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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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PYRIDAZINE DERVATIVES FOR MODULATING NUCLEIC ACID SPLICING

CLAIM OF PRIORITY

This application is a divisional of Australian Application No. 2021228286 filed 28 February 2021, is related to PCT/US2021/020160, and claims priority from U.S. Application No. 62/983,537 filed 28 February 2020; U.S. Application No. 63/007,134 filed 8 April 2020; U.S. Application No. 63/040,474 filed 17 June 2020; U.S. Application No. 63/072,781 filed 31 August 2020; and U.S. Application No. 63/126,491 filed 16 December 2020, entitled "Pyridazine derivatives for modulating nucleic add splicing" 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), (I-g), or (I-h)) 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), (I-g), or (I-h), and pharmaceutically acceptable

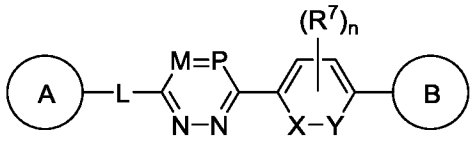
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salts, solvates, hydrates, tautomers, stereoisomers thereof), and compositions thereof, e.g., to target, and in embodiments bind or form a complex with, a nucleic acid (e.g., a pre-mRNA or nucleic acid component of a small nuclear ribonucleoprotein (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), (I-g), or (I-h), 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), (I-g), or (I-h), 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), (I-g), or (I-h), 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,

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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; L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^3)-, -S(O)$_x$-, -N(R^3)C(O)-, or -C(O)N(R^3)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4; M and P are each independently C(R^2) or N; X and Y are each independently C, C(R^{5a}), C(R^{5a})(R^{5b}), N, or N(R^{5c}), wherein the bond between X and Y may be a single or double bond as valency permits, and wherein X and Y may not both be C(R^{5a})(R^{5b}) or C(R^{5a}); 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, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^8; 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^8; each R^2 is independently hydrogen, halo, cyano, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, or –OR^A; each R^3 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^4 is 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 –$C(O)OR^D$; R^{5a} is 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, –NR^BR^C, or –OR^F; R^{5b} is hydrogen or C_1-C_6-alkyl; or R^{5a} and R^{5b}, together with the carbon atom to which they are attached, form an oxo group; each R^{5c} is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $C(O)R^D$; each R^7 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, halo, oxo, cyano, –OR^A, –NR^BR^C, $NR^BC(O)R^D$, –$C(O)NR^BR^C$, –$C(O)R^D$, or –SR^E, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more R^9; or two R^7 groups, together with the atoms to which they are attached (e.g., X or Y), form a 4-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9; R^8 and R^9 are each 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, –

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$C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each of 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, $-OR^A$; 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^{10}; 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; R^F is hydrogen, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl; R^{10} is C_1-C_6-alkyl or halo; 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 $-OR^A$; n is 0, 1, 2, 3, or 4; 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), or (I-h)), 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), (I-g), or (I-h)), 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), (I-g), or (I-h)) 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), (I-g), or (I-h)) 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), (I-g), or (I-h)) 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), (I-g), or (I-h))

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), (I-g), or (I-h)) 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), (I-g), or (I-h))) 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), (I-g), or (I-h)) 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 compositions for use in 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), (I-g), or (I-h)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or

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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), (I-g), or (I-h)) 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), (I-g), or (I-h))) 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), (I-g), or (I-h)), 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

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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

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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–C_{10} alkenyl. In certain embodiments, the alkenyl group is substituted C_2–C_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

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("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, $-CH_2-NH-OCH_3$

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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

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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.

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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.

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"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.

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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).

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.

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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 "$\sim\!\!\sim$" 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,

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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

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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

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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.

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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

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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 $R \cdot x\ H_2O$, 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 ($R \cdot 0.5\ H_2O$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2\ H_2O$) and hexahydrates ($R \cdot 6\ H_2O$)).

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.

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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

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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.

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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

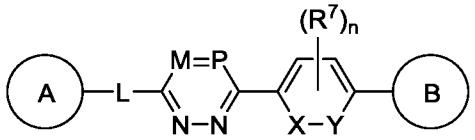
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proliferation of normally quiescent cells; 2) the pathological migration of cells from their normal location (*e.g.*, metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes such as the matrix metalloproteinases (*e.g.*, 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; L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^3)-, -S(O)$_x$-, -N(R^3)C(O)-, or -C(O)N(R^3)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4; M and P are each independently C(R^2) or N; X and Y are each independently C, C(R^{5a}), C(R^{5a})(R^{5b}), N, or N(R^{5c}), wherein the bond between X and Y may be a single or double bond as valency permits, and wherein X and Y may not both be C(R^{5a})(R^{5b}); 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, –$C(O)NR^BR^C$, –

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$C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^8; 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^8; each R^2 is independently hydrogen, halo, cyano, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, or $-OR^A$; each R^3 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^4 is 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 $-C(O)OR^D$; R^{5a} is 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, $-NR^BR^C$, or $-OR^F$; R^{5b} is hydrogen or C_1-C_6-alkyl; or R^{5a} and R^{5b}, together with the carbon atom to which they are attached, form an oxo group; each R^{5c} is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $C(O)R^D$; each R^7 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, halo, oxo, cyano, $-OR^A$, $-NR^BR^C$, $NR^BC(O)R^D$, $-C(O)NR^BR^C$, $-C(O)R^D$, or $-SR^E$, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more R^9; or two R^7 groups, together with the atoms to which they are attached (e.g., X or Y), form a 4-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9; R^8 and R^9 are each 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 of 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, $-OR^A$; 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^{10}; 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; R^F is hydrogen, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl; R^{10} is C_1-C_6-alkyl or halo; each R^{11} is independently C_1-C_6-

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alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$; n is 0, 1, 2, 3, or 4; and x is 0, 1, or 2.

As generally described herein, each of A or B are 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, either A or B is 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

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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, either A or B is 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, either A or B is 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 is monocyclic heterocyclyl and B is monocyclic heteroaryl or monocyclic heterocyclyl.

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

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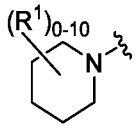
or B are independently heterocyclyl comprising at least 1, at least 2, at least 3, at least 4, at least 5, or at least 6 nitrogen atoms. In some embodiments, A is heterocyclyl comprising 1 nitrogen atom. In some embodiments, B is heterocyclyl comprising 1 nitrogen atom. In some embodiments, A is heterocyclyl 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 is a nitrogen-containing heterocyclyl comprising 1 nitrogen atom and B is a nitrogen-containing heteroaryl or nitrogen-containing heterocyclyl comprising 1, 2, or 3 nitrogen atoms.

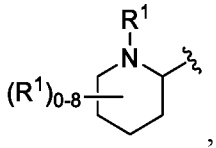
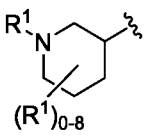
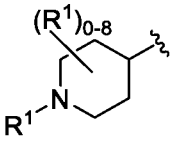
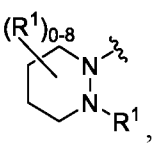
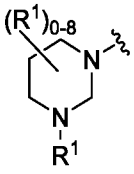
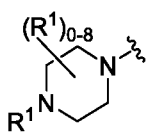
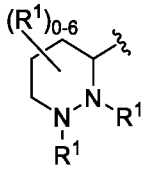
In some embodiments, A or B are independently a nitrogen-containing heteroaryl, e.g., heteroaryl comprising one or more nitrogen atom. The one or more nitrogen atom of the nitrogen-containing heteroaryl may be at any position of the ring. In some embodiments, the nitrogen-containing heteroaryl is monocyclic, 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.

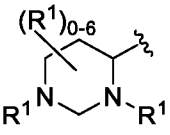
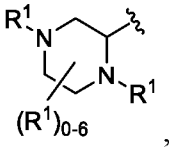
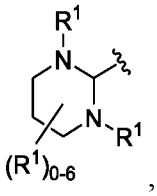
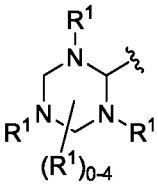
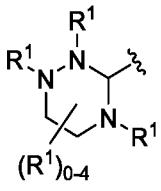
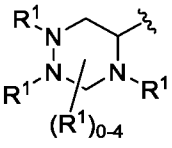
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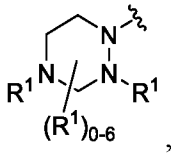
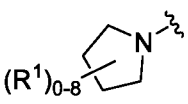
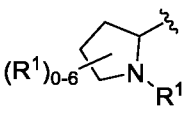
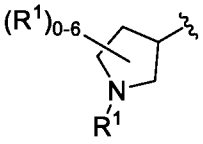
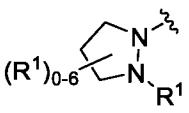
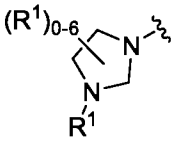
In some embodiments, A is a 6-membered nitrogen-containing heterocyclyl, e.g., a 6-membered heterocyclyl comprising one or more nitrogen. In some embodiments, A is a 6-membered heterocyclyl comprising 1 nitrogen atom. In some embodiments, A is a 6-membered heterocyclyl comprising 2 nitrogen atoms. In 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.

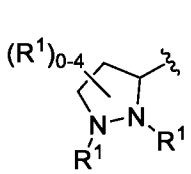
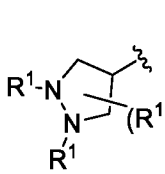
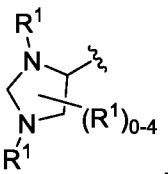
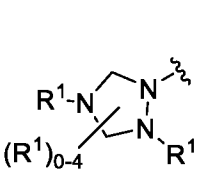
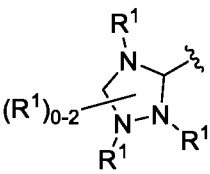
In some embodiments, B is a 5-membered nitrogen-containing heterocyclyl or heteroaryl, e.g., a 5-membered heterocyclyl or heteroaryl comprising one or more nitrogen. In some embodiments, B is a 5-membered heterocyclyl comprising 1 nitrogen atom. In some embodiments, B is a 5-membered heteroaryl comprising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

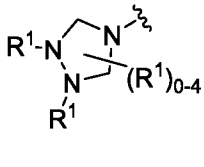
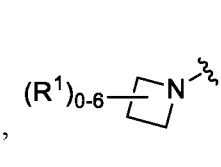
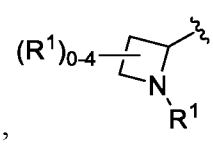
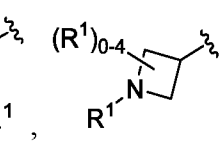
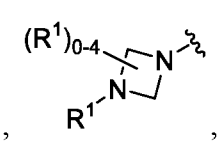
In some embodiments, each of A and B are independently selected from: ,

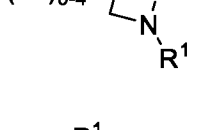
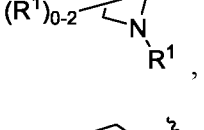
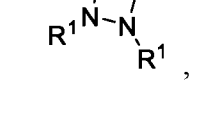
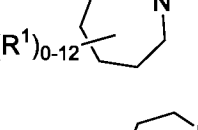
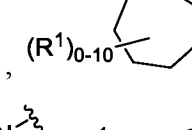
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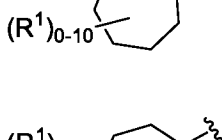
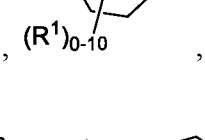
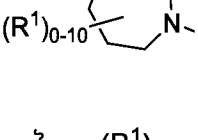
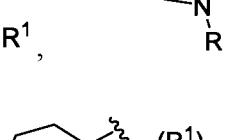
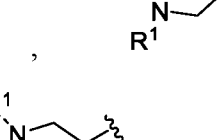
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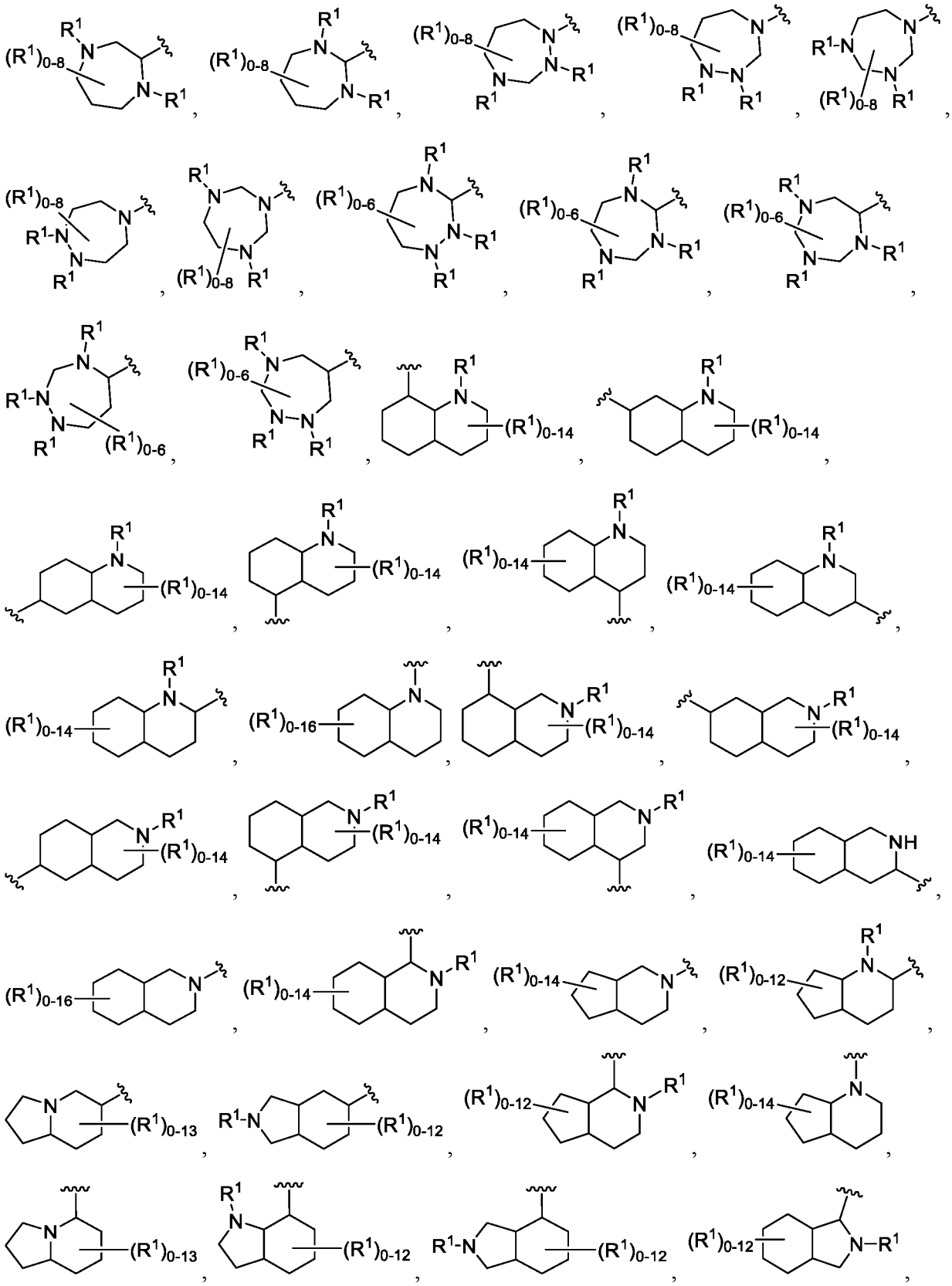
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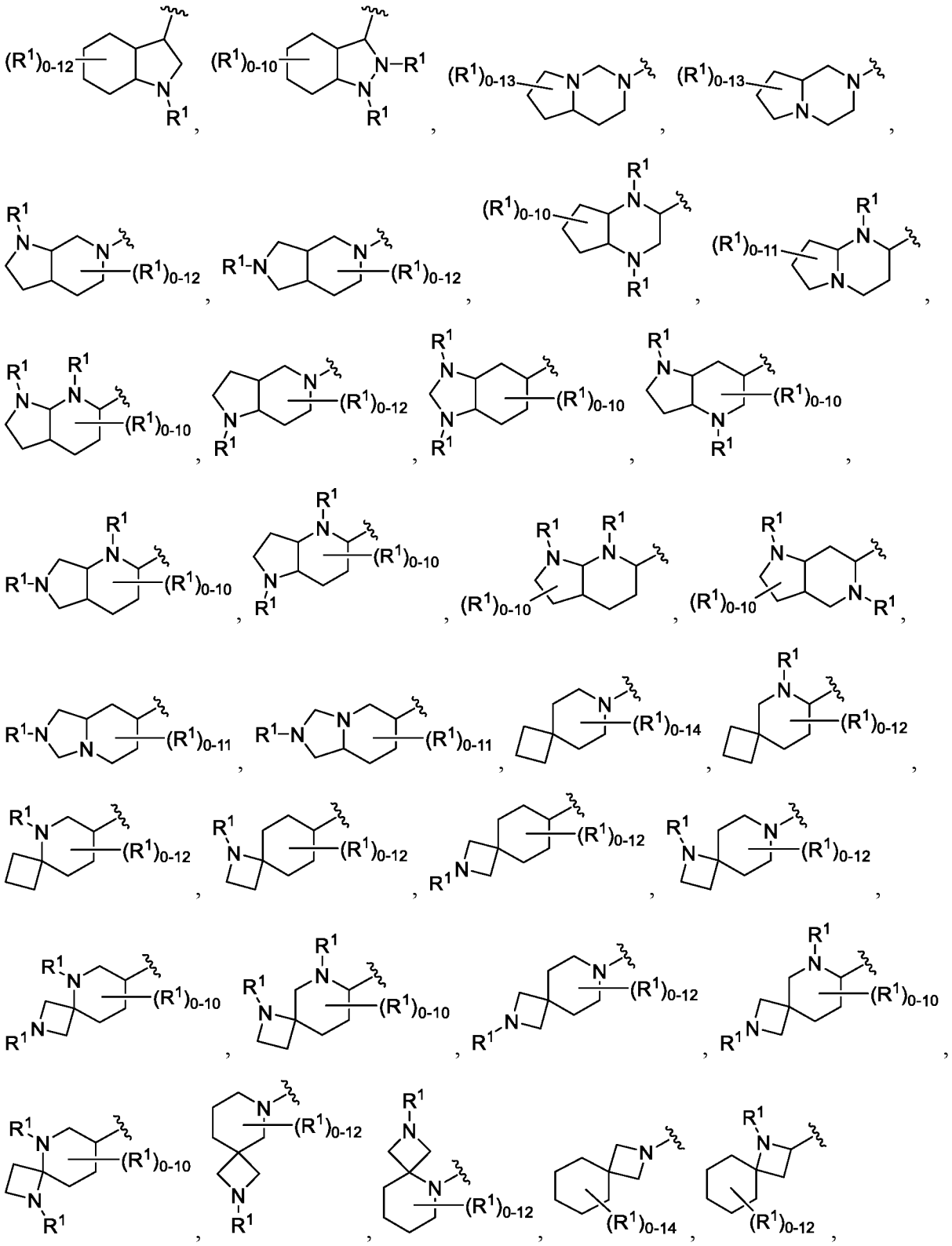
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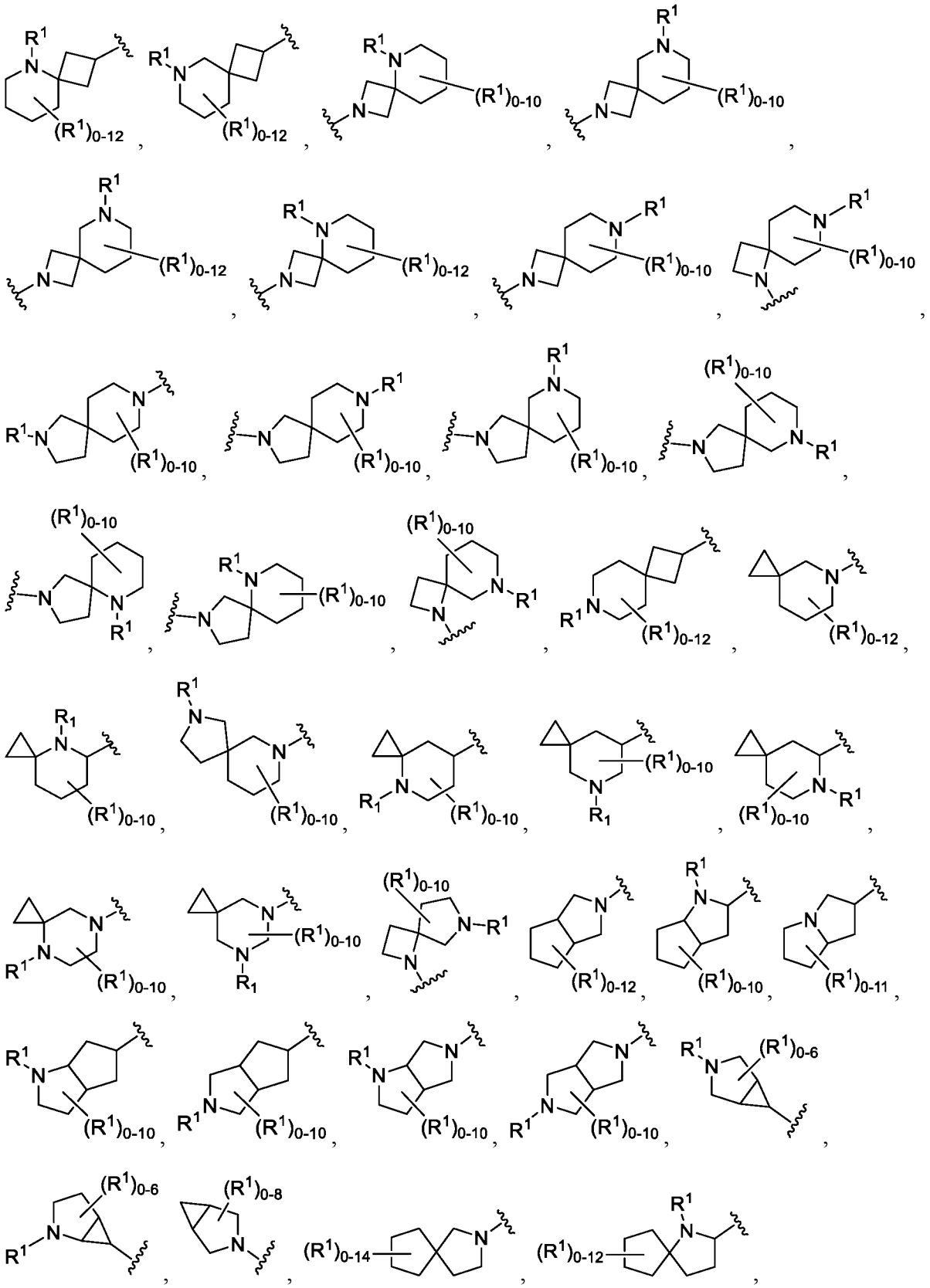
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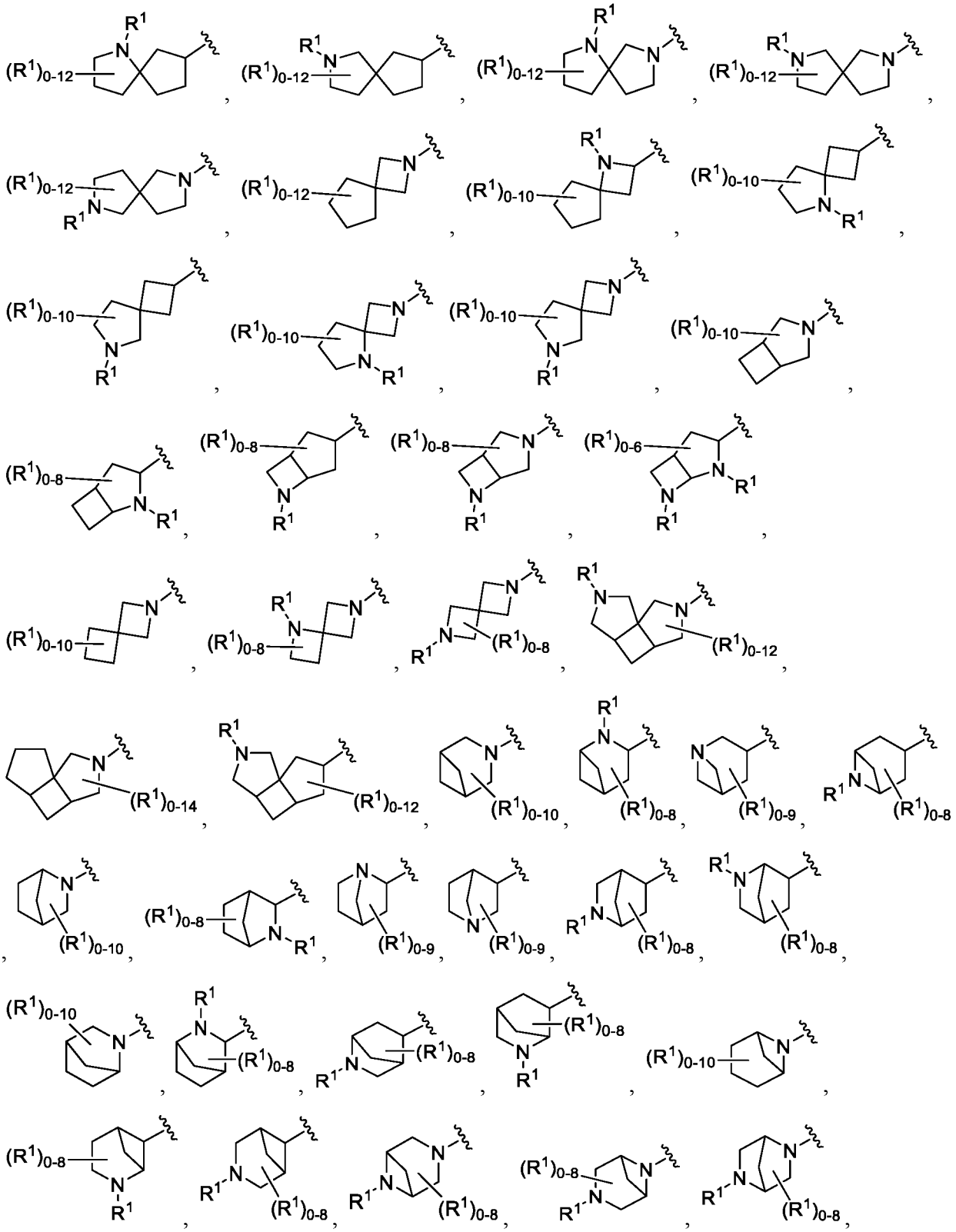
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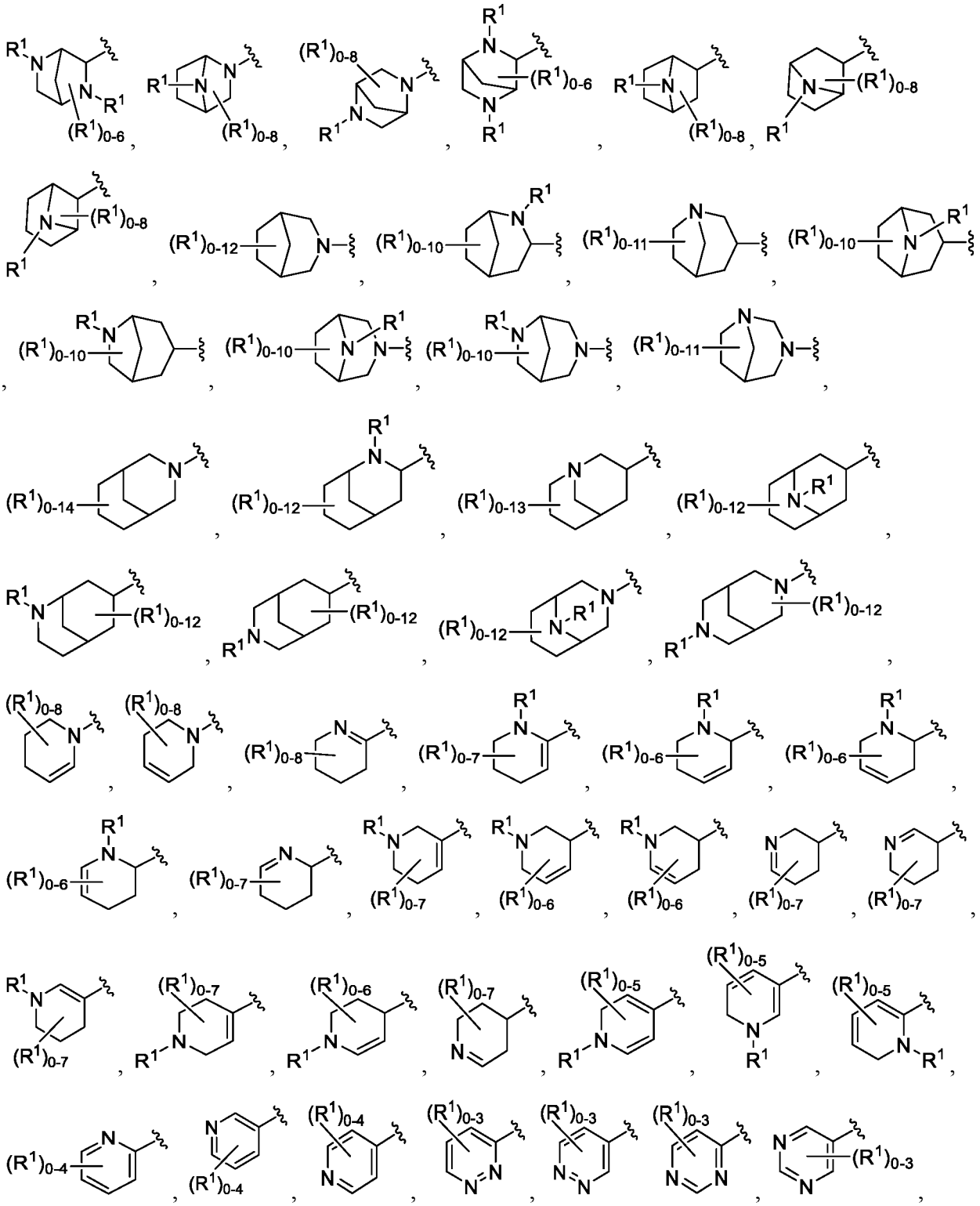
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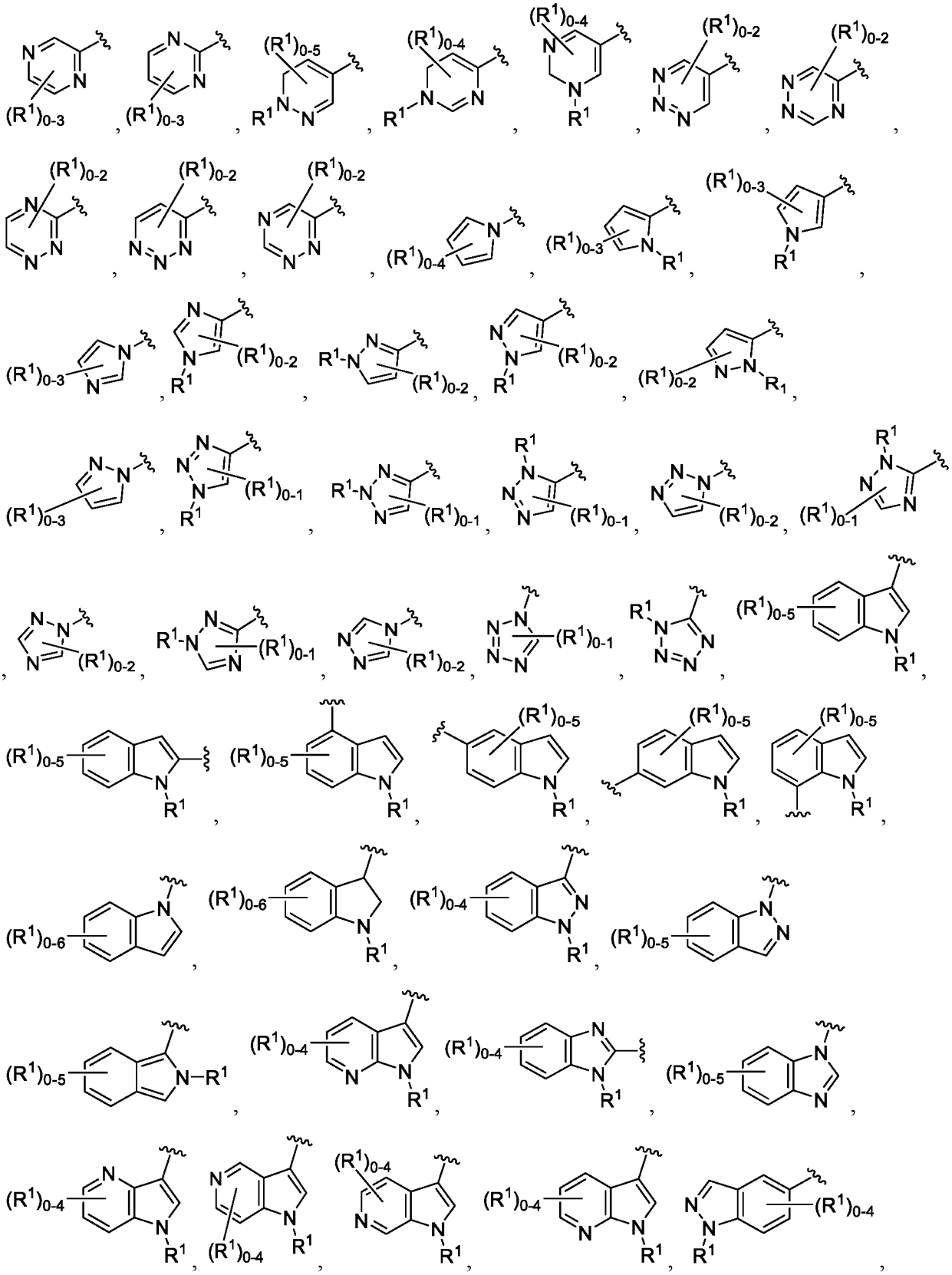


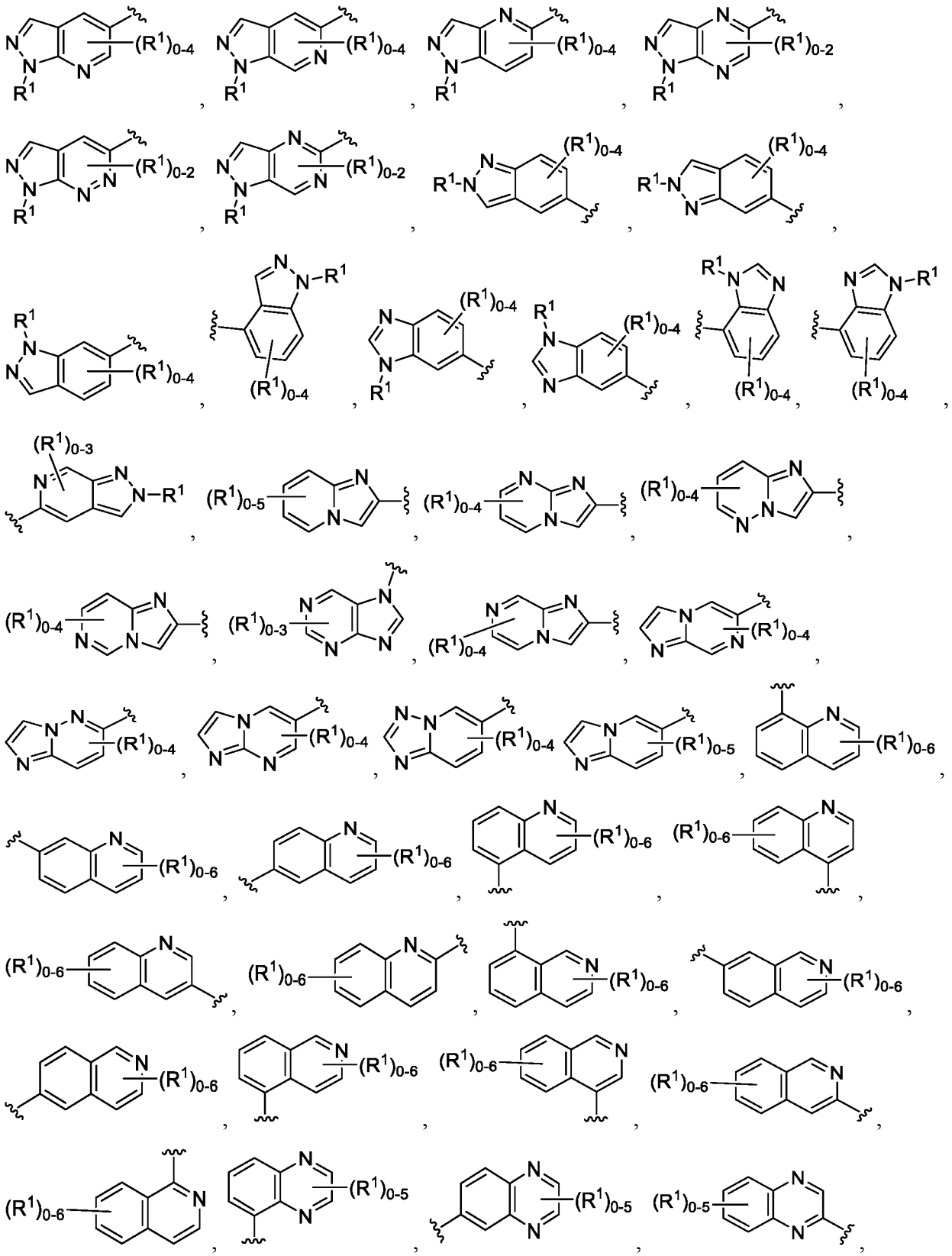


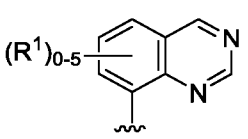
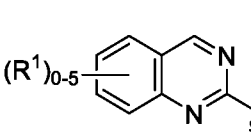
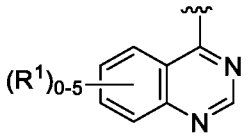
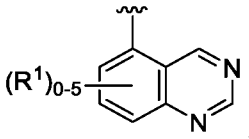
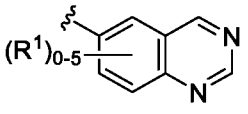
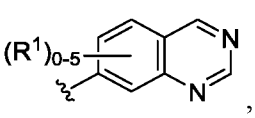
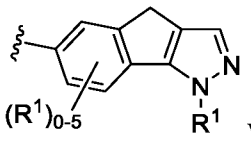


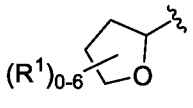


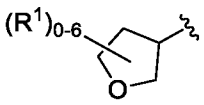
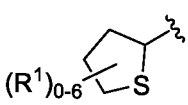
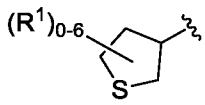
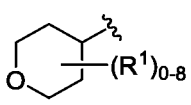
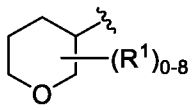
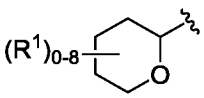
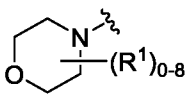
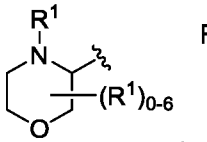
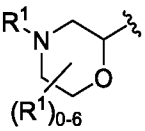
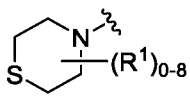
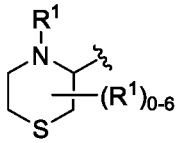
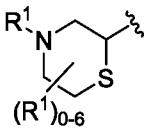
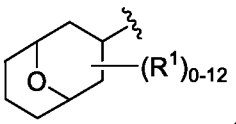
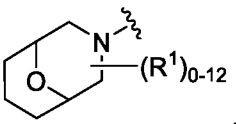
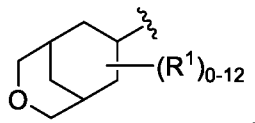
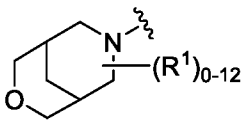
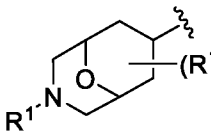
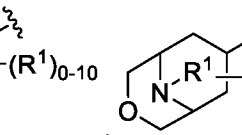
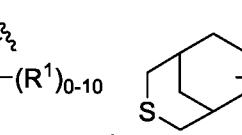
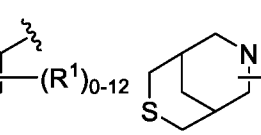
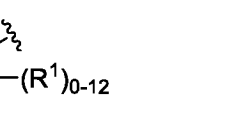
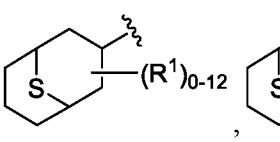
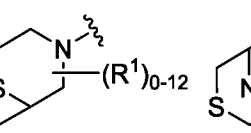
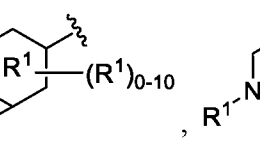
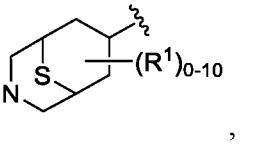
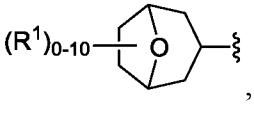
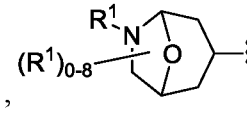
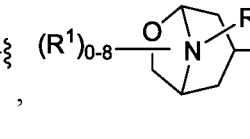
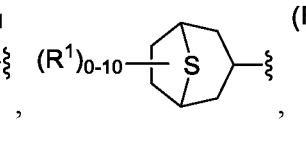




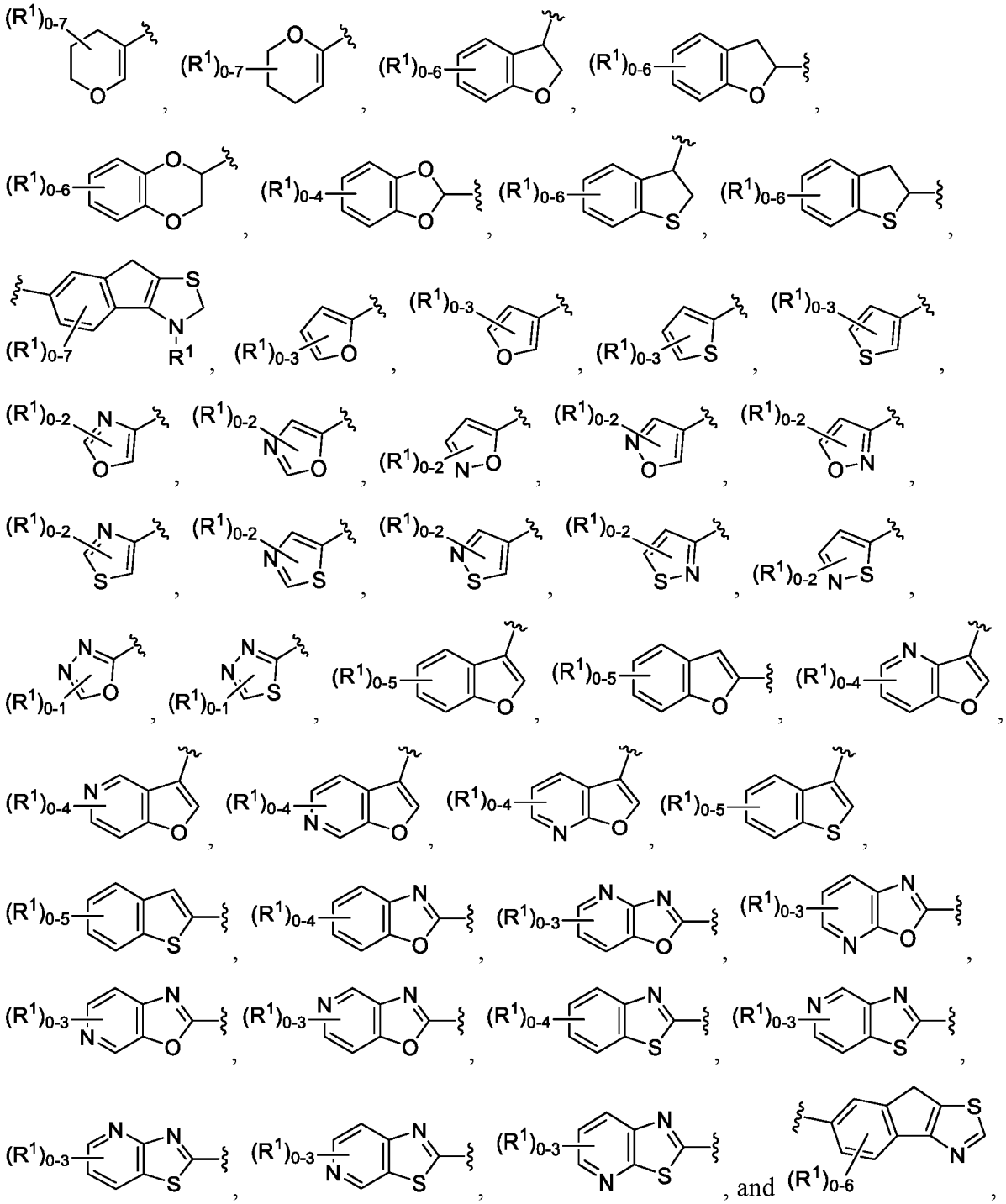








, and  wherein each R^1 is as defined herein. In an embodiment, A and B are each independently a saturated, partially saturated, or unsaturated (e.g., aromatic) derivative of one of the rings described above. In an embodiment, A and B are each independently a stereoisomer of one of the rings described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

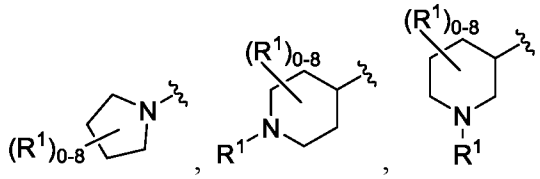
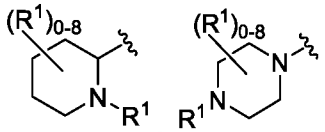
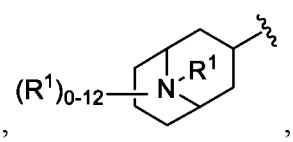
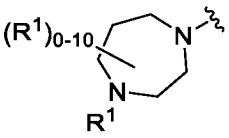
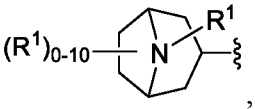
In some embodiments, each of A and B are independently selected from: ,

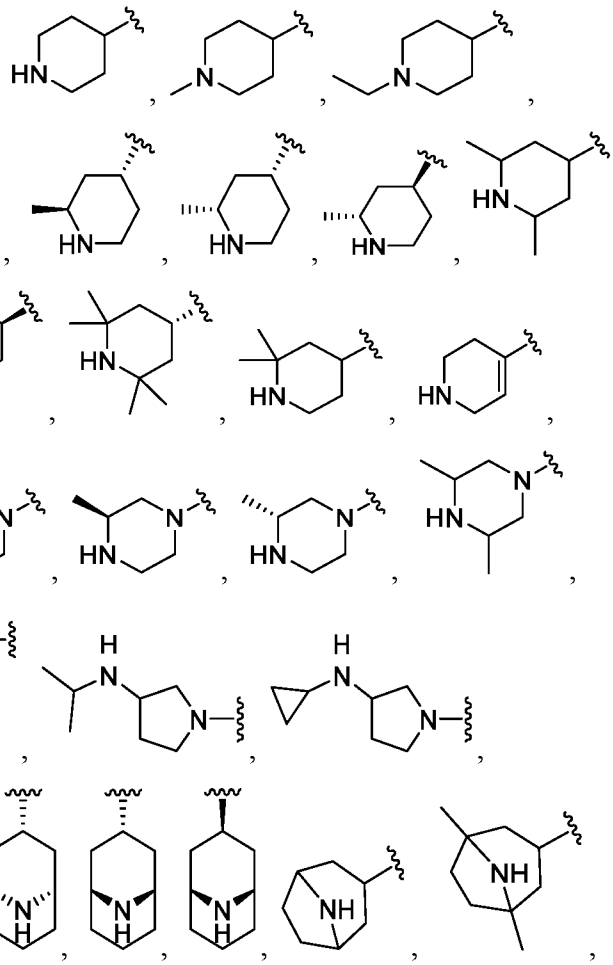






























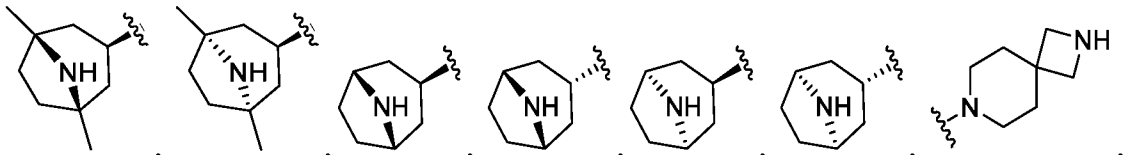
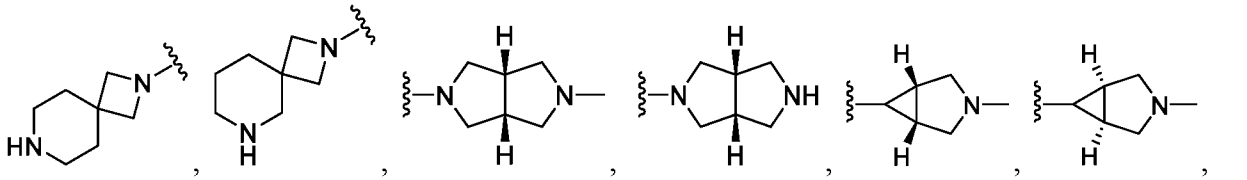
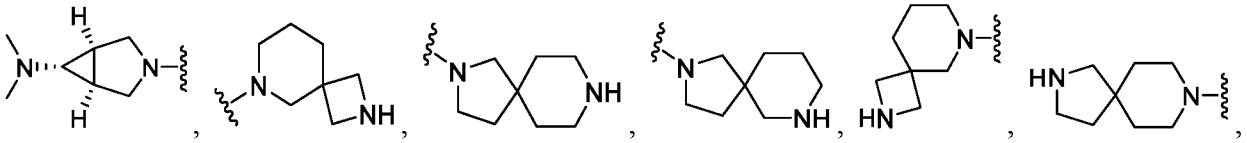
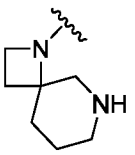


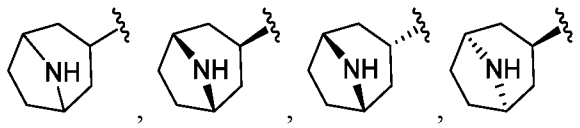
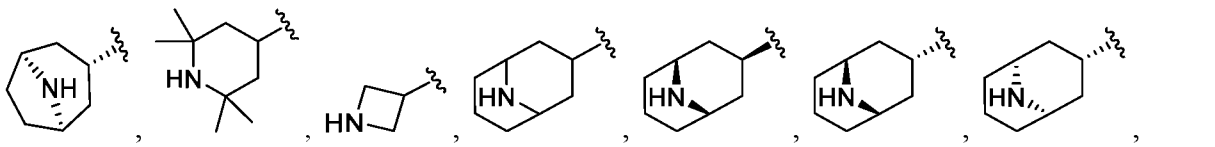
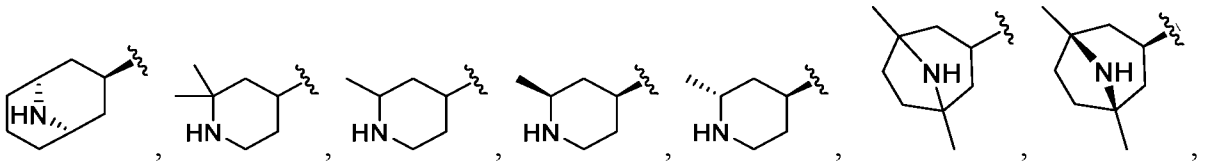
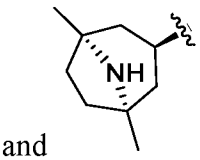


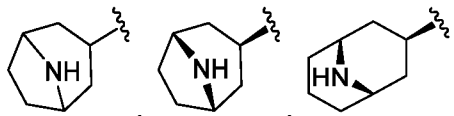
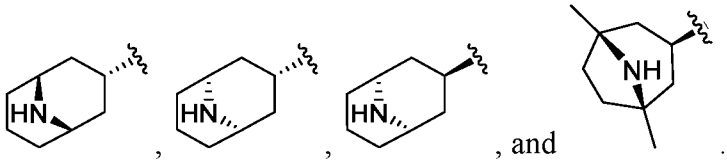
wherein each R^1 is as defined herein. In an embodiment, A and B are each independently a saturated, partially saturated, or unsaturated (e.g., aromatic) derivative of one of the rings described above. In an embodiment, A and B are each independently a stereoisomer of one of the rings described above.

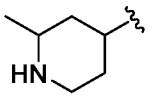
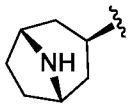
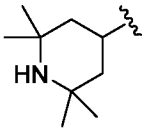
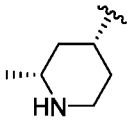
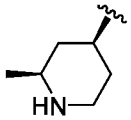
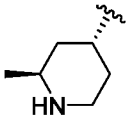
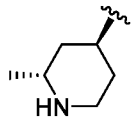
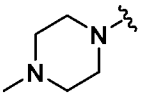
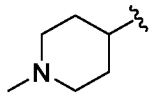
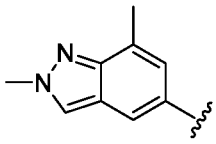
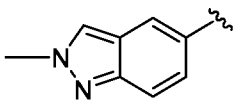
In some embodiments, A is selected from , , , , and , wherein R^1 is as defined herein.

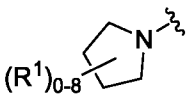
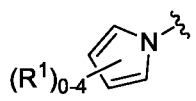
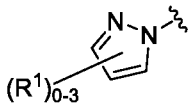
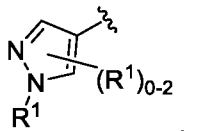
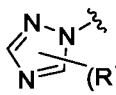
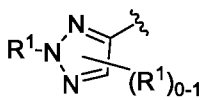
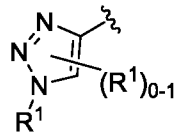
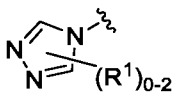
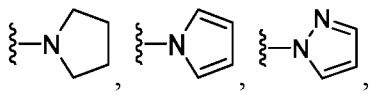
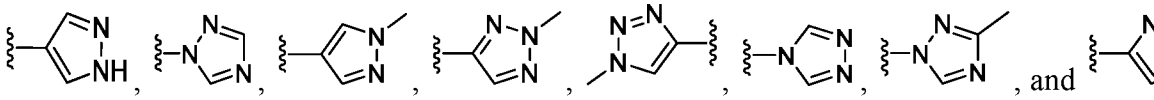
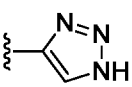
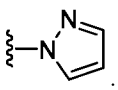
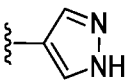
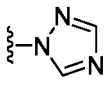
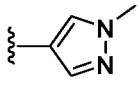
In some embodiments, A is selected from 

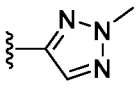
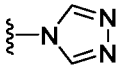
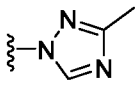
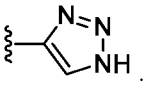




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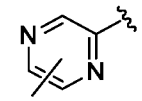
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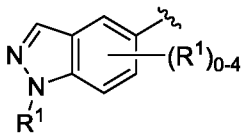
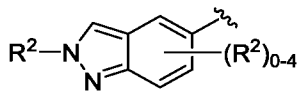
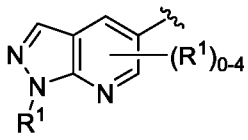
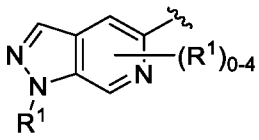
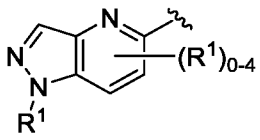
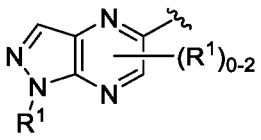
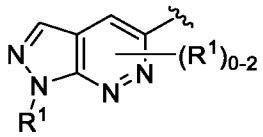
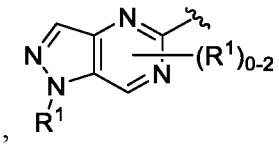
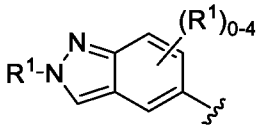
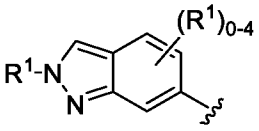
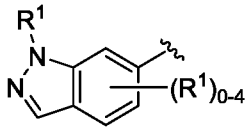
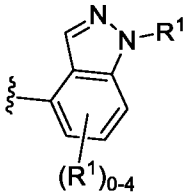
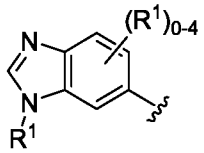
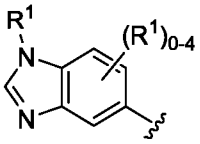
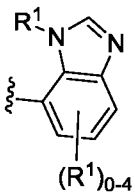
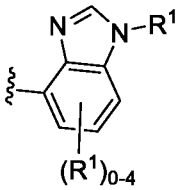
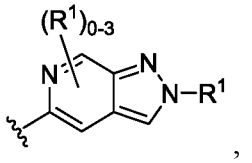
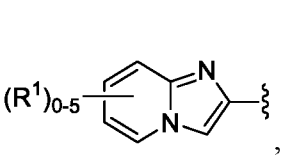
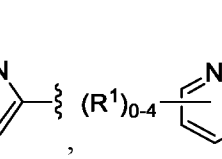
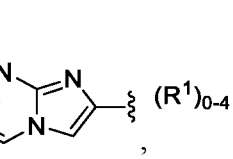
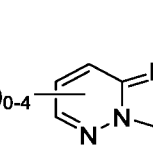
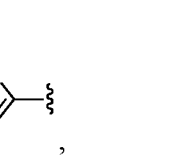
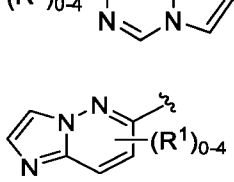
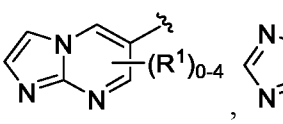
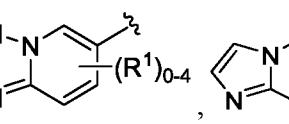
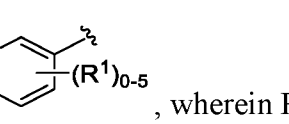
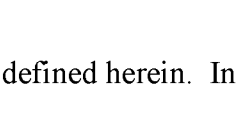
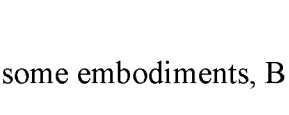
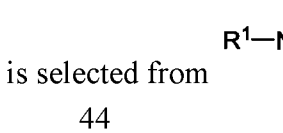
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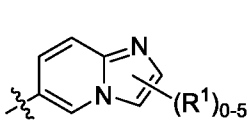
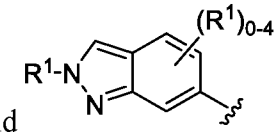
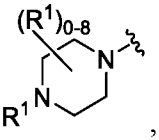
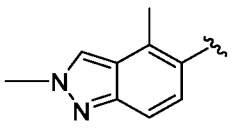
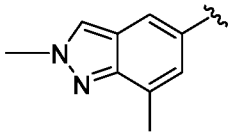
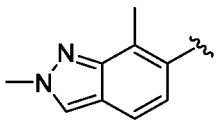
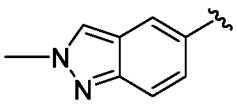
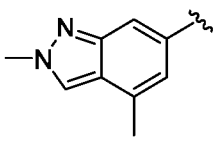
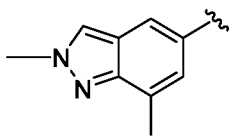
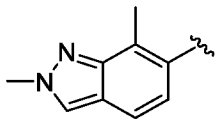
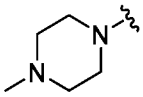
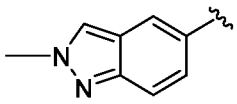
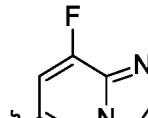
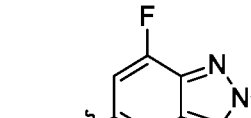
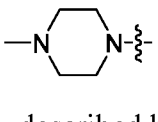
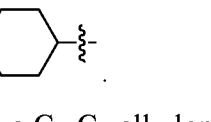
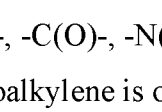
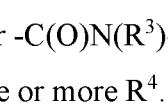
In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments,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

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

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

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As generally described herein, L may be absent or refer to a C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^3)-, -S(O)$_x$, -N(R^3)C(O)-, or -C(O)N(R^3)- group, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4. In some embodiments, L may be absent or refer to a C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^3)-, -N(R^3)C(O)-, or -C(O)N(R^3)- group, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4.

In some embodiments, L is absent. In some embodiments, L 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 is unsubstituted C_1-C_6 alkylene. In some embodiments, L is substituted C_1-C_6-alkylene, e.g., C_1-C_6 alkylene substituted with one or more R^4. In some embodiments, L is C_1-

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alkylene substituted with one R^4. In some embodiments, L is -CH_2- (or methylene). In some embodiments, L is -C(O)- (or carbonyl).

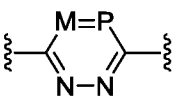
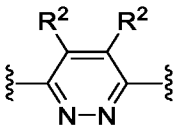
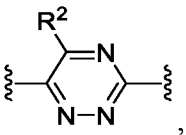
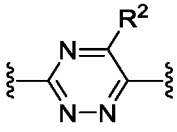
In some embodiments, L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -$N(R^3)C(O)$-, or -$C(O)N(R^3)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4.

In some embodiments, L 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 is unsubstituted C_1-C_6 heteroalkylene. In some embodiments, L is C_1-C_6-heteroalkylene substituted with one or more R^4. 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 is -$N(R^3)C(O)$-. In some embodiments, L is -$C(O)N(R^3)$-.

In some embodiments, L is oxygen. In some embodiments, L is nitrogen, which may be substituted with R^3. In some embodiments, L is nitrogen substituted with one R^3. In some embodiments, L is -$N(R^3)$-. In some embodiments, L is -$N(CH_3)$-. In some embodiments, L is -NH-. In some embodiments, L is -O-.

In some embodiments, L is -$S(O)_x$-. In some embodiments, x is 0, 1, or 2. In some embodiments, L is -S- or -$S(O)_2$-. In some embodiments, L is -S-.

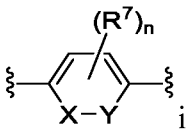
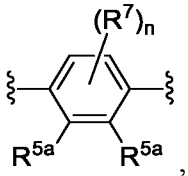
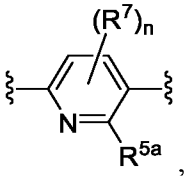
As generally described herein, each of M and P independently refer to $C(R^2)$ or N. In some embodiments, each of M and P are independently $C(R^2)$ or N. In some embodiments, M and P are each independently $C(R^2)$, e.g., CH. In some embodiments, one of M and P is $C(R^2)$, and the other of M and P is N. In some embodiments, M is $C(R^2)$. In some embodiments, M is N. In some embodiments, P is $C(R^2)$. In some embodiments, P is N. In some embodiments, M is $C(R^2)$ (e.g., CH) and P is N. In some embodiments, M is N and P is $C(R^2)$ (e.g., CH).

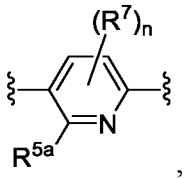
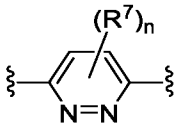
In some embodiments,  is selected from , , and , wherein R^2 is as defined above. In some embodiments, R^2 is hydrogen.

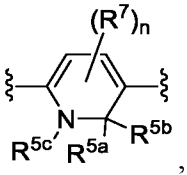
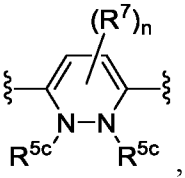
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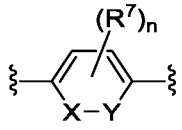
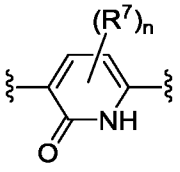
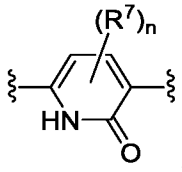
As generally described herein, each of X and Y independently refer to C, $C(R^{5a})$, $C(R^{5a})(R^{5b})$, N, or $N(R^{5c})$. In some embodiments, each of X and Y are independently C. In some embodiments, each of X and Y are $C(R^{5a})$. In some embodiments, X and Y are may not both be $C(R^{5a})$. In some embodiments, one of X and Y is $C(R^{5a})(R^{5b})$, and the other of X and Y is $N(R^{5c})$. In some embodiments, X is $N(R^{5c})$ and Y is $C(R^{5a})(R^{5b})$. In some embodiments, X is $N(R^{5c})$ and Y is $C(R^{5a})(R^{5b})$, where R^{5a} and R^{5b}, together with the carbon atom to which they are attached, form an oxo group. In some embodiments, one of X and Y is $C(R^{5a})$, and the other of X and Y is N. In some embodiments, Y is N and X is $C(R^{5a})$ (e.g., CH or $COCH_3$). In some embodiments, X is N and Y is $C(R^{5a})$ (e.g., CH or $COCH_3$). In some embodiments, one of X and Y is C(O) and the other of X and Y is NH. In some embodiments, X is NH and Y is C(O). In some embodiments, the bond between X and Y is a single bond. In some embodiments, the bond between X and Y is a double bond.

In some embodiments, when Y is N and X is $C(R^{5a})$ (e.g., CH), L is not $-N(R^3)-$ (e.g., $-N(CH_3)-$). In some embodiments, when Y is N and X is CH, L is not $-N(R^3)-$ (e.g., $-N(CH_3)-$). In some embodiments, when Y is N and X is $C(R^{5a})$ (e.g., CH), L is not $-N(CH_3)-$. In some embodiments, when Y is N and X is CH, L is not $-N(CH_3)-$. In some embodiments, when Y is N and L is $-N(R^3)$, R^3 is not C_1-C_6-alkylene. In some embodiments, when Y is N and L is $-N(R^3)$, R^3 is not CH_3. In some embodiments, when Y is N, X is also N. In some embodiments, when X is $C(R^{5a})$ (e.g., CH), Y is not N. In some embodiments, when Y comprises N, the bond between X and Y is not a double bond. In some embodiments, when Y comprises N, the bond between X and Y is a single bond. In some embodiments, when Y is N, B is not aryl or heteroaryl. In some embodiments, when Y is N, B is not aryl. In some embodiments, when Y is N, B is not heteroaryl. In some embodiments, when Y is N, B is cycloalkyl or heterocyclyl. In some embodiments, when Y is N, B is cycloalkyl. In some embodiments, when Y is N, B is heterocyclyl.

In some embodiments,  is selected from , ,


, and , wherein each of R^{5a}, R^{5b}, R^{5c}, R^7 and n are as defined herein.

In some embodiments,  is selected from  and , wherein each of R^7 and n are as defined herein.

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^8. In some embodiments, R^1 is C_2-C_6-alkenyl substituted with one or more R^8. In some embodiments, R^1 is C_2-C_6-alkynyl substituted with one or more R^8. In some embodiments, R^1 is C_1-C_6-heteroalkyl substituted with one or more R^8. In some embodiments, R^1 is C_1-C_6-haloalkyl substituted with one or more R^8. 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^8. In some embodiments, R^1 is heterocyclyl substituted with one or more R^8. In some embodiments, R^1 is aryl substituted with one or more R^8. In some embodiments, R^1 is C_1-C_6 alkylene-aryl substituted with one or

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more R^8. In some embodiments, R^1 is C_1-C_6 alkenylene-aryl substituted with one or more R^8. In some embodiments, R^1 is C_1-C_6 alkylene-heteroaryl substituted with one or more R^8. In some embodiments, R^1 is heteroaryl substituted with one or more R^8.

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^8.

In some embodiments, R^2 is hydrogen. 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 C_1-alkyl (e.g., methyl). In some embodiments, R^2 is methyl. In some embodiments, R^2 is $-OR^A$. In some embodiments, R^2 is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^2 is fluoro. In some embodiments, R^2 is cyano.

In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is C_1-C_6 alkyl. In some embodiments, R^3 is C_1-C_6 haloalkyl. In some embodiments, R^3 is C_1-alkyl (e.g., methyl). In some embodiments, R^3 is methyl.

In some embodiments, R^4 is C_1-C_6-alkyl. In some embodiments, R^4 is C_1-C_6-heteroalkyl. In some embodiments, R^4 is C_1-C_6-haloalkyl. In some embodiments, R^4 is cycloalkyl. In some embodiments, R^4 is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^4 is cyano. In some embodiments, R^4 is oxo. In some embodiments, R^4 is $-OR^A$. In some embodiments, R^4 is $-NR^BR^C$. In some embodiments, R^4 is $-C(O)R^D$ or $-C(O)OR^D$.

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In some embodiments, R^{5a} and R^{5b} are each independently hydrogen or C_1-C_6-alkyl. In some embodiments, R^{5a} is hydrogen. In some embodiments, R^{5b} is hydrogen. In some embodiments, R^{5a} and R^{5b} are taken together to form an oxo group. In some embodiments, R^{5c} is hydrogen. In some embodiments, R^{5c} is C_1-C_6-alkyl. In some embodiments, R^{5c} is C_1-C_6-haloalkyl (e.g., $-CF_3$ or $-CHF_2$). In some embodiments, R^{5c} is $-CF_3$. In some embodiments, R^{5c} is $-CHF_2$. In some embodiments, R^{5c} is $-C(O)R^D$ (e.g., $-C(O)CH_3$). In some embodiments, R^{5c} is $-C(O)CH_3$).

In some embodiments, R^{5d}, R^{5e}, and R^{5f} are each independently hydrogen, C_1-C_6-alkyl, halo, or R^{5d}, R^{5e} are taken together to form an oxo group. In some embodiments, R^{5d} is hydrogen. In some embodiments, R^{5e} is hydrogen. In some embodiments, R^{5f} is hydrogen. In some embodiments, R^{5e} and R^{5f}, are together to form an oxo group.

In some embodiments, R^7 is C_1-C_6-alkyl. In some embodiments, R^7 is C_2-C_6-alkenyl. In some embodiments, R^7 is C_2-C_6-alkynyl. In some embodiments, R^7 is C_1-C_6-heteroalkyl. In some embodiments, R^7 is C_1-C_6-haloalkyl. In some embodiments, R^7 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^7 is C_1-C_6-alkyl substituted with one or more R^9. In some embodiments, R^7 is C_2-C_6-alkenyl substituted with one or more R^9. In some embodiments, R^7 is C_2-C_6-alkynyl substituted with one or more R^9. In some embodiments, R^7 is C_1-C_6-heteroalkyl substituted with one or more R^9. In some embodiments, R^7 is C_1-C_6-haloalkyl substituted with one or more R^9. In some embodiments, R^7 is halo, e.g., fluoro, chloro, bromo, or iodo. In some embodiments, R^7 is fluoro. In some embodiments, R^7 is cyano. In some embodiments, R^7 is oxo. In some embodiments, R^7 is $NR^BC(O)R^D$. In some embodiments, R^7 is $-C(O)NR^BR^C$. In some embodiments, R^7 is $-C(O)R^D$. In some embodiments, R^7 is $-SR^E$.

In some embodiments, R^8 is C_1-C_6-alkyl. In some embodiments, R^8 is C_2-C_6-alkenyl. In some embodiments, R^8 is C_2-C_6-alkynyl. In some embodiments, R^8 is C_1-C_6-heteroalkyl. In some embodiments, R^8 is C_1-C_6-haloalkyl. In some embodiments, R^8 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^8 is C_1-C_6-alkyl substituted with one or more R^{11}. In some embodiments, R^8 is C_2-C_6-alkenyl substituted with one or more R^{11}. In some embodiments, R^8 is C_2-C_6-alkynyl substituted with one or more R^{11}. In some

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embodiments, R^8 is C_1-C_6-haloalkyl substituted with one or more R^{11}. In some embodiments, R^8 is C_1-C_6-heteroalkyl substituted with one or more R^{11}.

In some embodiments, R^8 is cycloalkyl. In some embodiments, R^8 is heterocyclyl. In some embodiments, R^8 is aryl. In some embodiments, R^8 is heteroaryl. In some embodiments, R^8 is unsubstituted cycloalkyl, unsubstituted heterocyclyl, unsubstituted aryl, or unsubstituted heteroaryl. In some embodiments, R^8 is cycloalkyl substituted with one or more R^{11}. In some embodiments, R^8 is heterocyclyl substituted with one or more R^{11}. In some embodiments, R^8 is aryl substituted with one or more R^{11}. In some embodiments, R^8 is heteroaryl substituted with one or more R^{11}.

In some embodiments, R^8 is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^8 is cyano. In some embodiments, R^8 is oxo. In some embodiments, R^8 is $-OR^A$. In some embodiments, R^8 is $-NR^BR^C$. In some embodiments, R^8 is $-NR^BC(O)R^D$. In some embodiments, R^8 is $-NO_2$. In some embodiments, R^8 is $-C(O)NR^BR^C$. In some embodiments, R^8 is $-C(O)R^D$. In some embodiments, R^8 is $-C(O)OR^D$. In some embodiments, R^8 is $-SR^E$. In some embodiments, R^8 is $-S(O)_xR^D$.

In some embodiments, R^9 is C_1-C_6-alkyl. In some embodiments, R^9 is C_2-C_6-alkenyl. In some embodiments, R^9 is C_2-C_6-alkynyl. In some embodiments, R^9 is C_1-C_6-heteroalkyl. In some embodiments, R^9 is C_1-C_6-haloalkyl. In some embodiments, R^9 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^9 is C_1-C_6-alkyl substituted with one or more R^{11}. In some embodiments, R^9 is C_2-C_6-alkenyl substituted with one or more R^{11}. In some embodiments, R^9 is C_2-C_6-alkynyl substituted with one or more R^{11}. In some embodiments, R^9 is C_1-C_6-haloalkyl substituted with one or more R^{11}. In some embodiments, R^9 is C_1-C_6-heteroalkyl substituted with one or more R^{11}.

In some embodiments, R^9 is cycloalkyl. In some embodiments, R^9 is heterocyclyl. In some embodiments, R^9 is aryl. In some embodiments, R^9 is heteroaryl. In some embodiments, R^9 is unsubstituted cycloalkyl, unsubstituted heterocyclyl, unsubstituted aryl, or unsubstituted heteroaryl. In some embodiments, R^9 is cycloalkyl substituted with one or more R^{11}. In some embodiments, R^9 is heterocyclyl substituted with one or more R^{11}. In some embodiments, R^9 is

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aryl substituted with one or more R^{11}. In some embodiments, R^9 is heteroaryl substituted with one or more R^{11}.

In some embodiments, R^9 is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^9 is cyano. In some embodiments, R^9 is oxo. In some embodiments, R^9 is $-OR^A$. In some embodiments, R^9 is $-NR^BR^C$. In some embodiments, R^9 is $-NR^BC(O)R^D$. In some embodiments, R^9 is $-NO_2$. In some embodiments, R^9 is $-C(O)NR^BR^C$. In some embodiments, R^9 is $-C(O)R^D$. In some embodiments, R^9 is $-C(O)OR^D$. In some embodiments, R^9 is $-SR^E$. In some embodiments, R^9 is $-S(O)_xR^D$.

In some embodiments, R^{10} is C_1-C_6-alkyl. In some embodiments, R^{10} is halo (e.g., fluoro, chloro, bromo, or iodo).

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 each 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^{10} (e.g., 1, 2, or 3 R^{10}).

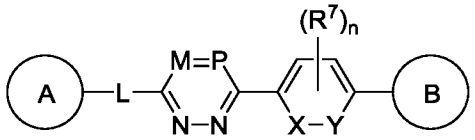
In some embodiments, R^D, R^E, or both are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl (e.g., benzyl), or C_1-C_6 alkylene-heteroaryl. In some

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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, m is an integer between 0 and 2 (e.g., 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, n is an integer between 0 and 4 (e.g., 0, 1, 2, 3, or 4). In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4. In some embodiments, x is an integer between 0 and 2 (e.g., 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 present disclosure features 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;

L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^3)-, -N(R^3)C(O)-, or -C(O)N(R^3)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4;

M and P are each independently C(R^2) or N;

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X and Y are each independently C, C(R^{5a}), C(R^{5a})(R^{5b}), N, or N(R^{5c}), wherein the bond between X and Y may be a single or double bond as valency permits, and wherein X and Y may not both be C(R^{5a})(R^{5b});

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, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^8; 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^8;

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

each R^3 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^4 is 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 $–C(O)OR^D$;

R^{5a} is hydrogen, C_1-C_6-alkyl, or $–OR^F$;

R^{5b} is hydrogen or C_1-C_6-alkyl; or

R^{5a} and R^{5b}, together with the carbon atom to which they are attached, form an oxo group;

each R^{5c} is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $C(O)R^D$;

each R^7 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, halo, oxo, cyano, $NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, or $–SR^E$, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more R^9; or

two R^7 groups, together with the atoms to which they are attached (e.g., X or Y), form a 4-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9;

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R^8 and R^9 are each 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 of 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, $-OR^A$; 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^{10};

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;

R^F is hydrogen or C_1-C_6-alkyl;

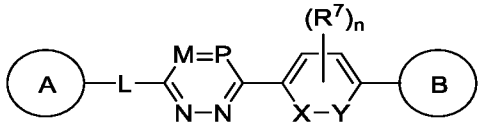
R^{10} is C_1-C_6-alkyl or halo;

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 $-OR^A$;

n is 0, 1, 2, 3, or 4; and

x is 0, 1, or 2.

In some embodiments, the present disclosure features 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;

L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^3)$-, $-N(R^3)C(O)$-, or $-C(O)N(R^3)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4;

M and P are each independently $C(R^2)$ or N;

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X and Y are each independently $C(R^{5a})$, $C(R^{5a})(R^{5b})$, N, or $N(R^{5c})$, wherein the bond between X and Y may be a single or double bond as valency permits, and wherein X and Y may not both be $C(R^{5a})(R^{5b})$ or $C(R^{5a})$;

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, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^8; 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^8;

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

each R^3 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^4 is 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 of R^{5a} and R^{5b} is 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, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

R^{5a} and R^{5b}, together with the carbon atom to which they are attached, form an oxo group;

each R^{5c} is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $C(O)R^D$;

each R^7 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, halo, oxo, cyano, $NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, or $–SR^E$, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more R^9;

R^8 and R^9 are each 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 $–S(O)_xR^D$,

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wherein each of 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, cycloalkyl, heterocyclyl, 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, $-OR^A$; 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^{10};

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;

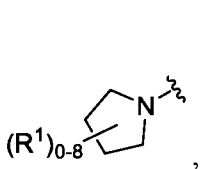
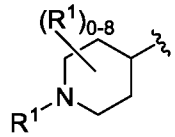
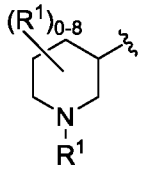
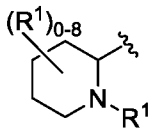
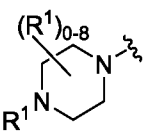
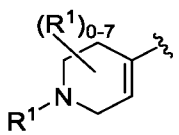
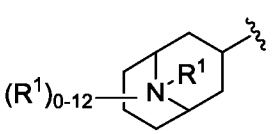
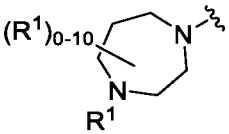
R^{10} is C_1-C_6-alkyl or halo;

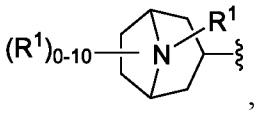
each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

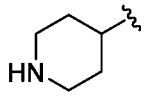
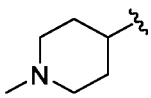
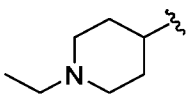
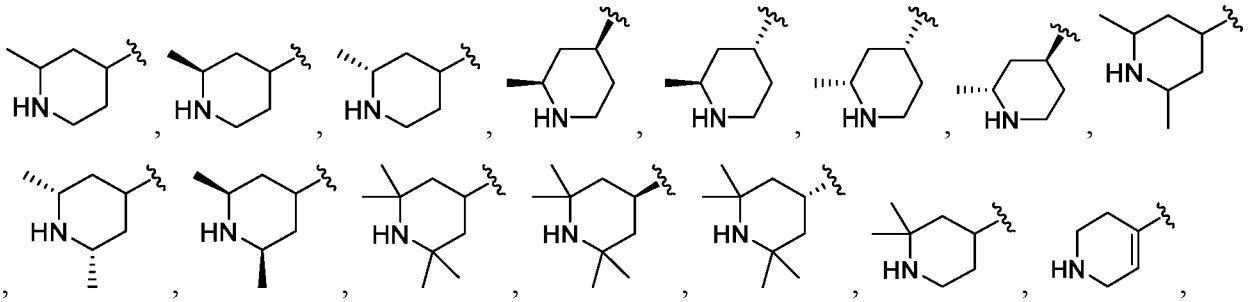
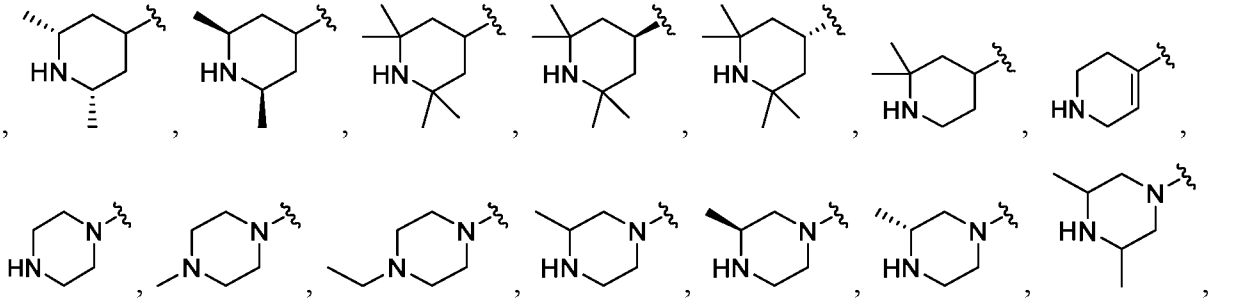
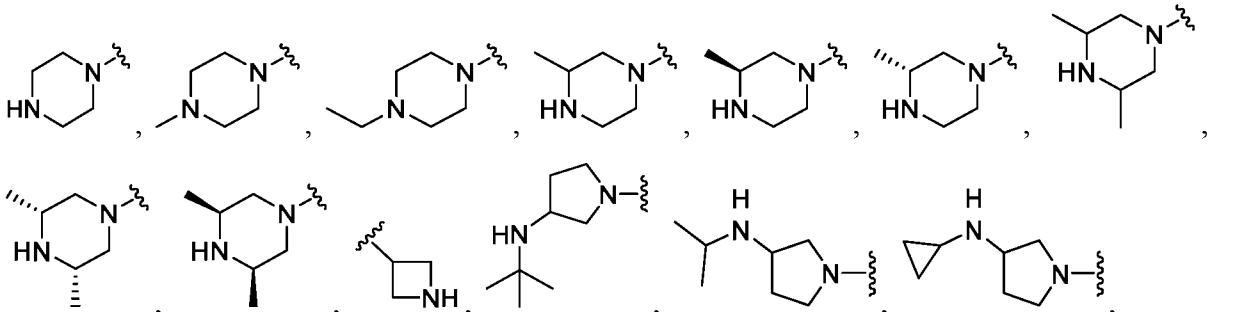
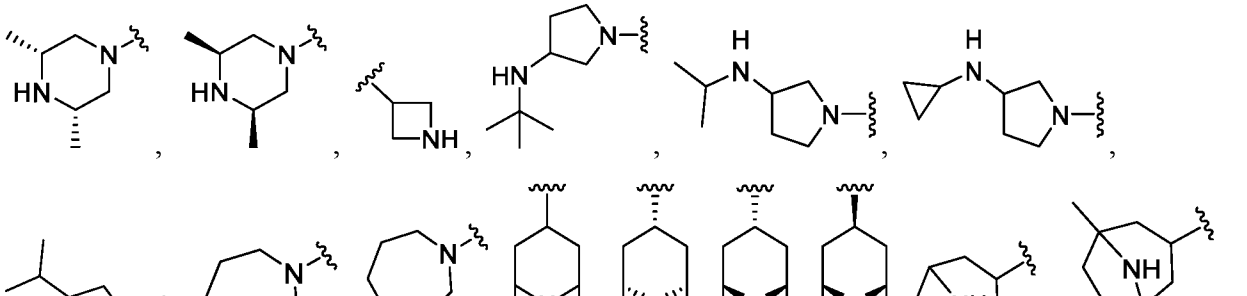
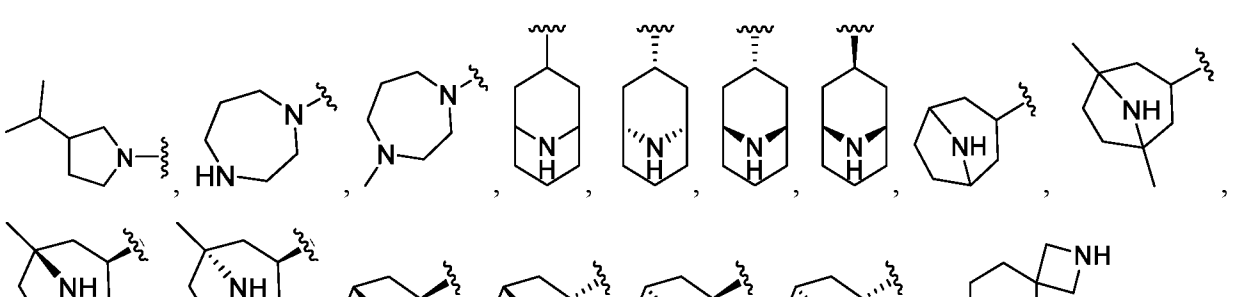
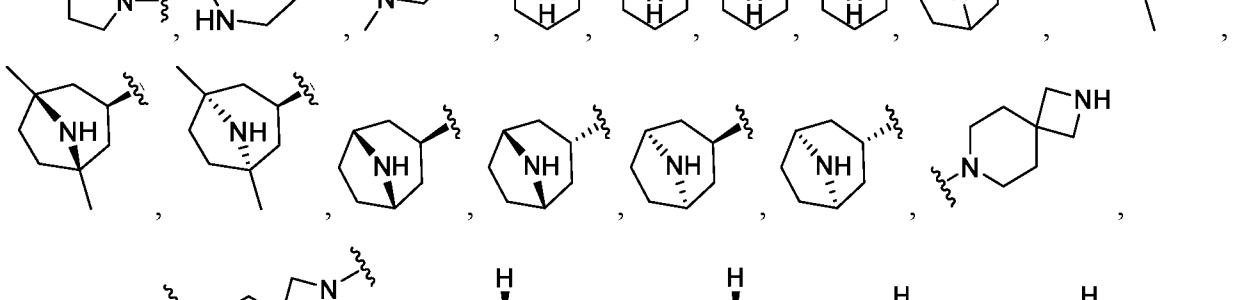
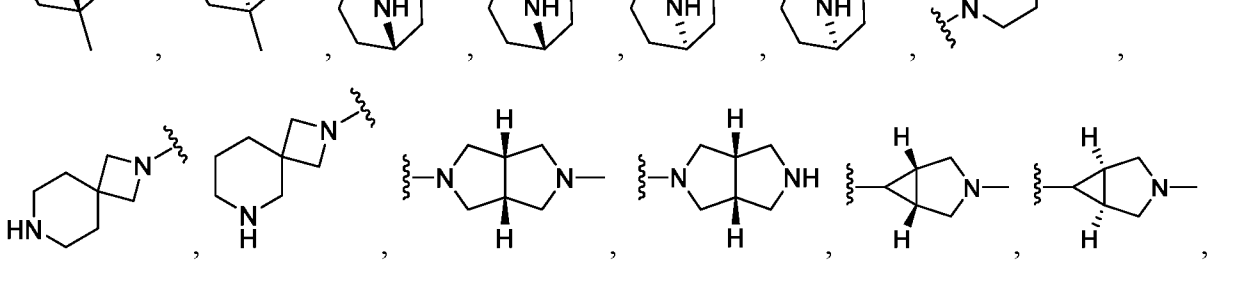
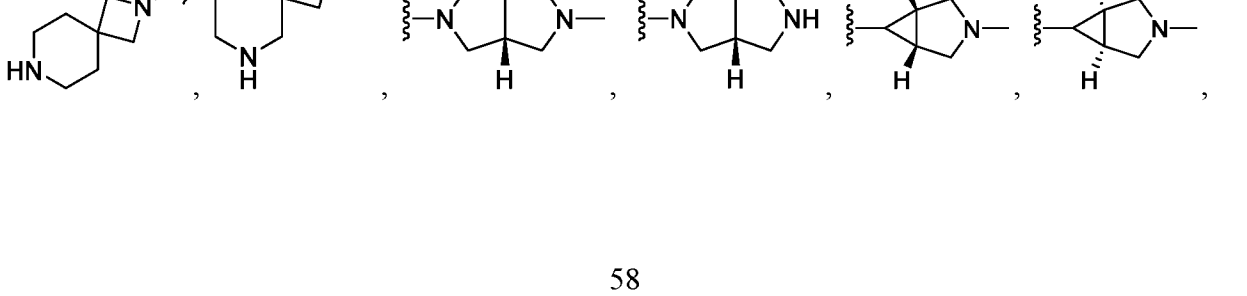
n is 0, 1, 2, 3, or 4; and

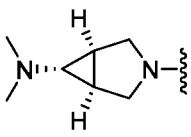
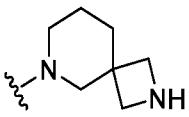
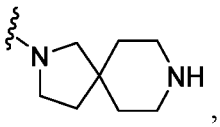
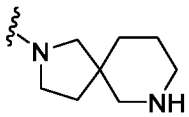
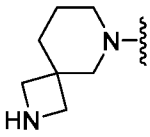
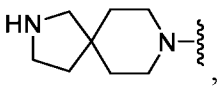
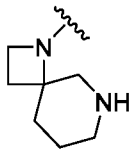
x is 0, 1, or 2.

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 azabicyclo[3.2.1]octanyl.

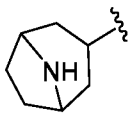
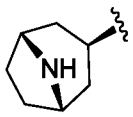
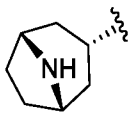
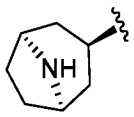
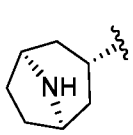
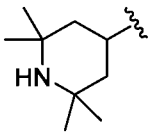
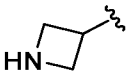
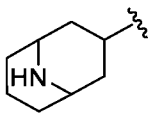
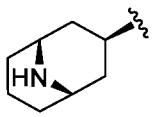
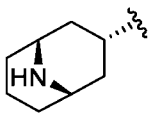
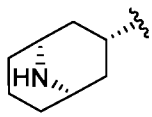
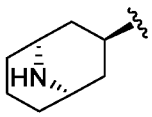
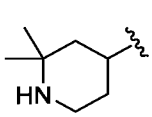
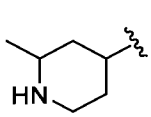
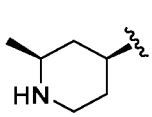
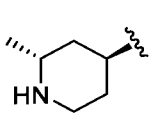
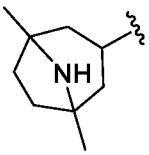
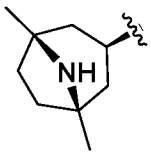
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, wherein R^1 is as defined herein.

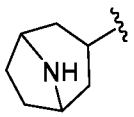
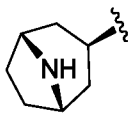
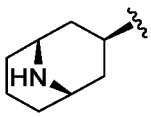
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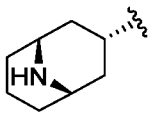
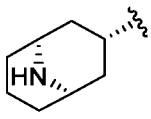
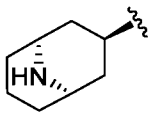
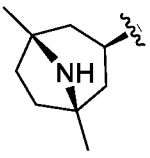








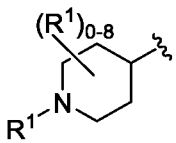
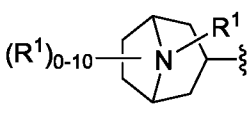
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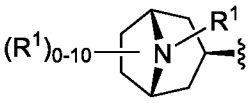
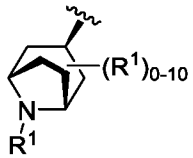
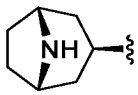
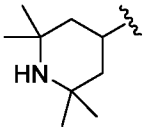
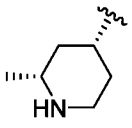
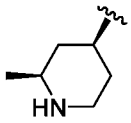
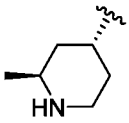
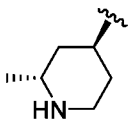
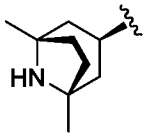
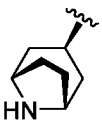
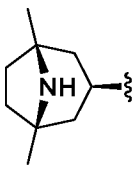
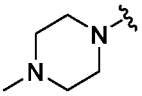
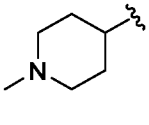
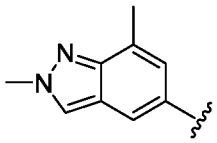
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In some embodiments, A is selected from , , ,

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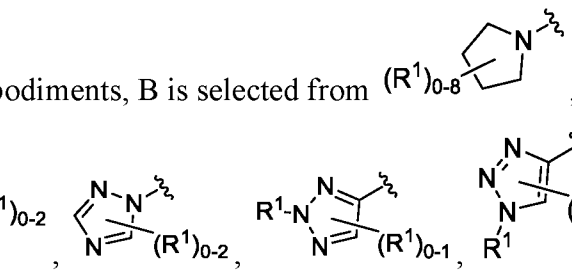
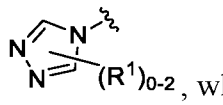
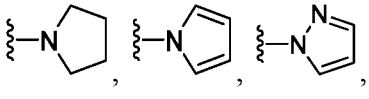
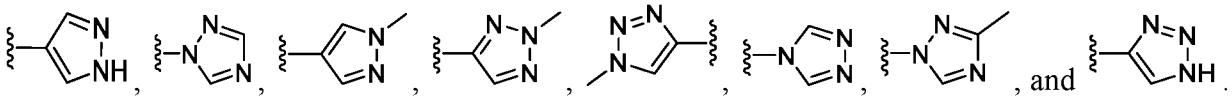
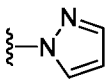
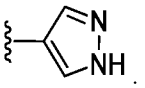
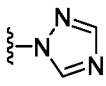
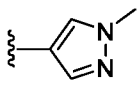
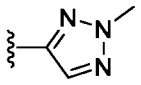
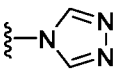
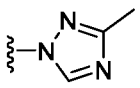
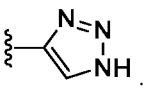
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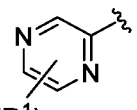
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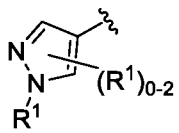
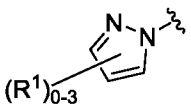
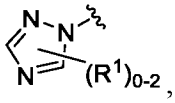
hydrogen or C_1-C_6-alkyl. In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments,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

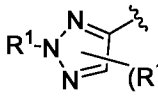
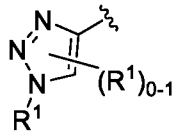
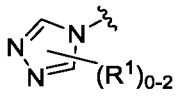
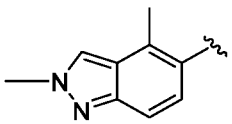
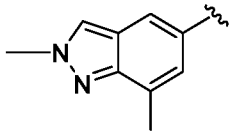
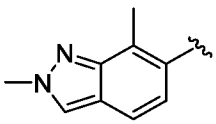
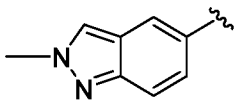
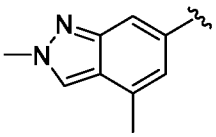
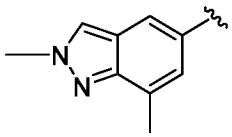
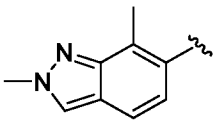
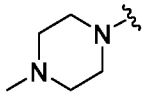
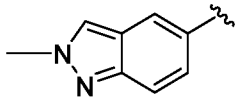
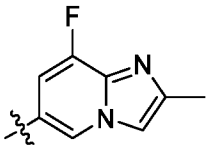
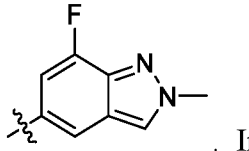
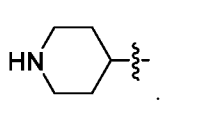
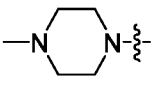
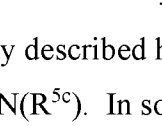
In some embodiments, L is absent. In some embodiments, L is oxygen. In some embodiments, L is nitrogen that is optionally substituted with R^3. In some embodiments, L is nitrogen substituted with R^3. In some embodiments, R^3 is C_1-C_6 alkyl. In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-.

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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 monocyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is selected from , and , wherein R^1 is as defined herein. 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 , wherein R^1 is as defined herein.

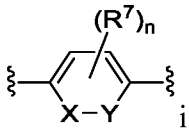
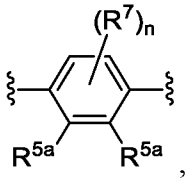
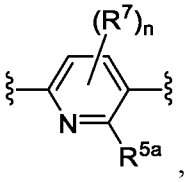
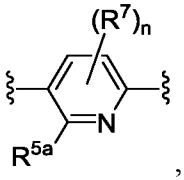
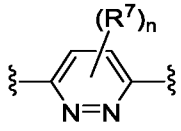
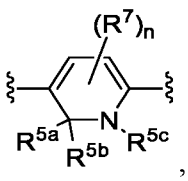
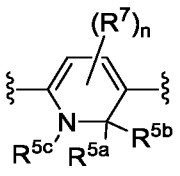
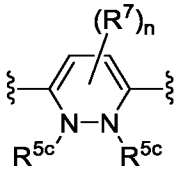
In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is

independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. 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 .

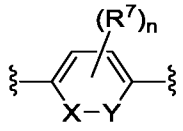
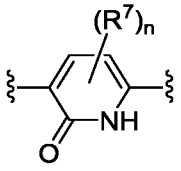
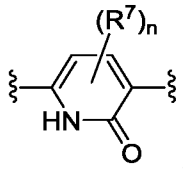
As generally described herein, each of X and Y independently refer to C, $C(R^{5a})$, $C(R^{5a})(R^{5b})$, N, or $N(R^{5c})$. In some embodiments, each of X and Y are independently C. In some embodiments, each of X and Y are $C(R^{5a})$. In some embodiments, one of X and Y is $C(R^{5a})(R^{5b})$, and the other of X and Y is $N(R^{5c})$. In some embodiments, X is $N(R^{5c})$ and Y is $C(R^{5a})(R^{5b})$. In some embodiments, X is $N(R^{5c})$ and Y is $C(R^{5a})(R^{5b})$, where R^{5a} and R^{5b},

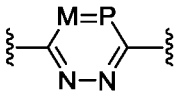
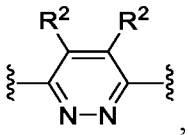
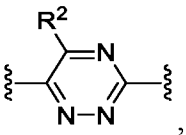
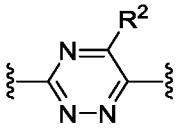
together with the carbon atom to which they are attached, form an oxo group. In some embodiments, one of X and Y is C(R^{5a}), and the other of X and Y is N. In some embodiments, Y is N and X is C(R^{5a}) (e.g., CH or $COCH_3$). In some embodiments, X is N and Y is C(R^{5a}) (e.g., CH or $COCH_3$). In some embodiments, one of X and Y is C(O) and the other of X and Y is NH. In some embodiments, X is NH and Y is C(O). In some embodiments, the bond between X and Y is a single bond. In some embodiments, the bond between X and Y is a double bond.

In some embodiments, when Y is N and X is C(R^{5a}) (e.g., CH), L is not -N(R^3)- (e.g., -N(CH_3)-). In some embodiments, when Y is N and X is CH, L is not -N(R^3)- (e.g., -N(CH_3)-). In some embodiments, when Y is N and X is C(R^{5a}) (e.g., CH), L is not -N(CH_3)-. In some embodiments, when Y is N and X is CH, L is not -N(CH_3)-. In some embodiments, when Y is N and L is -N(R^3), R^3 is not C_1-C_6-alkylene. In some embodiments, when Y is N and L is -N(R^3), R^3 is not CH_3. In some embodiments, when Y is N, X is also N. In some embodiments, when X is C(R^{5a}) (e.g., CH), Y is not N. In some embodiments, when Y comprises N, the bond between X and Y is not a double bond. In some embodiments, when Y comprises N, the bond between X and Y is a single bond. In some embodiments, when Y is N, B is not aryl or heteroaryl. In some embodiments, when Y is N, B is not aryl. In some embodiments, when Y is N, B is not heteroaryl. In some embodiments, when Y is N, B is cycloalkyl or heterocyclyl. In some embodiments, when Y is N, B is cycloalkyl. In some embodiments, when Y is N, B is heterocyclyl.

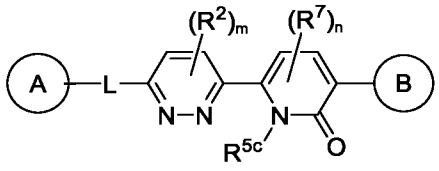
In some embodiments,  is selected from , , , , , , and , wherein each of R^{5a}, R^{5b}, R^{5c}, R^7 and n are as defined herein.

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In some embodiments,  is selected from  and , wherein each of R^7 and n are as defined herein.

In some embodiments,  is selected from , , and , wherein R^2 is as defined above. In some embodiments, R^2 is hydrogen.

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;

L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^3)-, -N(R^3)C(O)-, or -C(O)N(R^3)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4;

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, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^8; or

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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^8;

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

each R^3 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^4 is 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 $-C(O)OR^D$;

R^{5c} is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $C(O)R^D$;

each R^7 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, halo, oxo, cyano, $NR^BC(O)R^D$, $-C(O)NR^BR^C$, $-C(O)R^D$, or $-SR^E$, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more R^9; or

two R^7 groups, together with the atoms to which they are attached (e.g., X or Y), form a 4-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9;

R^8 and R^9 are each 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 of 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, $-OR^A$; 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^{10};

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;

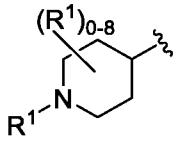
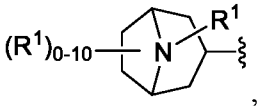
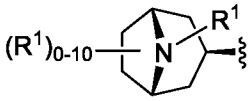
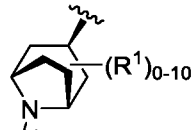
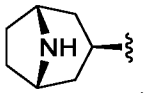
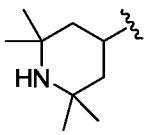
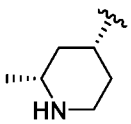
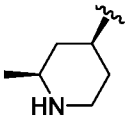
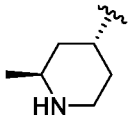
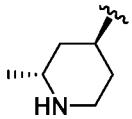
each R^{10} is independently C_1-C_6-alkyl or halo;

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 $-OR^A$;

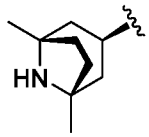
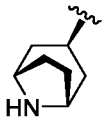
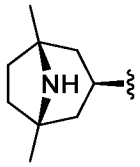
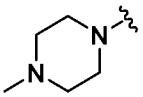
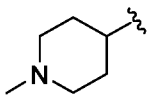
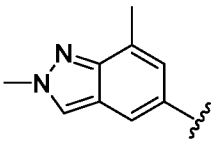
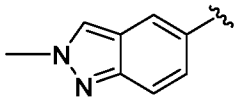
m is 0, 1, or 2

n is 0, 1, 2, 3, or 4; and

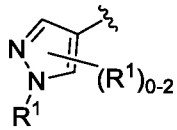
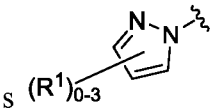
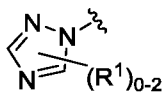
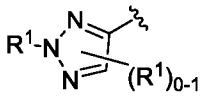
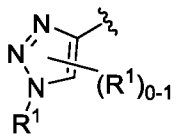
x is 0, 1, or 2.

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 azabicyclo[3.2.1]octanyl. In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. 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 . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is .

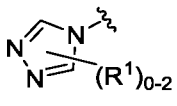
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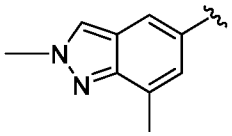
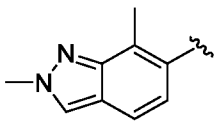
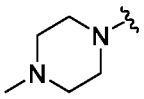
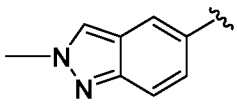
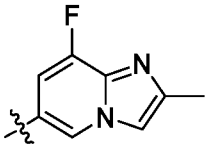
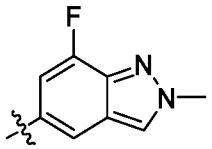
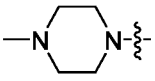
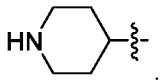
In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is .

In some embodiments, L is oxygen. In some embodiments, L is nitrogen that is optionally substituted with R^3. In some embodiments, L is nitrogen substituted with R^3. In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-.

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 monocyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each

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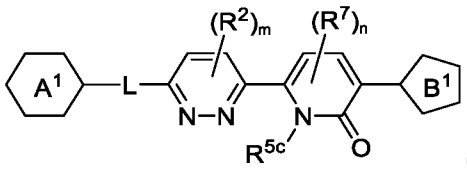
R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl.

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, R^1 is C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is methyl. In some embodiments, R^2 is hydrogen. In some embodiments, R^7 is hydrogen. In some embodiments, m and n are each 0. In some embodiments, R^{5c} is hydrogen.

In some embodiments, R^{5c} is hydrogen, C_1-C_6-alkyl. In some embodiments, R^{5c} is hydrogen. In some embodiments, R^{5c} is C_1-C_6-alkyl (e.g., CH_3).

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:

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A^1 is a 6-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

B^1 is a 5-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with R^1;

L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^3)-, -N(R^3)C(O)-, or -C(O)N(R^3)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4;

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, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^8; 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^8;

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

each R^3 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^4 is 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 $–C(O)OR^D$;

R^{5c} is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $C(O)R^D$;

each R^7 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, halo, oxo, cyano, $NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, or $–SR^E$, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more R^9; or

two R^7 groups, together with the atoms to which they are attached (e.g., X or Y), form a 4-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9;

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R^8 and R^9 are each 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 of 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, $-OR^A$; 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^{10};

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^{10} is independently C_1-C_6-alkyl or halo;

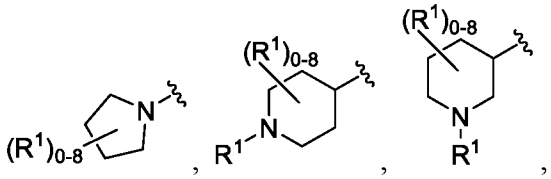
each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

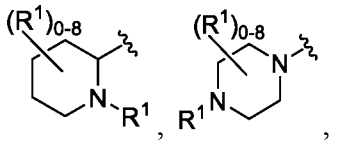
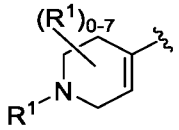
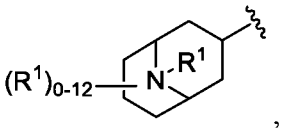
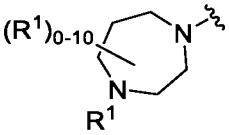
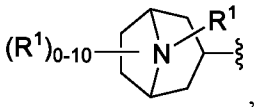
m is 0, 1, or 2

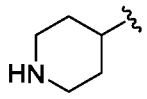
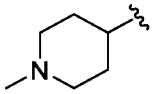
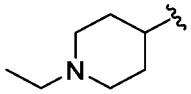
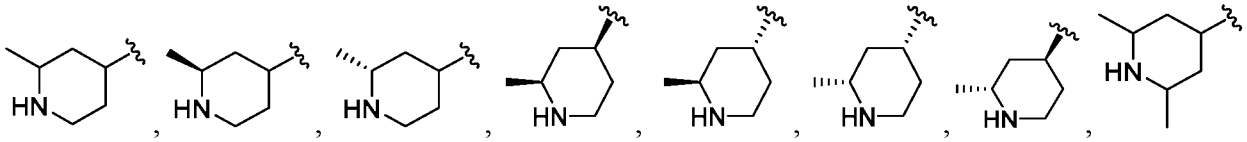
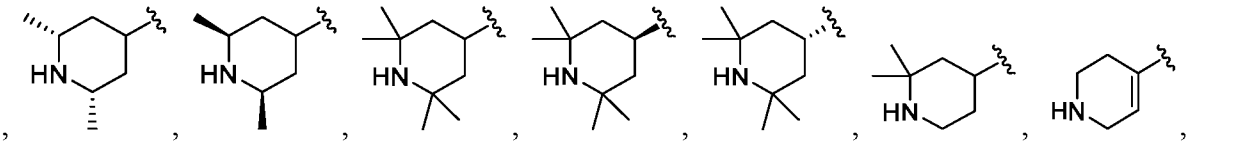
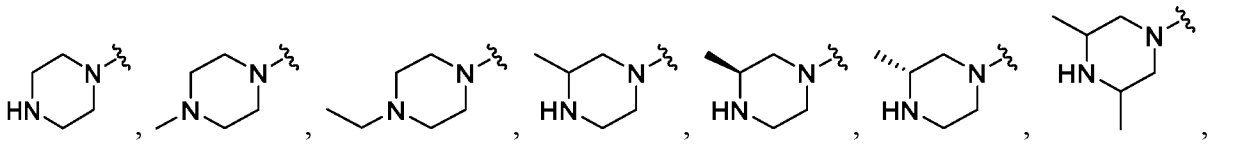
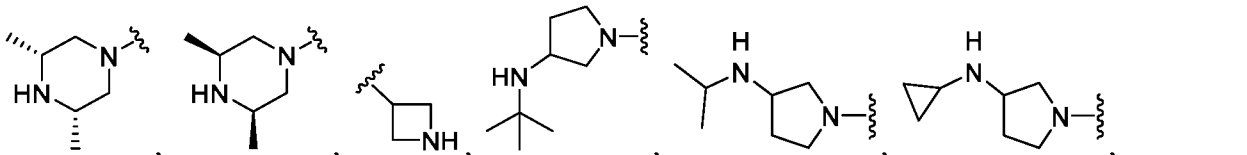
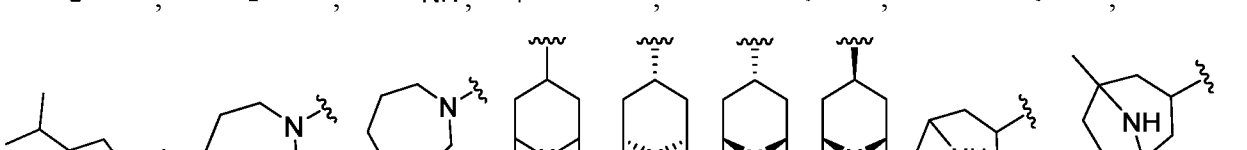
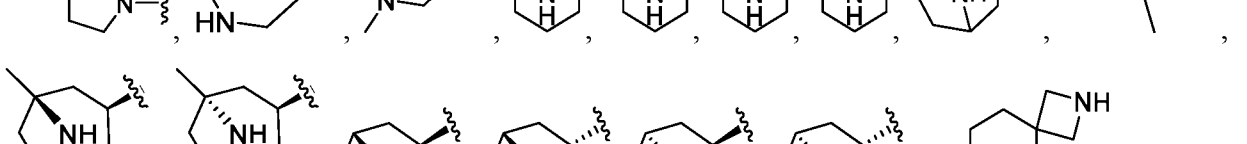
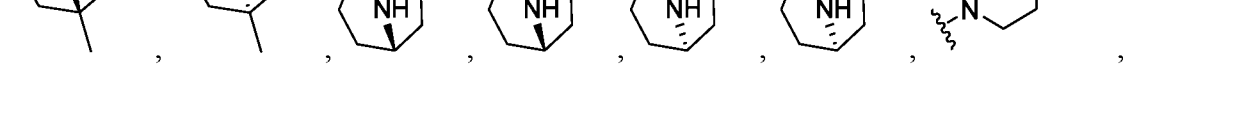
n is 0, 1, 2, 3, or 4; and

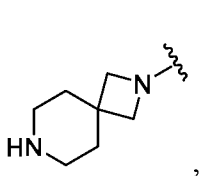
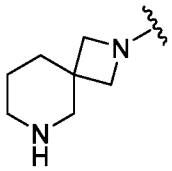
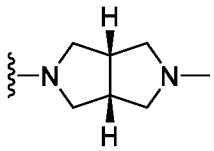
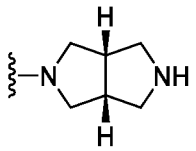
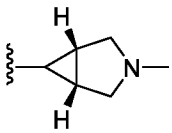
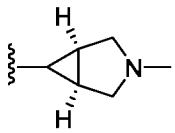
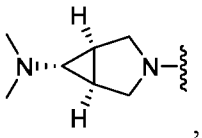
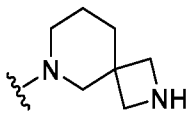
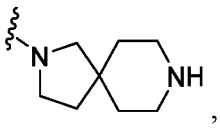
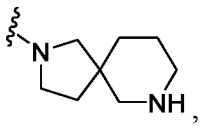
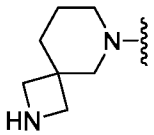
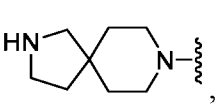
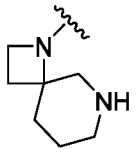
x is 0, 1, or 2.

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 azabicyclo[3.2.1]octanyl.

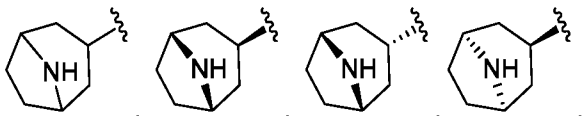
In some embodiments, A is selected from 

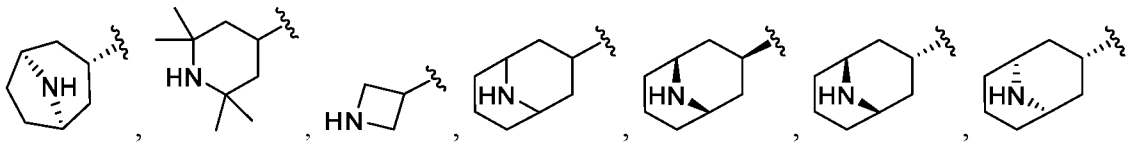

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, wherein R^1 is as defined herein.

In some embodiments, A is selected from 
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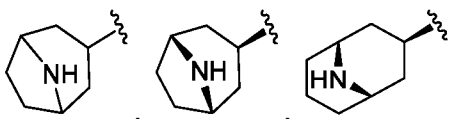














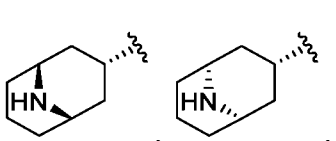
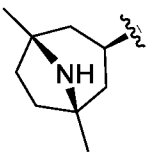
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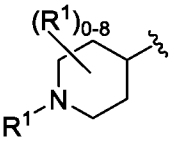
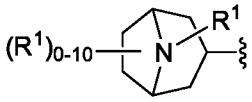
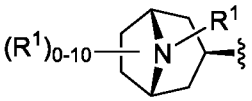
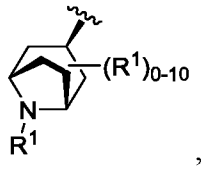
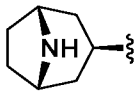
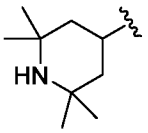
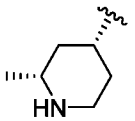
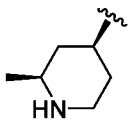
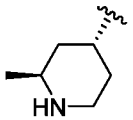
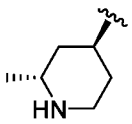
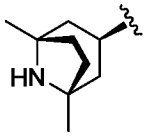
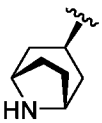
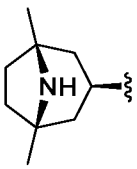
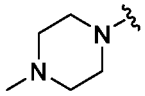
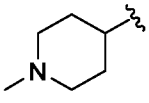
In some embodiments, A is selected from 



and .

In some embodiments, A is selected from 

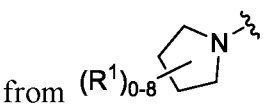
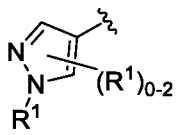
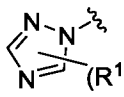
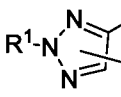
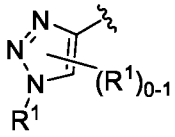
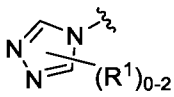
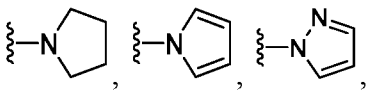
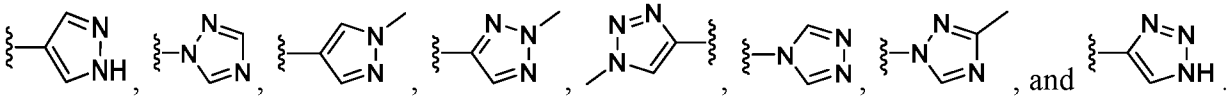
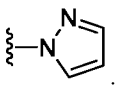
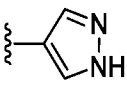
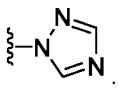
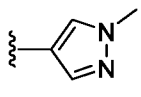
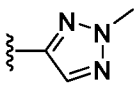
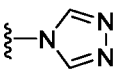
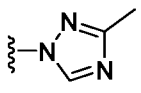
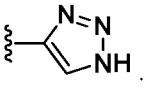

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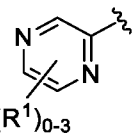
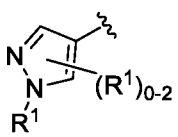
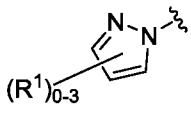
In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is . In some embodiments, A is . 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, L is absent. In some embodiments, L is oxygen. In some embodiments, L is nitrogen that is optionally substituted with R^3. In some embodiments, L is

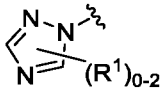
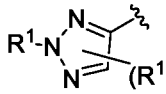
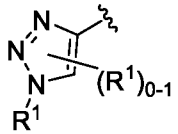
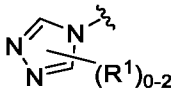
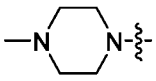
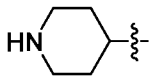
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nitrogen substituted with R^3. In some embodiments, R^3 is C_1-C_6 alkyl. In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-.

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 monocyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is selected from , , , , , , and , wherein R^1 is as defined herein. 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 .

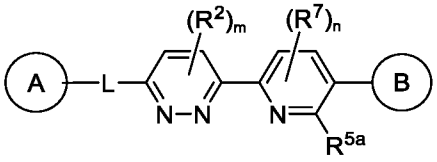
In some embodiments, B is . In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some

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embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is . In some embodiments, B is .

In some embodiments, R^1 is C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is methyl. In some embodiments, R^2 is hydrogen. In some embodiments, R^7 is hydrogen. In some embodiments, m and n are each 0. In some embodiments, R^{5c} is hydrogen.

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;

L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^3)-, -N(R^3)C(O)-, or -C(O)N(R^3)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4;

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, $-OR^A$, $-NR^BR^C$, –

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$NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^8; 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^8;

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

each R^3 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^4 is 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 $-C(O)OR^D$;

R^{5a} is 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, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

each R^7 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, halo, oxo, cyano, $NR^BC(O)R^D$, $-C(O)NR^BR^C$, $-C(O)R^D$, or $-SR^E$, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more R^9;

R^8 and R^9 are each 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 of 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, $-OR^A$; 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^{10};

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;

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R^F is hydrogen or C_1-C_6-alkyl;

each R^{10} is independently C_1-C_6-alkyl or halo;

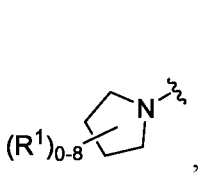
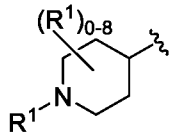
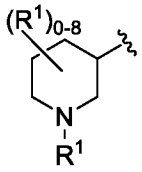
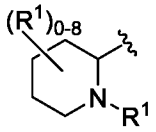
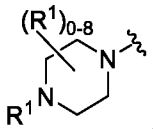
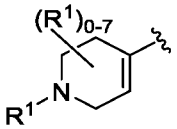
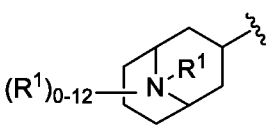
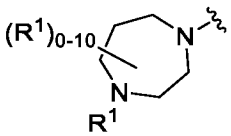
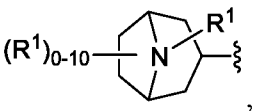
each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$;

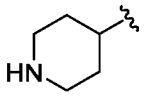
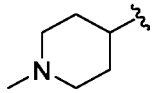
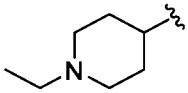
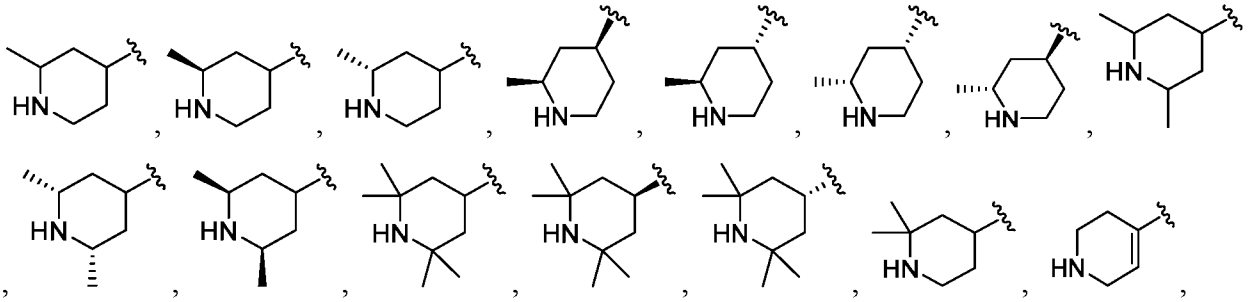
m is 0, 1, or 2

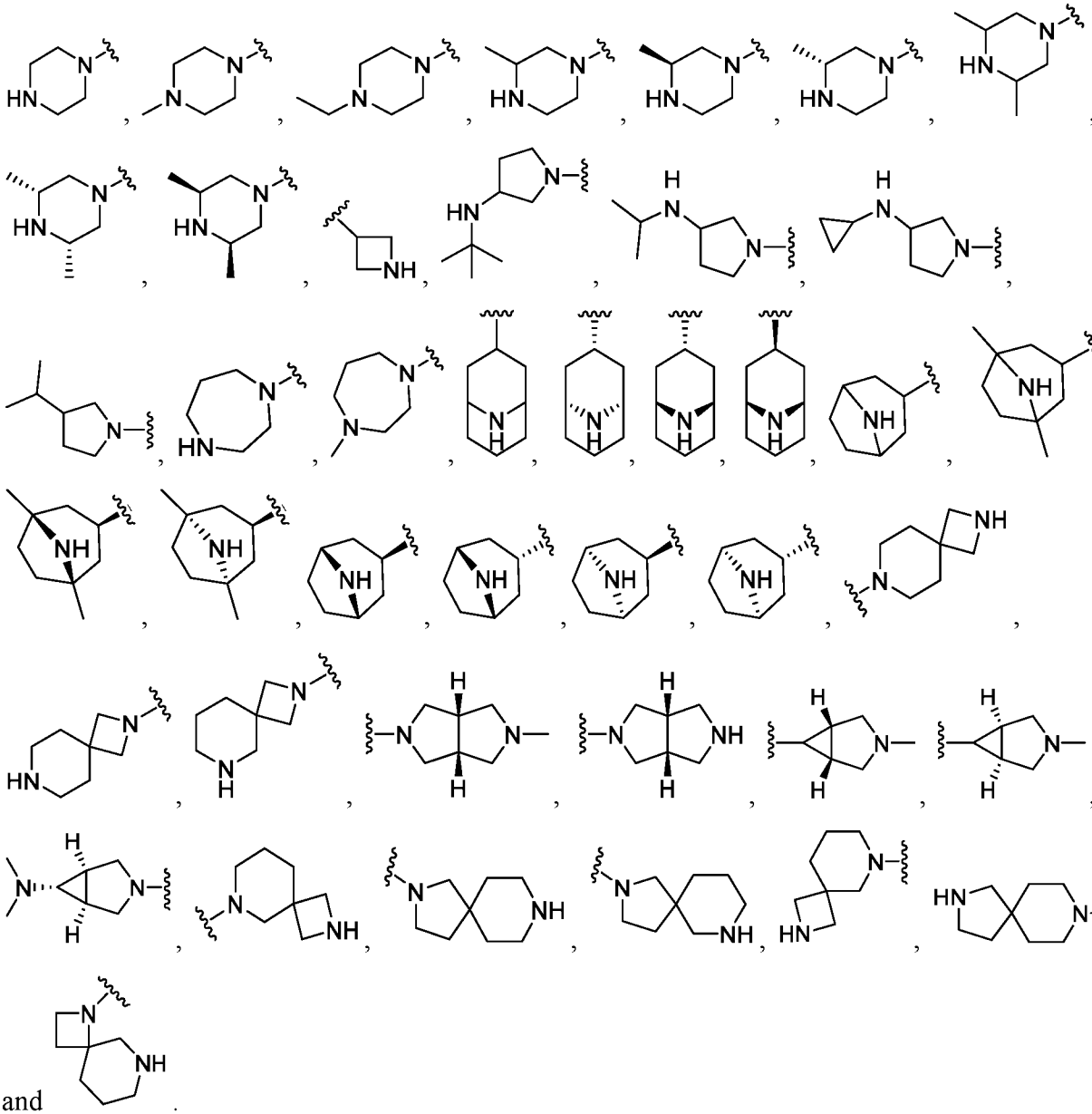
n is 0, 1, 2, 3, or 4; and

x is 0, 1, or 2.

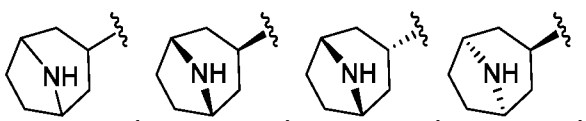
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl. In some embodiments, A is optionally substituted piperidinyl. In some embodiments, A is optionally substituted azabicyclo[3.2.1]octanyl.

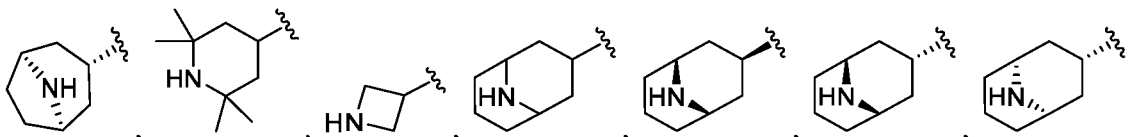
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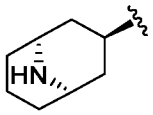
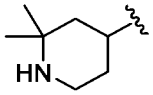
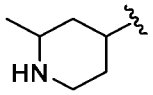
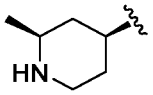
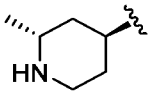
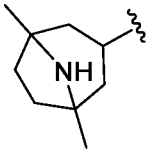
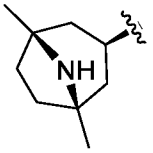
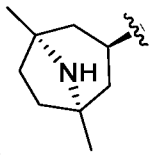
In some embodiments, A is selected from , , , .



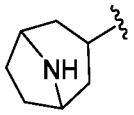
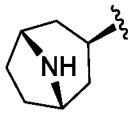
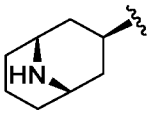
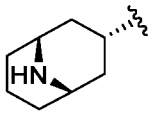
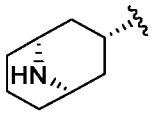
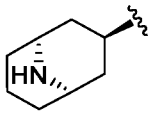
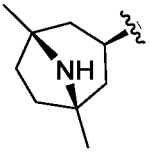
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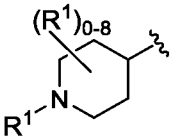
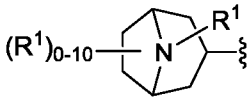
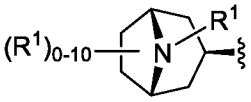
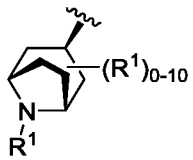
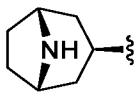
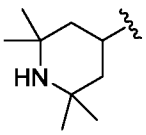
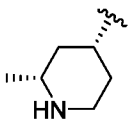
In some embodiments, A is selected from 

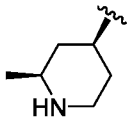
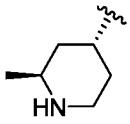
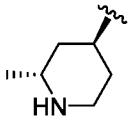
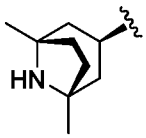
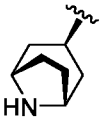
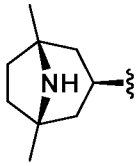
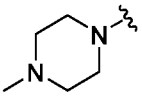
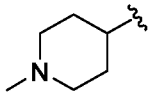


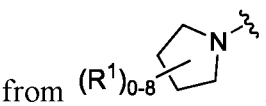
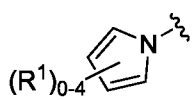
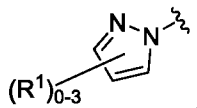
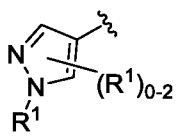
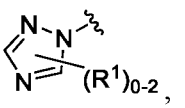
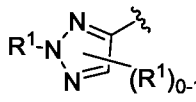
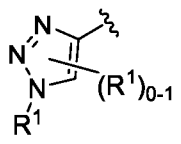
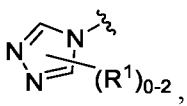
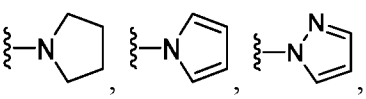
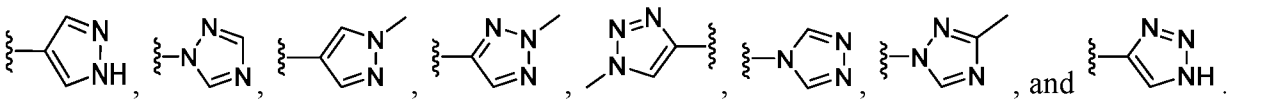
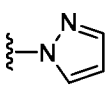
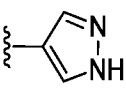
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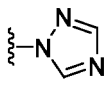
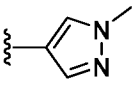
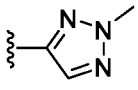
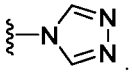
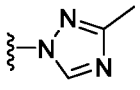
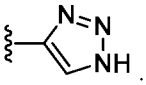
In some embodiments, A is selected from , , , , , , and .

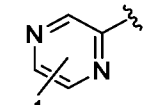
In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is , wherein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

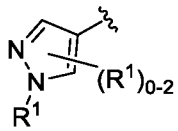
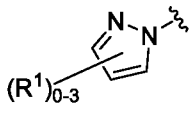
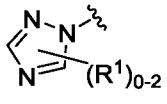
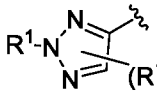
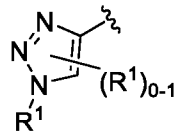
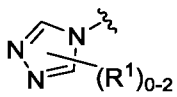
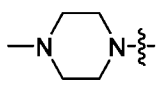
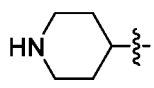
embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is .

In some embodiments, L is absent. In some embodiments, L is oxygen. In some embodiments, L is nitrogen that is optionally substituted with R^3. In some embodiments, L is nitrogen substituted with R^3. In some embodiments, R^3 is C_1-C_6 alkyl. In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-.

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 monocyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is selected from , , , , , , , and , wherein R^1 is as defined herein. 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 , wherein R^1 is as defined herein.

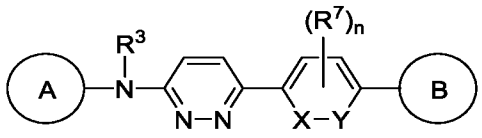
In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, B is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some In some embodiments, B is . In some embodiments, B is .

In some embodiments, R^1 is C_1-C_6 alkyl (e.g., methyl). In some embodiments, R^1 is methyl. In some embodiments, R^2 is hydrogen. In some embodiments, R^7 is hydrogen. In some embodiments, m and n are each 0. In some embodiments, R^{5c} is hydrogen.

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In some embodiments, R^{5a} is 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, halo, cyano, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$. In some embodiments, R^{5a} is hydrogen. In some embodiments, R^{5a} is C_1-C_6-alkyl. In some embodiments, R^{5a} is C_1-C_6-heteroalkyl. In some embodiments, R^{5a} is C_1-C_6-haloalkyl. In some embodiments, R^{5a} is cycloalkyl. In some embodiments, R^{5a} is halo. In some embodiments, R^{5a} is cyano. In some embodiments, R^{5a} is $-OR^A$.

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;

X and Y are each independently C, $C(R^{5a})$, $C(R^{5a})(R^{5b})$, N, or $N(R^{5c})$, wherein the bond between X and Y may be a single or double bond as valency permits, and wherein X and Y may not both be $C(R^{5a})(R^{5b})$;

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, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^8; 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^8;

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

each R^3 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^4 is 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 $-C(O)OR^D$;

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R^{5a} is hydrogen, C_1-C_6-alkyl, or $-OR^F$;

R^{5b} is hydrogen or C_1-C_6-alkyl; or

R^{5a} and R^{5b}, together with the carbon atom to which they are attached, form an oxo group;

each R^{5c} is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $C(O)R^D$;

each R^7 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, halo, oxo, cyano, $NR^BC(O)R^D$, $-C(O)NR^BR^C$, $-C(O)R^D$, or $-SR^E$, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more R^9; or

two R^7 groups, together with the atoms to which they are attached (e.g., X or Y), form a 4-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9;

R^8 and R^9 are each 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 of 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, $-OR^A$; 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^{10};

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;

R^F is hydrogen or C_1-C_6-alkyl;

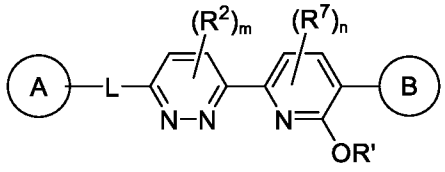
R^{10} is C_1-C_6-alkyl or halo;

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 $-OR^A$;

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n is 0, 1, 2, 3, or 4; and x is 0, 1, or 2.

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;

L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^3)-, -N(R^3)C(O)-, or -C(O)N(R^3)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4;

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, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^8; 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^8;

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

each R^3 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^4 is 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 $–C(O)OR^D$;

R' is 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, $–C(O)R^D$, or $–C(O)OR^D$;

each R^7 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, halo, oxo, cyano, $NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, or $–SR^E$, wherein

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alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more R^9;

R^8 and R^9 are each 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 of 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, $-OR^A$; 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^{10};

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^{10} is independently C_1-C_6-alkyl or halo;

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 $-OR^A$;

m is 0, 1, or 2;

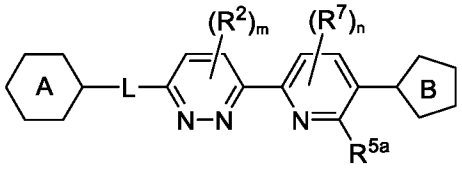
n is 0, 1, 2, 3, or 4; and

x is 0, 1, or 2.

In some embodiments, R' is 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. In some embodiments, R' is C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, or heterocyclyl. In some embodiments, R' is C_1-C_6-alkyl, C_1-C_6-haloalkyl, or cycloalkyl. In some embodiments, R' is C_1-C_6-alkyl. In some embodiments, R' is C_1-C_6-haloalkyl. In some embodiments, R' is cycloalkyl. In some embodiments, R' is hydrogen.

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

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(I-h)

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;

L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^3)-, -N(R^3)C(O)-, or -C(O)N(R^3)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4;

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, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^8; 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^8;

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

each R^3 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^4 is 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 $–C(O)OR^D$;

R^{5a} is 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, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

each R^7 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, halo, oxo, cyano, $NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, or $–SR^E$, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more R^9;

R^8 and R^9 are each independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-

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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 of 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, $-OR^A$; 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^{10};

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^{10} is independently C_1-C_6-alkyl or halo;

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 $-OR^A$;

m is 0, 1, or 2;

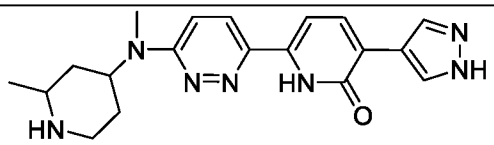
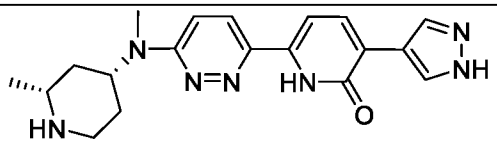
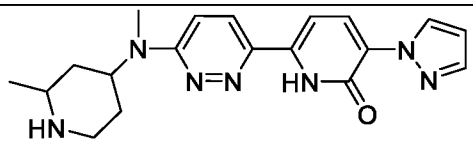
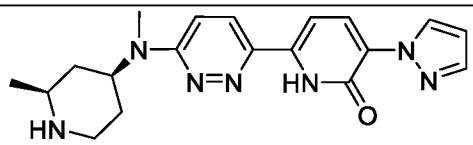
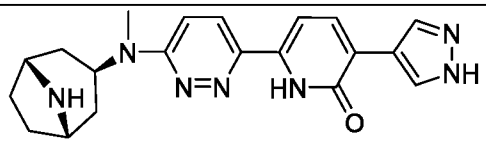
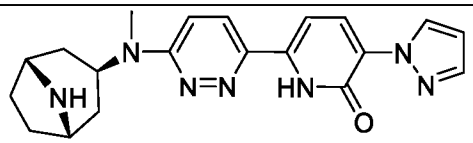
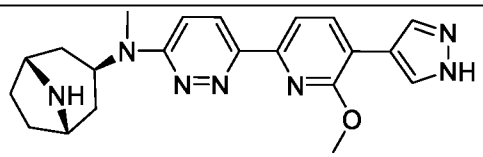
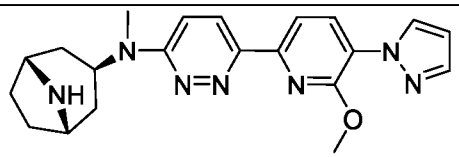
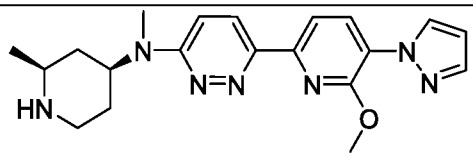
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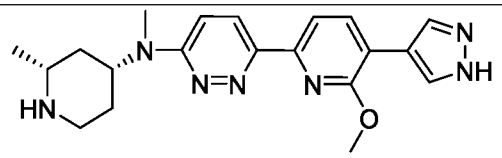
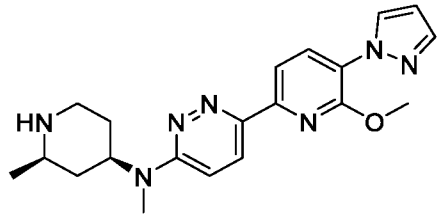
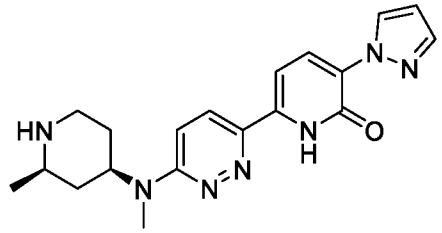
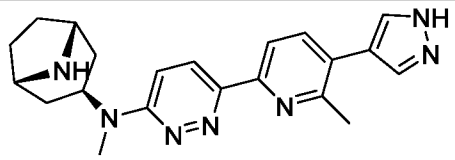
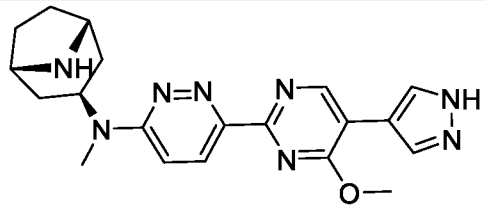
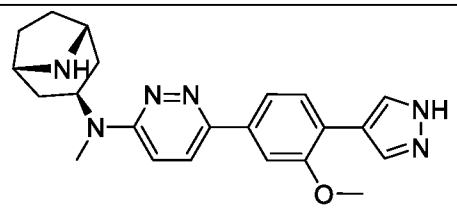
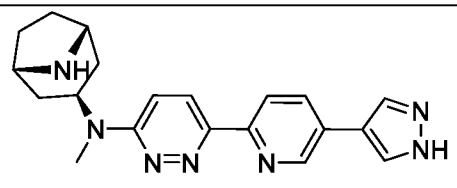
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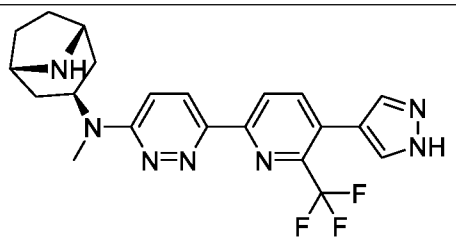
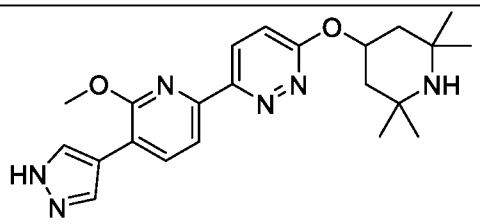
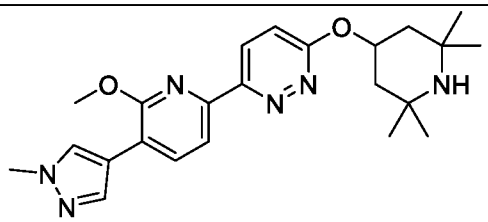
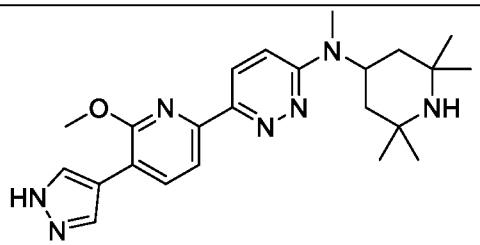
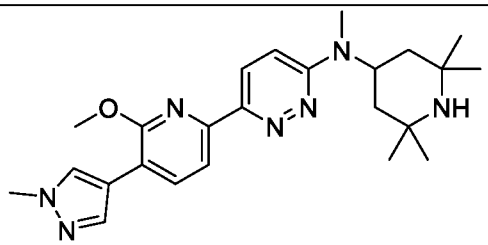
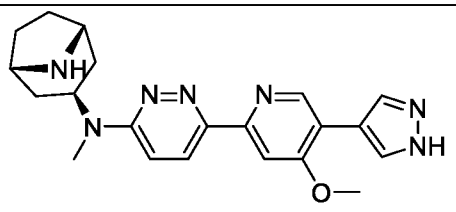
In some embodiments, R^{5a} is hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$. In some embodiments, R^{5a} is hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$. In some embodiments, R^{5a} is hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$. In some embodiments, R^{5a} is hydrogen. In some embodiments, R^{5a} is halo. In some embodiments, R^{5a} is C_1-C_6-haloalkyl. In some embodiments, R^{5a} is C_1-C_6-alkyl. In some embodiments, R^{5a} is $-OR^A$.

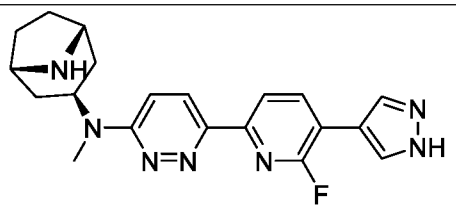
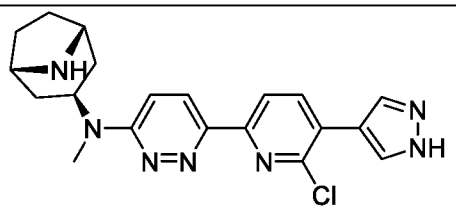
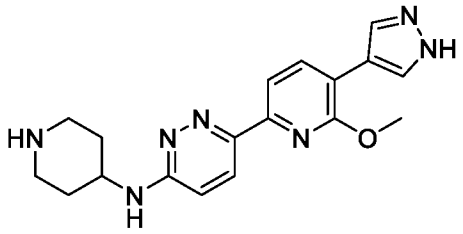
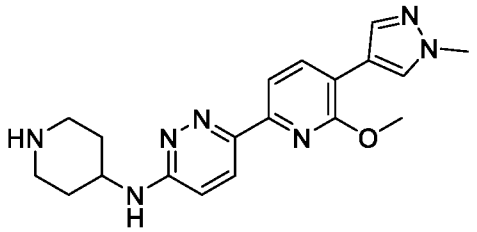
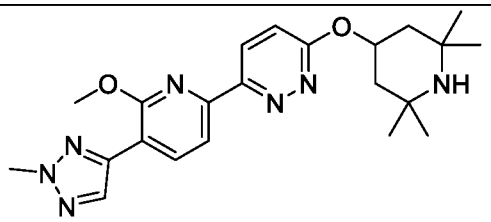
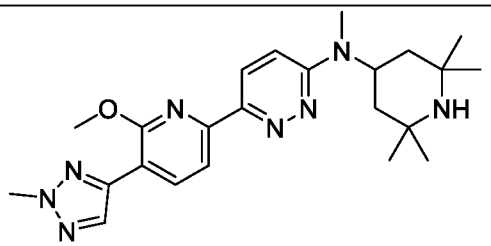
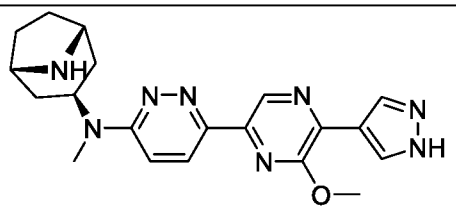
In some embodiments, the compound of Formula (I) is selected from a compound in Table 1, or a pharmaceutically acceptable salt thereof.

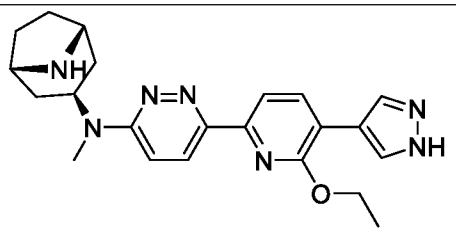
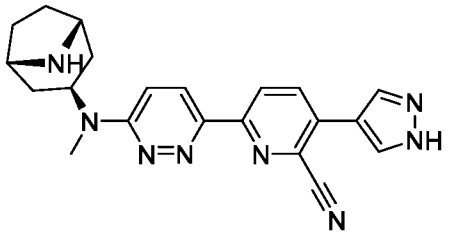
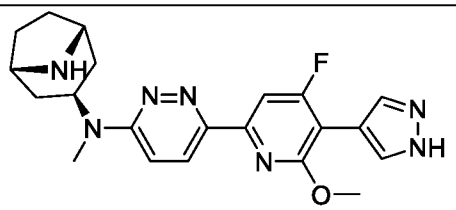
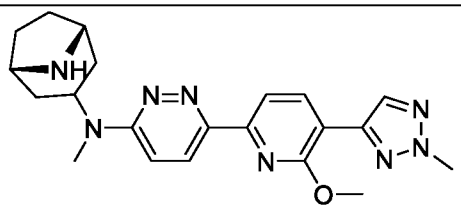
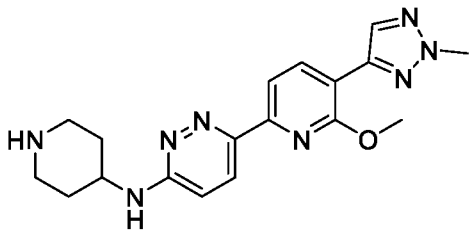
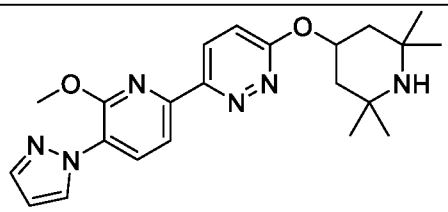
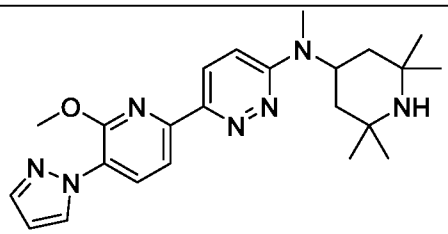
Table 1: Exemplary compounds

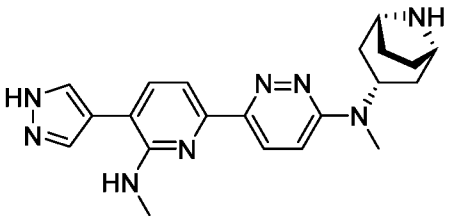
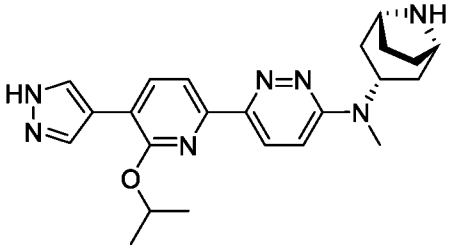
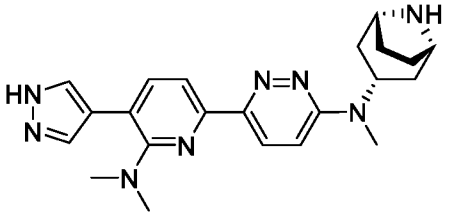
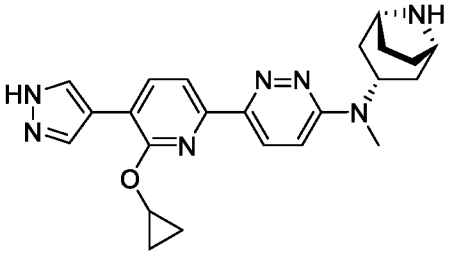
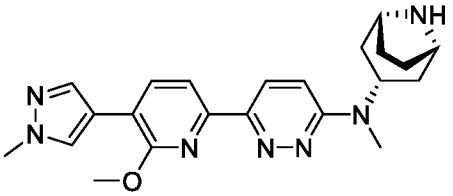
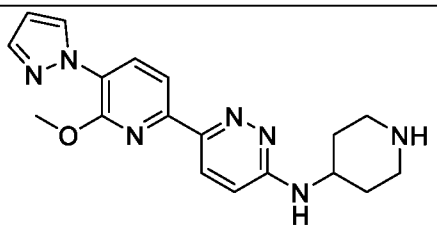
Compound No.	Structure
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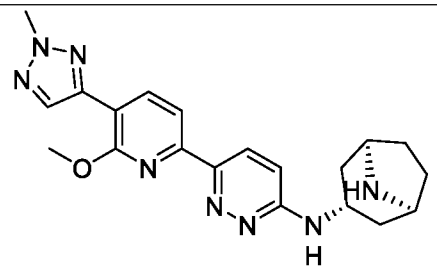
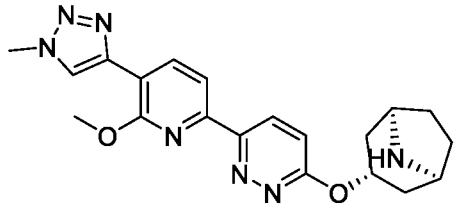
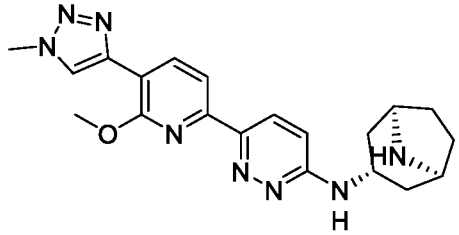
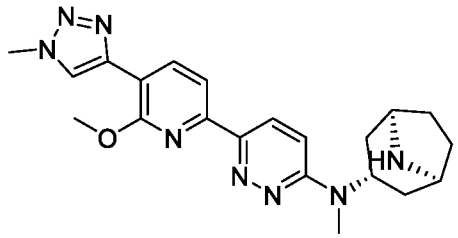
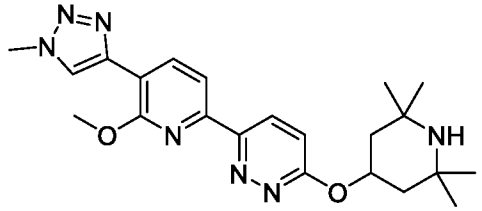
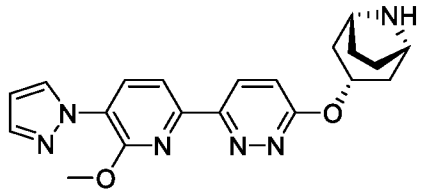
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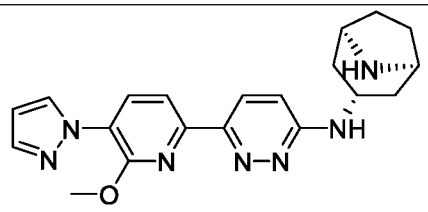
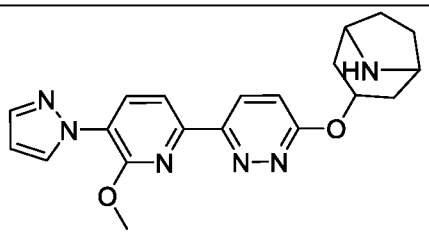
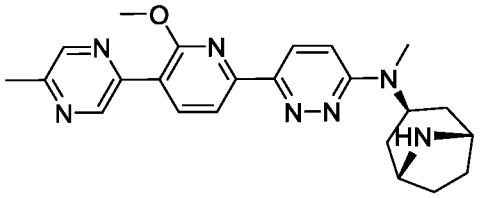
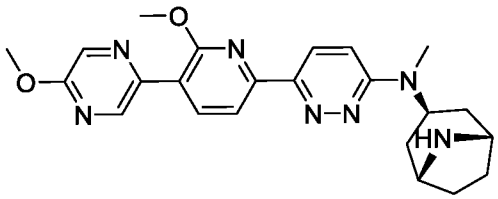
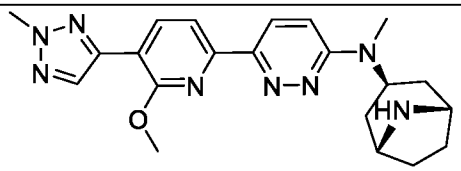
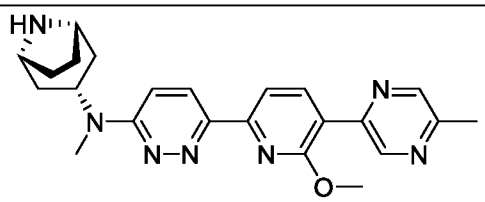
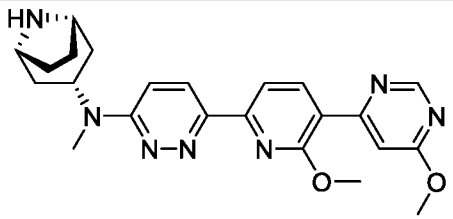
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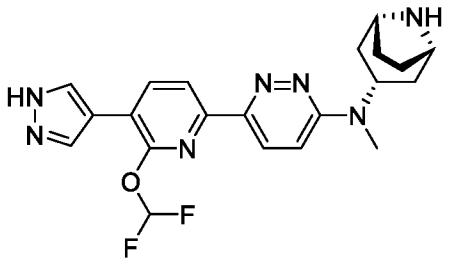
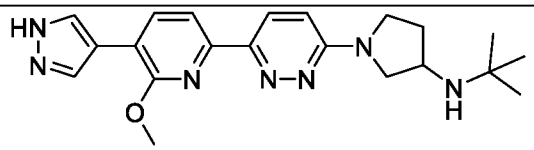
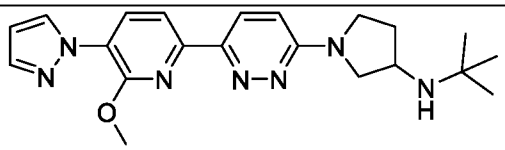
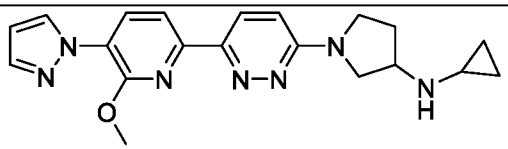
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In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., piperidinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH); X is N(R^{5c}) (e.g., NH); Y is C(R^{5a})(R^{5b}) (e.g., -C(O)-); and n is 0. In some embodiments, the compound of Formulas (I), (I-a), (I-b), (I-e), (I-f), and (I-h) is Compound 125, 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 is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH); X is N(R^{5c}) (e.g., NH); Y is C(R^{5a})(R^{5b}) (e.g., -C(O)-); and n is 0. In some embodiments, the compound of Formulas (I), (I-a), (I-d), (I-e), and (I-h) is Compound 126, 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 is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH); X is N(R^{5c}) (e.g., NH); Y is C(R^{5a})(R^{5b}) (e.g., -C(O)-); and n is

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0. In some embodiments, the compound of Formulas (I), (I-a), (I-b), (I-e), (I-f), and (I-h) is Compound 127, 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 is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH); X is N(R^{5c}) (e.g., NH); Y is C(R^{5a})(R^{5b}) (e.g., -C(O)-); and n is 0. In some embodiments, the compound of Formulas (I), (I-a), (I-b), (I-e), (I-f), and (I-h) is Compound 128, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heterocyclyl (e.g., azabicyclo[3.2.1]octanyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH); X is N(R^{5c}) (e.g., NH); Y is C(R^{5a})(R^{5b}) (e.g., -C(O)-); and n is 0. In some embodiments, the compound of Formulas (I), (I-a), (I-b), (I-e), and (I-h) is Compound 129, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heterocyclyl (e.g., azabicyclo[3.2.1]octanyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH); X is N(R^{5c}) (e.g., NH); Y is C(R^{5a})(R^{5b}) (e.g., -C(O)-); and n is 0. In some embodiments, the compound of Formulas (I), (I-a), (I-b), (I-e), and (I-h) is Compound 130, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heterocyclyl (e.g., azabicyclo[3.2.1]octanyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH); X is N; Y is C(R^{5a}) (e.g., -C(OMe)-); and n is 0. In some embodiments, the compound of Formulas (I), (I-g), and (I-h) is Compound 133, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heterocyclyl (e.g., azabicyclo[3.2.1]octanyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH); X is N; Y is C(R^{5a}) (e.g., -C(OMe)-); and n is

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0. In some embodiments, the compound of Formulas (I), (I-g), and (I-h) is Compound 134, 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 is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH); X is N; Y is C(R^{5a}) (e.g., -C(OMe)-); and n is 0. In some embodiments, the compound of Formulas (I), (I-g), and (I-h) is Compound 135, 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 is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH); X is N; Y is C(R^{5a}) (e.g., -C(OMe)-); and n is 0. In some embodiments, the compound of Formulas (I), (I-g), and (I-h) is Compound 136, 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 is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH); X is N or N(R^{5c}) (e.g., NH); Y is C(R^{5a}) (e.g., -C(OMe)-) or C(R^{5a})(R^{5b}) (e.g., -C(O)-); and n is 0. In some embodiments, the compound of Formulas (I), (I-f), and (I-g) is Compound 161, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-a), (I-e), (I-f), (I-g), (I-h) is Compound 162, 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 is -N(R^3)- (e.g., NMe); M and P are each independently C(R^2) (e.g., CH) or N; X is N or N(R^{5c}) (e.g., NH); Y is C(R^{5a}) (e.g., -C(CH_3), -C(OMe)-, C(CN), N(CH_3)$_2$, C(O-cycloalkyl)) or C(R^{5a})(R^{5b}) (e.g., -C(O)-); and n is 0. In some embodiments, the compound of Formulas (I), (I-f), and (I-g) is a compound selected from any one of Compounds 171, 217, 236, 244-305, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, the compound of Formula (I) is selected from any one of Compounds 133, 134, 245, 246, 247, 249, 250, 260, 261, 262, 268, 269, 272, 284, and 286. In some embodiments, the compound of Formula (I) is selected from any one of Compounds 249,

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250, 260, 261, 268, 269, 284, and 286. In some embodiments, the compound of Formula (I) is not Compound 207 or 208.

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.

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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

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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

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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

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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.

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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.

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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%,

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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,

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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, MTDH, MTERF3, MTF1, MTF2, MTIF2, MTHFR, MUC2, MUT, MVK, MYB, MYBL2, MYC, MYCBP2, MYH2, MYRF, MYT1, MY019, MY03A, MY09B, MYOM2, MYOM3, NAG, NARG1, NARG2, NCOA1, NDC80, NDFIP2, NEB, NEDD4, NEK1, NEK5, NEK11, NF1, NF2, NFATC2, NFE2L2, NFIA, NFIB, NFIX, NFKB1, NFKB2, NFKBIL2, NFRKB, NFYA, NFYB, NIPA2, NKAIN2, NKAP, NLRC3, NLRC5, NLRP3, NLRP7, NLRP8, NLRP13, NME1, NME1-NME2, NME2, NME7, NOL10, NOP561, NOS1, NOS2A, NOTCH1, NPAS4, NPM1, NR1D1, NR1H3, NR1H4, NR4A3, NR5A1, NRXN1, NSMAF, NSMCE2, NT5C, NT5C2, NT5C3, NUBP1, NUBPL, NUDT5, NUMA1, NUP88, NUP98, NUP160, NUPL1, OAT, OAZ1, OBFC2A, OBFC2B, OLIG2, OMA1, OPA1, OPN4, OPTN, OSBPL11, OSBPL8, OSGEPL1, OTC, OTX2, OVOL2, OXT, PA2G4, PADI4, PAH, PAN2, PAOX, PAPOLG, PARD3, PARP1, PARVB, PAWR, PAX3, PAX8, PBGD, PBRM1, PBX2, PCBP4, PCCA, PCGF2, PCNX, PCOTH, PDCD4, PDE4D, PDE8B, PDE10A, PD1A3, PDH1, PDLIM5, PDXK, PDZRN3, PELI2, PDK4, PDS5A, PDS5B, PGK1, PGM2, PHACTR4, PHEX, PHKB, PHLDB2, PHOX2B, PHTF1, PIAS1, PIEZO1, PIGF, PIGN, PIGT, PIK3C2G, PIK3CA, PIK3CD, PIK3CG, PIK3RI, PIP5K1A, PITRM1, PIWIL3, PKD1,

PKHD1L1, PKD2, PKIB, PKLR, PKM1, PKM2, PLAGL2, PLCB1, PLCB4, PLCG1, PLD1, PLEKHA5, PLEKHA7, PLEKHM1, PLKR, PLXNC1, PMFBP1, POLN, POLR3D, POMT2, POSTN, POU2AF1, POU2F2, POU2F3, PPARA, PPFIA2, PPP1R12A, PPP3CB, PPP4C, PPP4R1L, PPP4R2, PRAME, PRC1, PRDM1, PREX1, PREX2, PRIM1, PRIM2, PRKAR1A, PRKCA, PRKG1, PRMT7, PROC, PROCR, PROSC, PRODH, PROX1, PRPF40B, PRPF4B, PRRG2, PRUNE2, PSD3, PSEN1, PSMAL, PTCH1, PTEN, PTK2, PTK2B, PTPN2, PTPN3, PTPN4, PTPN11, PTPN22, PTPRD, PTPRK, PTPRM, PTPRN2, PTPRT, PUS10, PVRL2, PYGM, QRSL1, RAB11FIP2, RAB23, RAF1, RALBP1, RALGDS, RB1CC1, RBL2, RBM39, RBM45, RBPJ, RBSN, REC8, RELB, RFC4, RFT1, RFTN1, RHOA, RHPN2, RIF1, RIT1, RLN3, RMND5B, RNF11, RNF32, RNFT1, RNGTT, ROCK1, ROCK2, RORA, RP1, RP6KA3, RP11-265F1, RP13-36C9, RPAP3, RPN1, RPGR, RPL22, RPL22L1, RPS6KA6, RREB1, RRM1, RRP1B, RSK2, RTEL1, RTF1, RUFY1, RUNX1, RUNX2, RXRA, RYR3, SAAL1, SAE1, SALL4, SAT1, SATB2, SBCAD, SCN1A, SCN2A, SCN3A, SCN4A, SCN5A, SCN8A, SCNA, SCN11A, SCO1, SCYL3, SDC1, SDK1, SDK2, SEC24A, SEC24D, SEC31A, SEL1L, SENP3, SENP6, SENP7, SERPINA1, SETD3, SETD4, SETDB1, SEZ6, SFRS12, SGCE, SGOL2, SGPL1, SH2D1A, SH3BGRL2, SH3PXD2A, SH3PXD2B, SH3RF2, SH3TC2, SHOC2, SIPA1L2, SIPA1L3, SIVA1, SKAP1, SKIV2L2, SLC6A11, SLC6A13, SLC6A6, SLC7A2, SLC12A3, SLC13A1, SLC22A17, SLC25A14, SLC28A3, SLC33A1, SLC35F6, SLC38A1, SLC38A4, SLC39A10, SLC4A2, SLC6A8, SMARCA1, SMARCA2, SMARCA5, SMARCC2, SMC5, SMN2, SMOX, SMS, SMTN, SNCAIP, SNORD86, SNRK, SNRP70, SNX5, SNX6, SOD1, SOD10, SOS, SOS2, SOX5, SOX6, SOX8, SP1, SP2, SP3, SP110, SPAG9, SPATA13, SPATA4, SPATS1, SPECC1L, SPDEF, SPI1, SPINK5, SPP2, SPTA1, SRF, SRM, SRP72, SSX3, SSX5, SSX9, STAG1, STAG2, STAMBPLI, STARD6, STAT1, STAT3, STAT5A, STAT5B, STAT6, STK17B, STX3, STXBP1, SUCLG2, SULF2, SUPT6H, SUPT16H, SV2C, SYCP2, SYT6, SYCPI, SYTL3, SYTL5, TAF2, TARDBP, TBC1D3G, TBC1D8B, TBC1D26, TBC1D29, TBCEL, TBK1, TBP, TBPL1, TBR1, TBX, TCEB3, TCF3, TCF4, TCF7L2, TCFL5, TCF12, TCP11L2, TDRD3, TEAD1, TEAD3, TEAD4, TECTB, TEK, TERF1, TERF2, TET2, TFAP2A, TFAP2B, TFAP2C, TFAP4, TFDP1, TFRC, TG, TGM7, TGS1, THAP7, THAP12, THOC2, TIAL1, TIAM2, TIMM50, TLK2, TM4SF20, TM6SF1, TMEM27, TMEM77, TMEM156, TMEM194A, TMF1, TMPRSS6, TNFRSF10A, TNFRSF10B, TNFRSF8, TNK2, TNKS, TNKS2, TOM1L1, TOM1L2, TOP2B,

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TP53, TP53INP1, TP53BP2, TP53I3, TP63, TRAF3IP3, TRAPPC2, TRIM44, TRIM65, TRIML1, TRIML2, TRPM3, TRPM5, TRPM7, TRPS1, TSC1, TSC2, TSHB, TSPAN7, TTC17, TTF1, TTLL5, TTLL9, TTN, TTPAL, TTR, TUSC3, TXNDC10, UBE3A, UCK1, UGT1A1, UHRF1BP1, UNC45B, UNC5C, USH2A, USF2, USP1, USP6, USP18, USP38, USP39, UTP20, UTP15, UTP18, UTRN, UTX, UTY, UVRAG, UXT, VAPA, VEGFA, VPS29, VPS35, VPS39, VT11A, VT11B, VWA3B, WDFY2, WDR16, WDR17, WDR26, WDR44, WDR67, WDTC1, WRN, WRNIP1, WT1, WWC3, XBP1, XRN1, XRN2, XX-FW88277, YAP1, YARS, YBX1, YGM, YY1, ZBTB18, ZBTB20, ZC3HAV1, ZC3HC1, ZC3H7A, ZDHHC19, ZEB1, ZEB2, ZFPM1, ZFYVE1, ZFX, ZIC2, ZNF37A, ZNF91, ZNF114, ZNF155, ZNF169, ZNF205, ZNF236, ZNF317, ZNF320, ZNF326, ZNF335, ZNF365, ZNF367, ZNF407, ZNF468, ZNF506, ZNF511, ZNF511-PRAP1, ZNF519, ZNF521, ZNF592, ZNF618, ZNF763, and *ZWINT.*

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, AC012651.1, CAPN3, AC013489.1, DET1, AC016747.4, C2orf74, AC020907.6, FXYD3, AC021087.5, PDCD6, AHRR, AC022137.3, ZNF761, AC025283.3, NAA60, AC027644.4, RABGEF1, AC055811.2, FLCN, AC069368.3, ANKDD1A, AC073610.3, ARF3, AC074091.1,GPN1, AC079447.1, LIPT1, AC092587.1, AC079594.2, TRIM59, AC091060.1,C18orf21, AC092143.3, MC1R, AC093227.2, ZNF607, AC093512.2, ALDOA, AC098588.1, ANAPC10, AC107871.1, CALML4, AC114490.2, ZMYM6, AC138649.1, NIPA1, AC138894.1, CLN3, AC139768.1, AC242426.2, CHD1L, ACADM, ACAP3, ACKR2,RP11-141M3.5, KRBOX1, ACMSD, ACOT9, ACP5, ACPL2, ACSBG1, ACSF2, ACSF3, ACSL1, ACSL3, ACVR1, ADAL, ADAM29, ADAMTS10, ADAMTSL5, ADARB1, ADAT2, ADCK3, ADD3, ADGRG1, ADGRG2, ADH1B, ADIPOR1, ADNP, ADPRH, AGBL5, AGPAT1, AGPAT3, AGR2, AGTR1, AHDC1, AHI1, AHNAK, AIFM1, AIFM3, AIMP2, AK4, AKAP1, AKNAD1, CLCC1, AKR1A1, AKT1, AKT1S1, AKT2, AL139011.2, PEX19, AL157935.2, ST6GALNAC6,*

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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, AAGgcaggau, AAGgcaggca, AAGgcaggga, AAGgcagggg, AAGgcaggua, AAGgcaggug, AAGgcaucuc, AAGgcaugcu, AAGgcaugga, AAGgcauguu, AAGgcauuau, AAGgcgagcu,

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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, AUGguagguu, GAGgucuguc, CAGguaugug, CAAguacugc, CACgugcgua, CCGgugagcu, CAGguacuuc, CAGgcgagag, GAAgcaagua, AGGgugagca, CAGgcaaguc, AAGgugaggc, CAGguaagua, CCAguugggu, AAGgugugggg, CAGguuggag, CCGguaugaa, UGGguaaugu, CAGgugaggu, AGAguaauag, CAGguaugag, AUGguaaguu, UUGgugggguc, UUUguaagca, CUCguaugcc, UAGguaagag, UAGgcaaguu, GGAguuaagu, GAGguaugcc, AAGguguggu, CAGgugggug, UUAguaagua, AAGguuggcu, UGAguaugug, CCAgccuucc, CCUguacgug, CCUguaggua, CAGguacgcu, GAGguucuuc, AAGguugccu, CGUguucacu, CGGgugggga, UAGgugggau, CGGguaagga, AAGguacuau, GGGguaagcu, ACGguagagc, CAGgugaaga, GCGguaagag, CAGguguugu, GAAguuugug, AUGgugagca, CGGguucgug, AUUguccggc, GAUgugugug, AUGgucuguu, AAGguaggau, CCGguaagau, AAGguaaaga, GGGgugaguu, AGGguuggug, GGAgugagug, AGUguaagga, UAGguaacug, AAGgugaaga, UGGguaagug, CAGguaagag, UAGgugagcg, GAGguaaaaa, GCCguaaguu, AAGguuuugu, CAGgugagga, ACAgcccaug, GCGgugagcc, CAGguaugca, AUGguaccua, CAAguaugua, AUGguggugc, UAAguggcag, UAGguauagu, CUGguauuua, AGGguaaacg, AUAguaagug, UUGguacuga, GGUguaagcc, GAGguggaua, GAUguaagaa, ACGgucaguu, UAAguaaaca, AAGguaucug, AGGguauuug, AAGgugaaug, CUGgugaauu, CAGguuuuuu, CAUguaugug, UUGguagagg,

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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, AAGguguggc, AGAgugaucu, AAGguaucca, UUCguaagua, UAAgugggug, GCCgugaacg, GAGguugugg,

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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

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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

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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

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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

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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

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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

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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);

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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

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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

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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,

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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

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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

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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.

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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,

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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

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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

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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

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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

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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: Waters-2545, Column: X-Select CSH (C18 OBD 130Å, 5 μm, 30 mm X 150 mm). Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: acetonitrile, Gradient:5% B to 50% B in 8 min.

Condition 2: Shimadzu, Column: XBridge Prep C18 OBD Column, 5um,19 mm X 150 mm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: methanol, Gradient: 30% B up to 50% in 10 min.

Condition 3: Shimadzu, Column: Xselect CSH OBD Column, 30 mm X 150 mm, 5um, Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: acetonitrile, Gradient 1: 10% Phase B up to 60% in 8 min; Gradient 2: 5% Phase B up to 40% in 8 min

Condition 4: Shimadzu, Column: XBridge Prep OBD C18 Column, 30 X 150mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: acetonitrile; Gradient 1: 10 B to 44 B in 8 min; Gradient 2: 3 B to 33 B in 6 min; Gradient 3: 5 B to 35 B in 8 min; Gradient 4: 5 B to 24 B in 8 min; Gradient 5: 5 B to 43 B in 6 min; Gradient 6: hold 5 B in 2 min, up to 55 B in 6 min; Gradient 7: 5% B to 40% B in 8 min; Gradient 8: 35% B to 75% B in 8 min; Gradient 9: 10% B to 40% B in 8 min; Gradient 10: 40% B to 85% B in 10 min.

Condition 5: Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: water (10 mmol/L NH_4HCO_3); Mobile Phase B: acetonitrile; Flow rate: 60 mL/min; Gradient: 10 B to 35 B in 10 min.

Condition 6: Column, Xselect CSH OBD Column 30 x 150 mm 5 um; Mobile Phase A: water (0.1% HCl); Mobile Phase B: acetonitrile; Gradient 1: Hold 3% phase B for 2 min, then ramp up to 23% over 6 min.

Condition 7: Column, XBridge Shield RP18 OBD Column 19 x 150 mm, 5μm; Mobile Phase A: water (0.05% $NH_3.H_2O$), Mobile Phase B: acetonitrile; Flow rate: 20 mL/min; Gradient

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1: 41% B to 63% B in 8 min; Gradient 2: 16% B to 40% B in 7 min; Gradient 3: 20% B to 50% B in 7 min.; Gradient 4: 25% B to 55% B in 7 min; Gradient 5: 28% to 58% gradient in 7.2 min.

Condition 8: Column, XBridge Shield RP18 OBD Column 19 x 150 mm, 5μm; Mobile Phase A: water (0.05% NH_3 in water and 10 mmol NH_4HCO_3), Mobile Phase B: acetonitrile; Flow rate: 20 mL/min; Gradient 1: 25% B to 56% B in 7 min; Gradient 2: 22% B to 55% B in 7 min; Gradient 3: 35% B to 72% B in 8 min; Gradient 4: 25% B to 48% B in 7 min.

Condition 9: Column, SunFire Prep C18 OBD Column, 19 x 150 mm, 5μm 10nm; Mobile Phase A: water (0.05%HCl), Mobile Phase B: acetonitrile; Flow rate: 20 mL/min; Gradient 1: 15% B to 42% B in 7 min; Gradient 2: 12% B to 22% B in 7.2 min.

Condition 10: Column, Xselect CSH OBD Column 30 x 150mm 5um; Mobile Phase A, water (0.05% HCl), Mobile Phase B: acetonitrile; Flow rate: 60 mL/min; Gradient 1: 3% B to 35% B in 8 min; Gradient 2: 3% B to 3% B in 2 min; Gradient 3: 3% B to 43% B in 8 min.

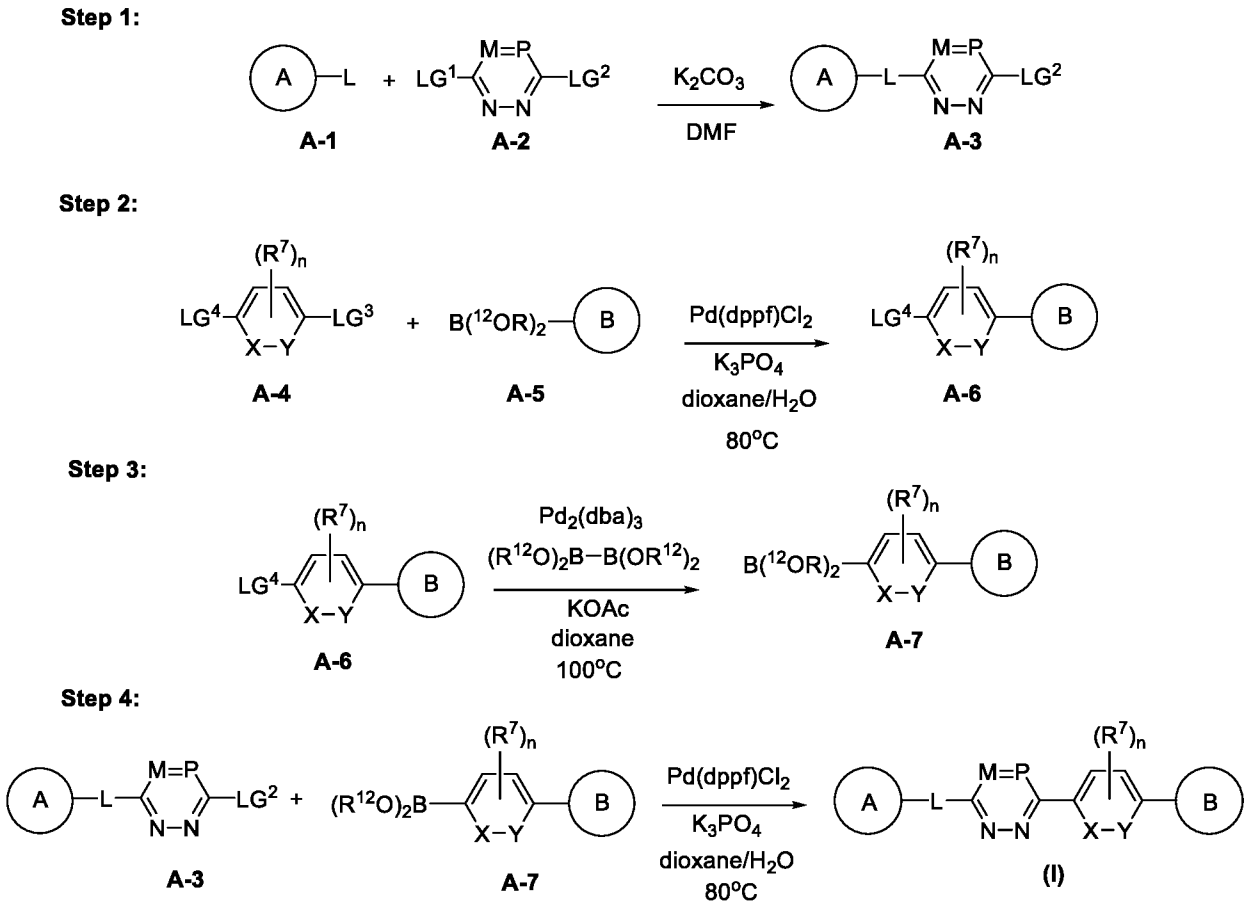
Condition 11: Column: YMC-Actus Triart C18, 30x150 mm, 5um; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: acetonitrile; Flow rate: 60 mL/min; Gradient 1: 5% B to 55% B in 8 min; Gradient 2: 5% B to 40% B in 8 min; Gradient 3: 15% B to 50% B in 8 min; Gradient 4: 5% B to 45% B in 8 min; Gradient 5: 5% B to 50% B in 8 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.

General Synthetic Scheme

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

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Scheme A. An exemplary method of preparing a compound of Formula (I); wherein A, B, L, M, P, X, Y, R^7, and n are as defined herein; LG^1, LG^2, LG^3, and LG^4 are each independently a leaving group (e.g., halo); and $–B(OR^{12})_2$ is a boronic ester (e.g., Bpin), wherein each R^{12} may be 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 of Formula (I) is provided in Scheme A. In this scheme, A-3 is prepared in Step 1 by incubating A-1 with A-2 in the presence of a base, for example, potassium carbonate (K_2CO_3) or sodium hydride (NaH) in *N*,*N*-dimethylformamide (DMF) or another suitable reagent. In some instances, A-3 is prepared by heating the reaction mixture to a suitable temperature, for example, 100 °C. In Step 2, A-6 is prepared by incubating A-4 with A-5. Step 2 may be carried out in the presence of 1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride ($Pd(dppf)Cl_2$), and tripotassium phosphate (K_3PO_4) or a similar reagent, for example, potassium carbonate (K_2CO_3). Alternative catalysts to $Pd(dppf)Cl_2$ may also be used, such as a suitable palladium catalyst (e.g., a catalyst

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suitable for a Suzuki reaction), for example, tetrakis(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$). The coupling of A-4 and A-5 may be carried out in a mixture of dioxane and water, or a similar solvent or mixture, and heated to 80 °C or temperature sufficient to provide A-6, for example, 100°C.

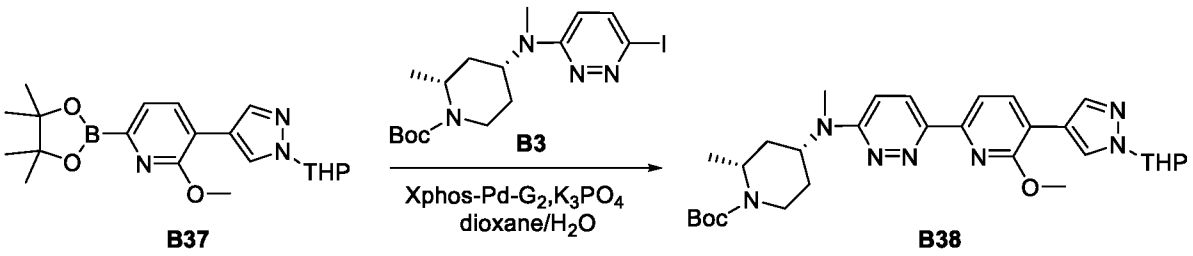
In Step 3, A-7 is prepared by incubating A-6 with a reagent suitable to displace LG^4 with a boronic ester group, such as $(R^{12}O)_2B–B(OR^{12})_2$ (e.g., bis(pinacolato)diboron (B_2pin_2)). Other common reagents for installing boronic ester groups (e.g., pinacol borane) can also be used. This reaction may involve the use of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), and potassium acetate (KOAc) or a suitable alternative, for example, tripotassium phosphate (K_3PO_4). Step 3 may also be carried out using an alternative catalyst to $Pd_2(dba)_3$, such as another palladium catalyst, for example, [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) ($Pd(dtbpf)Cl_2$) or chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (XPhos-Pd-G2). The reaction may be conducted in dioxane or a similar solvent, at 100 °C or a temperature sufficient to provide Fragment A-7, for example, 80 °C, 90 °C, 110 °C, or 120°C. The reaction may be conducted in a microwave reactor.

A-3 and A-7 are coupled to provide a compound of Formula (I) in Step 4. This coupling reaction may be conducted in the presence of $Pd(dppf)Cl_2$, and K_3PO_4 or a similar reagent, for example tripotassium carbonate (K_3PO_4). As in Step 2, alternative catalysts to $Pd(dppf)Cl_2$ may be used, such as any suitable palladium catalyst, for example, tetrakis(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$) or chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (XPhos-Pd-G2). The reaction of Step 4 is conducted in dioxane or a mixture of dioxane and water, or other suitable solvents, and the mixture is heated to 80 °C or a temperature sufficient to provide the compound of Formula (I) or a precursor to the compound of Formula (I) with one or more protecting group(s), for example, 100 °C. Compounds of Formula (I) may be purified using standard techniques and characterized using any method known in the art, such as nuclear magnetic resonance spectroscopy (NMR) or mass spectrometry (MS).

Example 1: Synthesis of Compound 126

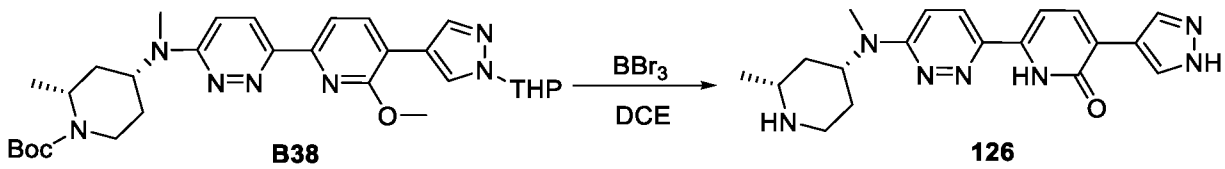
Synthesis of Intermediate B38

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2-methoxy-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (B37; 500.0 mg, 1.65 mmol, 1 equiv), *tert*-butyl (2*R*,4*R*)-4-[(6-iodopyridazin-3-yl)(methyl)amino]-2-methylpiperidine-1-carboxylate (B3; 855.7 mg, 1.98 mmol, 1.20 equiv), dioxane (16 mL), K_3PO_4 (875.3 mg, 4.12 mmol, 2.50 equiv), H_2O (4 mL), and XPhos palladium(II) biphenyl-2-amine chloride (64.9 mg, 0.08 mmol, 0.05 equiv) were added to a 40-mL vial, and the resulting solution was stirred for 4h at 80 °C. The reaction was then quenched by the addition of water/ice (2 mL), and the resulting solution was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (60%) to provide *tert*-butyl (2*R*,4*R*)-4-[(6-[6-methoxy-5-[1-(oxan-2-yl) pyrazol-4-yl] pyridin-2-yl]pyridazin-3-yl)(methyl)amino]-2-methylpiperidine-1-carboxylate (B38; 530 mg) as an oil. **LCMS** (ES, *m/z*): 564 $[M+H]^+$.

Synthesis of Compound 126



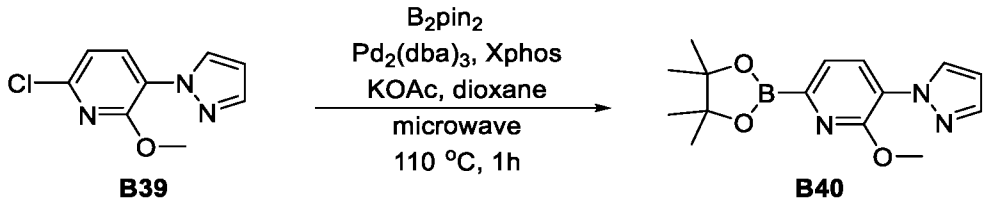
A 100-mL 3-necked round-bottom flask was purged and maintained under an atmosphere of nitrogen, and *tert*-butyl (2*R*,4*R*)-4-[(6-[6-methoxy-5-[1-(oxan-2-yl) pyrazol-4-yl] pyridin-2-yl]pyridazin-3-yl)(methyl)amino]-2-methylpiperidine-1-carboxylate (B38; 380.0 mg, 0.67 mmol, 1 equiv), dichloroethane (50 mL), and boron tribromide (1851.0 mg, 7.39 mmol, 11 equiv) were added to the flask, and the resulting solution was stirred for 0.5 h at 0 °C. The reaction mixture was then stirred for an additional 6 h at 80 °C. The reaction mixture was cooled with a water/ice bath and quenched by the addition of methanol. The resulting mixture was concentrated under vacuum, and the pH of the solution was adjusted to 8 using saturated aqueous $NaHCO_3$. The

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resulting solution was extracted with dichloromethane (3x10 mL) and the organic layers were combined. The crude product was purified by preparative HPLC (Condition 4, Gradient 3) to provide 6-(6-[methyl[(2R,4R)-2-methylpiperidin-4-yl]amino]pyridazin-3-yl)-3-(1H-pyrazol-4-yl)-1H-pyridin-2-one (Compound 126; 33.3 mg) as a solid. LC MS (ES, *m/z*): 366 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 12.88 (s, 1H), 8.28 (s, 2H), 8.04 (d, *J* = 9.8 Hz, 1H), 7.95 (d, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 9.8 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 4.63 (s, 1H), 3.30 (s, 1H), 3.07 – 3.00 (m, 1H), 2.98 (s, 3H), 2.69 – 2.60 (m, 1H), 2.48 (s, 5H), 1.67 – 1.52 (m, 3H), 1.31 (q, *J* = 11.4 Hz, 1H), 1.03 (d, *J* = 6.2 Hz, 3H).

Example 2: Synthesis of Compound 128

Synthesis of Intermediate B40

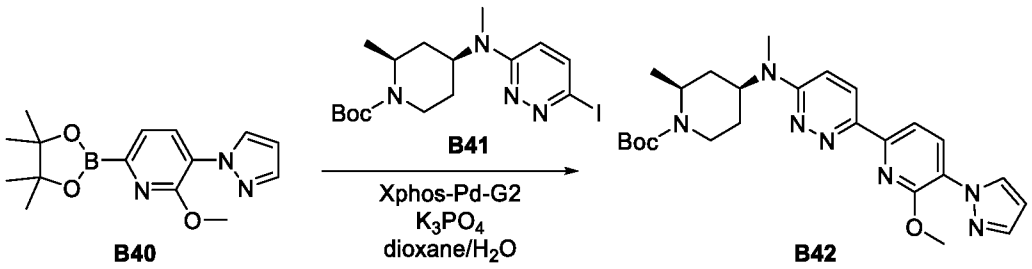


B39 **B40**

A mixture of 6-chloro-2-methoxy-3-(pyrazol-1-yl)pyridine (B39; 650.0 mg, 3.101 mmol, 1.0 equiv) , B_2Pin_2 (945.09 mg, 3.721 mmol, 1.2 equiv), KOAc (912.93 mg, 9.302 mmol, 3.0 equiv), XPhos (147.82 mg, 0.31 mmol, 0.1 equiv) and $Pd_2(dba)_3$ (283.94 mg, 0.310 mmol, 0.10 equiv) in dioxane (15 mL) was stirred for 1h at 110 °C under a nitrogen atmosphere. The reaction was quenched with H_2O (20 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate (20 mL x 3), and the resulting mixture was washed with saturated NaCl (20 mL), then dried with Na_2SO_4. The resulting mixture was filtered, and the filter cake was washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (3:1) to afford 2-methoxy-3-(pyrazol-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (B40; 600 mg) as a solid. **LCMS** (ES, *m/z*): 302 $[M+H]^+$.

Synthesis of Intermediate B42

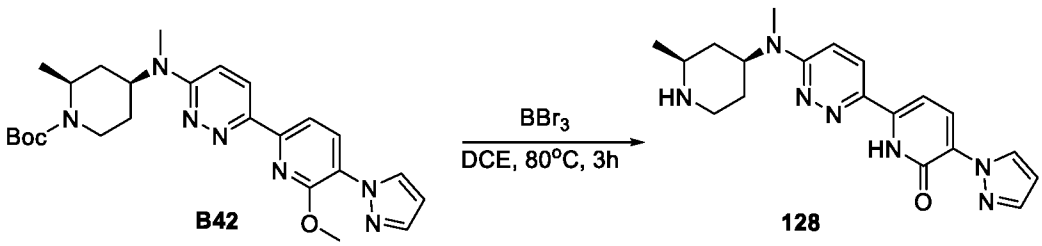
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A mixture of 2-methoxy-3-(pyrazolidin-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine (B40; 650.0 mg, 2.088 mmol, 1.0 equiv) , *tert*-butyl (2*S*,4*S*)-4-[(6-iodopyridazin-3-yl)(methyl)amino]-2-methylpiperidine-1-carboxylate (B41; 1083.44 mg, 2.506 mmol, 1.2 equiv), K_3PO_4 (1329.95 mg, 6.265 mmol, 3.0 equiv) and Xphos-Pd-G2 (164.16 mg, 0.209 mmol, 0.1 equiv) in dioxane (15mL) and H_2O (4 mL) was stirred for 4h at 80 °C under a nitrogen atmosphere in a 40-mL sample bottle. The reaction was quenched with H_2O (20 mL) at 0 °C, and the aqueous layer was extracted with ethyl acetate (20 mL x 2). The resulting mixture was washed with saturated NaCl (20 mL) and dried with Na_2SO_4. The mixture was then filtered, the filter cake was washed with ethyl acetate, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (4:1) to afford *tert*-butyl (2*S*,4*S*)-4-([6-[6-methoxy-5-(pyrazol-1-yl)pyridin-2-yl]pyridazin-3-yl](methyl)amino)-2-methylpiperidine-1-carboxylate (B42; 300 mg) as a solid.

LCMS (ES, *m/z*): 480 $[M+H]^+$.

Synthesis of Compound 128



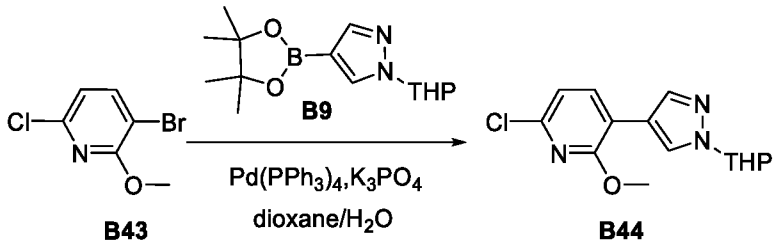
A mixture of *tert*-butyl (2*S*,4*S*)-4-([6-[6-methoxy-5-(pyrazol-1-yl)pyridin-2-yl]pyridazin-3-yl](methyl)amino)-2-methylpiperidine-1-carboxylate (B42; 300.0 mg, 0.626 mmol, 1 equiv) and boron tribromide (1567.12 mg, 6.255 mmol, 10 equiv) in dichloroethane (10 mL) was stirred for 4h at 80 °C under a nitrogen atmosphere in a 40-mL sample bottle. The pH of the mixture was then adjusted to 7-8 using saturated $NaHCO_3$. The crude product was purified by preparative HPLC (Condition 4, Gradient 3), to provide 6-(6-[methyl[(2S,4S)-2-methylpiperidin-4-

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yl]amino]pyridazin-3-yl)-3-(pyrazol-1-yl)-1H-pyridin-2-one (Compound 128; 1.5 mg) as a solid. **LCMS** (ES, *m/z*) 366 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.83 (d, *J* = 2.5 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 8.04 (d, *J* = 9.7 Hz, 1H), 7.75 (d, *J* = 1.7 Hz, 1H), 7.25 (d, *J* = 9.9 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.54 – 6.48 (m, 1H), 4.65 (s, 1H), 3.04 (s, 0H), 3.00 (s, 3H), 2.73 (s, 2H), 1.63 (d, *J* = 15.7 Hz, 3H), 1.35 (d, *J* = 11.8 Hz, 1H), 1.05 (d, *J* = 6.2 Hz, 3H).

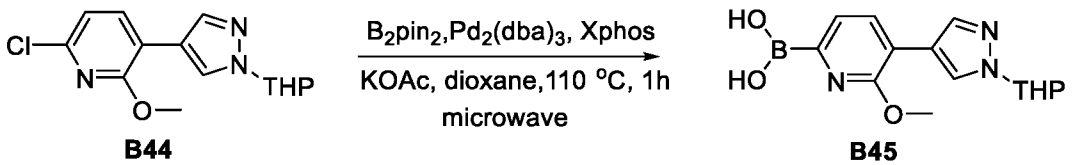
Example 3: Synthesis of Compound 129

Synthesis of Intermediate B44



A 250-mL 3-necked round-bottom flask was purged and maintained under an atmosphere of nitrogen, and 3-bromo-6-chloro-2-methoxypyridine (B43; 2 g, 8.99 mmol, 1 equiv), dioxane (80 mL), 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazole (B9; 3.0 g, 10.79 mmol, 1.20 equiv), K_3PO_4 (5.7 g, 26.97 mmol, 3 equiv), H_2O (20 mL), and $Pd(PPh_3)_4$ (519.4 mg, 0.45 mmol, 0.05 equiv) were added to the flask, and the resulting solution was stirred for 4h at 100 °C. The reaction was then quenched by the addition of water/ice (50 mL), and the resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were was washed with saturated aqueous NaCl (100 mL), then dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with ethyl acetate/petroleum ether (20%) to provide 6-chloro-2-methoxy-3-[1-(oxan-2-yl) pyrazol-4-yl]pyridine (B44; 2.3 g) as an oil. **LCMS** (ES, *m/z*): 294 $[M+H]^+$.

Synthesis of Intermediate B45

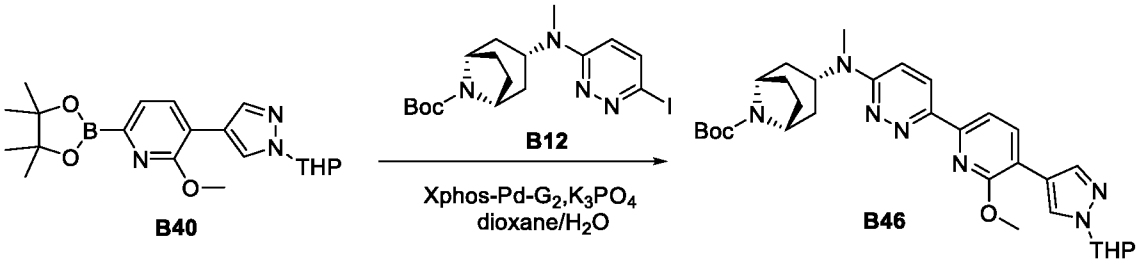


6-Chloro-2-methoxy-3-[1-(oxan-2-yl) pyrazol-4-yl]pyridine (B44; 1 g, 3.40mmol, 1 equiv), $B_2(pin)_2$ (1.6 g, 0.01 mmol, 1.8 equiv), KOAc (1 g, 0.01 mmol, 3 equiv), XPhos (0.49 g, 0.001

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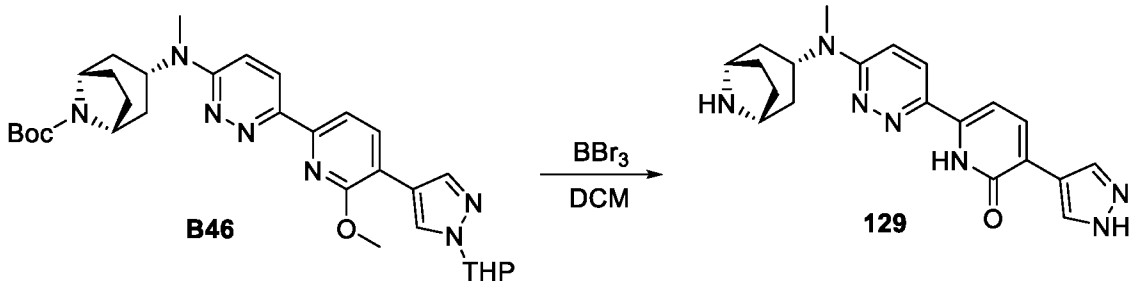
mmol, 0.3 equiv), $Pd_2(dba)_3$-$CHCl_3$ (0.28 g, 0.08 equiv), and dioxane (12 mL) were added to a 30-mL microwave tube, and the resulting solution was stirred for 1h at 110 °C in a microwave reactor. The mixture was then filtered, and the resulting crude product was added to the next step directly without further purification. **LCMS** (ES, *m/z*): 304 $[M+H]^+$.

Synthesis of Intermediate B46



2-methoxy-3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (B40; 500 mg, 1.65 mmol, 1 equiv), *tert*-butyl (1*R*,3*S*,5*S*)-3-[(6-iodopyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane -8-carboxylate (B12; 879.5 mg, 1.98 mmol, 1.2 equiv), dioxane (16 mL), K_3PO_4 (875.3 mg, 4.12 mmol, 2.5 equiv), H_2O (4 mL), and XPhos palladium(II) biphenyl-2-amine chloride (64.5 mg, 0.08 mmol, 0.05 equiv) were placed in a 40-mL vial, and the resulting solution was stirred for 4h at 80 °C. The reaction was then quenched by the addition of water/ice (2 mL). The resulting solution was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers washed with saturated aqueous NaCl (50 mL). The solids were filtered out. The resulting mixture was concentrated under vacuum, and the residue was purified by silica gel column chromatography, eluting with ethyl acetate/petroleum ether (3:2), to provide *tert*-butyl (1*R*,3*S*,5*S*)-3-[(6-[6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl]pyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B46; 380 mg) as an oil. **LCMS** (ES, *m/z*): 576 $[M+H]^+$.

Synthesis of Compound 129

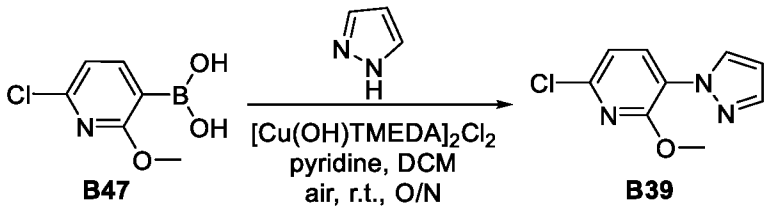


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A 100-mL 3-necked round-bottom flask was purged and maintained under an atmosphere of nitrogen, and *tert*-butyl (1*R*,3*S*,5*S*)-3-[(6-[6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl]pyridazin-3-yl)(methyl) amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B46; 410.0 mg, 0.28 mmol, 1 equiv), dichloroethane (60 mL), and boron tribromide (713.6mg, 2.85 mmol, 10 equiv) were added to the flask, and the resulting solution was stirred for 6h at 80 °C. The reaction mixture was then cooled with a water/ice bath and quenched by the addition of methanol. The pH of the solution was adjusted to 8 using saturated aqueous $NaHCO_3$, and the resulting solution was extracted with dichloromethane (3 x 20 mL) and the organic layers combined and concentrated under vacuum. The crude product was purified by preparative HPLC (Condition 4, Gradient 4), to provide 6-[6-[(1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl(methyl)amino]pyridazin-3-yl]-3-(1H-pyrazol-4-yl)-1H-pyridin-2-one (Compound 129; 5.6 mg) as a solid. LC MS (ES, *m/z*): 378 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 12.91 (s, 1H), 8.40 (s, 1H), 8.03 (d, *J* = 9.7 Hz, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 9.7 Hz, 1H), 7.04 (s, 1H), 6.57 (s, 1H), 5.11 (s, 1H), 3.49 (s, 3H), 2.93 (s, 3H), 2.48 (s, 18H), 1.84 – 1.70 (m, 2H), 1.73 (s, 5H), 1.53 (s, 2H), 1.24 (s, 1H), 0.84 (s, 1H).

Example 4: Synthesis of Compound 130

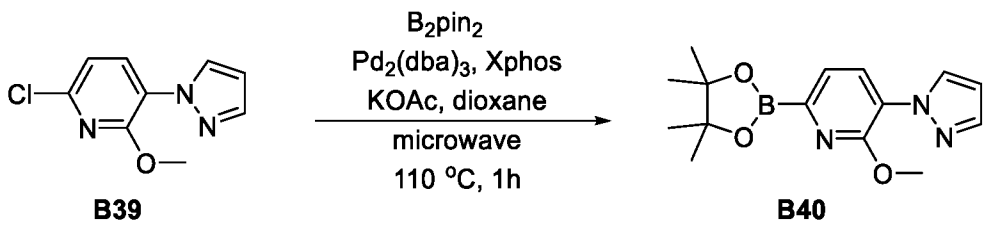
Synthesis of Intermediate B39



A mixture of pyrazole (2.18 g, 32.019 mmol, 2 equiv), $[Cu(OH)TMEDA]_2Cl_2$ (0.74 g, 1.601 mmol, 0.1 equiv) and pyridine were heated to 35 °C for 30 min, then 6-chloro-2-methoxypyridin-3-ylboronic acid (B47; 3.0 g, 16 mmol, 1.0 equiv) and dimethylformamide (100 mL) were slowly added, and the mixture stirred for overnight under a nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with ethyl acetate, and the filtrate was concentrated under reduced pressure. The aqueous layer was extracted with ethyl acetate (100 mL). The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (2:1) to afford 6-chloro-2-methoxy-3-(pyrazol-1-yl)pyridine (B39; 450 mg) as a solid. **LCMS** (ES, *m/z*): 210 $[M+H]^+$.

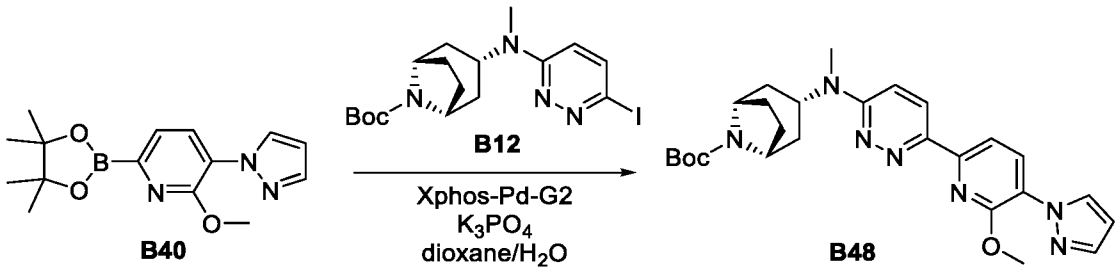
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Synthesis of Intermediate B40



A mixture of 6-chloro-2-methoxy-3-(pyrazol-1-yl), pyridine (B39; 500.0 mg, 2.385 mmol, 1 equiv), B_2Pin_2 (1211.66 mg, 4.770 mmol, 2 equiv), $Pd_2(dba)_3$-$CHCl_3$ (123.44 mg, 0.119 mmol, 0.05 equiv), XPhos (113.7 mg, 0.239 mmol, 0.1 equiv), KOAc (702.25 mg, 7.155 mmol, 3 equiv), and dioxane (15 mL) in a 30-mL microwave tube was stirred for 1h at 110 °C under a nitrogen atmosphere, with microwave irradiation. The resulting mixture was filtered, the filter cake was washed with ethyl acetate, and the filtrate was concentrated under reduced pressure, to provide 2-methoxy-3-(pyrazol-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (B40; 600 mg, 83.53%) as a solid. **LCMS** (ES, *m/z*):302 $[M+H]^+$.

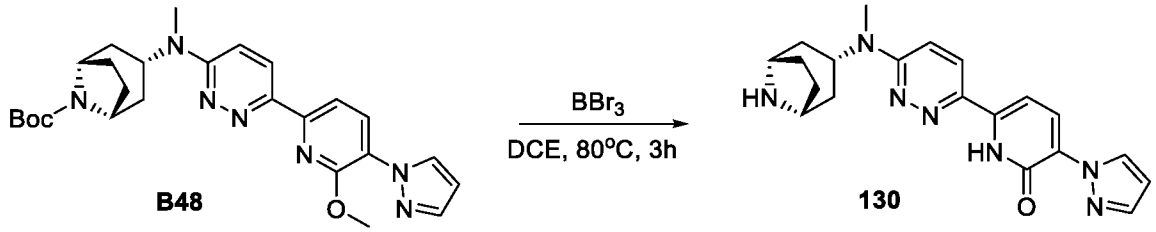
Synthesis of Intermediate B48



A mixture of 2-methoxy-3-(pyrazol-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (B40; 450.0 mg, 1.494 mmol, 1.0 equiv), *tert*-butyl (1*R*,3*S*,5*S*)-3-[(6-iodopyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B12; 796.72 mg, 1.793 mmol, 1.2 equiv), XPhos-Pd-G2 (117.45 mg, 0.149 mmol, 0.1 equiv), K_3PO_4 (951.55 mg, 4.483 mmol, 3.0 equiv), dioxane (12 mL), and H_2O (3 mL) in a 40-mL sample bottle was stirred for 2h at 100 °C under a nitrogen atmosphere. The reaction was then quenched with H_2O (20 mL) at 0 °C, and the aqueous layer was extracted with ethyl acetate (20 mL x 3), then washed with saturated NaCl (20 mL), and dried over Na_2SO_4. The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (3:1) to afford *tert*-butyl (1*R*,3*S*,5*S*)-3-([6-[6-methoxy-5-(pyrazol-1-yl)pyridin-2-yl]pyridazin-3-yl](methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (B48; 310 mg) as a solid. **LCMS** (ES, *m/z*): 492 $[M+H]^+$.

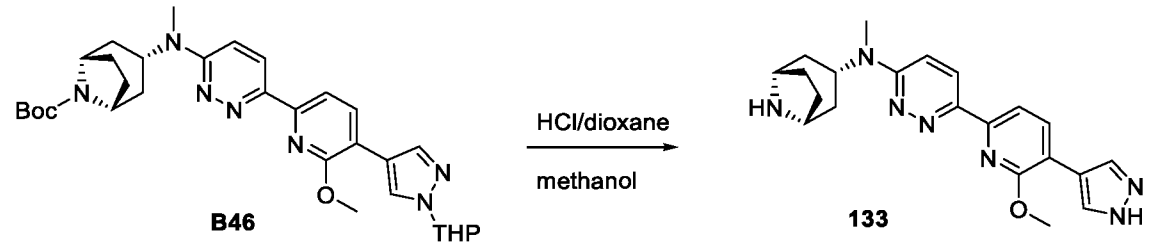
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Synthesis of Compound 130



A mixture of *tert*-butyl (1*R*,3*S*,5*S*)-3-([6-[6-methoxy-5-(pyrazol-1-yl)pyridine-2-yl]pyridazin-3-yl](methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (B48; 250.0 mg, 0.631 mmol, 1 equiv), boron tribromide (1274.01 mg, 6.306 mmol, 10 equiv), and dichloroethane (10 mL) in a 40-mL sample bottle was stirred for 4h at 80 °C under a nitrogen atmosphere. The pH of the mixture was then adjusted to pH 7-8 with saturated $NaHCO_3$. The crude product was concentrated under reduced pressure to provide in 6-[6-[(1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl(methyl)amino]pyridazin-3-yl]-3-(pyrazol-1-yl)-1H-pyridin-2-one (Compound 130; 25. 3mg) as a solid. **LCMS** (ES, *m/z*): 378[M+H] $^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.84 (d, J = 2.5 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.04 (d, J = 9.7 Hz, 1H), 7.75 (d, J = 1.7 Hz, 1H), 7.21 (d, J = 9.7 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 6.50 (t, J = 2.1 Hz, 1H), 5.13 (s, 1H), 3.59 (s, 2H), 2.95 (s, 3H), 1.85 (t, J = 12.3 Hz, 2H), 1.78 (s, 4H), 1.57 (s, 2H).

Example 5: Synthesis of Compound 133

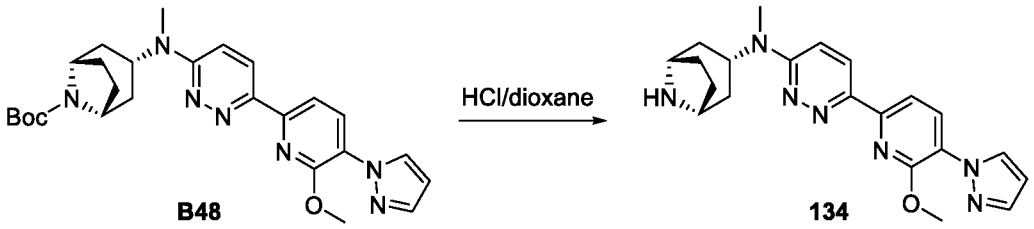


tert-Butyl (1*R*,3*S*,5*S*)-3-[(6-[6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl]pyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B46 from Example 17; 120 mg, 0.21 mmol, 1 equiv), dioxane (2 mL), and HCl in 1,4-dioxane (2 mL) were added to a 40-mL vial, followed by a small amount of methanol. The resulting solution was stirred for 3h at room temperature, then concentrated under vacuum. The crude product was purified by preparative HPLC (Condition 4, Gradient 3), to provide (1*R*,3*S*,5*S*)-N-[6-[6-methoxy-5-(1H-pyrazol-4-yl)pyridin-2-yl]pyridazin-3-yl]-N-methyl-8-azabicyclo[3.2.1]octan-3-amine (Compound 133; 43.3 mg) as a solid. LC MS (ES, *m/z*): 392 [M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 13.04

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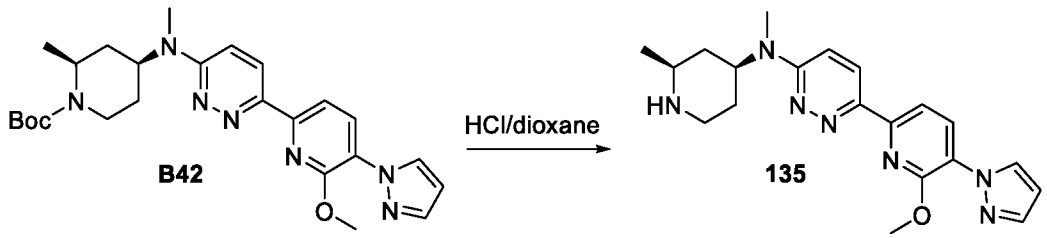
(s, 1H), 8.24 – 8.12 (m, 4H), 8.01 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 9.7 Hz, 1H), 5.10 (s, 1H), 4.10 (s, 3H), 3.50 (s, 2H), 2.93 (s, 3H), 1.79 (td, J = 13.2, 12.6, 3.7 Hz, 3H), 1.74 (s, 3H), 1.58 – 1.49 (m, 2H).

Example 6: Synthesis of Compound 134



A 50-mL 1-necked round-bottom flask was purged and maintained under a nitrogen atmosphere. *tert*-butyl (1*R*,3*S*,5*S*)-3-([6-[6-methoxy-5-(pyrazol-1-yl)pyridin-2-yl]pyridazin-3-yl](methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (B48 from Example 18; 50 mg), dioxane (1 mL), HCl in dioxane (1 mL), and MeOH (0.5 mL) were then added to the flask, and the mixture was stirred for 2h under a nitrogen atmosphere. The crude product was purified by preparative HPLC (Condition 4, Gradient 1) to provide (1*R*,3*S*,5*S*)-N-[6-[6-methoxy-5-(pyrazol-1-yl)pyridin-2-yl]pyridazin-3-yl]-N-methyl-8-azabicyclo[3.2.1]octan-3-amine (Compound 134; 6.8 mg) as a solid. **LCMS** (ES, *m/z*): 392[M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.37 (d, J = 2.5 Hz, 1H), 8.26 – 8.19 (m, 2H), 8.13 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 1.8 Hz, 1H), 7.19 (d, J = 9.6 Hz, 1H), 6.59 – 6.53 (m, 1H), 5.11 (s, 1H), 4.12 (s, 3H), 3.52 (s, 2H), 2.95 (s, 3H), 1.87 – 1.73 (m, 6H), 1.56 (t, J = 7.6 Hz, 2H), 1.15 (s).

Example 7: Synthesis of Compound 135

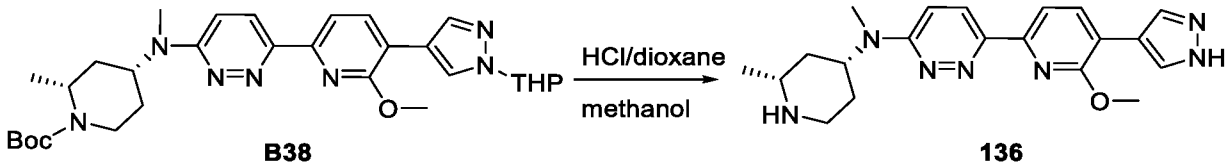


A mixture of *tert*-butyl (2*S*,4*S*)-4-([6-[6-methoxy-5-(pyrazol-1-yl)pyridin-2-yl]pyridazin-3-yl](methyl)amino)-2-methylpiperidine-1-carboxylate (B42 from Example 16; 100 mg), dioxane (2 mL), and HCl in dioxane (2 mL) was stirred for 2h at 0 °C under a nitrogen atmosphere in a 50-mL 3-necked bottle. The mixture was filtered, and the filtrate was concentrated under reduced pressure, and methanol (1 mL) was added to the residue. The crude product was purified

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by preparative HPLC (Condition 1), to afford 6-[6-methoxy-5-(pyrazol-1-yl)pyridin-2-yl]-N-methyl-N-[(2*S*,4*S*)-2-methylpiperidin-4-yl]pyridazin-3-amine (Compound 135; 22.7 mg) as a solid. LC MS (ES, *m/z*): 380[M+H] $^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.37 (d, *J* = 2.4 Hz, 1H), 8.25 – 8.18 (m, 2H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 1.7 Hz, 1H), 7.22 (d, *J* = 9.7 Hz, 1H), 6.56 (t, *J* = 2.2 Hz, 1H), 4.67 (s, 1H), 4.12 (s, 3H), 3.09 – 3.01 (m, 1H), 2.99 (s, 3H), 2.76 – 2.68 (m, 1H), 2.71 – 2.62 (m, 1H), 1.64 (qd, *J* = 11.4, 10.8, 4.0 Hz, 2H), 1.33 (q, *J* = 11.6 Hz, 1H), 1.05 (d, *J* = 6.2 Hz, 3H).

Example 8: Synthesis of Compound 136

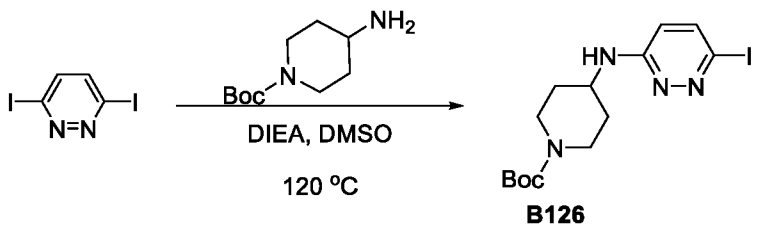


B38 **136**

tert-Butyl (2*R*,4*R*)-4-[(6-[6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl]pyridazin-3-yl)(methyl)amino]-2-methylpiperidine-1-carboxylate (B38 from Example 15; 140 mg, 0.25 mmol, 1 equiv), dioxane (2 mL), and HCl in 1,4-dioxane (2 mL) were added to a 40-mL vial, followed by the addition of a small amount of methanol. The resulting solution was stirred for 3h at room temperature. The crude product was purified by preparative HPLC (Condition 1), to provide 6-[6-methoxy-5-(1H-pyrazol-4-yl)pyridin-2-yl]-N-methyl-N-[(2R,4R)-2-methylpiperidin-4-yl]pyridazin-3-amine (Compound 136; 21.9 mg) as a solid. LC-MS (ES, *m/z*): 380 [M+H] $^+$. **^{1}H NMR** (400 MHz, DMSO-d6): δ 13.05 (s, 1H), 8.19 (t, *J* = 8.9 Hz, 3H), 8.13 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 9.7 Hz, 1H), 4.67 (s, 1H), 4.10 (s, 3H), 3.06 (d, *J* = 12.8 Hz, 1H), 2.97 (s, 3H), 2.77 – 2.64 (m, 2H), 1.71 – 1.57 (m, 3H), 1.40 – 1.22 (m, 1H), 1.05 (d, *J* = 6.2 Hz, 3H).

Example 9: Synthesis of Compound 256

Synthesis of Intermediate B126

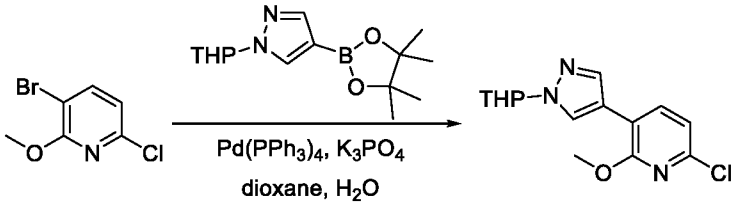


B126

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A mixture of 3,6-diiodopyridazine (2.00 g, 6.026 mmol, 1.00 equiv) , tert-butyl 4-aminopiperidine-1-carboxylate (1.45 g, 7.231 mmol, 1.2 equiv), and DIEA (2.34 g, 18.078 mmol, 3 equiv) in DMSO (20 mL) was stirred for 16 h at 120 °C. The reaction mixture was allowed to cool down to room temperature, then diluted with water. The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-100%) to afford tert-butyl 4-[(6-iodopyridazin-3-yl)amino]piperidine-1-carboxylate (600 mg, 24.63%) as a solid. **LCMS** (ES, *m/z*): 405 $[M+H]^+$

Synthesis of Intermediate B127

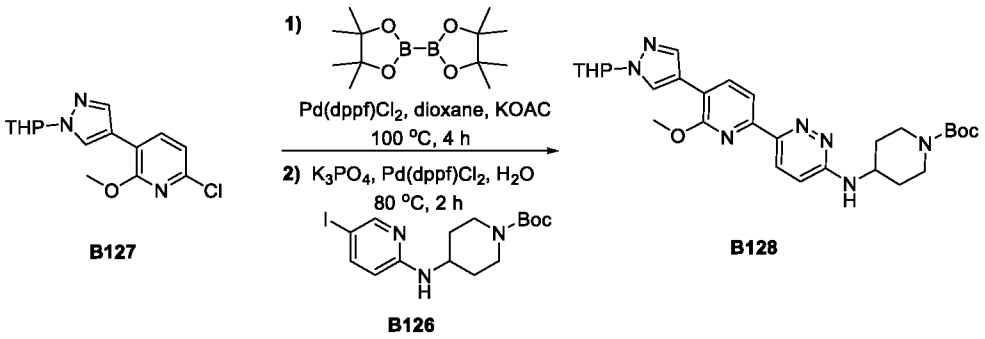


B127

A mixture of 3-bromo-6-chloro-2-methoxypyridine (2.50 g, 11.237 mmol, 1.00 equiv), 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (3.75 g, 13.484 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (6.49 g, 5.619 mmol, 0.5 equiv), and K_3PO_4 (7.16 g, 33.711 mmol, 3 equiv) in a mixture of dioxane (25 mL) and H_2O (5 mL) was stirred for 2 h at 80 °C under N_2 atmosphere. The reaction mixture was cooled to room temperature, then diluted with water. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-20%), to afford 6-chloro-2-methoxy-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine (3.00 g, 90.88%) as an oil. **LCMS** (ES, *m/z*):294 $[M+H]^+$.

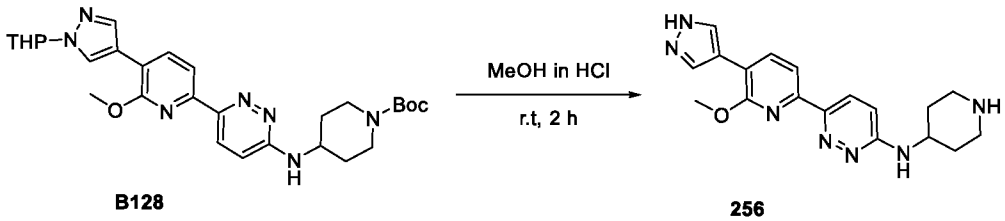
Synthesis of Intermediate B128

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A mixture of 6-chloro-2-methoxy-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine (120 mg, 0.409 mmol, 1.00 equiv), bis(pinacolato)diboron (124 mg, 0.491 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (149 mg, 0.204 mmol, 0.5 equiv), and KOAc (120 mg, 1.227 mmol, 3 equiv) in dioxane (2.40 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. To the reaction mixture was added tert-butyl 4-[(6-iodopyridazin-3-yl)amino]piperidine-1-carboxylate (173 mg, 0.429 mmol, 1 equiv), K_3PO_4 (315 mg, 1.485 mmol, 3 equiv), and $Pd(dppf)Cl_2$ (36 mg, 0.050 mmol, 0.1 equiv) in water (0.6 mL). The reaction mixture was stirred for 2 h at 80 °C under nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1), to afford tert-butyl 4-[(6-{6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl)amino]piperidine-1-carboxylate (120 mg, 52.24%) as a solid. **LCMS** (ES, *m/z*):536 $[M+H]^+$

Synthesis of Compound 256



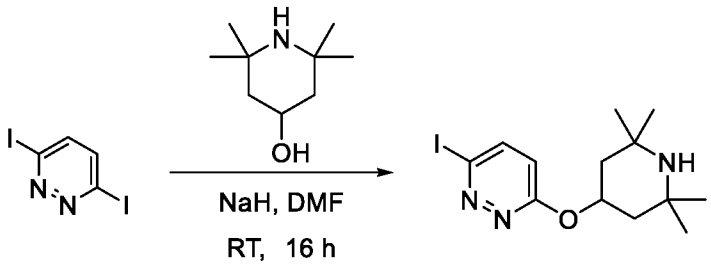
A mixture of 3-{6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}-6-[(2,2,6,6-tetramethylpiperidin -4-yl)oxy]pyridazine (85 mg, 0.173 mmol, 1.00 equiv) and HCl in methanol (1 mL) was stirred for 2 h at room temperature. The reaction mixture was quenched with $NH_3.H_2O$ at 5 °C, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 7, Gradient 1) to afford 3-[6-methoxy-5-(1H-pyrazol-4-yl)pyridin-2-yl]-6-[(2,2,6,6-tetramethylpiperidin-4-yl)oxy] pyridazine (7.5 mg, 12.35%) as a solid. **LCMS** (ES, m/z): 352 $[M+H]^+$. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 13 (m, J = 7.6 Hz, 1H), 8.19-8.08 (m, 4H), 7.95 (d, J = 7.8 Hz, 1H), 7.01 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 9.3 Hz, 1H),

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4.09 (s, 3H), 3.97 (s, 1H), 2.98 (d, J = 12.4 Hz, 2H), 2.58 (d, J = 12.3 Hz, 2H), 1.95 (d, J = 12.2 Hz, 2H), 1.34 (q, J = 11.0, 10.5 Hz, 2H).

Example 10: Synthesis of Compound 244

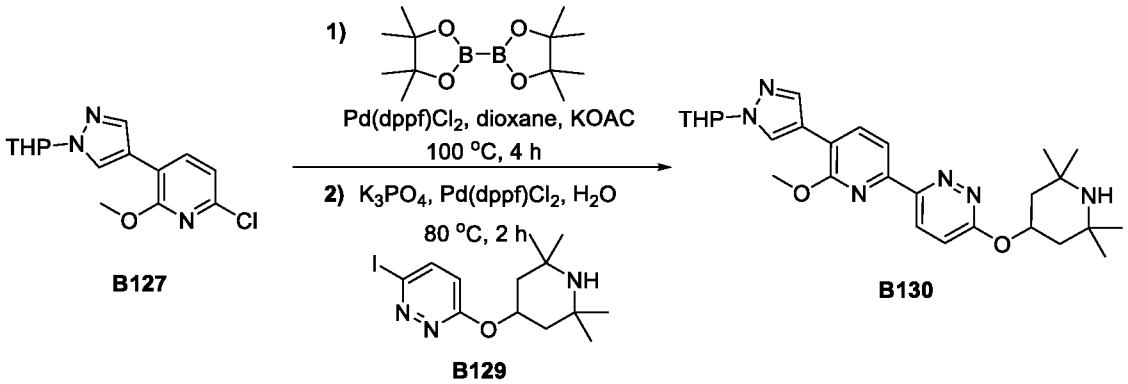
Synthesis of Intermediate B129



B129

To a stirred mixture of 3,6-diiodopyridazine (3.00 g, 9.0 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidin-4-ol (1.71 g, 10.8 mmol, 1.2 equiv) in DMF (30 mL) was added NaH (0.72 g, 18 mmol, 2 equiv) in portions at 0-5 °C .The reaction mixture was stirred 16 h at room temperature, then quenched with Water/Ice (100 mL) at 0-5 °C. The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-100%), to afford 3-iodo-6-[(2,2,6,6-tetramethylpiperidin-4-yl)oxy]pyridazine (2.00 g, 61.25%) as a solid. **LCMS** (ES, *m/z*): 362 $[M+H]^+$.

Synthesis of Intermediate B130



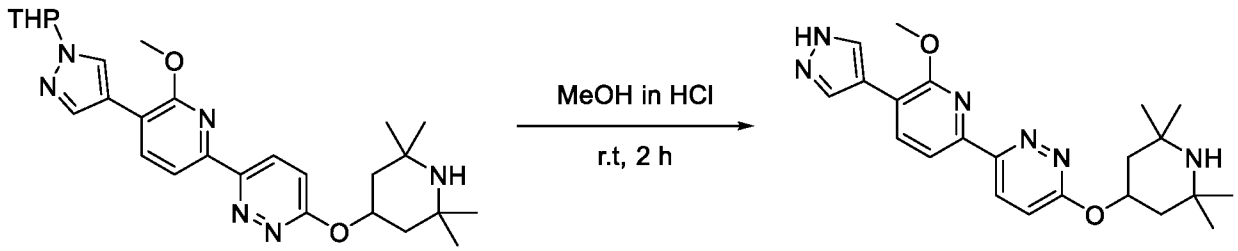
B127 **B129** **B130**

A mixture of 6-chloro-2-methoxy-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine (120 mg, 0.409 mmol, 1.00 equiv), bis(pinacolato)diboron (124 mg, 0.491 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (149 mg,

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0.204 mmol, 0.5 equiv), and KOAc (120 mg, 1.227 mmol, 3 equiv) in dioxane (2.4 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. After, the reaction mixture was cooled to room temperature, 3-iodo-6-[(2,2,6,6-tetramethylpiperidin-4-yl)oxy]pyridazine (155 mg, 0.429 mmol, 1 equiv), K_3PO_4 (315 mg, 1.485 mmol, 3 equiv) and $Pd(dppf)Cl_2$ (36 mg, 0.050 mmol, 0.1 equiv) in H_2O (0.6 mL) were added. The reaction mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10:1), to afford 3-{6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}-6-[(2,2,6,6-tetramethylpiperidin-4-yl)oxy]pyridazine (85 mg, 40.23%) as a solid. **LCMS** (ES, *m/z*):493 $[M+H]^+$.

Synthesis of Compound 244



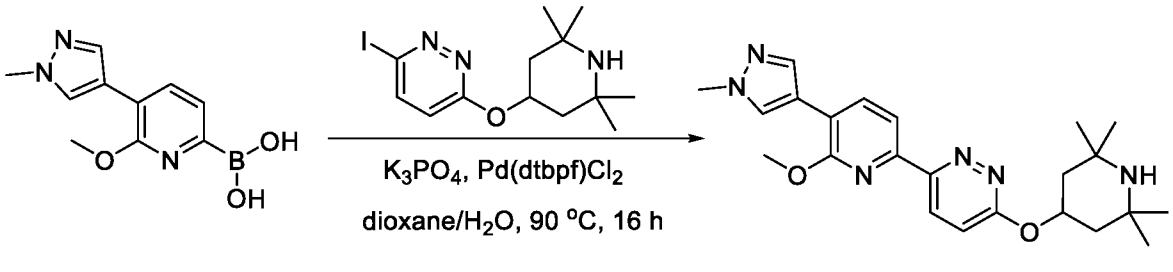
B130 **PH-RMT-2020-0966-0**

A mixture of 3-{6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}-6-[(2,2,6,6-tetramethylpiperidin -4-yl)oxy]pyridazine (85 mg, 0.173 mmol, 1.00 equiv) and HCl in methanol (0.85 mL) was stirred for 2 h at room temperature. The reaction mixture was quenched with $NH_3.H_2O$ at 5 °C, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 7, Gradient 1) to afford 3-[6-methoxy-5-(1H-pyrazol-4-yl)pyridin-2-yl]-6-[(2,2,6,6-tetramethylpiperidin-4-yl)oxy] pyridazine) (27 mg, 38.31%) as a solid. **LCMS** (ES, m/z): 409$[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 8.45 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 7.8 Hz, 3H), 8.09 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 9.2 Hz, 1H), 5.73 (tt, J = 11.2, 4.1 Hz, 1H), 4.12 (s, 3H), 2.15-2.06 (m, 2H), 1.46-1.34 (m, 1H), 1.25 (s, 8H), 1.12 (s, 6H).

Example 11: Synthesis of Compound 245

Synthesis of Compound 245

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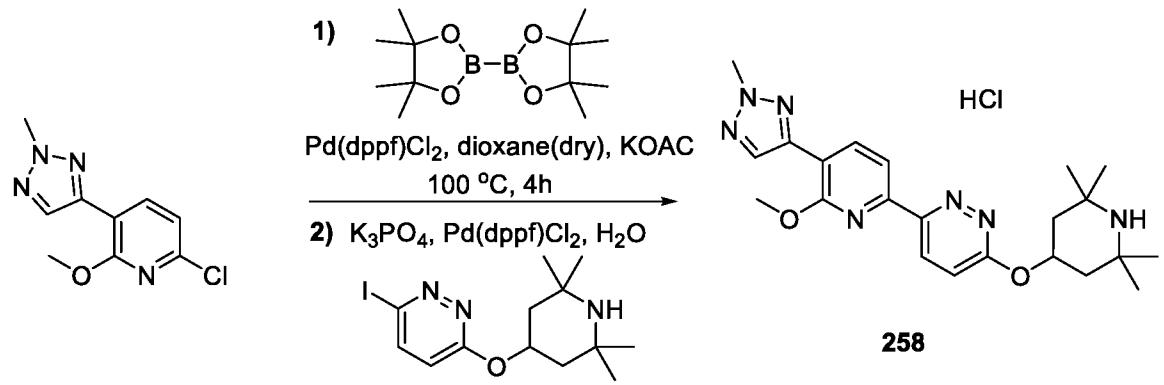


B245

A mixture of 6-methoxy-5-(1-methylpyrazol-4-yl)pyridin-2-ylboronic acid (80 mg, 0.343 mmol, 1.00 equiv), 3-iodo-6-[(2,2,6,6-tetramethylpiperidin-4-yl)oxy]pyridazine (124 mg, 0.343 mmol, 1.0 equiv), (phosphoperoxy)potassium; dipotassium (219 mg, 1.029 mmol, 3.0 equiv) and $Pd(dtbpf)Cl_2$ (22 mg, 0.034 mmol, 0.1 equiv) in dioxane (1.5 mL) and water (0.3 mL) was stirred for 16 h at 90 °C under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-10%), followed by Prep-HPLC (Condition 8, Gradient 1) to afford 3-[6-methoxy-5-(1-methylpyrazol-4-yl) pyridin-2-yl]-6-[(2,2,6,6-tetramethylpiperidin-4-yl)oxy]pyridazine (38.1 mg, 26.27%) as a solid. **LCMS** (ES, *m/z*): 423 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.44 (d, J = 9.2 Hz, 1H), 8.26 (s, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.12-8.04 (m, 2H), 7.29 (d, J = 9.2 Hz, 1H), 5.79-5.67 (m, 1H), 4.12 (s, 3H), 3.91 (s, 3H), 2.10 (dd, J = 11.9, 4.0 Hz, 2H), 1.37 (s, 1H), 1.29 (d, J = 11.5 Hz, 2H), 1.25 (s, 6H), 1.11 (s, 6H).

Example 12: Synthesis of Compound 258

Synthesis of Compound 258



258

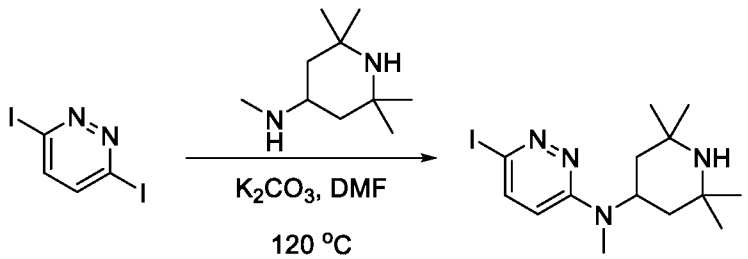
A mixture of 6-chloro-2-methoxy-3-(2-methyl-1,2,3-triazol-4-yl)pyridine (85 mg, 0.378 mmol, 1.00 equiv), 4,4,5-trimethyl-2-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane

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(102 mg, 0.454 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (43 mg, 0.038 mmol, 0.1 equiv) and KOAc (111 mg, 1.134 mmol, 3 equiv) in dioxane (1 mL) was stirred for 4 h at 80 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature. To the reaction mixture was added tert-butyl 4-[(5-bromopyridin-2-yl)amino] piperidine-1-carboxylate (137 mg, 0.385 mmol, 1 equiv), K_3PO_4 (315 mg, 1.485 mmol, 3 equiv), and $Pd(dppf)Cl_2$ (36 mg, 0.050 mmol, 0.1 equiv) in water (0.6 mL). The reaction mixture was stirred for 2 h at 80 °C under nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-10%), followed by Prep-HPLC (Condition 9, Gradient 1) to afford 3-[6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl) pyridin-2-yl]-6-[(2,2,6,6-tetramethylpiperidin-4-yl)oxy]pyridazine (20 mg, 23.85%) as a solid. **LCMS** (ES, *m/z*):424 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.37 (d, *J* = 12.1 Hz, 1H), 8.59-8.49 (m, 2H), 8.42 (d, *J* = 7.8 Hz, 1H), 8.22-8.14 (m, 2H), 7.40 (d, *J* = 9.3 Hz, 1H), 5.78 (tt, *J* = 10.9, 4.2 Hz, 1H), 4.25 (s, 3H), 4.16 (s, 3H), 2.34 (dd, *J* = 13.1, 4.1 Hz, 2H), 1.86 (t, *J* = 11.9 Hz, 2H), 1.54 (d, *J* = 7.8 Hz, 12H).

Example 13: Synthesis of Compound 246

Synthesis of Intermediate B131

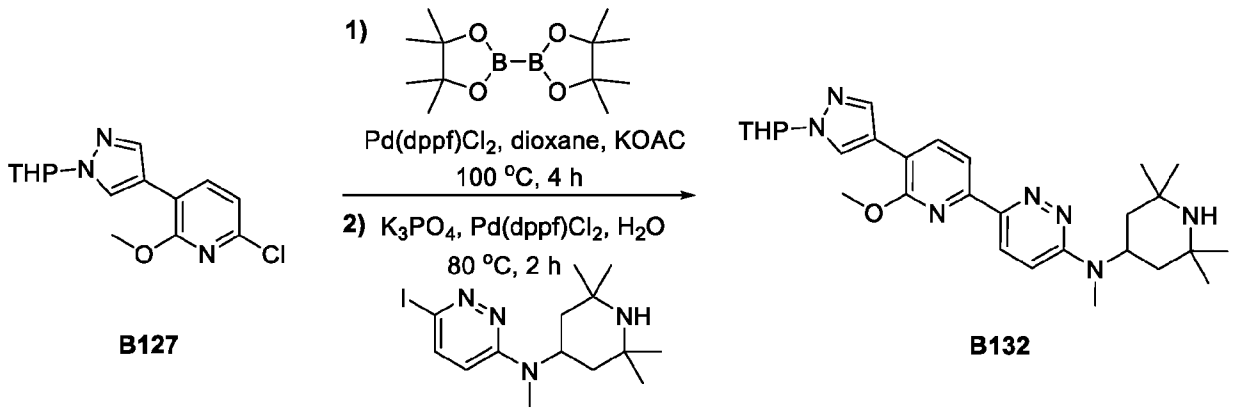


B131

A mixture of 3,6-diiodopyridazine (3.00 g, 9.039 mmol, 1.00 equiv), N,2,2,6,6-pentamethylpiperidin -4-amine (1.85 g, 10.847 mmol, 1.2 equiv), and K_2CO_3 (3.75 g, 27.117 mmol, 3 equiv) in DMF (30 mL) was stirred for 4 h at 120 °C. The reaction mixture was cooled to room temperature, then diluted with water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (1/1) to afford 6-iodo-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine (1.60 g, 47.29%) as a solid. **LCMS** (ES, *m/z*):375 $[M+H]^+$.

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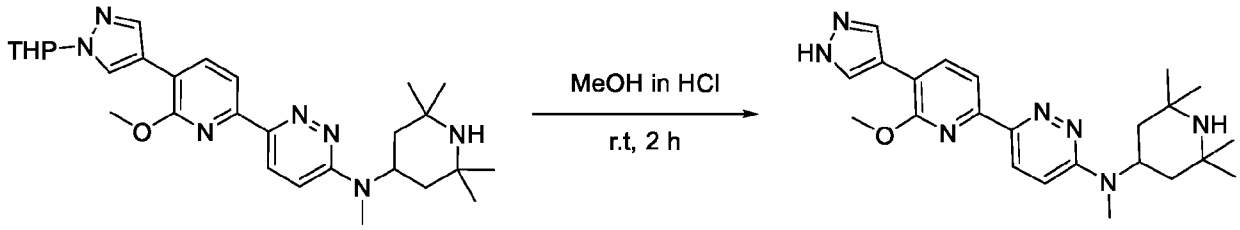
Synthesis of Intermediate B132



B127 **B131** **B132**

A mixture of 6-chloro-2-methoxy-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine (120 mg, 0.409 mmol, 1.00 equiv), bis(pinacolato)diboron (124 mg, 0.491 mmol, 1.2 equiv), $Pd(dppf)Cl_2$ (149 mg, 0.204 mmol, 0.5 equiv) and KOAc (120 mg, 1.227 mmol, 3 equiv) in dioxane (2.4 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature. To the reaction mixture was added 6-iodo-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine (185 mg, 0.495 mmol, 1 equiv), K_3PO_4 (315 mg, 1.485 mmol, 3 equiv), and $Pd(dppf)Cl_2$ (36 mg, 0.050 mmol, 0.1 equiv) in water (0.6 mL). The reaction mixture was stirred for an additional 2 h at 80 °C under nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10/1), to afford 6-{6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}-N-methyl-N- (2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine (200 mg, 79.93%) as a solid. **LCMS** (ES, *m/z*):506 $[M+H]^+$.

Synthesis of Compound 246



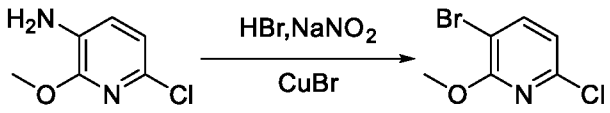
B132 **246**

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A solution of 6-{6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}-N-methyl-N-(2,2,6,6-tetra methylpiperidin-4-yl)pyridazin-3-amine (100 mg, 0.198 mmol, 1.00 equiv) in 4 M HCl in methanol (1 mL) was stirred for 2 h at room temperature. The reaction mixture was quenched with $NH_3.H_2O$ at 0-5 °C, then concentrated in vacuo to give a residue. The residue was purified by Prep-HPLC (Condition 7, Gradient 2) to afford 6-[6-methoxy-5-(1H-pyrazol-4-yl)pyridin-2-yl]-N-methyl-N-(2,2,6,6- tetramethylpiperidin-4-yl)pyridazin-3-amine (30.7 mg, 36.83%) as a white solid. **LCMS** (ES, m/z): 421 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 8.20 (dd, J = 23.3, 8.7 Hz, 3H), 8.02 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 9.7 Hz, 1H), 5.15 (s, 1H), 4.10 (s, 3H), 2.96 (s, 3H), 1.53 (dd, J = 12.0, 3.6 Hz, 2H), 1.44 (t, J = 12.0 Hz, 2H), 1.27 (s, 6H), 1.10 (s, 6H).

Example 14: Synthesis of Compound 247

Synthesis of Intermediate B133

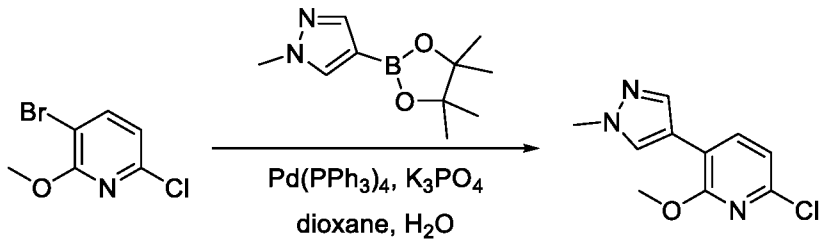


B133

To a stirred mixture of 6-chloro-2-methoxypyridin-3-amine (10.00 g, 63 mmol, 1 equiv) and 40% HBr in water (100 mL) was added $NaNO_2$ (4.57 g, 66 mmol, 1.05 equiv) in water (20 mL) dropwise at 0-5 °C. The reaction mixture was stirred for 30 min at 0-5 °C. To the reaction mixture was added copper(I) bromide (10.85 g, 75 mmol, 1.2 equiv) in portions. The resulting mixture was stirred for an additional 2 h at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-50%) to afford 3-bromo-6-chloro-2-methoxypyridine (13.00 g, 92.67%) as a solid. **LCMS** (ES, *m/z*): 222 $[M+H]^+$.

Synthesis of Intermediate B134

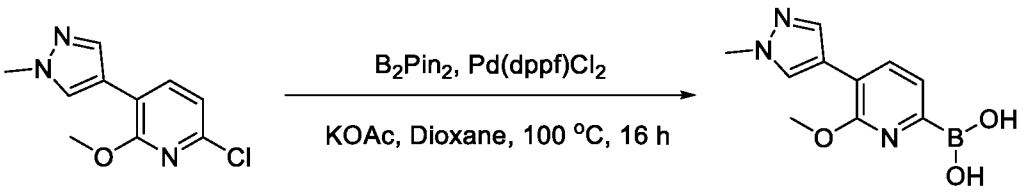
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B133 **B134**

To a mixture of 3-bromo-6-chloro-2-methoxypyridine (2.50 g, 11.237 mmol, 1.00 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (2.81 g, 13.484 mmol, 1.2 equiv) in dioxane (25 mL) and H_2O (5 mL) was added K_3PO_4 (7.16 g, 33.711 mmol, 3 equiv) and $Pd(PPh_3)_4$ (0.65 g, 0.562 mmol, 0.05 equiv). The reaction mixture was stirred for 2 h at 80 ° C under a nitrogen atmosphere, then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford 6-chloro-2-methoxy-3-(1-methylpyrazol-4-yl)pyridine (2.00 g, 79.57%) as a solid. **LCMS** (ES, *m/z*): 224.1 $[M+H]^+$.

Synthesis of Intermediate B135

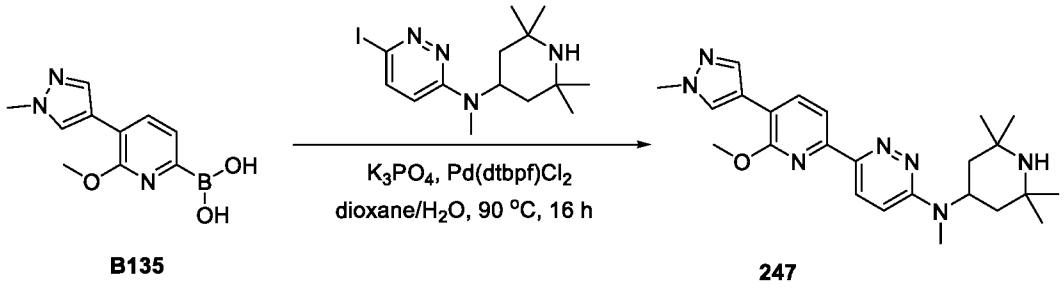


B134 **B135**

A solution of 6-chloro-2-methoxy-3-(1-methylpyrazol-4-yl)pyridine (700 mg, 3.130 mmol, 1.00 equiv), bis(pinacolato)diboron (1192 mg, 4.695 mmol, 1.5 equiv), potassium acetate (921 mg, 9.390 mmol, 3.0 equiv) and $Pd(dppf)Cl_2$ (229 mg, 0.313 mmol, 0.1 equiv) in dioxane (14 mL) was stirred for 16 h at 100 °C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-100%) to afford 6-methoxy-5-(1-methylpyrazol-4-yl)pyridin-2-ylboronic acid (350 mg, 47.99%) as a solid. **LCMS** (ES, *m/z*): 234.2 $[M+H]^+$

Synthesis of Compound 247

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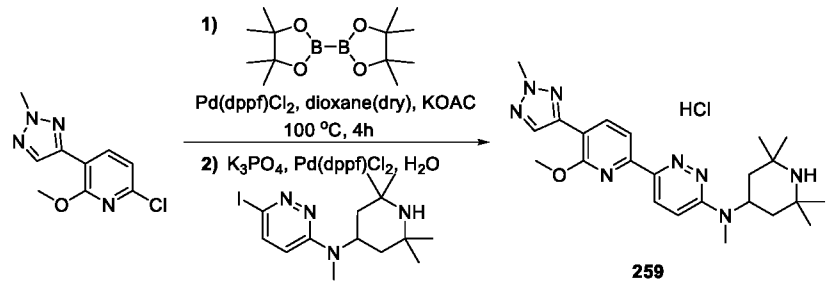


B135 247

A solution of 6-methoxy-5-(1-methylpyrazol-4-yl)pyridin-2-ylboronic acid (80 mg, 0.343 mmol, 1.00 equiv), 6-iodo-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine (128 mg, 0.343 mmol, 1.0 equiv), $Pd(dtbpf)Cl_2$ (22 mg, 0.034 mmol, 0.1 equiv), and (phosphoperoxy)potassium; dipotassium (219 mg, 1.029 mmol, 3.0 equiv) in dioxane (1.5 mL) and water (0.3 mL) was stirred for 16 h at 90 °C under nitrogen atmosphere, then concentrated under vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-10%), followed by Prep-HPLC (Condition 8, Gradient 2) to afford 6-[6-methoxy-5-(1-methylpyrazol-4-yl) pyridin-2-yl]-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine (77.1 mg, 51.56%) as a solid. **LCMS** (ES, m/z): 436.3 $[M+H]^+$ **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.25 – 8.19 (m, 2H), 8.13 (d, J = 7.8 Hz, 1H), 8.01 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 9.7 Hz, 1H), 5.14 (Brs, 1H), 4.10 (s, 3H), 3.91 (s, 3H), 2.96 (s, 3H), 1.53 (dd, J = 12.1, 3.6 Hz, 2H), 1.44 (t, J = 12.0 Hz, 2H), 1.26 (s, 6H), 1.10 (s, 6H).

Example 15: Synthesis of Compound 259

Synthesis of Compound 259



B131 259

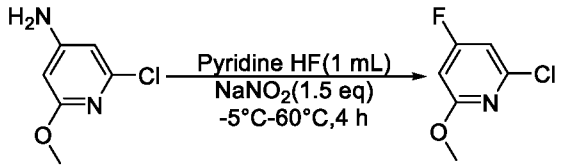
A mixture of 6-chloro-2-methoxy-3-(2-methyl-1,2,3-triazol-4-yl)pyridine (85 mg, 0.378 mmol, 1.00 equiv), 4,4,5-trimethyl-2-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (102 mg, 0.454 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (43 mg, 0.038 mmol, 0.1 equiv) and KOAc (111 mg, 1.134 mmol, 3 equiv) in dioxane (1 mL) was stirred for 4 h at 80 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature. To the reaction mixture was

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added 6-iodo-N-methyl-N-(2,2,6,6-tetramethyl piperidin-4-yl)pyridazin-3-amine (141 mg, 0.376 mmol, 1.1 equiv), K_3PO_4 (315 mg, 1.485 mmol, 3 equiv), and $Pd(dppf)Cl_2$ (36 mg, 0.050 mmol, 0.1 equiv) in water (0.6 mL). The reaction mixture was stirred for an additional 2 h at 80 °C under nitrogen atmosphere, then concentrated under vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-10%), followed by Prep-HPLC (Condition 9, Gradient 1) to afford 6-[6-methoxy-5-(2-methyl-1,2,3- triazol-4-yl)pyridin-2-yl]-N-methyl-N-(2,2,6-trimethylpiperidin-4-yl)pyridazin-3-amine (50 mg, 46.15%) as a solid. **LCMS** (ES, *m/z*):437 $[M+H]^+$. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 9.30 (d, J = 12.0 Hz, 1H), 8.46-8.39 (m, 3H), 8.35 (s, 1H), 8.19 (s, 1H), 7.61 (s, 1H), 5.15 (s, 1H), 4.31 (s, 3H), 4.08 (s, 3H), 3.05 (s, 3H), 2.07 (d, J = 12.5 Hz, 2H), 1.81 (s, 2H), 1.56 (s, 12H).

Example 16: Synthesis of Compound 268

Synthesis of Intermediate B136

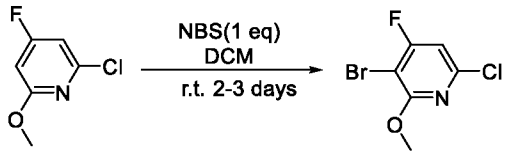


B136

To a fluoride bottle was added 2-chloro-6-methoxypyridin-4-amine (1.5 g, 9.458 mmol, 1.00 equiv) and HF-Pyridine (15 mL, 166.488 mmol, 17.60 equiv) at room temperature. The reaction mixture was stirred for 0.5 h at -5 °C. To the reaction mixture was added $NaNO_2$ (0.98 g, 14.187 mmol, 1.5 equiv) at -5 °C under nitrogen. The resulting mixture was stirred for 2 h at -5 °C, then for 1.5 h at 60 °C. The reaction mixture was used in the next step without further purification

LCMS (ES, *m/z*): 162 $[M+H]^+$

Synthesis of Intermediate B137



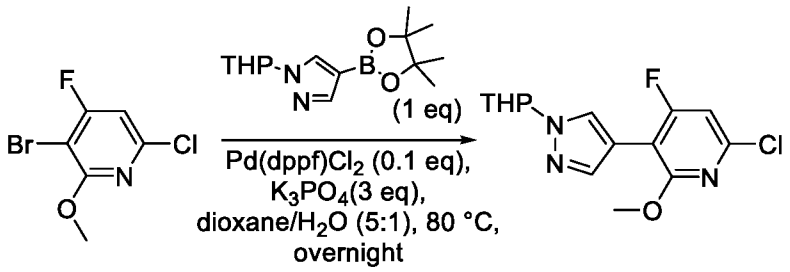
B136 **B137**

To the reaction mixture from the synthesis of B136 was added, NBS (1.65 g, 9.284 mmol, 1 equiv) and DCM (150 mL, 2359.507 mmol, 254.13 equiv). The resulting mixture was stirred for 3 days at room temperature, then basified to pH 7 with $NaHCO_3$, filtered, and the filter cake

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washed with DCM (3 x 20 mL). The filtrate was concentrated under reduced pressure to afford 3-bromo-6-chloro-4-fluoro-2-methoxypyridine (1.1 g, 24.64%) as a solid. **LCMS** (ES, *m/z*): 240 $[M+H]^+$.

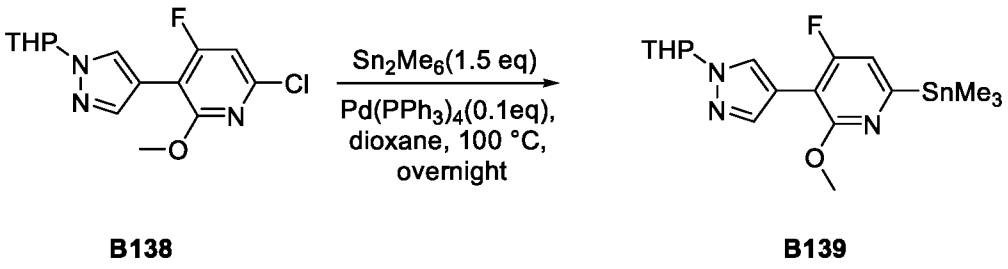
Synthesis of Intermediate B138



B137 **B138**

3-bromo-6-chloro-4-fluoro-2-methoxypyridine (900 mg, 1.946 mmol, 1.00 equiv) and K_3PO_4 (1239.38 mg, 5.838 mmol, 3 equiv) were combined in water (4 mL, 222.033 mmol, 114.08 equiv) at room temperature. The resulting mixture was stirred for overnight at 80 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, then quenched with water (50 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (1x40 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1), followed by Prep-HPLC (Condition 4, Gradient 8) to afford 6-chloro-4-fluoro-2-methoxy-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine potassium (93 mg, 13.62%) as a solid. **LCMS** (ES, *m/z*): 312 $[M+H]^+$.

Synthesis of Intermediate B139



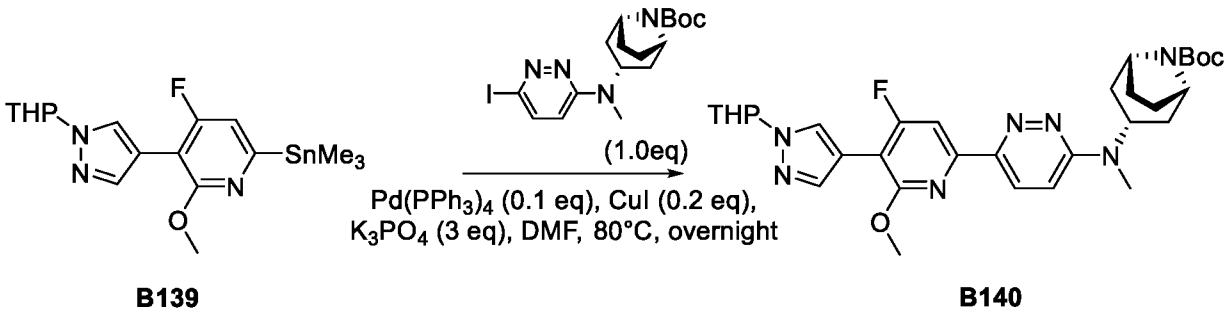
B138 **B139**

6-chloro-4-fluoro-2-methoxy-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine (90 mg, 0.289 mmol, 1.00 equiv), hexamethyldistannane (189.17 mg, 0.578 mmol, 2 equiv), tetrakis(triphenylphosphine)palladium(0) (33.36 mg, 0.029 mmol, 0.1 equiv) and dioxane (10

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mL, 118.041 mmol, 408.87 equiv) were combined at room temperature. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, then quenched by the addition of water/KF (20 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford 4-fluoro-2-methoxy-3-[1-(oxan-2-yl)pyrazol-4-yl]-6-(trimethylstannyl)pyridine (105 mg, 53.71%) as an oil. **LCMS** (ES, *m/z*): 442 $[M+H]^+$.

Synthesis of Intermediate B140

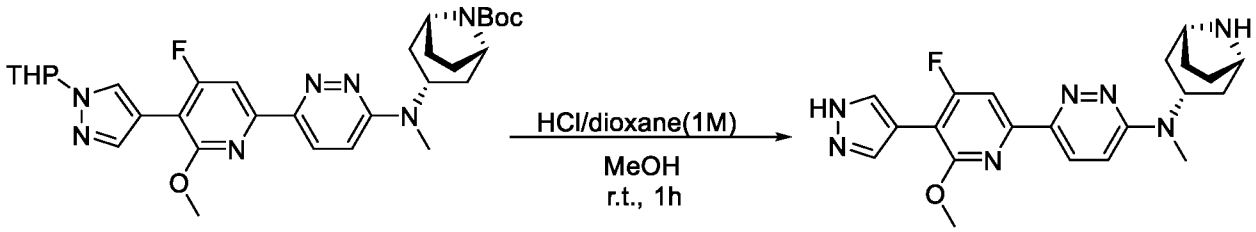


B139 **B140**

4-fluoro-2-methoxy-3-[1-(oxan-2-yl)pyrazol-4-yl]-6-(trimethylstannyl)pyridine (85 mg, 0.193 mmol, 1.00 equiv), tert-butyl (exo)-3-[(6-iodopyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (128.72 mg, 0.289 mmol, 1.5 equiv), (phosphoperoxy)potassium; dipotassium (122.99 mg, 0.579 mmol, 3 equiv), copper(I) iodide (7.36 mg, 0.039 mmol, 0.2 equiv), tetrakis(triphenylphosphine)palladium(0) (22.32 mg, 0.019 mmol, 0.1 equiv) and dimethylformamide (8 mL, 109.447 mmol, 566.68 equiv) were combined at room temperature. The reaction mixture was stirred for overnight at 80 °C under nitrogen atmosphere, then allowed to cool to room temperature. The reaction mixture was quenched with water (20 mL) at room temperature, then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with sub-saturation brine (3x20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford tert-butyl (exo)-3-[(6-{4-fluoro-6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (50 mg, 43.61%) as a solid. **LCMS** (ES, *m/z*): 594 $[M+H]^+$

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Synthesis of Compound 268

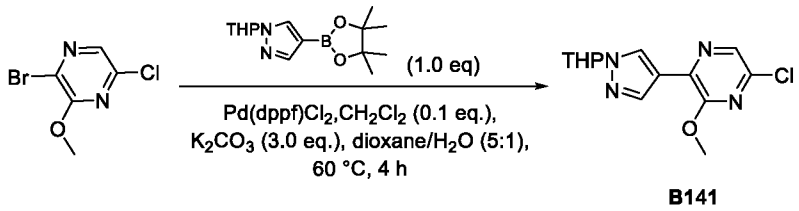


B140 **286**

A mixture of tert-butyl (exo)-3-[(6-{4-fluoro-6-methoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.084 mmol, 1.00 equiv), HCl (gas) in 1,4-dioxane (2 mL) and MeOH (2 mL, 49.398 mmol, 586.55 equiv) was stirred for 1 h at room temperature, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 4, Gradient 7) to afford (exo)-N-{6-[4-fluoro-6-methoxy-5-(1H-pyrazol-4-yl)pyridin-2-yl]pyridazin-3-yl}-N-methyl-8-azabicyclo[3.2.1]octan-3-amine (9.3 mg, 26.46%) as a solid. **LCMS** (ES, *m/z*): 410 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 8.19 (d, *J* = 9.7 Hz, 1H), 8.13 (s, 2H), 7.87 (d, *J* = 11.6 Hz, 1H), 7.18 (d, *J* = 9.7 Hz, 1H), 5.12 (s, 1H), 4.12 (s, 3H), 3.51 (s, 2H), 2.93 (s, 3H), 1.78 (d, *J* = 23.8 Hz, 6H), 1.59 – 1.51 (m, 2H).

Example 17: Synthesis of Compound 260

Synthesis of Intermediate B141



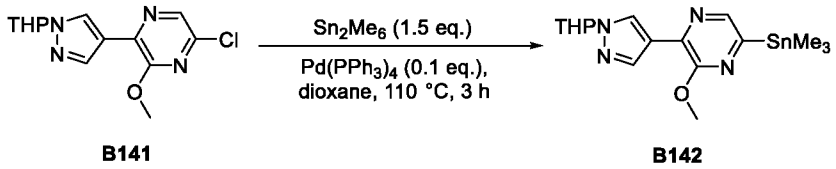
B141

To a solution of 2-bromo-5-chloro-3-methoxypyrazine (1.00 g, 4.47 mmol, 1.00 equiv) and 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazole (1.24 g, 4.47 mmol, 1.00 equiv) in dioxane (20 mL) and H_2O (4 mL) was added K_2CO_3 (1.86 g, 13.42 mmol, 3.00 equiv) and Pd(dppf)Cl_2.CH_2Cl_2 (0.36 g, 0.45 mmol, 0.10 equiv). After stirring overnight at 60 °C under a nitrogen atmosphere, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC/silica gel column chromatography, eluted with

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PE/EA (1:1) to afford 5-chloro-3-methoxy-2-[1-(oxan-2-yl) pyrazol-4-yl] pyrazine (1.05 g, 74.83%) as a solid. **LCMS** (ES, *m/z*):295 [M+H] $^+$

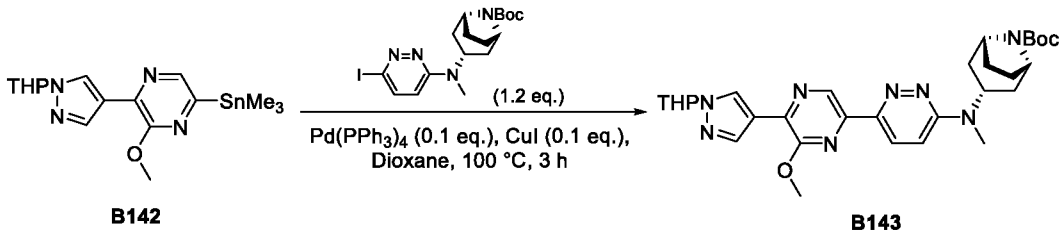
Synthesis of Intermediate B142



B141 **B142**

A mixture of 5-chloro-3-methoxy-2-[1-(oxan-2-yl) pyrazol-4-yl] pyrazine (200.00 mg, 0.68 mmol, 1.00 equiv), Sn_2Me_6 (333.48 mg, 1.02 mmol, 1.50 equiv) and $Pd(PPh_3)_4$ (78.41 mg, 0.07 mmol, 0.10 equiv) in dioxane (4 mL) was stirred overnight at 100 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, then quenched by the addition of 10% KF (aq.) at room temperature. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford 3-methoxy-2-[1-(oxan-2-yl) pyrazol-4-yl]-5-(trimethylstannyl) pyrazine (229.0 mg, 79.7%) as an oil. **LCMS** (ES, *m/z*):425 [M+H] $^+$

Synthesis of Intermediate B143



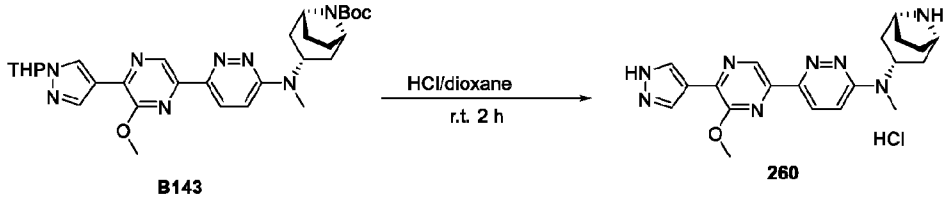
B142 **B143**

A mixture of 3-methoxy-2-[1-(oxan-2-yl) pyrazol-4-yl]-5-(trimethylstannyl) pyrazine (50.00 mg, 0.12 mmol, 1.00 equiv), tert-butyl (1R,3R,5S)-3-[(6-iodopyridazin-3-yl) (methyl)amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (63.01 mg, 0.142 mmol, 1.20 equiv), $Pd(PPh_3)_4$ (13.66 mg, 0.012 mmol, 0.10 equiv) and CuI (2.25 mg, 0.012 mmol, 0.10 equiv) in dioxane (1 mL) was stirred overnight at 60 °C under nitrogen atmosphere, then concentrated in vacuo to give a reisude. The residue was purified by reverse flash chromatography (Column, C18 silica gel; Mobile Phase, acetonitrile in water; Gradient 20% to 70% in 20 min; detector, UV 254 nm) to afford tert-butyl (1R,3R,5S)-3-[(6-{6-methoxy-5-[1-(oxan-2-yl) pyrazol-4-yl] pyrazin-2-yl}

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pyridazin-3-yl) (methyl)amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (15 mg, 22.0%) as a solid. **LCMS** (ES, *m/z*):577 $[M+H]^+$.

Synthesis of Compound 260

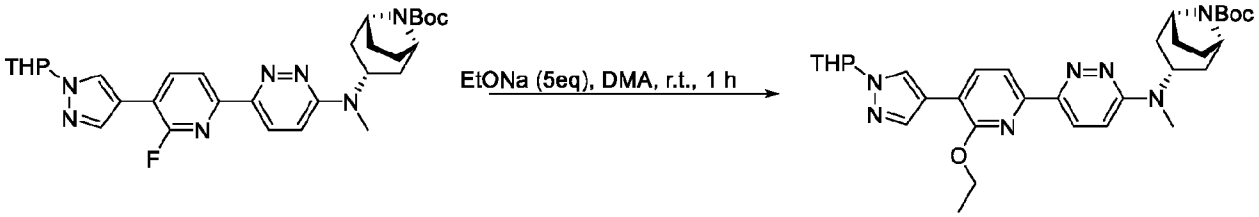


B143 260

A mixture of tert-butyl (1R,3R,5S)-3-[(6-{6-methoxy-5-[1-(oxan-2-yl) pyrazol-4-yl] pyrazin-2-yl} pyridazin-3-yl) (methyl)amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (50.00 mg, 0.087 mmol, 1.00 equiv) and HCl (gas)in 1,4-dioxane (0.5 mL) was stirred for 2 h at room temperature, then concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Condition 10, Gradient 1) to afford (1R,3R,5S)-N-{6-[6-methoxy-5-(1H-pyrazol-4-yl) pyrazin-2-yl] pyridazin-3-yl}-N-methyl-8-azabicyclo [3.2.1] octan-3-amine hydrochloride (8.7 mg, 25.5%) as a solid. **LCMS** (ES, *m/z*):393 $[M+H]^+$. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 9.00 (d, J = 1.8 Hz, 1H), 8.43 (d, J = 9.7 Hz, 1H), 8.35 (s, 2H), 7.84 (d, J = 10.5 Hz, 1H), 4.89 (s, 1H), 4.17 (s, 3H), 4.11 (d, J = 4.3 Hz, 2H), 3.14 – 3.03 (m, 3H), 2.27 (d, J = 10.9 Hz, 2H), 2.18 – 1.97 (m, 4H), 1.91 – 1.78 (m, 2H).

Example 18: Synthesis of Compound 261

Synthesis of Intermediate B144



B144

A mixture of tert-butyl (1R,3R,5S)-3-[(6-{6-fluoro-5-[1-(oxan-2-yl)pyrazol-4-yl] pyridin-2-yl}pyridazin-3-yl) (methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.106 mmol, 1.00 equiv) and EtONa (36.22 mg, 0.530 mmol, 5 equiv) in DMA (2 mL) was stirred for 1 h at room temperature. The resulting mixture was diluted with water (5 mL), and a precipitate formed. The solid was collected by filtration and washed with water (3x2 mL) to afford tert-butyl

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(1R,3R,5S)-3-[(6-{6-ethoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl) (methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (46 mg, 58.62%) as a solid. **LCMS** (ES, *m/z*): 590[M+H$^+$].

Synthesis of Compound 261

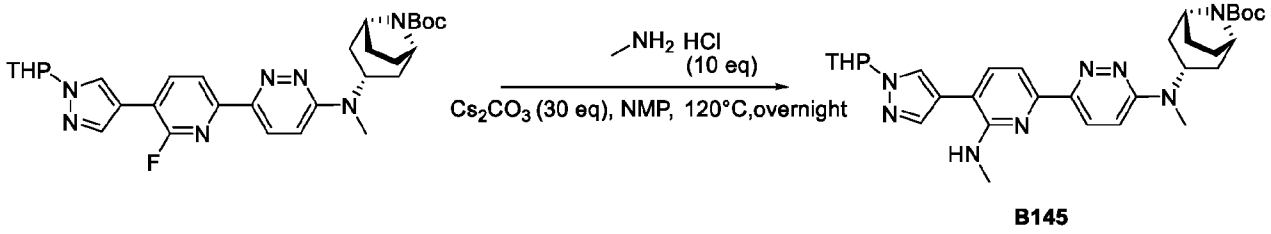


B144 261

A solution of tert-butyl (1R,3R,5S)-3-[(6-{6-ethoxy-5-[1-(oxan-2-yl)pyrazol-4-yl] pyridin-2-yl}pyridazin-3-yl) (methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (46 mg, 0.078 mmol, 1.00 equiv) in DCM (5 mL) was stirred for 30 min at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Condition 11, Gradient 1) to afford (1R,3R,5S)-N-{6-[6-ethoxy-5-(1H-pyrazol-4-yl) pyridin-2-yl]pyridazin-3-yl}-N-methyl-8-azabicyclo[3.2.1]octan-3-amine (13.6 mg, 41.66%) as a solid. **LCMS** (ES, *m/z*): 406[M+H$^+$]$^+$. **^{1}H-NMR**: (400 MHz, DMSO-d_6): δ 13.03 (s, 1H), 8.17 (ddd, *J* = 9.8, 5.5, 3.6 Hz, 4H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.20 – 7.13 (m, 1H), 5.09 (s, 1H), 4.55 (q, *J* = 7.0 Hz, 2H), 3.50 (s, 2H), 2.92 (s, 3H), 1.84 – 1.69 (m, 6H), 1.57 – 1.50 (m, 2H), 1.48 (t, *J* = 7.0 Hz, 3H).

Example 19: Synthesis of Compound 283

Synthesis of Intermediate B145



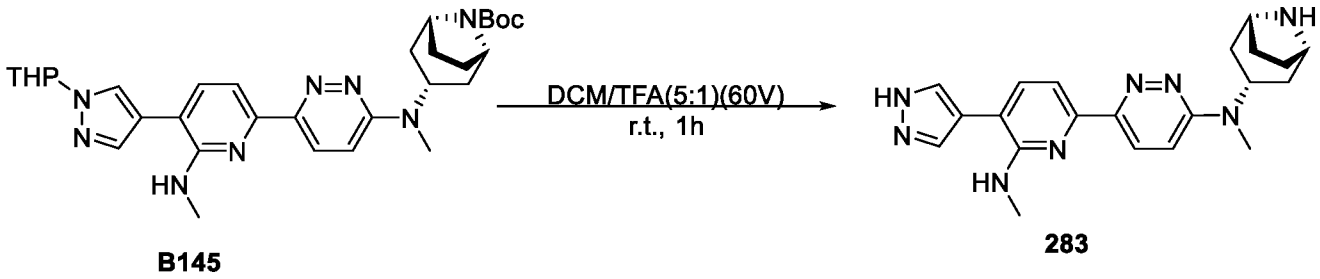
B145

A mixture of tert-butyl (1R,3R,5S)-3-[(6-{6-fluoro-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl) (methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.177 mmol, 1.00 equiv) and methanamine, hydrochloride (119.78 mg, 1.770 mmol, 10 equiv) and Cs_2CO_3 (1734.07 mg, 5.310 mmol, 30 equiv) in NMP (5 mL, 51.851 mmol, 292.27

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equiv) was stirred for overnight at 120 °C under nitrogen atmosphere. The reaction mixture was diluted with water (15 mL) and a precipitate formed. The solid was collected by filtration and washed with water (3x3 mL) to afford tert-butyl (1R,3R,5S)-3-[methyl({6-[6-(methylamino)-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl] pyridazin-3-yl})amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (80 mg, 62.77%) as a solid. **LCMS** (ES, *m/z*): 575[M+H$^+$].

Synthesis of Compound 283

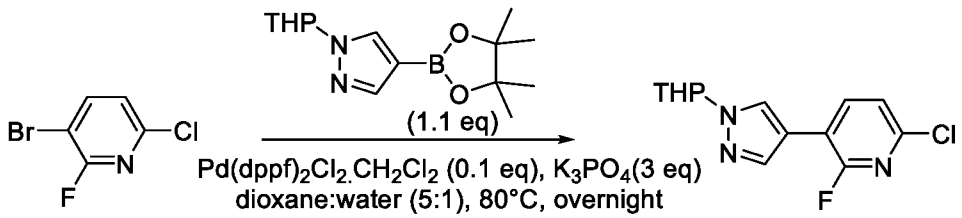


B145 **283**

A solution of tert-butyl (1R,3R,5S)-3-[methyl({6-[6-(methylamino)-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl] pyridazin-3-yl})amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (80 mg) in DCM (0.8 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Condition 11, Gradient 2) to afford (1R,3R,5S)-N-methyl-N-{6-[6-(methylamino)-5-(1H-pyrazol -4-yl)pyridin-2-yl]pyridazin-3-yl}-8-azabicyclo[3.2.1]octan-3-amine (16.5 mg, 29.46%) as a solid. **LCMS** (ES, *m/z*): 391[M+H$^+$]$^+$. **^{1}H-NMR**: (400 MHz, DMSO-*d6*, *ppm*): δ 13.07 (s, 1H), 8.21 (d, *J* = 9.5 Hz, 1H), 7.94 (s, 2H), 7.67 – 7.51 (m, 2H), 7.15 (d, *J* = 9.6 Hz, 1H), 5.90 (q, *J* = 4.7 Hz, 1H), 5.08 (s, 1H), 3.51 (s, 2H), 3.06 – 2.81 (m, 6H), 2.02 – 1.63 (m, 6H), 1.53 (d, *J* = 14.0 Hz, 2H).

Example 20: Synthesis of Compound 249

Synthesis of Intermediate B146

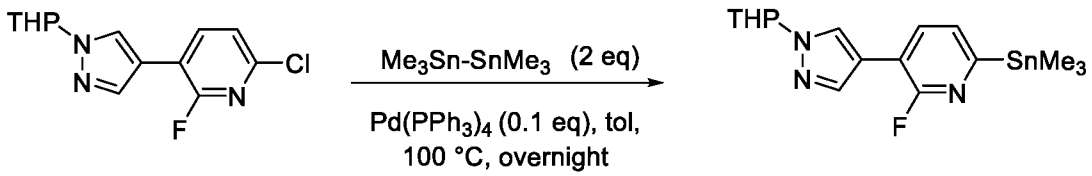


B146

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To a stirred mixture of 3-bromo-6-chloro-2-fluoropyridine (500 mg, 2.376 mmol, 1.00 equiv) and 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (727.03 mg, 2.614 mmol, 1.1 equiv) in dioxane (10 mL) was added K_3PO_4 (1513.09 mg, 7.128 mmol, 3 equiv)(in 2 mL water) dropwise at room temperature under nitrogen atmosphere. The reaction mixture was stirred overnight at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL), then extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford 6-chloro-2-fluoro-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine (600 mg) as an oil. **LCMS** (ES, *m/z*): 282[M+H$^+$].

Synthesis of Intermediate B147

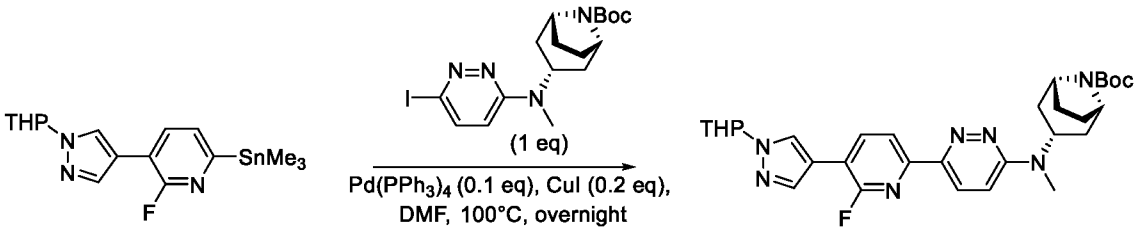


B146 **B147**

A mixture of 6-chloro-2-fluoro-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine (600 mg, 2.130 mmol, 1.00 equiv) and hexamethyldistannane (1395.56 mg, 4.260 mmol, 2 equiv) in dioxane (12 mL) was stirred overnight at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with KF (aq, 50 mL), then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by neutral Al_2O_3 column chromatography, eluted with PE/EA (10:1) to afford 2-fluoro-3-[1-(oxan-2-yl)pyrazol-4-yl]-6-(trimethylstannyl)pyridine (198 mg) as an oil. **LCMS** (ES, *m/z*): 412[M+H$^+$].

Synthesis of Intermediate B148

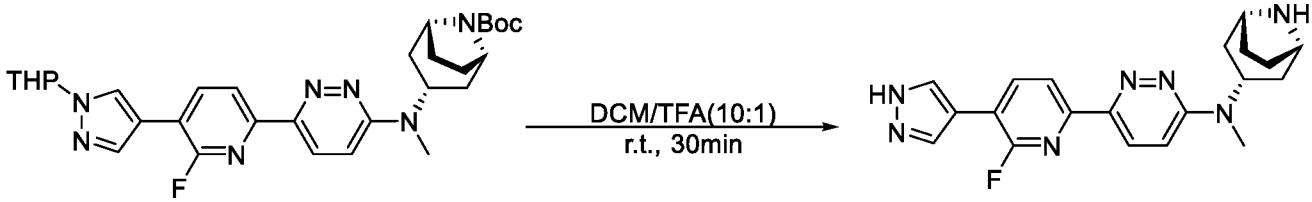
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B147 **B148**

A mixture of 2-fluoro-3-[1-(oxan-2-yl)pyrazol-4-yl]-6-(trimethylstannyl)pyridine (178 mg, 0.434 mmol, 1.00 equiv), tert-butyl (1R,3R,5S)-3-[(6-iodopyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (21.67 mg, 0.049 mmol, 1 equiv), $Pd(PPh_3)_4$ (50.16 mg, 0.043 mmol, 0.1 equiv), and CuI (16.53 mg, 0.087 mmol, 0.2 equiv) in DMF (4 mL, 230.007 mmol, 529.90 equiv) was stirred for overnight at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (30 mL), then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:8) to afford tert-butyl (1R,3R,5S)-3-[(6-{6-fluoro-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl} pyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (106 mg) as a solid. **LCMS** (ES, *m/z*): 564[$M+H^+$].

Synthesis of Compound 249



B148 **249**

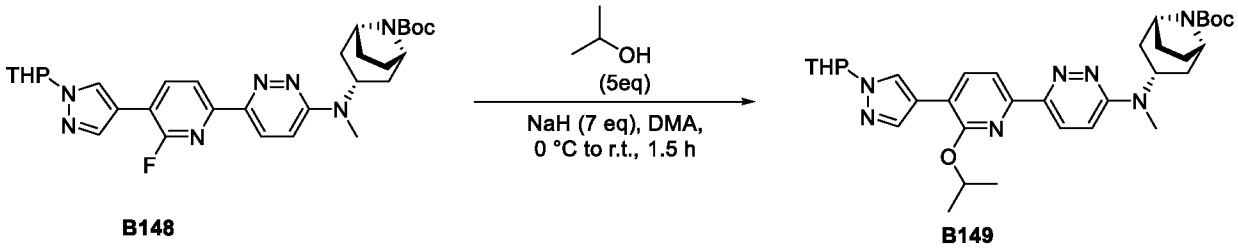
A mixture of tert-butyl (1R,3R,5S)-3-[(6-{6-fluoro-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl) (methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (106 mg, 1.00 equiv) in DCM (90 mL)/TFA (10 mL) was stirred for 0.5 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 10, Gradient 2, Gradient 3) to afford (1R,3R,5S)-N-{6-[6-fluoro-5-(1H-pyrazol-4-yl)pyridin-2-yl]pyridazin-3-yl}-N-methyl-8-

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azabicyclo[3.2.1]octan-3-amine hydrochloride (5.1 mg, HCl salt) as a solid. **LCMS** (ES, *m/z*): 380[M+H$^+$]$^+$. **^{1}H-NMR**: (400 MHz, 353K, DMSO-*d6*, *ppm*): δ 9.36 (s, 1H), 8.94 (s, 1H), 8.38 (ddd, *J* = 9.8, 7.8, 1.8 Hz, 1H), 8.30 (dt, *J* = 8.0, 2.1 Hz, 1H), 8.19 – 8.11 (m, 3H), 7.36 (dd, *J* = 9.8, 1.8 Hz, 1H), 5.19 (dt, *J* = 12.1, 6.3 Hz, 1H), 4.12 (s, 2H), 3.07 (d, *J* = 1.7 Hz, 3H), 2.36 (t, *J* = 12.3 Hz, 2H), 2.10 (s, 4H), 1.88 – 1.76 (m, 2H).

Example 21: Synthesis of Compound 284

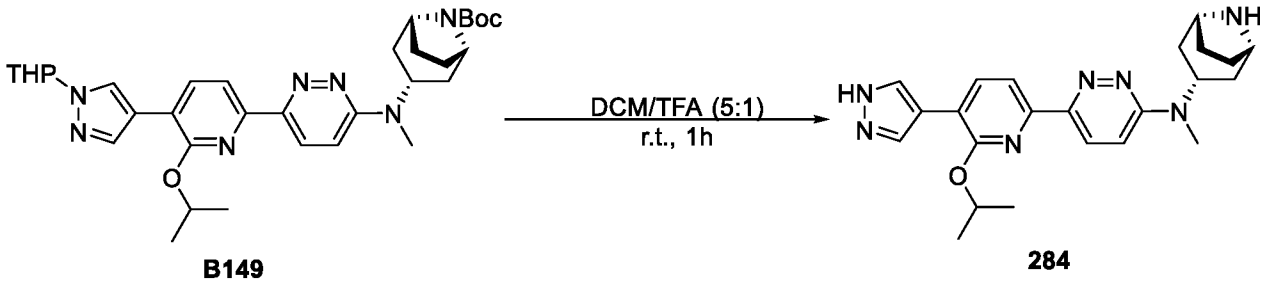
Synthesis of Intermediate B149



B148 **B149**

To a stirred solution of isopropyl alcohol (31.98 mg, 0.530 mmol, 5 equiv) in DMA (3 mL) was added NaH (17.88 mg, 0.742 mmol, 7 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0 °C under nitrogen atmosphere. To the reaction mixture was added tert-butyl (1R,3R,5S)-3-[(6-{6-fluoro-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.106 mmol, 1.00 equiv) at 0 °C, and the resulting mixture was stirred for an additional 1 h at room temperature. The resulting mixture was diluted with water (10 mL) to form a precipitate. The solid was collected by filtration and washed with water (3x3 mL) to afford tert-butyl (1R,3R,5S)-3-[(6-{6-isopropoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (60 mg, 70.02%). **LCMS** (ES, *m/z*): 604[M+H$^+$].

Synthesis of Compound 284



B149 **284**

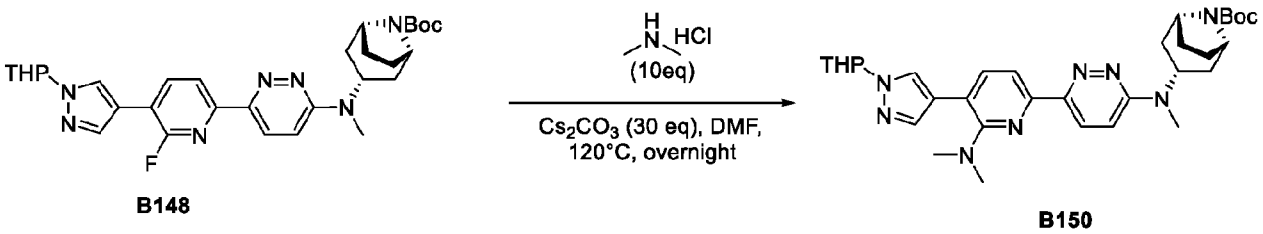
A mixture of tert-butyl (1R,3R,5S)-3-[(6-{6-isopropoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl) (methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (60 mg) and DCM

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(3 mL)/TFA (0.6 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Condition 4, Gradient 9) to afford (1R,3R,5S)-N-{6-[6-isopropoxy-5-(1H-pyrazol-4-yl)pyridin-2-yl]pyridazin-3-yl}-N-methyl-8-azabicyclo[3.2.1]octan-3-amine (8.1 mg) as a solid. **LCMS** (ES, *m/z*): 420[M+H$^+$]$^+$. **^{1}H-NMR**: (400 MHz, DMSO-*d*$_6$): δ 13.01 (s, 1H), 8.29 – 8.02 (m, 4H), 8.02 – 7.84 (m, 1H), 7.18 (d, *J* = 9.8 Hz, 1H), 5.58 – 5.41 (m, 1H), 5.07 (s, 1H), 3.49 (s, 2H), 2.93 (s, 3H), 1.77 (d, *J* = 20.5 Hz, 6H), 1.61 – 1.49 (m, 2H), 1.45 (d, *J* = 5.9 Hz, 6H).

Example 22: Synthesis of Compound 285

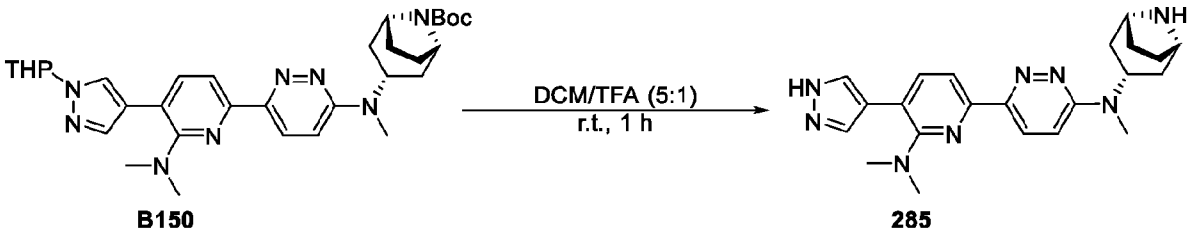
Synthesis of Intermediate B150



B148 **B150**

A mixture of tert-butyl (1R,3R,5S)-3-[(6-{6-fluoro-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl) (methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.177 mmol, 1.00 equiv), dimethylamine hydrochloride (144.66 mg, 1.770 mmol, 10 equiv), and Cs_2CO_3 (1734.07 mg, 5.310 mmol, 30 equiv) in DMF (5 mL, 51.851 mmol, 292.27 equiv) was stirred overnight at 120 °C under nitrogen atmosphere. The resulting mixture was diluted with water (15 mL) and a precipitate formed. The solid was collected by filtration and washed with water (3 x 3 mL) to afford tert-butyl (1R,3R,5S)-3-({6-[6-(dimethylamino)-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl] pyridazin-3-yl}(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (110 mg, 87.41%). **LCMS** (ES, *m/z*): 589[M+H]$^+$.

Synthesis of Compound 285



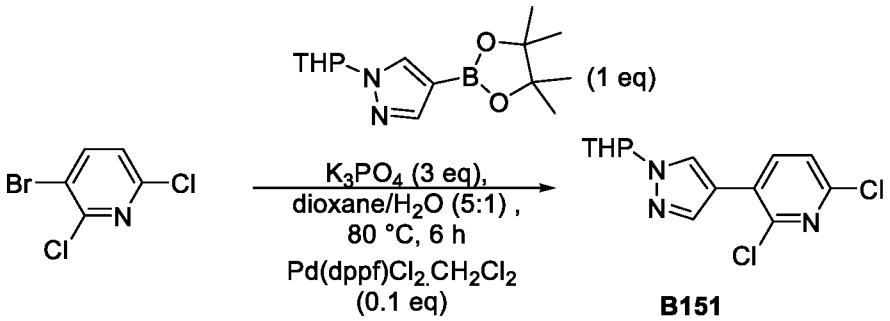
B150 **285**

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A solution of tert-butyl (1R,3R,5S)-3-({6-[6-(dimethylamino)-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl] pyridazin-3-yl}(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (110 mg) and DCM (5.5 mL)/TFA (1.1 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Condition 11, Gradient 3) to afford (1R,3R,5S)-N-{6-[6-(dimethylamino) -5-(1H-pyrazol-4-yl)pyridin-2-yl]pyridazin-3-yl}-N-methyl-8-azabicyclo[3.2.1]octan-3-amine (17.2 mg) as a solid. **LCMS** (ES, *m/z*): 405[M+H$^+$]. **^{1}H-NMR**: (400 MHz, DMSO-*d6*, *ppm*): δ 13.00 (s, 1H), 8.19 (d, *J* = 9.6 Hz, 1H), 8.02 (s, 2H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 9.6 Hz, 1H), 5.08 (tt, *J* = 11.8, 5.1 Hz, 1H), 3.50 (s, 2H), 2.92 (s, 3H), 2.77 (s, 6H), 1.92 – 1.64 (m, 6H), 1.54 (dt, *J* = 12.2, 4.2 Hz, 2H).

Example 23: Synthesis of Compound 250

Synthesis of Intermediate B151

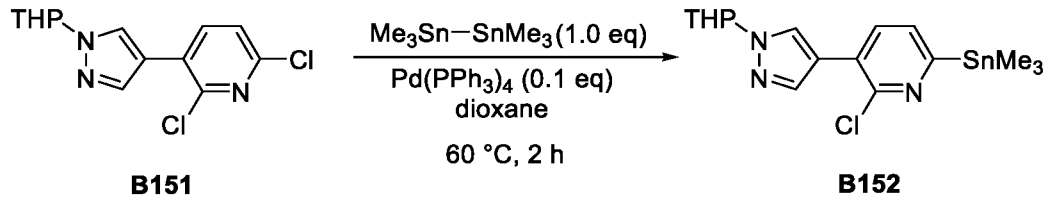


B151

3-bromo-2,6-dichloropyridine (1 g, 4.408 mmol, 1.00 equiv), 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.23 g, 4.408 mmol, 1 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.36 g, 0.441 mmol, 0.1 equiv), dioxane (20 mL, 236.082 mmol, 53.56 equiv) and (phosphoperoxy)potassium; dipotassium (2.81 g, 13.224 mmol, 3 equiv) were combined in water (4 mL, 222.037 mmol, 50.38 equiv) at room temperature. The resulting mixture was stirred for 4 h at 80 °C under nitrogen atmosphere, then quenched with water (20 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine (1x30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (4:1) to afford 2,6-dichloro-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine (1.095 g, 83.32%) as an oil. **LCMS** (ES, *m/z*): 298 [M+H]$^+$.

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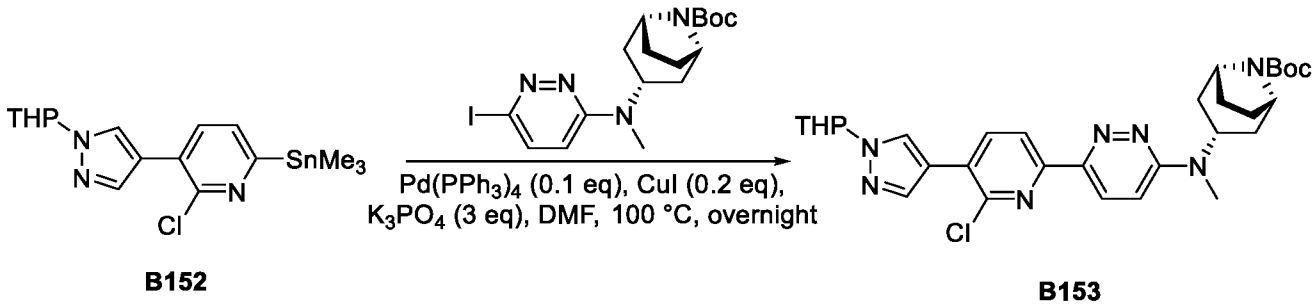
Synthesis of Intermediate B152



B151 **B152**

2,6-dichloro-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine (2 g, 6.708 mmol, 1.00 equiv), hexamethyldistannane (2.20 g, 6.708 mmol, 1 equiv), Pd(dppf)Cl_2.CH_2Cl_2 (546.41 mg, 0.671 mmol, 0.1 equiv) and dioxane (25 mL, 295.102 mmol, 44.00 equiv) were combined at room temperature. The resulting mixture was stirred for 3 h at 100 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, then quenched with water/KF (50 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by neutral alumina column chromatography, eluted with PE/EA (5:1) to afford 2-chloro-3-[1-(oxan-2-yl)pyrazol-4-yl]-6-(trimethylstannyl)pyridine (1.1 g, 0.35%) as an oil. **LCMS** (ES, *m/z*): 427 $[M+H]^+$

Synthesis of Intermediate B153



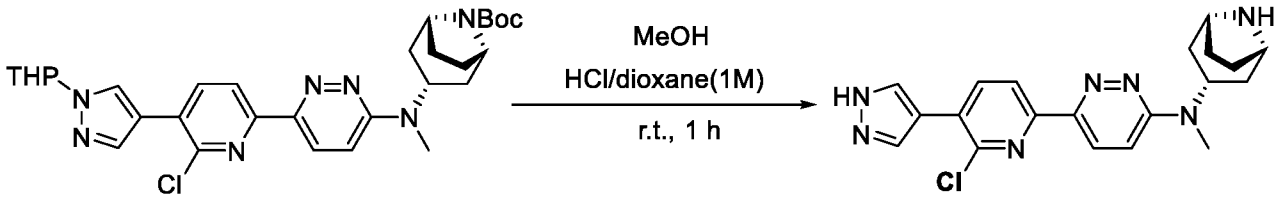
B152 **B153**

2-chloro-3-[1-(oxan-2-yl)pyrazol-4-yl]-6-(trimethylstannyl)pyridine (260 mg, 0.518 mmol, 1.00 equiv), tert-butyl (exo)-3-[(6-iodopyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (230.22 mg, 0.518 mmol, 1 equiv), copper(I) iodide (19.74 mg, 0.104 mmol, 0.2 equiv), tetrakis(triphenylphosphine)palladium(0) (59.88 mg, 0.052 mmol, 0.1 equiv), K_3PO_4 (329.95 mg, 1.554 mmol, 3 equiv), and dimethylformamide (757.46 mg, 10.360 mmol, 20 equiv) were combined at room temperature. The resulting mixture was stirred overnight at 60 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, then quenched with

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water (20 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with sub-saturation brine (3x20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1), followed by Prep-HPLC (Condition 4, Gradient 10) to afford tert-butyl (1R,3R,5S)-3-[(6-{6-chloro-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (40 mg, 13.31%) as a solid. **LCMS** (ES, *m/z*): 580 $[M+H]^+$.

Synthesis of Compound 250

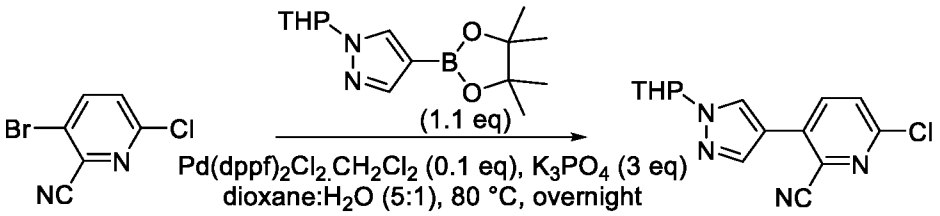


B153 **250**

A mixture of tert-butyl (exo)-3-[(6-{6-chloro-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (20 mg, 0.034 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (2 mL, 65.824 mmol, 1909.32 equiv) in methanol (2 mL, 49.398 mmol, 1432.86 equiv) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 11, Gradient 4) to afford (exo)-N-{6-[6-chloro-5-(1H-pyrazol-4-yl)pyridin-2-yl]pyridazin-3-yl}-N-methyl-8-azabicyclo[3.2.1]octan-3-amine (8.8 mg, 64.37%) as a solid. **LCMS** (ES, *m/z*): 396 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.23 (s, 1H), 8.37 (d, J = 8.1 Hz, 1H), 8.25 – 8.18 (m, 3H), 8.10 (d, J = 9.6 Hz, 1H), 7.17 (d, J = 9.7 Hz, 1H), 5.13 (s, 1H), 3.50 (s, 2H), 2.94 (s, 3H), 2.25 (s, 1H), 1.85 – 1.70 (m, 6H), 1.58 – 1.49 (m, 2H).

Example 24: Synthesis of Compound 262

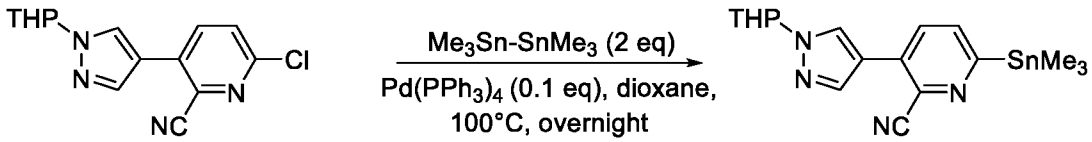
Synthesis of Intermediate B154



B154

To a stirred mixture of 3-bromo-6-chloropyridine-2-carbonitrile (2.5 g, 11.497 mmol, 1.00 equiv), 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (3.52 g, 12.647 mmol, 1.1 equiv), and Pd(dppf)Cl_2 CH_2Cl_2 (0.94 g, 1.150 mmol, 0.1 equiv) in dioxane (50 mL) was added K_3PO_4 (7.32 g, 34.491 mmol, 3 equiv)(in 10 mL water) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 °C under nitrogen atmosphere, then diluted with water (150 mL), and extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford 6-chloro-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine-2-carbonitrile (3 g, 90.37%) as an oil. **LCMS** (ES, *m/z*): 289[M+H]$^+$.

Synthesis of Intermediate B155

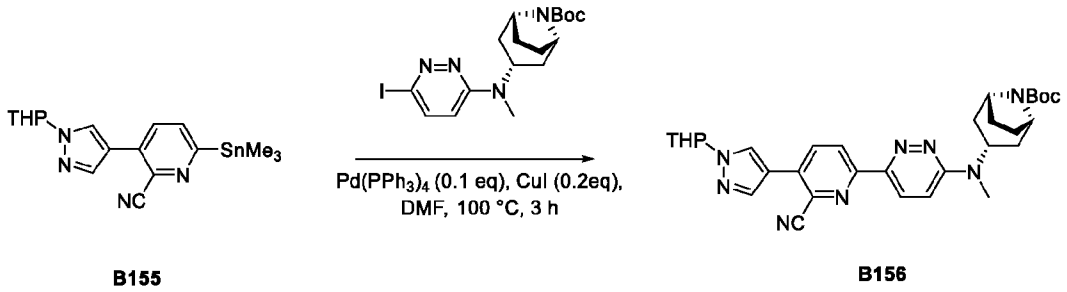


B154 **B155**

A mixture of 6-chloro-3-[1-(oxan-2-yl)pyrazol-4-yl]pyridine-2-carbonitrile (600 mg, 2.078 mmol, 1.00 equiv), Sn_2Bu_6 (2.41 g, 4.156 mmol, 2 equiv), and Pd(PPh_3)$_4$ (240.12 mg, 0.208 mmol, 0.1 equiv) in dioxane (12 mL) was stirred overnight at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL), then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (1x50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by neutral Al_2O_3 column chromatography, eluted with PE/EA

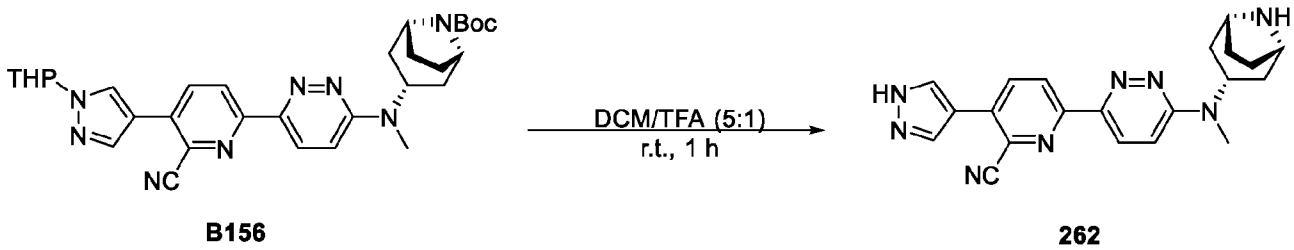
(10:1) to afford 3-[1-(oxan-2-yl)pyrazol-4-yl]-6-(trimethylstannyl)pyridine-2-carbonitrile (500 mg, 57.69%) as a solid. **LCMS** (ES, *m/z*): 419[M+H$^+$];

Synthesis of Intermediate B156



A mixture of 3-[1-(oxan-2-yl)pyrazol-4-yl]-6-(trimethylstannyl)pyridine-2-carbonitrile (200 mg, 0.480 mmol, 1.00 equiv), tert-butyl (1R,3R,5S)-3-[(6-iodopyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (213.05 mg, 0.480 mmol, 1 equiv), $Pd(PPh_3)_4$ (55.41 mg, 0.048 mmol, 0.1 equiv), and CuI (18.26 mg, 0.096 mmol, 0.2 equiv) in DMF (40 mL) was stirred for 3 h at 100 °C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by reverse flash chromatography (Column, C18 silica gel; Mobile Phase, acetonitrile in water (10mmol/L NH_4HCO_3); Gradient: 10% to 95% in 20 min; detector, UV 254 nm) to afford tert-butyl (1R,3R,5S)-3-[(6-{6-cyano-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin -3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (98 mg, 35.81%) as a solid. **LCMS** (ES, *m/z*): 571[M+H]$^+$.

Synthesis of Compound 262



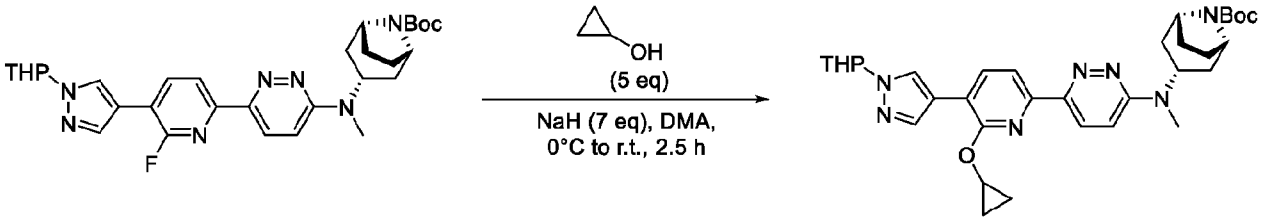
A mixture of tert-butyl (1R,3R,5S)-3-[(6-{6-cyano-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl) (methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (98 mg) and DCM (9 mL)/TFA (1 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 11, Gradient 5) to afford 6-{6-[(1R,3R,5S)-8-

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azabicyclo[3.2.1]octan -3-yl(methyl)amino]pyridazin-3-yl}-3-(1H-pyrazol-4-yl)pyridine-2-carbonitrile (34.7 mg) as a solid. **LCMS** (ES, *m/z*): 387[M+H$^+$].**^{1}H-NMR**: (400 MHz, DMSO-*d6*, *ppm*): δ 13.42 (s, 1H), 8.66 (d, *J* = 8.6 Hz, 1H), 8.35 (d, *J* = 8.6 Hz, 1H), 8.32 (s, 2H), 8.16 (d, *J* = 9.6 Hz, 1H), 7.20 (d, *J* = 9.7 Hz, 1H), 5.16 (s, 1H), 3.54 (s, 2H), 2.95 (s, 3H), 2.05 – 1.62 (m, 6H), 1.62 – 1.45 (m, 2H).

Example 25: Synthesis of Compound 286

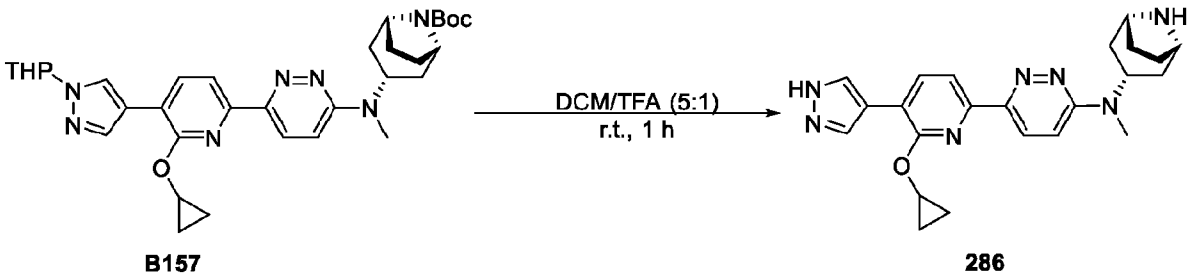
Synthesis of Intermediate B157



B148 **B157**

To a stirred solution of cyclopropanol (41.22 mg, 0.710 mmol, 5 equiv) in DMA (4 mL) was added NaH (23.84 mg, 0.994 mmol, 7 equiv) in portions at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. To the reaction mixture was added tert-butyl (1R,3R,5S)-3-[(6-{6-fluoro-5- [1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.142 mmol, 1.00 equiv) at 0 °C. The resulting mixture was stirred for an additional 2 h at room temperature. A precipitate formed, and the solid was collected by filtration and washed with water (3x3 mL) to afford tert-butyl (1R,3R,5S)-3-[(6-{6-cyclopropoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (80 mg, 74.00%). **LCMS** (ES, *m/z*): 602[M+H]$^+$.

Synthesis of Compound 286



B157 **286**

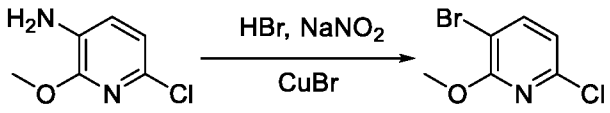
A mixture of tert-butyl (1R,3R,5S)-3-[(6-{6-cyclopropoxy-5-[1-(oxan-2-yl)pyrazol-4-yl]pyridin-2-yl}pyridazin -3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (80 mg) and DCM

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(4 mL)/TFA (0.8 mL) was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Condition 4, Gradient 7) to afford (1R,3R,5S)-N-{6-[6-cyclopropoxy-5- (1H-pyrazol-4-yl)pyridin-2-yl]pyridazin-3-yl}-N-methyl-8-azabicyclo[3.2.1]octan-3-amine (13.8 mg) as a solid. **LCMS** (ES, *m/z*): 418[M+H]$^+$. **^{1}H-NMR**: (400 MHz, DMSO-*d6*, *ppm*): δ 13.02 (s, 1H), 8.23 (d, *J* = 9.6 Hz, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 8.10 (s, 2H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 9.6 Hz, 1H), 5.17 – 5.00 (m, 1H), 4.54 (tt, *J* = 6.3, 3.3 Hz, 1H), 3.50 (s, 2H), 2.93 (s, 3H), 1.91 – 1.65 (m, 6H), 1.61 – 1.44 (m, 2H), 0.85 (dq, *J* = 9.3, 3.1, 2.6 Hz, 4H).

Example 26: Synthesis of Compound 287

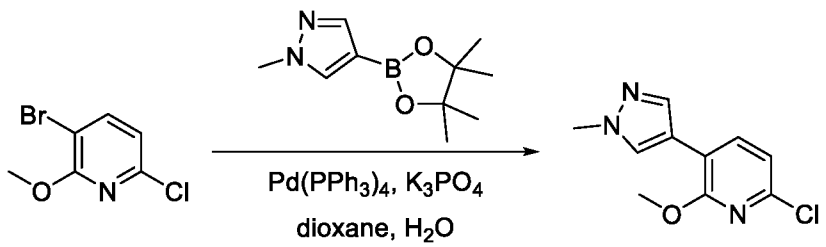
Synthesis of Intermediate B158



B158

To a stirred solution mixture of 6-chloro-2-methoxypyridin-3-amine (10.00 g, 63 mmol, 1 equiv) and 40% HBr in water (100 mL) was added $NaNO_2$ (4.57 g, 66 mmol, 1.05 equiv) in water (20 mL) dropwise at 0-5 °C. The resulting mixture was stirred for 30 min at 0-5 °C. To the reaction mixture was added copper(I) bromide (10.85 g, 75 mmol, 1.2 equiv) in portions. The resulting mixture was stirred for an additional 2 h at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-50%) to afford 3-bromo-6-chloro-2-methoxypyridine (13.00 g, 92.67%) as a solid. **LCMS** (ES, *m/z*): 222 [M+H]$^+$.

Synthesis of Intermediate B159

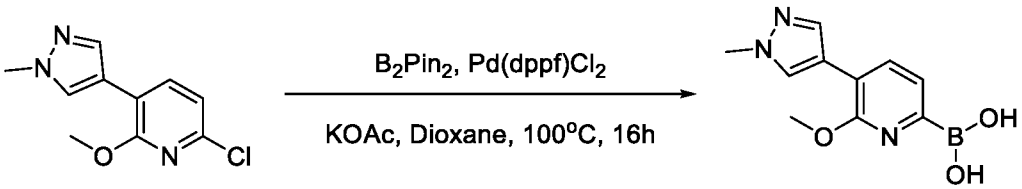


B158 **B159**

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To a mixture of 3-bromo-6-chloro-2-methoxypyridine (2.50 g, 11.237 mmol, 1.00 equiv) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (2.81 g, 13.484 mmol, 1.2 equiv) in dioxane (25 mL) and H_2O (5 mL) was added K_3PO_4 (7.16 g, 33.711 mmol, 3 equiv) and $Pd(PPh_3)_4$ (0.65 g, 0.562 mmol, 0.05 equiv). The reaction mixture was stirred for 2 h at 80 ° C under a nitrogen atmosphere, then concentrated under reduced pressure. The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1), to afford 6-chloro-2-methoxy-3-(1-methylpyrazol-4-yl)pyridine (2.00 g, 79.57%) as a solid. **LCMS** (ES, *m/z*): 224 $[M+H]^+$.

Synthesis of Intermediate B160

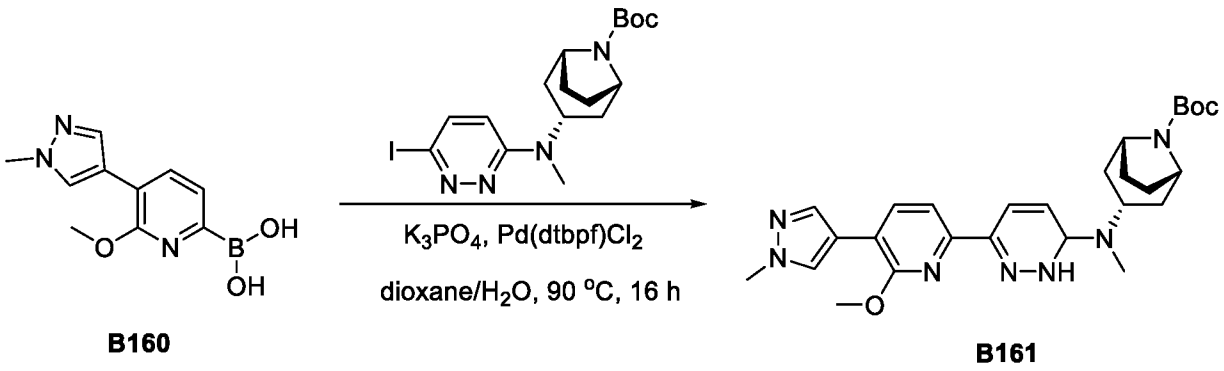


B159 **B160**

A mixture of 6-chloro-2-methoxy-3-(1-methylpyrazol-4-yl)pyridine (700 mg, 3.130 mmol, 1.00 equiv), bis(pinacolato)diboron (1192 mg, 4.695 mmol, 1.5 equiv), potassium acetate (921 mg, 9.390 mmol, 3.0 equiv), and $Pd(dppf)Cl_2$ (229 mg, 0.313 mmol, 0.1 equiv) in dioxane (14 mL) was stirred for 16 h at 100 °C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (0-100%) to afford 6-methoxy-5-(1-methylpyrazol-4-yl)pyridin-2-ylboronic acid (350 mg, 47.99%) as a solid. **LCMS** (ES, *m/z*): 234 $[M+H]^+$.

Synthesis of Intermediate B161

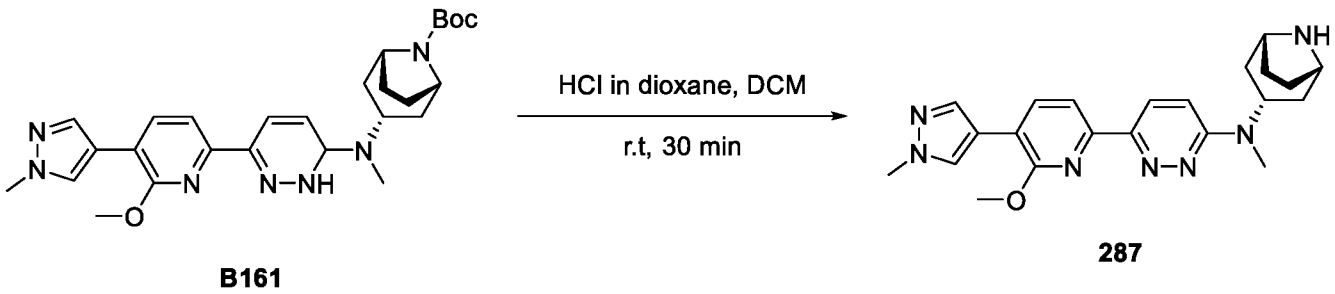
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B160 **B161**

To a stirred mixture of 6-methoxy-5-(1-methylpyrazol-4-yl) pyridin-2-ylboronic acid (100 mg, 0.429 mmol, 1.0 equiv) and tert-butyl 3-[(6-iodopyridazin-3-yl) (methyl)amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (191 mg, 0.429 mmol, 1 equiv) in dioxane (1.0 mL)/H_2O (0.2 mL) was added K_3PO_4 (273 mg, 1.287 mmol, 3.0 equiv) and Pd(dtbpf)Cl_2 (28 mg, 0.043 mmol, 0.1 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 90 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (1:1) to afford tert-butyl 3-({6-[6-methoxy-5-(1-methylpyrazol-4-yl) pyridin-2-yl] pyridazin-3-yl} (methyl)amino)-8-azabicyclo [3.2.1]octane-8-carboxylate (104 mg, 47.79%) as a solid. **LCMS** (ES, *m/z*): 508 $[M+H]^+$.

Synthesis of Compound 287



B161 **287**

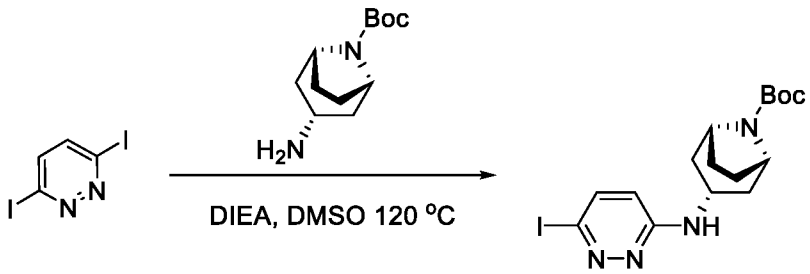
To a stirred solution of tert-butyl (1R,3s,5S)-3-((6-(6-methoxy-5-(1-methyl-1H-pyrazol-4-yl) pyridin-2-yl)-2,3-dihydropyridazin-3-yl) (methyl)amino)-8-azabicyclo [3.2.1] octane-8-carboxylate (104 mg, 1.0 equiv) in DCM (1.0 mL) was added HCl (gas) in 1,4-dioxane (1.0 mL, 4M) dropwise at room temperature. The resulting mixture was stirred for 30 min at room temperature, then concentrated under reduced pressure to give a residue. The residue was neutralized to pH 7 with saturated Na_2CO_3 (aq), then purified by Prep-HPLC (Condition 7,

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Gradient 3) to afford (1R,3s,5S)-N-(6-(6-methoxy-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)pyridazin-3-yl)-N-methyl-8-azabicyclo [3.2.1] octan-3-amine (43.4 mg, 52.24%) as a solid. **LCMS** (ES, *m/z*): 406 $[M+H]^+$. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.22-8.12 (m, 3H), 8.02 (s, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.17 (d, J = 9.7 Hz, 1H), 5.19-5.05(m, 1H), 4.09 (s, 3H), 3.90 (s, 3H), 3.65-3.54 (m, 2H), 2.93 (s, 3H), 1.97 -1.75 (m, 6H), 1.68-1.47 (m, 2H).

Example 27: Synthesis of Compound 269

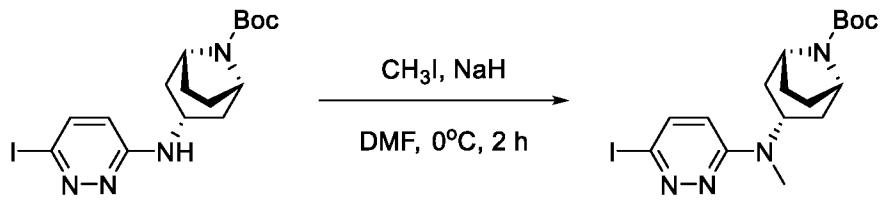
Synthesis of Intermediate B162



B162

A mixture of 3,6-diiodopyridazine (5.00 g, 15 mmol, 1 equiv), tert-butyl (1R,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (4.09 g, 18 mmol, 1.2 equiv), and DIEA (5.84 g, 45 mmol, 3 equiv) in DMSO (50 mL) was stirred overnight at 120 °C. The reaction mixture was cooled to room temperature, then diluted with water (50 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-100%), to afford tert-butyl (1R,5S)-3-[(6-iodopyridazin- 3-yl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (2.7 g, 41.65%) as a solid. **LCMS** (ES, *m/z*): 431 $[M+H]^+$.

Synthesis of Intermediate B163



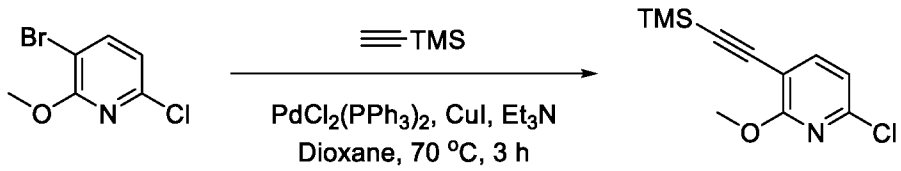
B162 **B163**

To a stirred solution of tert-butyl (1R,3S,5S)-3-[(6-iodopyridazin-3-yl) amino]-8-azabicyclo[3.2.1] octane-8-carboxylate (2.70 g, 6.27 mmol, 1.00 equiv) in DMF (27 mL) was

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added NaH (0.75 g, 18.8 mmol, 3 equiv, 60%) in portions at 0-5 °C . To the reaction mixture was added methyl iodide (1.78 g, 12.55 mmol, 2 equiv) dropwise at 0-5 °C. The resulting mixture was stirred for an additional 2 h at 0-5 °C, then quenched by the addition of water/ice. The resulting mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EtOAc/PE (0-100%), to afford tert-butyl (1R,3S,5S)-3-[(6-iodopyridazin-3-yl) (methyl)amino]-8-azabicyclo[3.2.1] octane-8-carboxylate (2.20 g, 78.91%) as a solid. **LCMS** (ES, *m/z*): 445 $[M+H]^+$.

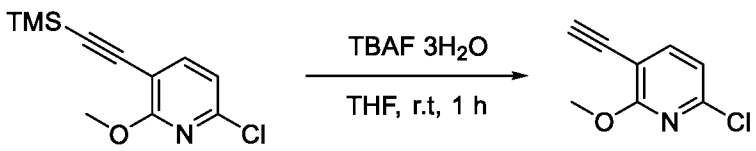
Synthesis of Intermediate B164



B163 **B164**

A solution of 3-bromo-6-chloro-2-methoxypyridine (4.00 g, 17.980 mmol, 1.00 equiv), trimethylsilylacetylene (2.12 g, 21.576 mmol, 1.2 equiv), and triethylamine (5.45 g, 53.940 mmol, 3.0 equiv) in 1,4-dioxane (40 mL) was stirred for 16 h at 70 °C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with EA / PE (1:10) to afford 6-chloro-2-methoxy-3-[2-(trimethylsilyl)ethynyl]pyridine (3.90 g, 90.47%) as an oil. **LCMS** (ES, *m/z*): 240 $[M+H]^+$.

Synthesis of Intermediate B165



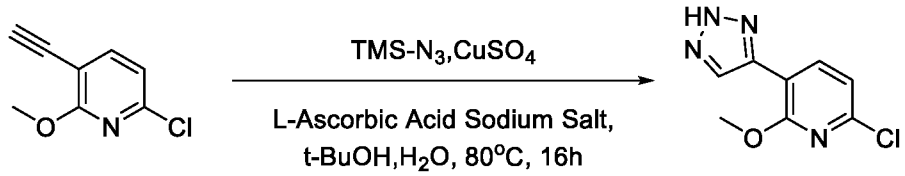
B164 **B165**

To a stirred solution of 6-chloro-2-methoxy-3-[2-(trimethylsilyl)ethynyl]pyridine (3.90 g, 16.266 mmol, 1.00 equiv) in tetrahydrofuran (39 mL) was added TBAF·$3H_2O$ (2.05 g, 6.506 mmol, 0.4 equiv) at room temperature. The reaction mixture was stirred at room temperature for 1 h, then

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diluted with water (100 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (1x100 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EA/PE (0-20%) to afford 6-chloro-3-ethynyl-2-methoxypyridine (2.60 g, 95.38%) as a solid. **LCMS** (ES, *m/z*): 168 $[M+H]^+$.

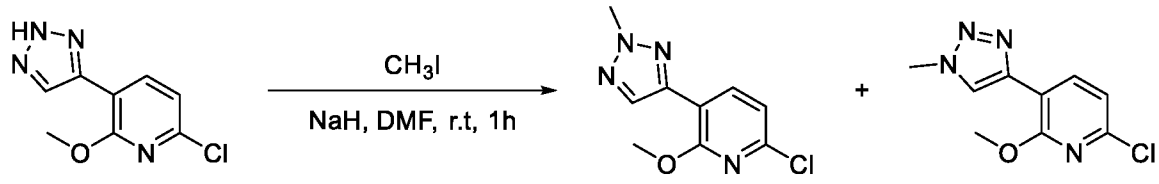
Synthesis of Intermediate B166



B165 **B166**

A mixture of 6-chloro-3-ethynyl-2-methoxypyridine (2.5 g, 14.917 mmol, 1.00 equiv), trimethylsilyl azide (3.44 g, 29.834 mmol, 2.0 equiv), L-Ascorbic Acid Sodium Salt (0.59 g, 2.983 mmol, 0.2 equiv), and dioxo(sulfonylidene)copper (0.24 g, 1.492 mmol, 0.1 equiv) in 2-methyl-2-propanol (50 mL) and water (12.5 mL) was stirred for 16 h at 80 °C under nitrogen atmosphere. The reaction mixture was quenched with water at room temperature, then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EA / PE (1:1) to afford 6-chloro-2-methoxy-3-(2H-1,2,3-triazol-4-yl)pyridine (1.80 g, 57.29%) as a solid.. **LCMS** (ES, m/z): 211 $[M+H]^+$.

Synthesis of Intermediate B167 and B167B



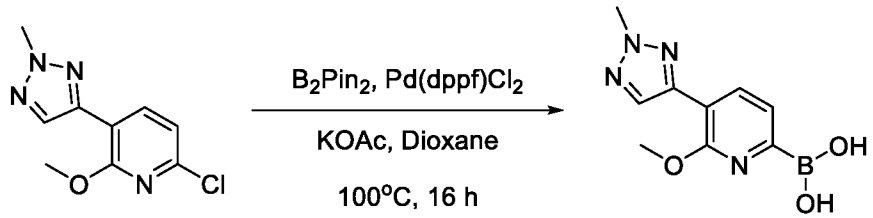
B166 **B167** **B167B**

To a stirred solution of 6-chloro-2-methoxy-3-(2H-1,2,3-triazol-4-yl)pyridine (1.75 g, 8.309 mmol, 1.00 equiv) in DMF (18 mL) was added 60% NaH (0.50 g, 12.463 mmol, 1.5 equiv) in portions at 5 °C, followed by the addition of methyl iodide (1.42 g, 9.971 mmol, 1.2 equiv) at 5

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°C. The reaction mixture was stirred at room temperature for 1 h, then quenched with water at 5 °C, and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (1x30 mL), brine (1x30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with EA/PE, (0-30%) to afford 6-chloro-2-methoxy-3-(2-methyl-1,2,3-triazol-4-yl)pyridine (800 mg, 42.86%) as a solid, then eluted with EA/PE (1:1) to afford 6-chloro-2-methoxy-3-(1-methyl-1,2,3-triazol-4-yl)pyridine (750 mg, 40.18%) as a solid. **LCMS** (ES, *m/z*): 225 $[M+H]^+$.

Synthesis of Intermediate B168

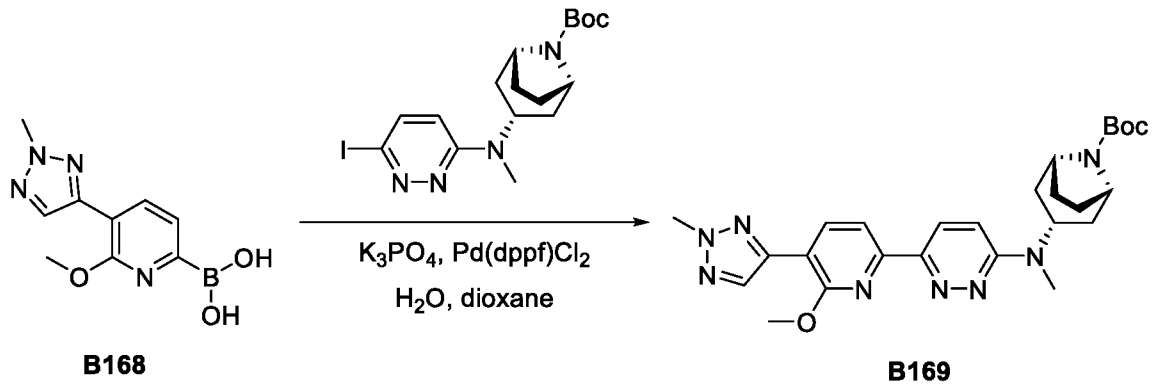


B167 **B168**

A mixture of 6-chloro-2-methoxy-3-(2-methyl-1,2,3-triazol-4-yl)pyridine (1.00 g, 4.451 mmol, 1.00 equiv), 4,4,5-trimethyl-2-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.21 g, 5.341 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (0.51 g, 0.445 mmol, 0.1 equiv) and KOAc (1.31 g, 13.353 mmol, 3 equiv) in 1,4-dioxane (20 mL) was stirred for 4 h at 80 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1), to afford 6-methoxy-5-(2H-1,2,3-triazol-4-yl)pyridin-2-ylboronic acid (670 mg, 68.42%) as a solid. **LCMS** (ES, *m/z*):235 $[M+H]^+$.

Synthesis of Intermediate B169

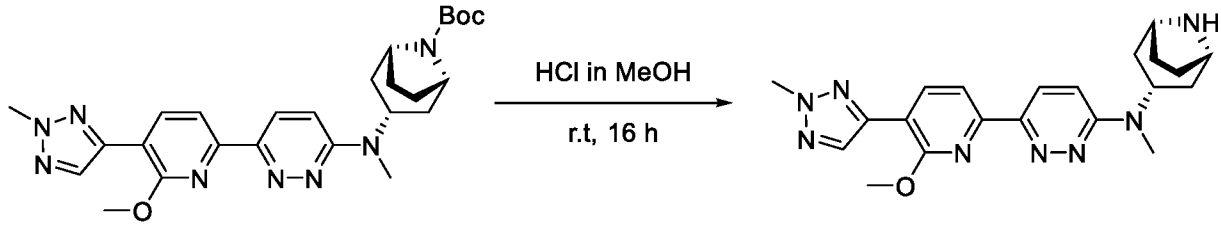
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B168 **B169**

A mixture of 6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl)pyridin-2-ylboronic acid (80 mg, 0.342 mmol, 1.00 equiv), tert-butyl 4-[(6-iodopyridazin-3-yl)amino]piperidine-1-carboxylate (153 mg, 0.380 mmol, 1.11 equiv), K_3PO_4 (244 mg, 1.155 mmol, 3 equiv), and $Pd(dtbpf)Cl_2$ (25 mg, 0.039 mmol, 0.1 equiv) in dioxane (1.3 mL) H_2O (0.3 mL) was stirred for 2 h at 80 ° C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl tert-butyl 4-({6-[6-methoxy-5-(2- methyl-1,2,3-triazol-4-yl)pyridin-2-yl]pyridazin-3-yl}amino)piperidine-1-carboxylate (102 mg, 63.95%) as a solid. **LCMS** (ES, *m/z*):507 $[M+H]^+$.

Synthesis of Compound 269



B169 **269**

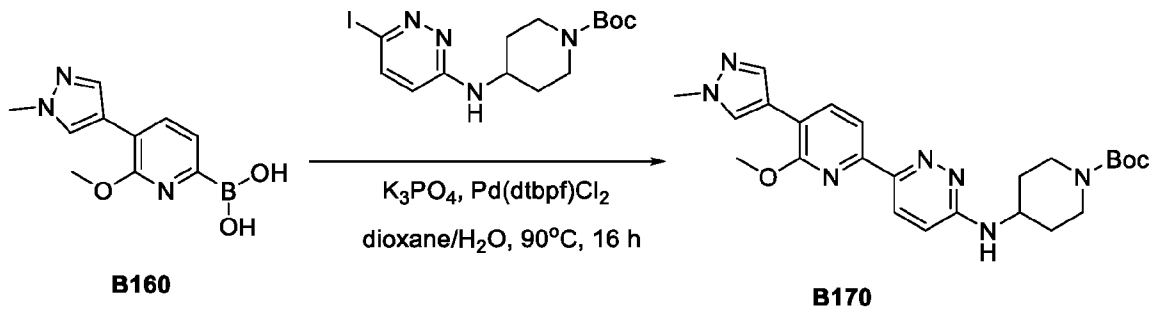
A mixture of tert-butyl 3-({6-[6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl)pyridin-2-yl]pyridazin-3-yl} (methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.197 mmol, 1.00 equiv) and HCl in methanol (1 mL) was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure and quenched with $NH_3.H_2O$ at 5 ° C. The residue was purified by Prep-HPLC (Condition 8, Gradient 3) to afford N-{6-[6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl)pyridin-2-yl] pyridazin-3-yl} -N-methyl-8-azabicyclo[3.2.1]octan-3-amine (3.5 mg, 4.36%) as a solid. **LCMS** (ES, m/z):407 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.35 (d, *J* =

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7.9 Hz, 1H), 8.23 (d, *J* = 9.6 Hz, 1H), 8.16 (s, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 9.6 Hz, 1H), 5.10 (s, 1H), 4.24 (s, 3H), 4.14 (s, 3H), 3.52 (s, 2H), 2.95 (s, 3H), 1.86-1.71 (m, 6H), 1.60-1.52 (m, 2H).

Example 28: Synthesis of Compound 257

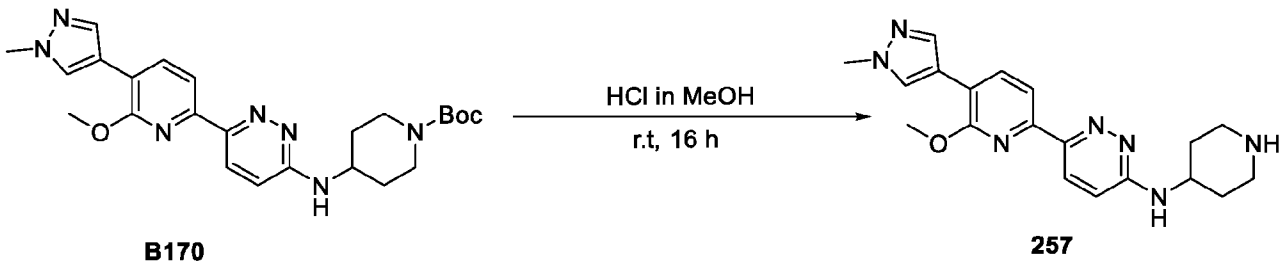
Synthesis of Intermediate B170



B160 **B170**

A solution of 6-methoxy-5-(1-methylpyrazol-4-yl)pyridin-2-ylboronic acid (80 mg, 0.343 mmol, 1.00 equiv), tert-butyl 4-[(6-iodopyridazin-3-yl)amino]piperidine-1-carboxylate (139 mg, 0.343 mmol, 1.0 equiv), K_3PO_4 (218 mg, 1.029 mmol, 3.0 equiv) and $Pd(dtbpf)Cl_2$ (22 mg, 0.034 mmol, 0.1 equiv) in dioxane (1.5 mL) and water (0.3 mL) was stirred for 16 h at 90°C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with EA / PE (0-100%) to afford tert-butyl 4-({6-[6-methoxy-5-(1-methylpyrazol-4-yl)pyridin-2-yl]pyridazin-3-yl} amino)piperidine-1-carboxylate (70 mg, 43.80%) as a solid. **LCMS** (ES, *m/z*): 466.3 $[M+H]^+$.

Synthesis of Compound 257



B170 **257**

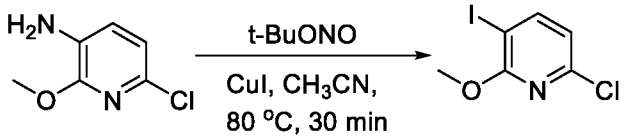
Into a solution of tert-butyl 4-({6-[6-methoxy-5-(1-methylpyrazol-4-yl)pyridin-2-yl]pyridazin-3-yl} amino)piperidine-1-carboxylate (70 mg, 0.150 mmol, 1.00 equiv) in methanol (0.7 mL) was added 4 M HCl in methanol (0.7 mL). The reaction mixture was stirred for 2 h at room temperature, then concentrated under reduced pressure and quenched with $NH_3.H_2O$ at 5 °C. The residue was purified by Prep-HPLC (Condition 8, Gradient 4) to afford 6-[6-methoxy-5-(1-

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methylpyrazol-4-yl)pyridin-2-yl]-N-(piperidin-4- yl)pyridazin-3-amine (26.5 mg, 48.23%)as a solid. **LCMS** (ES, m/z):366 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 8.12 (d, J = 8.3 Hz, 2H), 8.01 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 9.3 Hz, 1H), 4.09 (s, 3H), 3.97 (s, 1H), 3.90 (s, 3H), 2.98 (d, J = 12.2 Hz, 2H), 2.58 (d, J = 11.9 Hz, 2H), 1.95 (d, J = 11.9 Hz, 2H), 1.34 (m, J = 11.6, 3.9 Hz, 2H).

Example 29: Synthesis of Compound 288

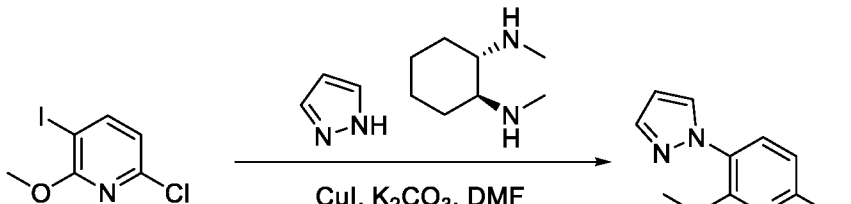
Synthesis of Intermediate B171



B171

To a stirred mixture of 6-chloro-2-methoxypyridin-3-amine (5.00 g, 31.528 mmol, 1.00 equiv) and CuI (9.01 g, 47.292 mmol, 1.5 equiv) in acetonitrile (100 mL) was added t-BuONO (3.90 g, 37.827 mmol, 1.20 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (250 mL), and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with water (300 mL), brine (300 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1), to afford 6-chloro-3-iodo-2-methoxypyridine (2.20 g, 25.90%) as a solid. **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.95 (d, J = 7.7 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 4.02 (s, 3H).

Synthesis of Intermediate B172



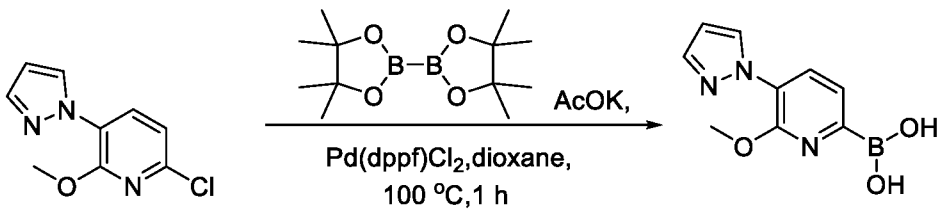
B171 **B172**

To a stirred mixture of 6-chloro-3-iodo-2-methoxypyridine (2.2 g, 8.164 mmol, 1.00 equiv) and pyrazole (0.61 g, 8.980 mmol, 1.1 equiv) in DMF (55 mL) was added K_3PO_4 (1.69 g, 12.246

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mmol, 1.5 equiv), CuI (0.31 g, 1.633 mmol, 0.2 equiv) and (1S,2S)-N1, N2-dimethylcyclohexane-1,2-diamine (0.23 g, 1.633 mmol, 0.2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 110 °C under nitrogen atmosphere. The resulting mixture was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with water (150 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1) to afford 6-chloro-2-methoxy-3-(1H-pyrazol-1-yl)pyridine (1.07 g, 62.52%) as a solid. **LCMS** (ES, *m/z*): 210.0 $[M+H]^+$

Synthesis of Intermediate B173

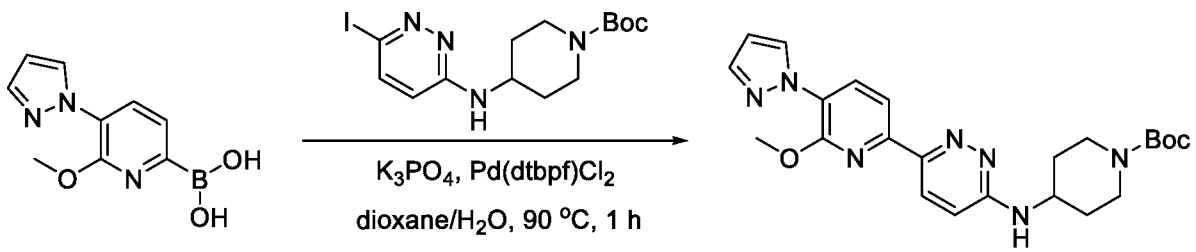


B172 **B173**

To a mixture of 6-chloro-2-methoxy-3-(1H-pyrazol-1-yl) pyridine (1.07 g, 5.104 mmol, 1.00 equiv) and bis (pinacolato) diboron (1.94 g, 7.656 mmol, 1.5 equiv) in 1,4-dioxane (22 mL) was added AcOK (1.50 g, 15.312 mmol, 3 equiv) and $Pd(dppf)Cl_2$ (0.37 g, 0.510 mmol, 0.1 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 100 °C under nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (10:1), to afford (6-methoxy-5-(1H-pyrazol-1-yl) pyridin-2-yl) boronic acid (1.50 g, 99.97%) as a oil. **LCMS** (ES, *m/z*): 220.0 $[M+H]^+$. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.36 (d, *J* = 2.6 Hz, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 1.8 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 6.47 (dd, *J* = 2.6, 1.8 Hz, 1H), 4.18 (s, 3H).

Synthesis of Intermediate B174

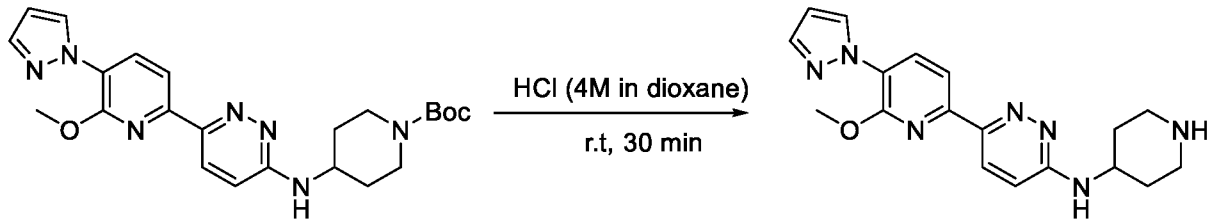
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B173 **B174**

To a stirred mixture of 6-methoxy-5-(pyrazol-1-yl) pyridin-2-ylboronic acid (80 mg, 0.365 mmol, 1.0 equiv) and tert-butyl 4-[(6-iodopyridazin-3-yl) amino] piperidine-1-carboxylate (148 mg, 0.365 mmol, 1.0 equiv) in dioxane/H_2O ((1.20 mL/0.24 mL) was added K_3PO_4 (233 mg, 1.095 mmol, 3.0 equiv) and Pd(DtBPF)Cl_2 (24 mg, 0.036 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 90 °C under nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:4) to afford tert-butyl 4-({6-[6-methoxy-5-(pyrazol-1-yl) pyridin-2-yl] pyridazin-3-yl} amino) piperidine-1-carboxylate (93 mg, 56.39%) as a solid. **LCMS** (ES, *m/z*): 452 $[M+H]^+$.

Synthesis of Compound 288



B174 **288**

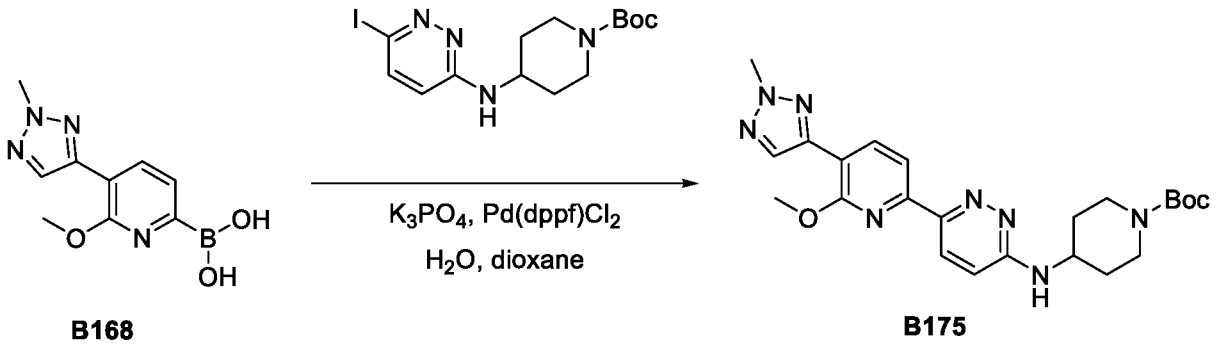
To a stirred solution of tert-butyl 4-({6-[6-methoxy-5-(pyrazol-1-yl)pyridin-2-yl]pyridazin-3-yl}amino) piperidine-1-carboxylate (93 mg, 1 equiv) in DCM (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL) dropwise at room temperature. The resulting mixture was stirred for 30 min at room temperature, then concentrated under reduced pressure, neutralized to pH 7 with saturated Na_2CO_3 (aq.). The resulting mixture was purified by Prep-HPLC (Condition 7, Gradient 4) to afford 6-[6-methoxy-5-(pyrazol-1-yl) pyridin-2-yl]-N-(piperidin-4-yl) pyridazin-3- amine (36.4 mg, 50.29%) as a solid. **LCMS** (ES, *m/z*): 352 $[M+H]^+$. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.29 (dd, J = 2.6, 0.6 Hz, 1H), 8.24 (d, J = 9.4 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 1.9 Hz, 1H), 6.98 (d, J = 9.4 Hz, 1H), 6.53 (dd, J = 2.6, 1.9

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Hz, 1H), 4.15 (s, 3H), 4.13-4.06 (m, 1H), 3.22 (dt, J = 12.7, 3.6 Hz, 2H), 2.90 (ddd, J = 12.8, 11.6, 2.8 Hz, 2H), 2.26-2.06 (m, 2H), 1.83-1.38 (m, 2H).

Example 30: Synthesis of Compound 270

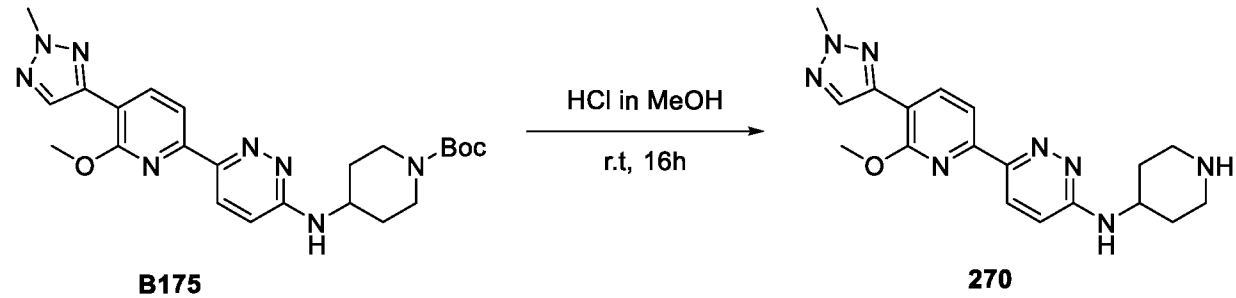
Synthesis of Intermediate B175



B168 **B175**

A mixture of 6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl)pyridin-2-ylboronic acid (80 mg, 0.342 mmol, 1.00 equiv), tert-butyl 4-[(5-bromopyridin-2-yl)amino]piperidine-1-carboxylate (137 mg, 0.385 mmol, 1 equiv), K_3PO_4 (244 mg, 1.155 mmol, 3 equiv) and $Pd(dtbpf)Cl_2$ (25 mg, 0.039 mmol, 0.1 equiv) in dioxane (1.3 mL) and H_2O (0.3 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl 4-({6-[6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl)pyridin-2-yl]pyridazin-3-yl}amino)piperidine-1-carboxylate (102 mg, 63.95%) as a solid. **LCMS** (ES, *m/z*):467 $[M+H]^+$.

Synthesis of Compound 270



B175 **270**

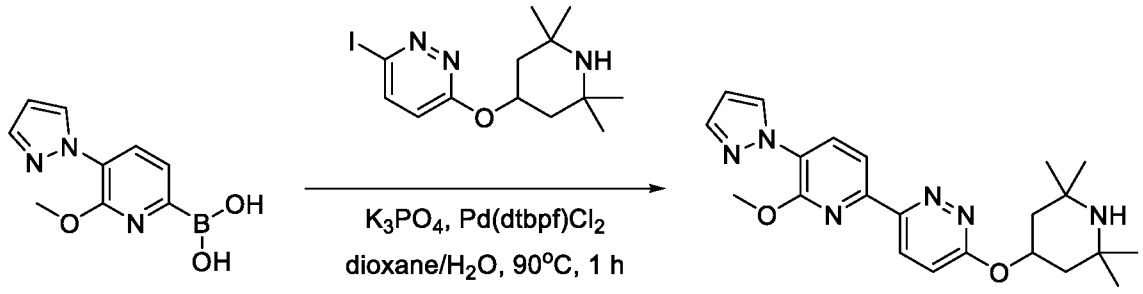
Tert-butyl 4-({6-[6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl)pyridin-2-yl]pyridazin-3-yl}amino)piperidine-1-carboxylate (100 mg, 0.214 mmol, 1.00 equiv) in methanol (1 mL) was added 4 M HCl in methanol (1 mL). The reaction mixture was stirred for 2 h at room temperature, then concentrated under reduced pressure and quenched with $NH_3.H_2O$ at 5 °C. The

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residue was purified by Prep-HPLC (Condition 8, Gradient 3) to afford 6-[6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl) pyridin-2-yl]-N-(piperidin-4-yl)pyridazin-3-amine (16.8 mg, 21.39%) as a solid. **LCMS** (ES, m/z):367 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.34 (d, J = 7.9 Hz, 1H), 8.19-8.12 (m, 2H), 8.05 (d, J = 7.9 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 9.3 Hz, 1H), 4.24 (s, 3H), 4.13 (s, 3H), 3.98 (s, 1H), 3.02-2.94 (m, 2H), 2.58 (d, J = 11.7 Hz, 3H), 1.94 (d, J = 12.0 Hz, 2H), 1.33 (t, J = 11.5, 6.2 Hz, 2H).

Example 31: Synthesis of Compound 271

Synthesis of Compound 271



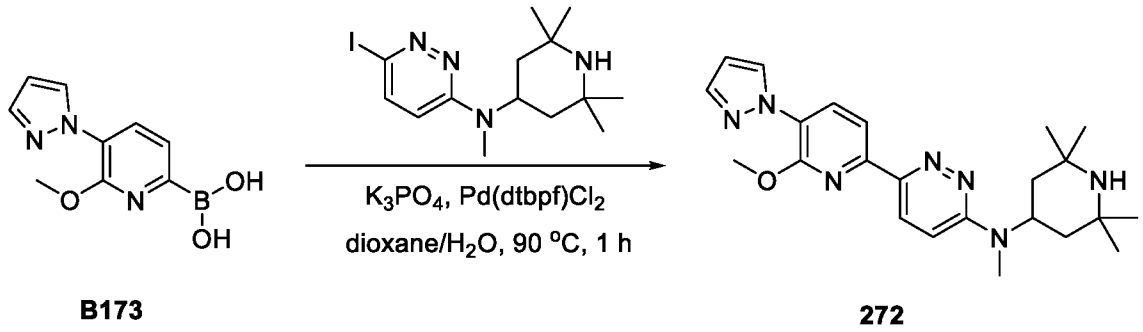
B173 **271**

To a stirred mixture of bis(6-methoxy-5-(pyrazol-1-yl) pyridin-2-ylboronic acid) (50 mg, 0.228 mmol, 1.0 equiv) and 3-iodo-6-[(2,2,6,6-tetramethylpiperidin-4-yl) oxy] pyridazine (83 mg, 0.228 mmol, 1.0 equiv) in dioxane /H_2O (0.75 mL/0.15mL) were added K_3PO_4 (145 mg, 0.685 mmol, 3.0 equiv) and $Pd(dtbpf)Cl_2$ (15 mg, 0.023 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 90 degrees C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:2) to afford crude prodcut. The crude product was purified by Prep-HPLC (Condition 7, Gradient 4) to afford bis(3-[6-methoxy-5-(pyrazol-1-yl) pyridin-2-yl]-6-[(2,2,6,6-tetramethylpiperidin-4-yl) oxy] pyridazine) (16.8 mg, 18.04%) as a solid. **LCMS** (ES, *m/z*): 409 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.47 (d, J = 9.2 Hz, 1H), 8.42 (d, J = 2.5 Hz, 1H), 8.29 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.32 (d, J = 9.2 Hz, 1H), 6.57 (t, J = 2.1 Hz, 1H), 5.93-5.54 (m, 1H), 4.14 (s, 3H), 2.11 (dd, J = 11.9, 4.0 Hz, 2H), 1.40-1.32 (m, 1H), 1.30 (d, J = 11.6 Hz, 2H), 1.25 (s, 6H), 1.11 (s, 6H).

Example 32: Synthesis of Compound 272

Synthesis of Compound 272

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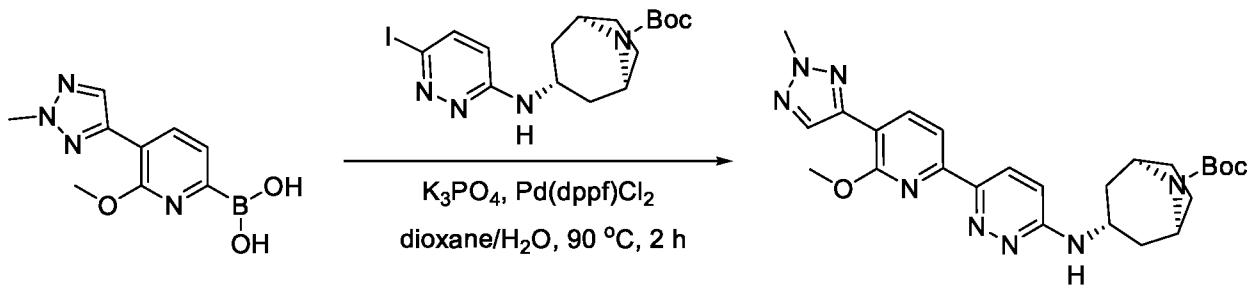


B173 **272**

To a stirred mixture of 6-methoxy-5-(pyrazol-1-yl) pyridin-2-ylboronic acid (70 mg, 0.320 mmol, 1.0 equiv) and 6-iodo-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine (118 mg, 0.320 mmol, 1.0 equiv) in 1,4-dioxane/H_2O (1.20 mL/0.24 mL) was added K_3PO_4 (203 mg, 0.960 mmol, 3.0 equiv) and Pd(dtbpf)Cl_2 (21 mg, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 90 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1), followed by Prep-HPLC (Condition 7, Gradient 4) to afford 6-[6-methoxy-5-(pyrazol-1-yl) pyridin-2-yl]-N- methyl -N-(2,2,6,6-tetramethylpiperidin-4-yl) pyridazin-3-amine (52.7 mg, 39.16%) as a solid. **LCMS** (ES, *m/z*): 422 $[M+H]^+$. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.37 (d, *J* = 2.5 Hz, 1H), 8.28-8.18 (m, 2H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 1.8 Hz, 1H), 7.20 (d, *J* = 9.7 Hz, 1H), 6.73-6.46 (m, 1H), 5.19-5.09 (m, 1H), 4.11 (s, 3H), 2.97 (s, 3H), 1.60-1.37 (m, 4H), 1.26 (s, 6H), 1.09 (s, 6H).

Example 33: Synthesis of Compound 289

Synthesis of Intermediate B176

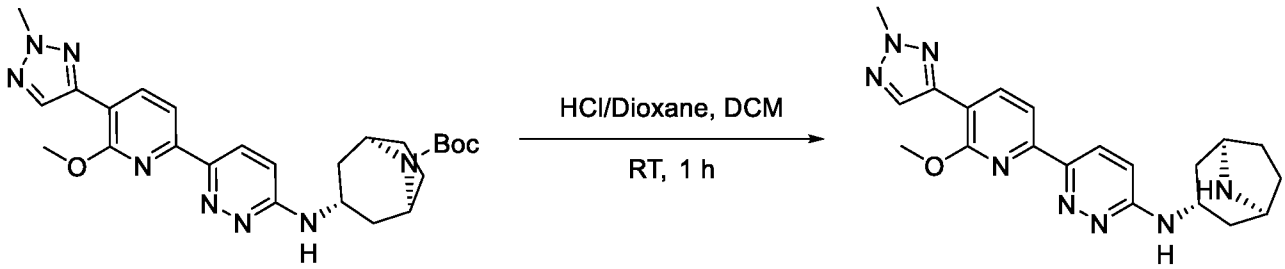


B168 **B176**

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To a stirred mixture of tert-butyl 3-[(6-iodopyridazin-3-yl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (92 mg, 0.214 mmol, 1 equiv) and 6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl)pyridin-2-ylboronic acid (50 mg, 0.214 mmol, 1.00 equiv) in dioxane (1 mL) and water (0.2 mL) was added K_3PO_4 (91 mg, 0.428 mmol, 2 equiv) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (17 mg, 0.021 mmol, 0.1 equiv) at room temperature. The resulting mixture was stirred for 2 h at 80 °Cunder nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10/1) to afford tert-butyl 3-({6-[6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl) pyridin-2-yl]pyridazin-3-yl}amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (20 mg, 19.00%) as a solid. **LCMS** (ES, *m/z*): 493 $[M+H]^+$.

Synthesis of Compound 289



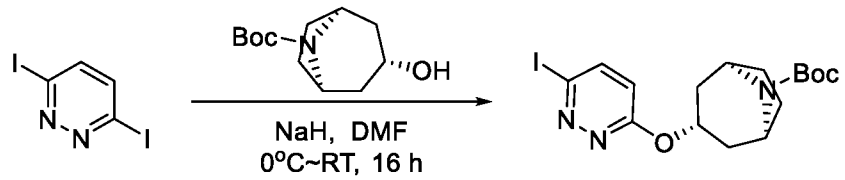
B176 **289**

A mixture of tert-butyl (1R,3S,5S)-3-({6-[6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl)pyridin-2-yl] pyridazin-3-yl}amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (20 mg, 0.041 mmol, 1.00 equiv) and 4 M HCl(gas) in 1,4-dioxane (0.5 mL) in DCM (0.5 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Condition 7, Gradient 5) to afford (1R,3S,5S)-N-{6-[6-methoxy-5-(2-methyl-1,2,3-triazol-4-yl)pyridin-2-yl]pyridazin-3-yl}-8-azabicyclo[3.2.1]octan-3-amine (4.1 mg, 25.73%) as a solid. **LCMS** (ES, *m/z*): 393 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.40 (d, J = 7.9 Hz, 1H), 8.26 (d, J = 9.4 Hz, 1H), 8.13 (s, 1H), 8.02 (m, 1H), 6.96 (d, J = 9.3 Hz, 1H), 4.48 (d, J = 5.5 Hz, 1H), 4.25 (s, 3H), 4.19 (s, 3H), 3.77 (d, J = 5.4 Hz, 2H), 2.25-2.16 (m, 2H), 2.11-1.96 (m, 4H), 1.71-1.60 (m, 2H).

Example 34: Synthesis of Compound 290

Synthesis of Intermediate B177

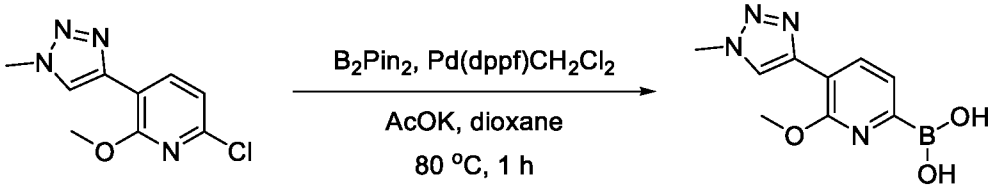
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B177

To a stirred solution of tert-butyl (1R,3S,5S)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (2.05 g, 9.039 mmol, 1 equiv) in DMF (50 mL) was added NaH (0.81 g, 13.558 mmol, 1.5 equiv) in portions at 0 °C under nitrogen atmosphere. To the reaction mixture was added 3,6-diiodopyridazine (3.00 g, 9.039 mmol, 1.00 equiv) at 0 °C. The resulting mixture was stirred for 16 h at room temperature under nitrogen atmosphere, then quenched with saturated NH_4Cl (50 mL) at room temperature, and extracted with ethyl acetate (3 x100 mL). The combined organic layers were washed with H_2O (3x100 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1), to afford tert-butyl (1R,3S,5S)-3-[(6-iodopyridazin-3-yl)oxy]-8-azabicyclo[3.2.1]octane-8-carboxylate (3.20 g, 82.08%) as a solid. **LCMS** (ES, *m/z*): 432 $[M+H]^+$.

Synthesis of Intermediate B178

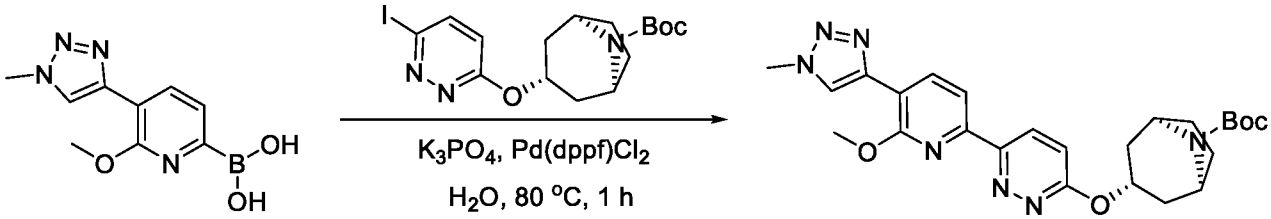


B178

To a stirred mixture of 6-chloro-2-methoxy-3-(1-methyl-1,2,3-triazol-4-yl)pyridine (420 mg, 1.870 mmol, 1.00 equiv), bis(pinacolato)diboron (570 mg, 2.244 mmol, 1.2 equiv), and KOAc (550 mg, 5.610 mmol, 3.0 equiv) in dioxane (6 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (76 mg, 0.094 mmol, 0.05 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 1 h at 80 °C under N_2 atmosphere, and then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10/1), to afford 2-methoxy-3-(1-methyl-1,2,3-triazol-4-yl)-6- (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (658 mg, crude) as a solid. **LCMS** (ES, *m/z*): 235 $[M+H]^+$.

Synthesis of Intermediate B179

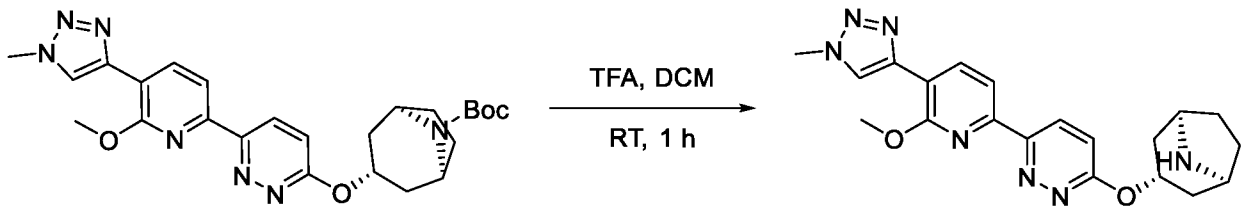
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B178 **B179**

To a stirred mixture of 6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-ylboronic acid (110 mg crude, 0.314 mmol, 1.00 equiv) and tert-butyl 3-[(6-iodopyridazin-3-yl)oxy]-8-azabicyclo[3.2.1]octane-8- carboxylate (135 mg, 0.314 mmol, 1.0 equiv) in dioxane (1.25 mL) and H_2O (0.25 mL) was added K_3PO_4 (200 mg, 0.942 mmol, 3.0 equiv) and Pd(DtBPF)Cl_2 (20 mg, 0.031 mmol, 0.1 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 1 h at 80 °C under N_2 atmosphere, and then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/1), to afford tert-butyl 3-({6-[6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-yl]pyridazin- 3-yl}oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (71 mg, 45.88%) as a solid. **LCMS** (ES, *m/z*): 494 $[M+H]^+$.

Synthesis of Compound 290



B179 **290**

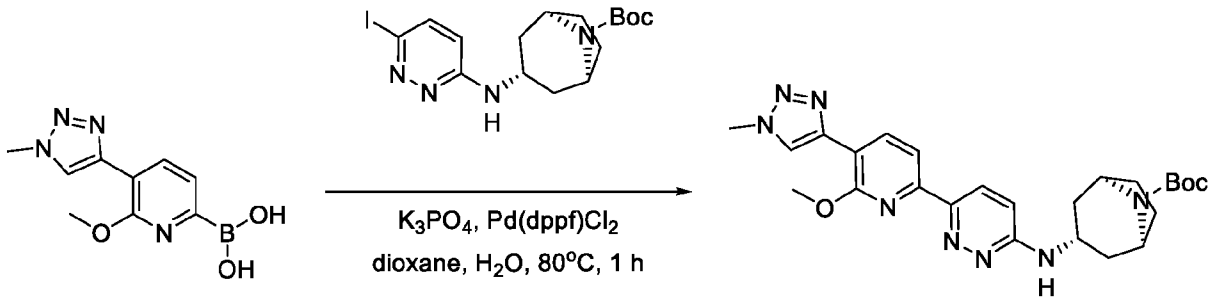
To a stirred solution of tert-butyl 3-({6-[6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-yl]pyridazin -3-yl}oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (71 mg, 0.144 mmol, 1.00 equiv) in DCM (2.1 mL) was added TFA (0.7 mL) at room temperature under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 9, Gradient 2) to afford 3-({6-[6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-yl]pyridazin-3-yl}oxy)-8- azabicyclo[3.2.1]octane (25.9 mg, 45.76%) as a solid. **LCMS** (ES, *m/z*): 394 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.91 (d, J = 9.4 Hz, 1H), 8.71 (d, J = 7.8 Hz, 1H), 8.56 (s, 1H), 8.16 (d, J = 7.9 Hz, 1H), 7.87 (d, J = 9.4 Hz, 1H),

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5.73-5.64 (m, 1H), 4.31 (s, 3H), 4.27 (s, 2H), 4.24 (s, 3H), 2.69-2.59 (m, 2H), 2.31-2.20 (m, 4H), 2.16-2.10 (m, 2H).

Example 36: Synthesis of Compound 291

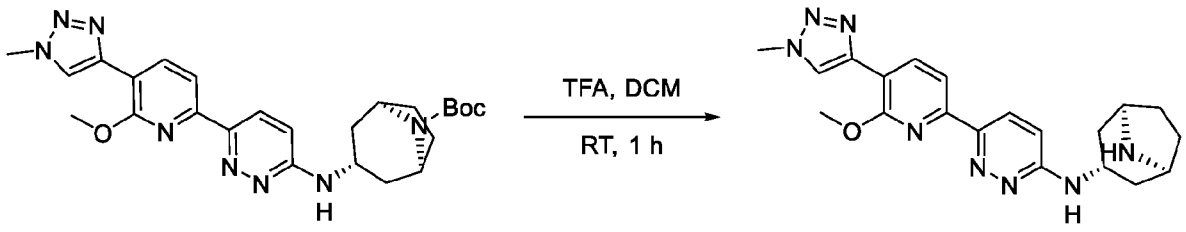
Synthesis of Intermediate B180



B178 **B180**

To a stirred mixture of 6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-ylboronic acid (110 mg, 0.314 mmol, 1.00 equiv), K_3PO_4 (200 mg, 0.942 mmol,3 equiv), and tert-butyl 3-[(6-iodopyridazin-3-yl) amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (135 mg, 0.314 mmol, 1.0 equiv) in dioxane (1.25 mL) and H_2O (0.5 mL) was added $Pd(DtBPF)Cl_2$ (20 mg, 0.031 mmol, 0.1 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 1 h at 80 °C under N_2 atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10/1), to afford tert-butyl 3-({6-[6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-yl] pyridazin-3-yl}amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (40 mg, 25.90%) as a solid. **LCMS** (ES, *m/z*): 493 $[M+H]^+$.

Synthesis of Compound 291



B180 **291**

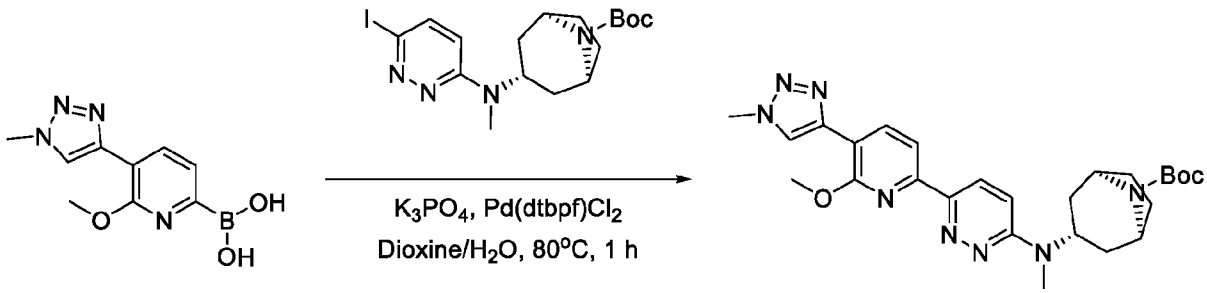
To a stirred solution of tert-butyl 3-({6-[6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-yl] pyridazin-3-yl}amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (40 mg, 0.081 mmol, 1.00 equiv) in DCM (1.2 mL) was added TFA (0.4 mL) at room temperature under N_2 atmosphere.

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The mixture was stirred for 1 h at room temperature, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 7, Gradient 4) to afford N-{6-[6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-yl]pyridazin-3-yl}-8-azabicyclo[3.2.1]octan-3- amine (10 mg, 31.38%) as a solid. **LCMS** (ES, *m/z*): 393 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.53 (d, *J* = 7.9 Hz, 1H), 8.36 (s, 1H), 8.23 (d, *J* = 9.4 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 9.4 Hz, 1H), 4.46-4.40 (m, 1H), 4.19 (s, 6H), 3.67 (s, 2H), 2.15-2.11 (m, 2H), 1.98-1.90 (m, 4H), 1.65-1.53 (m, 2H).

Example 37: Synthesis of Compound 292

Synthesis of Intermediate B181

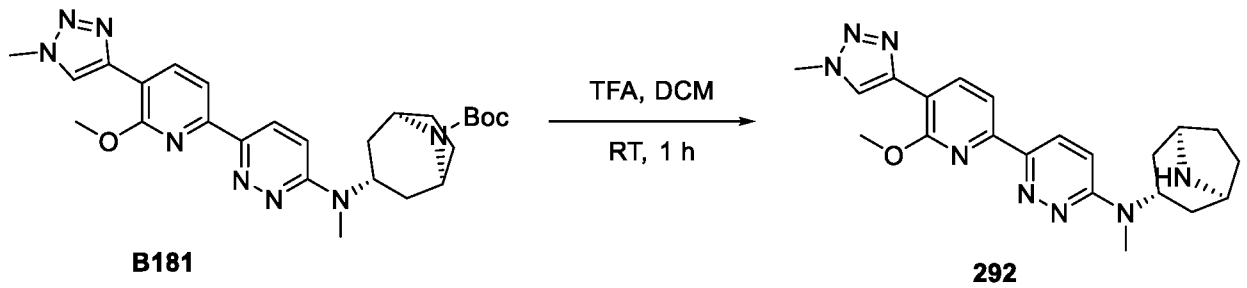


B178 **B181**

To a stirred mixture of 6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-ylboronic acid (110 mg, 0.470 mmol, 1.00 equiv), K_3PO_4 (200 mg, 0.940 mmol, 2 equiv), and tert-butyl 3-[(6-iodopyridazin-3-yl)(methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (209 mg, 0.470 mmol, 1 equiv) in dioxane (2 mL) and H_2O (0.4 mL) was added Pd(DtBPF)Cl_2 (31 mg, 0.047 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 80 °C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1), to afford tert-butyl 3-({6-[6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-yl]pyridazin-3-yl}(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (60 mg, 25.20%) as a solid. **LCMS** (ES, *m/z*): 507 $[M+H]^+$.

Synthesis of Compound 292

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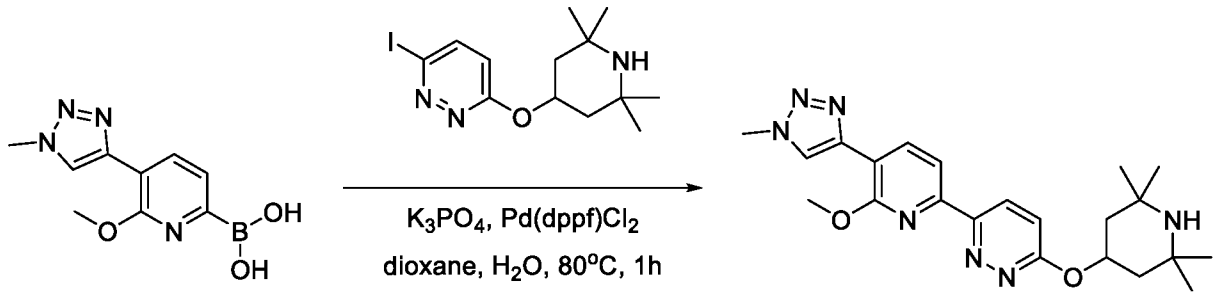


B181 **292**

To a stirred solution of tert-butyl 3-({6-[6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-yl] pyridazin-3-yl}(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (60 mg, 0.118 mmol, 1.00 equiv) in DCM (1.8 mL) was added TFA (0.6 mL) at room temperature under N_2 atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 7, Gradient 4) to afford 3-({6-[6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-yl]pyridazin-3-yl}oxy)-8-azabicyclo[3.2.1]octane (13 mg, 27.90%) as a solid. **LCMS** (ES, *m/z*): 407 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.54 (d, J = 7.9 Hz, 1H), 8.40-8.31 (m, 2H), 8.06 (d, J = 7.9 Hz, 1H), 7.19 (d, J = 9.6 Hz, 1H), 5.28-5.22 (m, 1H), 4.20 (d, J = 3.8 Hz, 6H), 3.70 (s, 2H), 3.02 (s, 3H), 1.99 (s, 3H), 1.96 (d, J = 3.6 Hz, 2H), 1.78-1.69 (m, 2H).

Example 38: Synthesis of Compound 293

Synthesis of Compound 293



B178 **293**

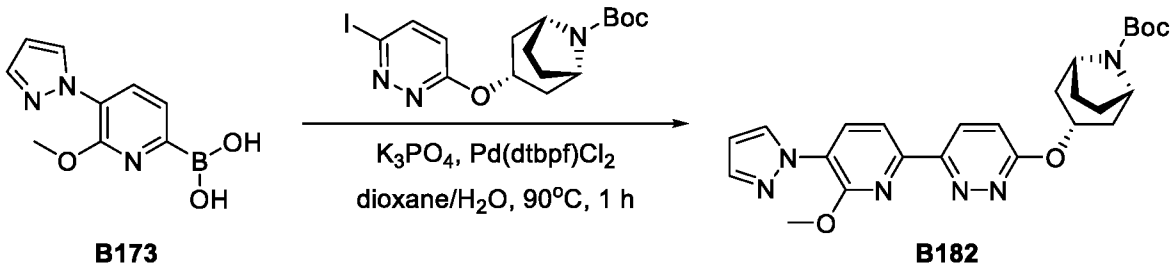
To a stirred mixture of 6-methoxy-5-(1-methyl-1,2,3-triazol-4-yl)pyridin-2-ylboronic acid (73 mg, 0.312 mmol, 1.00 equiv), K_3PO_4 (199 mg, 0.936 mmol, 3.0 equiv), and 3-iodo-6-[(2,2,6,6-tetramethylpiperidin-4-yl) oxy]pyridazine (113 mg, 0.312 mmol, 1.0 equiv) in dioxane/H_2O (2 mL/0.4 mL) was added $Pd(dppf)Cl_2$ (21 mg, 0.028 mmol, 0.09 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 80 °C under nitrogen atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue

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was purified by silica gel column chromatography, eluted with PE / EA (1:1), followed by Prep-HPLC to afford 3-[6-methoxy-5-(1-methyl-1,2,3- triazol-4-yl)pyridin-2-yl]-6-[(2,2,6,6-tetramethylpiperidin-4-yl)oxy]pyridazine (3.4 mg, 2.57%) as a solid. **LCMS** (ES, *m/z*): 424 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.58 (d, J = 7.9 Hz, 1H), 8.52 (d, J = 9.3 Hz, 1H), 8.39 (s, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 9.3 Hz, 1H), 5.84-5.79 (m, 1H), 4.19 (d, J = 7.9 Hz, 5H), 2.29-2.25 (m , 2H), 1.51-1.45 (m, 2H), 1.43 (s, 6H), 1.31 (s, 6H).

Example 39: Synthesis of Compound 294

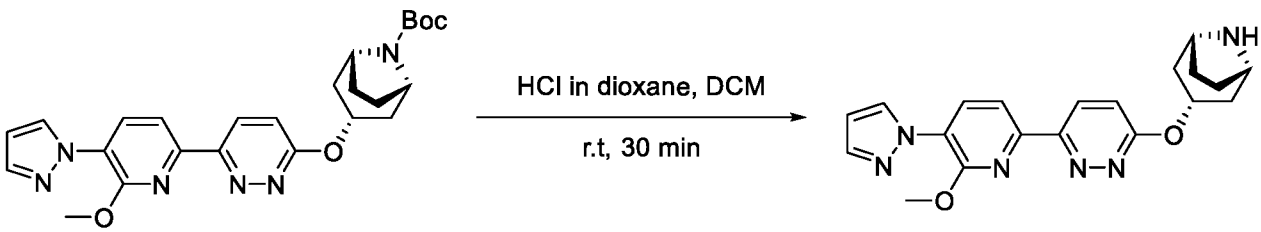
Synthesis of Intermediate B182



B173 **B182**

To a stirred mixture of (6-methoxy-5-(1H-pyrazol-1-yl) pyridin-2-yl) boronic acid (70 mg, 0.320 mmol, 1.0 equiv) and tert-butyl (1R,3s,5S)-3-((6-iodopyridazin-3-yl) oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (138 mg, 0.320 mmol, 1.0 equiv) in dioxane (1.0 mL)/H_2O (0.2 mL) was added K_3PO_4 (203 mg, 0.960 mmol, 3.0 equiv) and $Pd(dtbpf)Cl_2$ (21 mg, 0.032 mmol, 0.1 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 90 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (2:1), to afford tert-butyl (1R,3s,5S)-3-((6-(6-methoxy-5-(1H- pyrazol-1-yl)pyridin-2-yl)pyridazin-3-yl)oxy)-8-azabicyclo [3.2.1] octane-8-carboxylate (150 mg, 98.17%) as a solid. **LCMS** (ES, *m/z*): 479 $[M+H]^+$.

Synthesis of Compound 294



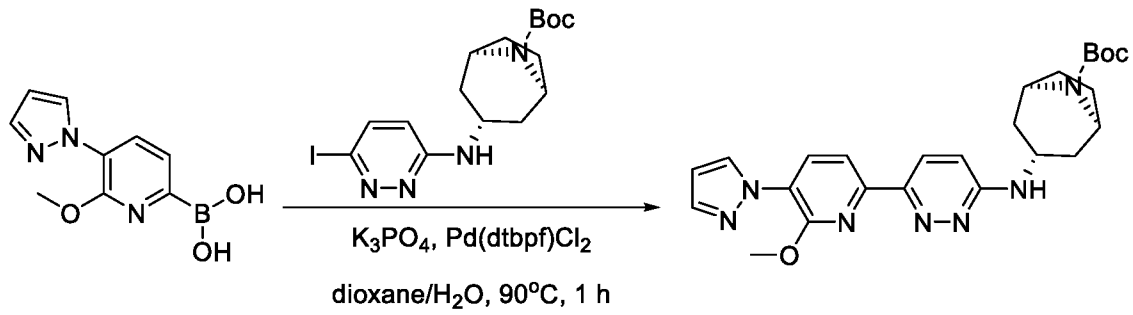
B182 **294**

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To a stirred solution of tert-butyl (1R,3s,5S)-3-((6-(6-methoxy-5-(1H-pyrazol-1-yl)pyridin-2-yl) pyridazin-3-yl)oxy)-8-azabicyclo[3.2.1] octane-8-carboxylate (150 mg, 0.314 mmol, 1.0 equiv) in DCM (1.5 mL) was added HCl (gas) in 1,4-dioxane (1.5 mL, 4M) dropwise at room temperature. The resulting mixture was stirred for 30 min at room temperature, then concentrated under reduced pressure, and neutralized to pH 7 with saturated Na_2CO_3 (aq.). The resulting mixture was purified by Prep-HPLC (Condition 7, Gradient 4) to afford (1R,3s,5S)-3-((6-(6-methoxy-5- (1H-pyrazol-1-yl)pyridin-2-yl)pyridazin-3-yl)oxy) -8-azabicyclo[3.2.1]octane (60.7 mg,51.17%) as a solid. **LCMS** (ES, *m/z*): 379 $[M+H]^+$. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.45 (d, J = 9.3 Hz, 1H), 8.41 (d, J = 2.5 Hz, 1H), 8.29 (d, J = 8.1 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.30 (d, J = 9.3 Hz, 1H), 6.61 - 6.53 (m, 1H), 5.58 (dt, J = 10.7, 5.0 Hz, 1H), 4.13 (s, 3H), 3.53 - 3.48 (m, 2H), 2.21 - 2.14 (m, 2H), 1.77 - 1.68 (m, 4H), 1.66 - 1.54 (m, 2H).

Example 40: Synthesis of Compound 295

Synthesis of Intermediate B183



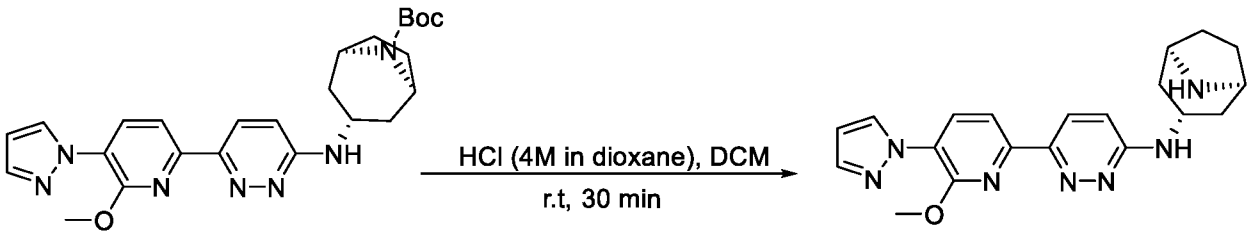
B173 **B183**

To a stirred mixture of (6-methoxy-5-(1H-pyrazol-1-yl) pyridin-2-yl) boronic acid (80.0 mg, 0.365 mmol, 1.00 equiv) and tert-butyl (1R,3s,5S)-3-((6-iodopyridazin-3-yl) amino)-8-azabicyclo [3.2.1] octane-8-carboxylate (157.1 mg, 0.365 mmol, 1.0 equiv) in dioxane (1.2 mL)/H_2O (0.2 mL) was added K_3PO_4 (232.6 mg, 1.095 mmol, 3.0 equiv) and $Pd(dtbpf)Cl_2$ (23.8 mg, 0.036 mmol, 0.1 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 90 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with ethyl acetate, to afford tert-butyl (1R,3s,5S)-3-((6-(6-

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methoxy-5-(1H-pyrazol-1-yl) pyridin-2-yl) pyridazin-3-yl) amino)-8-azabicyclo [3.2.1] octane-8-carboxylate (174 mg, 83.77%) as a solid. **LCMS** (ES, *m/z*): 478 $[M+H]^+$.

Synthesis of Compound 295



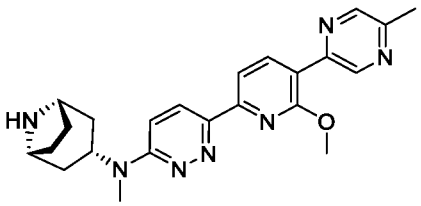
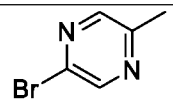
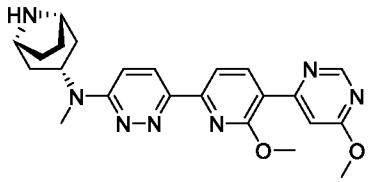
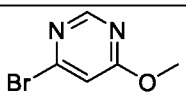
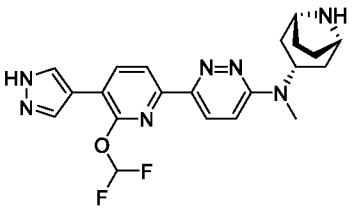
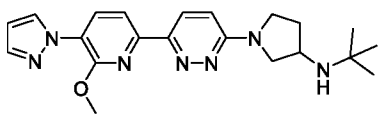
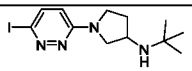
B183 **295**

To a stirred solution of tert-butyl (1R,3s,5S)-3-((6-(6-methoxy-5-(1H-pyrazol-1-yl) pyridin-2-yl) pyridazin-3-yl) amino)-8-azabicyclo [3.2.1] octane-8-carboxylate (174 mg, 0.365 mmol, 1.0 equiv) in DCM (1.7 mL) was added HCl (gas) in 1,4-dioxane (1.7 mL) (4M) dropwise at room temperature. The resulting mixture was stirred for 30 min at room temperature, then concentrated under reduced pressure to give a residue, and neutralized to pH 7 with saturated Na_2CO_3 (aq.). The resulting mixture was purified by Prep-HPLC (Condition 7, Gradient 4) to afford (1R,3s,5S)-N-(6-(6-methoxy-5-(1H-pyrazol-1-yl) pyridin-2-yl) pyridazin-3-yl)-8-azabicyclo [3.2.1] octan-3-amine (26.6 mg, 19.35%) as a solid. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.36 (d, J = 2.5 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 8.10 (dd, J = 13.3, 8.7 Hz, 2H), 7.79 (d, J = 1.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 6.91 (d, J = 9.4 Hz, 1H), 6.55 (t, J = 2.2 Hz, 1H), 4.41-4.27 (m, 1H), 4.10 (s, 3H), 3.47 (s, 2H), 1.95 (dt, J = 12.3, 4.2 Hz, 2H), 1.72 (s, 4H), 1.43 (td, J = 14.0, 12.7, 2.7 Hz, 2H).

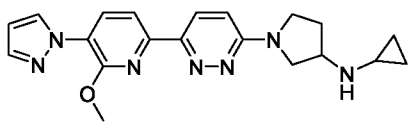
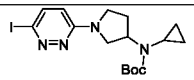
Example 41: Synthesis of Compounds 300-305

Compounds 300-305 were prepared according to the procedures outlined herein. outlined in this Example 32 and generalized by Scheme C. The table below provides intermediates used in these procedures and final compound characterization data.

Compound No. and Structure	**Coupling Reagent**	**LCMS (ESI, *m/z*) $[M+H]^+$**	**^{1}H NMR δ**

 **300**		418.2	(300 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.55 (dd, *J* = 18.8, 8.8 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.60-7.50 (m, 2H), 5.26-5.25 (m, 1H), 4.21-4.19 (m, 5H), 4.04 (s, 3H), 3.09 (s, 3H), 2.30-2.24 (m, 6H), 2.02-1.99 (m, 2H).δ 9.86 (s, 1H), 9.21-9.04 (m, 2H), 8.69 (s, 1H), 8.50 (dd, *J* = 16.9, 8.8 Hz, 2H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 9.7 Hz, 1H), 4.94 (s, 1H), 4.13 (m, 5H), 3.19 (s, 3H), 2.57 (s, 3H), 2.43-2.38 (m, 2H), 2.20-1.96 (m, 4H), 1.88-1.83 (m, 2H).
 **301**		434	(400 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 8.55 (dd, *J* = 18.8, 8.8 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.60-7.50 (m, 2H), 5.26-5.25 (m, 1H), 4.21-4.19 (m, 5H), 4.04 (s, 3H), 3.09 (s, 3H), 2.30-2.24 (m, 6H), 2.02-1.99 (m, 2H).8.81 (s, 1H), 8.55 (dd, *J* = 18.8, 8.8 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.60-7.50 (m, 2H), 5.26-5.25 (m, 1H), 4.21-4.19 (m, 5H), 4.04 (s, 3H), 3.09 (s, 3H), 2.30-2.24 (m, 6H), 2.02-1.99 (m, 2H).
 **302**		428	(400 MHz, DMSO-d_6): *δ* 13.18 (s, 1H), 8.35 (dd, *J* = 8.2, 3.4 Hz, 1H), 8.21 – 8.29 (m, 1H), 8.11 – 8.20 (m, 3H), 8.03 – 8.10 (m, 0.5H), 8.81 – 8.90 (m, 0.2H) 7.17 (dd, *J* = 9.7, 3.5 Hz, 1H), 5.13 (d, *J* = 13.1 Hz, 1H), 3.50 (s, 2H), 2.94 (d, *J* = 3.4 Hz, 3H), 1.77 (d, *J* = 22.2 Hz, 6H), 1.60 – 1.46 (m, 2H).
 **304**		394	(400 MHz, DMSO-*d*$_6$) δ 8.37 (d, *J* = 2.5 Hz, 1H), 8.25-8.18 (m, 2H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 1.9 Hz, 1H), 6.98 (d, *J* = 9.5 Hz, 1H), 6.56 (t, *J* = 2.2 Hz, 1H), 4.12 (s, 3H), 3.81 (d, *J* = 10.3 Hz, 1H), 3.68 (s, 1H), 3.56 (t, *J* = 7.3 Hz, 1H), 3.46 (q, *J* = 9.2, 8.7 Hz, 1H), 3.11 (t, *J* = 8.9 Hz, 1H), 2.20-2.19 (m, 1H), 1.82-1.71 (m, 2H), 1.10 (s, 9H).

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 **305**		378	(400 MHz, DMSO-d_6) δ 8.37 (d, J = 2.5 Hz, 1H), 8.21 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 1.9 Hz, 1H), 6.98 (d, J = 9.5 Hz, 1H), 6.55 (t, J = 2.1 Hz, 1H), 4.12 (s, 3H), 3.71 (dd, J = 10.8, 5.9 Hz, 1H), 3.63 (d, J = 8.3 Hz, 1H), 3.53 (p, J = 6.1 Hz, 2H), 3.44-3.36 (m, 1H), 2.22-2.06 (m, 2H), 1.95-1.90 (m, 1H), 0.47-0.36 (m, 2H), 0.28-0.21 (m, 2H).

Example 42: 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

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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

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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

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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)**
126	D	D
129	C	C
130	C	B
133	B	A
134	B	B
135	D	D
136	C	C
171	C	C
207	C	C
208	B	B
217	B	B

Compound No.	**HTT AJ AC_{50} (nM)**	**HTT CJ AC_{50} (nM)**
236	D	D
244	B	B
245	B	B
246	B	A
247	B	B
248	D	D
249	A	A
250	A	A
256	C	C
257	C	C
258	C	B

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Compound No.	HTT AJ AC_{50} (nM)	HTT CJ AC_{50} (nM)
259	C	B
260	B	B
261	A	A
262	B	A
268	A	A
269	B	B
270	C	D

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ AC_{50} (nM)
271	C	C
272	B	B
284	C	A
286	A	A
287	B	A
288	D	D
290	D	B

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
130	B	C	A
133	A	A	A
134	B	B	D
135	D	-	A
136	C	B	-
171	C	B	C
207	C	C	C
208	B	A	B

Compound No.	HTT	SMN2	Target C
217	B	D	C
236	D	-	D
244	A	-	B
245	A	-	B
246	A	-	B
247	A	-	B
248	D	-	D
249	A	-	A

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Compound No.	HTT	SMN2	Target C
250	A	-	B
256	B	-	C
257	C	-	C
258	B	-	C
259	B	-	B
260	A	-	A
261	A	-	A
262	A	-	A
268	A	-	A

Compound No.	HTT	SMN2	Target C
269	A	-	B
270	C	-	C
271	C	-	C
272	C	-	C
284	A	-	B
286	A	-	A
287	A	-	A
288	D	-	D
290	B	-	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-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;

L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^3)-, -N(R^3)C(O)-, or -C(O)N(R^3)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^4;

M and P are each independently C(R^2) or N;

X and Y are each independently C(R^{5a}), C(R^{5a})(R^{5b}), N, or N(R^{5c}), wherein the bond between X and Y may be a single or double bond as valency permits, and wherein X and Y may not both be C(R^{5a})(R^{5b}) or C(R^{5a});

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, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^8; 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^8;

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

each R^3 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^4 is 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 –$C(O)OR^D$;

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each of R^{5a} and R^{5b} is 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, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$;

R^{5a} and R^{5b}, together with the carbon atom to which they are attached, form an oxo group;

each R^{5c} is hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $C(O)R^D$;

each R^7 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, halo, oxo, cyano, $NR^BC(O)R^D$, $-C(O)NR^BR^C$, $-C(O)R^D$, or $-SR^E$, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more R^9;

R^8 and R^9 are each 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 of 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, cycloalkyl, heterocyclyl, 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, $-OR^A$; 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^{10};

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;

R^{10} is C_1-C_6-alkyl or halo;

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 $-OR^A$;

n is 0, 1, 2, 3, or 4; and

x is 0, 1, or 2.

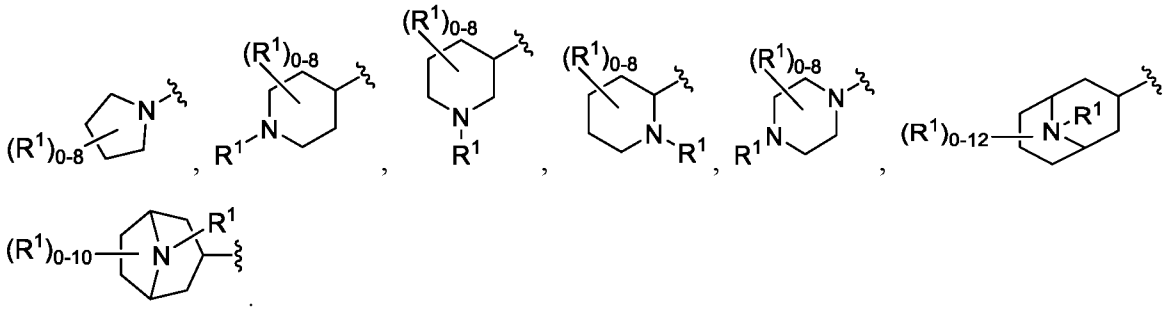
2. The compound of claim 1, wherein A is a monocyclic or bicyclic heterocyclyl.

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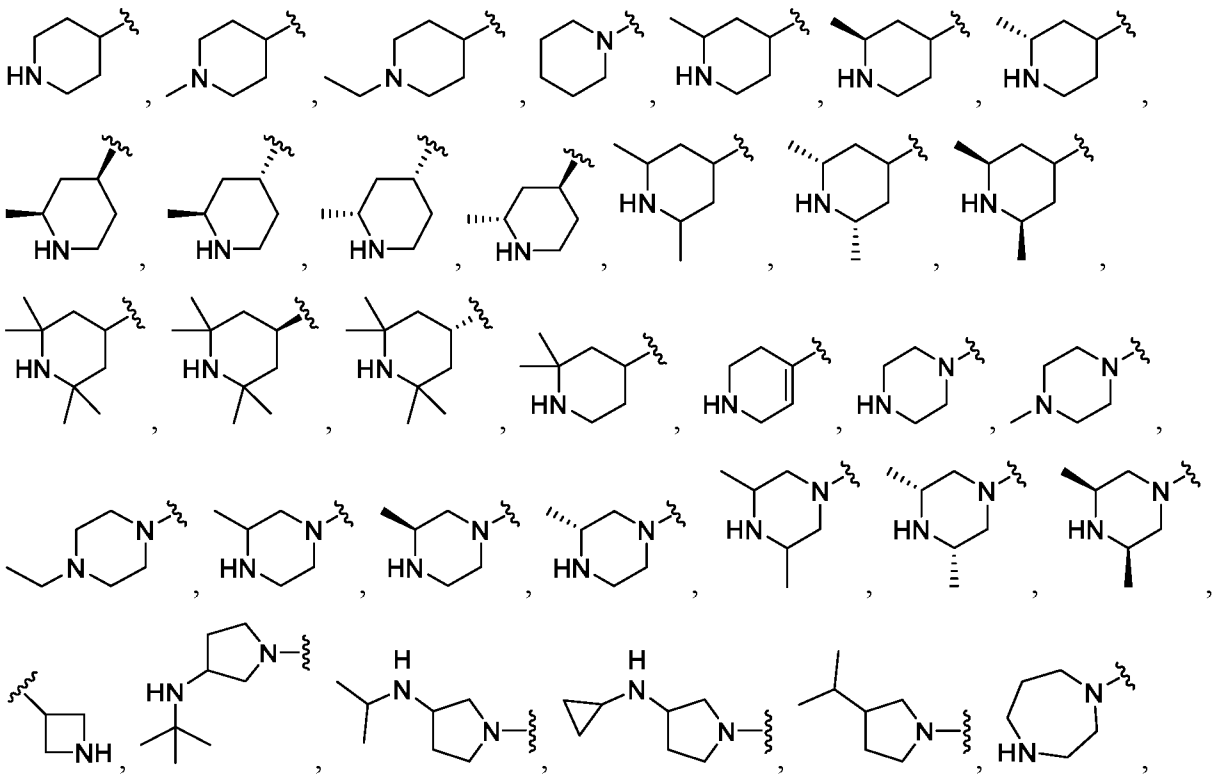
3. The compound of any one of the preceding claims, wherein A is monocyclic heterocyclyl.

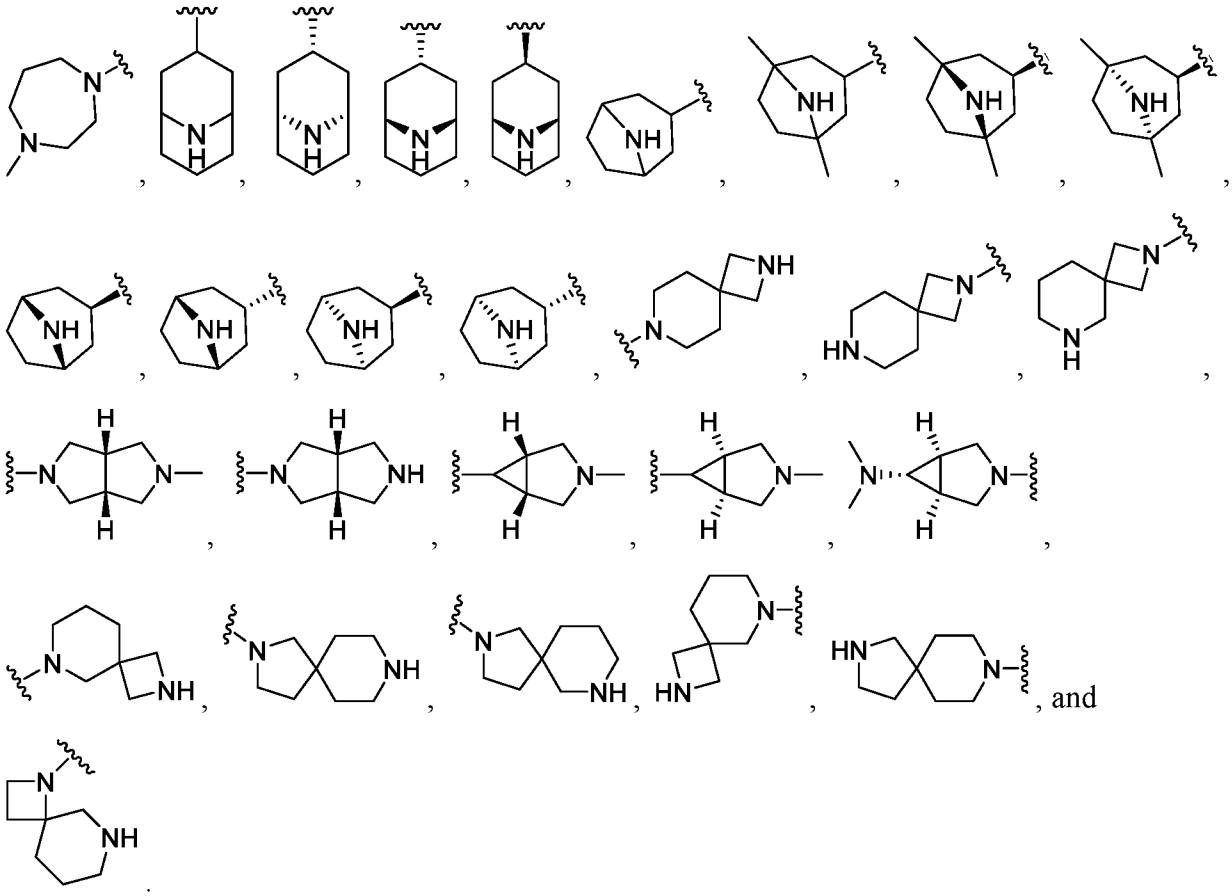
4. The compound of any one of the preceding claims, wherein A is a nitrogen-containing heterocyclyl.

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

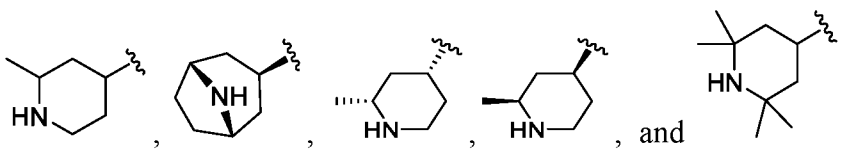


6. The compound of any one of the preceding claims, wherein A is selected from

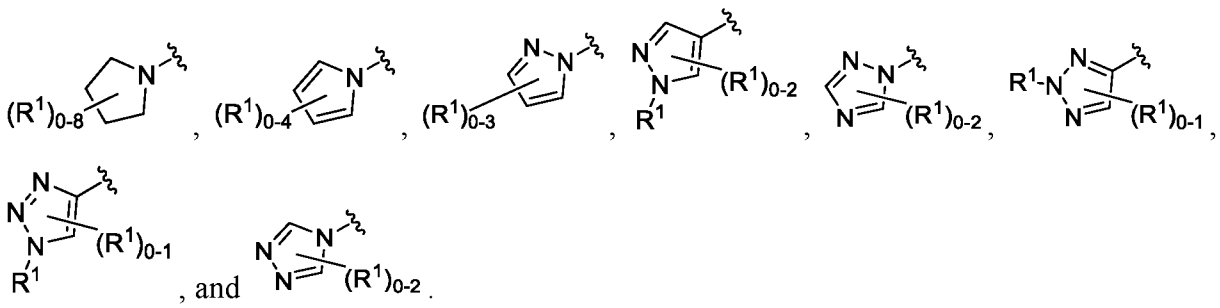




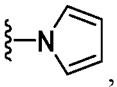
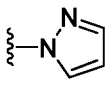
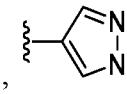
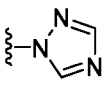
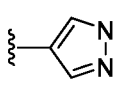
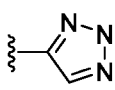
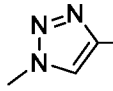
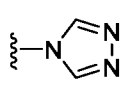
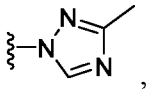
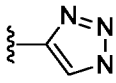
7. The compound of any one of the preceding claims, wherein A is selected from

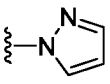
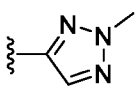
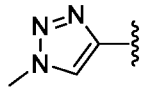
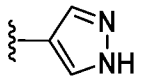


8. The compound of any one of the preceding claims, wherein B is selected from



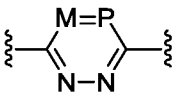
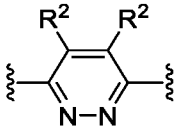
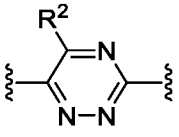
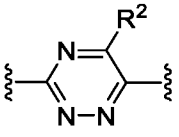
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9. The compound of any one of the preceding claims, wherein B is selected from , , , , , , , , , and .

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

11. The compound of any one of the preceding claims, wherein L is absent, -O- or -N(R^3)- (e.g., -N(CH_3)- or -NH-).

12. The compound of any one of the preceding claims, wherein L is -N(R^3)- (e.g., -N(CH_3)- or -NH-).

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

14. The compound of any one of the preceding claims, wherein each of M and P is independently C(R^2) (e.g., CH).

15. The compound of any one of the preceding claims, wherein one of X and Y is C(R^{5a})(R^{5b}) and the other of X and Y is N(R^{5c}).

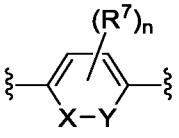
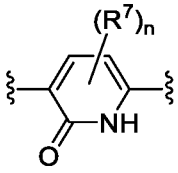
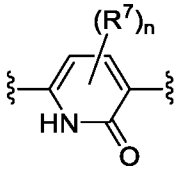
16. The compound of claim 15, wherein R^{5a} and R^{5b}, together with the carbon atom to which they are attached, form an oxo group.

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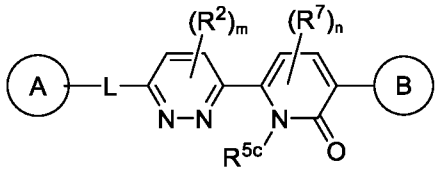
17. The compound of any one of the preceding claims, wherein X is $N(R^{5c})$ (e.g., NH) and Y is $C(R^{5a})(R^{5b})$ (e.g., C(O)).

18. The compound of any one of the preceding claims, wherein X is N and Y is $C(R^{5a})$ (e.g., $C(OCH_3)$).

19. The compound of any one of the preceding claims, wherein one of X and Y is C(O) and the other of X and Y is NH.

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

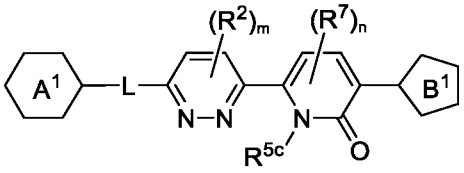
21. The compound of any one of claims 1-19, wherein the compound is a compound of Formula (I-c):



(I-c),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L, R^2, R^{5c}, R^7, m, n, and subvariables thereof are as described in claim 1.

22. The compound of any one of claims 1-19, wherein the compound is a compound of Formula (I-d):



(I-d),

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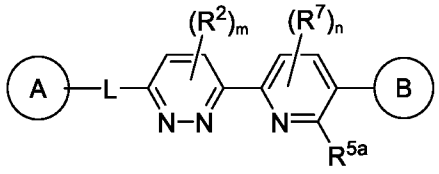
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

A^1 is 6-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

B^1 is 5-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; and

L, R^1, R^2, R^{5c}, R^7, m, n, and subvariables thereof are as described in claim 1.

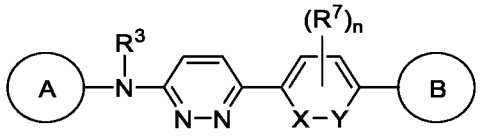
23. The compound of any one of claims 1-20, wherein the compound is a compound of Formula (I-e):



(I-e),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L, R^2, R^{5a}, R^7, m, n, and subvariables thereof are as described in claim 1.

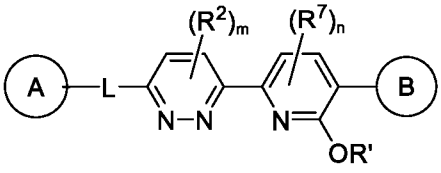
24. The compound of any one of claims 1-20, wherein the compound is a compound of Formula (I-f):



(I-f),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, X, Y, R^3, R^7, n, and subvariables thereof are as described in claim 1.

25. The compound of any one of claims 1-20, wherein the compound is a compound of Formula (I-g):

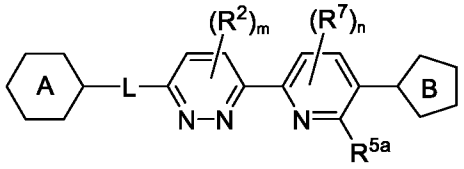


(I-g),

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or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L, R', R^2, R^7, m, n, and subvariables thereof are as described in claim 1, R' is 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, $-C(O)R^D$, or $-C(O)OR^D$..

26. The compound of any one of claims 1-20, wherein the compound is a compound of Formula (I-h):



(I-h),

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

A^1 is 6-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1;

B^1 is 5-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; and

L, R^{5a}, R^2, R^7, m, n, and subvariables thereof are as described in claim 1.

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

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

29. The compound of any one of claims 1-27, or the pharmaceutical composition of claim 28, wherein the compound alters a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

30. The compound of any one of claims 1-27, or the pharmaceutical composition of claim 28, wherein the compound binds to a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

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31. The compound of any one of claims 1-27, or the pharmaceutical composition of claim 28, wherein the compound stabilizes a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

32. The compound of any one of claims 1-27, or the pharmaceutical composition of claim 28, 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.

33. The compound of any one of claims 1-27, or the pharmaceutical composition of claim 28, 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 %.

34. 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 1-27, comprising contacting the nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA) with a compound of Formula (I).

35. The method of claim 34, wherein the component of a spliceosome is recruited to the nucleic acid in the presence of the compound of Formula (I).

36. 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 1-27 or the pharmaceutical composition of claim 28.

37. The method of claim 36, wherein the altering comprises forming a bulge in the nucleic acid.

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38. The method of claim 36, wherein the altering comprises stabilizing a bulge in the nucleic acid.

39. The method of claim 36, wherein the altering comprises reducing a bulge in the nucleic acid.

40. The method of any one of any one of claims 36-39, wherein the nucleic acid comprises a splice site.

41. 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 1-27 or the pharmaceutical composition of claim 28.

42. The composition for use of claim 41, wherein the disease or disorder comprises a proliferative disease (e.g., cancer, a benign neoplasm, or angiogenesis).

43. The composition for use of claim 41, 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.

44. The composition for use of claim 41, wherein the disease or disorder comprises neurological disease or disorder.

45. The composition for use of claim 41, wherein the disease or disorder comprises Huntington's disease.