94 (m, 1H), 6.88 (dd, J = 5.1, 3.4 Hz, 1H), 6.47 (s, 1H), 4.65 (s, 2H), 2.02 (s, 3H).	427.8
49	13,9	(400 MHz, Methanol-d4) δ 7.30 (dt, J = 5.1, 1.2 Hz, 1H), 7.07 (dd, J = 3.4, 1.3 Hz, 1H), 6.98 (ddd, J = 5.0, 3.4, 1.3 Hz, 1H), 6.61 – 6.54 (m, 1H), 4.76 (d, J = 3.4 Hz, 2H), 3.51 – 3.38 (m, 1H), 3.11 – 3.01 (m, 1H), 2.13 (s, 4H), 2.01 – 1.78 (m, 4H), 1.56 – 1.39 (m, 3H).	400.0
50	13,9	(300 MHz, Methanol-d_4) δ 7.32 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.09 (dt, *J* = 3.4, 1.1 Hz, 1H), 7.00 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.56 (s, 1H), 4.78 (d, *J* = 0.9 Hz, 2H), 3.85 (q, *J* = 8.4 Hz, 1H), 3.61 (q, *J* = 9.0 Hz, 1H), 2.43 – 2.24 (m, 1H), 2.13 (s, 5H), 1.92 (p, *J* = 9.7 Hz, 1H).	372.0
51	13,9	(300 MHz, Methanol-d_4) δ 7.32 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.09 (dt, *J* = 3.4, 1.1 Hz, 1H), 7.00 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.56 (s, 1H), 4.78 (d, *J* = 0.9 Hz, 2H), 3.85 (q, *J* = 8.4 Hz, 1H), 3.61 (q, *J* = 9.0 Hz, 1H), 2.36 – 2.26 (m, 1H), 2.23 – 2.08 (m, 5H), 1.92 (p, *J* = 9.7 Hz, 1H).	372.0

Compound #	General Synthesis Scheme	^{1}H-NMR data	LC/MS Ion
52	13,9	(400 MHz, Methanol-d4) δ 7.30 (dd, J = 5.1, 1.2 Hz, 1H), 7.07 (dq, J = 3.4, 1.1 Hz, 1H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.61 (s, 1H), 4.80 – 4.77 (m, 2H), 3.60 (q, J = 12.3, 11.6 Hz, 1H), 3.42 (q, J = 12.3, 11.6 Hz, 1H), 2.47 – 2.15 (m, 4H), 2.10 – 2.14 (m, 3H), 2.02 (q, J = 12.3, 11.6 Hz, 1H), 1.66 (q, J = 12.3, 11.6 Hz, 1H).	435.9

Example 11: ATXN3 Quantitative Splicing Assay.

[00384] 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.

[00385] The primers and probes are listed below in **Table 4**.

Table 4.

Target Sequence	**Forward Primer**	**Probe**	**Reverse Primer**
ATXN3 E4skpping -FAM	SEQ ID NO: 2 5’ GCAGCCTTCTGGAAA TATGG 3’	SEQ ID NO: 3 5’ TTCTCTATTCAGAAAT GAAAGATCATT 3’	SEQ ID NO: 4 5’ CTGGACCCGTCAAGA GAGAA 3’
ATXN3 E4E5-Cy5	SEQ ID NO: 5	SEQ ID NO: 6 5’ AGGCTCAGGATCGAT	SEQ ID NO: 7

Target Sequence	Forward Primer	Probe	Reverse Primer
	5’ TGTTCAACAGTCCAG AGTATCAG 3’	CCTATAAATGAAAGA 3’	5’ ACCCGTCAAGAGAGA ATTCAAG 3’
ATXN3 E8E9-total-FAM	SEQ ID NO: 8 5’ GATGAGGAGGATTTG CAGAGG 3’	SEQ ID NO: 9 5’ ATGTTTCTGGAACTAC CTTGCATACTTAGCTG 3’	SEQ ID NO: 10 5’ CCTGATGTCTGTGTCA TATCTTGA 3’
TBP-YAK (endogenous control)	SEQ ID NO: 11 5’ TCGGAGAGTTCTGGG ATT 3’	SEQ ID NO: 12 5’ CCGCAGCTGCAAAAT ATTGTATCCACA 3’	SEQ ID NO: 13 5’ AAGTGCAATGGTCTTT AGGT 3’

Example 12: ATXN3 total protein assay.

[00386] 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.

[00387] 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.

[00388] 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.

Example 13: ATXN3 HiBiT assay.

[00389] To monitor ATXN3 protein levels by luminescence, a Kelly-ATXN3-HiBiT cell line with homozygous knock-in of HiBiT at the C-terminus of the endogenous ATXN3 gene was used (knock-in of the HiBiT-tag coding sequence SEQ ID NO. 14: 5’GTGAGCGGCTGGCGGCTGTTCAAGAAGATTAGC3’ into exon 11 of ATXN3 –

position 1114 of ATXN3 RefSeq NM_004993.6). Manipulations of the Kelly-ATXN3-HiBiT cell line that result in downregulation of the ATXN3-HiBiT protein (through modulation of ATXN3-HiBiT pre-mRNA splicing) can be followed by monitoring the luminescence signal of the HiBiT tag using the Nano Glo HiBiT Lytic Detection System (Promega, #N3050). Kelly-ATXN3-HiBiT cells were maintained in in RPMI 1640 w/ Glutamax (Gibco, #61870010), 10% FBS (Sigma Aldrich, # F8687), 1 % Penicillin/Streptomycin (Gibco, #15140-122) at 37 °C, 5 % CO_2. To assess HiBiT-luminescence signal upon compound treatment, 2000 Kelly-ATXN3-HiBiT cells were seeded per well in 384 plate format. Compounds were added 24 h after seeding. ATXN3-HiBiT-luminescence signal was read out 48 h after addition of the compound using the Nano Glo HiBiT Lytic Detection System (Promega, #N3050) according to the manufacturer's instructions. To control for cell viability, an identically prepared sister plate was read out with the CellTiter-Glo® 2.0 Assay (Promega, #G9243) according to the manufacturer's instructions. Fold changes of ATXN3-HiBiT-luminescence and of CellTiter-Glo viability signals were calculated relative to a DMSO control condition.

[00390] Compounds were tested as outlined in Examples 11-13 above and the results are shown below in **Table 5**.

Table 5

ATXN3 E4E5 IC50 (nM): $0.01 \leq A \leq 100$; $101 \leq B \leq 500$; $501 \leq C \leq 5000$; $5001 \leq D \leq 10000$; $10001 \leq E \leq 40{,}000$.

ATXN3 Protein IC50 (nM): $0.01 \leq A \leq 100$; $101 \leq B \leq 500$; $501 \leq C \leq 5000$; $5001 \leq D \leq 10000$; $10001 \leq E \leq 40{,}000$.

ATXN3 HiBit EC50 (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 E4E5 IC50 (nM)	ATXN3 Protein IC50 (nM)	ATXN3 HiBit EC50 (nM)
1	B	B	B
2	B	B	B
3	B	B	B
4	B	B	B
5	A	A	A

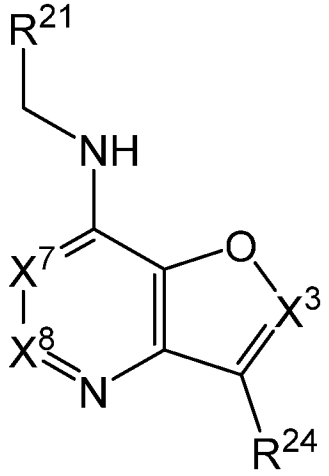
Compound #	ATXN3 E4E5 IC50 (nM)	ATXN3 Protein IC50 (nM)	ATXN3 HiBit EC50 (nM)
6	A	A	A
7	B	B	B
8	B	C	B
9	C	C	C
10	C	C	C
11	A	B	A
12	A	B	A
13			C
14			E
15	C	C	C
16	B	B	B
19	B	B	B
21	A	B	A
22	B	C	C
23	D	E	C
24	C	C	C
25	E	E	D
26	B	C	B
27	C	C	C
28	C	C	C
31			A
33	B	C	B
34			A
35			A
36	C	C	C
37	C		
38	B	B	B
39	B	A	A
40			A

Compound #	ATXN3 E4E5 IC50 (nM)	ATXN3 Protein IC50 (nM)	ATXN3 HiBit EC50 (nM)
41	A	A	A
42			A
43			A
44			A
45			A
46	A	B	A
47			A
48			A
49	A		
50	C		
51	C		
52	A		

CLAIMS

WHAT IS CLAIMED IS:

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



Formula (I)

wherein,

- X^3 is selected from the group consisting of N and CR^{23};
- X^7 is CR^{27} or N;

X^8 is CR^{28} or N;

- R^{21} is selected from the group consisting of phenyl, 5-6 membered heteroaryl, and 5-6 membered heterocycloalkyl, each of which is unsubstituted or substituted with 1, 2, 3 or 4, 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_{1-4} haloalkoxy, 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_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl, 4- 10 membered heterocycloalkyl, -(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_{1-6} alkylene)-C_{6-10} aryl, -(C_{1-6} alkylene)-5-10 membered heteroaryl, -(C_{1-6} heteroalkylene)-C_{6-10} aryl, -(C_{1-6} heteroalkylene)-5-10 membered heteroaryl, -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_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl,

and 4- 10 membered heterocycloalkyl, are each unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups;

- R^{24} is -C≡C-R^{20d} or C_{3-6} alkynyl, wherein the C_{3-6} alkynyl is optionally substituted with 1, 2, 3, or 4 independently selected R^{20d} groups;

R^{27} is selected from the group consisting of H, azido, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, -CN, -NO_2, -OR^{a7}, -C(=O)R^{b7}, -C(=O)OR^{b7}, -$NR^{c7}R^{d7}$, -C(=O)$NR^{c7}R^{d7}$, -OC(=O)$NR^{c7}R^{d7}$, -NR^{c7}C(=O)R^{b7}, -NR^{c7}C(=O)OR^{b7}, -NR^{c7}C(=O)$NR^{c7}R^{d7}$, -NR^{c7}S(=O)$_2R^{b7}$, and -NR^{c7}S(=O)$_2NR^{c7}R^{d7}$, wherein the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups;

- R^{28} is selected from the group consisting of H, azido, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} heteroalkyl, -CN, -NO_2, -OR^{a8}, -C(=O)R^{b8}, -C(=O)OR^{b8}, -$NR^{c8}R^{d8}$, -C(=O)$NR^{c8}R^{d8}$, -OC(=O)$NR^{c8}R^{d8}$, -NR^{c8}C(=O)R^{b8}, -NR^{c8}C(=O)OR^{b8}, -NR^{c8}C(=O)$NR^{c8}R^{d8}$, -NR^{c8}S(=O)$_2R^{b8}$, and -NR^{c8}S(=O)$_2NR^{c8}R^{d8}$, wherein the C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl 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^{a7}, R^{b7}, R^{c7}, R^{d7}, R^{a8}, R^{b8}, R^{c8}, and R^{d8} 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 each of which is unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups;

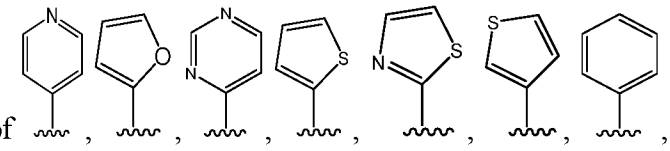
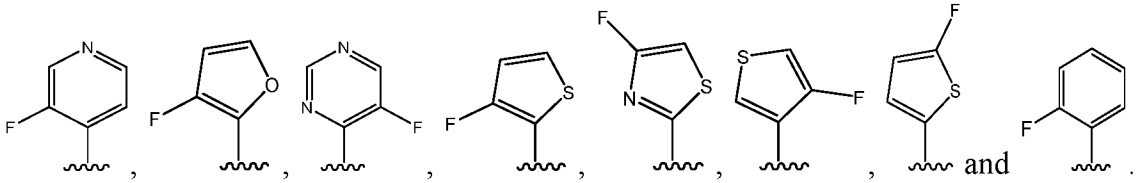
or R^{c3} and R^{d3} together with the N atom to which they are connected, come together to form a 5-10 membered heteroaryl or a 4-10 membered heterocycloalkyl ring, each of which is unsubstituted or substituted with 1, 2, 3, or 4 independently selected R^{20} groups; and

- each R^{20} is independently selected from the group consisting of -OH, -SH, -CN, -NO_2, halo, oxo, amino, carbamyl, carbamoyl, 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_{6-10} aryl, 4-6 membered heteroaryl, 5-6 membered heterocycloalkyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} alkylcarbamyl, di(C_{1-4} alkyl)carbamyl, 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; and

each R^{20d} is independently selected from the group consisting of -OH, -SH, -CN, -NO_2, halogen, oxo, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} haloalkyl, C_{1-4} heteroalkyl, 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, and di(C_{1-4} alkyl)aminocarbonylamino.

2. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein R^{21} is selected from the group consisting of phenyl and 5-6 membered heteroaryl, each of which is unsubstituted or substituted with 1, 2, 3 or 4, 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.

3. The compound of claim 2, or pharmaceutically acceptable salt thereof, wherein R^{21} is selected from the group consisting of  ,  , and .

4. The compound of any one of claims 1-3, or pharmaceutically acceptable salt thereof, wherein, X^3 is CH.

5. The compound of any one of claims 1-3, or pharmaceutically acceptable salt thereof, wherein, X^3 is CR^{23}.

6. The compound of claim 5, or pharmaceutically acceptable salt thereof, 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 thereof, wherein X^3 is $CCH_2CH(NH_2)CH_3$.

8. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein X^3 is $CCH_2CH(NH_2)CH_2OH$.

9. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein X^3 is $CCH_2CH(NH_2)CH_2CH_3$.

10. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein X^3 is $CCH_2CH(NH_2)CH_2CH_2OH$.

11. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein X^3 is $CCH_2CH(NH_2)CH_2CH_2F$.

12. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein X^3 is $CCH_2CH(NH_2)CH_2CHF_2$.

13. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein X^3 is $CCH_2CH(NH_2)CH_2CH(CH_3)_2$.

14. The compound of any one of claims 1-13, or pharmaceutically acceptable salt thereof, wherein, R^{24} is ethynyl.

15. The compound of any one of claims 1-13, or pharmaceutically acceptable salt thereof, wherein, R^{24} is propynyl.

16. The compound of any one of claims 1-15, or pharmaceutically acceptable salt thereof, wherein, X^8 is N.

17. The compound of any one of claims 1-15, or pharmaceutically acceptable salt thereof, wherein, X^8 is CR^{28}.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein X^7 is CR^{27}.

19. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt thereof, wherein X^7 is N.

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

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

22. 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 according to any one of claims 1-20 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 21.

23. A method of modulating splicing of a Ataxin3 (ATXN3) pre-mRNA, comprising contacting a compound according to any one of claims 1-20 or a pharmaceutically acceptable salt thereof,, or a pharmaceutical composition of claim 21, 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.

24. Use of a compound according to any one of claims 1-20, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 21, in the manufacture of a medicament for the treatment of a condition or disease associated with Ataxin 3 (ATXN3) expression level or activity level.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/022135

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. ☐ 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

International application No
PCT/US2023/022135

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/04 A61K31/4355 A61P25/14
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

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020/167628 A1 (PTC THERAPEUTICS INC [US]) 20 August 2020 (2020-08-20) claims; examples	1-24

☐ 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
18 August 2023	28/08/2023

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	Beyss-Kahana, Ellen

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/022135

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2020167628 A1	20-08-2020	AU 2020222881 A1	09-09-2021
		CA 3129067 A1	20-08-2020
		CL 2021002137 A1	25-02-2022
		CN 113795304 A	14-12-2021
		CO 2021010598 A2	30-08-2021
		EA 202192170 A1	15-11-2021
		EP 3924049 A1	22-12-2021
		IL 285399 A	30-09-2021
		JP 2022520822 A	01-04-2022
		KR 20210137040 A	17-11-2021
		PE 20220139 A1	27-01-2022
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