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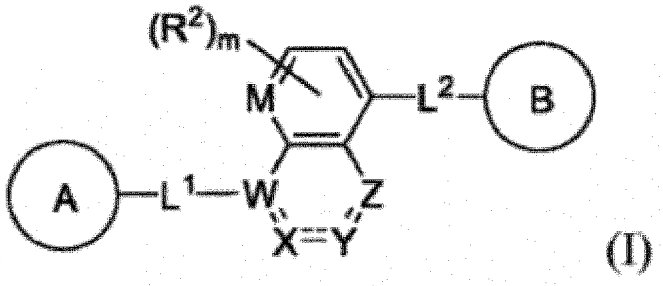
(54) Title: FUSED BICYCLIC COMPOUNDS USEFUL FOR MODULATING NUCLEIC ACID SPLICING



(I)

(57) Abstract: The present disclosure features compounds and related compositions that, *inter alia*, modulate nucleic acid splicing, e.g., splicing of a pre-mRNA, as well as methods of use thereof.

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FUSED BICYCLIC COMPOUNDS USEFUL FOR MODULATING NUCLEIC ACID SPLICING

CLAIM OF PRIORITY

This application claims priority to U.S. Application No. 62/983,541, filed February 28, 2020; U.S. Application No. 63/007,333, filed April 8, 2020; U.S. Application No. 63/040,484, filed June 17, 2020; U.S. Application No. 63/072,790, filed August 31, 2020; and U.S. Application No. 63/126,492, filed December 16, 2020. The disclosure of each of the foregoing applications is incorporated herein by reference in its entirety.

BACKGROUND

Alternative splicing is a major source of protein diversity in higher eukaryotes and is frequently regulated in a tissue-specific or development stage-specific manner. Disease associated alternative splicing patterns in pre-mRNAs are often mapped to changes in splice site signals or sequence motifs and regulatory splicing factors (Faustino and Cooper (2003), *Genes Dev* 17(4):419-37). Current therapies to modulate RNA expression involve oligonucleotide targeting and gene therapy; however, each of these modalities exhibit unique challenges as currently presented. As such, there is a need for new technologies to modulate RNA expression, including the development of small molecule compounds that target splicing.

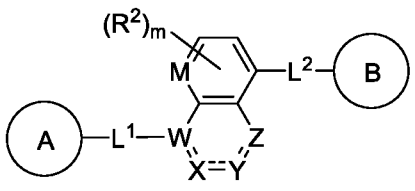
SUMMARY

The present disclosure features compounds and related compositions that, *inter alia*, modulate nucleic acid splicing, e.g., splicing of a pre-mRNA, as well as methods of use thereof. In an embodiment, the compounds described herein are compounds of Formula (I) (e.g., a compound of Formulas (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) and pharmaceutically acceptable salts, solvates, hydrates, tautomers, or stereoisomers thereof. The present disclosure additionally provides methods of using the compounds of the invention (e.g., compounds of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers thereof), and compositions thereof, e.g., to target, and in embodiments bind or form a complex with, a nucleic acid (e.g., a pre-mRNA or nucleic acid component of a small nuclear ribonucleoprotein (snRNP) or spliceosome), a protein (e.g., a protein component of an snRNP or spliceosome, e.g., a member of the splicing machinery, e.g.,

one or more of the U1, U2, U4, U5, U6, U11, U12, U4atac, U6atac snRNPs), or a combination thereof. In another aspect, the compounds described herein may be used to alter the composition or structure of a nucleic acid (e.g., a pre-mRNA or mRNA (e.g., a pre-mRNA and the mRNA which arises from the pre-mRNA), e.g., by increasing or decreasing splicing at a splice site. In some embodiments, increasing or decreasing splicing results in modulating the level of a gene product (e.g., an RNA or protein) produced.

In another aspect, the compounds described herein may be used for the prevention and/or treatment of a disease, disorder, or condition, e.g., a disease, disorder or condition associated with splicing, e.g., alternative splicing. In some embodiments, the compounds described herein (e.g., compounds of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers thereof) and compositions thereof are used for the prevention and/or treatment of a proliferative disease, disorder, or condition (e.g., a disease, disorder, or condition characterized by unwanted cell proliferation, e.g., a cancer or a benign neoplasm) in a subject. In some embodiments, the compounds described herein (e.g., compounds of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers thereof) and compositions thereof are used for the prevention and/or treatment of a non-proliferative disease, disorder, or condition. In some embodiments, the compounds described herein (e.g., compounds of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers thereof) and compositions thereof are used for the prevention and/or treatment of a neurological disease or disorder, an autoimmune disease or disorder, immunodeficiency disease or disorder, a lysosomal storage disease or disorder, a cardiovascular disease or disorder, a metabolic disease or disorder, a respiratory disease or disorder, a renal disease or disorder, or an infectious disease in a subject.

In one aspect, the present disclosure provides compounds of Formula (I):



(I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

W is N, C, or C(R^{3a}); X, Y, and Z are each independently C(R^{3a}), C(R^{3a})(R^{3b}), N, N(R^{3c}), or O, wherein the bonds in the ring comprising W, X, Y, and Z may be single or double bonds as valency permits; M is C(R^2) or N; L^1 and L^2 are each independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –SR^E, or –$S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6; or two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more R^6; each R^2 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or –OR^A; R^{3a} and R^{3b} are each independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, –OR^A, –NR^BR^C, –$C(O)R^D$, or –$C(O)OR^D$; or each of R^{3a} and R^{3b}, together with the carbon atom to which they are attached, form an oxo group; R^{3c} is hydrogen or C_1-C_6-alkyl; each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$C(O)R^D$, or –$C(O)OR^D$; each R^6 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –SR^E, or –$S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11}; each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, –$C(O)R^D$, or –$S(O)_xR^D$;each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or –OR^A; or R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^7; each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl; each R^7 is C_1-C_6-alkyl, halo,

cyano, oxo, or $-OR^{A1}$; each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^{A}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m is 0, 1, or 2; and x is 0, 1, or 2.

In another aspect, the present invention provides pharmaceutical compositions comprising a compound of Formula (I) (e.g., a compound of Formulas (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), or (I-i)), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient. In an embodiment, the pharmaceutical compositions described herein include an effective amount (e.g., a therapeutically effective amount) of a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In another aspect, the present disclosure provides methods for modulating splicing, e.g., splicing of a nucleic acid (e.g., a DNA or RNA, e.g., a pre-mRNA) with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In another aspect, the present disclosure provides compositions for use in modulating splicing, e.g., splicing of a nucleic acid (e.g., a DNA or RNA, e.g., a pre-mRNA) with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. Modulation of splicing may comprise impacting any step involved in splicing and may include an event upstream or downstream of a splicing event. For example, in some embodiments, the compound of Formula (I) binds to a target, e.g., a target nucleic acid (e.g., DNA or RNA, e.g., a precursor RNA, e.g., a pre-mRNA), a target protein, or combination thereof (e.g., an snRNP and a pre-mRNA). A target may include a splice site in a pre-mRNA or a component of the splicing machinery, such as the U1 snRNP. In some embodiments, the compound of Formula (I) alters a target nucleic acid (e.g., DNA or RNA, e.g., a precursor RNA, e.g., a pre-mRNA), target protein, or combination thereof. In some embodiments, the compound of Formula (I) increases or decreases splicing at a splice site on a target nucleic acid (e.g., an RNA, e.g., a precursor RNA, e.g., a pre-mRNA) by about 0.5% or more (e.g., about 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 75%, 90%, 95%, or more), relative to a reference (e.g., the absence of a compound of Formula (I), e.g., in a healthy or diseased cell or tissue). In some embodiments, the presence of a

compound of Formula (I) results an increase or decrease of transcription of a target nucleic acid (e.g., an RNA) by about 0.5% or more (e.g., about 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, 40%, 50%, 75%, 90%, 95%, or more), relative to a reference (e.g., the absence of a compound of Formula (I), e.g., in a healthy or diseased cell or tissue).

In another aspect, the present disclosure provides methods for preventing and/or treating a disease, disorder, or condition in a subject by administering a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, or related compositions. In some embodiments, the disease or disorder entails unwanted or aberrant splicing. In some embodiments, the disease or disorder is a proliferative disease, disorder, or condition. Exemplary proliferative diseases include cancer, a benign neoplasm, or angiogenesis. In other embodiments, the present disclosure provides methods for treating and/or preventing a non-proliferative disease, disorder, or condition. In still other embodiments, the present disclosure provides methods for treating and/or preventing a neurological disease or disorder, autoimmune disease or disorder, immunodeficiency disease or disorder, lysosomal storage disease or disorder, cardiovascular disease or disorder, metabolic disease or disorder, respiratory disease or disorder, renal disease or disorder, or infectious disease.

In another aspect, the present disclosure provides methods of down-regulating the expression of (e.g., the level of or the rate of production of) a target protein with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another aspect, the present disclosure provides methods of up-regulating the expression of (e.g., the level of or the rate of production of) a target protein with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another aspect, the present disclosure provides methods of altering the isoform of a target protein with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g))) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. Another aspect of the disclosure relates to methods of inhibiting the activity of a target protein in a biological sample or subject. In some embodiments, administration of a compound

of Formula (I) to a biological sample, a cell, or a subject comprises inhibition of cell growth or induction of cell death.

In another aspect, the present disclosure provides compositions for use in preventing and/or treating a disease, disorder, or condition in a subject by administering a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, or related compositions. In some embodiments, the disease or disorder entails unwanted or aberrant splicing. In some embodiments, the disease or disorder is a proliferative disease, disorder, or condition. Exemplary proliferative diseases include cancer, a benign neoplasm, or angiogenesis. In other embodiments, the present disclosure provides methods for treating and/or preventing a non-proliferative disease, disorder, or condition. In still other embodiments, the present disclosure provides methods for treating and/or preventing a neurological disease or disorder, autoimmune disease or disorder, immunodeficiency disease or disorder, lysosomal storage disease or disorder, cardiovascular disease or disorder, metabolic disease or disorder, respiratory disease or disorder, renal disease or disorder, or infectious disease.

In another aspect, the present disclosure provides compositions for use in down-regulating the expression of (e.g., the level of or the rate of production of) a target protein with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another aspect, the present disclosure provides compositions for use in up-regulating the expression of (e.g., the level of or the rate of production of) a target protein with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another aspect, the present disclosure provides compositions for use in altering the isoform of a target protein with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g))) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. Another aspect of the disclosure relates to compositions for use in inhibiting the activity of a target protein in a biological sample or subject. In some embodiments, administration of a compound of Formula (I) to a biological sample, a cell, or a subject comprises inhibition of cell growth or induction of cell death.

In another aspect, the present disclosure features kits comprising a container with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer thereof, or a pharmaceutical composition thereof. In certain embodiments, the kits described herein further include instructions for administering the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer thereof, or the pharmaceutical composition thereof.

In any and all aspects of the present disclosure, in some embodiments, the compound, target nucleic acid (e.g., DNA, RNA, e.g., pre-mRNA), or target protein described herein is a compound, target nucleic acid (e.g., DNA, RNA, e.g., pre-mRNA), or target protein other than a compound, target nucleic acid (e.g., DNA, RNA, e.g., pre-mRNA), or target protein described one of U.S. Patent No. 8,729,263, U.S. Publication No. 2015/0005289, WO 2014/028459, WO 2016/128343, WO 2016/196386, WO 2017/100726, WO 2018/232039, WO 2018/098446, WO 2019/028440, WO 2019/060917, and WO 2019/199972. In some embodiments, the compound, target nucleic acid (e.g., DNA, RNA, e.g., pre-mRNA), or target protein described herein is a compound, target nucleic acid (e.g., DNA, RNA, e.g., pre-mRNA), or target protein described one of U.S. Patent No. 8,729,263, U.S. Publication No. 2015/0005289, WO 2014/028459, WO 2016/128343, WO 2016/196386, WO 2017/100726, WO 2018/232039, WO 2018/098446, WO 2019/028440, WO 2019/060917, and WO 2019/199972, each of which is incorporated herein by reference in its entirety.

The details of one or more embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the **Detailed Description**, the **Examples**, and the **Claims**.

DETAILED DESCRIPTION

Selected Chemical Definitions

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas

Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "C_1-C_6 alkyl" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_1-C_6, C_1-C_5, C_1-C_4, C_1-C_3, C_1-C_2, C_2-C_6, C_2-C_5, C_2-C_4, C_2-C_3, C_3-C_6, C_3-C_5, C_3-C_4, C_4-C_6, C_4-C_5, and C_5-C_6 alkyl.

The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

As used herein, "alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 24 carbon atoms ("C_1-C_{24} alkyl"). In some embodiments, an alkyl group has 1 to 12 carbon atoms ("C_1-C_{12} alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("C_1-C_8 alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("C_1-C_6 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("C_2-C_6 alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). Examples of C_1-C_6alkyl groups include methyl (C_1), ethyl (C_2), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8) and the like. Each instance of an alkyl group may be independently optionally substituted, i.e., unsubstituted (an "unsubstituted alkyl") or substituted (a "substituted alkyl") with one or more substituents; e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkyl group is unsubstituted C_1–C_{10} alkyl (e.g., –CH_3). In certain embodiments, the alkyl group is substituted C_1–C_6 alkyl.

As used herein, "alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 24 carbon atoms, one or more carbon–carbon double bonds, and no triple

bonds ("C_2-C_{24} alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_2-C_{10} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_2-C_8 alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_2-C_6 alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_2-C_4 alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of C_2-C_6 alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Each instance of an alkenyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkenyl group is unsubstituted C_{1-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-6} alkenyl.

As used herein, the term "alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 24 carbon atoms, one or more carbon–carbon triple bonds ("C_2-C_{24} alkenyl"). In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_2-C_{10} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_2-C_8 alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_2-C_6 alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C_2-C_4 alkynyl groups include ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Each instance of an alkynyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkynyl group is unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-6} alkynyl.

As used herein, the term "haloalkyl," refers to a non-cyclic stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one halogen selected from the group consisting of F, Cl, Br, and I. The halogen(s) F, Cl, Br, and I may be

placed at any position of the haloalkyl group. Exemplary haloalkyl groups include, but are not limited to: $-CF_3$, $-CCl_3$, $-CH_2-CF_3$, $-CH_2-CCl_3$, $-CH_2-CBr_3$, $-CH_2-CI_3$, $-CH_2-CH_2-CH(CF_3)-CH_3$, $-CH_2-CH_2-CH(Br)-CH_3$, and $-CH_2-CH=CH-CH_2-CF_3$. Each instance of a haloalkyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted haloalkyl") or substituted (a "substituted haloalkyl") with one or more substituents *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent

As used herein, the term "heteroalkyl," refers to a non-cyclic stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P, S, and Si may be placed at any position of the heteroalkyl group. Exemplary heteroalkyl groups include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, and $-O-CH_2-CH_3$. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as $-CH_2O$, $-NR^CR^D$, or the like, it will be understood that the terms heteroalkyl and $-CH_2O$ or $-NR^CR^D$ are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as $-CH_2O$, $-NR^CR^D$, or the like. Each instance of a heteroalkyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent

As used herein, "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.,* bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.,* having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_6-C_{14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.,* phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.,* naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.,* anthracyl). An aryl group may be described as, e.g.,

a C_6-C_{10}-membered aryl, wherein the term "membered" refers to the non-hydrogen ring atoms within the moiety. Aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl. Each instance of an aryl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_6-C_{14} aryl. In certain embodiments, the aryl group is substituted C_6-C_{14} aryl.

As used herein, "heteroaryl" refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system (*e.g.,* having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur ("5–10 membered heteroaryl"). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.,* indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.,* either the ring bearing a heteroatom (*e.g.,* 2–indolyl) or the ring that does not contain a heteroatom (*e.g.,* 5–indolyl). A heteroaryl group may be described as, e.g., a 6-10-membered heteroaryl, wherein the term "membered" refers to the non-hydrogen ring atoms within the moiety. Each instance of a heteroaryl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent

Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing four heteroatoms include, without

limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Other exemplary heteroaryl groups include heme and heme derivatives.

As used herein, "cycloalkyl" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C_3-C_{10} cycloalkyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_3-C_8 cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_3-C_6 cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_3-C_6 cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_5-C_{10} cycloalkyl"). A cycloalkyl group may be described as, e.g., a C_4-C_7-membered cycloalkyl, wherein the term "membered" refers to the non-hydrogen ring atoms within the moiety. Exemplary C_3-C_6 cycloalkyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_3-C_8 cycloalkyl groups include, without limitation, the aforementioned C_3-C_6 cycloalkyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), cubanyl (C_8), bicyclo[1.1.1]pentanyl (C_5), bicyclo[2.2.2]octanyl (C_8), bicyclo[2.1.1]hexanyl (C_6), bicyclo[3.1.1]heptanyl (C_7), and the like. Exemplary C_3-C_{10} cycloalkyl groups include, without limitation, the aforementioned C_3-C_8 cycloalkyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the

like. As the foregoing examples illustrate, in certain embodiments, the cycloalkyl group is either monocyclic ("monocyclic cycloalkyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic cycloalkyl") and can be saturated or can be partially unsaturated. "Cycloalkyl" also includes ring systems wherein the cycloalkyl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is on the cycloalkyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the cycloalkyl ring system. Each instance of a cycloalkyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C_3-C_{10} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_3-C_{10} cycloalkyl.

"Heterocyclyl" as used herein refers to a radical of a 3– to 10–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("3–10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more cycloalkyl groups wherein the point of attachment is either on the cycloalkyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. A heterocyclyl group may be described as, e.g., a 3-7-membered heterocyclyl, wherein the term "membered" refers to the non-hydrogen ring atoms, i.e., carbon, nitrogen, oxygen, sulfur, boron, phosphorus, and silicon, within the moiety. Each instance of heterocyclyl may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted

3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin–2–one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl (e.g., 2,2,6,6-tetramethylpiperidinyl), tetrahydropyranyl, dihydropyridinyl, pyridinonyl (e.g., 1-methylpyridin2-onyl), and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, pyridazinonyl (2-methylpyridazin-3-onyl), pyrimidinonyl (e.g., 1-methylpyrimidin-2-onyl, 3-methylpyrimidin-4-onyl), dithianyl, dioxanyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5–membered heterocyclyl groups fused to a C_6 aryl ring (also referred to herein as a 5,6–bicyclic heterocyclyl ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 5–membered heterocyclyl groups fused to a heterocyclyl ring (also referred to herein as a 5,5–bicyclic heterocyclyl ring) include, without limitation, octahydropyrrolopyrrolyl (e.g., octahydropyrrolo[3,4-c]pyrrolyl), and the like. Exemplary 6-membered heterocyclyl groups fused to a heterocyclyl ring (also referred to as a 4,6-membered heterocyclyl ring) include, without limitation, diazaspirononanyl (e.g., 2,7-diazaspiro[3.5]nonanyl). Exemplary 6–membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6–bicyclic heterocyclyl ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like. Exemplary 6–membered heterocyclyl

groups fused to a cycloalkyl ring (also referred to herein as a 6,7-bicyclic heterocyclyl ring) include, without limitation, azabicyclooctanyl (e.g., (1,5)-8-azabicyclo[3.2.1]octanyl). Exemplary 6–membered heterocyclyl groups fused to a cycloalkyl ring (also referred to herein as a 6,8-bicyclic heterocyclyl ring) include, without limitation, azabicyclononanyl (e.g., 9-azabicyclo[3.3.1]nonanyl).

The terms "alkylene," "alkenylene," "alkynylene," "haloalkylene," "heteroalkylene," "cycloalkylene," or "heterocyclylene," alone or as part of another substituent, mean, unless otherwise stated, a divalent radical derived from an alkyl, alkenyl, alkynyl, haloalkylene, heteroalkylene, cycloalkyl, or heterocyclyl respectively. For example, the term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene. An alkylene, alkenylene, alkynylene, haloalkylene, heteroalkylene, cycloalkylene, or heterocyclylene group may be described as, e.g., a C_1-C_6-membered alkylene, C_2-C_6-membered alkenylene, C_2-C_6-membered alkynylene, C_1-C_6-membered haloalkylene, C_1-C_6-membered heteroalkylene, C_3-C_8-membered cycloalkylene, or C_3-C_8-membered heterocyclylene, wherein the term "membered" refers to the non-hydrogen atoms within the moiety. In the case of heteroalkylene and heterocyclylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -$C(O)_2R'$- may represent both -$C(O)_2R'$- and –$R'C(O)_2$-.

As used herein, the terms "cyano" or "–CN" refer to a substituent having a carbon atom joined to a nitrogen atom by a triple bond, *e.g.*, C≡N.

As used herein, the terms "halogen" or "halo" refer to fluorine, chlorine, bromine or iodine.

As used herein, the term "hydroxy" refers to –OH.

As used herein, the term "nitro" refers to a substitutent having two oxygen atoms bound to a nitrogen atom, e.g., -NO_2.

As used herein, the term "nucleobase" as used herein, is a nitrogen-containing biological compounds found linked to a sugar within a nucleoside—the basic building blocks of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The primary, or naturally occurring, nucleobases are cytosine (DNA and RNA), guanine (DNA and RNA), adenine (DNA and RNA),

thymine (DNA) and uracil (RNA), abbreviated as C, G, A, T, and U, respectively. Because A, G, C, and T appear in the DNA, these molecules are called DNA-bases; A, G, C, and U are called RNA-bases. Adenine and guanine belong to the double-ringed class of molecules called purines (abbreviated as R). Cytosine, thymine, and uracil are all pyrimidines. Other nucleobases that do not function as normal parts of the genetic code, are termed non-naturally occurring. In an embodiment, a nucleobase may be chemically modified, for example, with an alkyl (e.g., methyl), halo, -O-alkyl, or other modification.

As used herein, the term "nucleic acid" refers to deoxyribonucleic acids (DNA) or ribonucleic acids (RNA) and polymers thereof in either single- or double-stranded form. The term "nucleic acid" includes a gene, cDNA, pre-mRNA, or an mRNA. In one embodiment, the nucleic acid molecule is synthetic (*e.g.,* chemically synthesized) or recombinant. Unless specifically limited, the term encompasses nucleic acids containing analogues or derivatives of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (*e.g.,* degenerate codon substitutions), alleles, orthologs, SNPs, and complementarity sequences as well as the sequence explicitly indicated.

As used herein, "oxo" refers to a carbonyl, i.e., -C(O)-.

The symbol "〰" as used herein in relation to a compound of Formula (I) refers to an attachment point to another moiety or functional group within the compound.

Alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted. In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (*e.g.,* a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.,* a substituent which upon substitution results in a stable compound, *e.g.,* a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, such as any of the substituents described herein that result in

the formation of a stable compound. The present disclosure contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocyclyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

The compounds provided herein may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to: cis- and trans-forms; E- and Z-forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and half chair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. In an embodiment, the stereochemistry depicted in a compound is relative rather than absolute. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*,

Tetrahedron 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). This disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

As used herein, a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (i.e., in enantiomeric excess). In other words, an "S" form of the compound is substantially free from the "R" form of the compound and is, thus, in enantiomeric excess of the "R" form. The term "enantiomerically pure" or "pure enantiomer" denotes that the compound comprises more than 75% by weight, more than 80% by weight, more than 85% by weight, more than 90% by weight, more than 91% by weight, more than 92% by weight, more than 93% by weight, more than 94% by weight, more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 99% by weight, more than 99.5% by weight, or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

In the compositions provided herein, an enantiomerically pure compound can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising an enantiomerically pure R–compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure R–compound. In certain embodiments, the enantiomerically pure R–compound in such compositions can, for example, comprise, at least about 95% by weight R–compound and at most about 5% by weight S–compound, by total weight of the compound. For example, a pharmaceutical composition comprising an enantiomerically pure S–compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure S–compound. In certain embodiments, the enantiomerically pure S–compound in such compositions can, for example, comprise, at least about 95% by weight S–compound and at most about 5% by weight R–compound, by total weight of the compound.

In some embodiments, a diastereomerically pure compound can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising a diastereometerically pure exo compound can comprise, for example, about 90% excipient and about 10% diastereometerically pure exo compound. In certain embodiments, the

diastereometerically pure exo compound in such compositions can, for example, comprise, at least about 95% by weight exo compound and at most about 5% by weight endo compound, by total weight of the compound. For example, a pharmaceutical composition comprising a diastereometerically pure endo compound can comprise, for example, about 90% excipient and about 10% diastereometerically pure endo compound. In certain embodiments, the diastereometerically pure endo compound in such compositions can, for example, comprise, at least about 95% by weight endo compound and at most about 5% by weight exo compound, by total weight of the compound.

In some embodiments, an isomerically pure compound can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising a isomerically pure exo compound can comprise, for example, about 90% excipient and about 10% isomerically pure exo compound. In certain embodiments, the isomerically pure exo compound in such compositions can, for example, comprise, at least about 95% by weight exo compound and at most about 5% by weight endo compound, by total weight of the compound. For example, a pharmaceutical composition comprising an isomerically pure endo compound can comprise, for example, about 90% excipient and about 10% isomerically pure endo compound. In certain embodiments, the isomerically pure endo compound in such compositions can, for example, comprise, at least about 95% by weight endo compound and at most about 5% by weight exo compound, by total weight of the compound.

In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

Compound described herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D or deuterium), and ^{3}H (T or tritium); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; N may be in any isotopic form, including ^{14}N and ^{15}N; F may be in any isotopic form, including ^{18}F, ^{19}F, and the like.

The term "pharmaceutically acceptable salt" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base,

either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, e.g., Berge et al, *Journal of Pharmaceutical Science* 66: 1-19 (1977)). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. These salts may be prepared by methods known to those skilled in the art. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for the present invention.

In addition to salt forms, the present disclosure provides compounds in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

The term "solvate" refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds of Formula (I) may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate

will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

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

The term "tautomer" refers to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane that are likewise formed by treatment with acid or base. Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

Other Definitions

The following definitions are more general terms used throughout the present disclosure.

The articles "a" and "an" refer to one or more than one (*e.g.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element. The term "and/or" means either "and" or "or" unless indicated otherwise.

The term "about" is used herein to mean within the typical ranges of tolerances in the art. For example, "about" can be understood as about 2 standard deviations from the mean. In certain embodiments, about means ±10%. In certain embodiments, about means ±5%. When about is present before a series of numbers or a range, it is understood that "about" can modify each of the numbers in the series or range.

"Acquire" or "acquiring" as used herein, refer to obtaining possession of a value, e.g., a

numerical value, or image, or a physical entity (e.g., a sample), by "directly acquiring" or "indirectly acquiring" the value or physical entity. "Directly acquiring" means performing a process (e.g., performing an analytical method or protocol) to obtain the value or physical entity. "Indirectly acquiring" refers to receiving the value or physical entity from another party or source (e.g., a third-party laboratory that directly acquired the physical entity or value). Directly acquiring a value or physical entity includes performing a process that includes a physical change in a physical substance or the use of a machine or device. Examples of directly acquiring a value include obtaining a sample from a human subject. Directly acquiring a value includes performing a process that uses a machine or device, e.g., mass spectrometer to acquire mass spectrometry data.

The terms "administer," "administering," or "administration," as used herein refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing an inventive compound, or a pharmaceutical composition thereof.

As used herein, the terms "condition," "disease," and "disorder" are used interchangeably.

An "effective amount" of a compound of Formula (I) refers to an amount sufficient to elicit the desired biological response, *i.e.*, treating the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of Formula (I) may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment. For example, in treating cancer, an effective amount of an inventive compound may reduce the tumor burden or stop the growth or spread of a tumor.

A "therapeutically effective amount" of a compound of Formula (I) is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. In some embodiments, a therapeutically effective amount is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy,

reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

The terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprised therein. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types.

"Prevention," "prevent," and "preventing" as used herein refers to a treatment that comprises administering a therapy, e.g., administering a compound described herein (e.g., a compound of Formula (I)) prior to the onset of a disease, disorder, or condition in order to preclude the physical manifestation of said disease, disorder, or condition. In some embodiments, "prevention," "prevent," and "preventing" require that signs or symptoms of the disease, disorder, or condition have not yet developed or have not yet been observed. In some embodiments, treatment comprises prevention and in other embodiments it does not.

A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle–aged adult, or senior adult)) and/or other non–human animals, for example, mammals (*e.g.*, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs) and birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys). In certain embodiments, the animal is a mammal. The animal may be a male or female and at any stage of development. A non–human animal may be a transgenic animal.

As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of one or more of a symptom, manifestation, or underlying cause of a disease, disorder, or condition (e.g., as described herein), e.g., by administering a therapy, e.g., administering a compound described herein (e.g., a compound of Formula (I)). In an embodiment, treating comprises reducing, reversing, alleviating, delaying the onset of, or inhibiting the progress of a symptom of a disease, disorder,

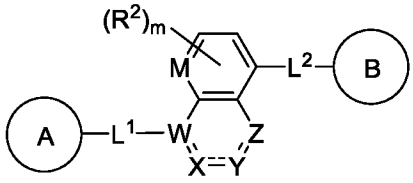
or condition. In an embodiment, treating comprises reducing, reversing, alleviating, delaying the onset of, or inhibiting the progress of a manifestation of a disease, disorder, or condition. In an embodiment, treating comprises reducing, reversing, alleviating, reducing, or delaying the onset of, an underlying cause of a disease, disorder, or condition. In some embodiments, "treatment," "treat," and "treating" require that signs or symptoms of the disease, disorder, or condition have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease or condition, e.g., in preventive treatment. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence. Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence. In some embodiments, treatment comprises prevention and in other embodiments it does not.

A "proliferative disease" refers to a disease that occurs due to abnormal extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be associated with: 1) the pathological proliferation of normally quiescent cells; 2) the pathological migration of cells from their normal location (*e.g.*, metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes such as the matrix metalloproteinases (*e.g.*, collagenases, gelatinases, and elastases); 4) the pathological angiogenesis as in proliferative retinopathy and tumor metastasis; or 5) evasion of host immune surveillance and elimination of neoplastic cells. Exemplary proliferative diseases include cancers (*i.e.*, "malignant neoplasms"), benign neoplasms, and angiogenesis.

A "non-proliferative disease" refers to a disease that does not primarily extend through the abnormal multiplication of cells. A non-proliferative disease may be associated with any cell type or tissue type in a subject. Exemplary non-proliferative diseases include neurological diseases or disorders (e.g., a repeat expansion disease); autoimmune disease or disorders; immunodeficiency diseases or disorders; lysosomal storage diseases or disorders; inflammatory diseases or disorders; cardiovascular conditions, diseases, or disorders; metabolic diseases or disorders; respiratory conditions, diseases, or disorders; renal diseases or disorders; and infectious diseases.

Compounds

The present disclosure features a compound of Formula (I):



(I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

W is N, C, or $C(R^{3a})$;

X, Y, and Z are each independently $C(R^{3a})$, $C(R^{3a})(R^{3b})$, N, $N(R^{3c})$, or O, wherein the bonds in the ring comprising W, X, Y, and Z may be single or double bonds as valency permits;

M is $C(R^2)$ or N;

L^1 and L^2 are each independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)$-, $-N(R^4)C(O)$-, or $-C(O)N(R^4)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5;

each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6; or

two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more R^6;

each R^2 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$;

$R^{3a}$and R^{3b} are each independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$; or

each of R^{3a} and R^{3b}, together with the carbon atom to which they are attached, form an oxo group;

R^{3c} is hydrogen or C_1-C_6-alkyl;

each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^5 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

each R^6 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11};

each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, or $-S(O)_xR^D$;

each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^7;

each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

each R^7 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$;

each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

each R^{A1} is hydrogen or C_1-C_6-alkyl;

m is 0, 1, or 2; and

x is 0, 1, or 2.

As generally described herein, A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1.

In some embodiments, each of A and B are independently a monocyclic ring, e.g., monocyclic cycloalkyl, monocyclic heterocyclyl, monocyclic aryl, or monocyclic heteroaryl. The monocyclic ring may be saturated, partially unsaturated, or fully unsaturated (e.g., aromatic). In some embodiments, A or B are independently a monocyclic ring comprising between 3 and 10 ring atoms (e.g., 3, 4, 5, 6, 7, 8, 9, or 10 ring atoms). In some embodiments, A is a 4-membered

monocyclic ring. In some embodiments, B is a 4-membered monocyclic ring. In some embodiments, A is a 5-membered monocyclic ring. In some embodiments, B is a 5-membered monocyclic ring. In some embodiments, A is a 6-membered monocyclic ring. In some embodiments, B is a 6-membered monocyclic ring. In some embodiments, A is a 7-membered monocyclic ring. In some embodiments, B is a 7-membered monocyclic ring. In some embodiments, A is an 8-membered monocyclic ring. In some embodiments, B is an 8-membered monocyclic ring. In some embodiments, A or B are independently a monocyclic ring optionally substituted with one or more R^1.

In some embodiments, A or B are independently a bicyclic ring, e.g., bicyclic cycloalkyl, bicyclic heterocyclyl, bicyclic aryl, or bicyclic heteroaryl. The bicyclic ring may be saturated, partially unsaturated, or fully unsaturated (e.g., aromatic). In some embodiments, A or B are independently a bicyclic ring comprising a fused, bridged, or spiro ring system. In some embodiments, A or B are independently a bicyclic ring comprising between 4 and 18 ring atoms (e.g., 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 ring atoms). In some embodiments, A is a 6-membered bicyclic ring. In some embodiments, B is a 6-membered bicyclic ring. In some embodiments, A is a 7-membered bicyclic ring. In some embodiments, B is a 7-membered bicyclic ring. In some embodiments, A is an 8-membered bicyclic ring. In some embodiments, B is an 8-membered bicyclic ring. In some embodiments, A is a 9-membered bicyclic ring. In some embodiments, B is a 9-membered bicyclic ring. In some embodiments, A is a 10-membered bicyclic ring. In some embodiments, B is a 10-membered bicyclic ring. In some embodiments, A is an 11-membered bicyclic ring. In some embodiments, B is an 11-membered bicyclic ring. In some embodiments, A is a 12-membered bicyclic ring. In some embodiments, B is a 12-membered bicyclic ring. In some embodiments, A or B are independently a bicyclic ring optionally substituted with one or more R^1.

In some embodiments, A or B are independently a tricyclic ring, e.g., tricyclic cycloalkyl, tricyclic heterocyclyl, tricyclic aryl, or tricyclic heteroaryl. The tricyclic ring may be saturated, partially unsaturated, or fully unsaturated (e.g., aromatic). In some embodiments, A or B are independently a tricyclic ring that comprises a fused, bridged, or spiro ring system, or a combination thereof. In some embodiments, A or B are independently a tricyclic ring comprising between 6 and 24 ring atoms (e.g., 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 ring atoms). In some embodiments, A is an 8-membered tricyclic ring. In

some embodiments, B is an 8-membered tricyclic ring. In some embodiments, A is a 9-membered tricyclic ring. In some embodiments, B is a 9-membered tricyclic ring. In some embodiments, A is a 10-membered tricyclic ring. In some embodiments, B is a 10-membered tricyclic ring. In some embodiments, A or B are independently a tricyclic ring optionally substituted with one or more R^1.

In some embodiments, A or B are independently monocyclic cycloalkyl, monocyclic heterocyclyl, monocyclic aryl, or monocyclic heteroaryl. In some embodiments, A or B are independently bicyclic cycloalkyl, bicyclic heterocyclyl, bicyclic aryl, or bicyclic heteroaryl. In some embodiments, A or B are independently tricyclic cycloalkyl, tricyclic heterocyclyl, tricyclic aryl, or tricyclic heteroaryl. In some embodiments, A is monocyclic heterocyclyl. In some embodiments, B is monocyclic heterocyclyl. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, B is bicyclic heterocyclyl. In some embodiments, A is monocyclic heteroaryl. In some embodiments, B is monocyclic heteroaryl. In some embodiments, A is bicyclic heteroaryl. In some embodiments, B is bicyclic heteroaryl.

In some embodiments, A or B are independently a nitrogen-containing heterocyclyl, e.g., heterocyclyl comprising one or more nitrogen atom. The one or more nitrogen atom of the nitrogen-containing heterocyclyl may be at any position of the ring. In some embodiments, the nitrogen-containing heterocyclyl is monocyclic, bicyclic, or tricyclic. In some embodiments, A or B are independently heterocyclyl comprising at least 1, at least 2, at least 3, at least 4, at least 5, or at least 6 nitrogen atoms. In some embodiments, A is heterocyclyl comprising 1 nitrogen atom. In some embodiments, B is heterocyclyl comprising 1 nitrogen atom. In some embodiments, A is heterocyclyl comprising 2 nitrogen atoms. In some embodiments, B is heterocyclyl comprising 2 nitrogen atoms. In some embodiments, A is heterocyclyl comprising 3 nitrogen atoms. In some embodiments, B is heterocyclyl comprising 3 nitrogen atoms. In some embodiments, A is heterocyclyl comprising 4 nitrogen atoms. In some embodiments, B is heterocyclyl comprising 4 nitrogen atoms. In some embodiments, A or B are independently a nitrogen-containing heterocyclyl comprising one or more additional heteroatoms, e.g., one or more of oxygen, sulfur, boron, silicon, or phosphorus. In some embodiments, the one or more nitrogen of the nitrogen-containing heterocyclyl is substituted, e.g., with R^1.

In some embodiments, A or B are independently a nitrogen-containing heteroaryl, e.g., heteroaryl comprising one or more nitrogen atom. The one or more nitrogen atom of the

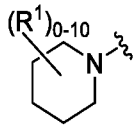
nitrogen-containing heteroaryl may be at any position of the ring. In some embodiments, the nitrogen-containing heteroaryl is monocyclic, bicyclic, or tricyclic. In some embodiments, A or B are independently heteroaryl comprising at least 1, at least 2, at least 3, at least 4, at least 5, or at least 6 nitrogen atoms. In some embodiments, A is heteroaryl comprising 1 nitrogen atom. In some embodiments, B is heteroaryl comprising 1 nitrogen atom. In some embodiments, A is heteroaryl comprising 2 nitrogen atoms. In some embodiments, B is heteroaryl comprising 2 nitrogen atoms. In some embodiments, A is heteroaryl comprising 3 nitrogen atoms. In some embodiments, B is heteroaryl comprising 3 nitrogen atoms. In some embodiments, A is heteroaryl comprising 4 nitrogen atoms. In some embodiments, B is heteroaryl comprising 4 nitrogen atoms. In some embodiments, A or B are independently a nitrogen-containing heteroaryl comprising one or more additional heteroatoms, e.g., one or more of oxygen, sulfur, boron, silicon, or phosphorus. In some embodiments, the one or more nitrogen of the nitrogen-containing heteroaryl is substituted, e.g., with R^1.

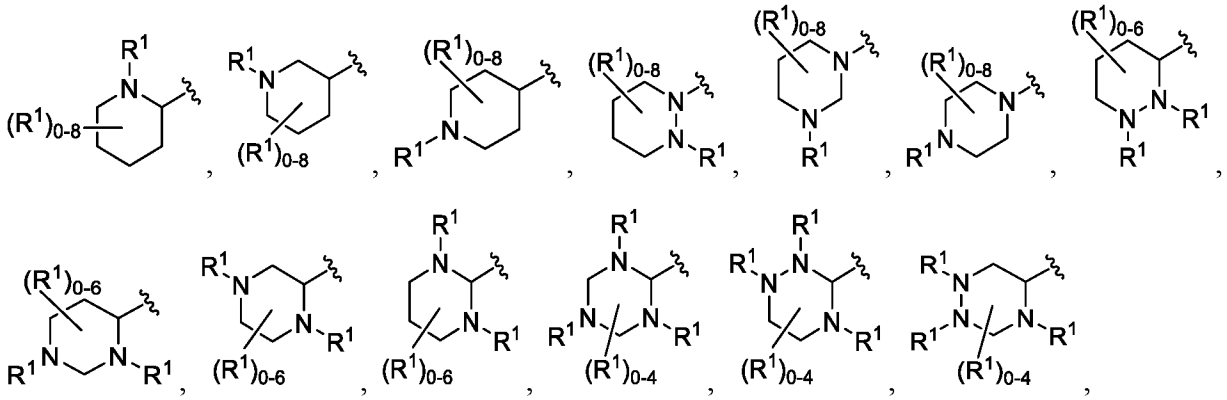
In some embodiments, A is a 6-membered nitrogen-containing heterocyclyl, e.g., a 6-membered heterocyclyl comprising one or more nitrogen. In some embodiments, A is a 6-membered heterocyclyl comprising 1 nitrogen atom. In some embodiments, A is a 6-membered heterocyclyl comprising 2 nitrogen atoms. In some embodiments, A is a 6-membered heterocyclyl comprising 3 nitrogen atoms. In some embodiments, A is a 6-membered heterocyclyl comprising 4 nitrogen atoms. The one or more nitrogen atom of the 6-membered nitrogen-containing heterocyclyl may be at any position of the ring. In some embodiments, A is a 6-membered nitrogen-containing heterocyclyl optionally substituted with one or more R^1. In some embodiments, the one or more nitrogen of the 6-membered nitrogen-containing heterocyclyl is substituted, e.g., with R^1. In some embodiments, A is a 6-membered nitrogen-containing heterocyclyl comprising one or more additional heteroatoms, e.g., one or more of oxygen, sulfur, boron, silicon, or phosphorus.

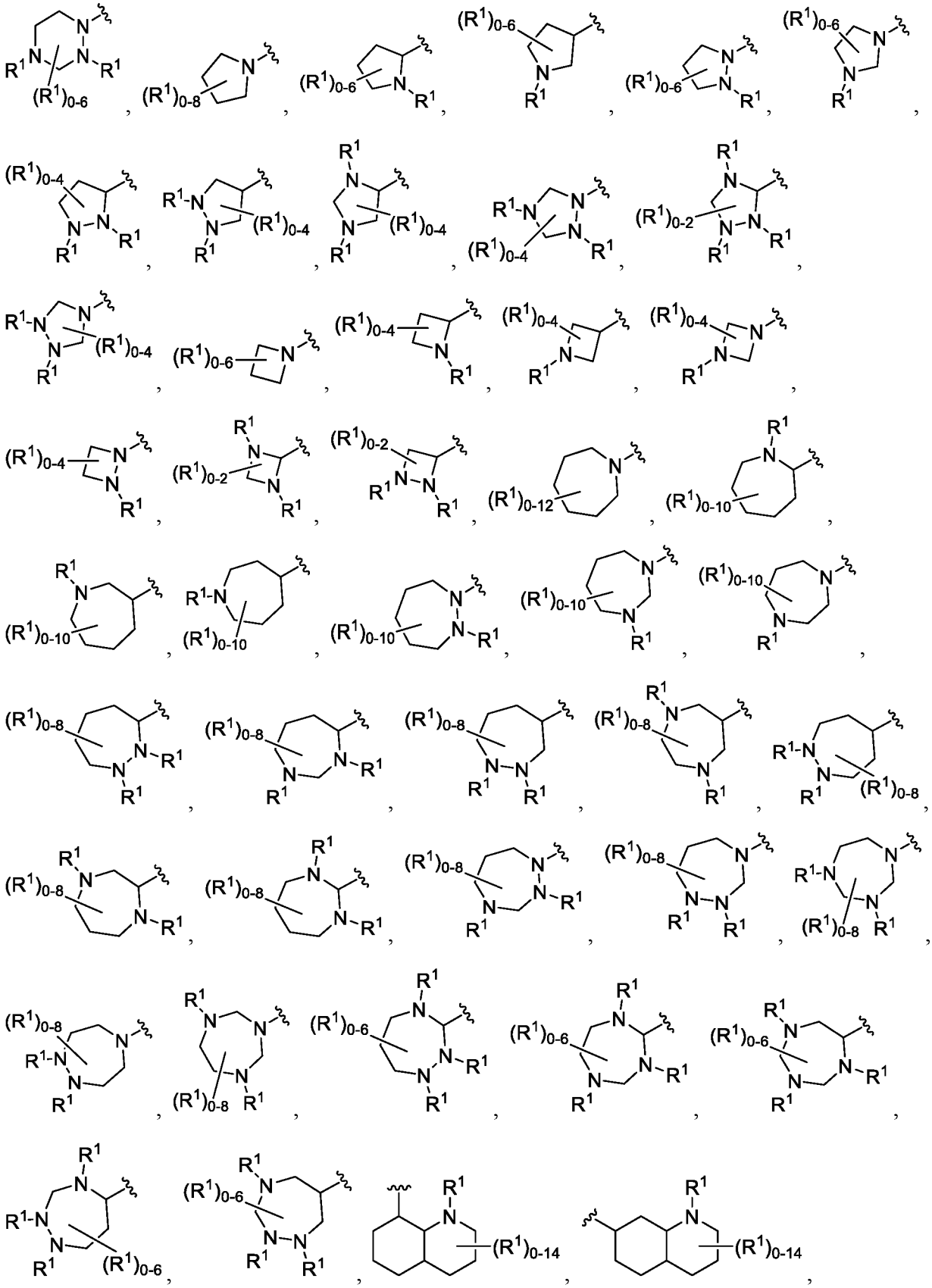
In some embodiments, B is a 5-membered nitrogen-containing heterocyclyl or heteroaryl, e.g., a 5-membered heterocyclyl or heteroaryl comprising one or more nitrogen. In some embodiments, B is a 5-membered heterocyclyl comprising 1 nitrogen atom. In some embodiments, B is a 5-membered heteroaryl comprising 1 nitrogen atom. In some embodiments, B is a 5-membered heterocyclyl comprising 2 nitrogen atoms. In some embodiments, B is a 5-membered heteroaryl comprising 2 nitrogen atoms. In some embodiments, B is a 5-membered

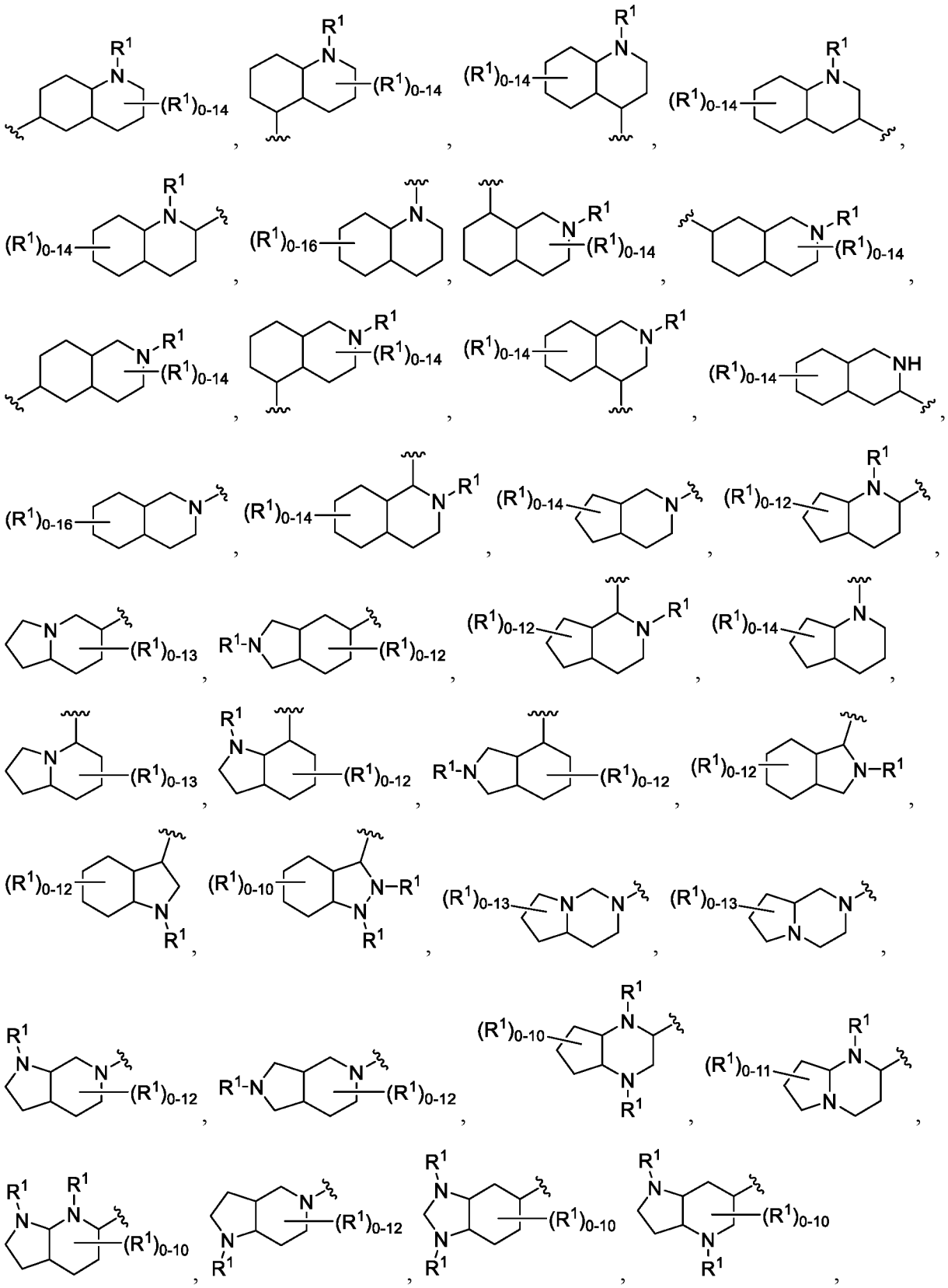
heterocyclyl comprising 3 nitrogen atoms. In some embodiments, B is a 5-membered heteroaryl comprising 3 nitrogen atoms. The one or more nitrogen atom of the 5-membered nitrogen-containing heterocyclyl or heteroaryl may be at any position of the ring. In some embodiments, B is a 5-membered nitrogen-containing heterocyclyl optionally substituted with one or more R^1. In some embodiments, B is a 5-membered nitrogen-containing heteroaryl optionally substituted with one or more R^1. In some embodiments, the one or more nitrogen of the 5-membered nitrogen-containing heterocyclyl or heteroaryl is substituted, e.g., with R^1. In some embodiments, B is a 5-membered nitrogen-containing heterocyclyl or heteroaryl comprising one or more additional heteroatoms, e.g., one or more of oxygen, sulfur, boron, silicon, or phosphorus.

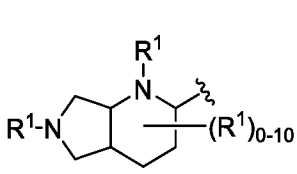
In some embodiments, B is a nitrogen-containing bicyclic heteroaryl (e.g., a 9-membered nitrogen-containing bicyclic heteroaryl), that is optionally substituted with one or more R^1. In some embodiments, B is a 9-membered bicyclic heteroaryl comprising 1 nitrogen atom. In some embodiments, B is a 9-membered bicyclic heteroaryl comprising 2 nitrogen atoms. In some embodiments, B is a 9-membered bicyclic heteroaryl comprising 3 nitrogen atoms. In some embodiments, B is a 9-membered bicyclic heteroaryl comprising 4 nitrogen atoms. The one or more nitrogen atom of the 9-membered bicyclic heteroaryl may be at any position of the ring. In some embodiments, B is a 9-membered bicyclic heteroaryl substituted with one or more R^1.

In some embodiments, each of A and B are independently selected from:  ,





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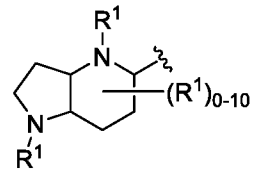
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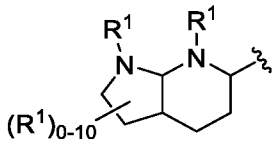
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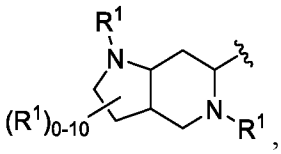
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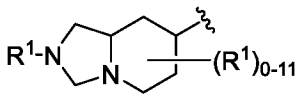
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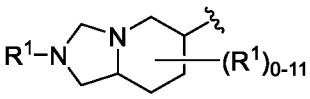
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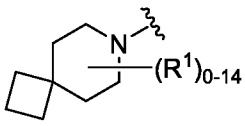
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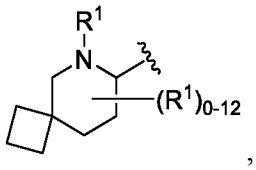
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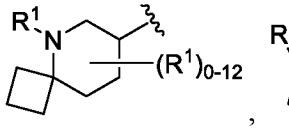
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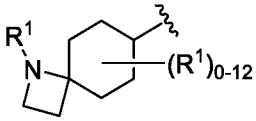
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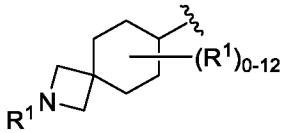
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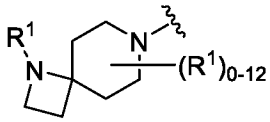
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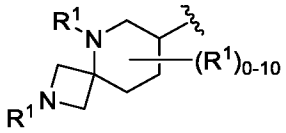
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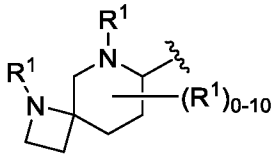
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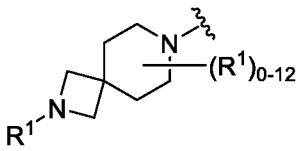
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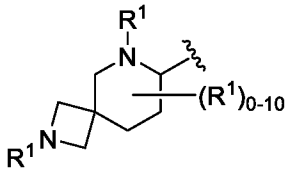
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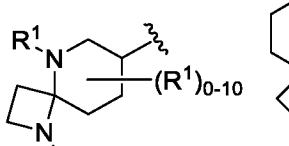
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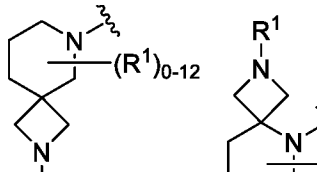
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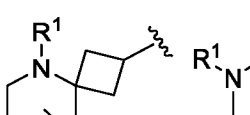
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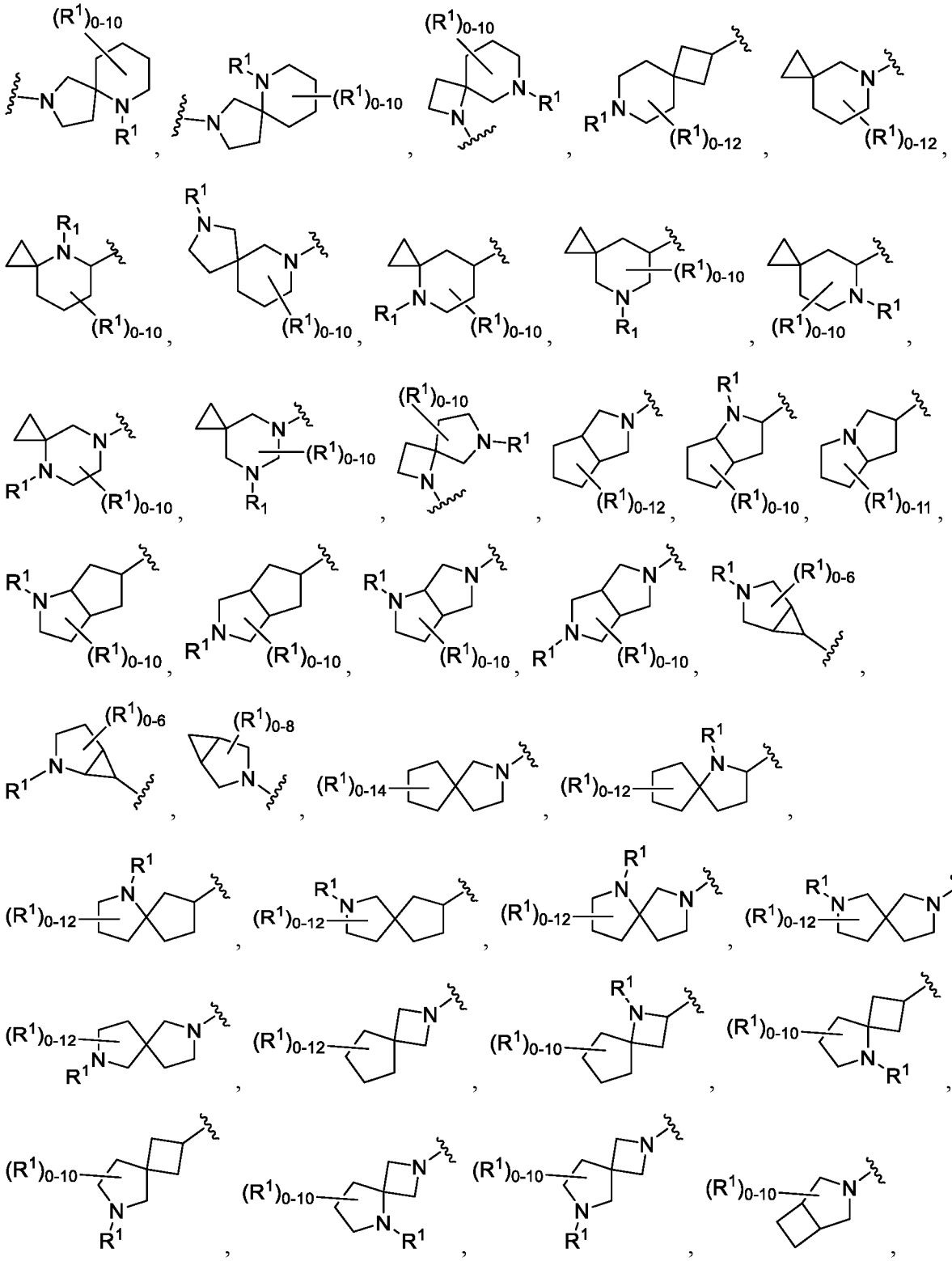
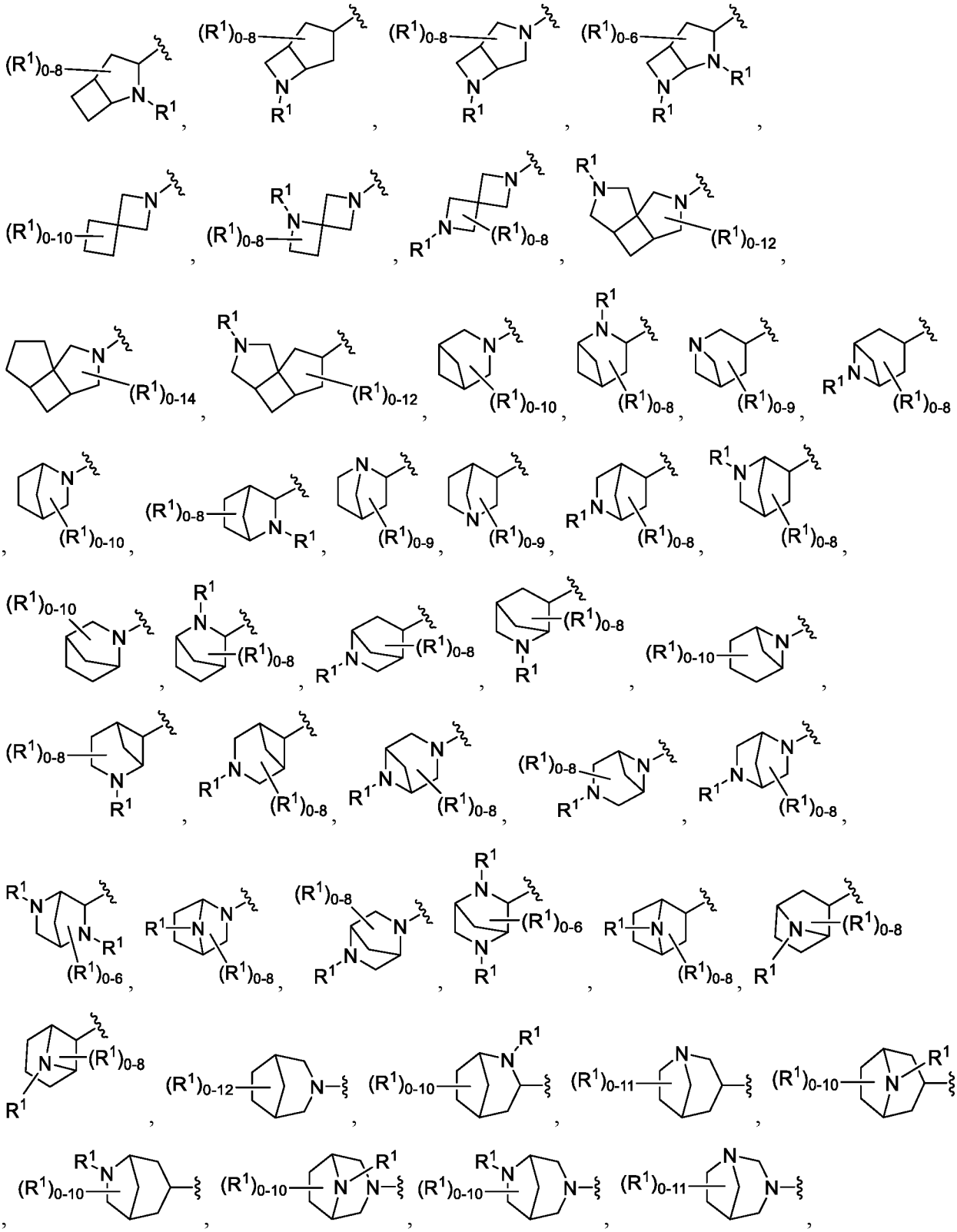
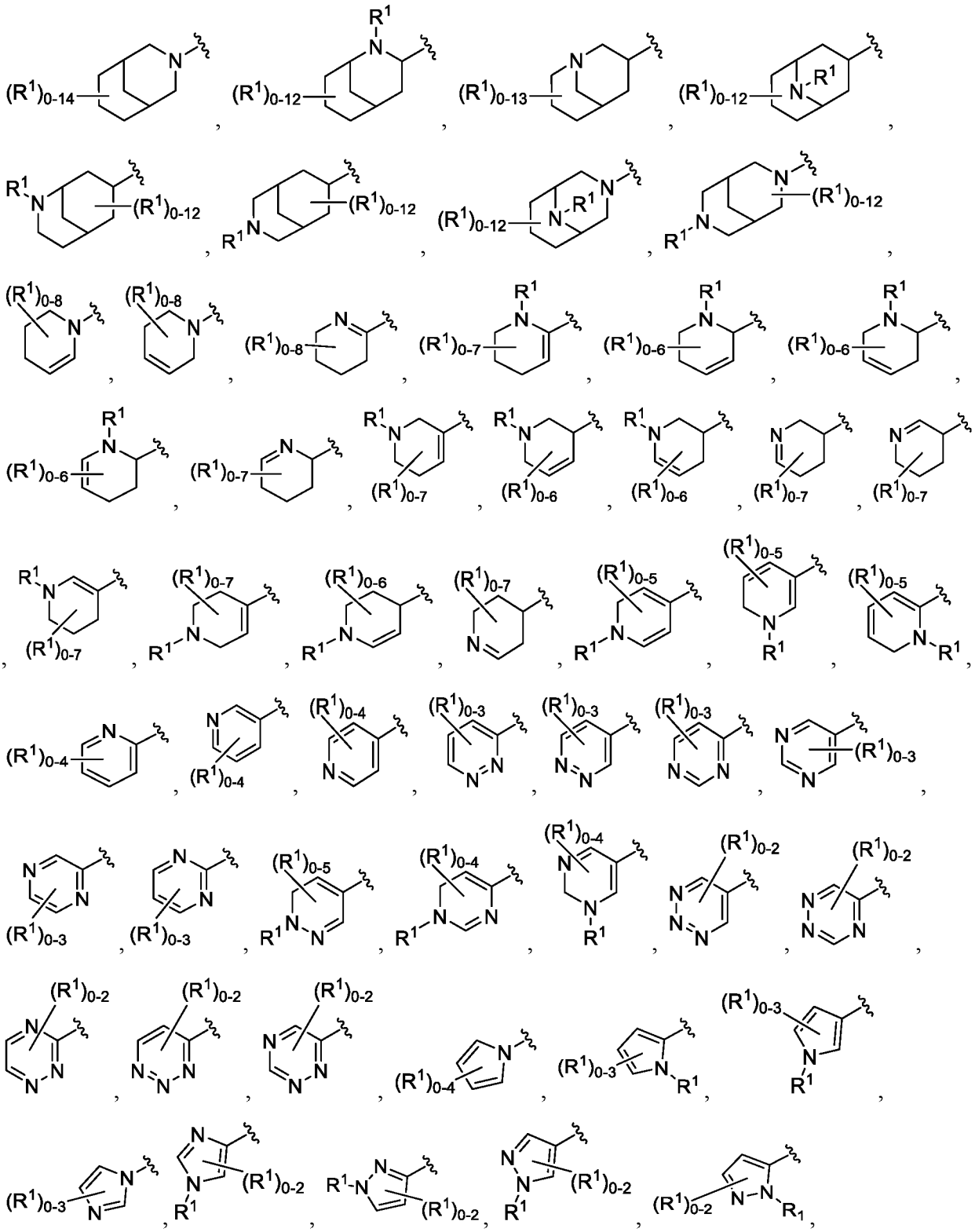
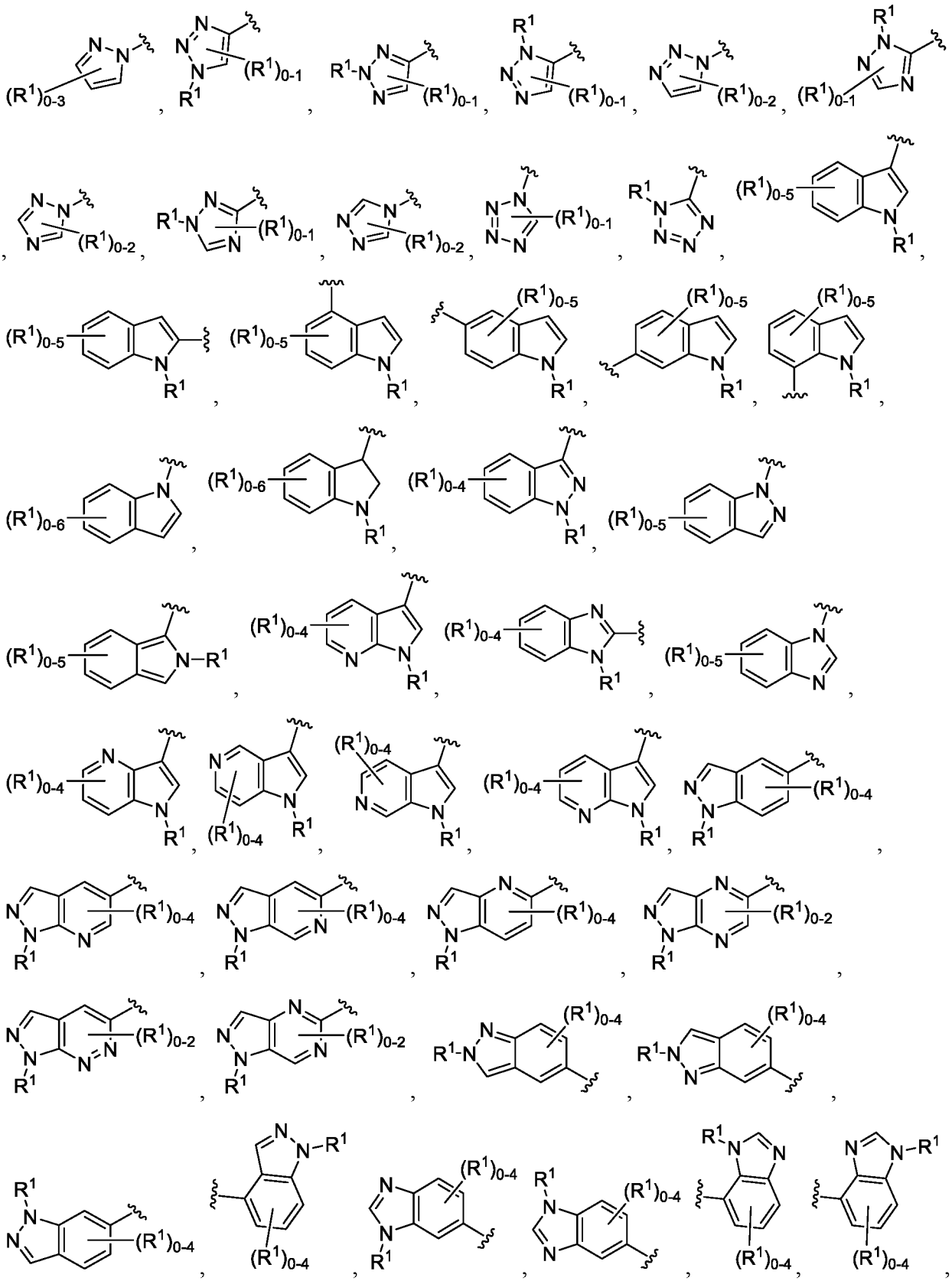
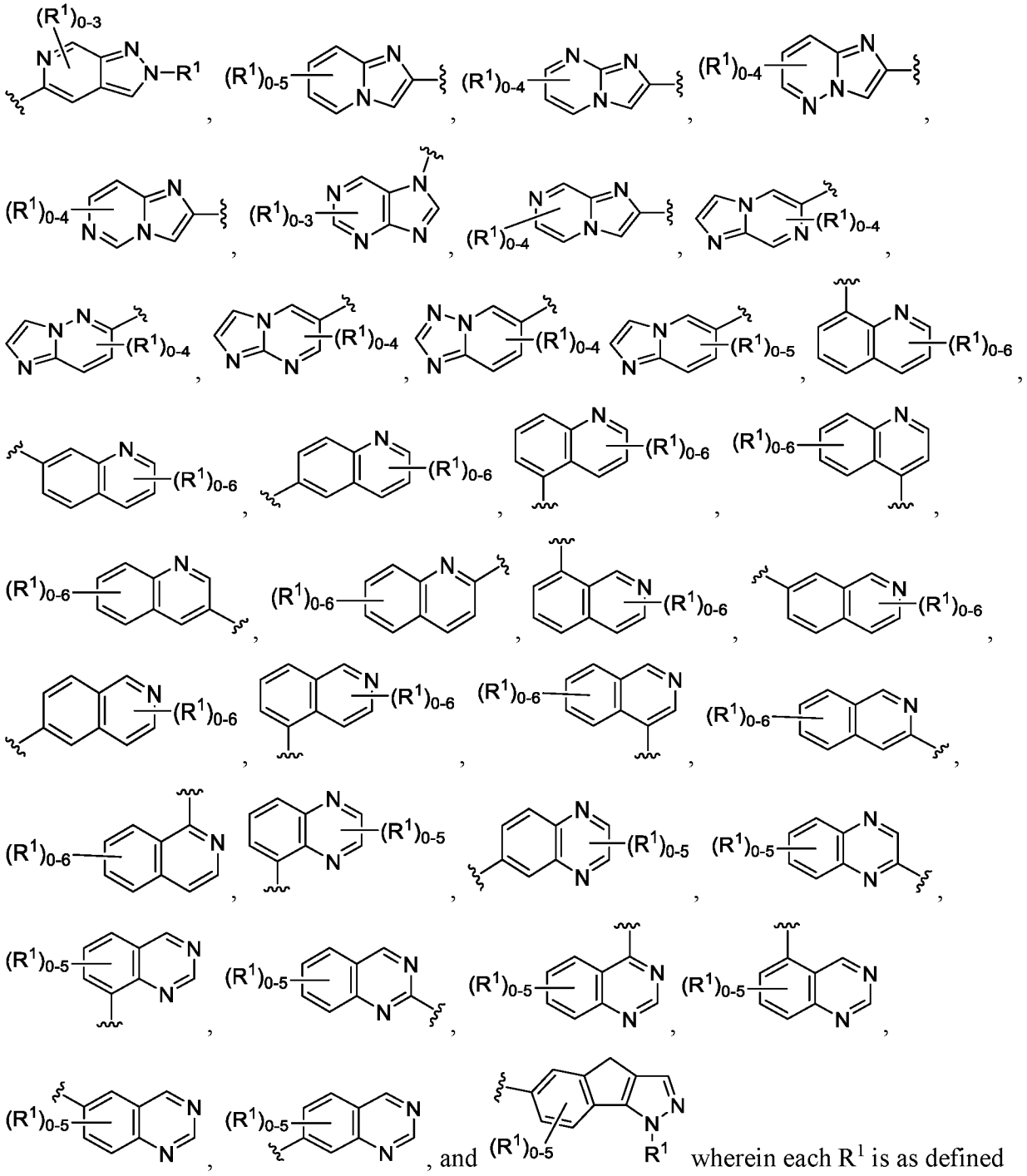


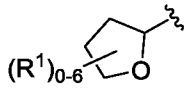


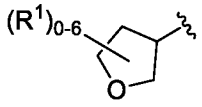
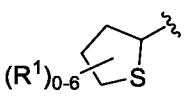
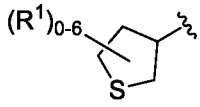
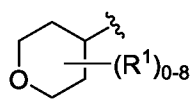
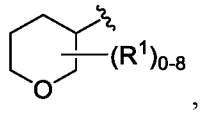


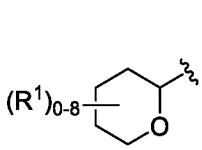
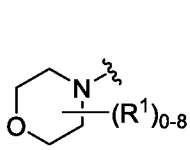
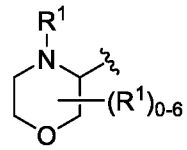
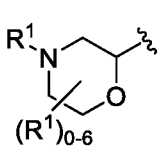
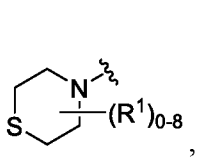
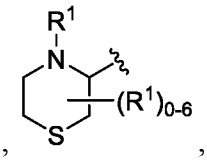


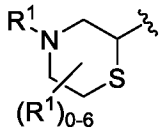
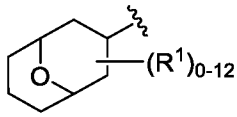
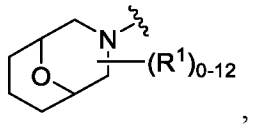
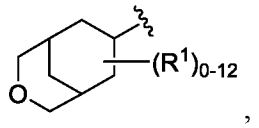
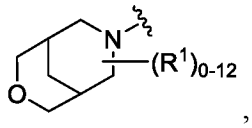


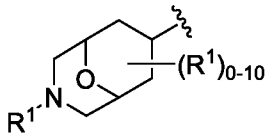
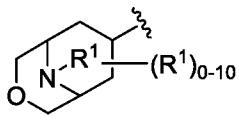
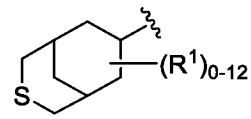
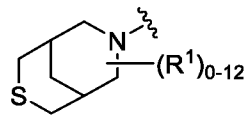
herein. In an embodiment, A and B are each independently a saturated, partially saturated, or unsaturated (e.g., aromatic) derivative of one of the rings described above. In an embodiment, A and B are each independently a stereoisomer of one of the rings described above.

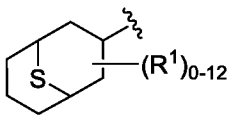
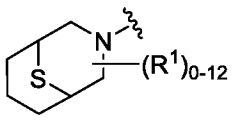
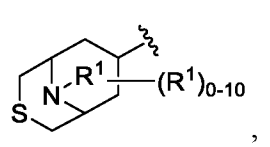
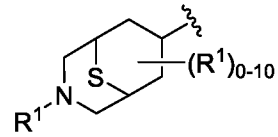
In some embodiments, each of A and B are independently selected from:  ,

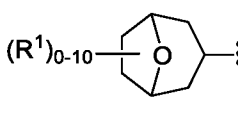
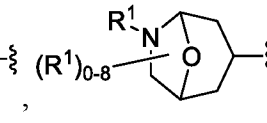
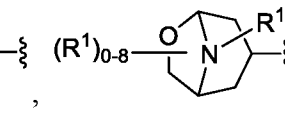
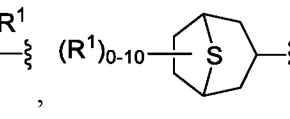
 ,  ,  ,  ,  ,

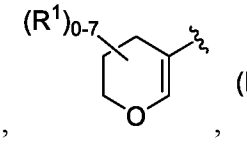
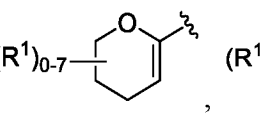
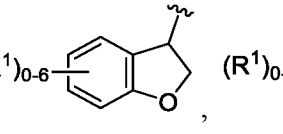
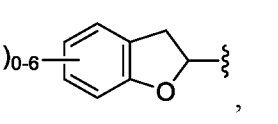
 ,  ,  ,  ,  ,  ,

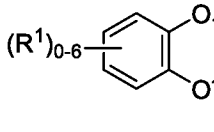
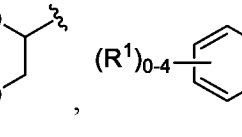
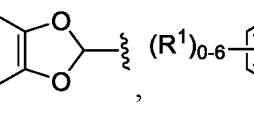
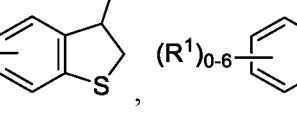
 ,  ,  ,  ,  ,

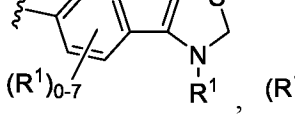
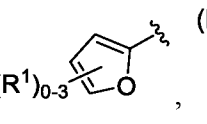
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  , ,

 ,  ,  ,  ,

 ,  , , , ,

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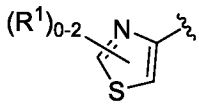
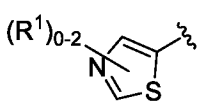
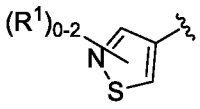
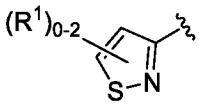
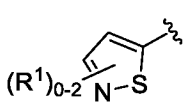
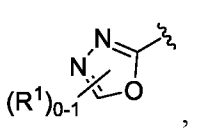
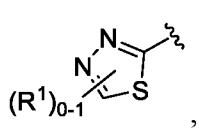
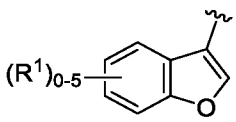
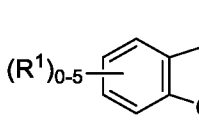
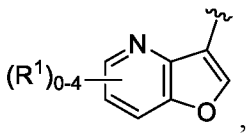
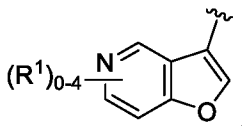
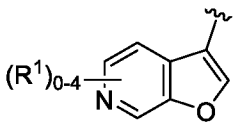
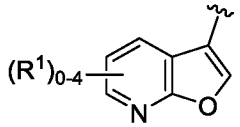
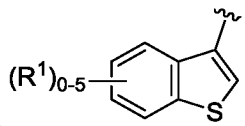
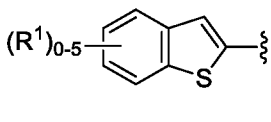
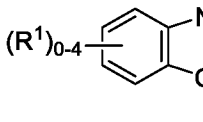
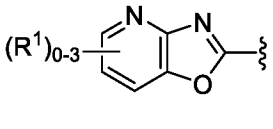
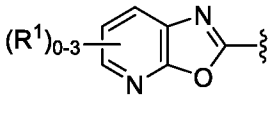
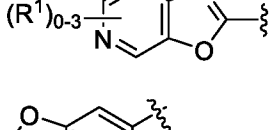
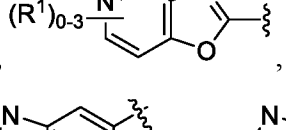
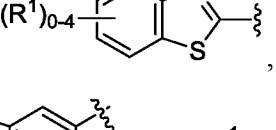
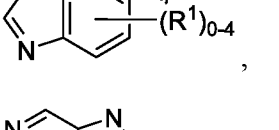
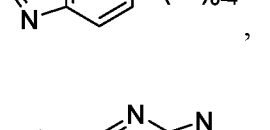
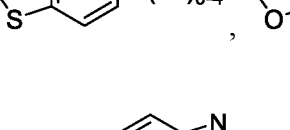
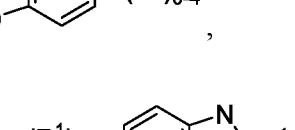
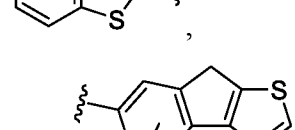
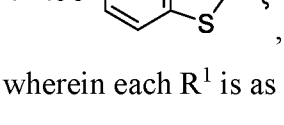
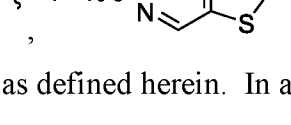
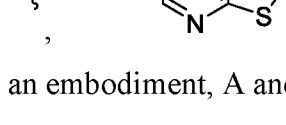
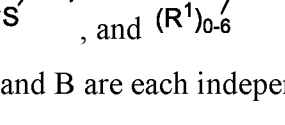
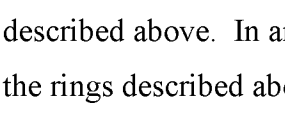
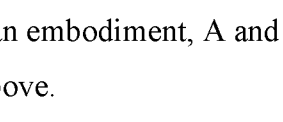
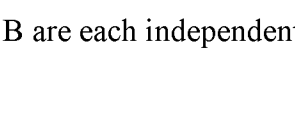
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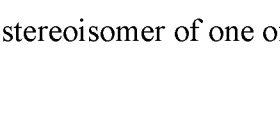
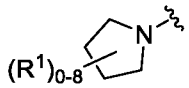
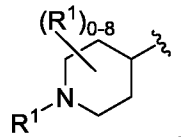
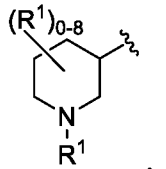
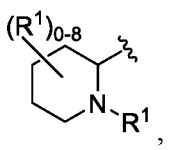
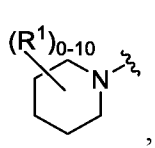
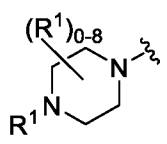
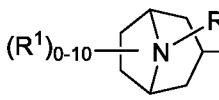
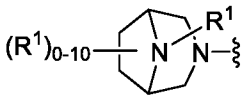
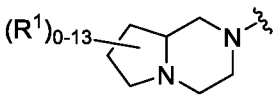
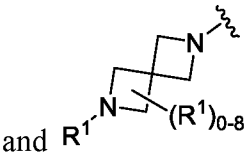
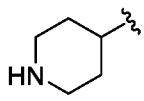
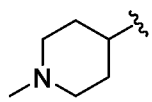
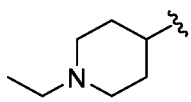
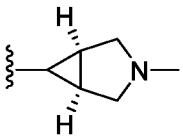
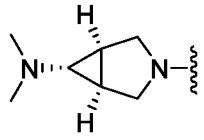
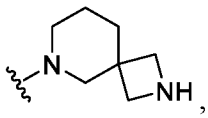
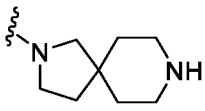
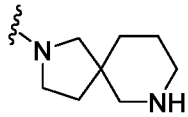
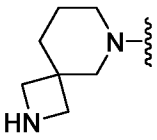


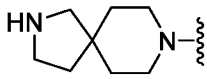
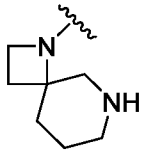
wherein each R^1 is as defined herein. In an embodiment, A and B are each independently a saturated, partially saturated, or unsaturated (e.g., aromatic) derivative of one of the rings described above. In an embodiment, A and B are each independently a stereoisomer of one of the rings described above.

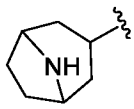
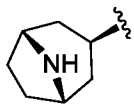
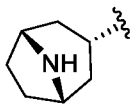
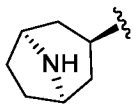
In some embodiments, A is selected from







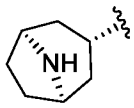
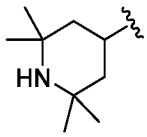
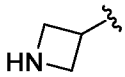
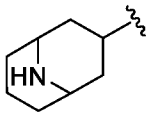
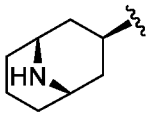
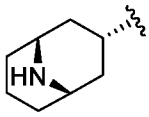
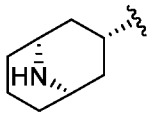



, and  , wherein R^1 is as defined herein.

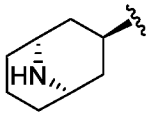
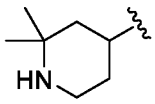
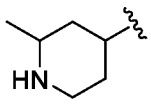
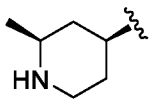
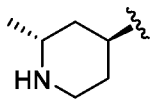
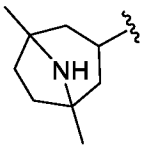
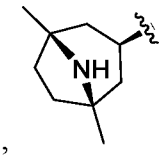
In some embodiments, A is selected from 



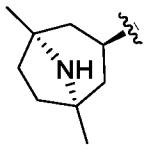
 ,  ,  ,  ,  ,  ,

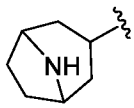
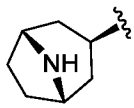
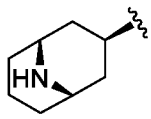
 , and  .

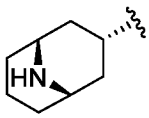
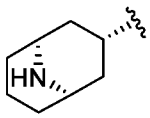
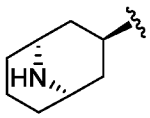
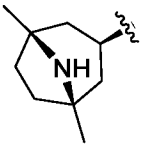
In some embodiments, A is selected from  ,  ,  ,  ,

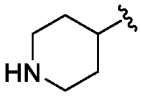
 ,  ,  ,  ,  ,  ,  ,

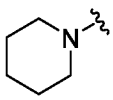
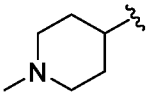
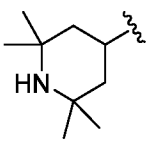
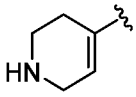
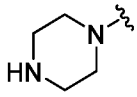
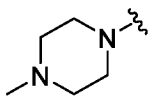
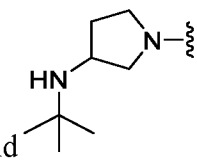
 ,  ,  ,  ,  ,  ,  , and

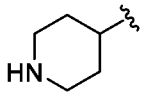
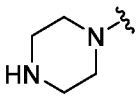
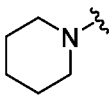
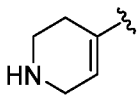
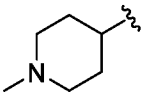
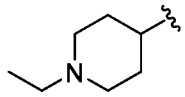
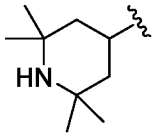
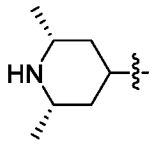
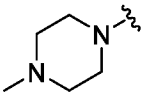
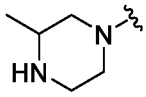
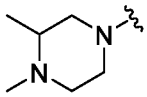
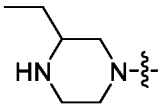
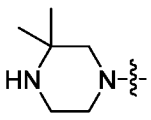
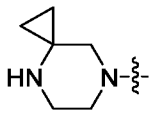
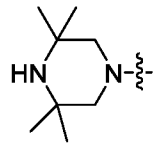
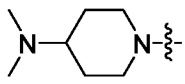
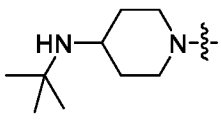
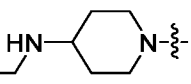
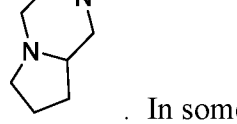
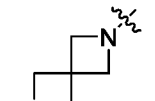
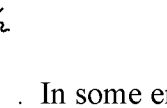
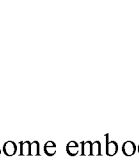
 .

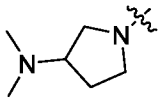
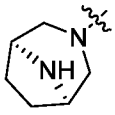
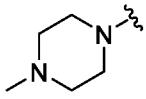
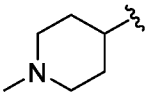
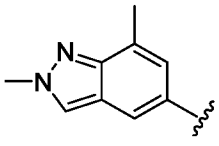
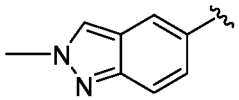
In some embodiments, A is selected from  ,  ,  ,

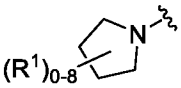
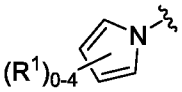
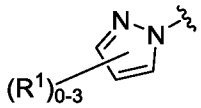
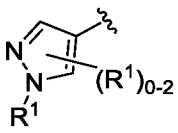
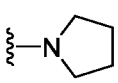
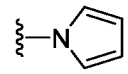
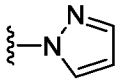
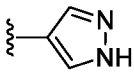
 ,  ,  , and  .

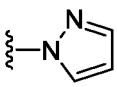
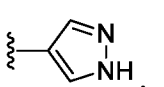
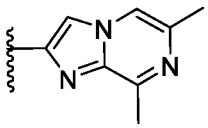
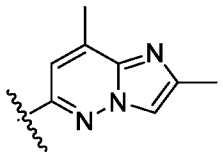
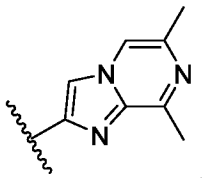
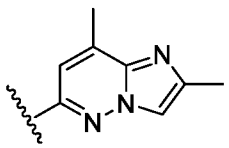
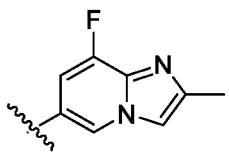
In some embodiments, A is selected from wherein A is selected from  ,

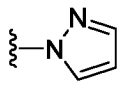
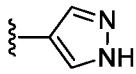
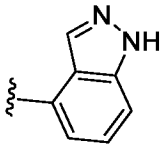
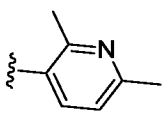
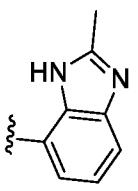
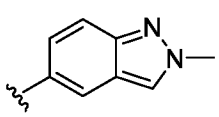
 ,  ,  ,  ,  ,  , and  .

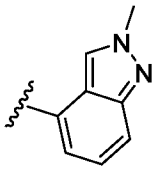
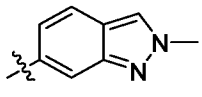
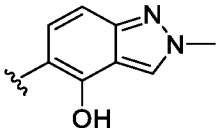
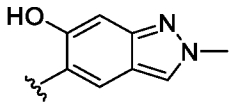
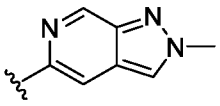
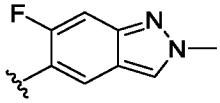
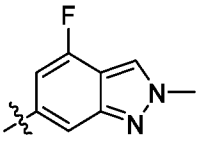
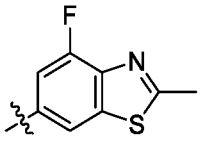
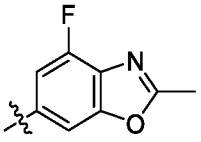
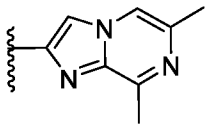
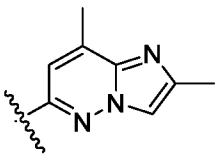
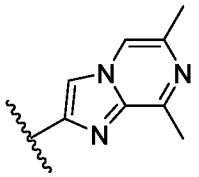
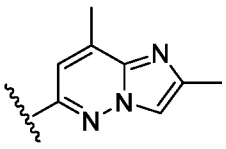
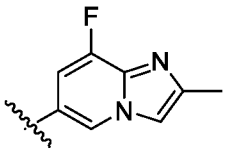
In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is

 . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  . In some embodiments, A is  .

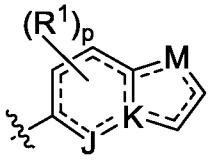
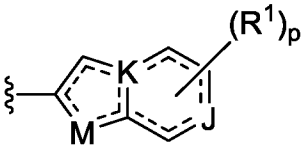
In some embodiments, B is selected from  ,  ,  ,  , wherein R^1 is as defined herein. In some embodiments, B is selected from  ,  ,  , and  .

In some embodiments, B is selected from  ,  ,  ,  ,  ,  , and  .

In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  .

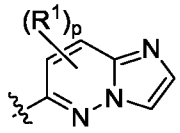
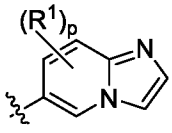
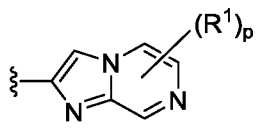
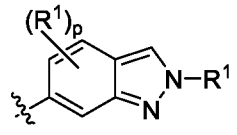
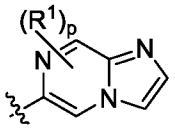
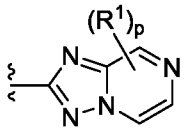
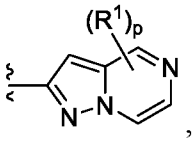
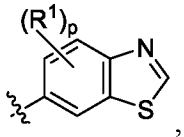
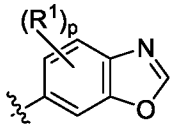
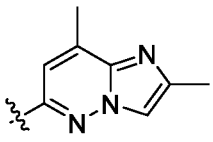
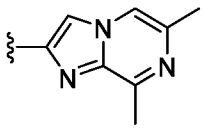
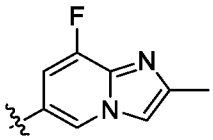
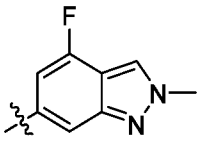
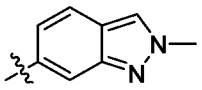
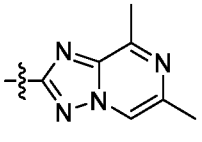
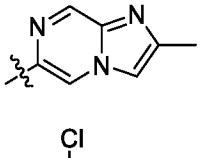
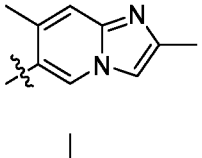
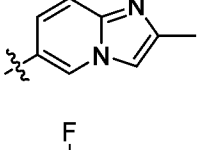
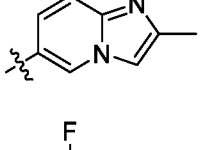
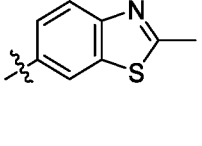
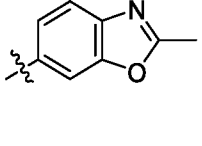
embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is selected is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  .

In some embodiments, B is a structure of Formula (A) or Formula (B):

 (A) or  (B),

wherein each of J, K, and M is selected from N and C(R'); R^1 is as defined above; R' is hydrogen, halo (e.g., fluoro), or C_1-C_6-alkyl (e.g., methyl); and p is 0, 1, 2, 3, or 4; wherein at least one of J, K, and M is N; and the bonds in the ring comprising J, K, and M may be single or double bonds as valency permits.

In some embodiments, J, K, and M are each independently N. In some embodiments, J is C(R') and K and M are each independently M. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2. In some embodiments, p is 3. In some embodiments, p is 4.

In some embodiments, B is selected from  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is . In some embodiments, B is .

As generally described herein, L^1 and L^2 each independently may be absent or refer to a C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)- group, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5.

In some embodiments, L^1 is absent. In some embodiments, L^1 is C_1-C_6-alkylene (e.g., C_1-alkylene, C_2-alkylene, C_3-alkylene, C_4-alkylene, C_5-alkylene, or C_6-alkylene). In some embodiments, L^1 is unsubstituted C_1-C_6 alkylene. In some embodiments, L^1 is substituted C_1-C_6-alkylene, e.g., C_1-C_6 alkylene substituted with one or more R^5. In some embodiments, L^1 is C_1-alkylene substituted with one R^5. In some embodiments, L^1 is -CH_2- (or methylene). In some embodiments, L^1 is -C(O)- (or carbonyl).

In some embodiments, L^1 is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5.

In some embodiments, L^1 is C_1-C_6 heteroalkylene (e.g., C_1-heteroalkylene, C_2-heteroalkylene, C_3-heteroalkylene, C_4-heteroalkylene, C_5-heteroalkylene, or C_6-heteroalkylene). In some embodiments, L^1 is unsubstituted C_1-C_6 heteroalkylene. In some embodiments, L^1 is substituted heteroalkylene, e.g., C_1-C_6 heteroalkylene substituted with one or more R^5. In some embodiments, the heteroalkylene comprises 1 or more heteroatoms. In some embodiments, the heteroalkylene comprises one or more of oxygen, sulfur, nitrogen, boron, silicon, or phosphorus. In some embodiments, L^1 is -N(R^4)C(O)-. In some embodiments, L^1 is -C(O)N(R^4)-. In some embodiments, L^1 is -C(O)N(H)-.

In some embodiments, L^1 is oxygen. In some embodiments, L^1 is nitrogen which is optionally substituted with R^4. In some embodiments, L^1 is nitrogen substituted with R^4. In some embodiments, L^1 is -N(R^4)-, e.g., -N(CH_3)-. In some embodiments, L^1 is -NH-. In some embodiments, L^1 is -O-.

In some embodiments, L^2 is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5. In some embodiments, L^2 is unsubstituted C_1-C_6 heteroalkylene. In some embodiments, L^2 is substituted heteroalkylene, e.g., C_1-C_6 heteroalkylene substituted with one or more R^5. In some embodiments, the heteroalkylene comprises 1 or more heteroatoms. In some embodiments, the heteroalkylene comprises one or more of oxygen, sulfur, nitrogen, boron,

silicon, or phosphorus. In some embodiments, L^2 is -N(R^4)C(O)-. In some embodiments, L^2 is -C(O)N(R^4)-. In some embodiments, L^2 is -C(O)N(H)-.

In some embodiments, L^2 is nitrogen which is optionally substituted with R^4. In some embodiments, L^2 is nitrogen substituted with R^4. In some embodiments, L^2 is -N(R^4)-, e.g., -N(CH_3)-. In some embodiments, L^2 is -NH-.

As generally described herein, W refers to N, C, or (CR^{3a}) (e.g., CH). In some embodiments, W is N. In some embodiments, W is C. In some embodiments, W is (R^{3a}).

As generally described herein, X, Y, and Z each independently refer to C(R^{3a}), C(R^{3a})(R^{3b}), N, N(R^{3c}), or O. In some embodiments, at least one of X, Y, and Z is N, N(R^{3c}), or O. In some embodiments, at least one of X, Y, and Z is N or N(R^{3c}). In some embodiments, at least two of X, Y, and Z is N or N(R^{3c}). In some embodiments, X is N. In some embodiments, X is N(R^{3c}). In some embodiments, X is C(R^{3a})(R^{3b}) (e.g., C(O)). In some embodiments, X is C(R^{3a}) (e.g., CH). In some embodiments, Y is N. In some embodiments, Y is C(R^{3a}) (e.g., CH). In some embodiments, Y is C(R^{3a})(R^{3b}) (e.g., C(O)). In some embodiments, Z is N. In some embodiments, Z is C(R^{3a}) (e.g., CH). In some embodiments, Z is N(R^{3c}) (e.g., NH). In some embodiments, two of X, Y, and Z are N, and the other of X, Y, and Z is C(R^{3a}) (e.g., CH). In some embodiments, one of X, Y, and Z is C(R^{3a}) (e.g., CH), and the others of X, Y, and Z are each independently N. In some embodiments, X and Y are each independently N, and Z is C(R^{3a}) (e.g., CH). In some embodiments, X is C(R^{3a}) (e.g., CH), and Y and Z are each independently N. In some embodiments, X is C(R^{3a}) (e.g., CH), Y is C(R^{3a})(R^{3b}) (e.g., C(O)), and Z is C(R^{3c}) (e.g., NH). In some embodiments, X is CH, Y is C(O), and Z is NH. In some embodiments, X is C(R^{3a})(R^{3b}) (e.g., C(O)), and Y and Z are each independently C(R^{3a}) (e.g., CH). In some embodiments, X is C(O), and Y and Z are each independently CH.

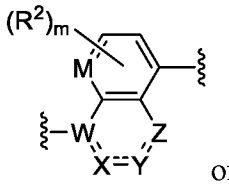
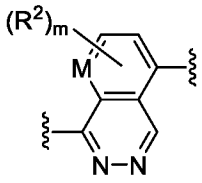
In some embodiments, X, Y, and Z are each independently N or C(R^{3a}), wherein at least one of X, Y, and Z is N and the bonds in the ring comprising X, Y, and Z may be single or double bonds as valency permits.

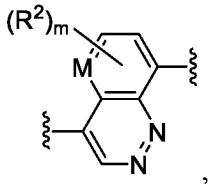
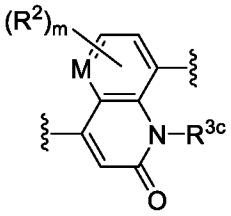
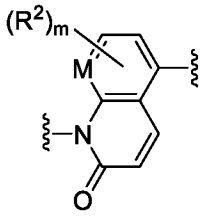
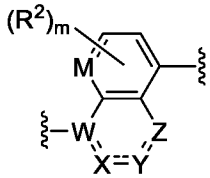
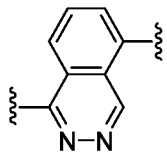
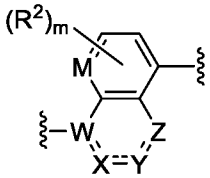
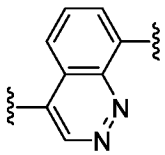
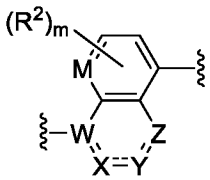
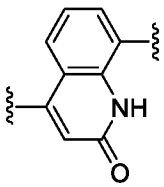
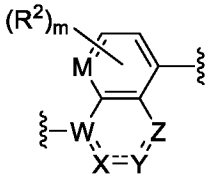
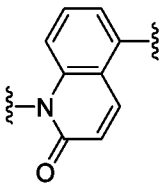
In some embodiments, W is N and X is C(R^{3a})(R^{3b}) (e.g., C(O)). In some embodiments, W is N and X is C(O). In some embodiments, W is N, X is C(R^{3a})(R^{3b}) (e.g., C(O)), and the bond between W and X is a single bond. In some embodiments, W is C and X is C(R^{3a}) (e.g., CH). In some embodiments, W is C and X is CH. In some embodiments, W is C, X is C(R^{3a}) (e.g., CH), and the bond between W and X is a double bond. In some embodiments, W is C, X is C(R^{3a})

(e.g., CH), and each of Y and Z are independently $C(R^{3a})(R^{3b})$ (e.g., C(O)) or $N(R^{3c})$. In some embodiments, W is C, X is $C(R^{3a})$ (e.g., CH), Y is $C(R^{3a})(R^{3b})$ (e.g., C(O)), and Z is $N(R^{3c})$. In some embodiments, W is C, X is $C(R^{3a})$ (e.g., CH), and the bond between Y and Z is a single bond. In some embodiments, W is N, X is $C(R^{3a})(R^{3b})$ (e.g., C(O)), and Y and Z are each independently $C(R^{3a})$ (e.g., CH). In some embodiments, W is N, X is $C(R^{3a})(R^{3b})$ (e.g., C(O)), the bond between Y and Z is a double bond.

In some embodiments, W is N and each of X, Y, and Z is independently $C(R^{3a})(R^{3b})$ (e.g., C(O) or CH). In some embodiments, X is CO and each of Y and Z is independently CH.

As generally described herein, M refers to $C(R^2)$ or N. In some embodiments, M is $C(R^2)$ (e.g., CH). In some embodiments, M is CH. In some embodiments, M is N.

In some embodiments,  of Formula (I) is selected from 

 ,  , and  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  .

In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_1-C_6-alkyl. In some embodiments, R^1 is C_2-C_6-alkenyl. In some embodiments, R^1 is C_2-C_6-alkynyl. In some embodiments, R^1 is C_1-C_6-heteroalkyl. In some embodiments, R^1 is C_1-C_6-haloalkyl (e.g., -CF_3). In some embodiments, R^1 is C_1-alkyl (e.g., methyl). In some embodiments, R^1 is unsubstituted C_1-C_6-alkyl, unsubstituted C_2-C_6-alkenyl, unsubstituted C_2-C_6-alkynyl, unsubstituted C_1-C_6-heteroalkyl, or unsubstituted C_1-C_6-haloalkyl. In some embodiments, R^1 is C_1-C_6-alkyl substituted with one or more R^6. In some embodiments, R^1 is C_2-C_6-alkenyl substituted with one or more R^6. In some embodiments, R^1 is C_2-C_6-alkynyl substituted with one or more R^6. In some embodiments, R^1 is C_1-C_6-heteroalkyl substituted with one or more R^6. In some embodiments, R^1 is C_1-C_6-haloalkyl substituted with one or more R^6. In some embodiments, R^1 is methyl.

In some embodiments, R^1 is cycloalkyl (e.g., 3-7 membered cycloalkyl). In some embodiments, R^1 is heterocyclyl (e.g., 3-7 membered heterocyclyl). In some embodiments, R^1 is aryl. In some embodiments, R^1 is C_1-C_6 alkylene-aryl (e.g., benzyl). In some embodiments, R^1 is C_1-C_6 alkenylene-aryl. In some embodiments, R^1 is C_1-C_6 alkylene-heteroaryl. In some embodiments, R^1 is heteroaryl. In some embodiments, R^1 is unsubstituted cycloalkyl, unsubstituted heterocyclyl, unsubstituted aryl, unsubstituted C_1-C_6 alkylene-aryl, unsubstituted C_1-C_6 alkenylene-aryl, unsubstituted C_1-C_6 alkylene-heteroaryl, or unsubstituted heteroaryl. In some embodiments, R^1 is cycloalkyl substituted with one or more R^6. In some embodiments, R^1 is heterocyclyl substituted with one or more R^6. In some embodiments, R^1 is aryl substituted with one or more R^6. In some embodiments, R^1 is C_1-C_6 alkylene-aryl substituted with one or more R^6. In some embodiments, R^1 is C_1-C_6 alkenylene-aryl substituted with one or more R^6. In some embodiments, R^1 is C_1-C_6 alkylene-heteroaryl substituted with one or more R^6. In some embodiments, R^1 is heteroaryl substituted with one or more R^6.

In some embodiments, R^1 is $-OR^A$. In some embodiments, R^1 is $-NR^BR^C$ (e.g., NH_2 or NMe_2). In some embodiments, R^1 is $-NR^BC(O)R^D$. In some embodiments, R^1 is$-C(O)NR^BR^C$. In some embodiments, R^1 is $-C(O)R^D$. In some embodiments, R^1 is $-C(O)OR^D$. In some embodiments, R^1 is$-SR^E$. In some embodiments, R^1 is $-S(O)_xR^D$. In some embodiments, R^1 is halo, e.g., fluoro, chloro, bromo, or iodo. In some embodiments, R^1 is cyano. In some embodiments, R^1 is nitro (-NO_2). In some embodiments, R^1 is oxo.

In some embodiments, two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl. In some embodiments, two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered heterocyclyl. In some embodiments, two R^1 groups, together with the atoms to which they are attached, form a 5- or 6-membered aryl. In some embodiments, two R^1 groups, together with the atoms to which they are attached, form a 5- or 6-membered heteroaryl. The cycloalkyl, heterocyclyl, aryl, or heteroaryl may be substituted with one or more R^6.

In some embodiments, R^2 is hydrogen. In some embodiments, R^2 is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^2 is cyano. In some embodiments, R^2 is C_1-C_6-alkyl. In some embodiments, R^2 is C_2-C_6-alkenyl. In some embodiments, R^2 is C_2-C_6-alkynyl. In some embodiments, R^2 is $-OR^A$ (e.g., –OH).

In some embodiments, R^{3a}, R^{3b}, or both are independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$. In some embodiments, R^{3a} and R^{3b} are each independently hydrogen or C_1-C_6-alkyl. In some embodiments, R^{3a} is hydrogen. In some embodiments, R^{3b} is hydrogen. In some embodiments, R^{3a} is C_1-C_6-alkyl (e.g., methyl). In some embodiments, R^{3b} is C_1-C_6-alkyl (e.g., methyl). In some embodiments, R^{3a} is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^{3b} is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^{3a} is cyano. In some embodiments, R^{3b} is cyano. In some embodiments, R^{3a} is $-OR^A$ (e.g., –OH). In some embodiments, R^{3b} is $-OR^A$ (e.g., –OH). In some embodiments, R^{3a} is $-NR^BR^C$. In some embodiments, R^{3b} is $-NR^BR^C$. In some embodiments, R^{3a} is $-C(O)R^D$. In some embodiments, R^{3b} is $-C(O)R^D$. In some embodiments, R^{3a} is $-C(O)OR^D$. In some embodiments, R^{3b} is $-C(O)OR^D$. In some embodiments, each of R^{3a} and R^{3b}, together with the carbon atom to which they are attached, form an oxo group.

In some embodiments, R^{3c} is hydrogen. In some embodiments, R^{3c} is C_1-C_6-alkyl. In some embodiments, R^{3c} is methyl.

In some embodiments, R^4 is hydrogen. In some embodiments, R^4 is C_1-C_6 alkyl. In some embodiments, R^4 is C_1-C_6 haloalkyl (e.g., $-CF_3$ or $-CHF_2$). In some embodiments, R^4 is methyl.

In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is C_1-C_6-alkyl. In some embodiments, R^5 is C_1-C_6-heteroalkyl. In some embodiments, R^5 is C_1-C_6-haloalkyl. In

some embodiments, R^5 is cycloalkyl. In some embodiments, R^5 is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^5 is cyano. In some embodiments, R^5 is oxo. In some embodiments, R^5 is $-OR^A$. In some embodiments, R^5 is $-NR^BR^C$. In some embodiments, R^5 is $-C(O)R^D$ or $-C(O)OR^D$.

In some embodiments, R^6 is C_1-C_6-alkyl. In some embodiments, R^6 is C_2-C_6-alkenyl. In some embodiments, R^6 is C_2-C_6-alkynyl. In some embodiments, R^6 is C_1-C_6-heteroalkyl. In some embodiments, R^6 is C_1-C_6-haloalkyl. In some embodiments, R^6 is unsubstituted C_1-C_6-alkyl, unsubstituted C_2-C_6-alkenyl, unsubstituted C_2-C_6-alkynyl, unsubstituted C_1-C_6-haloalkyl, or unsubstituted C_1-C_6-heteroalkyl. In some embodiments, R^6 is C_1-C_6-alkyl substituted with one or more R^{11}. In some embodiments, R^6 is C_2-C_6-alkenyl substituted with one or more R^{11}. In some embodiments, R^6 is C_2-C_6-alkynyl substituted with one or more R^{11}. In some embodiments, R^6 is C_1-C_6-haloalkyl substituted with one or more R^{11}. In some embodiments, R^6 is C_1-C_6-heteroalkyl substituted with one or more R^{11}.

In some embodiments, R^6 is cycloalkyl. In some embodiments, R^6 is heterocyclyl. In some embodiments, R^6 is aryl. In some embodiments, R^6 is heteroaryl. In some embodiments, R^6 is unsubstituted cycloalkyl, unsubstituted heterocyclyl, unsubstituted aryl, or unsubstituted heteroaryl. In some embodiments, R^6 is cycloalkyl substituted with one or more R^{11}. In some embodiments, R^6 is heterocyclyl substituted with one or more R^{11}. In some embodiments, R^6 is aryl substituted with one or more R^{11}. In some embodiments, R^6 is heteroaryl substituted with one or more R^{11}.

In some embodiments, R^6 is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^6 is cyano. In some embodiments, R^6 is oxo. In some embodiments, R^6 is $-OR^A$. In some embodiments, R^6 is $-NR^BR^C$. In some embodiments, R^6 is $-NR^BC(O)R^D$. In some embodiments, R^6 is $-NO_2$. In some embodiments, R^6 is $-C(O)NR^BR^C$. In some embodiments, R^6 is $-C(O)R^D$. In some embodiments, R^6 is $-C(O)OR^D$. In some embodiments, R^6 is $-SR^E$. In some embodiments, R^6 is $-S(O)_xR^D$.

In some embodiments, R^7 is C_1-C_6-alkyl. In some embodiments, R^7 is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^7 is cyano. In some embodiments, R^7 is oxo. In some embodiments, R^7 is $-OR^{A1}$ (e.g., –OH).

In some embodiments, R^{11} is C_1-C_6-alkyl. In some embodiments, R^{11} is C_1-C_6-heteroalkyl. In some embodiments, R^{11} is C_1-C_6-haloalkyl (e.g., $-CF_3$). In some embodiments,

R^{11} is cycloalkyl. In some embodiments, R^{11} is heterocyclyl. In some embodiments, R^{11} is aryl. In some embodiments, R^{11} is heteroaryl. In some embodiments, R^{11} is halo. In some embodiments, R^{11} is cyano. In some embodiments, R^{11} is oxo. In some embodiments, R^{11} is $-OR^A$.

In some embodiments, R^A is hydrogen. In some embodiments, R^A is C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^A is C_1-C_6 haloalkyl. In some embodiments, R^A is aryl. In some embodiments, R^A is heteroaryl. In some embodiments, R^A is C_1-C_6 alkylene-aryl (e.g., benzyl). In some embodiments, R^A is C_1-C_6 alkylene-heteroaryl. In some embodiments, R^A is $C(O)R^D$. In some embodiments, R^A is $-S(O)_xR^D$.

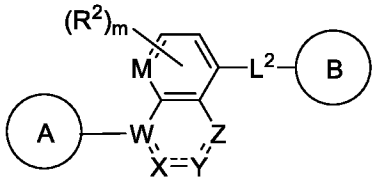
In some embodiments, R^B, R^C, or both are independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$. In some embodiments, each of R^B and R^C is independently hydrogen. In some embodiments, each of R^B and R^C is independently C_1-C_6 alkyl. In some embodiments, one of R^B and R^C is hydrogen, and the other of R^B and R^C is C_1-C_6 alkyl. In some embodiments, R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more of R^7.

In some embodiments, R^D, R^E, or both are independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl (e.g., benzyl), or C_1-C_6 alkylene-heteroaryl. In some embodiments, each of R^D and R^E is independently hydrogen. In some embodiments, each of R^D and R^E is independently C_1-C_6 alkyl. In some embodiments, R^D is hydrogen. In some embodiments, R^E is hydrogen. In some embodiments, R^D is C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^E is C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^D is C_1-C_6 heteroalkyl. In some embodiments, R^E is C_1-C_6 heteroalkyl. In some embodiments, R^D is C_1-C_6 haloalkyl. In some embodiments, R^E is C_1-C_6 haloalkyl. In some embodiments, R^D is cycloalkyl. In some embodiments, R^E is cycloalkyl. In some embodiments, R^D is heterocyclyl. In some embodiments, R^E is heterocyclyl. In some embodiments, R^D is aryl. In some embodiments, R^E is aryl. In some embodiments, R^D is heteroaryl. In some embodiments, R^E is heteroaryl. In some embodiments, R^D is C_1-C_6 alkylene-aryl (e.g., benzyl). In some embodiments, R^E is C_1-C_6 alkylene-aryl (e.g., benzyl). In some embodiments, R^D is C_1-C_6 alkylene-heteroaryl. In some embodiments, R^E is C_1-C_6 alkylene-heteroaryl.

In some embodiments, R^{A1} is hydrogen. In some embodiments, R^{A1} is C_1-C_6-alkyl (e.g., methyl).

In some embodiments, m is 0, 1, or 2. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, x is 0, 1, or 2). In some embodiments, x is 0. In some embodiments, x is 1. In some embodiments, x is 2.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-a):



(I-a), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

W is N, C, or $C(R^{3a})$;

X, Y, and Z are each independently $C(R^{3a})$, $C(R^{3a})(R^{3b})$, N, or $N(R^{3c})$, or O, wherein at least one of X, Y, and Z is N, $N(R^{3c})$, or O, and the bonds in the ring comprising W, X, Y, and Z may be single or double bonds as valency permits;

M is $C(R^2)$ or N;

L^2 is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)$-, $-N(R^4)C(O)$-, or $-C(O)N(R^4)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5;

each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6; or

two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more R^6;

each R^2 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$;

$R^{3a}$and R^{3b} are each independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$; or

each of R^{3a} and R^{3b}, together with the carbon atom to which they are attached, form an oxo group;

R^{3c} is hydrogen or C_1-C_6-alkyl;

each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^5 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

each R^6 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11};

each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, or $-S(O)_xR^D$;

each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^7;

each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

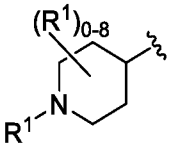
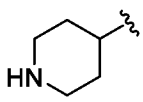
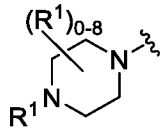
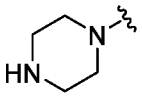
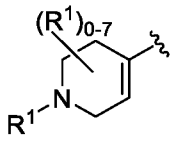
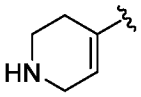
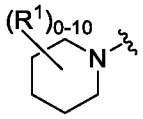
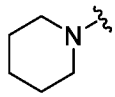
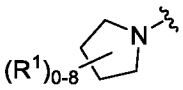
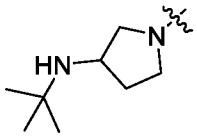
each R^7 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$;

each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

each R^{A1} is hydrogen or C_1-C_6-alkyl;

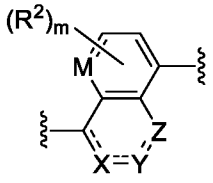
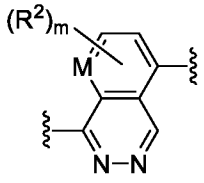
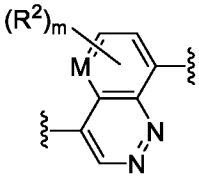
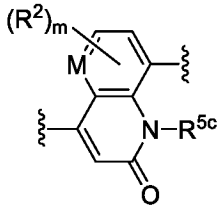
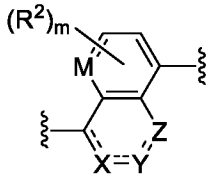
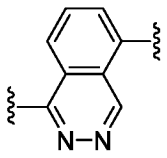
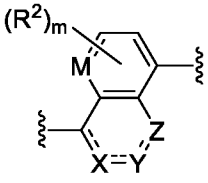
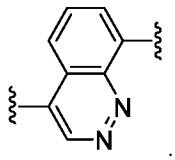
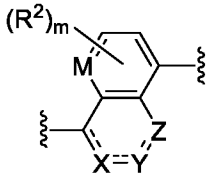
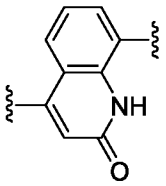
m is 0, 1, or 2; and

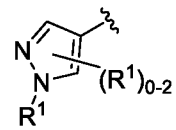
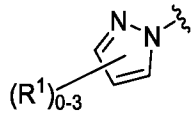
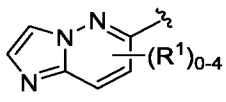
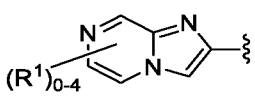
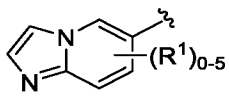
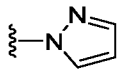
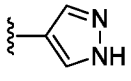
x is 0, 1, or 2.

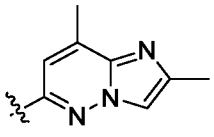
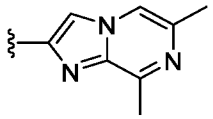
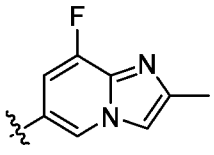
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl. In some embodiments, A is optionally substituted piperidinyl. In some embodiments, A is optionally substituted piperazinyl. In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen, C_1-C_6-alkyl, or $-NR^BR^C$, and wherein each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen, C_1-C_6-alkyl, or $-NR^BR^C$, and wherein each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl. In some embodiments, A is  .

In some embodiments, L^2 is absent. In some embodiments, L^2 is C_1-C_6-heteroalkylene, that is optionally substituted with one or more R^5. In some embodiments, L^2 is $-C(O)N(R^4)-$. In some embodiments, L^2 is $-C(O)N(H)-$.

In some embodiments, M is C(R^2) (e.g., CH). In some embodiments, M is CH. In some embodiments, M is N. In some embodiments, X is N, Y is N, and Z is C(R^{3a}). In some embodiments, X is C(R^{3a}), Y is N, and Z is N. In some embodiments, X is C(R^{3a}), Y is C(R^{3a})(R^{3b}), and Z is N(R^{3c}) (e.g., NH).

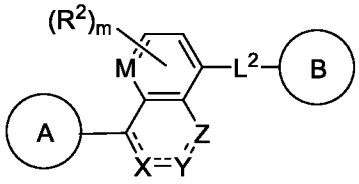
In some embodiments,  is selected from  ,  ,  , and  . In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  .

In some embodiments, B is heteroaryl optionally substituted with one or more R^1. In some embodiments, B is monocyclic heteroaryl. In some embodiments, B is bicyclic heteroaryl. In some embodiments, B is monocyclic nitrogen-containing heteroaryl. In some embodiments, B is bicyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is selected from  ,  ,  ,  , and  wherein each R^1 is as defined above. In some embodiments, B is  . In some embodiments, B is  . In some

embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  .

In some embodiments, R^2 is C_1-C_6-alkyl. In some embodiments, R^2 is halo (e.g., fluoro). In some embodiments, R^2 is $-OR^A$ (e.g., –OH). In some embodiments, m is 0.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-b):



(I-b)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

X, Y, and Z are each independently $C(R^{3a})$, $C(R^{3a})(R^{3b})$, N, or $N(R^{3c})$, wherein at least one of X, Y, and Z is N, or $N(R^{3c})$, and the bonds in the ring comprising X, Y, and Z may be single or double bonds as valency permits;

M is $C(R^2)$ or N;

L^2 is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)$-, $-N(R^4)C(O)$-, or $-C(O)N(R^4)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5;

each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6; or

two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more R^6;

each R^2 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$;

$R^{3a}$and R^{3b} are each independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$; or

each of R^{3a} and R^{3b}, together with the carbon atom to which they are attached, form an oxo group;

R^{3c} is hydrogen or C_1-C_6-alkyl;

each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^5 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

each R^6 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11};

each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, or $-S(O)_xR^D$;

each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^7;

each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

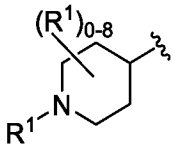
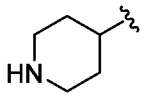
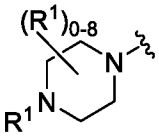
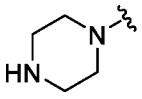
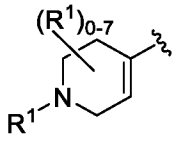
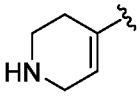
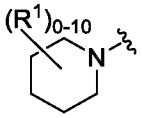
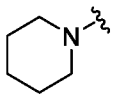
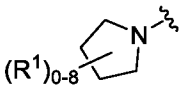
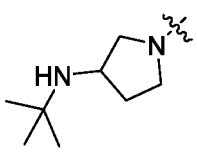
each R^7 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$;

each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

each R^{A1} is hydrogen or C_1-C_6-alkyl;

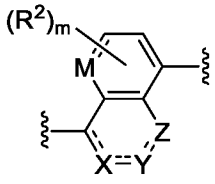
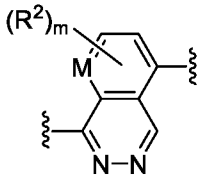
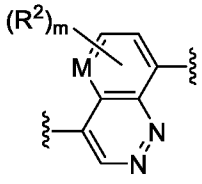
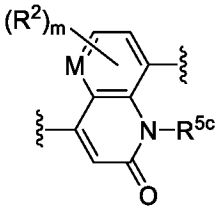
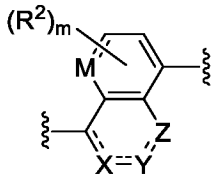
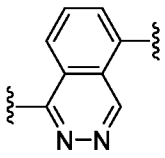
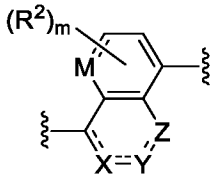
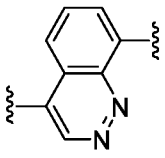
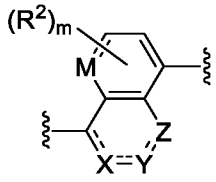
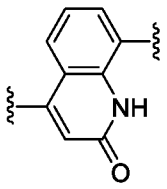
m is 0, 1, or 2; and

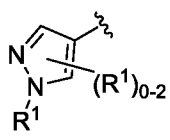
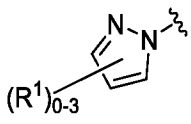
x is 0, 1, or 2.

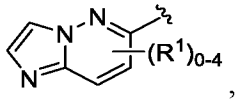
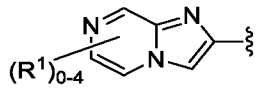
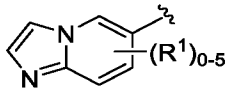
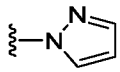
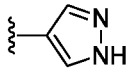
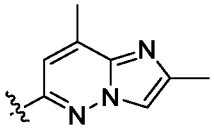
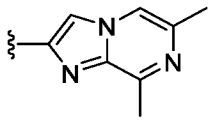
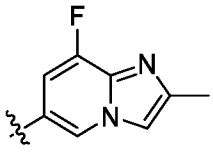
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl. In some embodiments, A is optionally substituted piperidinyl. In some embodiments, A is optionally substituted piperazinyl. In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen, C_1-C_6-alkyl, or $-NR^BR^C$, and wherein each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen, C_1-C_6-alkyl, or $-NR^BR^C$, and wherein each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl. In some embodiments, A is  .

In some embodiments, L^2 is absent. In some embodiments, L^2 is C_1-C_6-heteroalkylene, that is optionally substituted with one or more R^5. In some embodiments, L^2 is -C(O)N(R^4)-. In some embodiments, L^2 is -C(O)N(H)-.

In some embodiments, M is C(R^2) (e.g., CH). In some embodiments, M is CH. In some embodiments, M is N. In some embodiments, X is N, Y is N, and Z is C(R^{3a}). In some embodiments, X is C(R^{3a}), Y is N, and Z is N. In some embodiments, X is C(R^{3a}), Y is C(R^{3a})(R^{3b}), and Z is N(R^{3c}) (e.g., NH).

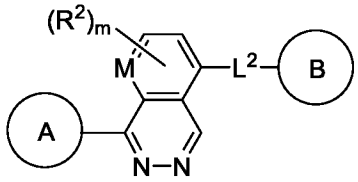
In some embodiments,  is selected from  ,  ,  and  . In some embodiments,  is . In some embodiments,  is  . In some embodiments,  is  .

In some embodiments, B is heteroaryl optionally substituted with one or more R^1. In some embodiments, B is monocyclic heteroaryl. In some embodiments, B is bicyclic heteroaryl. In some embodiments, B is monocyclic nitrogen-containing heteroaryl. In some embodiments, B is bicyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is selected from  ,  ,

 ,  , and  wherein each R^1 is as defined above. In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  .

In some embodiments, R^2 is C_1-C_6-alkyl. In some embodiments, R^2 is halo (e.g., fluoro). In some embodiments, R^2 is $-OR^A$ (e.g., –OH). In some embodiments, m is 0.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-c):



(I-c),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

M is $C(R^2)$ or N;

L^2 is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)-$, $-N(R^4)C(O)-$, or $-C(O)N(R^4)-$, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5;

each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6; or

two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6;

each R^2 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$;

each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^5 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

each R^6 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11};

each R^7 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$;

each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, or $-S(O)_xR^D$;

each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^7;

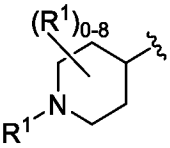
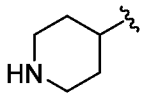
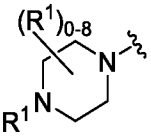
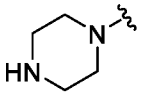
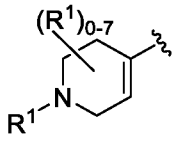
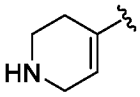
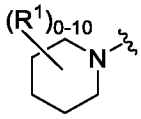
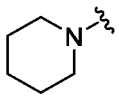
each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

each R^{A1} is hydrogen or C_1-C_6-alkyl;

m is 0, 1, or 2; and

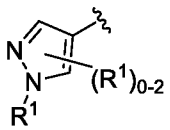
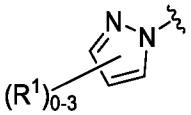
x is 0, 1, or 2.

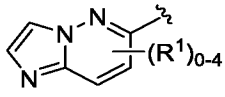
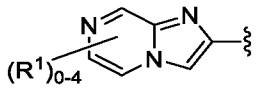
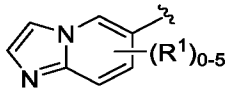
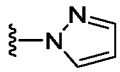
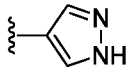
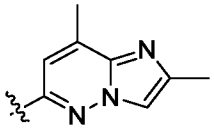
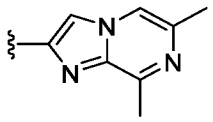
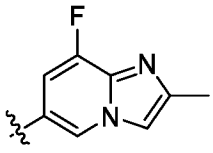
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing

heterocyclyl. In some embodiments, A is optionally substituted piperidinyl. In some embodiments, A is optionally substituted piperazinyl. In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen, C_1-C_6-alkyl, or $-NR^BR^C$, and wherein each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl. In some embodiments, A is  .

In some embodiments, L^2 is absent. In some embodiments, L^2 is C_1-C_6-heteroalkylene, that is optionally substituted with one or more R^5. In some embodiments, L^2 is -C(O)N(R^4)-. In some embodiments, L^2 is -C(O)N(H)-.

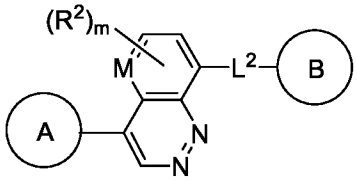
In some embodiments, M is C(R^2) (e.g., CH). In some embodiments, M is CH. In some embodiments, M is N.

In some embodiments, B is heteroaryl optionally substituted with one or more R^1. In some embodiments, B is monocyclic heteroaryl. In some embodiments, B is bicyclic heteroaryl. In some embodiments, B is monocyclic nitrogen-containing heteroaryl. In some embodiments, B is bicyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is selected from  ,  ,

 ,  , and  wherein each R^1 is as defined above. In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  .

In some embodiments, R^2 is C_1-C_6-alkyl. In some embodiments, R^2 is halo (e.g., fluoro). In some embodiments, R^2 is $-OR^A$ (e.g., –OH). In some embodiments, m is 0.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-d):



(I-d)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

M is $C(R^2)$ or N;

L^2 is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)$-, $-N(R^4)C(O)$-, or $-C(O)N(R^4)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5;

each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6; or

two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more R^6;

each R^2 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$;

each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^5 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

each R^6 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11};

each R^7 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$;

each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, or $-S(O)_xR^D$;

each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^7;

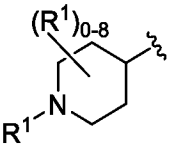
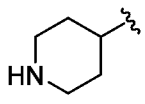
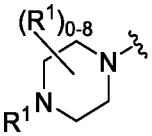
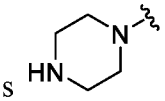
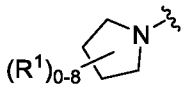
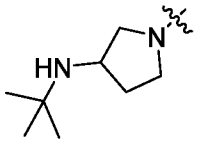
each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

each R^{A1} is hydrogen or C_1-C_6-alkyl;

m is 0, 1, or 2; and

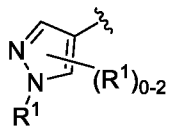
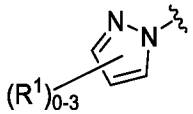
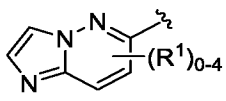
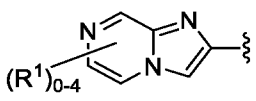
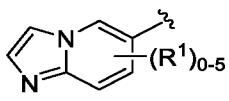
x is 0, 1, or 2.

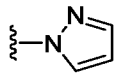
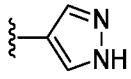
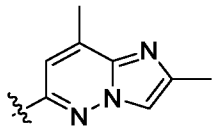
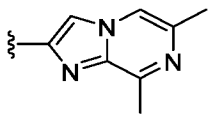
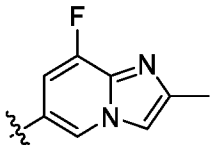
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing

heterocyclyl. In some embodiments, A is optionally substituted piperidinyl. In some embodiments, A is optionally substituted piperazinyl. In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen, C_1-C_6-alkyl, or $-NR^BR^C$, and wherein each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl. In some embodiments, A is  .

In some embodiments, L^2 is absent. In some embodiments, L^2 is C_1-C_6-heteroalkylene, that is optionally substituted with one or more R^5. In some embodiments, L^2 is -C(O)N(R^4)-. In some embodiments, L^2 is -C(O)N(H)-.

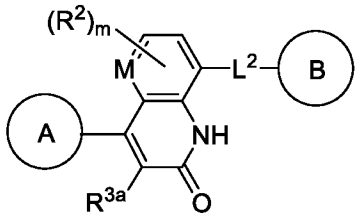
In some embodiments, M is C(R^2) (e.g., CH). In some embodiments, M is CH. In some embodiments, M is N.

In some embodiments, B is heteroaryl optionally substituted with one or more R^1. In some embodiments, B is monocyclic heteroaryl. In some embodiments, B is bicyclic heteroaryl. In some embodiments, B is monocyclic nitrogen-containing heteroaryl. In some embodiments, B is bicyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is selected from  ,  ,  ,  , and  wherein each R^1 is as defined

above. In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  .

In some embodiments, R^2 is C_1-C_6-alkyl. In some embodiments, R^2 is halo (e.g., fluoro). In some embodiments, R^2 is $-OR^A$ (e.g., –OH). In some embodiments, m is 0.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-e):



(I-e)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

M is $C(R^2)$ or N;

L^2 is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)$-, $-N(R^4)C(O)$-, or $-C(O)N(R^4)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5;

each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6; or

two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more R^6;

each R^2 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$;

R^{3a} is hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

R^{3c} is hydrogen or C_1-C_6-alkyl;

each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^5 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

each R^6 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11};

each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, or $-S(O)_xR^D$;

each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^7;

each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

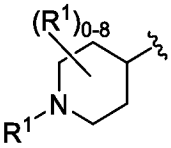
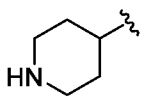
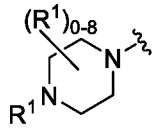
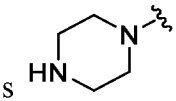
each R^7 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$;

each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

each R^{A1} is hydrogen or C_1-C_6-alkyl;

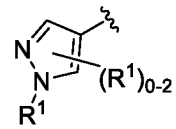
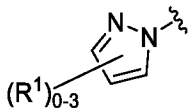
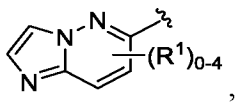
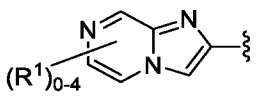
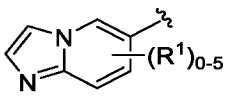
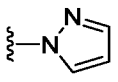
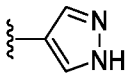
m is 0, 1, or 2; and

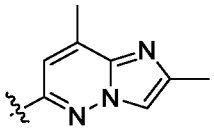
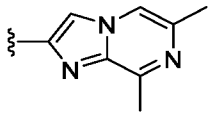
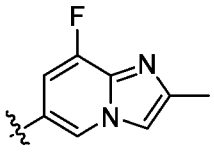
x is 0, 1, or 2.

In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl. In some embodiments, A is optionally substituted piperidinyl. In some embodiments, A is optionally substituted piperazinyl. In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  .

In some embodiments, L^2 is absent. In some embodiments, L^2 is C_1-C_6-heteroalkylene, that is optionally substituted with one or more R^5. In some embodiments, L^2 is -C(O)N(R^4)-. In some embodiments, L^2 is -C(O)N(H)-.

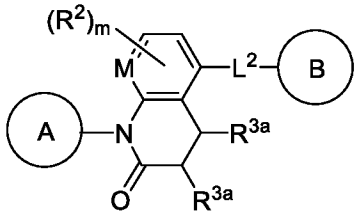
In some embodiments, M is C(R^2) (e.g., CH). In some embodiments, M is CH. In some embodiments, M is N.

In some embodiments, B is heteroaryl optionally substituted with one or more R^1. In some embodiments, B is monocyclic heteroaryl. In some embodiments, B is bicyclic heteroaryl. In some embodiments, B is monocyclic nitrogen-containing heteroaryl. In some embodiments, B is bicyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is selected from  ,  ,  ,  , and  wherein each R^1 is as defined above. In some embodiments, B is  . In some embodiments, B is  . In some

embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  .

In some embodiments, R^2 is C_1-C_6-alkyl. In some embodiments, R^2 is halo (e.g., fluoro). In some embodiments, R^2 is $-OR^A$ (e.g., –OH). In some embodiments, m is 0. In some embodiments, R^{3a} is hydrogen. In some embodiments, R^{3c} is hydrogen.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-f):



(I-f),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

M is $C(R^2)$ or N;

L^2 is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)$-, $-N(R^4)C(O)$-, or $-C(O)N(R^4)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5;

each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6; or

two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more R^6;

each R^2 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$;

each R^{3a} is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^5 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

each R^6 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11};

each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, or $-S(O)_xR^D$;

each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^7;

each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

each R^7 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$;

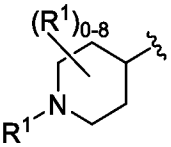
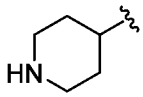
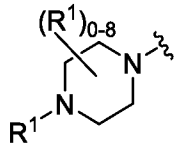
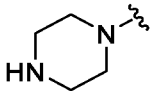
each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

each R^{A1} is hydrogen or C_1-C_6-alkyl;

m is 0, 1, or 2; and

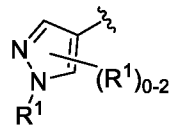
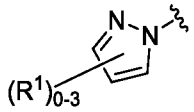
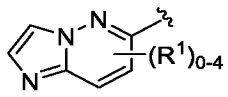
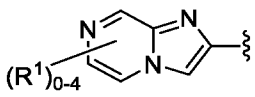
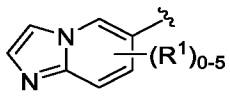
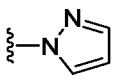
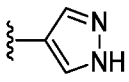
x is 0, 1, or 2.

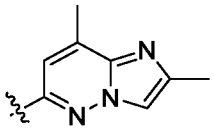
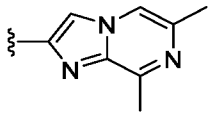
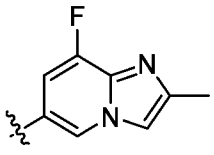
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl. In some embodiments, A is optionally substituted piperidinyl. In some

embodiments, A is optionally substituted piperazinyl. In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  .

In some embodiments, L^2 is absent. In some embodiments, L^2 is C_1-C_6-heteroalkylene, that is optionally substituted with one or more R^5. In some embodiments, L^2 is -C(O)N(R^4)-. In some embodiments, L^2 is -C(O)N(H)-.

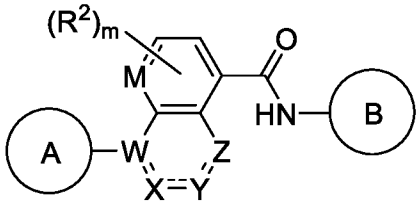
In some embodiments, M is C(R^2) (e.g., CH). In some embodiments, M is CH. In some embodiments, M is N.

In some embodiments, B is heteroaryl optionally substituted with one or more R^1. In some embodiments, B is monocyclic heteroaryl. In some embodiments, B is bicyclic heteroaryl. In some embodiments, B is monocyclic nitrogen-containing heteroaryl. In some embodiments, B is bicyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is selected from  ,  ,  ,  , and  wherein each R^1 is as defined above. In some embodiments, B is  . In some embodiments, B is  . In some

embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  .

In some embodiments, R^2 is C_1-C_6-alkyl. In some embodiments, R^2 is halo (e.g., fluoro). In some embodiments, R^2 is $-OR^A$ (e.g., –OH). In some embodiments, m is 0. In some embodiments, each R^{3a} is hydrogen.

In some embodiments, the compound of Formula (I) is a compound of Formula (I-g):



(I-g)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

W is N, C, or $C(R^{3a})$;

X, Y, and Z are each independently $C(R^{3a})$, $C(R^{3a})(R^{3b})$, N, $N(R^{3c})$, or O, wherein at least one of X, Y, and Z is N, $N(R^{3c})$, or O, and the bonds in the ring comprising W, X, Y, and Z may be single or double bonds as valency permits;

M is $C(R^2)$ or N;

each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6; or

two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more R^6;

each R^2 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$;

$R^{3a}$and R^{3b} are each independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$; or

each of R^{3a} and R^{3b}, together with the carbon atom to which they are attached, form an oxo group;

R^{3c} is hydrogen or C_1-C_6-alkyl;

each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^6 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11};

each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, or $-S(O)_xR^D$;

each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^7;

each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

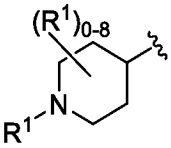
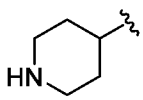
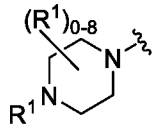
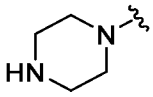
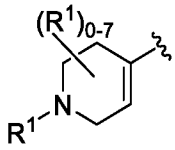
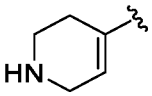
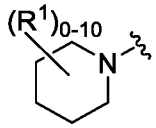
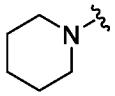
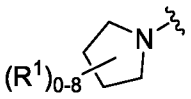
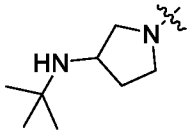
each R^7 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$;

each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

each R^{A1} is hydrogen or C_1-C_6-alkyl;

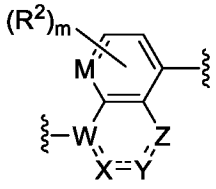
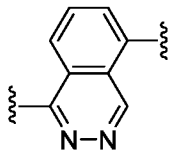
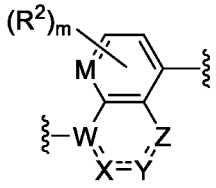
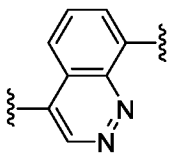
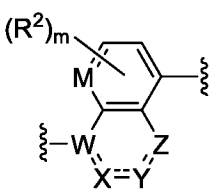
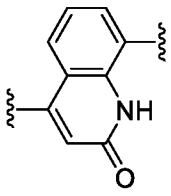
m is 0, 1, or 2; and

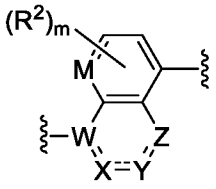
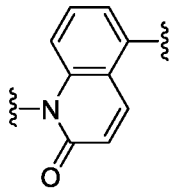
x is 0, 1, or 2

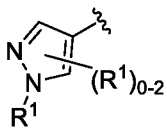
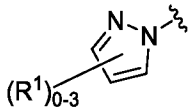
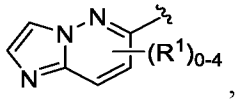
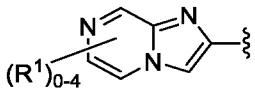
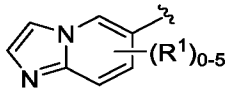
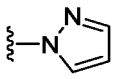
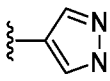
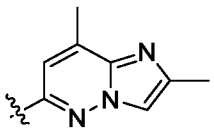
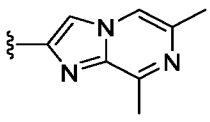
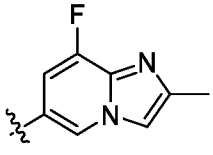
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl. In some embodiments, A is optionally substituted piperidinyl. In some embodiments, A is optionally substituted piperazinyl. In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen, C_1-C_6-alkyl, or $-NR^BR^C$, and wherein each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl. In some embodiments, A is  . In some embodiments, A is  , wherein each R^1 is independently hydrogen, C_1-C_6-alkyl, or $-NR^BR^C$, and wherein each of R^B and R^C is independently hydrogen or C_1-C_6 alkyl. In some embodiments, A is  .

In some embodiments, M is $C(R^2)$ (e.g., CH). In some embodiments, M is CH. In some embodiments, M is N. In some embodiments, W is C. in some embodiments, W is N. In some

embodiments, X is N, Y is N, and Z is C(R^{3a}). In some embodiments, X is C(R^{3a}), Y is N, and Z is N. In some embodiments, X is C(R^{3a}), Y is C(R^{3a})(R^{3b}), and Z is N(R^{3c}) (e.g., NH).

In some embodiments,  is  . In some embodiments,  is  . In some embodiments,  is  .

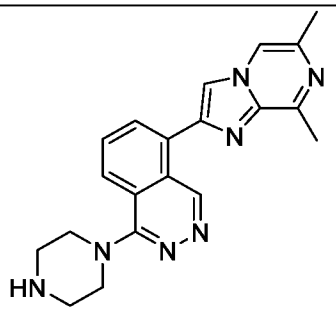
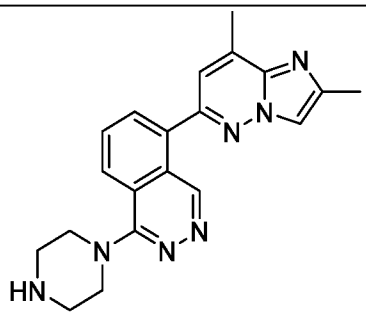
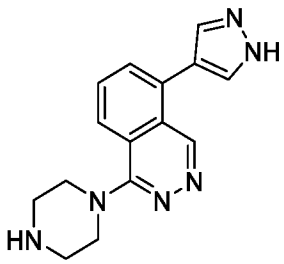
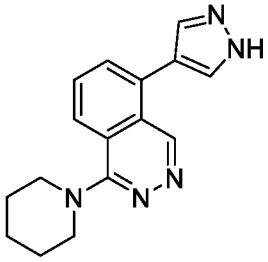
In some embodiments,  is  .

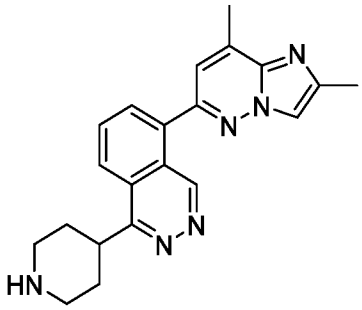
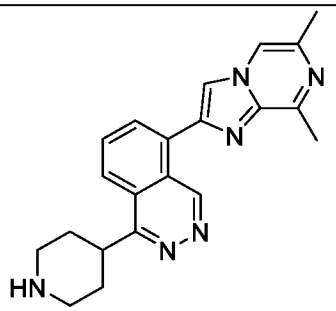
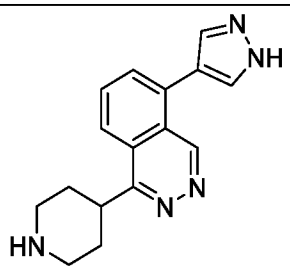
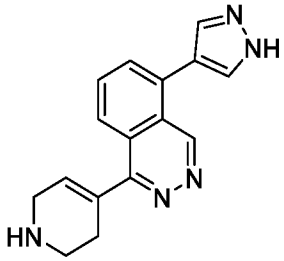
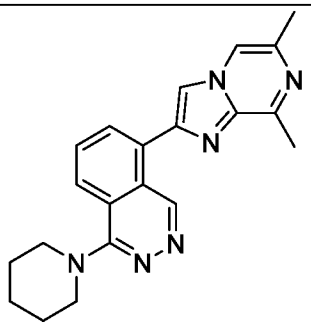
In some embodiments, B is heteroaryl optionally substituted with one or more R^1. In some embodiments, B is monocyclic heteroaryl. In some embodiments, B is bicyclic heteroaryl. In some embodiments, B is monocyclic nitrogen-containing heteroaryl. In some embodiments, B is bicyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is selected from  ,  ,  ,  , and  wherein each R^1 is as defined above. In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  . In some embodiments, B is  .

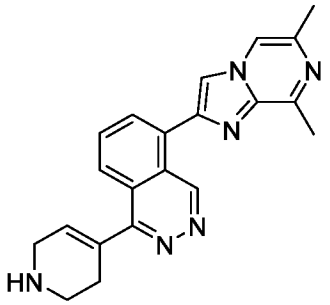
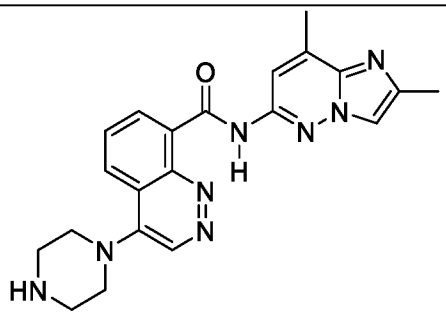
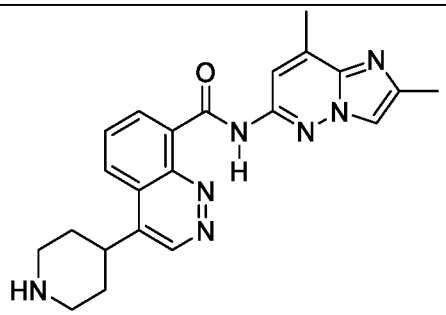
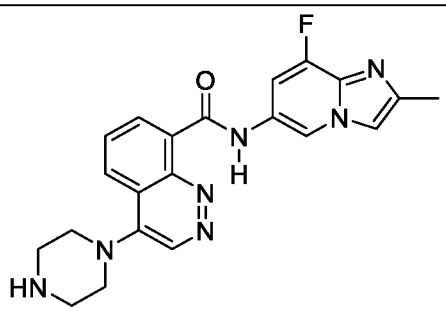
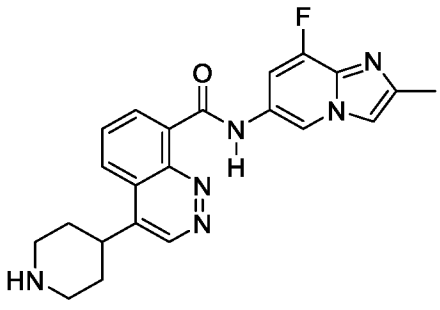
In some embodiments, R^2 is C_1-C_6-alkyl. In some embodiments, R^2 is halo (e.g., fluoro). In some embodiments, R^2 is $-OR^A$ (e.g., –OH). In some embodiments, m is 0. In some embodiments, each R^{3a} is hydrogen.

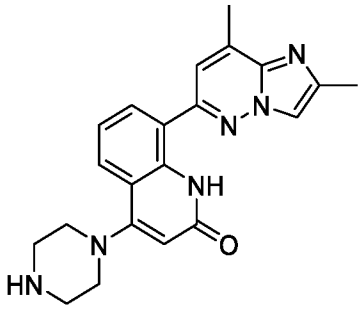
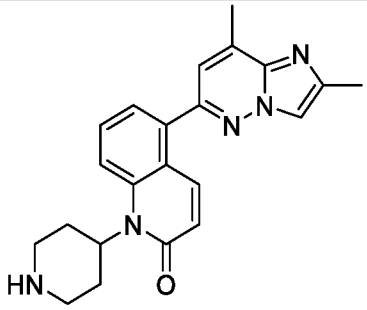
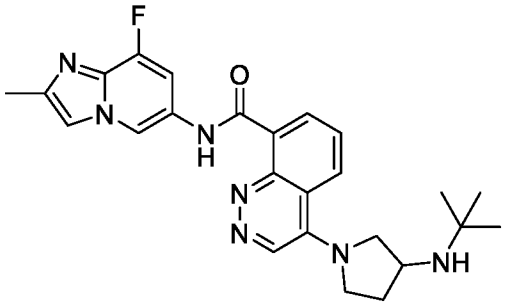
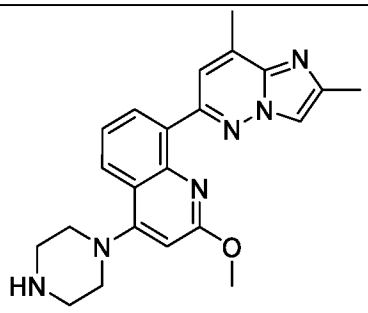
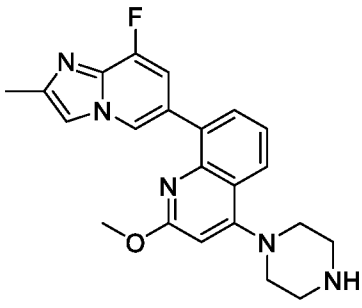
In some embodiments, the compound of Formula (I) is selected from a compound in Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

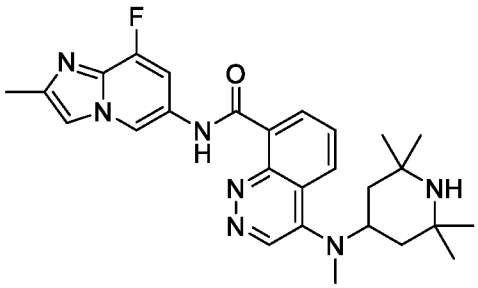
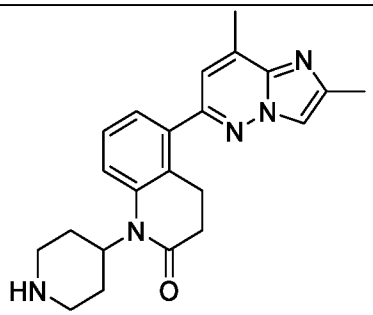
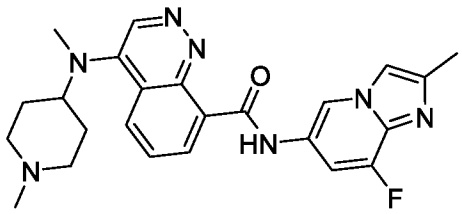
Table 1: Exemplary compounds of Formula (I).

Compound No.	**Structure**
100	
101	
102	
103	

104	
105	
106	
107	
108	

109	
111	
112	
113	
114	

120	
121	
122	
134	
138	

184	
185	
213	

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperazinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*a*]pyrazinyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is C; X and Y are each independently N; Z is $C(R^{3a})$ (e.g., CH); and m is 0. In some embodiments, the compound of Formulas (I), (I-a), and (I-b) is Compound 100, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperazinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*b*]pyridazinyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is C; X and Y are each independently N; Z is $C(R^{3a})$ (e.g., CH); and m is 0. In some embodiments, the compound of Formulas (I), (I-a), and (I-b) is Compound 101, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperazinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is C; X and Y are each independently N; Z is $C(R^{3a})$ (e.g., CH); and m is 0. In some embodiments, the

compound of Formulas (I), (I-a), and (I-b) is Compound 102, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperidinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is C; X and Y are each independently N; Z is $C(R^{3a})$ (e.g., CH); and m is 0. In some embodiments, the compound of Formulas (I), (I-a), and (I-b) is Compound 103, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperidinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*b*]pyridazinyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is C; X and Y are each independently N; Z is $C(R^{3a})$ (e.g., CH); and m is 0. In some embodiments, the compound of Formulas (I), (I-a), and (I-b) is Compound 104, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperidinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*a*]pyrazinyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is C; X and Y are each independently N; Z is $C(R^{3a})$ (e.g., CH); and m is 0. In some embodiments, the compound of Formulas (I), (I-a), and (I-b) is Compound 105, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperidinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is C; X and Y are each independently N; Z is $C(R^{3a})$ (e.g., CH); and m is 0. In some embodiments, the compound of Formulas (I), (I-a), and (I-b) is Compound 106, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., tetrahydropyridyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is C; X and Y are each independently N; Z is $C(R^{3a})$ (e.g., CH); and m is 0. In some embodiments, the compound of Formulas (I), (I-a), and (I-b) is Compound 107, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperidinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*a*]pyrazinyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is C; X and Y are each independently N; Z is $C(R^{3a})$ (e.g., CH); and m is 0. In some embodiments,

the compound of Formulas (I), (I-a), and (I-b) is Compound 108, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., tetrahydropyridyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*a*]pyrazinyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is C; X and Y are each independently N; Z is $C(R^{3a})$ (e.g., CH); and m is 0. In some embodiments, the compound of Formulas (I), (I-a), and (I-b) is Compound 109, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperazinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*b*]pyridazinyl); L^2 is $-C(O)N(R^4)-$ (e.g., -C(O)N(H)-); M is $C(R^2)$ (e.g., CH); W is C; X is $C(R^{3a})$ (e.g., CH); Y and Z are each independently N; and m is 0. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-f) is Compound 111, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperidinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*b*]pyridazinyl); L^2 is $-C(O)N(R^4)-$ (e.g., -C(O)N(H)-); M is $C(R^2)$ (e.g., CH); W is C; X is $C(R^{3a})$ (e.g., CH); Y and Z are each independently N; and m is 0. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-f) is Compound 112, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperazinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*a*]pyridinyl); L^2 is $-C(O)N(R^4)-$ (e.g., -C(O)N(H)-); M is $C(R^2)$ (e.g., CH); W is C; X is $C(R^{3a})$ (e.g., CH); Y and Z are each independently N; and m is 0. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-f) is Compound 113, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperidinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*a*]pyridinyl); L^2 is $-C(O)N(R^4)-$ (e.g., -C(O)N(H)-); M is $C(R^2)$ (e.g., CH); W is C; X is $C(R^{3a})$ (e.g., CH); Y and Z are each independently N; and m is 0. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-f) is Compound 114, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperazinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*b*]pyridazinyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is C; X is $C(R^{3a})$ (e.g., CH); Y is $C(R^{3a})(R^{3b})$ (e.g., -C(O)-); Z is $N(R^{3c})$ (e.g., -N(H)-); and m is

0. In some embodiments, the compound of Formulas (I), (I-a), and (I-d) is Compound 120, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperidinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*b*]pyridazinyl); L^2 is absent; M is $C(R^2)$ (e.g., CH); W is N; X is $C(R^{3a})(R^{3b})$ (e.g., -C(O)-); Y and Z are each independently $C(R^{3a})$ (e.g., CH); and m is 0. In some embodiments, the compound of Formulas (I) and (I-e) is Compound 121, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperazinyl or pyrrolyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*b*]pyridazinyl or imidazo[1,2-*a*]pyridinyl); L^2 is absent or $-C(O)N(R^4)-$ (e.g., -C(O)NH; M is $C(R^2)$ (e.g., CH); W is C; X is $C(R^{3a})$ (e.g., CH); Y is N or $C(R^{3a})$ (e.g., C(OMe); Z is N; and m is 0. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-f) is Compound 122, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-a), and (I-d) is Compound 134 or 138, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperazinyl); B is bicyclic heteroaryl (e.g., imidazo[1,2-*b*]pyridazinyl or imidazo[1,2-*a*]pyridinyl); L^2 is absent, $N(R^4)-$ (e.g., NCH_3), or $-C(O)N(R^4)-$ (e.g., -C(O)NH; M is $C(R^2)$ (e.g., CH); W is N or C; X is $C(R^{3a})$ (e.g., CH) or $C(R^{3a})(R^{3b})$ (e.g., C(O)); Y is N or $C(R^{3a})$ (e.g., C(OMe); Z is N or $C(R^{3a})(R^{3b})$ (e.g., CH_2); and m is 0. In some embodiments, the compound of Formulas (I) and (I-a) is Compound 184, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I) and (I-a) is Compound 185, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I) and (I-a) is Compound 213, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

Pharmaceutical Compositions, Kits, and Administration

The present invention provides pharmaceutical compositions comprising a compound of Formula (I), *e.g.*, a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer, as described herein, and optionally a pharmaceutically

acceptable excipient. In certain embodiments, the pharmaceutical composition described herein comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount.

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

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

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

The term "pharmaceutically acceptable excipient" refers to a non-toxic carrier, adjuvant, diluent, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable excipients useful in the manufacture of the pharmaceutical compositions of the invention are any of those that are well known in the art of pharmaceutical formulation and include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Pharmaceutically acceptable excipients useful in the manufacture of the pharmaceutical compositions of the invention include, but are not

limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

Compositions of the present invention may be administered orally, parenterally (including subcutaneous, intramuscular, intravenous and intradermal), by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. In some embodiments, provided compounds or compositions are administrable intravenously and/or orally.

The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intraocular, intravitreal, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intraperitoneal intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, subcutaneously, intraperitoneally, or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or

coloring agents may also be added. In some embodiments, a provided oral formulation is formulated for immediate release or sustained/delayed release. In some embodiments, the composition is suitable for buccal or sublingual administration, including tablets, lozenges and pastilles. A provided compound can also be in micro-encapsulated form.

Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions or in an ointment such as petrolatum.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

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

Compounds provided herein are typically formulated in dosage unit form, e.g., single unit dosage form, for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity

of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

In certain embodiments, the compounds of Formula (I) may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

It will be also appreciated that a compound or composition, as described herein, can be

administered in combination with one or more additional pharmaceutical agents. The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional pharmaceutical agents, which may be useful as, *e.g.*, combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the additional pharmaceutical agents and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

Exemplary additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-diabetic agents, anti-inflammatory agents, immunosuppressant agents, and a pain-relieving agent. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells.

Also encompassed by the invention are kits (*e.g.*, pharmaceutical packs). The inventive kits may be useful for preventing and/or treating a proliferative disease or a non-proliferative disease, e.g., as described herein. The kits provided may comprise an inventive pharmaceutical

composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of an inventive pharmaceutical composition or compound. In some embodiments, the inventive pharmaceutical composition or compound provided in the container and the second container are combined to form one-unit dosage form.

Thus, in one aspect, provided are kits including a first container comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, or a pharmaceutical composition thereof. In certain embodiments, the kit of the disclosure includes a first container comprising a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the kits are useful in preventing and/or treating a disease, disorder, or condition described herein in a subject (e.g., a proliferative disease or a non-proliferative disease). In certain embodiments, the kits further include instructions for administering the compound, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, or a pharmaceutical composition thereof, to a subject to prevent and/or treat a proliferative disease or a non-proliferative disease.

Methods of Use

Described herein are compounds useful for modulating splicing. In some embodiments, a compound of Formula (I) may be used to alter the amount, structure, or composition of a nucleic acid (e.g., a precursor RNA, e.g., a pre-mRNA, or the resulting mRNA) by increasing or decreasing splicing at a splice site. In some embodiments, increasing or decreasing splicing results in modulating the level or structure of a gene product (e.g., an RNA or protein) produced. In some embodiments, a compound of Formula (I) may modulate a component of the splicing machinery, e.g., by modulating the interaction with a component of the splicing machinery with another entity (e.g., nucleic acid, protein, or a combination thereof). The splicing machinery as referred to herein comprises one or more spliceosome components. Spliceosome components may comprise, for example, one or more of major spliceosome members (U1, U2, U4, U5, U6 snRNPs), or minor spliceosome members (U11, U12, U4atac, U6atac snRNPs) and their accessory splicing factors.

In another aspect, the present disclosure features a method of modifying of a target (e.g., a precursor RNA, e.g., a pre-mRNA) through inclusion of a splice site in the target, wherein the method comprises providing a compound of Formula (I). In some embodiments, inclusion of a splice site in a target (e.g., a precursor RNA, e.g., a pre-mRNA, or the resulting mRNA) results in addition or deletion of one or more nucleic acids to the target (e.g., a new exon, e.g. a skipped exon). Addition or deletion of one or more nucleic acids to the target may result in an increase in the levels of a gene product (e.g., RNA, e.g., mRNA, or protein).

In another aspect, the present disclosure features a method of modifying a target (e.g., a precursor RNA, e.g., a pre-mRNA, or the resulting mRNA) through exclusion of a splice site in the target, wherein the method comprises providing a compound of Formula (I). In some embodiments, exclusion of a splice site in a target (e.g., a precursor RNA, e.g., a pre-mRNA) results in deletion or addition of one or more nucleic acids from the target (e.g., a skipped exon, e.g. a new exon). Deletion or addition of one or more nucleic acids from the target may result in a decrease in the levels of a gene product (e.g., RNA, e.g., mRNA, or protein). In other embodiments, the methods of modifying a target (e.g., a precursor RNA, e.g., a pre-mRNA, or the resulting mRNA) comprise suppression of splicing at a splice site or enhancement of splicing at a splice site (e.g., by more than about 0.5%, e.g., 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more), e.g., as compared to a reference (e.g., the absence of a compound of Formula (I), or in a healthy or diseased cell or tissue).

The methods described herein can be used to modulate splicing, e.g., of a nucleic acid comprising a particular sequence (e.g., a target sequence). Exemplary genes encoding a target sequence (e.g., a target sequence comprising DNA or RNA, e.g., pre-mRNA) include, *inter alia*, *ABCA4, ABCA9, ABCB1, ABCB5, ABCC9, ABCD1, ACADL, ACADM, ACADSB, ACSS2, ACTB, ACTG2, ADA, ADAL, ADAM10, ADAM15, ADAM22, ADAM32, ADAMTS12, ADAMTS13, ADAMTS20, ADAMTS6, ADAMTS9, ADAR, ADCY3, ADCY10, ADCY8, ADNP, ADRBK2, AFP, AGL, AGT, AHCTF1, AHR, AKAP10, AKAP3, AKNA, ALAS1, ALS2CL, ALB, ALDH3A2, ALG6, AMBRA1, ANK3, ANTXR2, ANXA10, ANXA11, ANGPTL3, AP2A2, AP4E1, APC, APOA1, APOB, APOC3, APOH, AR, ARID2, ARID3A, ARID3B, ARFGEF1 , ARFGEF2, ARHGAP1, ARHGAP8, ARHGAP18, ARHGAP26, ARHGEF18, ARHGEF2, ARPC3, ARS2, ASH1L, ASH1L-IT1, ASNSD1, ASPM, ATAD5, ATF1, ATG4A, ATG16L2, ATM, ATN1, ATP11C, ATP6V1G3,*

ATP13A5, ATP7A, ATP7B, ATR, ATXN2, ATXN3, ATXN7, ATXN10, AXIN1, B2M, B4GALNT3, BBS4, BCL2, BCL2L1, BCL2-like 11 (BIM), BCL11B, BBOX1, BCS1L, BEAN1, BHLHE40, BMPR2, BMP2K, BPTF, BRAF, BRCA1, BRCA2, BRCC3, BRSK1, BRSK2, BTAF1, BTK, C2orf55, C4orf29, C6orf118, C9orf43, C9orf72, C10orf137, C11orf30, C11orf65, C11orf70, C11orf87, C12orf51, C13orf1, C13orf15, C14orf10l, C14orf118, C15orf29, C15orf42, C15orf60, C16orf33, C16orf38, C16orf48, C18orf8, C19orf42, C1orf107, C1orf114, C1orf130, C1orf149, C1orf27, C1orf71, C1orf94, C1R, C20orf74, C21orf70, C3orf23, C4orf18, C5orf34, C8B, C8orf33, C9orf114, C9orf86, C9orf98, C3, CA11, CAB39, CACHD1, CACNA1A, CACNA1B, CACNA1C, CACNA2D1, CACNA1G, CACNA1H, CALCA, CALCOCO2, CAMK1D, CAMKK1, CAPN3, CAPN9, CAPSL, CARD11, CARKD, CASZ1, CAT, CBLB, CBX1, CBX3, CCDC102B, CCDC11, CCDC15, CCDC18, CCDC5, CCDC81, CCDC131, CCDC146, CD4, CD274, CD1B, CDC14A, CDC16, CDC2L5, CDC42BPB, CDCA8, CDH10, CDH11, CDH24, CDH8, CDH9, CDK5RAP2, CDK6, CDK8, CDK11B, CD33, CD46, CDH1, CDH23, CDK6, CDK11B, CDK13, CEBPZ, CEL, CELSR3, CENPA, CENPI, CENPT, CENTB2, CENTG2, CEP110, CEP170, CEP192, CETP, CFB, CFTR, CFH, CGN, CGNL1, CHAF1A, CHD9, CHIC2, CHL1, CHN1, CHM, CLEC16A, CL1C2, CLCN1, CLINT1, CLK1, CLPB, CLPTM1, CMIP, CMYA5, CNGA3, CNOT1, CNOT7, CNTN6, COG3, COL11A1, COL11A2, COL12A1, COL14A1, COL15A1, COL17A1, COL19A1, COL1A1, COL1A2, COL2A1, COL3A1, COL4A1, COL4A2, COL4A5, COL4A6, COL5A2, COL6A1, COL7A1, COL9A1, COL9A2, COL22A1, COL24A1, COL25A1, COL29A1, COLQ, COMTD1, COPA, COPB2, COPS7B, COPZ2, CPSF2, CPXM2, CR1, CRBN, CRYZ, CREBBP, CRKRS, CSE1L, CSTB, CSTF3, CT45-6, CTNNB1, CUBN, CUL4B, CUL5, CXorf41, CXXC1, CYBB, CYFIP2, CYP3A4, CYP3A43, CYP3A5, CYP4F2, CYP4F3, CYP17, CYP19, CYP24A1, CYP27A1, DAB1, DAZ2, DCBLD1, DCC, DCTN3, DCUN1D4, DDA1, DDEF1, DDX1, DDX24, DDX4, DENND2D, DEPDC2, DES, DGAT2, DHFR, DHRS7, DHRS9, DHX8, DIP2A, DMD, DMTF1, DNAH3, DNAH8, DNAI1, DNAJA4, DNAJC13, DNAJC7, DNMT1, DNTTIP2, DOCK4, DOCK5, DOCK10, DOCK11, DOT1L, DPP3, DPP4, DPY19L2P2, DR1, DSCC1, DVL3, DUX4, DYNC1H1, DYSF, E2F1, E2F3, E2F8, E4F1, EBF1, EBF3, ECM2, EDEM3, EFCAB3, EFCAB4B, EFNA4, EFTUD2, EGFR, EIF3A, ELA1, ELA2A, ELF2, ELF3, ELF4, EMCN, EMD, EML5, ENO3, ENPP3, EP300, EPAS1, EPB41L5, EPHA3, EPHA4, EPHB1, EPHB2, EPHB3, EPS15, ERBB4, ERCC1, ERCC8, ERGIC3, ERMN, ERMP1, ERN1, ERN2, ESR1, ESRRG, ETS2, ETV3, ETV4, ETV5,

ETV6, EVC2, EWSR1, EXO1, EXOC4, F3, F11, F13A1, F5, F7, F8, FAH, FAM13A1, FAM13B1, FAM13C1, FAM134A, FAM161A, FAM176B, FAM184A, FAM19A1, FAM20A, FAM23B, FAM65C, FANCA, FANCC, FANCG, FANCM, FANK1, FAR2, FBN1, FBXO15, FBXO18, FBXO38, FCGBP, FECH, FEZ2, FGA, FGD6, FGFR2, FGFR1OP, FGFR1OP2, FGFR2, FGG, FGR, FIX, FKBP3, FLI1, FLJ35848, FLJ36070, FLNA, FN1, FNBP1L, FOLH1, FOSL1, FOSL2, FOXK1, FOXM1, FOXO1, FOXP4, FRAS1, FUT9, FXN, FZD3, FZD6, GAB1, GABPA, GALC, GALNT3, GAPDH, GART, GAS2L3, GATA3, GATAD2A, GBA, GBGT1, GCG, GCGR, GCK, GFI1, GFM1, GH1, GHR, GHV, GJA1, GLA, GLT8D1, GNA11, GNAQ, GNAS, GNB5, GOLGB1, GOLT1A, GOLT1B, GPATCH1, GPR158, GPR160, GPX4, GRAMD3, GRHL1, GRHL2, GRHPR, GRIA1, GRIA3, GRIA4, GRIN2B, GRM3, GRM4, GRN, GSDMB, GSTCD, GSTO2, GTF2I, GTPBP4, HADHA, HAND2, HBA2, HBB, HCK, HDAC3, HDAC5, HDX, HEPACAM2, HERC1, HES7, HEXA, HEXB, HHEX, HIPK3, HLA-DPB1, HLA-G, HLCS, HLTF, HMBS, HMGA1, HMGCL, HNF1A, HNF1B, HNF4A, HNF4G, HNRNPH1, HOXC10, HP1BP3, HPGD, HPRT1, HPRT2, HSF1, HSF4, HSF2BP, HSPA9, HSPG2, HTT, HXA, ICA1, IDH1, IDS, IFI44L, IKBKAP, IKZF1, IKZF3, IL1R2, IL5RA, IL7RA, IMMT, INPP5D, INSR, INTS3, INTU, IP04, IP08, IQGAP2, IRF2, IRF4, IRF8, IRX3, ISL1, ISL2, ITFG1, ITGA6, ITGAL, ITGB1, ITGB2, 1TGB3, ITGB4, ITIH1, ITPR2, IWS1, JAK1, JAK2, JAG1, JMJD1C, JPH3, KALRN, KAT6A, KATNAL2, KCNN2, KCNT2, KDM2A, KIAA0256, KIAA0528, KIAA0564, KIAA0586, KIAA1033, KIAA1166, KIAA1219, KIAA1409, KIAA1622, KIAA1787, KIF3B, KIF15, KIF16B, KIF5A, KIF5B, KIF9, KIN, KIR2DL5B, KIR3DL2, KIR3DL3, KIT, KLF3, KLF5, KLF7, KLF10, KLF12, KLF16, KLHL20, KLK12, KLKB1, KMT2A, KMT2B, KPNA5, KRAS, KREMEN1, KRIT1, KRT5, KRTCAP2, KYNU, L1CAM, L3MBTL, L3MBTL2, LACE1, LAMA1, LAMA2, LAMA3, LAMB1, LARP7, LDLR, LEF1, LENG1, LGALS3, LGMN, LHCGR, LHX3, LHX6, LIMCH1, LIMK2, LIN28B, LIN54, LMBRD1, LMBRD2, LMLN, LMNA, LMO2, LMO7, LOC389634, LOC390110, LPA, LPCAT2, LPL, LRP4, LRPPRC, LRRK2, LRRC19, LRRC42, LRWD1, LUM, LVRN, LYN, LYST, MADD, MAGI1, MAGT1, MALT1, MAP2K1, MAP4K4, MAPK8IP3, MAPK9, MAPT, MARC1, MARCH5, MATN2, MBD3, MCF2L2, MCM6, MDGA2, MDM4, ASXL1, FUS, SPR54, MECOM, MEF2C, MEF2D, MEGF10, MEGF11, MEMO1, MET, MGA, MGAM, MGAT4A, MGAT5, MGC16169, MGC34774, MKKS, MIB1, MIER2, MITF, MKL2, MLANA, MLH1, MLL5, MLX, MME, MPDZ, MPI, MRAP2, MRPL11, MRPL39, MRPS28, MRPS35, MS4A13, MSH2, MSH3, MSMB, MST1R,

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Additional exemplary genes encoding a target sequence (e.g., a target sequence comprising DNA or RNA, e.g., pre-mRNA) include genes include *A1CF, A4GALT, AAR2, ABAT, ABCA11P, ZNF721, ABCA5, ABHD10, ABHD13, ABHD2, ABHD6, AC000120.3, KRIT1, AC004076.1, ZNF772, AC004076.9, ZNF772, AC004223.3, RAD51D, AC004381.6, AC006486.1, ERF, AC007390.5, AC007780.1, PRKAR1A, AC007998.2, INO80C, AC009070.1, CMC2, AC009879.2, AC009879.3, ADHFE1, AC010487.3, ZNF816-ZNF321P, ZNF816, AC010328.3, AC010522.1, ZNF587B, AC010547.4, ZNF19, AC012313.3, ZNF497,*

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In some embodiments, the gene encoding a target sequence comprises the HTT gene.

Exemplary genes that may be modulated by the compounds of Formula (I) described herein may also include, *inter alia*, AC005258.1, AC005943.1, AC007849.1, AC008770.2, AC010487.3, AC011477.4, AC012651.1, AC012531.3, AC034102.2, AC073896.4, AC104472.3, AL109811.3, AL133342.1, AL137782.1, AL157871.5, AF241726.2, AL355336.1, AL358113.1, AL360181.3, AL445423.2, AL691482.3, AP001267.5, RF01169, and RF02271.

The compounds described herein may further be used to modulate a sequence comprising a particular splice site sequence, e.g., an RNA sequence (e.g., a pre-mRNA sequence). In some embodiments, the splice site sequence comprises a 5' splice site sequence. In some embodiments, the splice site sequence comprises a 3' splice site sequence. Exemplary gene sequences and splice site sequences (e.g., 5' splice site sequences) include AAAgcaaguu, AAAguaaaaa, AAAguaaaau, AAAguaaagu, AAAguaaaua, AAAguaaaug, AAAguaaauu, AAAguaacac, AAAguaacca, AAAguaacuu, AAAguaagaa, AAAguaagac, AAAguaagag, AAAguaagau, AAAguaagca, AAAguaagcc, AAAguaagcu, AAAguaagga, AAAguaaggg, AAAguaaggu, AAAguaagua, AAAguaaguc, AAAguaagug, AAAguaaguu, AAAguaaucu, AAAguaauua, AAAguacaaa, AAAguaccgg, AAAguacuag, AAAguacugg, AAAguacuuc, AAAguacuug, AAAguagcuu, AAAguaggag, AAAguaggau, AAAguagggg, AAAguaggua, AAAguaguaa, AAAguauauu, AAAguauccu, AAAguaucuc, AAAguaugga, AAAguaugua, AAAguaugug, AAAguauguu, AAAguauugg, AAAguauuuu, AAAgucagau, AAAgucugag, AAAgugaaua, AAAgugagaa, AAAgugagac, AAAgugagag, AAAgugagau, AAAgugagca, AAAgugagcu, AAAgugaggg, AAAgugagua, AAAgugaguc, AAAgugagug, AAAgugaguu, AAAgugcguc, AAAgugcuga, AAAgugggguc, AAAgugggguu, AAAgugguaa, AAAguguaug, AAAgugugug, AAAguguguu, AAAguuaagu, AAAguuacuu, AAAguuagug, AAAguuaugu, AAAguugagu, AAAguuugua, AACguaaaac, AACguaaagc, AACguaaagg, AACguaagca, AACguaaggg, AACguaaguc, AACguaagug, AACguaaugg, AACguaguga, AACguaugua, AACguauguu, AACgugagca, AACgugagga, AACgugauuu, AACgugggau, AACgugggua, AACguguguu, AACguuggua, AAGgcaaauu, AAGgcaagag, AAGgcaagau, AAGgcaagcc, AAGgcaagga, AAGgcaaggg, AAGgcaagug, AAGgcaaguu, AAGgcacugc, AAGgcagaaa,

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Additional exemplary gene sequences and splice site sequences (e.g., 5' splice site sequences) include AAGgcaagau, AUGguaugug, GGGgugaggc, CAGguaggug, AAGgucagua, AAGguuagag, AUGgcacuua, UAAguaaguc, UGGgugagcu, CGAgcugggc, AAAgcacccc, UAGgugggggg, AGAguaacgu, UCGgugaugu, AAUgucaguu, AGGgucugag, GAGgugacug,

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Additional exemplary gene sequences and splice site sequences (e.g., 5' splice site sequences) include UCCguaaguu, GUGguaaacg, CGGgugcggu, CAUguacuuc, AGAguaaagg, CGCgugagua, AGAgugggca, AGAguaagcc, AGAguaaaca, GUGguuauga, AGGguaauaa, UGAguaagac, AGAguuuguu, CGGgucugca, CAGguaaguc, AAGguagaau, CAGgucccuc, AGAguaaugg, GAGgucuaag, AGAguagagu, AUGgucagua, GAGgccuggg, AAGgugguggc,

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UGCguccagc, AAAguggagu, CGUgugagcc, AGAguacugu, CAGguauagc, UACguaagga, AAGgucuuua, AAGguggucu, GGGguaaauu, UCAgugagga, AGAguacguu, GAGgucguca, UAGguuugau, CAUguaaacc, AAGguggcac, CAGguagaug, AACguaaaag, UAGgucucug, AUAguaggug, UAGgcaagag, UAGgcacggc, AAGgucuuca, CCAguaugcu, CAAgugaguu, CAGgucucaa, CAGguuacau, GGAgugagca, AGAguacgca, CUGguguugg, AAGguacuca, CUAguaaggg, AGAguaaaag, AAGguaacga, CUGgucccg, UAAguauggg, GAGgucgagc, UUGguauaua, AAAgucaagg, AAGgucuagg, CGAguagguc, AGGguucguu, GAGgcaggcc, CUAguauuac, ACGguaugug, UAGgugguuc, AGAguauaac, UUGgugcguc, ACCguuaucu, CCAgugauga, GAAguaugca, GAAguauggc, CCGguaggac, AAUguaagca, AGAguaauug, AGGguugguu, GUGguaggag, AAGgcaguuu, CAAguaagcc, CUGgcaagua, CAGgcaugau, AGGguaauug, GGGguaaccu, AAAguaacua, UAGgucugcc, ACGguaugaa, AGUguauggg, UGGguuggca, UAGguaaacu, AGAgugggua, AGAguauuug, AGUguaggaa, CUUguacgua, GAUgugagau, CAGgcagcca, AAGgucacug, AAGgucugac, UAGguuccuu, CUGgugcuuu, UGAguuggug, UUGgugggau, UGAguagggu, UCGgugaggu, AAAguaaaga, AAGgcaaguc, CGGguaaagc, AAAguuaguu, UUAguaagca, GAGgucacau, UAAgugguau, UAGgugcuuu, GGAguaggca, UGAguaagga, CAGguggagc, GAUguagaag, AAUgccugcc, AUGguaaggc, UGGguaauau, CUGguaccuc, CACgugagcc, UGAguuugug, CCGguagugu, AAAgugacaa, GAAguggguu, CAGgugcagc, GAGgugggcc, UAUgugcguc, GGGguacugg, CUGguagguu, UUGgcauguu, AAUguaauac, UAGgccggug, AGAgucagua, UAAguaaauc, CAGguuccuc, UAGguacgau, AGAguuagug, GCAguaagug, AGGgugguag, GGAguaaugu, GAUguaaguc, CCAguuucgu, AAGguucggg, AUGguggagu, AAGguaccgg, GAAgugcgaa, UGGgucaguu, AAGguguaga, UGGguaggcc, CCAgugaguc, AAGgucacuu, AGCgugaggc, UCCgugguaa, AGAguacuua, GGGgucagau, AAGguggacc, AGAgugagcg, AGAgucagau, UAAguauuac, AGAguauuuc, AGAguucagc, AUGgugaagu, UAGgugaucc, GGAguaagau, UAGguaccaa, AGAguugguc, GAAgugagac, AUCguagguu, GAGguacgcu, ACGguaaggg, CAGgcauguc, UUAguaagau, UGAguagguu, AGGguacgaa, ACGguauguu, AGGguacugu, UUGguaugga, UAAguaacug, GCGgucagcc, UUUgugaguc, GUGgucagug, CUGgucugua, GAGguucuua, AUGguacuga, AAUgugcuuu, AGGguggcgu, CCGgcaggaa, CAUguggguc, UUGguuuguu, CAGguucugu, ACGguaagcg, CUGgucagua, UCAguaggcu, UGAguaggac, CAGguuuuaa, GAGguguccc, AGGguggguu, GUGgugagac, CACguaggga, GUGguauuuu, GAGauauccu, AAGgugaaca, UAAguagggc, CUGgugcggg, CUGgucaaua, AGAguaaaaa, AAGgugcagu,

CGGguaagca, AAAgugagcc, AUGguaauca, GCAguacgug, AUGguacaug, AAGguuaaga, CGGguaaaug, GAGguucgca, GAGgcucugg, AUGgugggac, AACgugguag, AAGgugauag, GGGguuugca, CAUguaaggg, UCAguugagu, AAAgugcggc, AGAgugagcc, AUGgcaagaa, ACAguaaggu, AAGgucucua, GUGguaaaaa, AAAguaggug, UAGgugcacu, GUCgugguau, CAGguauagg, UGAgugagag, ACUgugagcc, AUCguuaguu, UUUguaccaa, UGGgugagau, AGAgugagaa, AGAguagggg, AGGgcaagua, CGGgucagua, UUGguaugcc, CGGguuagau, GGGgugaagu, CCCgugugaa, GCAguuugga, UGCguaagac, AGAgucugua, CACgugagca, AGGguaaaag, CAGgcugggu, GAAgucuuca, AAGgcaaaaa, GUAguaaaua, CUAgugagag, GAAguuucug, CCUguacgua, GAGgugcgcg, AAGguguaaa, CCAguauguu, CCGgucagcu, AUGguuccug, CAAguuaaau, AGAguaggcu, AUGgugggca, GGAguaagac, AGGgucacga, UAGgugauau, GAAguaaguc, CGGguaagau, CAAguagcua, UGAguaaaau, GUCguacgug, AUGguacgua, CAGgucucgg, GAGgcauguc, AGAgugggau, GUGguuagag, UGGgugguga, AAGguuaaac, CUUguuagcu, AAAguaggaa, UAGguuguau, AGGgugcgcc, AAGgugggcu, UAAguaucug, AAGguaacgu, AUGguggggc, CAAguacacg, GGCguaagug, AUAguaggac, AGAgugaggu, UUUguaaaaa, GAAguuugua, CUAguaaucu, AAGguuuuua, GAGgugcguu, UAGgcgagua, ACCgugagua, CAGgucccga, AUGguacugg, UGAguucagu, AAUguguggu, UCCguugguu, CAGgucagag, CAGgucccua, UAGguagacu, CAAguuaagg, GAGgugugcg, GAAgcugccc, CGAguacgug, CGGguaggua, UUGguauuga, AUUguaugau, UUGguaugaa, GAGgugguca, GCUguaugaa, CAGguguugc, CAGguaaaac, AUAguaaggu, CUGguuagag, AGCgugugag, AAGguuaucu, CACgugagua, AGGgucagua, GAGguauaau, CAGguuauuu, AGGguggacu, AUUguaauuc, UUUguggguu, AUGguacgug, AAGguguucc, CAGgugacgc, GAGguacuaa, ACAguucagu, GAGgucacgg, CAAguaaggc, AAGguuuggg, AAAgugggcu, GCGguucuug, GAGguggagc, UGAgucagug, CAGgucaagg, AGUguaagcu, GAGgcagaaa, AAGgucacac, GAAguagguu, GUCguaaguu, AGAguaugca, CCUgugcaaa, ACGgugaaaa, CAGguacgaa, CAUgugagga, AGCgugagua, GGUguguagg, AACgugagcu, GAGgugaacu, AGAguucagu, AACgugugua, CAGguugugg, AAGguacuag, UCAgugaaaa, AAUgucuggu, ACGguaaaau, CUGguguaag, GAGgugcgaa, AGGguuucuc, CAGguagccc, AUUguauugg, AUGguacuua, GAGgcccgac, UCGguaagac, CGGgcuguag, UAUgugugug, UAGguagaaa, GUGgucauua, UAGgugaaag, ACUguaauuc, GCAguacagg, UCGgugaguc, UAUguaggga, AUGguauguc, GUGgugugug, CUGgugaccu, AAUgugaaua, UAGgucucac, GAGguuauug, UGAguaggcu, CGGgcacgua, GCAguaaaua, CCGgugagag, UAAguugguc, CCGgugagcc,

AAGguuguca, CUGguauuau, GGGguauggg, AAAgucagua, UUUguaugua, UAAguacugc, CAGguaccaa, GAAguucaga, AUGgugcggu, GUGgugaggu, UGAguaagcc, UAUguaaggg, GUGguggaaa, GAGgugauug, GGAguuugua, AAGgucacga, GUGguagagg, UAAguauauc, AAGgugucca, UAUgugguau, GAGguacaau, AAGgugggggg, GGAguaggug, and UAGgugacuu.

In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises AGA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises AAA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises AAC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises AAU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises AAG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises ACA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises AUA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises AUU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises AUG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises AUC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises CAA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises CAU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises CAC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises CAG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GAA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GAC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GAU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GAG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GGA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GCA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GGG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GGC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GUU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GGU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GUC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises GUA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises

GUG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UCU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UCC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UCA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UCG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UUU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UUC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UUA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UUG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UGU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UAU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
GGA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
CUU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
CUC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
CUA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
CUG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
CCU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
CCC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
CCA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
CCG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
ACU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
ACC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
ACG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
AGC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
AGU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
AGG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
CGU. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UAC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UAA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
UAG. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises
CGC. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises

CGA. In some embodiments, the splice site sequence (e.g., 5' splice site sequence) comprises CGG. In some embodiments, the splice site sequence comprises AGAguaaggg.

In an embodiment, a gene sequence or splice site sequence provided herein is related to a proliferative disease, disorder, or condition (e.g., cancer, benign neoplasm, or inflammatory disease). In an embodiment, a gene sequence or splice site sequence provided herein is related to a non-proliferative disease, disorder, or condition. In an embodiment, a gene sequence or splice site sequence provided herein is related to a neurological disease or disorder; autoimmune disease or disorder; immunodeficiency disease or disorder; lysosomal storage disease or disorder; cardiovascular condition, disease or disorder; metabolic disease or disorder; respiratory condition, disease, or disorder; renal disease or disorder; or infectious disease in a subject. In an embodiment, a gene sequence or splice site sequence provided herein is related to a neurological disease or disorder (e.g., Huntington's disease). In an embodiment, a gene sequence or splice site sequence provided herein is related to an immunodeficiency disease or disorder. In an embodiment, a gene sequence or splice site sequence provided herein is related to a lysosomal storage disease or disorder. In an embodiment, a gene sequence or splice site sequence provided herein is related to a cardiovascular condition, disease or disorder. In an embodiment, a gene sequence or splice site sequence provided herein is related to a metabolic disease or disorder. In an embodiment, a gene sequence or splice site sequence provided herein is related to a respiratory condition, disease, or disorder. In an embodiment, a gene sequence or splice site sequence provided herein is related to a renal disease or disorder. In an embodiment, a gene sequence or splice site sequence provided herein is related to an infectious disease.

In an embodiment, a gene sequence or splice site sequence provided herein is related to a mental retardation disorder. In an embodiment, a gene sequence or splice site sequence provided herein is related to a mutation in the SETD5 gene. In an embodiment, a gene sequence or splice site sequence provided herein is related to an immunodeficiency disorder. In an embodiment, a gene sequence and splice site sequence provided herein is related to a mutation in the GATA2 gene.

In some embodiments, a compound of Formula (I) described herein interacts with (*e.g.*, binds to) a splicing complex component (e.g., a nucleic acid (e.g., an RNA) or a protein). In some embodiments, the splicing complex component is selected from 9G8, Al hnRNP, A2 hnRNP, ASD-1, ASD-2b, ASF, BRR2, B1 hnRNP, C1 hnRNP, C2 hnRNP, CBP20, CBP80,

CELF, F hnRNP, FBP11, Fox-1, Fox-2, G hnRNP, H hnRNP, hnRNP 1, hnRNP 3, hnRNP C, hnRNP G, hnRNP K, hnRNP M, hnRNP U, Hu, HUR, I hnRNP, K hnRNP, KH-type splicing regulatory protein (KSRP), L hnRNP, LUC7L, M hnRNP, mBBP, muscle-blind like (MBNL), NF45, NFAR, Nova-1, Nova-2, nPTB, P54/SFRS11, polypyrimidine tract binding protein (PTB), a PRP protein (e.g., PRP8, PRP6, PRP31, PRP4, PRP3, PRP28, PRP5, PRP2, PRP19), PRP19 complex proteins, RBM42, R hnRNP, RNPC1, SAD1, SAM68, SC35, SF, SF1/BBP, SF2, SF3A complex, SF3B complex, SFRS10, an Sm protein (such as B, D1, D2, D3, F, E, G), SNU17, SNU66, SNU114, an SR protein, 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, Ul 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.

In some embodiments, the splicing complex component comprises RNA (*e.g.,* snRNA). In some embodiments, a compound described herein binds to a splicing complex component comprising snRNA. The snRNA may be selected from, *e.g.,* U1 snRNA, U2 snRNA, U4 snRNA, U5 snRNA, U6 snRNA, U11 snRNA, U12 snRNA, U4atac snRNA, and any combination thereof.

In some embodiments, the splicing complex component comprises a protein, *e.g.,* a protein associated with an snRNA. In some embodiments, the protein comprises SC35, SRp55, SRp40, SRm300, SFRS10, TASR-1, TASR-2, SF2/ASF, 9G8, SRp75, SRp30c, SRp20 and P54/SFRS11. In some embodiments, the splicing complex component comprises a U2 snRNA auxiliary factor (e.g., U2AF65, U2AF35), Urp/U2AF1-RS2, SF1/BBP, CBP80, CBP 20, SF1 or PTB/hnRNP1. In some embodiments, the splicing complex component comprises a heterogenous ribonucleoprotein particle (hnRNP), e.g., an hnRNP protein. In some embodiments, the hnRNP protein comprises A1, A2/B1, L, M, K, U, F, H, G, R, I or 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*.

In one aspect, the compounds of Formula (I) and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, and compositions thereof, may modulate (e.g., increase or decrease) a splicing event of a target nucleic acid sequence (e.g., DNA, RNA, or a

pre-mRNA), for example, a nucleic acid encoding a gene described herein, or a nucleic acid encoding a protein described herein, or a nucleic acid comprising a splice site described herein. In an embodiment, the splicing event is an alternative splicing event.

In an embodiment, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, and compositions thereof increases splicing at splice site on a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA), by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, e.g., as determined by a known method in the art, e.g., qPCR. In an embodiment, the compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, and compositions thereof decreases splicing at splice site on a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA), by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, e.g., as determined by a known method in the art, e.g., qPCR.

In another aspect, the present disclosure features a method of forming a complex comprising a component of a spliceosome (e.g., a major spliceosome component or a minor spliceosome component), a nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA), and a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or composition thereof, comprising contacting the nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA) with said compound of Formula (I). In an embodiment, the component of a spliceosome is selected from the U1, U2, U4, U5, U6, U11, U12, U4atac, U6atac small nuclear ribonucleoproteins (snRNPs), or a related accessory factor. In an embodiment, the component of a spliceosome is recruited to the nucleic acid in the presence of the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or composition thereof.

In another aspect, the present disclosure features a method of altering the structure or conformation of a nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA) comprising contacting the nucleic acid with a compound of Formula (I) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer, or composition thereof. In an embodiment, the altering comprises forming a bulge or kink in the nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA). In an embodiment, the altering comprises stabilizing a bulge or a kink in the nucleic acid (e.g., a

DNA, RNA, e.g., a pre-mRNA). In an embodiment, the altering comprises reducing a bulge or a kink in the nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA). In an embodiment, the nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA) comprises a splice site. In an embodiment, the compound of Formula (I) interacts with a nucleobase, ribose, or phosphate moiety of a nucleic acid (e.g., a DNA, RNA, e.g., pre-mRNA).

The present disclosure also provides methods for the treatment or prevention of a disease, disorder, or condition. In an embodiment, the disease, disorder or condition is related to (e.g., caused by) a splicing event, such as an unwanted, aberrant, or alternative splicing event. In an embodiment, the disease, disorder or condition comprises a proliferative disease (e.g., cancer, benign neoplasm, or inflammatory disease) or non-proliferative disease. In an embodiment, the disease, disorder, or condition comprises a neurological disease, autoimmune disorder, immunodeficiency disorder, cardiovascular condition, metabolic disorder, lysosomal storage disease, respiratory condition, renal disease, or infectious disease in a subject. In another embodiment, the disease, disorder, or condition comprises a haploinsufficiency disease, an autosomal recessive disease (e.g., with residual function), or a paralogue activation disorder. In another embodiment, the disease, disorder, or condition comprises an autosomal dominant disorder (e.g., with residual function). Such methods comprise the step of administering to the subject in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer thereof, or a pharmaceutical composition thereof. In certain embodiments, the methods described herein include administering to a subject an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

In certain embodiments, the subject being treated is a mammal. In certain embodiments, the subject is a human. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal such as a dog or cat. In certain embodiments, the subject is a livestock animal such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal such as a rodent, dog, or non-human primate. In certain embodiments, the subject is a non-human transgenic animal such as a transgenic mouse or transgenic pig.

A proliferative disease, disorder, or condition may also be associated with inhibition of

apoptosis of a cell in a biological sample or subject. All types of biological samples described herein or known in the art are contemplated as being within the scope of the disclosure. The compounds of Formula (I) and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, and compositions thereof, may induce apoptosis, and therefore, be useful in treating and/or preventing proliferative diseases, disorders, or conditions.

In certain embodiments, the proliferative disease to be treated or prevented using the compounds of Formula (I) is cancer. As used herein, the term "cancer" refers to a malignant neoplasm (Stedman's Medical Dictionary, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990). All types of cancers disclosed herein or known in the art are contemplated as being within the scope of the disclosure. Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (e.g., lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (e.g., cholangiocarcinoma); bladder cancer; breast cancer (e.g., adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (e.g., meningioma, glioblastomas, glioma (e.g., astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (e.g., cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (e.g., colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (e.g., Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (e.g., uterine cancer, uterine sarcoma); esophageal cancer (e.g., adenocarcinoma of the esophagus, Barrett's adenocarcinoma); Ewing's sarcoma; eye cancer (e.g., intraocular melanoma, retinoblastoma); familiar hypereosinophilia; gall bladder cancer; gastric cancer (e.g., stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (e.g., head and neck squamous cell carcinoma, oral cancer (e.g., oral squamous cell carcinoma), throat cancer (e.g., laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematopoietic cancers (e.g., leukemia such as acute lymphocytic leukemia (ALL) (e.g., B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (e.g., B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (e.g., B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (e.g., B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (e.g., B-cell HL, T-cell HL) and non-Hodgkin

lymphoma (NHL) (e.g., B-cell NHL such as diffuse large cell lymphoma (DLCL) (e.g., diffuse large B-cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (e.g., mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (i.e., Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (e.g., cutaneous T-cell lymphoma (CTCL) (e.g., mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (e.g., alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (e.g., nephroblastoma a.k.a. Wilms' tumor, renal cell carcinoma); liver cancer (e.g., hepatocellular cancer (HCC), malignant hepatoma); lung cancer (e.g., bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (e.g., systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (e.g., polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) a.k.a. myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (e.g., neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (e.g., gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (e.g., bone cancer); ovarian cancer (e.g., cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (e.g., pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (e.g., Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (e.g., prostate

adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (e.g., squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (e.g., appendix cancer); soft tissue sarcoma (e.g., malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma; testicular cancer (e.g., seminoma, testicular embryonal carcinoma); thyroid cancer (e.g., papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (e.g., Paget's disease of the vulva).

In some embodiments, the proliferative disease is associated with a benign neoplasm. For example, a benign neoplasm may include adenoma, fibroma, hemangioma, tuberous sclerosis, and lipoma. All types of benign neoplasms disclosed herein or known in the art are contemplated as being within the scope of the disclosure.

In some embodiments, the proliferative disease is associated with angiogenesis. All types of angiogenesis disclosed herein or known in the art are contemplated as being within the scope of the disclosure.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat a non-proliferative disease. Exemplary non-proliferative diseases include a neurological disease, autoimmune disorder, immunodeficiency disorder, lysosomal storage disease, cardiovascular condition, metabolic disorder, respiratory condition, inflammatory disease, renal disease, or infectious disease.

In certain embodiments, the non-proliferative disease is a neurological disease. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat a neurological disease, disorder, or condition. A neurological disease, disorder, or condition may include a neurodegenerative disease, a psychiatric condition, or a musculoskeletal disease. A neurological disease may further include a repeat expansion disease, e.g., which may be characterized by the expansion of a nucleic acid sequence in the genome. For example, a repeat expansion disease includes myotonic dystrophy, amyotrophic lateral sclerosis, Huntington's disease, a trinucleotide repeat disease, or a polyglutamine disorder (e.g., ataxia,

fragile X syndrome). In some embodiments, the neurological disease comprises a repeat expansion disease, e.g., Huntington's disease. Additional neurological diseases, disorders, and conditions include Alzheimer's disease, Huntington's chorea, a prion disease (*e.g.*, Creutzfeld-Jacob disease, bovine spongiform encephalopathy, Kuru, or scrapie), a mental retardation disorder (e.g., a disorder caused by a SETD5 gene mutation, e.g., intellectual disability-facial dysmorphism syndrome, autism spectrum disorder), Lewy Body disease, diffuse Lewy body disease (DLBD), dementia, progressive supranuclear palsy (PSP), progressive bulbar palsy (PBP), psuedobulbar palsy, spinal and bulbar muscular atrophy (SBMA), primary lateral sclerosis, Pick's disease, primary progressive aphasia, corticobasal dementia, Parkinson's disease, Down's syndrome, multiple system atrophy, spinal muscular atrophy (SMA), progressive spinobulbar muscular atrophy (e.g., Kennedy disease), post-polio syndrome (PPS), spinocerebellar ataxia, pantothenate kinase-associated neurodegeneration (PANK), spinal degenerative disease/motor neuron degenerative diseases, upper motor neuron disorder, lower motor neuron disorder, Hallervorden-Spatz syndrome, cerebral infarction, cerebral trauma, chronic traumatic encephalopathy, transient ischemic attack, Lytigo-bodig (amyotrophic lateral sclerosis-parkinsonism dementia), Guam-Parkinsonism dementia, hippocampal sclerosis, corticobasal degeneration, Alexander disease, Apler's disease, Krabbe's disease, neuroborreliosis, neurosyphilis, Sandhoff disease, Tay-Sachs disease, Schilder's disease, Batten disease, Cockayne syndrome, Kearns-Sayre syndrome, Gerstmann-Straussler-Scheinker syndrome and other transmissible spongiform encephalopathies, hereditary spastic paraparesis, Leigh's syndrome, a demyelinating diseases, neuronal ceroid lipofuscinoses, epilepsy, tremors, depression, mania, anxiety and anxiety disorders, sleep disorders (*e.g.*, narcolepsy, fatal familial insomnia), acute brain injuries (*e.g.*, stroke, head injury), autism, Machado-Joseph disease, or a combination thereof. In some embodiments, the neurological disease comprises Friedrich's ataxia or Sturge Weber syndrome. In some embodiments, the neurological disease comprises Huntington's disease. All types of neurological diseases disclosed herein or known in the art are contemplated as being within the scope of the disclosure.

In certain embodiments, the non-proliferative disease is an autoimmune disorder or an immunodeficiency disorder. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat an autoimmune disease,

disorder, or condition, or an immunodeficiency disease, disorder, or condition. Exemplary autoimmune and immunodeficiency diseases, disorders, and conditions include arthritis (e.g., rheumatoid arthritis, osteoarthritis, gout), Chagas disease, chronic obstructive pulmonary disease (COPD), dermatomyositis, diabetes mellitus type 1, endometriosis, Goodpasture's syndrome, Graves' disease, Guillain-Barrė syndrome (GBS), Hashiomoto's disease, Hidradenitis suppurativa, Kawasaki disease, ankylosing spondylitis, IgA nephropathy, idiopathic thrombocytopenic purpura, inflammatory bowel disease, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischemic colitis, diversion colitis, Behcet's syndrome, infective colitis, indeterminate colitisinterstitial cystitis, lupus (e.g., systemic lupus erythematosus, discoid lupus, drug-induced lupus, neonatal lupus), mixed connective tissue disease, morphea, multiple sclerosis, myasthenia gravis, narcolepsy, neuromyotonia, pemphigus vulgaris, pernicious anemia, psoriasis, psoriatic arthritis, polymyositis, primary biliary cirrhosis, relapsing polychondritis, scleroderma, Sjögren's syndrome, Stiff person syndrome, vasculitis, vitiligo, a disorder caused by a GATA2 mutation (e.g., GATA2 deficiency; GATA2 haploinsufficiency; Emberger syndrome; monocytopenia and mycobacterium avium complex/dendritic cell, monocyte, B and NK lymphocyte deficiency; familial myelodysplastic syndrome; acute myeloid leukemia; chronic myelomonocytic leukemia), neutropenia, aplastic anemia, and Wegener's granulomatosis. In some embodiments, the autoimmune or immunodeficiency disorder comprises chronic mucocutaneous candidiasis. All types of autoimmune disorders and immunodeficiency disorders disclosed herein or known in the art are contemplated as being within the scope of the disclosure.

In certain embodiments, the non-proliferative disease is a cardiovascular condition. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat a cardiovascular disease, disorder, or condition. A cardiovascular disease, disorder, or condition may include a condition relating to the heart or vascular system, such as the arteries, veins, or blood. Exemplary cardiovascular diseases, disorders, or conditions include angina, arrhythmias (atrial or ventricular or both), heart failure, arteriosclerosis, atheroma, atherosclerosis, cardiac hypertrophy, cardiac or vascular aneurysm, cardiac myocyte dysfunction, carotid obstructive disease, endothelial damage after PTCA (percutaneous transluminal coronary angioplasty), hypertension including essential hypertension, pulmonary

hypertension and secondary hypertension (renovascular hypertension, chronic glomerulonephritis), myocardial infarction, myocardial ischemia, peripheral obstructive arteriopathy of a limb, an organ, or a tissue; peripheral artery occlusive disease (PAOD), reperfusion injury following ischemia of the brain, heart or other organ or tissue, restenosis, stroke, thrombosis, transient ischemic attack (TIA), vascular occlusion, vasculitis, and vasoconstriction. All types of cardiovascular diseases, disorders, or conditions disclosed herein or known in the art are contemplated as being within the scope of the disclosure.

In certain embodiments, the non-proliferative disease is a metabolic disorder. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat a metabolic disease, disorder, or condition. A metabolic disease, disorder, or condition may include a disorder or condition that is characterized by abnormal metabolism, such as those disorders relating to the consumption of food and water, digestion, nutrient processing, and waste removal. A metabolic disease, disorder, or condition may include an acid-base imbalance, a mitochondrial disease, a wasting syndrome, a malabsorption disorder, an iron metabolism disorder, a calcium metabolism disorder, a DNA repair deficiency disorder, a glucose metabolism disorder, hyperlactatemia, a disorder of the gut microbiota. Exemplary metabolic conditions include obesity, diabetes (Type I or Type II), insulin resistance, glucose intolerance, lactose intolerance, eczema, hypertension, Hunter syndrome, Krabbe disease, sickle cell anemia, maple syrup urine disease, Pompe disease, and metachromatic leukodystrophy. All types of metabolic diseases, disorders, or conditions disclosed herein or known in the art are contemplated as being within the scope of the disclosure.

In certain embodiments, the non-proliferative disease is a respiratory condition. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat a respiratory disease, disorder, or condition. A respiratory disease, disorder, or condition can include a disorder or condition relating to any part of the respiratory system, such as the lungs, alveoli, trachea, bronchi, nasal passages, or nose. Exemplary respiratory diseases, disorders, or conditions include asthma, allergies, bronchitis, allergic rhinitis, chronic obstructive pulmonary disease (COPD), lung cancer, oxygen toxicity, emphysema, chronic bronchitis, and acute respiratory distress syndrome. All types of respiratory diseases, disorders, or conditions

disclosed herein or known in the art are contemplated as being within the scope of the disclosure.

In certain embodiments, the non-proliferative disease is a renal disease. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat a renal disease, disorder, or condition. A renal disease, disorder, or condition can include a disease, disorder, or condition relating to any part of the waste production, storage, and removal system, including the kidneys, ureter, bladder, urethra, adrenal gland, and pelvis. Exemplary renal diseases include acute kidney failure, amyloidosis, Alport syndrome, adenovirus nephritis, acute lobar nephronia, tubular necrosis, glomerulonephritis, kidney stones, urinary tract infections, chronic kidney disease, polycystic kidney disease, and focal segmental glomerulosclerosis (FSGS). In some embodiments, the renal disease, disorder, or condition comprises HIV-associated nephropathy or hypertensive nephropathy. All types of renal diseases, disorders, or conditions disclosed herein or known in the art are contemplated as being within the scope of the disclosure.

In certain embodiments, the non-proliferative disease is an infectious disease. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat an infectious disease, disorder, or condition. An infectious disease may be caused by a pathogen such as a virus or bacteria. Exemplary infectious diseases include human immunodeficiency syndrome (HIV), acquired immunodeficiency syndrome (AIDS), meningitis, African sleeping sickness, actinomycosis, pneumonia, botulism, chlamydia, Chagas disease, Colorado tick fever, cholera, typhus, giardiasis, food poisoning, ebola hemorrhagic fever, diphtheria, Dengue fever, gonorrhea, streptococcal infection (e.g., Group A or Group B), hepatitis A, hepatitis B, hepatitis C, herpes simplex, hookworm infection, influenza, Epstein-Barr infection, Kawasaki disease, kuru, leprosy, leishmaniasis, measles, mumps, norovirus, meningococcal disease, malaria, Lyme disease, listeriosis, rabies, rhinovirus, rubella, tetanus, shingles, scarlet fever, scabies, Zika fever, yellow fever, tuberculosis, toxoplasmosis, or tularemia. In some embodiments, the infectious disease comprises cytomegalovirus. All types of infectious diseases, disorders, or conditions disclosed herein or known in the art are contemplated as being within the scope of the disclosure.

In certain embodiments, the disease, disorder, or condition is a haploinsufficiency

disease. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat a haploinsufficiency disease, disorder, or condition. A haploinsufficiency disease, disorder, or condition may refer to a monogenic disease in which an allele of a gene has a loss-of-function lesion, e.g., a total loss of function lesion. In an embodiment, the loss-of-function lesion is present in an autosomal dominant inheritance pattern or is derived from a sporadic event. In an embodiment, the reduction of gene product function due to the altered allele drives the disease phenotype despite the remaining functional allele (i.e. said disease is haploinsufficient with regard to the gene in question). In an embodiment, a compound of Formula (I) increases expression of the haploinsufficient gene locus. In an embodiment, a compound of Formula (I) increases one or both alleles at the haploinsufficient gene locus. Exemplary haploinsufficiency diseases, disorders, and conditions include Robinow syndrome, cardiomyopathy, cerebellar ataxia, pheochromocytoma, Charcot-Marie-Tooth disease, neuropathy, Takenouchi-Kosaki syndrome, Coffin-Siris syndrome 2, chromosome 1p35 deletion syndrome, spinocerebellar ataxia 47, deafness, seizures, dystonia 9, GLUT1 deficiency syndrome 1, GLUT1 deficiency syndrome 2, stomatin-deficient cryohydrocytosis, basal cell carcinoma, basal cell nevus syndrome, medulloblastoma, somatic, brain malformations, macular degeneration, cone-rod dystrophy, Dejerine-Sottas disease, hypomyelinating neuropathy, Roussy-Levy syndrome, glaucoma, autoimmune lymphoproliferative syndrome, pituitary hormone deficiency, epileptic encephalopathy, early infantile, popliteal pterygium syndrome, van der Woude syndrome, Loeys-Dietz syndrome, Skraban-Deardorff syndrome, erythrocytosis, megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome, mental retardation, CINCA syndrome, familial cold inflammatory syndrome 1, keratoendothelitis fugax hereditaria, Muckle-Wells syndrome, Feingold syndrome 1, Acute myeloid leukemia, Heyn-Sproul-Jackson syndrome, Tatton-Brown-Rahman syndrome, Shashi-Pena syndrome, Spastic paraplegia, autosomal dominant, macrophthalmia, colobomatous, with microcornea, holoprosencephaly, schizencephaly, endometrial cancer, familial, colorectal cancer, hereditary nonpolyposis, intellectual developmental disorder with dysmorphic facies and behavioral abnormalities, ovarian hyperstimulation syndrome, schizophrenia, Dias-Logan syndrome, premature ovarian failure, dystonia, dopa-responsive, due to sepiapterin reductase deficiency, Beck-Fahrner syndrome, chromosome 2p12-p11.2 deletion syndrome, neuronopathy, spastic paraplegia,

familial adult myoclonic, colorectal cancer, hypothyroidism, Culler-Jones syndrome, holoprosencephaly, myelokathexis, WHIM syndrome, Mowat-Wilson syndrome, mental retardation, an intellectual developmental disorder, autism spectrum disorder, epilepsy, epileptic encephalopathy, Dravet syndrome, migraines, a mental retardation disorder (e.g., a disorder caused by a SETD5 gene mutation, e.g., intellectual disability-facial dysmorphism syndrome, autism spectrum disorder), a disorder caused by a GATA2 mutation (e.g., GATA2 deficiency; GATA2 haploinsufficiency; Emberger syndrome; monocytopenia and mycobacterium avium complex/dendritic cell, monocyte, B and NK lymphocyte deficiency; familial myelodysplastic syndrome; acute myeloid leukemia; chronic myelomonocytic leukemia), and febrile seizures.

In certain embodiments, the disease, disorder, or condition is an autosomal recessive disease, e.g., with residual function. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat an autosomal recessive disease, disorder, or condition. An autosomal recessive disease with residual function may refer to a monogenic disease with either homozygous recessive or compound heterozygous heritability. These diseases may also be characterized by insufficient gene product activity (e.g., a level of gene product greater than 0%). In an embodiment, a compound of Formula (I) may increase the expression of a target (e.g., a gene) related to an autosomal recessive disease with residual function. Exemplary autosomal recessive diseases with residual function include Friedreich's ataxia, Stargardt disease, Usher syndrome, chlorioderma, fragile X syndrome, achromatopsia 3, Hurler syndrome, hemophilia B, alpha-1-antitrypsin deficiency, Gaucher disease, X-linked retinoschisis, Wiskott-Aldrich syndrome, mucopolysaccharidosis (Sanfilippo B), DDC deficiency, epidermolysis bullosa dystrophica, Fabry disease, metachromatic leukodystrophy, and odontochondrodysplasia.

In certain embodiments, the disease, disorder, or condition is an autosomal dominant disease. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat an autosomal dominant disease, disorder, or condition. An autosomal dominant disease may refer to a monogenic disease in which the mutated gene is a dominant gene. These diseases may also be characterized by insufficient gene product activity (e.g., a level of gene product greater than 0%). In an embodiment, a compound of Formula (I)

may increase the expression of a target (e.g., a gene) related to an autosomal dominant disease. Exemplary autosomal dominant diseases include Huntington's disease, achondroplasia, antithrombin III deficiency, Gilbert's disease, Ehlers-Danlos syndrome, hereditary hemorrhagic telangiectasia, intestinal polyposis, hereditary elliptosis, hereditary spherocytosis, marble bone disease, Marfan's syndrome, protein C deficiency, Treacher Collins syndrome, Von Willebrand's disease, tuberous sclerosis, osteogenesis imperfecta, polycystic kidney disease, neurofibromatosis, and idiopathic hypoparathyroidism.

In certain embodiments, the disease, disorder, or condition is a paralogue activation disorder. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat a paralogue activation disease, disorder, or condition. A paralogue activation disorder may comprise a homozygous mutation of genetic locus leading to loss-of-function for the gene product. In these disorders, there may exist a separate genetic locus encoding a protein with overlapping function (e.g. developmental paralogue), which is otherwise not expressed sufficiently to compensate for the mutated gene. In an embodiment, a compound of Formula (I) activates a gene connected with a paralogue activation disorder (e.g., a paralogue gene).

The cell described herein may be an abnormal cell. The cell may be *in vitro* or *in vivo*. In certain embodiments, the cell is a proliferative cell. In certain embodiments, the cell is a cancer cell. In certain embodiments, the cell is a non-proliferative cell. In certain embodiments, the cell is a blood cell. In certain embodiments, the cell is a lymphocyte. In certain embodiments, the cell is a benign neoplastic cell. In certain embodiments, the cell is an endothelial cell. In certain embodiments, the cell is an immune cell. In certain embodiments, the cell is a neuronal cell. In certain embodiments, the cell is a glial cell. In certain embodiments, the cell is a brain cell. In certain embodiments, the cell is a fibroblast. In certain embodiment, the cell is a primary cell, e.g., a cell isolated from a subject (e.g., a human subject).

In certain embodiments, the methods described herein comprise the additional step of administering one or more additional pharmaceutical agents in combination with the compound of Formula (I), a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof. Such additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-diabetic agents,

anti-inflammatory agents, immunosuppressant agents, and a pain-relieving agent. The additional pharmaceutical agent(s) may synergistically augment the modulation of splicing induced by the inventive compounds or compositions of this disclosure in the biological sample or subject. Thus, the combination of the inventive compounds or compositions and the additional pharmaceutical agent(s) may be useful in treating, for example, a cancer or other disease, disorder, or condition resistant to a treatment using the additional pharmaceutical agent(s) without the inventive compounds or compositions.

EXAMPLES

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

The compounds provided herein can be prepared from readily available starting materials using modifications to the specific synthesis protocols set forth below that would be well known to those of skill in the art. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, *etc.*) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by those skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in Greene *et al.*, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

Reactions can be purified or analyzed according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance (NMR) spectroscopy (*e.g.*, ^{1}H or ^{13}C), infrared (IR) spectroscopy,

spectrophotometry (*e.g.*, UV-visible), mass spectrometry (MS), or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

Proton NMR: ^{1}H NMR spectra were recorded in $CDCl_3$ solution in 5-mm o.d. tubes (Wildmad) at 24 °C and were collected on a BRUKER AVANCE NEO 400 at 400 MHz for ^{1}H. The chemical shifts (δ) are reported relative to tetramethylsilane (TMS = 0.00 ppm) and expressed in ppm.

LC/MS: Liquid chromatography-mass spectrometry (LC/MS) was performed on Shimadzu-2020EV using column: Shim-pack XR-ODS (C18, Ø4.6 x 50 mm, 3 μm, 120 Å, 40 °C) operating in ESI(+) ionization mode; flow rate = 1.2 mL/min. Mobile phase = 0.05% TFA in water or CH_3CN; or on Shimadzu-2020EV using column : Poroshell HPH-C18 (C18, Ø4.6 x 50 mm, 3 μm, 120 Å, 40 °C) operating in ESI(+) ionization mode; flow rate = 1.2 mL/min. Mobile phase A: Water/5mM NH_4HCO_3, Mobile phase B: CH_3CN.)

Analytical chiral HPLC: Analytical chiral HPLC was performed on a Agilent 1260 using column: CHIRALPAK IG-3, CHIRALPAK IC-3 or CHIRALPAK OJ-3, with flow rate = 1.2 mL/min. Mobile phase = MTBE(DEA):EtOH=50:50).

Preparative HPLC purification: prep-HPLC purification was performed using one of the following HPLC conditions:

Condition 1: Shimadzu, Column: XBridge Prep OBD C18 Column, 30Å—150mm 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3) Mobile Phase B: acetonitrile; Flow rate:60 mL/min; Gradient 1: 3 B to 3 B in 2 min; Gradient 2: 5% B to 35% B in 6 min; Gradient 3: 3 B to 33 B in 6 min; Gradient 4: 5% B up to 45% in 6 min; Gradient 5: 3% B to 23% B in 6 min; Gradient 6: 10% B to 60% B in 8 min; Gradient 7: 5 B to 45 B in 10 min; Gradient 8: 10% B up to 47% B in 10 min; Gradient 9: 10% B up to 50% B in 8 min; Gradient 9: 5% B to 35% B in 8 min; Gradient 10: 10% B to 48% B in 10 min; Gradient 11: 20% B to 52% B in 8 min; Gradient 12: 20% B to 50% B in 6 min; Gradient 13: 20% B to 43% B in 8 min; Gradient 14: 15% B to 45% B in 8 min; Gradient 14: 10% B to 55% B in 8 min; Gradient 15: 5% B to 38% B in 10 min; Gradient 16: 10% B to 35% B in 8 min; Gradient 17: 5% B to 42% B in 8 min; Gradient 18: 5% B to 30 %B in 8 min; Gradient 18: 5% B to 40% B in 8 min; Gradient 19: 5% B to 45% B in 8 min; Gradient 21: 5% B to 37% B in 8 min; Gradient 22: 5% B to 65% B in 8 min.

Condition 2: Column: Xselect CSH OBD Column 30*150mm 5 μm, n; Mobile Phase A: water (10mmol/L NH_4HCO_3); Mobile Phase B: acetonitrile; Flow rate: 60 mL/min; Gradient 1:

10 B to 55 B in 8 min; Gradient 2: 5 B to 50 B in 8 min; Gradient 3: 10 B to 60 B in 10 min; Gradient 4: 10 B to 40 B in 8 min; Gradient 5: 5 B to 65 B in 8 min; Gradient 6: 3% B to 63% B in 6 min; Gradient 7: 10% B to 52% B in 8 min; Gradient 8: 5% B to 37% B in 8 min; Gradient 9: 10% B to 38% B in 8 min; Gradient 10: 3% B to 75% B in 8 min; Gradient 11: 10% B to 42% B in 8 min; Gradient 12: 15% B to 40% B in 10 min; Gradient 13: 10% B to 60% B in 8 min; Gradient 14: 5% B to 35% B in 8 min.

Condition 3: Column: EP-C18M 10 μm 120A; Mobile Phase A: water (1mmol/L HCl); Mobile Phase B: acetonitrile; Flow rate:100 mL/min; Gradient: 40% B to 70% B in 35 min.

Condition 4: Column: Poroshell HPH-C18, 3.0*50 mm,2.7um; Mobile Phase A: water (5 mM NH_4HCO_3); Mobile Phase B: acetonitrile; Flow rate: 1.2 mL/min; Gradient 1:10% B to 95% B in 1.2 min, hold 0.5 min.

Condition 5: Column: X Select CSH OBD 30 x 150 mm 5 μm; Mobile phase A: water (0.1% formic acid); Mobile phase B: acetonitrile; Gradient 1: 3% phase B up to 18% in 6 min.

Condition 6: Column: X Select CSH OBD 30 x 150 mm 5 μm; Mobile phase A: water (0.05% HCl); Mobile phase B: acetonitrile; Flow rate: 60 mL/min; Gradient 1: 3% phase B up to 3% in 2 min.

Condition 7: Column: X Select CSH OBD 30 x 150 mm 5 μm; Mobile phase A: water (0.05% formic acid); Mobile phase B: acetonitrile; Flow rate: 60 mL/min; Gradient 1: 3% phase B up to 20% in 8 min.

Condition 8: Column: YMC-Actus Triart C18, 30 mm x 150 mm, 5 μm; Mobile phase A: water (0.05% HCl); Mobile phase B: acetonitrile; Gradient 1: 5% B to 35% B in 8 min.

Condition 9: Column: YMC-Actus Triart C18, 30 mm x 150 mm, 5 μm; Mobile phase A: water (10 mmol/L NH_4HCO_3); Mobile phase B: acetonitrile; Flow rate: 60 mL/min Gradient 1: 10% B to 70% B in 8 min; Gradient 2: 15% B to 55% B in 8 min; Gradient 3: 5% B to 65% B in 8 min; Gradient 3: 5% B to 45% B in 8 min; Gradient 4:15% B to 45% B in 10 min.

Preparative chiral HPLC: purification by chiral HPLC was performed on a Gilson-GX 281 using column: CHIRALPAK IG-3, CHIRALPAK IC-3 or CHIRALPAK OJ-3.

Condition 1: Column: CHIRALPAK IG, 3 x 25 cm, 5 μm; Mobile Phase A: MTBE (0.1%DEA), Mobile Phase B: ethanol; Flow rate:20 mL/min; Gradient 1: 50 B to 50 B in 18 min.

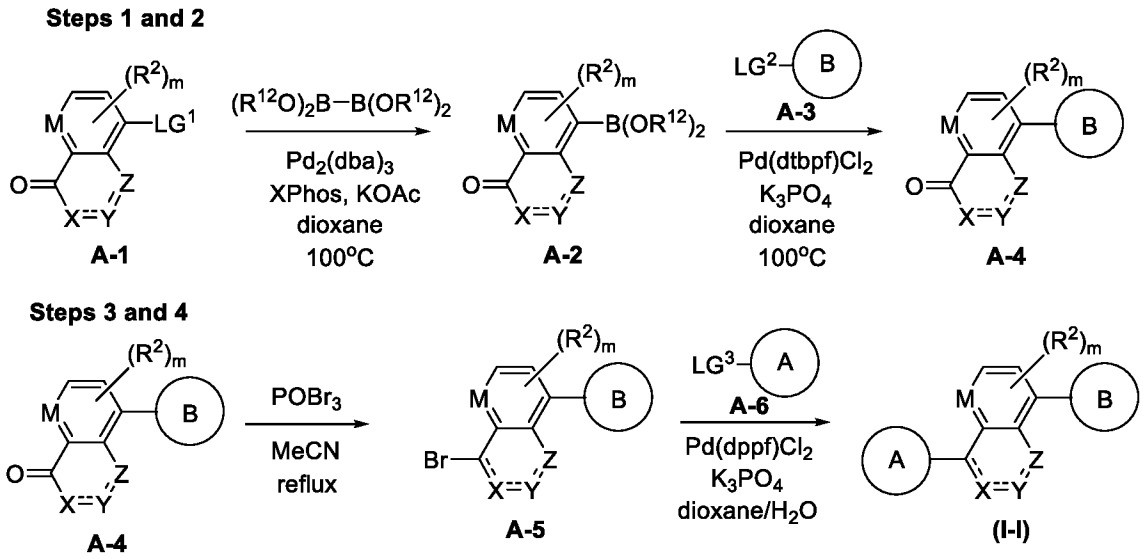
Reverse flash chromagraphy: purification by reverse flash chromatography was performed using one of the following conditions:

Condition 1: Column, C18; Mobile phase: MeOH in water; Gradient 1, 10% to 50% in 1 0 min; Detector, UV 254 nm.

Condition 2: Column, silica gel; Mobile phase: MeOH in water; Gradient 1: 10% to 50% in 10 min; Detector, UV 254 nm.

General Synthetic Scheme

Compounds of the present disclosure may be prepared using a synthetic protocol illustrated in Scheme A.



Scheme A. An exemplary method of preparing a compound of Formula (I); wherein A, B, M, X, Y, Z, R^2, and m are as defined herein; LG^1, LG^2, and LG^3 are each independently a leaving group (e.g., halo, $-B(OR^{12})_2$); and $-B(OR^{12})_2$ is a boronic acid or ester (e.g., Bpin), wherein each R^{12} may be hydrogen, C_1-C_6-alkyl, C_2-C_6-heteroalkyl, aryl, or heteroaryl; or two R^{12} groups, together with the atoms to which they are attached, form a heterocyclyl or heteroaryl.

An exemplary method of preparing a compound described herein, e.g., a compound of Formula (I-I), is provided in Scheme A. In Step 1, A-2 is prepared by incubating A-1 with a reagent suitable to displace LG^1 with a boronic ester group, such as $(R^{12}O)_2B–B(OR^{12})_2$ (e.g., bis(pinacolato)diboron (B_2pin_2)). Other common reagents for installing boronic ester groups (e.g., pinacol borane) can also be used. This reaction may involve the use of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) and potassium acetate (KOAc) or a suitable alternative. Step 1 may also be carried out using an alternative catalyst to $Pd_2(dba)_3$, such as another palladium catalyst, or using an alternative ligand to XPhos (e.g., another phosphine ligand). The reaction

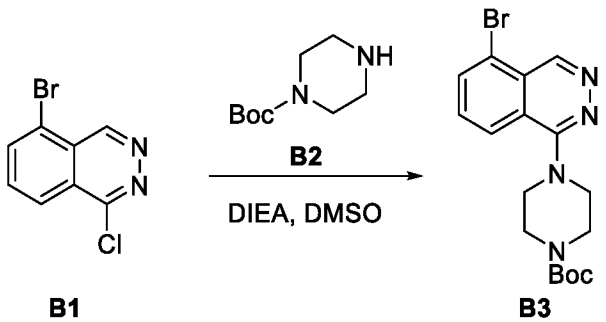
may be conducted in dioxane or a similar solvent, at 100 °C or a temperature sufficient to provide A-2.

In Step 2, A-4 is prepared by incubating A-2 with A-3. Step 2 may be carried out in the presence of [1,1′-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) ($Pd(dtbpf)Cl_2$) and tripotassium phosphate (K_3PO_4) or a similar reagent. Alternative catalysts to $Pd(dtbpf)Cl_2$ may also be used, such as a suitable palladium catalyst (e.g., a catalyst suitable for a Suzuki reaction). The coupling of A-2 and A-3 may be carried out in dioxane or a similar solvent, and heated to 100 °C or temperature sufficient to provide A-4. In Step 3, A-5 is prepared by treating A-4 with phosphoryl bromide ($POBr_3$) in acetonitrile (MeCN), or by using a similar reagent or solvent. The conversion of A-4 may be conducted at reflux, or at a temperature sufficient to provide A-5.

A-5 and A-6 are coupled to provide a compound of Formula (I-I) in Step 4. This coupling reaction may be conducted in the presence of 1,1'-bis(diphenylphosphino)ferrocene)-palladium(II) dichloride ($Pd(dppf)Cl_2$), and K_3PO_4 or a similar reagent. Alternative catalysts to $Pd(dppf)Cl_2$ may be used, such as any suitable palladium catalyst. The reaction of Step 4 is conducted in a mixture of dioxane and water, or other suitable solvents, at a temperature sufficient to provide the compound of Formula (I-I). Each starting material and/or intermediate in Scheme A may be protected and deprotected using standard protecting group methods. In addition, purification and characterization of each intermediate as well as the final compound of Formula (I) may be afforded by any accepted procedure.

Example 1: Synthesis of Compound 100

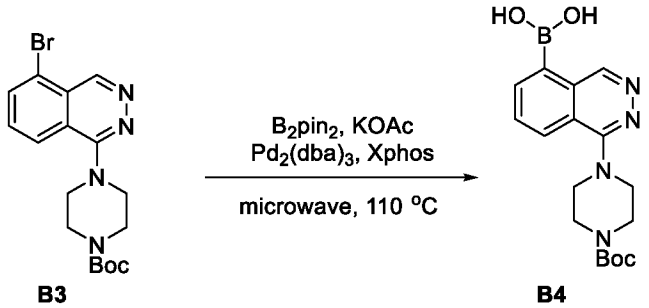
Synthesis of Intermediate B3



N,N-Diisopropylethylamine (DIEA, 2.39 g, 18.48 mmol, 3 equiv) was added dropwise to a mixture of 5-bromo-1-chlorophthalazine (B1 from Example 3; 1.50 g, 6.16 mmol, 1 equiv) and *tert*-butyl piperazine-1-carboxylate (B2; 1.38 g, 7.39 mmol, 1.2 equiv) in dimethyl sulfoxide (DMSO; 20 mL) at room temperature, and the resulting mixture was stirred for 2 h at 100 °C.

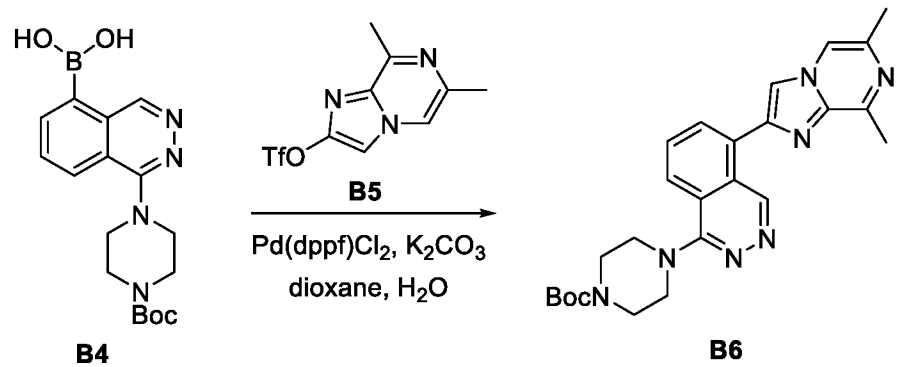
The residue was purified by reverse-phase flash chromatography using a C18 silica gel column, eluting with acetonitrile in water (0% to 100% gradient over 10 min, to provide *tert*-butyl 4-(5-bromophthalazin-1-yl)piperazine-1-carboxylate (B3; 1 g) as a solid. **LCMS** (ES, *m/z*): 393 $[M+H]^+$.

Synthesis of Intermediate B4



Potassium acetate (374 mg, 3.81 mmol, 3 equiv), X-Phos (182, 0.38 mmol, 0.3 equiv) and $Pd_2(dba)_3$ (93 mg, 0.1 mmol, 0.08 equiv) were added in portions to a mixture of *tert*-butyl 4-(5-bromophthalazin-1-yl)piperazine-1-carboxylate (B3; 500 mg, 1.27 mmol, 1 equiv) and bis(pinacolato)diboron (646 mg, 2.54 mmol, 2 equiv) in dioxane (12 mL) at room temperature under a nitrogen atmosphere, and the reaction mixture was then irradiated with microwave radiation for 4h at 110 °C. The resulting mixture was concentrated under reduced pressure, and the residue was purified by reverse phase flash chromatography using a C18 silica gel column, eluting with acetonitrile in water (0% to 50% gradient over 10 min), to provide 1-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]phthalazin-5-ylboronic acid (B4; 200 mg) as a solid. **LCMS** (ES, *m/z*): 359 $[M+H]^+$.

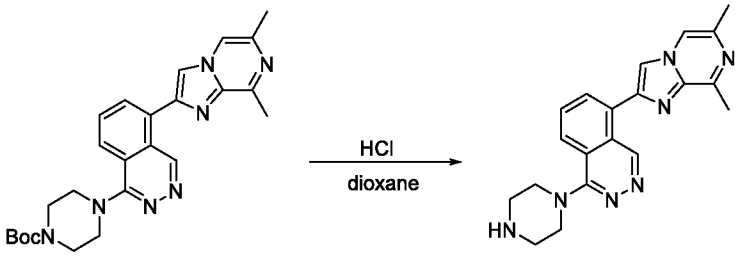
Synthesis of Intermediate B6



Potassium carbonate (174 mg, 1.26 mmol, 3 equiv) and $Pd(dppf)Cl_2$ (31 mg, 0.04 mmol, 0.1 equiv) were added in portions to a mixture of 1-[4-(*tert*-butoxycarbonyl)piperazin-1-

yl]phthalazin-5-ylboronic acid (B4; 150 mg, 0.42 mmol, 1 equiv) and 6,8-dimethylimidazo[1,2-a]pyrazin-2-yl trifluoromethanesulfonate (B5; 148 mg, 0.50 mmol, 1.2 equiv) in dioxane (7.5 mL) and H_2O (1.5 mL) at room temperature under a nitrogen atmosphere, and the resulting mixture was stirred for 2h at 80 °C. The reaction was quenched with water at room temperature and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (3:1) to afford *tert*-butyl 4-(5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]phthalazin-1-yl)piperazine-1-carboxylate (B6; 100 mg) as a solid. **LCMS** (ES, *m/z*): 460 $[M+H]^+$.

Synthesis of Compound 100

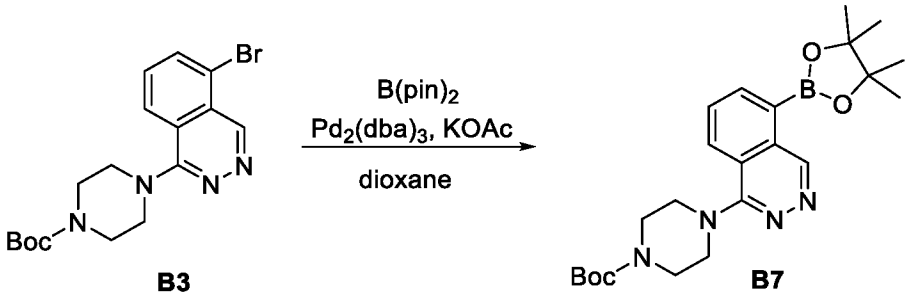


B6 100

A mixture of *tert*-butyl 4-(5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]phthalazin-1-yl)piperazine-1-carboxylate (B6; 100 mg, 0.22 mmol, 1 equiv) and HCl in 1,4-dioxane (5 mL) was stirred for 1h at room temperature under air. The crude product was purified by preparative HPLC (Condition 1; Gradient 1) to afford 5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]-1-(piperazin-1-yl)phthalazine (Compound 100; 12.9 mg) as a solid. **LCMS** (ES, m/z): 360 $[M+H]^+$. **^{1}H NMR** (400 MHz, Chloroform-d) δ 9.99 (s, 1H), 8.20-8.11 (m, 2H), 7.95-7.86 (m, 3H), 3.55 (t, J = 4.9 Hz, 4H), 3.21 (t, J = 4.9 Hz, 4H), 2.98 (s, 3H), 2.56 (s, 3H).

Example 2: Synthesis of Compound 101

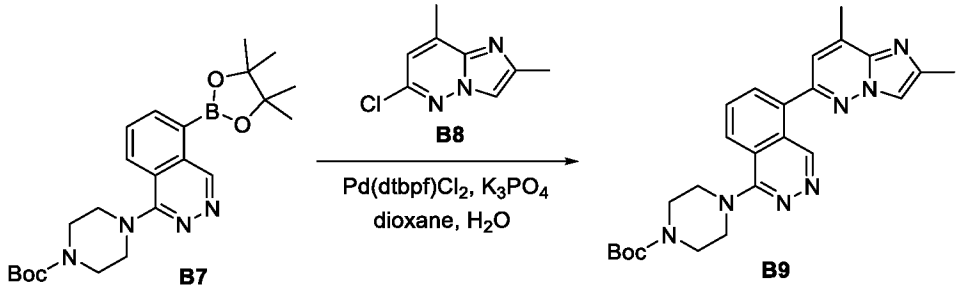
Synthesis of Intermediate B7



B3 B7

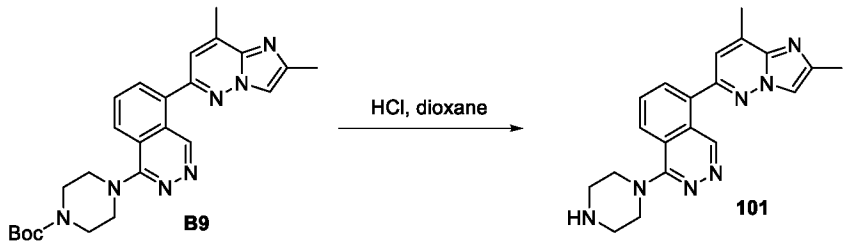
A 20-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-(5-bromophthalazin-1-yl)piperazine-1-carboxylate (B3 from Example 1; 1 g, 2.5 mmol, 1 equiv), bis(pinacolato)diboron (1.16 g, 4.5 mmol, 1.8 equiv), KOAc (0.75 g, 7.62 mmol, 3 equiv), $Pd_2(dba)_3$ (186 mg, 0.2 mmol, 0.08 equiv), XPhos (363 mg, 0.76 mmol, 0.3 equiv), and 1,4-dioxane (10 mL) were added to the vial, and the mixture was irradiated with microwave radiation for 1.5h at 110 °C. The mixture was then cooled to 25 °C and extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were concentrated to provide crude *tert*-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phthalazin-1-yl]piperazine-1-carboxylate (B7; 1.2 g) as a solid. **LCMS** (ES, *m/z*): 441 $[M+H]^+$.

Synthesis of Intermediate B9



A 20-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phthalazin-1-yl]piperazine-1-carboxylate (B7; 1 g, 2.27 mmol, 1 equiv), 6-chloro-2,8-dimethylimidazo[1,2-b]pyridazine (B8; 0.49 g, 2.72 mmol, 1.2 equiv), $Pd(dtbpf)Cl_2$ (74 mg, 0.114 mmol, 0.05 equiv), K_3PO_4 (1.45 g, 6.81 mmol, 3.0 equiv), 1.4-dioxane (8 mL), and H_2O (2 mL) were added to the flask, and the mixture was irradiated with microwave radiation for 1.5h at 110 °C. The reaction was quenched by the addition of water/ice, and the resulting solution was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography eluting with ethyl acetate/hexanes (1:1) to provide *tert*-butyl 4-(5-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]phthalazin-1-yl)piperazine-1-carboxylate (B9; 400 mg) as a solid. **LCMS** (ES, *m/z*): 460 $[M+H]^+$.

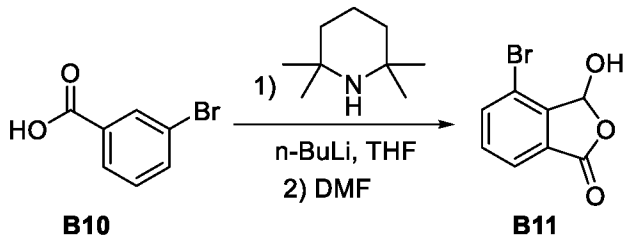
Synthesis of Compound 101



A 10-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-(5-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]phthalazin-1-yl)piperazine-1-carboxylate (B9; 350 mg, 1 equiv), dioxane (1 mL), and 4M HCl in dioxane (3 mL) were added to the flask, and the resulting solution was stirred for 3h at 25 °C. The mixture was then concentrated, and purified by preparative HPLC (Condition 1, Gradient 2) to provide 5-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]-1-(piperazin-1-yl)phthalazine (Compound 101; 51.3 mg) as a solid. **LCMS** (ES, *m/z*): 460 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.12 - 8.19 (m, 2H), 8.07 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 1.3 Hz, 1H), 3.34 - 3.38 (m, 5H), 3.01 - 3.05 (m, 4H), 2.65 (s, 3H), 2.45 (s, 3H).

Example 3: Synthesis of Compound 102

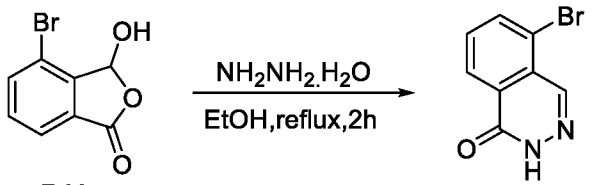
Synthesis of Intermediate B11



n-Butyllithium (1.6 M in tetrahydrofuran, 200 mL, 2.2 equiv,) and tetrahydrofuran (200 mL) were added to a 1000-mL 3-necked round-bottom flask that was purged and maintained under an atmosphere of nitrogen. 2,2,6,6-Tetramethylpiperidine (46.38 g, 328.33 mmol, 2.2 equiv) was then added dropwise over 5 min with stirring at 0 °C, followed by the dropwise addition of *m*-bromobenzoic acid (B10; 30 g, 149.24 mmol, 1 equiv) over 5 min with stirring at 0 °C, and the resulting solution was stirred for an additional 0.5h at 25 °C. Dimethylformamide (43.63 g, 596.96 mmol, 4 equiv) was then added dropwise with stirring over 5 min at 0 °C, and the resulting solution was stirred for 2h at 25 °C. The reaction was then quenched by the addition of water/ice (200 mL), and the resulting solution was extracted with ethyl acetate (2 x 100 mL) and the aqueous layers were combined. The pH of the solution was adjusted to 3 with 1M HCl, and the resulting solution was extracted with ethyl acetate (3 x 100 mL) and the combined organic

layers were dried over anhydrous sodium sulfate and concentrated, to provide crude 4-bromo-3-hydroxy-3H-2-benzofuran-1-one (B11; 27 g) as a solid, which was used directly in the subsequent step.

Synthesis of Intermediate B12

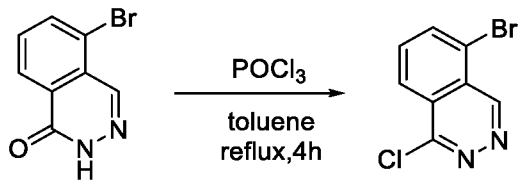


B11 B12

A 1000-mL 3-necked round-bottom flask was purged and maintained under an atmosphere of nitrogen, then 4-bromo-3-hydroxy-3H-2-benzofuran-1-one (B11; 27 g, 117.9 mmol, 1 equiv), ethanol (300 mL), and hydrazine hydrate (32.81 g, 655.5 mmol, 5.6 equiv) were added to the flask, and the resulting solution was stirred for 2h at 80 °C. The solids were collected by filtration and washed with ethanol to provide 5-bromo-2H-phthalazin-1-one (B12; 9 g) as a solid.

LCMS (ES, *m/z*): 225 $[M+H]^+$.

Synthesis of Intermediate B1

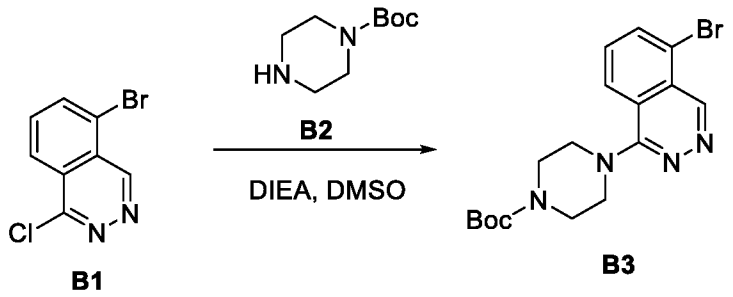


B12 B1

A 50-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, and 5-bromo-2H-phthalazin-1-one (B12; 1 g, 4.44 mmol, 1 equiv), toluene (5 mL), and phosphorus oxychloride (5 mL) were added to the flask, and the resulting solution was stirred for 2h at 80 °C. The resulting mixture was concentrated and washed with tetrahydrofuran (10 mL). The solids were collected by filtration, to provide 5-bromo-1-chlorophthalazine (B1; 1 g) as a solid.

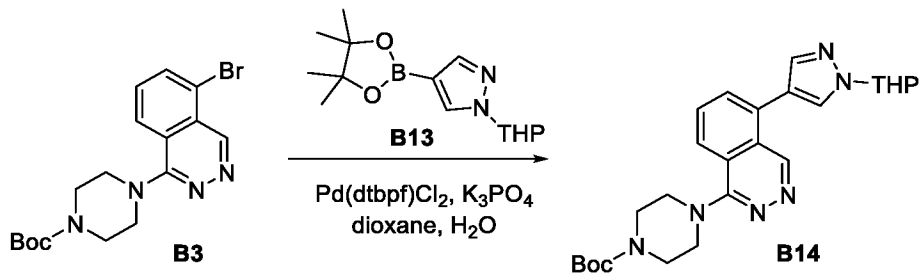
LCMS (ES, *m/z*): 243 $[M+H]^+$.

Synthesis of Intermediate B3



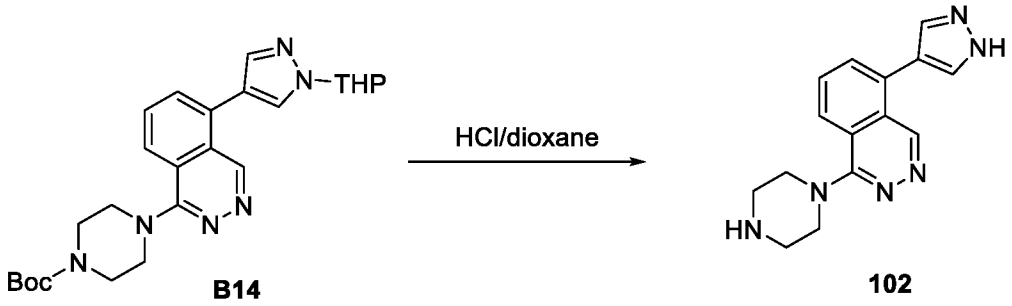
A 20-mL round-bottom flask was purged and maintained under an inert atmosphere of nitrogen, then 5-bromo-1-chlorophthalazine (B1; 750 mg, 3.08 mmol, 1 equiv), dimethyl sulfoxide (8 mL), N,N-diisopropylethylamine (DIEA; 1.59 g, 12.3 mmol, 4 equiv), and *tert*-butyl piperazine-1-carboxylate (B2; 631 mg, 3.39 mmol, 1.1 equiv) were added to the flask, and the resulting solution was stirred for 2 min at 100 °C. The reaction was then quenched by the addition of water/ice (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated, to provide *tert*-butyl 4-(5-bromophthalazin-1-yl)piperazine-1-carboxylate (B3; 690 mg) as a solid. **LCMS** (ES, *m/z*): 393 $[M+H]^+$.

Synthesis of Intermediate B13



A 40-mL 3-necked round-bottom flask was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-(5-bromophthalazin-1-yl)piperazine-1-carboxylate (B3; 600 mg, 1.53 mmol, 1 equiv), 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (B13; 466.8 mg, 1.68 mmol, 1.1 equiv), $Pd(dtbpf)Cl_2$ (49.72 mg, 0.076 mmol, 0.05 equiv), dioxane (8 mL), K_3PO_4 (971.5 mg, 4.58 mmol, 3 equiv), and H_2O (2 mL) were added to the flask, and the resulting solution was stirred for 2h at 80 °C. The mixture was then concentrated and purified with silica gel column chromatography eluting with ethyl acetate/hexanes (1:1), to provide *tert*-butyl 4-[5-[1-(oxan-2-yl)pyrazol-4-yl]phthalazin-1-yl]piperazine-1-carboxylate (B14; 290 mg) as a solid. **LCMS** (ES, *m/z*): 465 $[M+H]^+$.

Synthesis of Compound 102

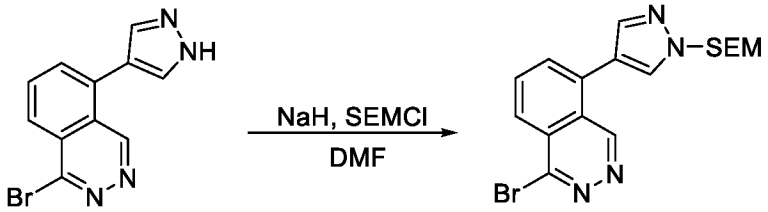


B14 102

A 100-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-[5-[1-(oxan-2-yl)pyrazol-4-yl]phthalazin-1-yl]piperazine-1-carboxylate (B14; 250 mg), dioxane (1 mL), and HCl in dioxane (5 mL) were added to the flask, and the resulting solution was stirred for 1h at 25 °C. The resulting mixture was concentrated, and purified by preparative HPLC (Condition 1, Gradient 3) to provide 1-(piperazin-1-yl)-5-(1H-pyrazol-4-yl)phthalazine (Compound 102; 11.9 mg) as a solid. **LCMS** (ES, *m/z*): 281 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ: 13.29 (brs, 1H), 9.34 - 9.40 (m, 1H), 8.10 (s, 2H), 7.98 - 8.05 (m, 1H), 7.90 - 7.97 (m, 2H), 3.40 - 3.83 (m, 2H), 3.17 - 3.29 (m, 3H), 2.99 (t, J = 4.8 Hz, 3H).

Example 4: Synthesis of Compound 103

Synthesis of Intermediate B16

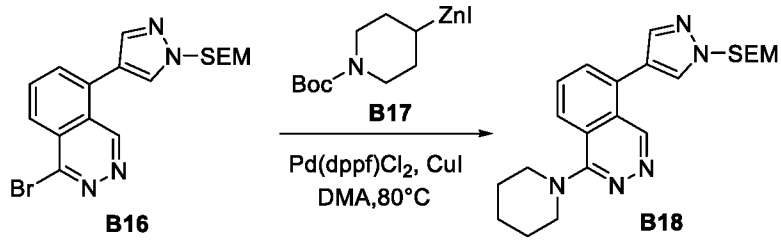


B15 B16

A 10-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then 1-bromo-5-(1H-pyrazol-4-yl)phthalazine (B15 from Example 6; 400 mg, 1.45 mmol, 1 equiv) and dimethylformamide (3 mL) were added to the flask, and the mixture was cooled to 0 °C before adding sodium hydride (52 mg, 2.18 mmol, 1.5 equiv). The mixture was then stirred at 0°C for 0.5h, before adding 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl; 266 mg, 1.6 mmol, 1.1 equiv), and the solution was stirred for an additional 1h at 25 °C in a water/ice bath. The reaction was then quenched by the addition of water/ice (5 mL), and the solution was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated, to provide 1-bromo-5-(1-[[2-

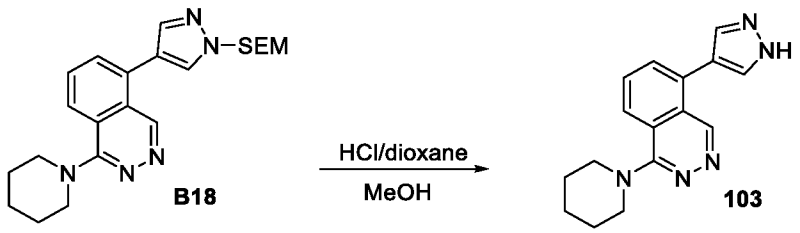
(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)phthalazine (B16; 450 mg) as an oil. **LCMS** (ES, *m/z*): 405 $[M+H]^+$.

Synthesis of Intermediate B17



A 20-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then 1-bromo-5-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)phthalazine (B16; 450 mg, 1.11 mmol, 1 equiv), $Pd(dppf)Cl_2$ (40 mg, 0.056 mmol, 0.05 equiv), CuI (21 mg, 0.11 mmol, 0.1 equiv), dimethylacetamide (4 mL), and [1-(tert-butoxycarbonyl)piperidin-4-yl](iodo)zinc (B17; 4.4 mL) were added to the flask, and the resulting solution was stirred for 80h at 5 °C. The reaction was then quenched by the addition of ice/salt (10 mL) and extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography eluting with dichloromethane/methanol (10:1) to provide 1-(piperidin-1-yl)-5-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)phthalazine (B18; 120 mg) as a solid. **LCMS** (ES, *m/z*): 410 $[M+H]^+$.

Synthesis of Compound 103

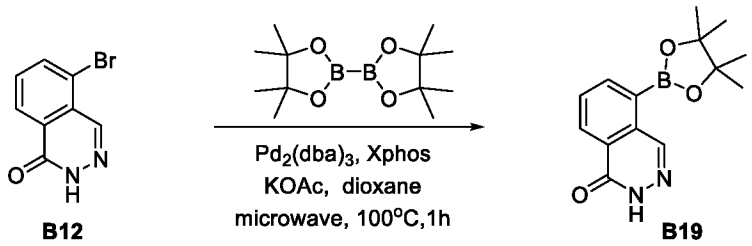


A 10-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then 1-(piperidin-1-yl)-5-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)phthalazine (B18; 120 mg) and 4M HCl in 1,4-dioxane (3 mL) were added to the flask, and the resulting solution was stirred for 1h at 25 °C. The mixture was then concentrated and purified by preparative HPLC (Condition 2, Gradient 1) to provide 1-(piperidin-1-yl)-5-(1H-pyrazol-4-yl)phthalazine (Compound 103; 7.9 mg) as a solid. **LCMS** (ES, *m/z*): 280 $[M+H]^+$. **^{1}H NMR** (400 MHz,

Methanol-d_4) δ 9.32 - 9.38 (m, 1H), 8.09 - 8.13 (m, 2H), 7.92 - 8.02 (m, 3H), 3.50 (t, J = 5.3 Hz, 4H), 1.90 - 1.95 (m, 4H), 1.80 - 1.85 (m, 2H).

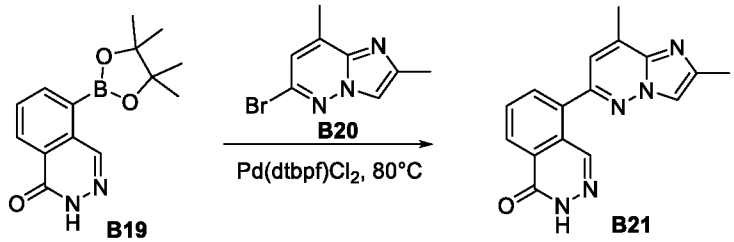
Example 5: Synthesis of Compound 104

Synthesis of Intermediate B19



A 20-mL sealed tube was purged and maintained under an atmosphere of nitrogen, then 5-bromo-2H-phthalazin-1-one (B12 from Example 3; 1 g, 4.44 mmol, 1 equiv), bis(pinacolato)diboron (2.03 g, 7.99 mmol, 1.8 equiv), $Pd_2(dba)_3$ (0.33 g, 0.35 mmol, 0.08 equiv), Xphos (0.64 g, 1.33 mmol, 0.3 equiv), KOAc (1.31 g, 13.33 mmol, 3 equiv), and dioxane (10 mL) were added to the flask, and the mixture was irradiated with microwave radiation for 1.5h at 110 °C. The reaction was then quenched by the addition of ice/salt (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were concentrated to provide 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-phthalazin-1-one (B19; 1.2) as an oil. **LCMS** (ES, *m/z*): 273 $[M+H]^+$.

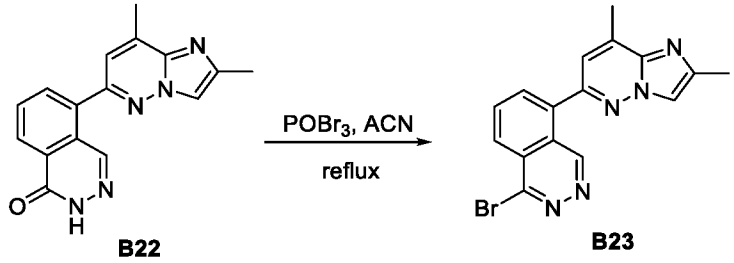
Synthesis of Intermediate B21



A 40-mL vial was purged and maintained under an atmosphere of nitrogen, then 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-phthalazin-1-one (B19; 1.1 g, 4.04 mmol, 1 equiv), 6-bromo-2,8-dimethylimidazo[1,2-b]pyridazine (B20; 1.01 g, 4.45 mmol, 1.1 equiv), $Pd(dtbpf)Cl_2$ (0.13 g, 0.20 mmol, 0.05 equiv), K_3PO_4 (2.57 g, 12.12 mmol, 3 equiv), dioxane (8 mL), and H_2O (2 mL) were added to the vial, and the resulting solution was stirred for 1h at 80 °C. The reaction was then quenched by the addition of ice/salt (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and

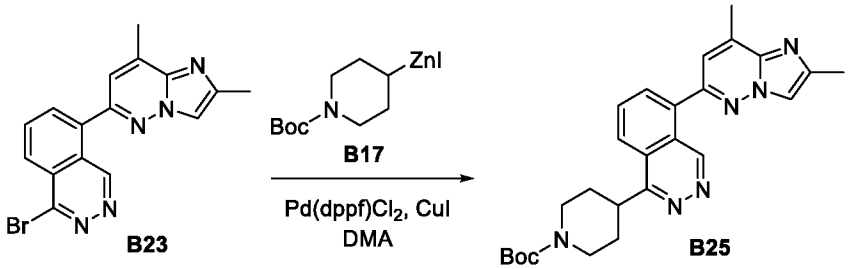
concentrated, and the residue was purified by silica gel column chromatography eluting with dichloromethane/methanol (10:1) to provide 5-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]-2H-phthalazin-1-one (B21; 1 g) as a solid. **LCMS** (ES, *m/z*): 292 $[M+H]^+$.

Synthesis of Intermediate B23



A 20-mL vial was purged and maintained under an atmosphere of nitrogen, then 5-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]-2H-phthalazin-1-one (B22; 1 g, 3.43 mmol, 1 equiv), acetonitrile (10 mL) and $POBr_3$ (5.9 g, 20.59 mmol, 6 equiv) were added to the vial, and the resulting solution was stirred for 3h at 100 °C. The reaction was quenched by the addition of water/ice (10 mL), and the pH of the solution was adjusted to 9 with saturated $NaHCO_3$. The resulting solution was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated, to provide 1-bromo-5-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]phthalazine (B23; 500 mg) as a solid. **LCMS** (ES, *m/z*): 354 $[M+H]^+$.

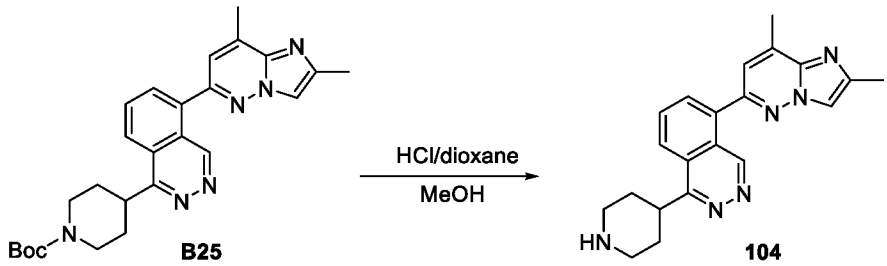
Synthesis of Intermediate B25



A 20-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then 1-bromo-5-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]phthalazine (B23; 500 mg, 1.41 mmol, 1 equiv), $Pd(dppf)Cl_2$ (51 mg, 0.071 mmol, 0.05 equiv), CuI (26 mg, 0.14 mmol, 0.1 equiv), dimethylacetamide (5 mL), and [1-(tert-butoxycarbonyl)piperidin-4-yl](iodo)zinc (B17; 5.6 mL) were added to the flask, and the resulting solution was stirred for 3h at 80 °C. The reaction was then quenched by the addition of water/ice (10 mL), extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were concentrated. The residue was purified by silica gel

column chromatography eluting with dichloromethane/methanol (10:1) to provide *tert*-butyl 4-(5-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]phthalazin-1-yl)piperidine-1-carboxylate (B25; 50 mg) as a solid. **LCMS** (ES, *m/z*): 459 $[M+H]^+$.

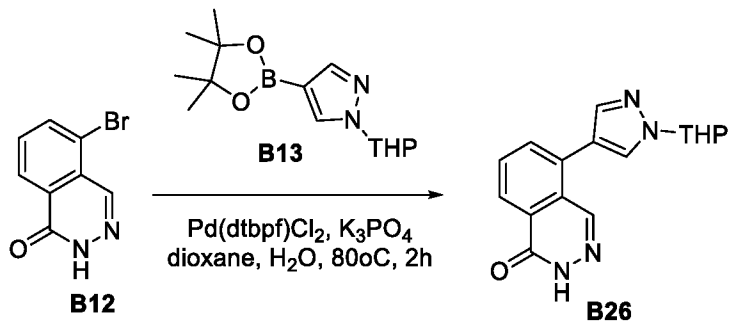
Synthesis of Compound 104



An 8-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-(5-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]phthalazin-1-yl)piperidine-1-carboxylate (B25; 50 mg), methanol (0.5 mL), and 4M HCl in 1,4-dioxane (0.5 mL) were added to the flask, and the resulting solution was stirred for 1h at 25 °C, and then concentrated. The crude product was purified by preparative HPLC (Condition 1, Gradient 4) to provide 5-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]-1-(piperidin-4-yl)phthalazine (Compound 104; 2.7 mg) as a solid. **LCMS** (ES, *m/z*): 359 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 9.78 (s, 1H), 8.59 (d, *J* = 8.3 Hz, 1H), 8.17 - 8.28 (m, 2H), 8.01 - 8.06 (m, 1H), 7.45 (d, *J* = 1.2 Hz, 1H), 4.01 (s, 1H), 3.33 - 3.35 (m, 2H), 3.04 - 3.08 (s, 2H), 2.75 (d, *J* = 1.1 Hz, 3H), 2.56 (d, *J* = 0.8 Hz, 3H), 2.16 - 2.25 (m, 4H).

Example 6: Synthesis of Compound 107

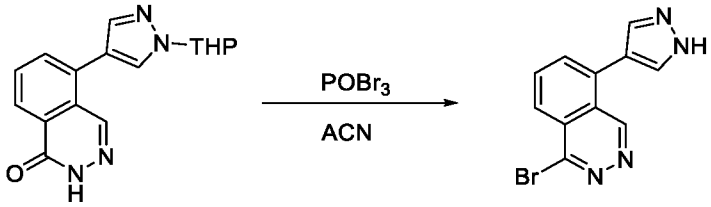
Synthesis of Intermediate B26



A 20-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, and 5-bromo-2H-phthalazin-1-one (B12 from Example 3; 1 g, 4.44 mmol, 1 equiv), 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (B13; 1.36 g, 4.88 mmol, 1.1 equiv), $Pd(dtbpf)Cl_2$ (144 mg, 0.22 mmol, 0.05 equiv), K_3PO_4 (2.83 g, 13.331 mmol, 3 equiv), dioxane

(8 mL), and H_2O (2 mL) were added to the flask, and the resulting solution was stirred for 2h at 80 °C. The solution was then extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:1) to provide 5-[1-(oxan-2-yl)pyrazol-4-yl]-2H-phthalazin-1-one (B26; 1.1 g) as a solid. **LCMS** (ES, *m/z*): 297 $[M+H]^+$.

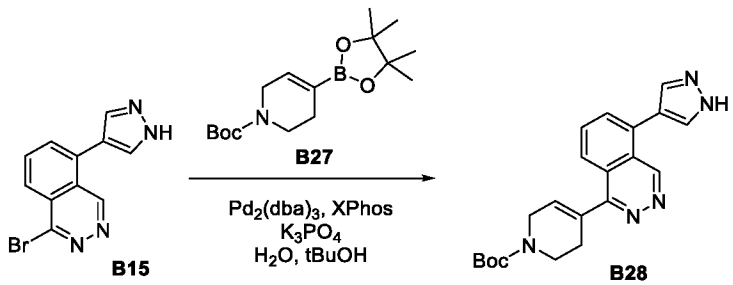
Synthesis of Intermediate B15



B26 B15

A 20-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then 5-[1-(oxan-2-yl)pyrazol-4-yl]-2H-phthalazin-1-one (B26; 1.1 g, 3.71 mmol, 1 equiv), acetonitrile (10 mL), and $POBr_3$ (6.39 g, 22.27 mmol, 6 equiv) were added to the flask, and the resulting solution was stirred for 2h at 100 °C. The reaction was quenched by the addition of water/ice (10 mL), and the pH of the solution was adjusted to 9 with saturated Na_2CO_3. The resulting solution was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate and concentrated, to provide 1-bromo-5-(1H-pyrazol-4-yl)phthalazine (B15; 800 mg) as a solid. **LCMS** (ES, *m/z*): 275 $[M+H]^+$.

Synthesis of Intermediate B28

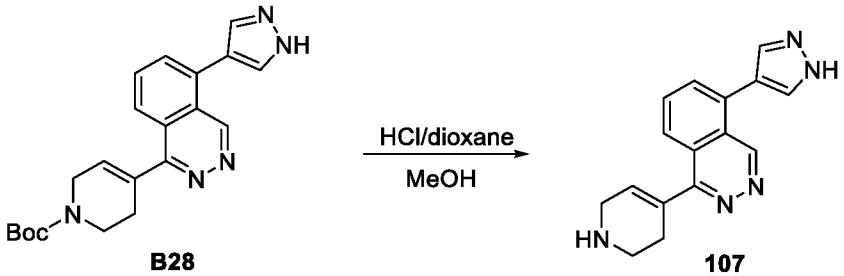


B15 B28

A 20-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then 1-bromo-5-(1H-pyrazol-4-yl)phthalazine (B15; 700 mg, 2.54 mmol, 1 equiv), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (B27; 1.02 g, 3.308 mmol, 1.3 equiv), $Pd_2(dba)_3$ (163 mg, 0.17 mmol, 0.07 equiv), XPhos (181 mg, 0.38 mmol, 0.15 equiv), K_3PO_4 (1.62 g, 7.63 mmol, 3 equiv), and H_2O/tBuOH (10 mL, 1:4) were

added to the flask, and the resulting solution was stirred for 3h at 100 °C. The reaction was quenched by the addition of ice/salt (10 mL), and the residue was purified by silica gel column chromatography eluting with dichloromethane/methanol (10:1), and dried over anhydrous sodium sulfate and concentrated, to provide *tert*-butyl 4-[5-(1H-pyrazol-4-yl)phthalazin-1-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (B28; 80 mg) as a solid. **LCMS** (ES, *m/z*): 378 $[M+H]^+$.

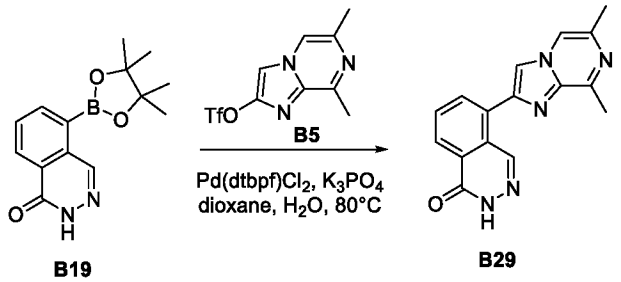
Synthesis of Compound 107



A 10-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-[5-(1H-pyrazol-4-yl)phthalazin-1-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (B28; 80 mg), methanol (1 mL), and 4M HCl in 1,4-dioxane (2 mL) were added to the flask, and the resulting solution was stirred for 2h at 25 °C. The mixture was then concentrated and purified by preparative HPLC (Condition 1, Gradient 5), to provide 5-(1H-pyrazol-4-yl)-1-(1,2,3,6-tetrahydropyridin-4-yl)phthalazine (Compound 107; 10.2 mg) as a solid. **LCMS** (ES, *m/z*): 278 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 9.67 (d, *J* = 1.0 Hz, 1H), 8.27 - 8.36 (m, 1H), 8.01 - 8.12 (m, 4H), 6.16 - 6.19 (m, 1H), 3.65 - 3.67 (m, 2H), 3.22 - 3.32 (m, 2H), 2.68 - 6.71 (m, 2H).

Example 7: Synthesis of Compound 108

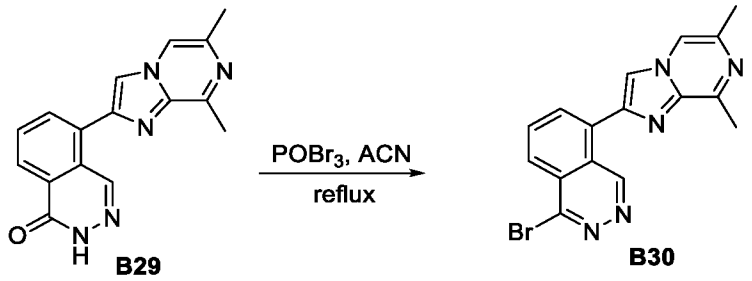
Synthesis of Intermediate B29



A 10-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-phthalazin-1-one (B19 from Example 5; 500 mg, 1.84 mmol, 1 equiv), 6,8-dimethylimidazo[1,2-a]pyrazin-2-yl trifluoromethanesulfonate (B5; 705 mg, 2.39 mmol, 1.3 equiv), $Pd(dtbpf)Cl_2$ (59 mg, 0.092 mmol, 0.05 equiv), K_3PO_4

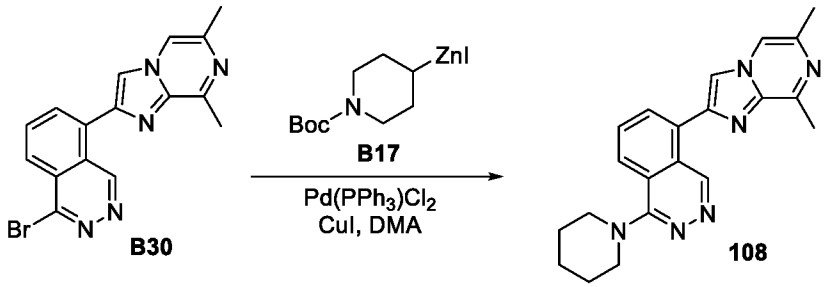
(1.17 g, 5.51 mmol, 3 equiv), 1,4-dioxane (4 mL), and H_2O (1 mL) were added to the flask, and the resulting solution was stirred for 2h at 80 °C. The reaction was then quenched by the addition of water/ice (10 mL), and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:1) to provide 5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]-2H-phthalazin-1-one (B29; 450 mg) as a solid. **LCMS** (ES, *m/z*): 292 $[M+H]^+$.

Synthesis of Intermediate B30



A 40-mL vial was purged and maintained under an atmosphere of nitrogen, then 5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]-2H-phthalazin-1-one (B29; 450 mg, 1.55 mmol, 1 equiv), acetonitrile (4 mL), and $POBr_3$ (2.66 g, 9.27 mmol, 6 equiv) were added to the vial, and the resulting solution was stirred for 5h at 80 °C. The reaction was quenched by the addition of water/ice (10 mL), and the pH of the solution was adjusted to 9 with saturated Na_2CO_3. The resulting solution was extracted with ethyl acetate (3x 20 mL) and the combined organic layers were dried over anhydrous sodium sulfate and concentrated, to provide 1-bromo-5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]phthalazine (B30; 400 mg) as a solid. **LCMS** (ES, *m/z*): 354 $[M+H]^+$.

Synthesis of Compound 108

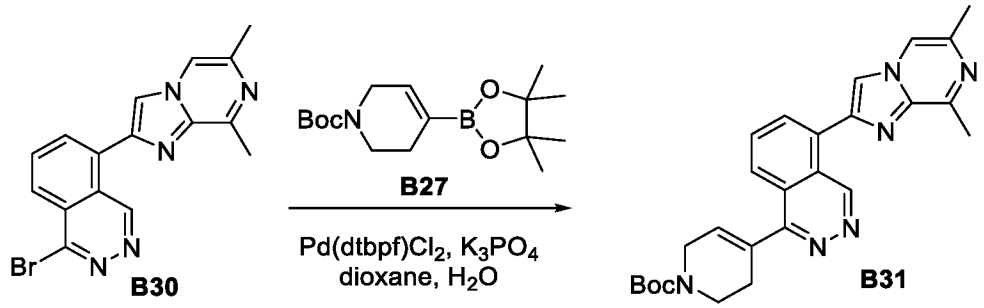


A 40-mL vial was purged and maintained under an atmosphere of nitrogen, then 1-bromo-5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]phthalazine (B30; 400 mg, 1.13 mmol, 1 equiv),

$Pd(dppf)Cl_2$ (41 mg, 0.056 mmol, 0.05 equiv), CuI (22 mg, 0.11 mmol, 0.1 equiv), dimethylacetamide (2 mL), and [1-(tert-butoxycarbonyl)piperidin-4-yl](iodo)zinc (B17; 6 mL, 0.5M in tetrahydrofuran) were added to the vial, and the resulting solution was stirred overnight at 90 °C. The reaction was then quenched by the addition of water/ice (10 mL), and the resulting solution was extracted with ethyl acetate (10 mL), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated. The crude product was purified by preparative HPLC (Condition 1, Gradient 6) to provide 5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]-1-(piperidin-1-yl)phthalazine (Compound 108; 5.6 mg) as a solid. **LCMS** (ES, m/z): 359 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.59 (s, 1H), 8.27 - 8.37 (m, 2H), 8.11 (d, *J* = 8.1 Hz, 1H), 8.00 - 8.08 (m, 1H), 3.33 - 3.35 (m, 4H), 2.82 (s, 3H), 2.48 (s, 3H), 2.44 (s, 3H), 1.80 - 1.90 (m, 4H), 1.71 - 1.75 (m, 2H).

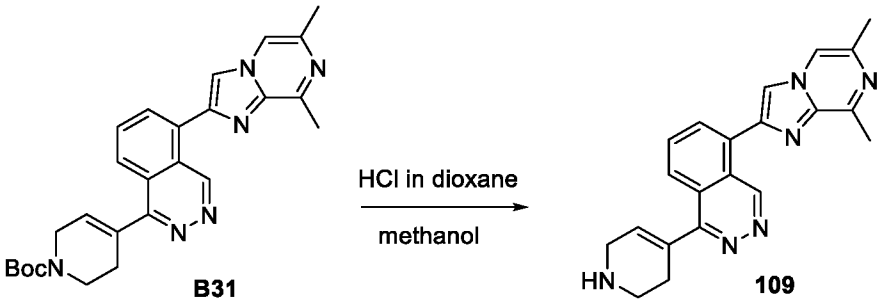
Example 8: Synthesis of Compound 109

Synthesis of Intermediate B31



A 20-mL vial was purged and maintained under an atmosphere of nitrogen, then 1-bromo-5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]phthalazine (B30 from Example 7; 300 mg, 0.85 mmol, 1 equiv), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (B27; 314.3 mg, 1.02 mmol, 1.2 equiv), $Pd(dtbpf)Cl_2$ (27.6 mg, 0.04 mmol, 0.05 equiv), K_3PO_4 (539.3 mg, 2.54 mmol, 3 equiv), 1,4-dioxane (4.5 mL), and H_2O (1.5 mL) were added to the vial, and the resulting solution was stirred for 2h at 80 °C. The mixture was then concentrated, and the residue was purified by silica gel column chromatography eluting with ethyl acetate/hexanes (100:1), to provide *tert*-butyl 4-(5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]phthalazin-1-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (B31; 200 mg) as a solid. **LCMS** (ES, *m/z*): 225 $[M+H]^+$.

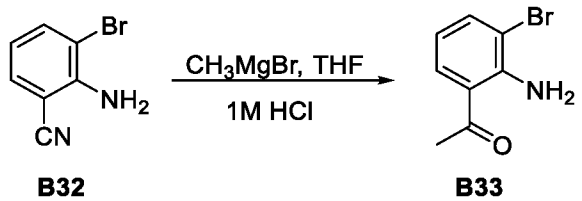
Synthesis of Compound 109



An 8-mL vial was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-(5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]phthalazin-1-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (B31; 70 mg), methanol (0.5 mL), and HCl in 1,4-dioxane (1 mL) were added to the vial, and the resulting solution was stirred for 1h at 25 °C, then concentrated. The crude product was purified by preparative HPLC (Condition 1, Gradient 2), to provide 5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]-1-(1,2,3,6-tetrahydropyridin- 4-yl)phthalazine (Compound 109; 5.4 mg) as a solid. **LCMS** (ES, *m/z*): 357 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d4) δ 10.39 (d, *J* = 0.9 Hz, 1H), 8.41 - 8.45 (m, 2H), 8.38 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.29 (t, *J* = 1.1 Hz, 1H), 8.14 (dd, *J* = 8.3, 7.4 Hz, 1H), 6.20 (dp, *J* = 3.2, 1.7 Hz, 1H), 3.67 (q, *J* = 2.9 Hz, 2H), 3.25 (t, *J* = 5.7 Hz, 2H), 2.93 (s, 3H), 2.71 (td, *J* = 5.7, 2.8 Hz, 2H), 2.53 (d, *J* = 1.0 Hz, 3H).

Example 9: Synthesis of Compound 111

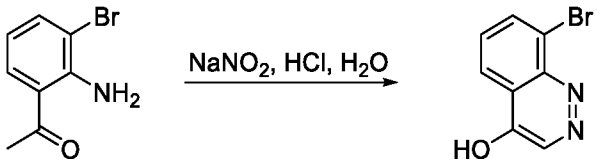
Synthesis of Intermediate B33



A 1-L round-bottom flask was purged and maintained under an atmosphere of nitrogen, then CH_3MgBr (35 mL, 304.48 mmol, 3 equiv) and tetrahydrofuran (200 mL) were added to the flask, and the mixture was cooled to 0 °C. 2-Amino-3-bromobenzonitrile (B32; 20 g, 101.5 mmol, 1 equiv) was then added, and the resulting solution was stirred overnight at room temperature. The reaction mixture was then cooled to 0 °C with a water/ice bath and quenched by the addition of 1N HCl (1 L). The pH of the solution was adjusted to 8 with $NaHCO_3$, and the resulting solution was extracted with dichloromethane (1 L), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography eluting with

dichloromethane/methanol (10:1) to provide 1-(2-amino-3-bromophenyl)ethanone (B33; 19.3 g) as a solid. **LCMS** (ES, *m/z*): 214 $[M+H]^+$.

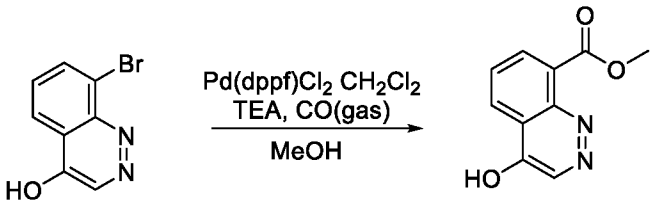
Synthesis of Intermediate B34



B33 **B34**

A 250-mL 3-necked round-bottom flask was purged and maintained under an atmosphere of nitrogen, then 1-(2-amino-3-bromophenyl)ethanone (B33; 19.6 g, 91.56 mmol, 1 equiv) and 1N HCl (63 mL) were added to the flask, and the mixture was cooled to -5 °C, before adding $NaNO_2$ (6.95 g, 100.7 mmol, 1.1 equiv) in H_2O (20 mL). The resulting solution was stirred for 3h at 65 °C, then cooled to 25°C with a water/ice bath. The solids were collected by filtration, and the residue was washed with ether and filtered, then dissolved in water, before $NaHCO_3$ was added and the mixture was stirred for 1h at room temperature, and filtered again. The filter cake was washed with ether and filtered, to provide 8-bromocinnolin-4-ol (B4; 18.9 g) as a solid. **LCMS** (ES, *m/z*): 225 $[M+H]^+$.

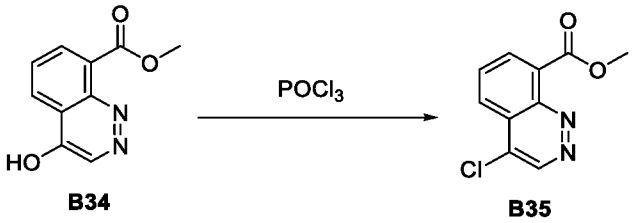
Synthesis of Intermediate B35



B34 **B35**

A mixture of 8-bromocinnolin-4-ol (B34; 19.3 g, 85.76 mmol, 1 equiv), $Pd(dppf)Cl_2$ (3.14 g, 4.23 mmol, 0.05 equiv), triethylamine (26.03 g, 257.28 mmol, 3 equiv), and methanol (200 mL) was stirred overnight at 50 °C under an atmosphere of carbon monoxide (8 psi). The resulting mixture was cooled to room temperature, filtered, washed with water, and extracted with ethyl acetate (200 mL x 3). The combined organic layers were dried with Na_2SO_4 and concentrated under a vacuum, and the residue was purified by silica gel column chromatography eluting with ethyl acetate/hexanes (0 to 50%) to provide methyl-4-hydroxycinnoline-8-carboxylate (B35; 15.9 g) as a solid. **LCMS** (ES, *m/z*): 205 $[M+H]^+$.

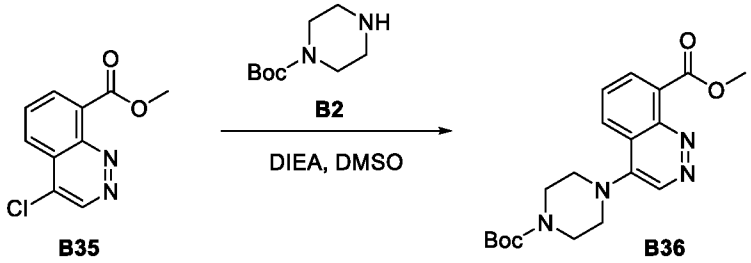
Synthesis of Intermediate B35



B34 B35

A 40-mL vial was purged and maintained under an inert atmosphere of nitrogen, then methyl 4-hydroxycinnoline-8-carboxylate (B34; 2 g) and phosphorus oxychloride (20 mL) were added to the vial, and the resulting solution was stirred for 5h at 80 °C, and then concentrated, to provide methyl 4-chlorocinnoline-8-carboxylate (B35; 2 g) as a solid. **LCMS** (ES, *m/z*): 223 $[M+H]^+$.

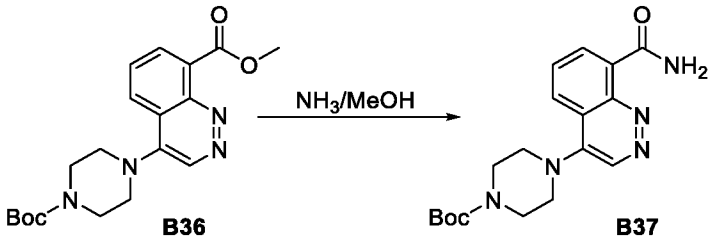
Synthesis of Intermediate B36



B35 B36

A 40-mL vial was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl piperazine-1-carboxylate (1.25 g, 6.74 mmol, 1.5 equiv), N,N-diisopropylethylamine (DIEA; 1.74 g, 13.5 mmol, 3 equiv), dimethyl sulfoxide (10 mL), and methyl 4-chlorocinnoline-8-carboxylate (B35; 1 g, 4.49 mmol, 1 equiv) were added to the vial, and the resulting solution was stirred for 2h at 80 °C. The reaction was then quenched by the addition of water/ice and extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography eluting with ethyl acetate/hexanes (1:1) to provide methyl 4-[4-(tert-butoxycarbonyl)piperazin-1-yl]cinnoline-8-carboxylate (B36; 650 mg) as a solid. **LCMS** (ES, *m/z*): 373 $[M+H]^+$.

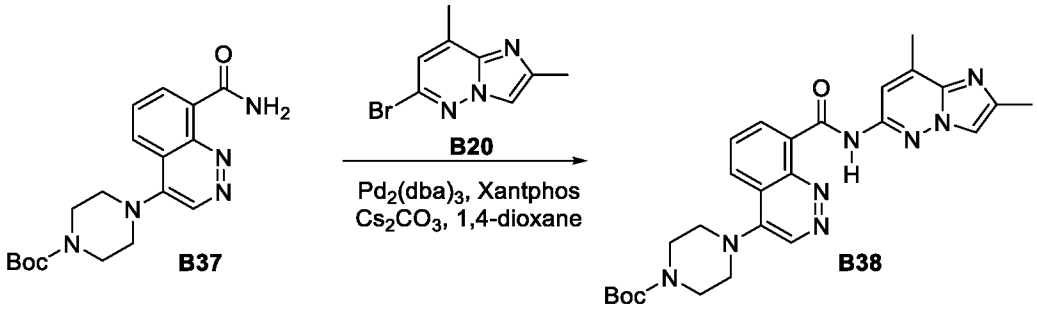
Synthesis of Intermediate B37



B36 B37

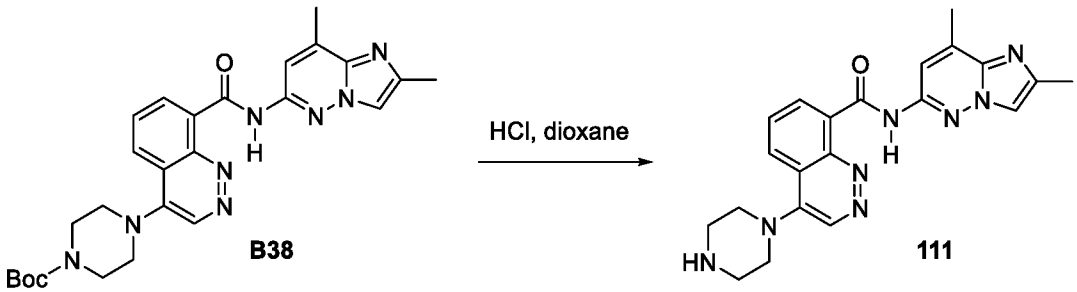
A 20-mL sealed tube was purged and maintained under an atmosphere of nitrogen, then methyl 4-[4-(tert-butoxycarbonyl)piperazin-1-yl]cinnoline-8-carboxylate (B36; 700 mg), followed by NH_3 in MeOH (7N, 7 mL) were added to the vial at 25 °C, and the resulting solution was stirred for 2h at 60 °C. The mixture was then concentrated to provide *tert*-butyl 4-(8-carbamoylcinnolin-4-yl)piperazine-1-carboxylate (B37; 650 mg) as a solid. **LCMS** (ES, *m/z*): 358 $[M+H]^+$.

Synthesis of Intermediate B38



A 10-mL vial was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-(8-carbamoylcinnolin-4-yl)piperazine-1-carboxylate (B37; 300 mg, 0.84 mmol, 1 equiv), 6-bromo-2,8-dimethylimidazo[1,2-b]pyridazine (B20; 227 mg, 1.01 mmol, 1.2 equiv), $Pd_2(dba)_3$ (192 mg, 0.21 mmol, 0.25 equiv), Xantphos (4 mg, 0.01 mmol, 0.01 equiv), Cs_2CO_3 (328 mg, 1.01 mmol, 1.20 equiv), and 1,4-dioxane (3 mL) were added to the vial, and the resulting solution was stirred for 4h at 100 °C. The mixture was then concentrated, and the residue was purified by silica gel column chromatography eluting with ethyl acetate/hexanes (9:1) to provide *tert*-butyl 4-[8-([2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]carbamoyl)cinnolin-4-yl]piperazine-1-carboxylate (B38; 100 mg) as a solid. **LCMS** (ES, *m/z*): 503 $[M+H]^+$.

Synthesis of Compound 111

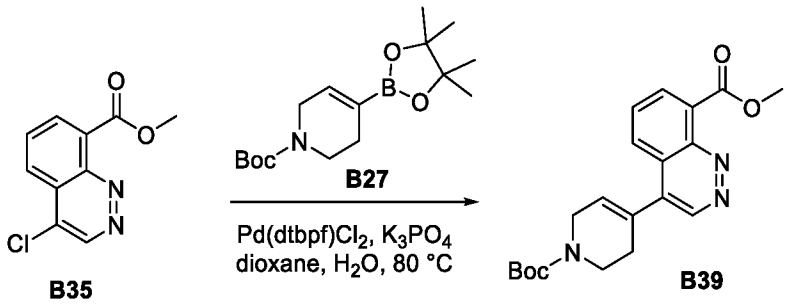


A 10-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-[8-([2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]carbamoyl)cinnolin-4-yl]piperazine-1-carboxylate (B38; 100 mg, 1 equiv) and 4M HCl in 1,4-dioxane (1mL) were added to the flask,

and the resulting solution was stirred for 2h at 25 °C, and then concentrated. The crude product was purified by preparative HPLC (Condition 1, Gradient 4) to provide N-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]-4-(piperazin-1-yl)cinnoline-8-carboxamide (Compound 111; 30.1 mg) as a solid. **LCMS** (ES, *m/z*): 403 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.94 (s, 1H), 9.15 (s, 1H), 8.70 (d, *J* = 7.2 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 8.10 (s, 1H), 7.98 (s, 1H), 7.89 (t, *J* = 7.9 Hz, 1H), 3.52 (t, *J* = 4.8 Hz, 4H), 3.07 (t, *J* = 4.8 Hz, 4H), 2.60 (s, 3H), 2.39 (s, 3H).

Example 10: Synthesis of Compound 112

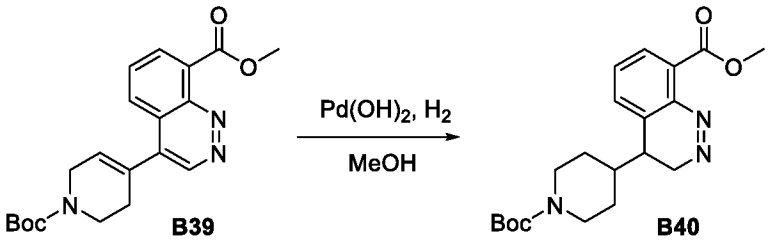
Synthesis of Intermediate B39



A 40-mL round-bottom flask was purged and maintained under an atmosphere of nitrogen, then methyl 4-chlorocinnoline-8-carboxylate (B35; 2 g, 8.98 mmol, 1 equiv), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (B27; 3.1 g, 9.88 mmol, 1.1 equiv), Pd(dtbpf)Cl_2 (0.29 g, 0.45 mmol, 0.05 equiv), 1,4-dioxane (16 mL), K_3PO_4 (5.72 g, 26.95 mmol, 3 equiv), and H_2O (4 mL) were added to the flask, and the resulting solution was stirred for 2h at 80 °C. The reaction was then quenched by the addition of water/ice (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were concentrated, and the residue was purified by silica gel column chromatography eluting with dichloromethane/methanol (10:1), to provide methyl 4-[1-(*tert*-butoxycarbonyl)-3,6-dihydro-2H-pyridin-4-yl]cinnoline-8-carboxylate (B39; 600 mg) as an oil.

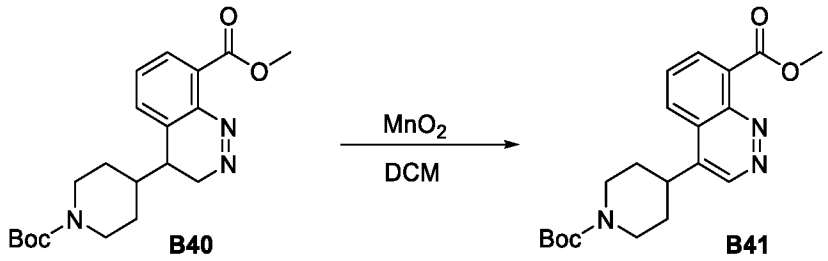
LCMS (ES, *m/z*): 370 $[M+H]^+$.

Synthesis of Intermediate B40



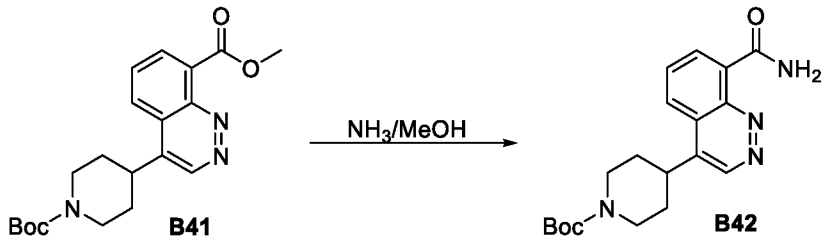
A mixture of *tert*-butyl 4-(5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]phthalazin-1-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (B39; 20 mg, 0.044 mmol), $Pd(OH)_2$ (5 mg), and methanol (2 mL) was stirred at 50 °C under a hydrogen atmosphere (20 Pa) for 5h. The solids were then removed by filtration, and the filtrate was concentrated to provide *tert*-butyl 4-(5-[6,8-dimethylimidazo[1,2-a]pyrazin-2-yl]phthalazin-1-yl)piperidine-1-carboxylate (B40; 400 mg) as a solid. **LCMS** (ES, *m/z*): 374 $[M+H]^+$.

Synthesis of Intermediate B41



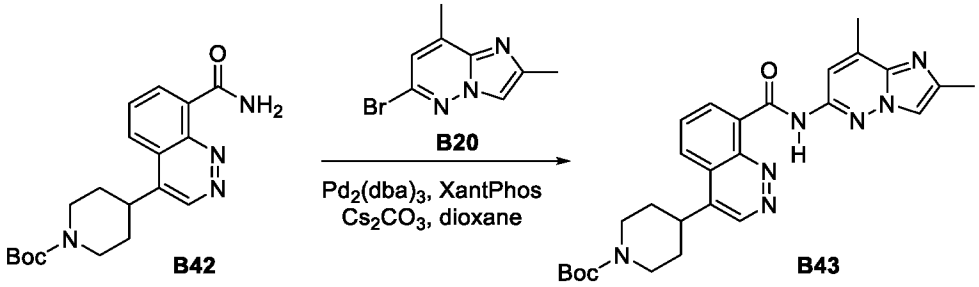
A 20-mL vial was purged and maintained under an atmosphere of nitrogen, then methyl 4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-3,4-dihydrocinnoline-8-carboxylate (B40; 400 mg, 1.07 mmol, 1 equiv), dichloromethane (4 mL), and MnO_2 (1.86 g, 21.42 mmol, 20 equiv) were added to the vial, and the resulting solution was stirred for 6h at 60 °C. The solids were then removed by filtration, and the filtrate was concentrated to provide methyl 4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]cinnoline-8-carboxylate (B41; 380 mg) as a solid. **LCMS** (ES, *m/z*): 372 $[M+H]^+$.

Synthesis of Intermediate B42



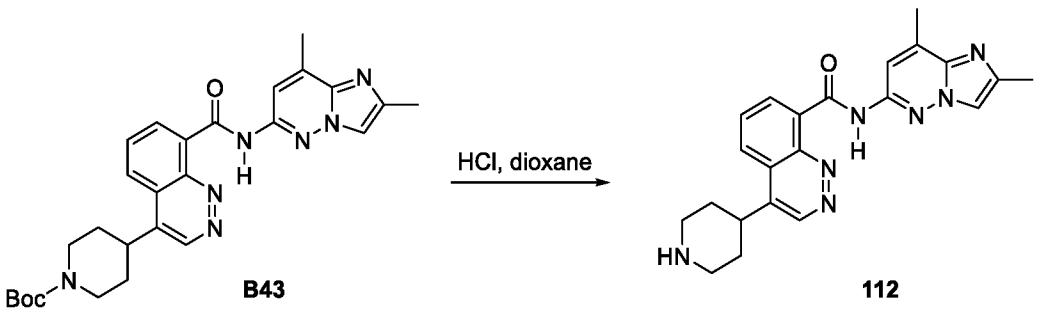
A 10-mL vial was purged and maintained under an atmosphere of nitrogen, then methyl 4-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]cinnoline-8-carboxylate (B41; 380 mg, 1 equiv) and NH_3 in methanol (4 mL) were added to the vial, and the resulting solution was stirred for 4h at 60 °C. The mixture was then concentrated to provide *tert*-butyl 4-(8-carbamoylcinnolin-4-yl)piperidine-1-carboxylate (B42; 330 mg) as a solid. **LCMS** (ES, *m/z*): 357 $[M+H]^+$.

Synthesis of Intermediate B43



A 10-mL vial was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-(8-carbamoylcinnolin-4-yl)piperidine-1-carboxylate (B42; 150 mg, 0.42 mmol, 1 equiv), 6-bromo-2,8-dimethylimidazo[1,2-b]pyridazine (B20; 114 mg, 0.51 mmol, 1.2 equiv), $Pd_2(dba)_3$ (48.2 mg, 0.053 mmol, 0.12 equiv), XantPhos (12.2 mg, 0.021 mmol, 0.05 equiv), Cs_2CO_3 (164.5 mg, 0.51 mmol, 1.2 equiv), and 1,4-dioxane (2 mL) were added to the vial, and the resulting solution was stirred for 2h at 80 °C. The mixture was then concentrated, and the residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (100:1), to provide *tert*-butyl 4-[8-([2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]carbamoyl)cinnolin-4-yl]piperidine-1-carboxylate (B43; 80 mg) as a solid. **LCMS** (ES, *m/z*): 502 $[M+H]^+$.

Synthesis of Compound 112

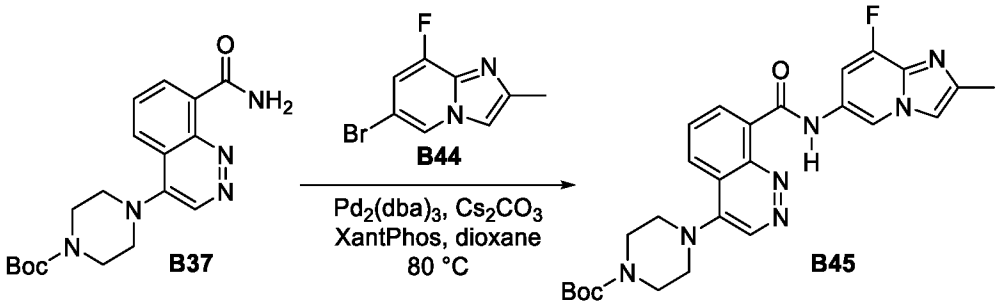


A 10-mL vial was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-[8-([2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]carbamoyl)cinnolin-4-yl]piperidine-1-carboxylate (B43; 80 mg) and HCl in 1,4-dioxane (1 mL) were added to the vial, and the resulting solution was stirred for 1h at 25 °C. The mixture was then concentrated, and the crude product was

purified by preparative HPLC (Condition 1, Gradient 4) to provide N-[2,8-dimethylimidazo[1,2-b]pyridazin-6-yl]-4-(piperidin-4-yl)cinnoline-8-carboxamide (Compound 112; 8.2 mg) as a solid. **LCMS** (ES, *m/z*): 402 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d4) δ 9.48 (s, 1H), 8.91 (dd, *J* = 7.3, 1.3 Hz, 1H), 8.66 (dd, *J* = 8.7, 1.3 Hz, 1H), 8.17 (d, *J* = 1.5 Hz, 1H), 8.10 (dd, *J* = 8.6, 7.2 Hz, 1H), 7.78 (s, 1H), 3.68 - 3.85 (m, 1H), 3.33 - 3.35 (m, 1H), 3.03 (t, *J* = 12.2 Hz, 2H), 2.67 (d, *J* = 1.1 Hz, 3H), 2.48 (d, *J* = 0.9 Hz, 3H), 2.08 (d, *J* = 13.0 Hz, 2H), 1.97 (td, *J* = 12.7, 3.8 Hz, 2H).

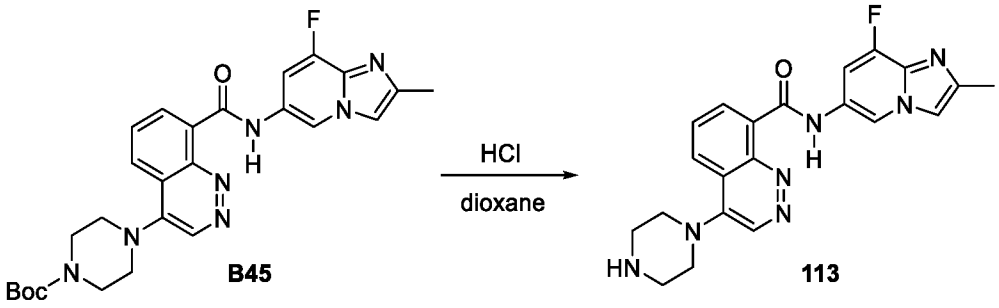
Example 11: Synthesis of Compound 113

Synthesis of Intermediate B45



A 10-mL vial was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-(8-carbamoylcinnolin-4-yl)piperazine-1-carboxylate (B37 from Example 9; 300 mg, 0.84 mmol, 1 equiv), 6-bromo-8-fluoro-2-methylimidazo[1,2-a]pyridine (B44; 230 mg, 1 mmol, 1.2 equiv), $Pd_2(dba)_3$ (192 mg, 0.21 mmol, 0.25 equiv), XantPhos (48 mg, 0.08 mmol, 0.1 equiv), Cs_2CO_3 (328 mg, 1 mmol, 1.2 equiv), and 1,4-dioxane (3 mL) were added to the vial, and the resulting solution was stirred for 5h at 80 °C. The reaction was then quenched by the addition of water/ice (5 mL), and the resulting solution was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were concentrated, and the residue was purified by silica gel column chromatography eluting with ethyl acetate/hexanes (9:1), to provide *tert*-butyl 4-[8-([8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl]carbamoyl)cinnolin-4-yl]piperazine-1-carboxylate (B45; 80 mg) as a solid. **LCMS** (ES, *m/z*): 506 $[M+H]^+$.

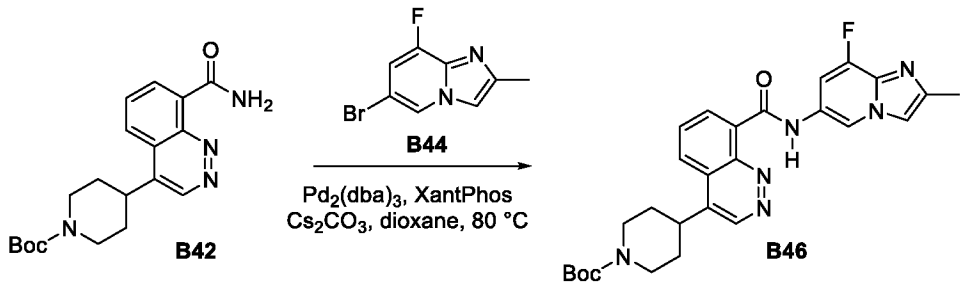
Synthesis of Compound 113



A 10-mL round-bottom flask was purged and maintained under an inert atmosphere of nitrogen, then *tert*-butyl 4-[8-([8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl]carbamoyl)cinnolin-4-yl]piperazine-1-carboxylate (B45; 80 mg), methanol (1 mL), and 4 M HCl in 1,4-dioxane (1 mL) were added to the flask, and the resulting solution was stirred for 3h at 25 °C. The mixture was then concentrated, and the crude product was purified by preparative HPLC (Condition 1, Gradient 4) to provide N-[8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl]-4-(piperazin-1-yl)cinnoline-8-carboxamide (Compound 113; 8.6 mg) as a solid. **LCMS** (ES, *m/z*): 406 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 9.22 (d, *J* = 1.6 Hz, 1H), 9.07 (s, 1H), 8.76 (d, *J* = 7.3 Hz, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 7.88 (t, *J* = 7.9 Hz, 1H), 7.75 (d, *J* = 2.9 Hz, 1H), 7.40 (d, *J* = 11.9 Hz, 1H), 3.55 - 3.59 (m, 4H), 3.16 - 3.23 (m, 4H), 2.45 (s, 3H). **^{19}F NMR** (376 MHz, Methanol-d4) δ -163.03 (d), -345.71.

Example 12: Synthesis of Compound 114

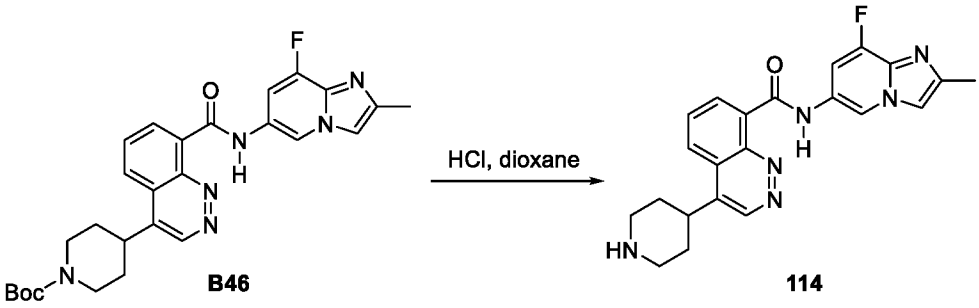
Synthesis of Intermediate B46



A 10-mL vial was purged and maintained under an atmosphere of nitrogen, then *tert*-butyl 4-(8-carbamoylcinnolin-4-yl)piperidine-1-carboxylate (B42 from Example 10; 150 mg, 0.42 mmol, 1 equiv), 6-bromo-8-fluoro-2-methylimidazo[1,2-a]pyridine (B44; 115.7 mg, 0.5 mmol, 1.2 equiv), $Pd_2(dba)_3$ (46.25 mg, 0.05 mmol, 0.12 equiv), XantPhos (12.18 mg, 0.021 mmol, 0.05 equiv), Cs_2CO_3 (164.5 mg, 0.5 mmol, 1.2 equiv), and 1,4-dioxane (2 mL) were added to the vial, and the resulting solution was stirred for 4h at 80 °C. The resulting mixture was concentrated, and the residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum

ether (100:1), to provide *tert*-butyl 4-[8-([8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl]carbamoyl)cinnolin-4-yl]piperidine-1-carboxylate (B46; 60 mg) as a solid. **LCMS** (ES, *m/z*): 505 $[M+H]^+$.

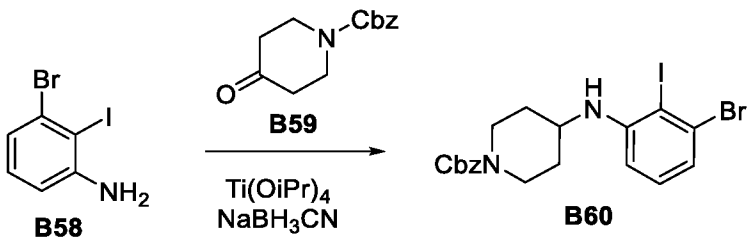
Synthesis of Compound 114



tert-Butyl 4-[8-([8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl]carbamoyl)cinnolin-4-yl]piperidine-1-carboxylate (B46; 60 mg) and HCl in 1,4-dioxane (1 mL) were added to an 8-mL round-bottom flask, and the resulting solution was stirred for 1h at 25 °C. The mixture was then concentrated, and the crude product was purified by preparative HPLC (Condition 1, Gradient 4), to provide N-[8-fluoro-2-methylimidazo[1,2-a]pyridin- 6-yl]-4-(piperidin-4-yl)cinnoline-8-carboxamide (Compound 114; 8.2 mg) as a solid. **LCMS** (ES, *m/z*): 505 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d4): δ 9.49 (s, 1H), 9.26 (d, *J* = 1.6 Hz, 1H), 8.82 (dd, *J* = 7.2, 1.3 Hz, 1H), 8.64 (dd, *J* = 8.8, 1.3 Hz, 1H), 8.10 (dd, J = 8.6, 7.2 Hz, 1H), 7.78 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.38 - 7.46 (m, 1H), 3.63 - 3.89 (m, 1H), 3.37 (s, 2H), 3.04 (td, *J* = 12.4, 2.8 Hz, 2H), 2.46 (d, *J* = 0.9 Hz, 3H), 2.02 - 2.13 (m, 2H), 1.99 (dd, *J* = 12.8, 3.8 Hz, 2H).

Example 13: Synthesis of Compound 121

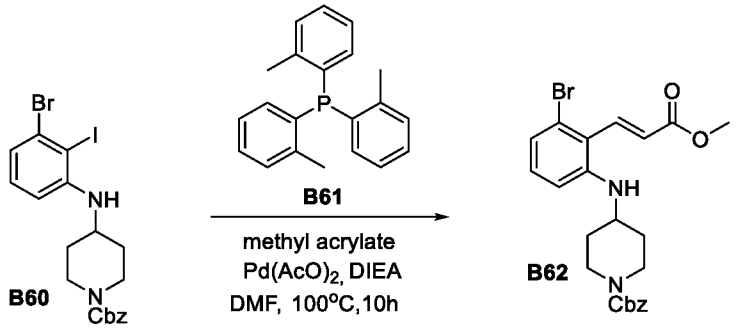
Synthesis of Intermediate B60



A mixture of 3-bromo-2-iodoaniline (B58; 3 g, 10 mmol), benzyl 4-oxopiperidine-1-carboxylate (B59; 3.52 g, 15 mmol), and titanium(IV)isopropoxide (20 mL) was stirred for 12 h at 25 °C under an atmosphere of nitrogen. Sodium cyanoborohydride (2.53 g, 40 mmol) in methanol (10 mL) was then added to the reaction, and the resulting solution was stirred for 4 h at 25 °C. The

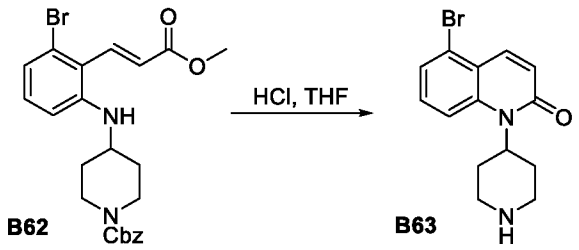
reaction was then quenched by the addition of $NaHCO_3$, filtered, and the filtrate was extracted with dichloromethane (3x30 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated, and purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:10) to afford benzyl 4-[(3-bromo-2-iodophenyl) amino]piperidine-1-carboxylate (B60; 1.4 g) as an oil. **LCMS** (ES, *m/z*): 515 $[M+H]^+$.

Synthesis of Intermediate B62



A mixture of benzyl 4-[(3-bromo-2-iodophenyl)amino]piperidine-1-carboxylate (B60; 1.3 g, 2.52 mmol), methyl acrylate (0.22 g, 2.52 mmol), tris(2-methylphenyl)phosphane (B61; 0.15 g, 0.51 mmol), diisopropylethylamine, and $Pd(OAc)_2$ (0.06 g, 0.25 mmol) in dimethyl formamide (13 mL) was stirred for 16 h at 100 °C under an atmosphere of nitrogen. The reaction mixture was cooled to 25 °C and quenched by the addition of water/ice (10 mL). The resulting solution was extracted with ethyl acetate (3x10 mL) and the combined organic layers were dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (10:1) to afford benzyl 4-([3-bromo-2-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]phenyl]amino)piperidine-1-carboxylate (B62; 700 mg) as a solid. **LCMS** (ES, *m/z*): 473 $[M+H]^+$.

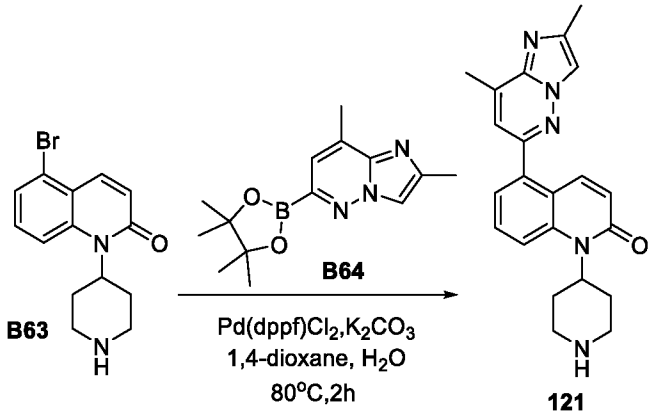
Synthesis of Intermediate B63



A mixture of benzyl 4-([3-bromo-2-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]phenyl]amino)piperidine-1-carboxylate (B62; 300 mg), tetrahydrofuran (1.5 mL), and HCl (1.5 mL) was stirred for 5 h at 80 °C, and then cooled to 25°C. The pH value of the solution was

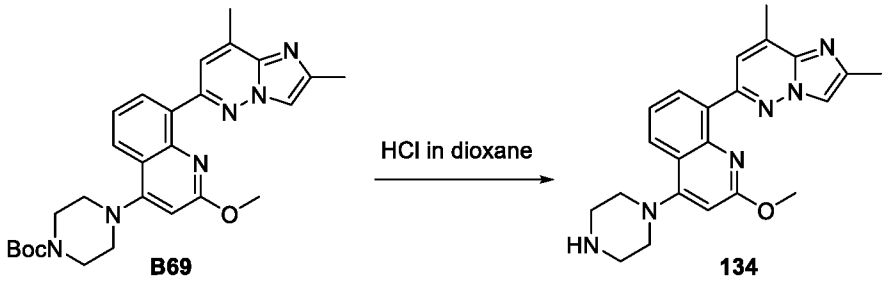
adjusted to 9 with Na_2CO_3, and the resulting solution was extracted with ethyl acetate (3x10 mL) and the combined organic layers were concentrated. The crude product was purified by reverse phase chromatography (IntelFlash-1, C18 silica gel) eluting with acetonitrile/water (20:100; increasing to 60:100) to afford 5-bromo-1-(piperidin-4-yl)quinolin-2-one (B63; 70 mg) as a solid. **LCMS** (ES, *m/z*): 307 $[M+H]^+$.

Synthesis of Compound 121



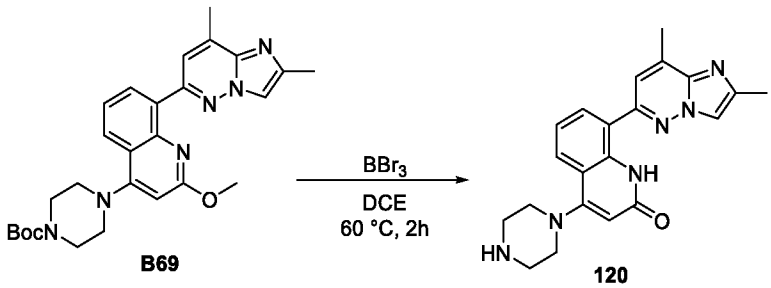
A mixture of 5-bromo-1-(piperidin-4-yl)quinolin-2-one (B63; 70 mg, 0.23 mmol), 2,8-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine (B64; 93 mg, 0.34 mmol), $Pd(dppf)Cl_2$ (8.3 mg, 0.011 mmol), and K_2CO_3 (94 mg, 0.68 mmol) in 1,4-dioxane (0.8 mL) and H_2O (0.2 mL) was stirred for 2 h at 80 °C under an atmosphere of nitrogen. The reaction mixture was cooled, and extracted with ethyl acetate (3x2 mL), and the combined organic layers were concentrated. The crude product was purified by preparative HPLC (Condition 1, Gradient 7) to afford 5-[2,8-dimethylimidazo[1,2-b] pyridazin-6-yl]-1-(piperidin-4-yl)quinolin-2-one (Compound 121; 10.3 mg) as a solid. **LCMS** (ES, *m/z*): 374 $[M+H]^+$. **^{1}HNMR** (400 MHz, DMSO-d_6, *ppm*) δ 8.06 (d, *J* = 14.4 Hz, 2H), 7.85 (d, *J* = 9.7 Hz, 1H), 7.71 (dd, *J* = 8.8, 7.4 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 1.3 Hz, 1H), 6.56 (d, *J* = 9.7 Hz, 1H), 4.37 - 5.54 (m, 1H), 3.10 (d, *J* = 7.5 Hz, 2H), 2.63 - 2.84 (m, 4H), 2.60 (d, *J* = 1.0 Hz, 3H), 2.43 (s, 3H), 1.58 (d, *J* = 7.1 Hz, 2H).

Example 14: Synthesis of Compound 134



A mixture of tert-butyl 4-(8-[2,8-dimethylimidazo[1,2-b] pyridazin-6-yl]-2-methoxyquinolin-4-yl) piperazine-1-carboxylate (B69; 50 mg, 0.1 mmol) and HCl in 1,4-dioxane (1 mL) was stirred for 1 h at room temperature under an atmosphere of nitrogen. The mixture was then filtered, concentrated under reduced pressure, and purified by preparative HPLC (Condition 1, Gradient 6) to afford 8-[2,8-dimethylimidazo[1,2-b] pyridazin-6-yl]-2-methoxy-4-(piperazin-1-yl) quinoline (Compound 134; 3.6 mg) as a solid. **LCMS** (ES, *m/z*): 389 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.09 (dd, J = 8.3, 1.6 Hz, 1H), 8.03 (d, J = 1.1 Hz, 1H), 7.92 (dd, J = 7.2, 1.5 Hz, 1H), 7.68 (d, J = 1.3 Hz, 1H), 7.53 (dd, J = 8.3, 7.2 Hz, 1H), 6.53 (s, 1H), 3.83 (s, 3H), 3.23 – 3.05 (m,6H), 2.58 (d, J = 1.1 Hz, 2H), 2.48 (s, 2H), 2.42 (d, J = 0.8 Hz, 2H).

Example 15: Synthesis of Compound 120

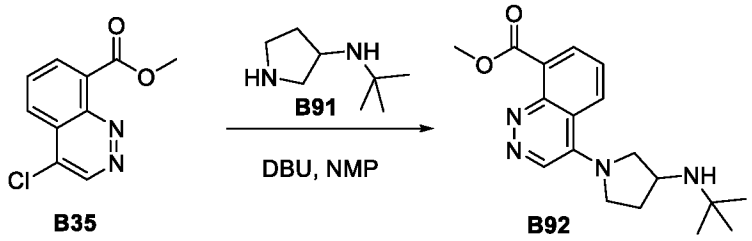


Boron tribromide (4.1 mL, 4.1 mmol) was added in portions to a solution of tert-butyl 4-(8-[2,8-dimethylimidazo[1,2-b] pyridazin-6-yl]-2-methoxyquinolin-4-yl) piperazine-1-carboxylate (B69 from Example 17; 200 mg, 0.41 mmol) in dichloroethane (2 mL) at room temperature under a nitrogen atmosphere, and the resulting mixture was stirred overnight at 60 °C. The reaction was quenched with methanol at room temperature, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (Condition 2, Gradient 3) to afford 8-[2,8-dimethylimidazo[1,2-b] pyridazin-6-yl]-4-(piperazin-1-yl)-1H-quinolin-2-one (Compound 120; 8.3 mg) as a solid. **LCMS** (ES, *m/z*): 375 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6): δ 11.07 (s,

1H), 8.10 (s, 1H), 7.86 (d, J = 7.8 Hz, 2H), 7.51 – 7.20 (m, 2H), 5.94 (s, 1H), 3.00 (dd, J = 15.1, 5.4 Hz, 8H), 2.61 (s, 3H), 2.43 (s, 3H).

Example 16: Synthesis of Compound 122

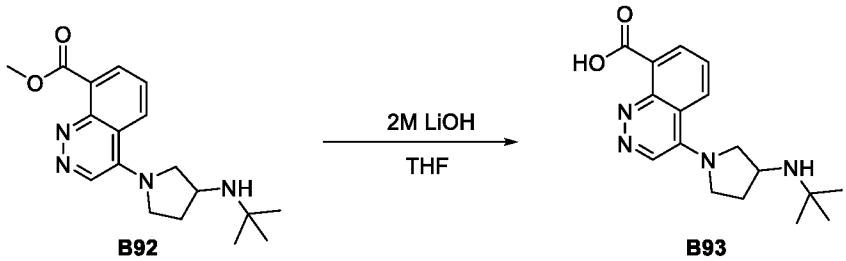
Synthesis of Intermediate B92



B35 B92

A mixture of methyl 4-chlorocinnoline-8-carboxylate (B35 from Example 9; 300 mg, 1.35 mmol) N-tert-butylpyrrolidin-3-amine (B91; 192 mg, 1.35 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.05 g, 13. 5 mmol) in N-methyl-2-pyrrolidone (5 mL) was stirred for 5h at 80 °C, then quenched with water at room temperature. The resulting mixture was extracted with dichloromethane (4 x 10mL), and the combined organic layers were washed with brine (2x3 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse flash chromatography eluting with methanol (10% to 50% gradient over 10 min) in water, to afford methyl 4-[3-(tert-butylamino)pyrrolidin-1-yl] cinnoline-8-carboxylate (B92; 80 mg) as a solid. **LCMS** (ES, *m/z*): 329 $[M+H]^+$.

Synthesis of Intermediate B93

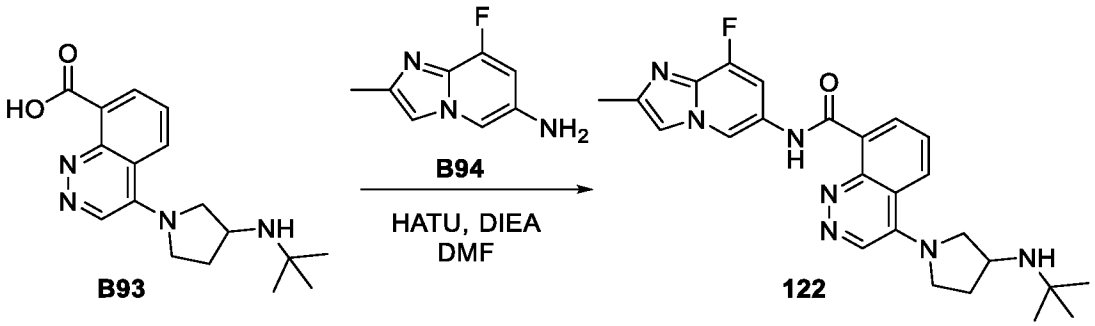


B92 B93

A mixture of methyl 4-[3-(tert-butylamino)pyrrolidin-1-yl]cinnoline-8-carboxylate (B92; 70 mg), and aqueous lithium hydroxide (2 mL) in tetrahydrofuran (2 mL), was stirred for 1 h at room temperature. The reaction was quenched with water at room temperature, and the pH was adjusted to 6 using concentrated hydrochloric acid. The resulting mixture was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were washed with brine (2x5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford

4-[3-(tert-butylamino)pyrrolidin-1-yl]cinnoline-8-carboxylic acid (B93; 60 mg) as a solid. **LCMS** (ES, *m/z*): 315 $[M+H]^+$.

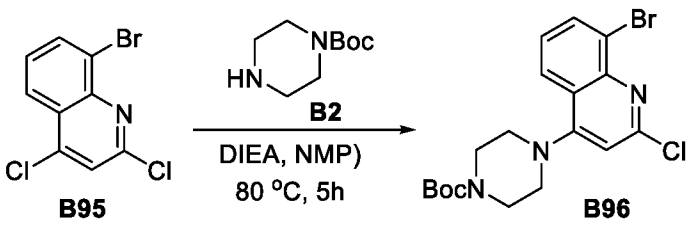
Synthesis of Compound 122



A mixture of 4-[3-(tert-butylamino)pyrrolidin-1-yl]cinnoline-8-carboxylic acid (B93; 55 mg, 0.18 mmol), hexafluorophosphate azabenzotriazole tetramethyl uronium (66.5 mg, 0.18 mmol), and diisopropylethylamine (67.8 mg, 0.53 mmol), in dimethylformamide (2 mL) was stirred for 30 min at room temperature. Then 8-fluoro-2-methylimidazo[1,2-a]pyridin-6-amine (29 mg, 0.18 mmol) was added in portions at room temperature, and the resulting mixture was stirred for 2h at room temperature. The reaction was quenched with water at room temperature and extracted with ethyl acetate (3 x5 mL). The combined organic layers were washed with brine (2x5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (Condition 4, Gradient 1), to afford 4-[3-(tert-butylamino)pyrrolidin-1-yl]-N-[8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl]cinnoline-8-carboxamide (Compound 122; 1.6 mg) as a solid. **LCMS** (ES, *m/z*): 462 $[M+H]^+$. **^{1}HNMR** (400 MHz, DMSO-d_6, *ppm*) δ 13.56 (s, 1H), 9.22 (d, *J* = 1.7 Hz, 1H), 8.72 (s, 1H), 8.59 – 8.52 (m, 2H), 7.94 (d, *J* = 3.2 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.31 (dd, *J* = 12.3, 1.7 Hz, 1H), 4.03 (d, *J* = 4.0 Hz, 1H), 3.90 (s, 2H), 3.60 (s, 2H), 2.47 (s, 13H), 2.37 (s, 2H), 2.23 – 2.18 (m, 1H), 1.85 (s, 1H), 1.25 (s, 1H), 1.10 (s, 9H), 0.85 (s, 1H).

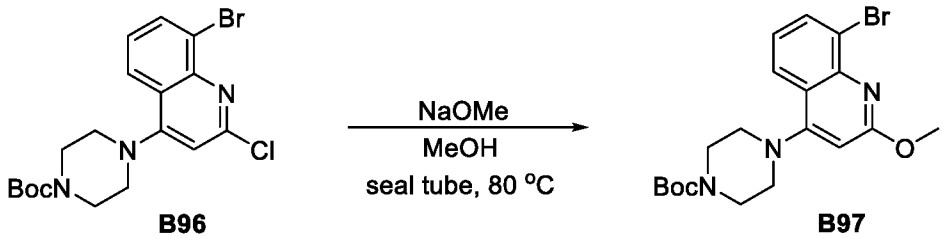
Example 17: Synthesis of Compound 138

Synthesis of Intermediate B96



To a solution of 8-bromo-2,4-dichloroquinoline (B95; 1 g, 3.6 mmol) in N-methyl-2-pyrrolidone (10 mL) was added tert-butyl piperazine-1-carboxylate (B2; 740 mg, 4.0 mmol) and diisopropylethylamine (1.4 g, 10.8 mmol) in portions at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 5 h at 80 °C and then quenched with water at room temperature. The resulting mixture was extracted with ethyl acetate (2 x 10 mL), and the combined organic layers were washed with brine (2x10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (5:1) to afford tert-butyl 4-(8-bromo-2-chloroquinolin-4-yl) piperazine-1-carboxylate (B96; 300 mg) as a solid. **LCMS** (ES, *m/z*): 426 $[M+H]^+$.

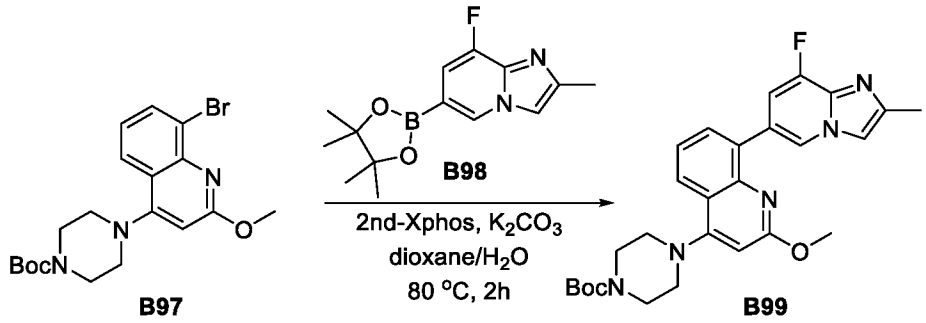
Synthesis of Intermediate B97



B96 **B97**

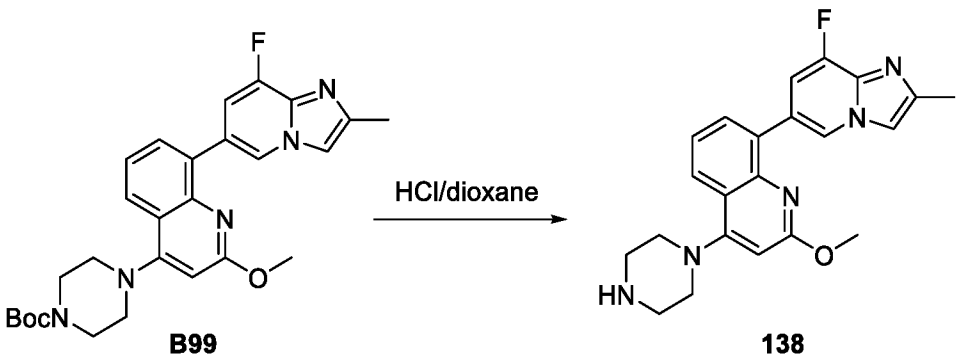
To a solution of tert-butyl 4-(8-bromo-2-chloroquinolin-4-yl) piperazine-1-carboxylate (B96; 300 mg, 0.7 mmol) in methanol (1 mL) was added sodium methoxide (76 mg, 1.4 mmol) in portions at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 4 days at 80 °C, then filtered. The filtrate was concentrated under reduced pressure and quenched with water at room temperature. The mixture was basified to pH 7 with HCl, then extracted with ethyl acetate (2 x 2 mL). The combined organic layers were washed with brine (2x2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, to afford tert-butyl 4-(8-bromo-2-methoxyquinolin-4-yl) piperazine-1-carboxylate (B97; 260 mg) as a solid. **LCMS** (ES, *m/z*): 422 $[M+H]^+$.

Synthesis of Intermediate B99



To a mixture of tert-butyl 4-(8-bromo-2-methoxyquinolin-4-yl) piperazine-1-carboxylate (B97; 620 mg, 0.62 mmol) and 8-fluoro-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo [1,2-a]pyridine (B98; 255 mg, 0.92 mmol) in dioxane (1 mL) and H_2O (1 mL) were added K_2CO_3 (248 mg, 1.8 mmol) and 2nd Generation XPhos precatalyst (47 mg, 0.06 mmol) in portions at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 °C, then filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (4:1), to afford 4-(8-[8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl]-2-methoxyquinolin-4-yl)piperazin-1-yl 2,2-dimethylpropanoate (B99; 200 mg) as a solid. **LCMS** (ES, *m/z*): 492 $[M+H]^+$.

Synthesis of Compound 138

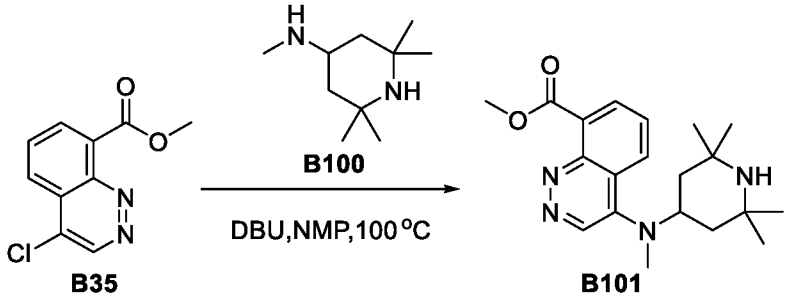


To a solution of 4-(8-[8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl]-2-methoxyquinolin-4-yl) piperazin-1-yl 2,2-dimethylpropanoate (B99; 100 mg, 0.2 mmol) in dioxane (1 mL) was added HCl in dioxane (1 mL, 4 mmol) in portions at room temperature under a nitrogen atmosphere. The resulting mixture was stirred 1h at room temperature, and was then concentrated under reduced pressure, and purified by preparative HPLC (Condition 2, Gradient 3), to afford 8-[8-fluoro-2-methylimidazo[1,2-a]pyridin-6-yl]-2-methoxy-4-(piperazin-1-yl) quinoline (Compound 138; 18.6 mg) as a solid. **LCMS** (ES, *m/z*): 392 $[M+H]^+$. **^{1}HNMR** (400 MHz, DMSO-d_6) δ 8.74 (d, J = 1.4 Hz, 1H), 7.99 (dd, J = 8.3, 1.5 Hz, 1H), 7.87 (dd, J = 3.1, 1.0 Hz, 1H), 7.79 (dd, J =

7.2, 1.4 Hz, 1H), 7.57 (dd, *J* = 12.8, 1.4 Hz, 1H), 7.49 (dd, *J* = 8.3, 7.2 Hz, 1H), 6.50 (s, 1H), 3.85 (s, 3H), 3.08 (ddd, *J* = 26.8, 6.7, 3.7 Hz, 8H), 2.39 (d, *J* = 0.8 Hz, 3H). **^{19}F NMR** (376 MHz, DMSO-d_6) δ -135.00.

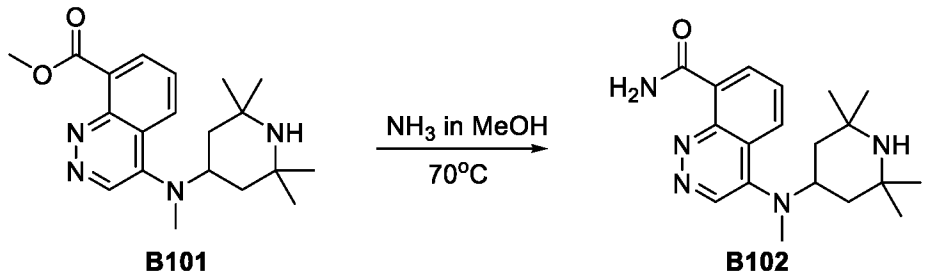
Example 18: Synthesis of Compound 184

Synthesis of Intermediate B101



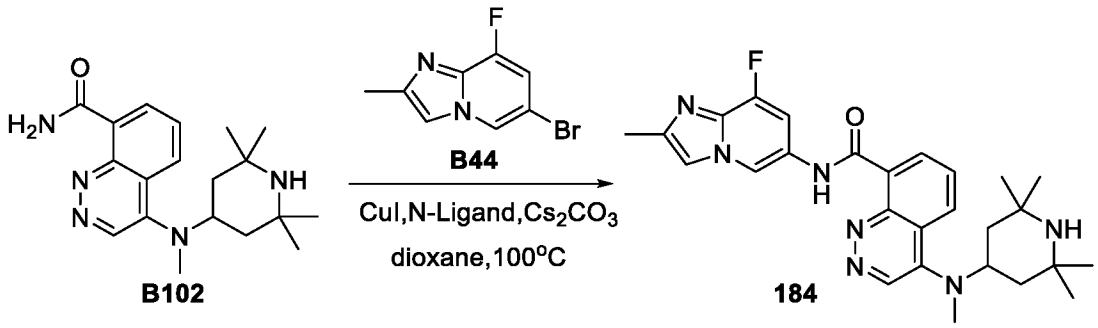
A mixture of methyl 4-chlorocinnoline-8-carboxylate (B35; 1 g, 4.5 mmol) N,2,2,6,6-pentamethylpiperidin-4-amine (B100; 0.76 g, 4.5 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (6.84 g, 45 mmol) in N-methyl-2-pyrrolidone (10 mL) was stirred overnight at 100 °C. The resulting mixture was diluted with water (20 mL), extracted with dichloromethane (3 x 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse flash chromatography on a C18 column, eluting with acetonitrile (10% to 50% gradient over 20 min) in water, to afford methyl 4-[methyl(2,2,6,6-tetramethylpiperidin-4-yl) amino]cinnoline-8-carboxylate (B101; 400 mg) as a solid. **LCMS** (ES, *m/z*): 357 $[M+H]^+$.

Synthesis of Intermediate B102



A mixture of methyl 4-[methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino]cinnoline-8-carboxylate (B101; 400 mg), and ammonia in methanol (10 mL) was stirred for 4 h at 70 °C, then concentrated under reduced pressure, to afford 4-[methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino] cinnoline-8-carboxamide (B102; 400 mg) as a solid. **LCMS** (ES, *m/z*): 342 $[M+H]^+$.

Synthesis of Compound 184



To a solution of 4-[methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino]cinnoline-8-carboxamide (B102; 20 mg, 0.06 mmol) and 6-bromo-8-fluoro-2-methylimidazo[1,2-a]pyridine (B44; 13.4 mg) in dioxane was added copper(I) iodide (1.12 mg, 0.006 mmol), N,N-dimethylcyclohexanamine (1.5 mg, 0.012 mmol), and cesium carbonate (57 mg, 0.18 mmol), and the mixture was stirred for 24 h at 100 °C under a nitrogen atmosphere. The mixture was then extracted with dichloromethane (3 x 5 mL), and the combined organic layers were washed with brine (2x4 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by preparative HPLC to afford N-[8-fluoro-2-methylimidazo[1,2-a] pyridin-6-yl]-4-[methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino]cinnoline-8-carboxamide (Compound 184; 6.5 mg) as a solid. **LCMS** (ES, *m/z*): 490 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 9.24 (d, *J* = 1.6 Hz, 1H), 8.99 (s, 1H), 8.76 (dd, *J* = 7.2, 1.3 Hz, 1H), 8.26 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.83 (dd, *J* = 8.6, 7.3 Hz, 1H), 7.76 (dd, *J* = 3.1, 1.0 Hz, 1H), 7.42 (dd, *J* = 11.9, 1.6 Hz, 1H), 4.61 (s, 1H), 4.40 (t, *J* = 12.2 Hz, 1H), 3.20 (s, 3H), 2.45 (d, *J* = 0.9 Hz, 3H), 1.94 (d, *J* = 12.3 Hz, 2H), 1.81 (t, *J* = 12.5 Hz, 2H), 1.28 (d, *J* = 3.8 Hz, 12H), 0.12 (s, 1H).

Example 19: Exemplary splicing assay for monitoring expression levels of splice variants

Compounds described herein were used to modulate RNA transcript abundance in cells. The expression of a target mRNA was measured by detecting the formation of an exon-exon junction in the canonical transcript (CJ). A compound mediated exon-inclusion event was detected by observing an increase in formation of a new junction with an alternative exon (AJ). Real-time qPCR assays were used to detect these splicing switches and interrogate the potency of various compounds towards different target genes. A high-throughput real time quantitative PCR (RT-qPCR) assay was developed to measure these two isoforms of the mRNA (CJ and AJ) for an exemplary gene, HTT, together with a control housekeeping gene, GAPDH or GUSB or PPIA, used for normalization. Briefly, the A673 or K562 cell line was treated with various compounds

described herein (e.g., compounds of Formula (I)). After treatment, the levels of the HTT mRNA targets were determined from each sample of cell lysate by cDNA synthesis followed by qPCR.

Materials:

Cells-to-C_T 1-step kit: ThermoFisher A25602, Cells-to-C_T lysis reagent: ThermoFisher 4391851C, TaqMan™ Fast Virus 1-Step Master Mix: ThermoFisher 4444436

GAPDH: VIC-PL, ThermoFisher 4326317E (Assay: Hs99999905_m1) – used for K562/suspension cell lines

GUSB: VIC-PL, ThermoFisher 4326320E (Assay: Hs99999908_m1) – used for K562/suspension cell lines

PPIA: VIC-PL, ThermoFisher 4326316E (Assay: Hs99999904_m1) – used for A673/adherent cell lines

Probe/primer sequences

Canonical junction (CJ)

HTT Primer 1: TCCTCCTGAGAAAGAGAAGGAC

HTT Primer 2: GCCTGGAGATCCAGACTCA

HTT CY5-Probe: /5Cy5/TGGCAACCCTTGAGGCCCTGTCCT/3IAbRQSp/

Alternative junction (AJ)

HTT Primer 1: TCCTGAGAAAGAGAAGGACATTG

HTT Primer 2: CTGTGGGCTCCTGTAGAAATC

HTT FAM-Probe: /56-FAM/TGGCAACCC/ZEN/TTGAGAGGCAAGCCCT/3IABkFQ/

Description

The A673 cell line was cultured in DMEM with 10% FBS. Cells were diluted with full growth media and plated in a 96-well plate (15,000 cells in 100ul media per well). The plate was incubated at 37°C with 5% CO_2 for 24 hours to allow cells to adhere. An 11-point 3-fold serial dilution of the compounds was made in DMSO then diluted in media in an intermediate plate. Compounds were transferred from the intermediate plate to the cell plate with the top dose at a final concentration of 10uM in the well. Final DMSO concentration was kept at or below 0.25%. The cell plate was returned to the incubator at 37°C with 5% CO_2 for an additional 24 hours.

The K562 cell line was cultured in IMDM with 10% FBS. For K562, cells were diluted with full growth media and plated in either a 96-well plate (50,000 cells in 50uL media per well) or a 384-well plate (8,000-40,000 cells in 45uL media per well). An 11-point 3-fold serial

dilution of the compounds were made in DMSO then diluted in media in an intermediate plate. Compound was transferred from the intermediate plate to the cell plate with the top dose at a final concentration of 10uM in the well. Final DMSO concentration was kept at or below 0.25%. Final volume was 100uL for 96-well plate and 50uL for 384-well plate. The cell plate was then placed in an incubator at 37°C with 5% CO2 for 24 hours.

The cells were then gently washed with 50uL – 100uL cold PBS before proceeding to addition of lysis buffer. 30uL – 50uL of room temperature lysis buffer with DNAse I (and optionally RNAsin) was added to each well. Cells were shaken/mixed thoroughly at room temperature for 5-10 minutes for lysis to take place and then 3uL – 5uL of room temperature stop solution was added and wells were shaken/mixed again. After 2-5 minutes, the cell lysate plate was transferred to ice for RT-qPCR reaction setup. The lysates could also be frozen at -80°C for later use.

In some cases, a direct lysis buffer was used. An appropriate volume of 3X lysis buffer (10 mM Tris, 150 mM NaCl, 1.5%-2.5% Igepal and 0.1-1 U/uL RNAsin, pH 7.4) was directly added to either K562 or A673 cells in media and mixed by pipetting 3 times. The plates were then incubated at room temperature with shaking/rocking for 20-50 minutes to allow for lysis to take place. After this time, the cell lysate plate was transferred to ice to set up for the RT-qPCR reactions. The lysates could also be frozen at -80°C for later use.

To set up 10 uL RT-qPCR reactions, cell lysates were transferred to 384-well qPCR plates containing the master mix according to the table below. The plates were sealed, gently vortexed, and spun down before the run. The volumes were adjusted accordingly in some instances where the reaction was carried in 20 uL. The table below summarizes the components of the RT-qPCR reactions:

Component	**1X**
Taqman 1-step RT-qPCR mix (4X)	2.5
20X AJ Primers+Probe (FAM)	0.5
20X CJ Primers+Probe (CY5)	0.5
20X PPIA Control (VIC)	0.5
Cell lysate (1X)	1-2
H_2O	4-5
Total volume	**10**

The RT-qPCR reaction was performed using a QuantStudio (ThermoFisher) under the following fast cycling conditions. All samples and standards were analyzed at least in duplicate. In some instances, bulk room temperature (RT) step of 5-10 minutes was completed for all plates before proceeding with qPCR. The table below summarizes the PCR cycle:

Step	# cycles	Temp.	Time
RT step	1	50°C	5 min
RT inactivation/initial denaturation	1	95°C	20 sec
Amplification	40	95°C	3 sec
		60°C	30 sec

The data analysis was performed by first determining the ΔCt vs the housekeeper gene. This ΔCt was then normalized against the DMSO control (ΔΔCt) and converted to RQ (relative quantification) using the 2^(-ΔΔCt) equation. The RQ were then converted to a percentage response by arbitrarily setting an assay window of 3.5 ΔCt for HTT-CJ and an assay window of 9 ΔCt for HTT-AJ. These assay windows correspond to the maximal modulation observed at high concentration of the most active compounds. The percentage response was then fitted to the 4 parametric logistic equation to evaluate the concentration dependence of compound treatment. The increase in AJ mRNA is reported as AC_{50} (compound concentration having 50% response in AJ increase) while the decrease in CJ mRNA levels is reported as IC_{50} (compound concentration having 50% response in CJ decrease).

A summary of these results is illustrated in Table 2, wherein "A" represents an AC_{50}/IC_{50} of less than 100 nM; "B" represents an AC_{50}/IC_{50} of between 100 nM and 1 μM; and "C" represents an AC_{50}/IC_{50} of between 1 μM and 10 μM; and "D" represents an AC_{50}/IC_{50} of greater than 10 μM.

Table 2: Modulation of RNA Splicing by Exemplary Compounds

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ AC_{50} (nM)
100	D	D

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ AC_{50} (nM)
101	C	D

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ AC_{50} (nM)
102	D	D
104	D	-
108	D	D
109	D	D
111	D	D
112	D	D
113	C	D
114	D	D

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ AC_{50} (nM)
119	C	B
121	D	D
122	D	D
134	C	C
138	D	D
184	C	C
185	D	C
213	C	C

Additional studies were carried out for a larger panel of genes using the protocol provided above. The junction between flanking upstream and downstream exons was used to design canonical junction qPCR assays. At least one of the forward primer, reverse primer or the CY5-labeled 5′ nuclease probe (with 3' quencher such as ZEN / Iowa Black FQ) was designed to overlap with the exon junction to capture the CJ mRNA transcript. BLAST was used to confirm the specificity of the probeset and parameters such as melting temperature, GC content, amplicon size, and primer dimer formation are considered during their design. Data for the decrease in CJ mRNA levels for three exemplary genes (HTT, SMN2, and Target C) analyzed in this panel are reported as IC_{50} (compound concentration having 50% response in CJ decrease).

A summary of the results from the panel is illustrated in Table 3, wherein "A" represents an IC_{50} of less than 100 nM; "B" represents an IC_{50} of between 100 nM and 1 μM; and "C" represents an IC_{50} of between 1 μM and 10 μM; and "D" represents an IC_{50} of greater than 10 μM.

Table 3: Modulation of RNA Splicing by Exemplary Compounds

Compound No.	HTT	SMN2	Target C
101	-	-	C
102	D	D	-
108	-	-	C
109	-	-	C
112	-	-	C
113	D	A	A

Compound No.	HTT	SMN2	Target C
121	D	D	-
134	-	-	C
138	D	B	D
184	C	C	C
185	C	D	-
213	C	C	C

EQUIVALENTS AND SCOPE

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

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, Figures, or Examples but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

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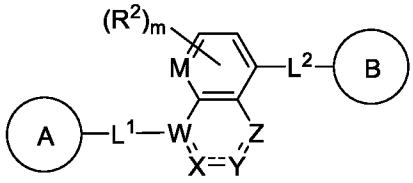
CLAIMS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

W is N, C, or $C(R^{3a})$;

X, Y, and Z are each independently $C(R^{3a})$, $C(R^{3a})(R^{3b})$, N, $N(R^{3c})$, or O, wherein the bonds in the ring comprising W, X, Y, and Z may be single or double bonds as valency permits;

M is $C(R^2)$ or N;

L^1 and L^2 are each independently is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)$-, $-N(R^4)C(O)$-, or $-C(O)N(R^4)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5;

each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6; or

two R^1 groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more R^6;

each R^2 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $–OR^A$;

R^{3a} and R^{3b} are each independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$; or

each of R^{3a} and R^{3b}, together with the carbon atom to which they are attached, form an oxo group;

R^{3c} is hydrogen or C_1-C_6-alkyl;

each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^5 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

each R^6 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11};

each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, or $-S(O)_xR^D$;

each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^7;

each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

each R^7 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$;

each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

each R^{A1} is hydrogen or C_1-C_6-alkyl;

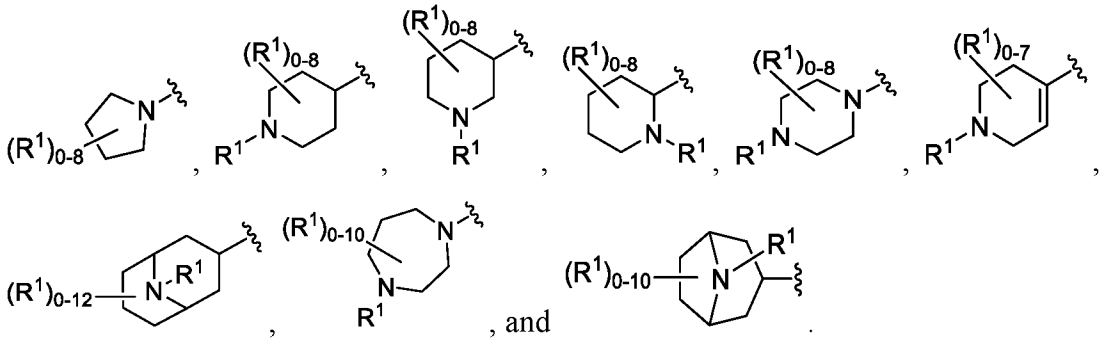
m is 0, 1, or 2; and

x is 0, 1, or 2.

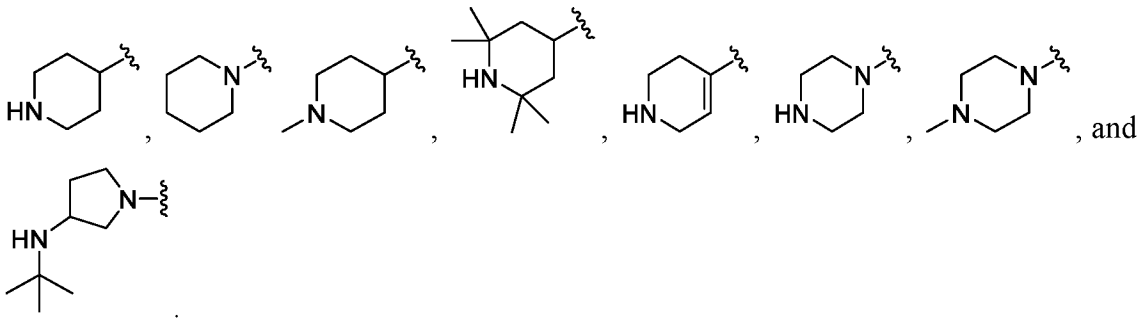
2. The compound of claim 1, wherein A is a monocyclic or bicyclic heterocyclyl.

3. The compound of any one of the preceding claims, wherein A is a nitrogen-containing heterocyclyl.

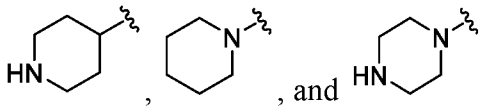
4. The compound of any one of the preceding claims, wherein A is selected from



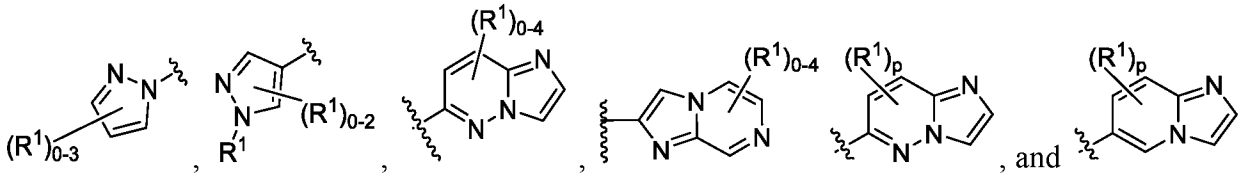
5. The compound of any one of the preceding claims, wherein A is selected from

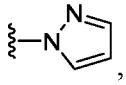
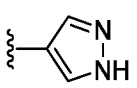
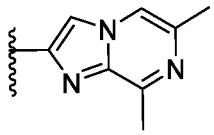
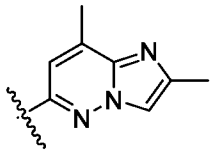
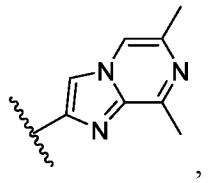
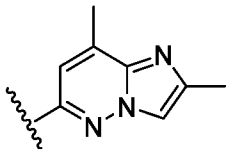
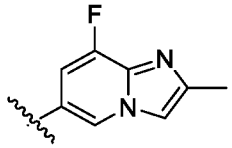


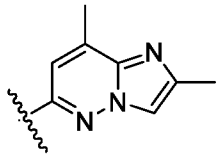
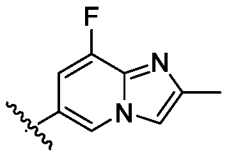
6. The compound of any one of the preceding claims, wherein A is selected from



7. The compound of any one of the preceding claims, wherein B is selected from



8. The compound of any one of the preceding claims, wherein B is selected from  ,  ,  ,  ,  ,  , and  .

9. The compound of any one of the preceding claims, wherein B is selected from  and  .

10. The compound of any one of the preceding claims, wherein L^1 and L^2 is each independently absent, -N(R^4)- (e.g., -N(CH_3)-), -N(R^4)C(O)- (e.g., -NHC(O)-), or O.

11. The compound of any one of the preceding claims, wherein L^1 and L^2 is each independently absent.

12. The compound of any one of the preceding claims, wherein one of L^1 and L^2 is independently absent and the other of L^1 and L^2 is -N(R^4)- (e.g., -N(CH_3)-) or -N(R^4)C(O)- (e.g., -NHC(O)-).

13. The compound of any one of the preceding claims, wherein L^1 is absent and L^2 is -N(R^4)C(O)- (e.g., -NHC(O)-).

14. The compound of any one of the preceding claims, wherein W is N, C, or (CR^{3a}) (e.g., CH).

15. The compound of any one of the preceding claims, wherein W is N or C.

16. The compound of any one of the preceding claims, wherein at least one of X, Y, and Z is N or N(R^{3c}).

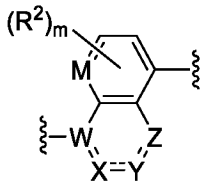
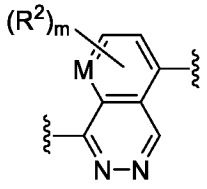
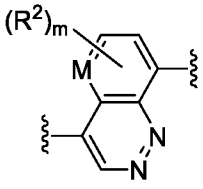
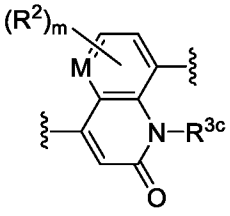
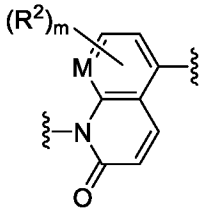
17. The compound of any one of the preceding claims, wherein one of X, Y, and Z is C(R^{3a}) (e.g., CH), and the others of X, Y, and Z are each independently N.

18. The compound of any one of the preceding claims, wherein W is N and X is C(R^{3a})(R^{3b}) (e.g., C(O)).

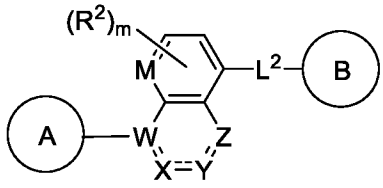
19. The compound of any one of the preceding claims, wherein W is C, X is C(R^{3a}) (e.g., CH), and the bond between Y and Z is a single bond.

20. The compound of any one of the preceding claims, wherein W is N, X is C(R^{3a})(R^{3b}) (e.g., C(O)), the bond between Y and Z is a double bond.

21. The compound of any one of the preceding claims, wherein M is N or CH.

22. The compound of any one of the preceding claims, wherein  is selected from  ,  ,  , and  .

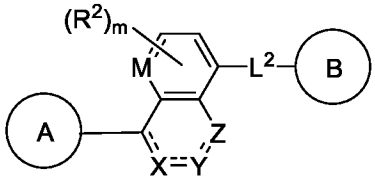
23. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound Formula (I-a):



(I-a)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, X, Y, Z, M, L^2, R^2, m, and subvariables thereof are defined as in claim 1.

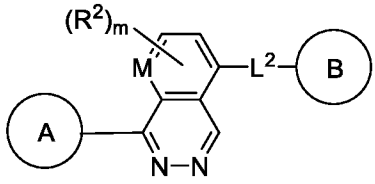
24. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-b):



(I-b)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, X, Y, Z, M, L^2, R^2, m, and subvariables thereof are defined as in claim 1.

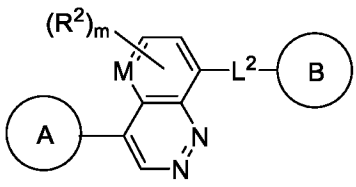
25. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-c):



(I-c),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, M, L^2, R^2, m, and subvariables thereof are defined as in claim 1.

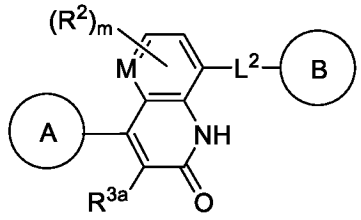
26. The compound of any one of claims 1-21, wherein the compound of Formula (I) is a compound of Formula (I-d):



(I-d)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, M, L^2, R^2, m, and subvariables thereof are defined as in claim 1.

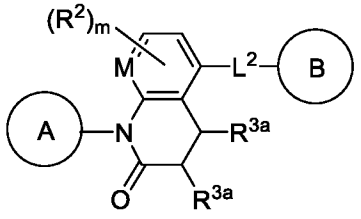
27. The compound of any one of claims 1-21, wherein the compound of Formula (I) is a compound of Formula (I-e):



(I-e)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, M, L^2, R^2, R^{3c}, m, and subvariables thereof are defined as in claim 1.

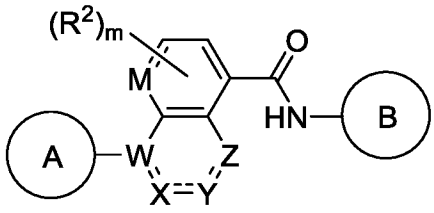
28. The compound of any one of claims 1-21, wherein the compound of Formula (I) is a compound of Formula (I-f):



(I-f),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, M, L^2, R^2, R^{3a}, m, and subvariables thereof are defined as in claim 1.

29. The compound of any one of claims 1-21, wherein the compound of Formula (I) is a compound of Formula (I-g):



(I-g)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, W, X, Y, Z, M, R^2, m, and subvariables thereof are defined as in claim 1.

30. The compound of any one of the preceding claims, wherein the compound is selected from a compound of Table 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

31. A pharmaceutical composition comprising a compound of any one of the preceding claims and a pharmaceutically acceptable excipient.

32. The compound of any one of claims 1-30, or the pharmaceutical composition of claim 31, wherein the compound alters a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

33. The compound of any one of claims 1-30, or the pharmaceutical composition of claim 31, wherein the compound binds to a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

34. The compound of any one of claims 1-30, or the pharmaceutical composition of claim 31, wherein the compound stabilizes a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

35. The compound of any one of claims 1-30, or the pharmaceutical composition of claim 31, wherein the compound increases splicing at splice site on a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA), by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, e.g., as determined by qPCR.

36. The compound of any one of claims 1-30, or the pharmaceutical composition of claim 31, wherein the compound decreases splicing at splice site on a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA), by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, e.g., as determined by qPCR %.

37. A method of forming a complex comprising a component of a spliceosome (e.g., a major spliceosome component or a minor spliceosome component), a nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA), and a compound of Formula (I) according to any one of claims 1-30,

comprising contacting the nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA) with a compound of Formula (I).

38. The method of claim 37, wherein the component of a spliceosome is recruited to the nucleic acid in the presence of the compound of Formula (I).

39. A method of altering the conformation of a nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA) comprising contacting the nucleic acid with a compound of Formula (I) according to any one of claims 1-30 or the pharmaceutical composition of claim 31.

40. The method of claim 39, wherein the altering comprises forming a bulge in the nucleic acid.

41. The method of claim 39, wherein the altering comprises stabilizing a bulge in the nucleic acid.

42. The method of claim 39, wherein the altering comprises reducing a bulge in the nucleic acid.

43. The method of any one of any one of claims 39-41, wherein the nucleic acid comprises a splice site.

44. A composition for use in treating a disease or disorder in a subject comprising administering to the subject a compound of Formula (I) according to any one of claims 1-30 or the pharmaceutical composition of claim 31.

45. The composition for use of claim 44, wherein the disease or disorder comprises a proliferative disease (e.g., cancer, a benign neoplasm, or angiogenesis).

46. The composition for use of claim 44, wherein the disease or disorder comprises a neurological disease or disorder, autoimmune disease or disorder, immunodeficiency disease or

disorder, lysosomal storage disease or disorder, cardiovascular disease or disorder, metabolic disease or disorder, respiratory disease or disorder, renal disease or disorder, or infectious disease.

47. The composition for use of claim 44, wherein the disease or disorder comprises neurological disease or disorder.

48. The composition for use of claim 44, wherein the disease or disorder comprises Huntington's disease.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/020152

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 C07D403/14 A61P25/28 A61P35/00 A61K31/495
C07D401/14 C07D471/04
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, 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.
X,P	REED CARSON W. ET AL: "Discovery of VU6027459: A First-in-Class Selective and CNS Penetrant mGlu 7 Positive Allosteric Modulator Tool Compound", ACS MEDICINAL CHEMISTRY LETTERS, vol. 11, no. 9, 20 August 2020 (2020-08-20), pages 1773-1779, XP055805108, US ISSN: 1948-5875, DOI: 10.1021/acsmedchemlett.0c00432 table 2 ----- -/--	1-4,7,8, 10,11, 14-16, 21,31, 44,46,47

[X] Further documents are listed in the continuation of Box C.

[X] 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
17 June 2021	25/06/2021

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	Johnson, Claire

3

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/148922 A1 (MITSUBISHI TANABE PHARMA CORP [JP]; INOUE SHINYA [JP] ET AL.) 1 December 2011 (2011-12-01) claim 1; compounds B281-B284	1-3,10, 11, 14-17, 21,31, 44,46
X	SMITS ROGIER A ET AL: "Ligand based design of novel histamine H4receptor antagonists; fragment optimization and analysis of binding kinetics", BIORGANIC & MEDICINAL CHEMISTRY LETTERS, ELSEVIER, AMSTERDAM , NL, vol. 22, no. 1, 11 November 2011 (2011-11-11), pages 461-467, XP029121530, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2011.10.104 table 1	1-5,10, 11, 14-17, 21,31, 44,46
X	ANGELA SCHÖFFMANN ET AL: "Efficient Modulation of [gamma]-Aminobutyric Acid Type A Receptors by Piperine Derivatives", JOURNAL OF MEDICINAL CHEMISTRY, vol. 57, no. 13, 10 July 2014 (2014-07-10) , pages 5602-5619, XP055375728, US ISSN: 0022-2623, DOI: 10.1021/jm5002277 compound 62	1-3,5,6, 14,15, 21,31, 44,46,47
A	CA 3 105 174 A1 (REBORNA BIOSCIENCES INC [JP]) 2 January 2020 (2020-01-02) claims 1,12	1-48
A	WO 2016/196386 A1 (PTC THERAPEUTICS INC [US]) 8 December 2016 (2016-12-08) cited in the application claim 1	1-48

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/020152

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-29, 31-48(all partially)
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 1-29, 31-48(all partially)

The present claims are directed to compounds of a very broadly defined general formula (I) which covers an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds claimed, namely the compounds disclosed in Table 1 on pp. 78-82 and a reasonable generalization thereof. Furthermore, independent of the lack of support and disclosure, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. For these reasons, a complete search has only been performed for compounds of formula (I), compositions comprising them and their uses, wherein A is as defined in claims 5 or 6, B is as defined in claims 7-9 and L1 and L2 are as defined in claims 10-13. Claims lacking one or more of these features have not been exhaustively searched. The present report is therefore only complete for subject matter having all these features.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/020152

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011148922 A1	01-12-2011	TW 201202230 A	16-01-2012
		WO 2011148922 A1	01-12-2011
CA 3105174 A1	02-01-2020	AU 2019293757 A1	04-02-2021
		BR 112020026637 A2	30-03-2021
		CA 3105174 A1	02-01-2020
		CL 2020003386 A1	14-05-2021
		CN 112469707 A	09-03-2021
		CO 2021000808 A2	30-04-2021
		EP 3816160 A1	05-05-2021
		KR 20210025625 A	09-03-2021
		SG 11202013088Y A	25-02-2021
		WO 2020004594 A1	02-01-2020
WO 2016196386 A1	08-12-2016	EP 3310169 A1	25-04-2018
		US 2018161456 A1	14-06-2018
		US 2021069350 A1	11-03-2021
		WO 2016196386 A1	08-12-2016