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(54) Title: COMPOUNDS AND METHODS FOR MODULATING SPLICING

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

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COMPOUNDS AND METHODS FOR MODULATING SPLICING

CLAIM OF PRIORITY

This application claims priority to U.S. Application No. 62/983,539, filed February 28, 2020; U.S. Application No. 63/007,145, filed April 8, 2020; U.S. Application No. 63/040,477, filed June 17, 2020; U.S. Application No. 63/072,919, filed August 31, 2020; and U.S. Application No. 63/126,324, filed December 16, 2020. The disclosure of each of the foregoing applications is incorporated herein by reference in its entirety.

BACKGROUND

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

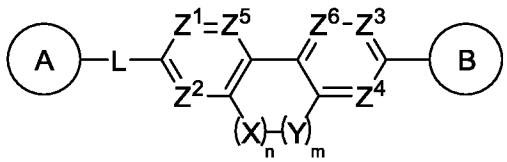
SUMMARY

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

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

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

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



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

absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -S-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) or N; X and Y are each independently O, C(R^{7a})(R^{7b}), or N(R^{7c}), wherein X and Y are not both O; 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, heteroaryl, C_1-C_6 alkylene-aryl, C_2-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, C_2-C_6 alkenylene-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^4 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, or heterocyclyl, wherein each alkyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^{12}; each R^5 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$C(O)R^D$, or –$C(O)OR^D$; R^6 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, aryl, heteroaryl, halo, cyano, –OR^A, –NR^BR^C, –$C(O)R^D$, or –$C(O)OR^D$; R^{7a}, R^{7b}, and R^{7c} are each independently hydrogen, C_1-C_6-alkyl, or halo; or R^{7a} and R^{7b}, together with the carbon atom to which they are attached, form an oxo group; each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –SR^E, or –$S(O)_xR^D$, wherein each 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-cycloalkyl, C_1-C_6 alkylene-heterocyclyl, 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, aryl, heteroaryl, C_1-C_6 alkylene-cycloalkyl, C_1-C_6 alkylene-heterocyclyl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, or –OR^A; or R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl or heteroaryl 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-cycloalkyl, C_1-C_6 alkylene-heterocyclyl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl; each R^{10} is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{11} is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$; each R^{12} is independently deuterium, halo, cyano, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-C(O)R^D$; each R^{A1} is hydrogen or C_1-C_6-alkyl; each of m and n is independently 1 or 2; and x is 0, 1, or 2.

In another aspect, the present invention provides pharmaceutical compositions comprising a compound of Formula (I) (e.g., a compound of Formulas (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), or (I-i)), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient. In an embodiment, the pharmaceutical compositions described herein include an effective amount (e.g., a therapeutically effective amount) of a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), or (I-i)), 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), (I-h), or (I-i)) 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), (I-h), or (I-i)) 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), (I-h), or (I-i)) 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), (I-h), or (I-i)) 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), (I-h), or (I-i)) 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), (I-h), or (I-i))) 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), (I-h), or (I-i)) 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), (I-h), or (I-i)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another aspect, the present disclosure provides compositions for use in up-regulating the expression of (e.g., the level of or the rate of production of) a target protein with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), or (I-i)) 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), (I-h), or (I-i))) 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), (I-h), or (I-i)), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer thereof, or a pharmaceutical composition thereof. In certain embodiments, the kits described herein further include instructions for administering the compound of Formula (I) or the pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer thereof, or the pharmaceutical composition thereof.

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

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

DETAILED DESCRIPTION

Selected Chemical Definitions

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

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

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

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

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

substituted (a "substituted alkyl") with one or more substituents; e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkyl group is unsubstituted $C_{1-}C_{10}$ alkyl (e.g., $-CH_3$). In certain embodiments, the alkyl group is substituted $C_{1-}C_6$ alkyl.

As used herein, "alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 24 carbon atoms, one or more carbon–carbon double bonds, and no triple bonds ("C_2-C_{24} alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_2-C_{10} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_2-C_8 alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_2-C_6 alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_2-C_4 alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of C_2-C_6 alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Each instance of an alkenyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkenyl group is unsubstituted $C_{1-}C_{10}$ 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 ("C_2-C_{24} alkenyl"). In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_2-C_{10} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_2-C_8 alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_2-C_6 alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C_2-C_4 alkynyl groups include ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Each instance of an alkynyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents *e.g.*, for instance from 1 to 5

substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkynyl group is unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-6} alkynyl.

As used herein, the term "haloalkyl," refers to a non-cyclic stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one halogen selected from the group consisting of F, Cl, Br, and I. The halogen(s) F, Cl, Br, and I may be placed at any position of the haloalkyl group. Exemplary haloalkyl groups include, but are not limited to: $-CF_3$, $-CCl_3$, $-CH_2-CF_3$, $-CH_2-CCl_3$, $-CH_2-CBr_3$, $-CH_2-CI_3$, $-CH_2-CH_2-CH(CF_3)-CH_3$, $-CH_2-CH_2-CH(Br)-CH_3$, and $-CH_2-CH=CH-CH_2-CF_3$. Each instance of a haloalkyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted haloalkyl") or substituted (a "substituted haloalkyl") with one or more substituents *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

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

As used herein, "aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_6-C_{14} aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} aryl"; *e.g.*, anthracyl). An aryl group may be described as, e.g., a C_6-C_{10}-membered aryl, wherein the term "membered" refers to the non-hydrogen ring atoms within the moiety. Aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl. Each instance of an aryl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_6-C_{14} aryl. In certain embodiments, the aryl group is substituted C_6-C_{14} aryl.

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

or more substituents *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent

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

As used herein, "cycloalkyl" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C_3-C_{10} cycloalkyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_3-C_8 cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_3-C_6 cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_3-C_6 cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_5-C_{10} cycloalkyl"). A cycloalkyl group may be described as, e.g., a C_4-C_7-membered cycloalkyl, wherein the term "membered" refers to the non-hydrogen ring atoms within the moiety. Exemplary C_3-C_6 cycloalkyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5),

cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_3-C_8 cycloalkyl groups include, without limitation, the aforementioned C_3-C_6 cycloalkyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), cubanyl (C_8), bicyclo[1.1.1]pentanyl (C_5), bicyclo[2.2.2]octanyl (C_8), bicyclo[2.1.1]hexanyl (C_6), bicyclo[3.1.1]heptanyl (C_7), and the like. Exemplary C_3-C_{10} cycloalkyl groups include, without limitation, the aforementioned C_3-C_8 cycloalkyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. As the foregoing examples illustrate, in certain embodiments, the cycloalkyl group is either monocyclic ("monocyclic cycloalkyl") or contain a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic cycloalkyl") and can be saturated or can be partially unsaturated. "Cycloalkyl" also includes ring systems wherein the cycloalkyl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is on the cycloalkyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the cycloalkyl ring system. Each instance of a cycloalkyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted cycloalkyl") or substituted (a "substituted cycloalkyl") with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C_3-C_{10} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_3-C_{10} cycloalkyl.

"Heterocyclyl" as used herein refers to a radical of a 3– to 10–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("3–10 membered heterocyclyl"). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic ("monocyclic heterocyclyl") or a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl"), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more cycloalkyl groups wherein the point of attachment is either on the cycloalkyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on

the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. A heterocyclyl group may be described as, e.g., a 3-7-membered heterocyclyl, wherein the term "membered" refers to the non-hydrogen ring atoms, i.e., carbon, nitrogen, oxygen, sulfur, boron, phosphorus, and silicon, within the moiety. Each instance of heterocyclyl may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

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

heterocyclyl ring (also referred to herein as a 5,5–bicyclic heterocyclyl ring) include, without limitation, octahydropyrrolopyrrolyl (e.g., octahydropyrrolo[3,4-c]pyrrolyl), and the like. Exemplary 6-membered heterocyclyl groups fused to a heterocyclyl ring (also referred to as a 4,6-membered heterocyclyl ring) include, without limitation, diazaspirononanyl (e.g., 2,7-diazaspiro[3.5]nonanyl). Exemplary 6–membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6–bicyclic heterocyclyl ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like. Exemplary 6–membered heterocyclyl groups fused to a cycloalkyl ring (also referred to herein as a 6,7-bicyclic heterocyclyl ring) include, without limitation, azabicyclooctanyl (e.g., (1,5)-8-azabicyclo[3.2.1]octanyl). Exemplary 6–membered heterocyclyl groups fused to a cycloalkyl ring (also referred to herein as a 6,8-bicyclic heterocyclyl ring) include, without limitation, azabicyclononanyl (e.g., 9-azabicyclo[3.3.1]nonanyl).

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

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

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

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

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

As used herein, the term "nucleobase" as used herein, is a nitrogen-containing biological compounds found linked to a sugar within a nucleoside—the basic building blocks of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The primary, or naturally occurring, nucleobases are cytosine (DNA and RNA), guanine (DNA and RNA), adenine (DNA and RNA), thymine (DNA) and uracil (RNA), abbreviated as C, G, A, T, and U, respectively. Because A, G, C, and T appear in the DNA, these molecules are called DNA-bases; A, G, C, and U are called RNA-bases. Adenine and guanine belong to the double-ringed class of molecules called purines (abbreviated as R). Cytosine, thymine, and uracil are all pyrimidines. Other nucleobases that do not function as normal parts of the genetic code, are termed non-naturally occurring. In an embodiment, a nucleobase may be chemically modified, for example, with an alkyl (e.g., methyl), halo, -O-alkyl, or other modification.

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

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

The symbol "$\sim\!\!\sim$" 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,

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 disclosure, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

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

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

Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or

geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. In an embodiment, the stereochemistry depicted in a compound is relative rather than absolute. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). This disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

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

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

pure S–compound. In certain embodiments, the enantiomerically pure S–compound in such compositions can, for example, comprise, at least about 95% by weight S–compound and at most about 5% by weight R–compound, by total weight of the compound.

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

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

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

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

form, including ^{16}O and ^{18}O; N may be in any isotopic form, including ^{14}N and ^{15}N; F may be in any isotopic form, including ^{18}F, ^{19}F, and the like.

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

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

reservoir with a suitable enzyme or chemical reagent.

The term "solvate" refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds of Formula (I) may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

The term "hydrate" refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x\ H_2O$, 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.

Other Definitions

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

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

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

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

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

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

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

or stop the growth or spread of a tumor.

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

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

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

A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle–aged adult, or senior adult)) and/or other non–human animals, for example, mammals (*e.g.*, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or

dogs) and birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys). In certain embodiments, the animal is a mammal. The animal may be a male or female and at any stage of development. A non–human animal may be a transgenic animal.

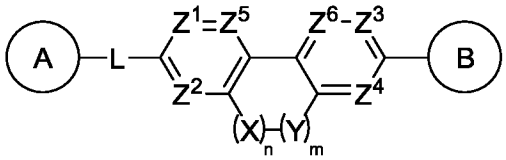
As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of one or more of a symptom, manifestation, or underlying cause of a disease, disorder, or condition (e.g., as described herein), e.g., by administering a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

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

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

Compounds

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



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -S-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) or N; X and Y are each independently O, C(R^{7a})(R^{7b}), or N(R^{7c}), wherein X and Y are not both O; 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, heteroaryl, C_1-C_6 alkylene-aryl, C_2-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, C_2-C_6 alkenylene-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^4 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, or heterocyclyl, wherein each alkyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one

or more R^{12}; each R^5 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$; R^6 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, aryl, heteroaryl, halo, cyano, $-OR^A$, $-NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$; R^{7a}, R^{7b}, and R^{7c} are each independently hydrogen, C_1-C_6-alkyl, or halo; or R^{7a} and R^{7b}, together with the carbon atom to which they are attached, form an oxo group; each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each 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-cycloalkyl, C_1-C_6 alkylene-heterocyclyl, 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, aryl, heteroaryl, C_1-C_6 alkylene-cycloalkyl, C_1-C_6 alkylene-heterocyclyl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, or $-OR^A$; or R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl or heteroaryl 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-cycloalkyl, C_1-C_6 alkylene-heterocyclyl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl; each R^{10} is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{11} is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$; each R^{12} is independently deuterium, halo, cyano, -OR^A, $-NR^BR^C$, $-NR^BC(O)R^D$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-C(O)R^D$; each R^{A1} is hydrogen or C_1-C_6-alkyl; each of m and n is independently 1 or 2; 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 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.

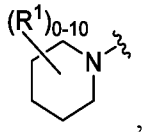
In some embodiments, A or B are independently a nitrogen-containing heterocyclyl, e.g., heterocyclyl comprising one or more nitrogen atom. The one or more nitrogen atom of the nitrogen-containing heterocyclyl may be at any position of the ring. In some embodiments, the nitrogen-containing heterocyclyl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

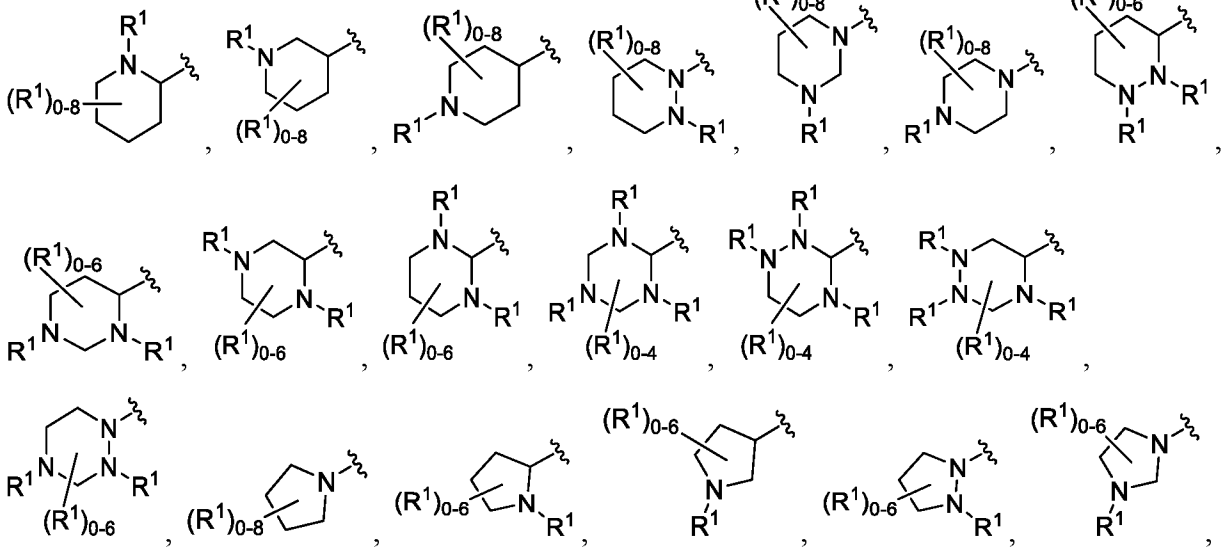
nitrogen of the nitrogen-containing heterocyclyl is substituted, e.g., with R^1. In some embodiments, A is a nitrogen-containing heterocyclyl comprising 1 nitrogen atom and B is a nitrogen-containing heteroaryl or nitrogen-containing heterocyclyl comprising 1, 2, or 3 nitrogen atoms.

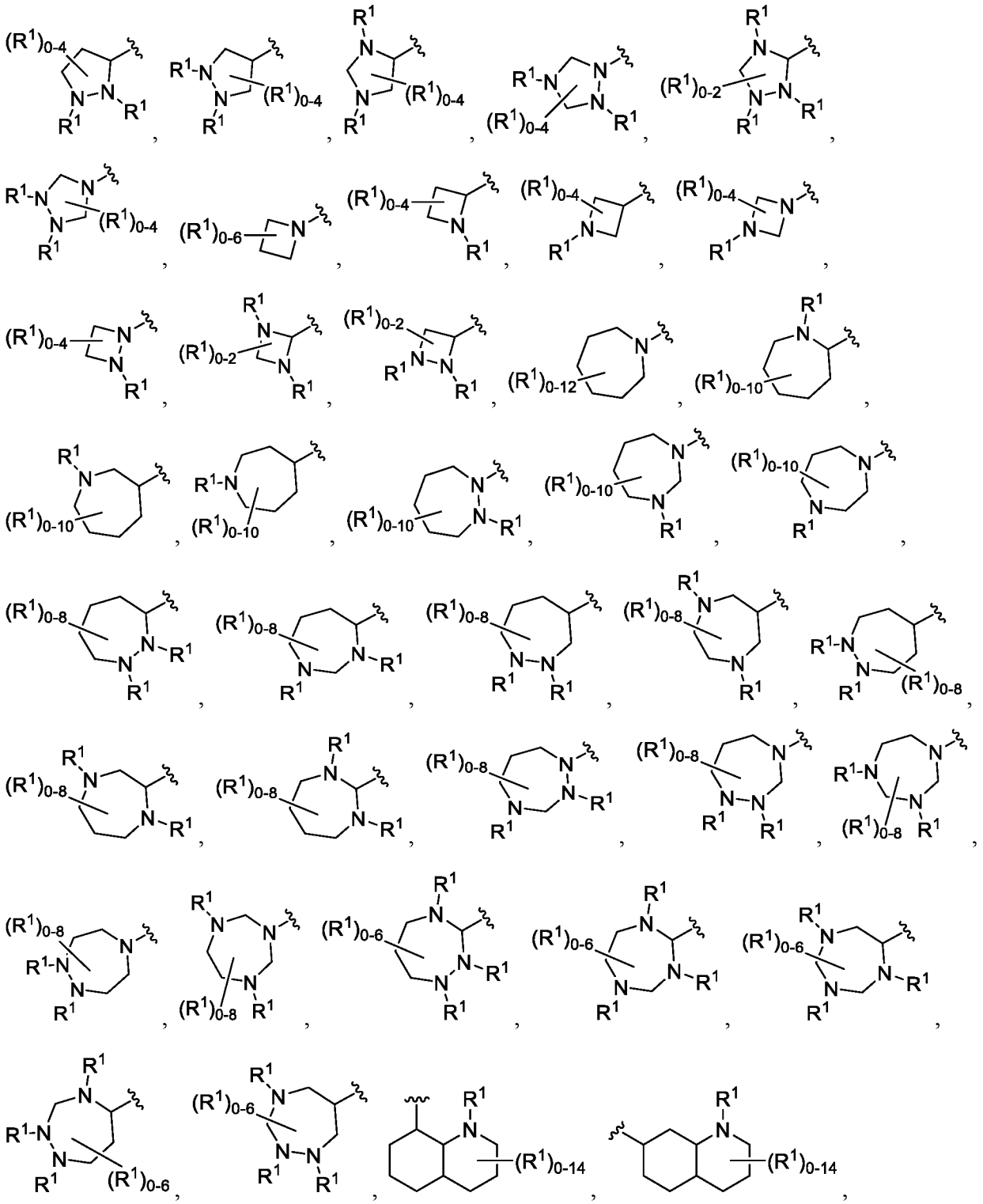
In some embodiments, A or B are independently a nitrogen-containing heteroaryl, e.g., heteroaryl comprising one or more nitrogen atom. The one or more nitrogen atom of the nitrogen-containing heteroaryl may be at any position of the ring. In some embodiments, the nitrogen-containing heteroaryl is monocyclic,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

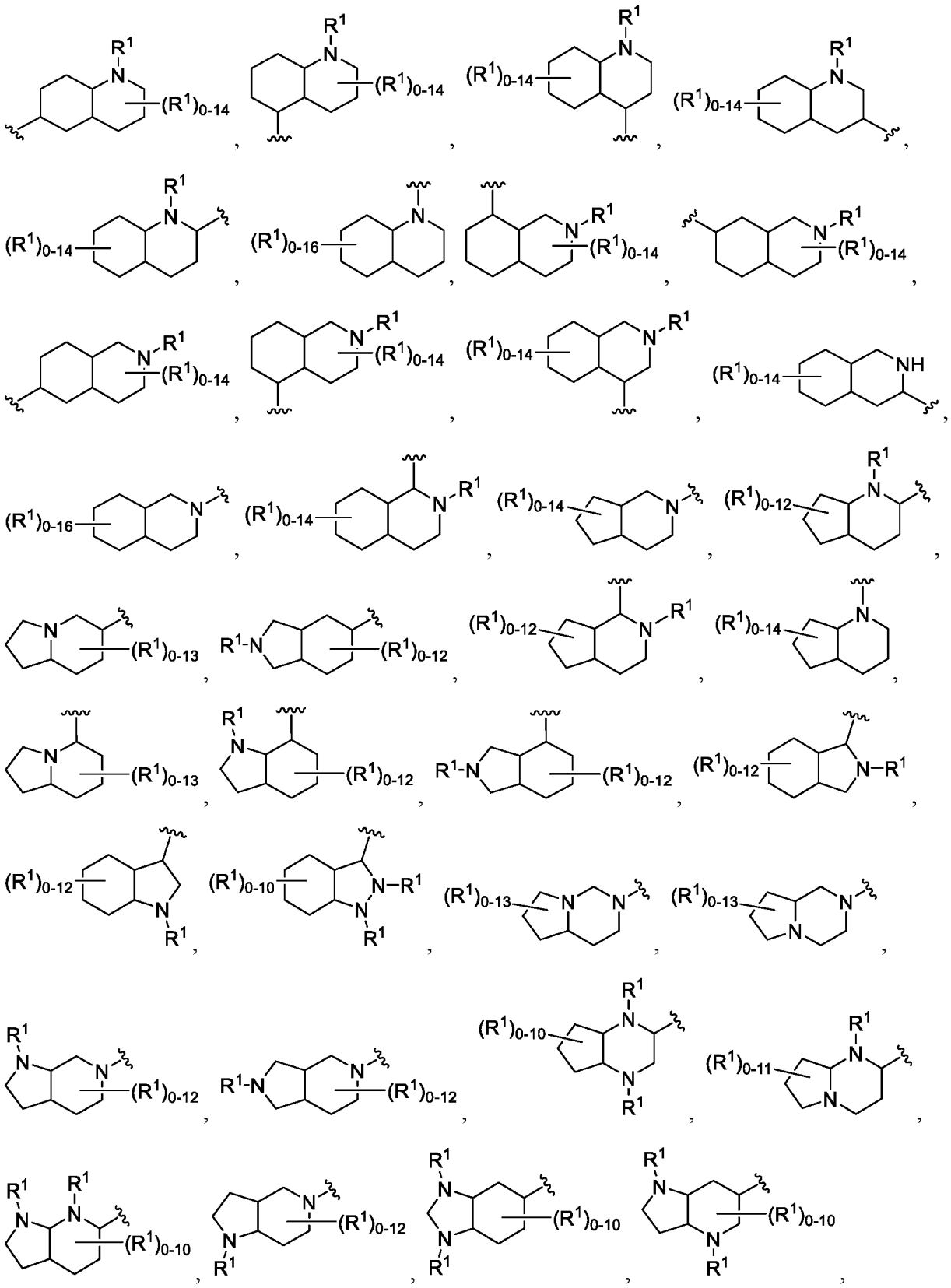
In some embodiments, A is a 6-membered nitrogen-containing heterocyclyl, e.g., a 6-membered heterocyclyl comprising one or more nitrogen. In some embodiments, A is a 6-membered heterocyclyl comprising 1 nitrogen atom. In some embodiments, A is a 6-membered heterocyclyl comprising 2 nitrogen atoms. In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

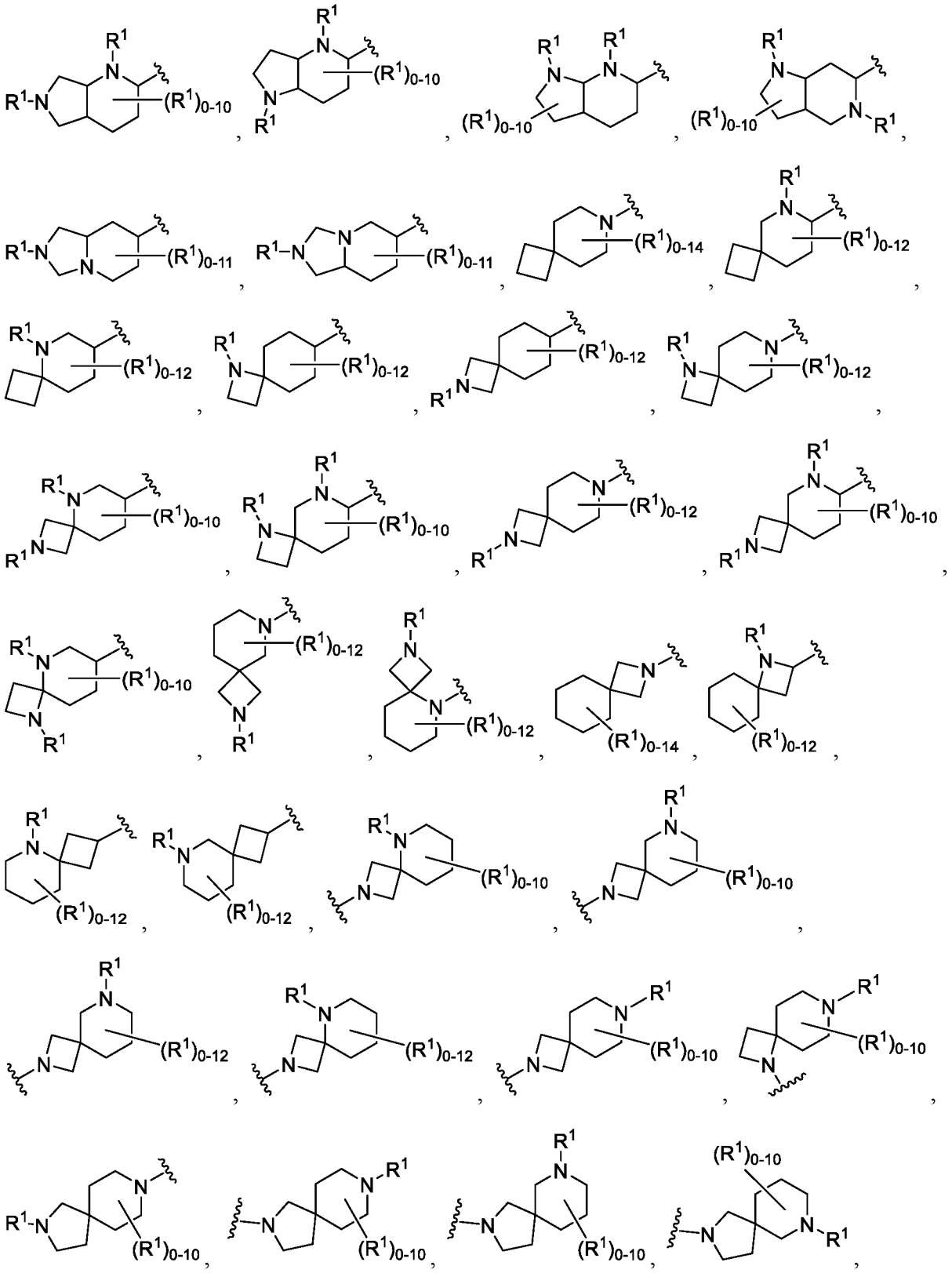
In some embodiments, B is a 5-membered nitrogen-containing heterocyclyl or heteroaryl, e.g., a 5-membered heterocyclyl or heteroaryl comprising one or more nitrogen. In some embodiments, B is a 5-membered heterocyclyl comprising 1 nitrogen atom. In some embodiments, B is a 5-membered heteroaryl comprising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

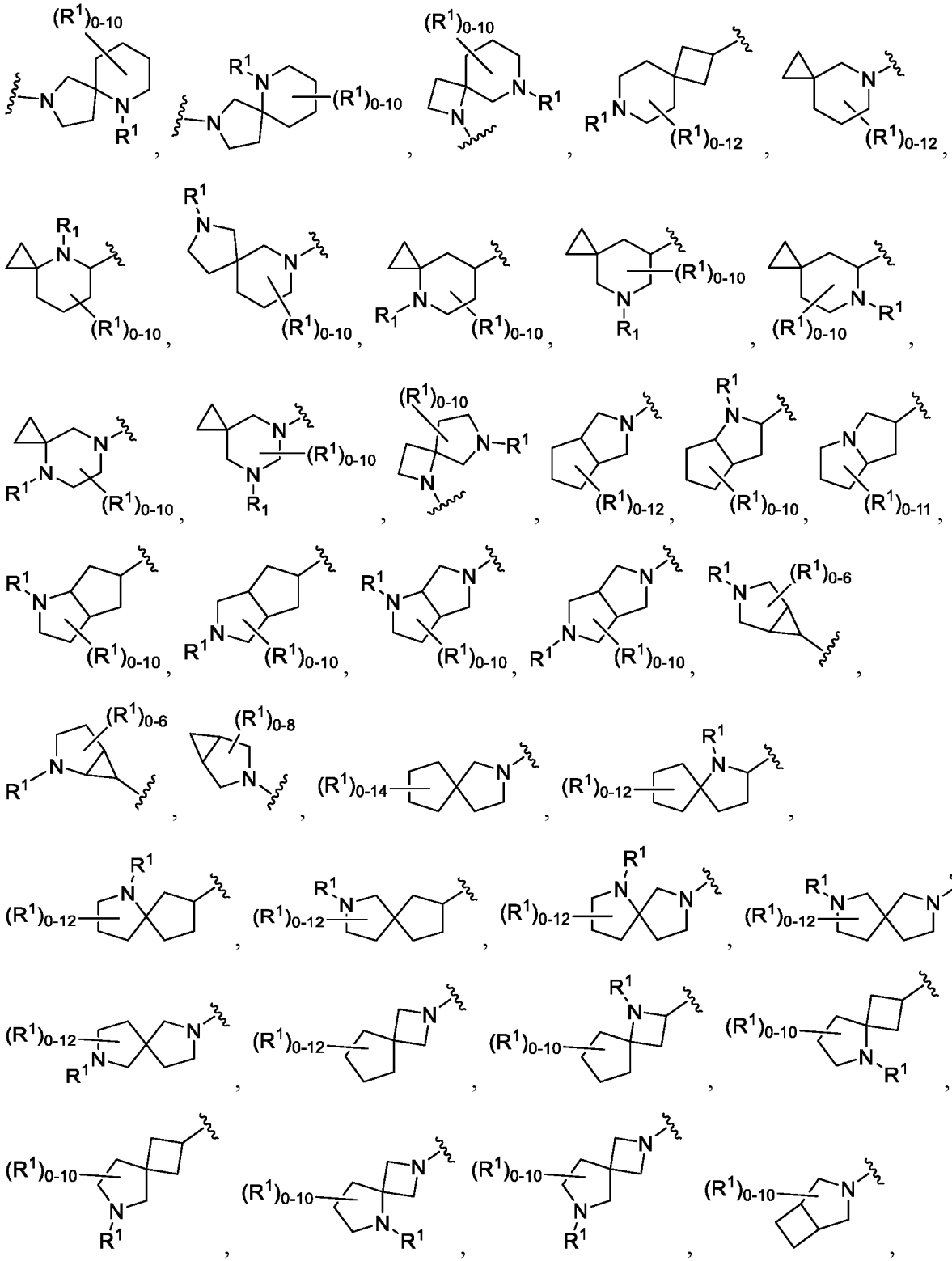
In some embodiments, each of A and B are independently selected from: ,

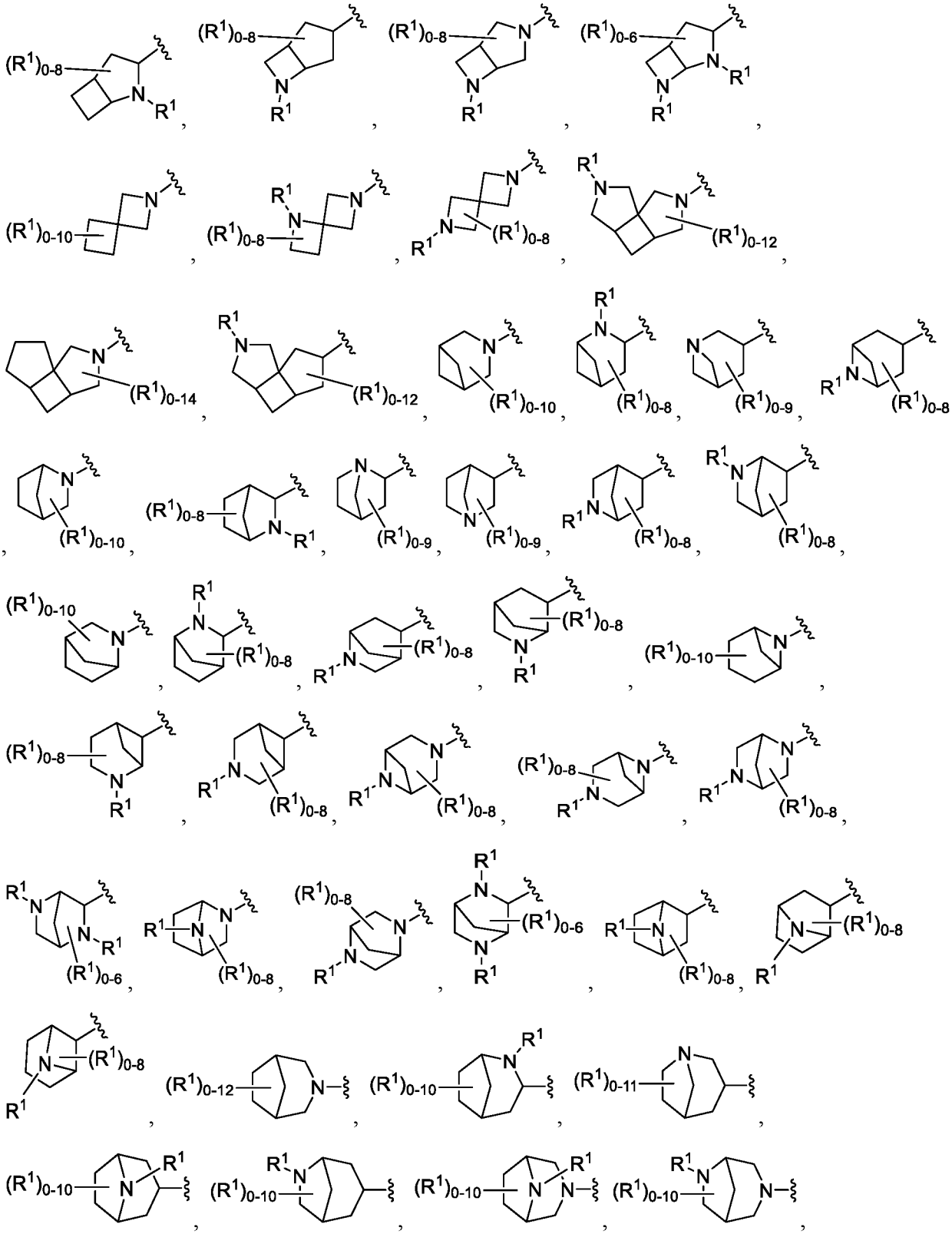


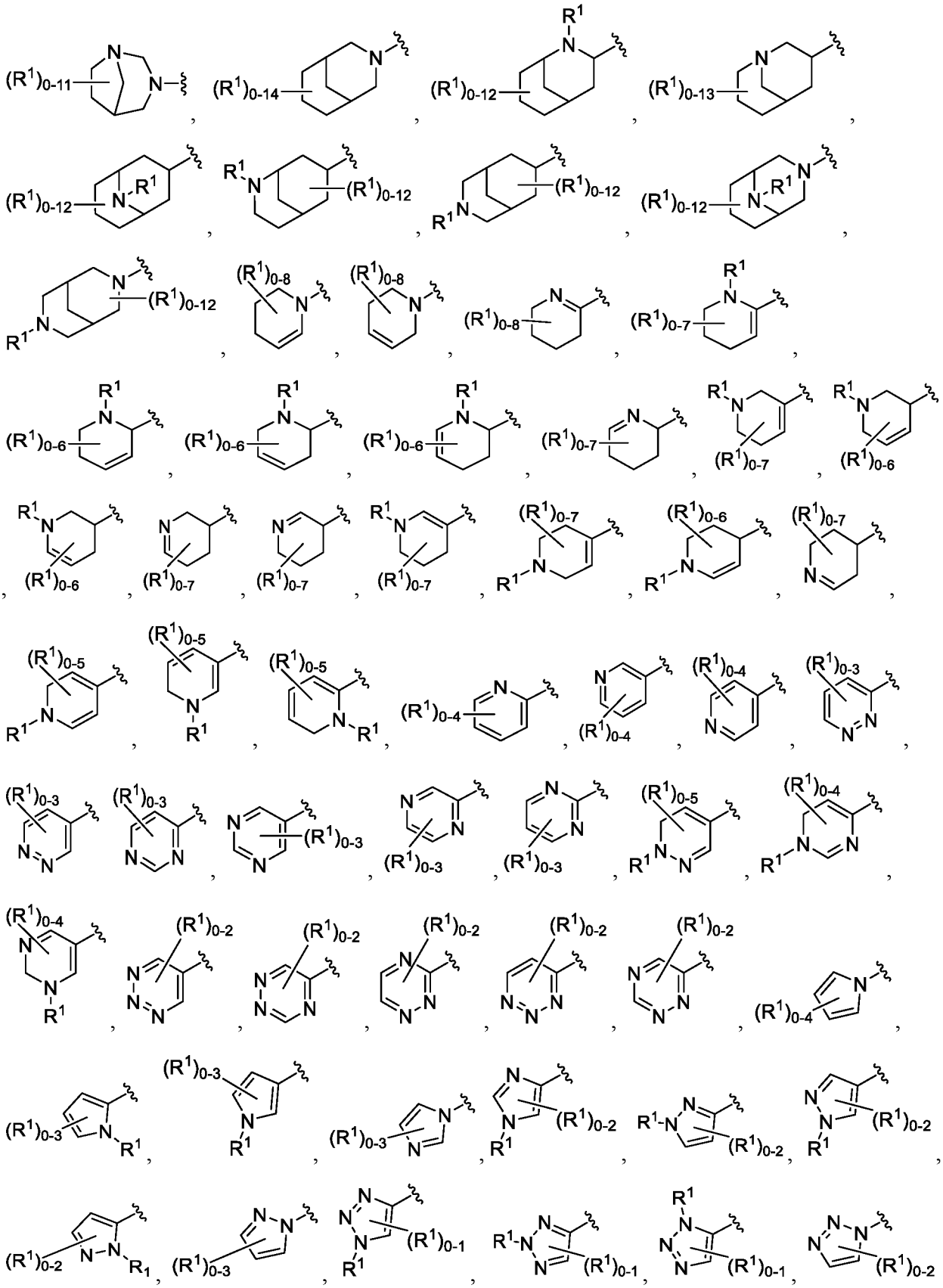


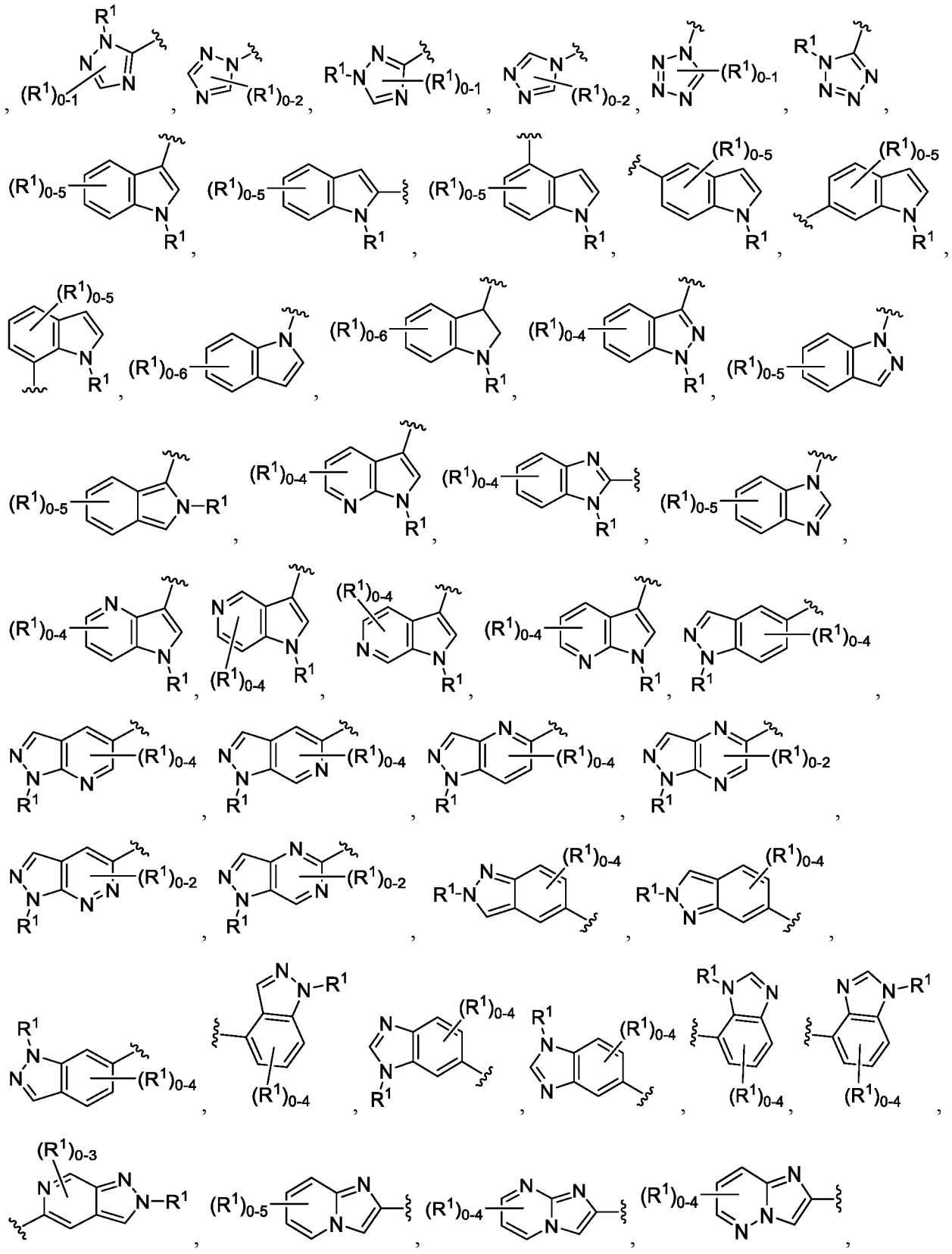


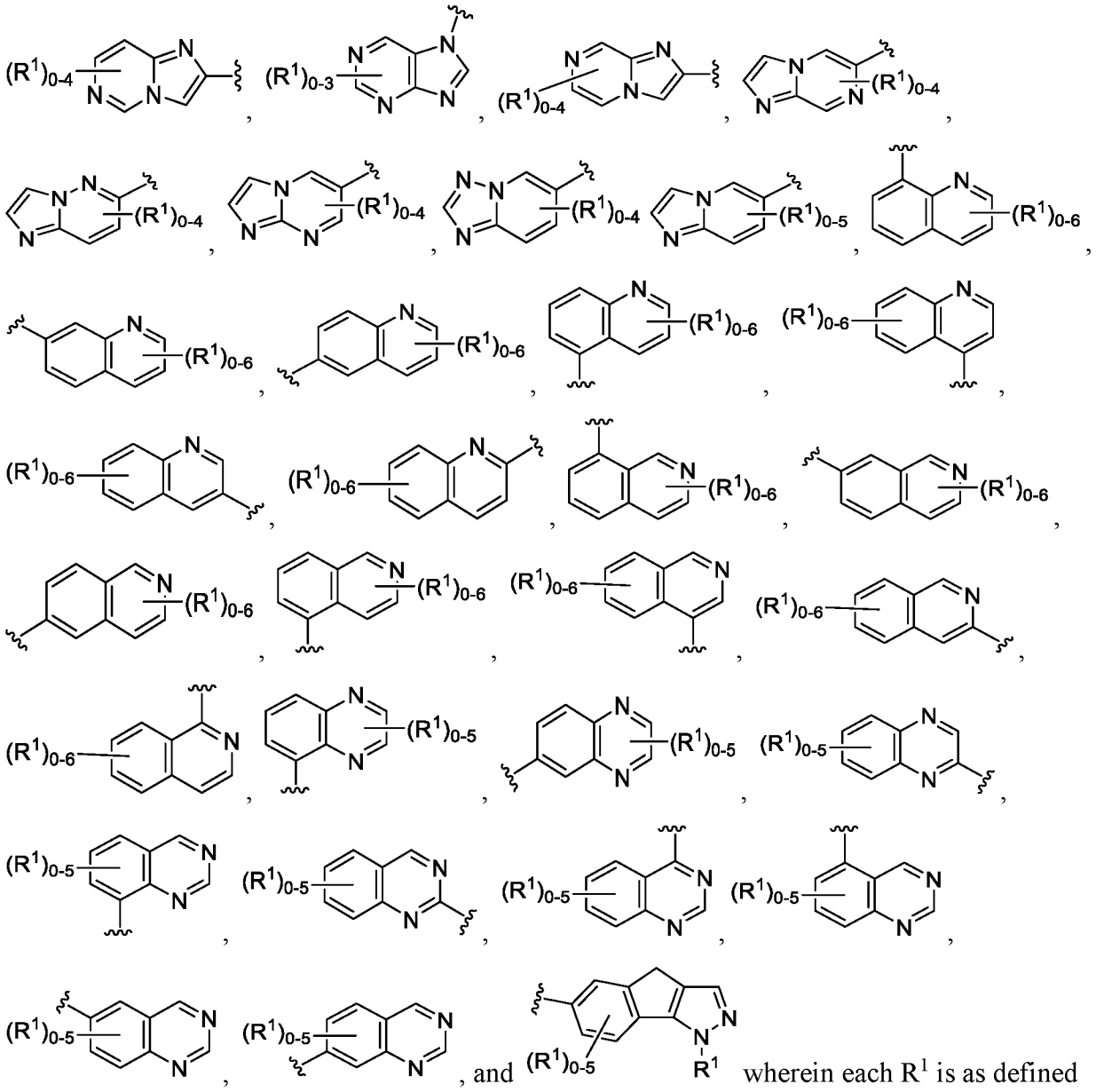






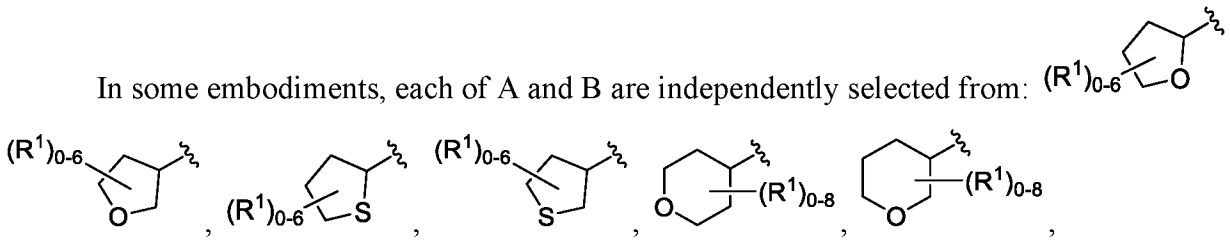


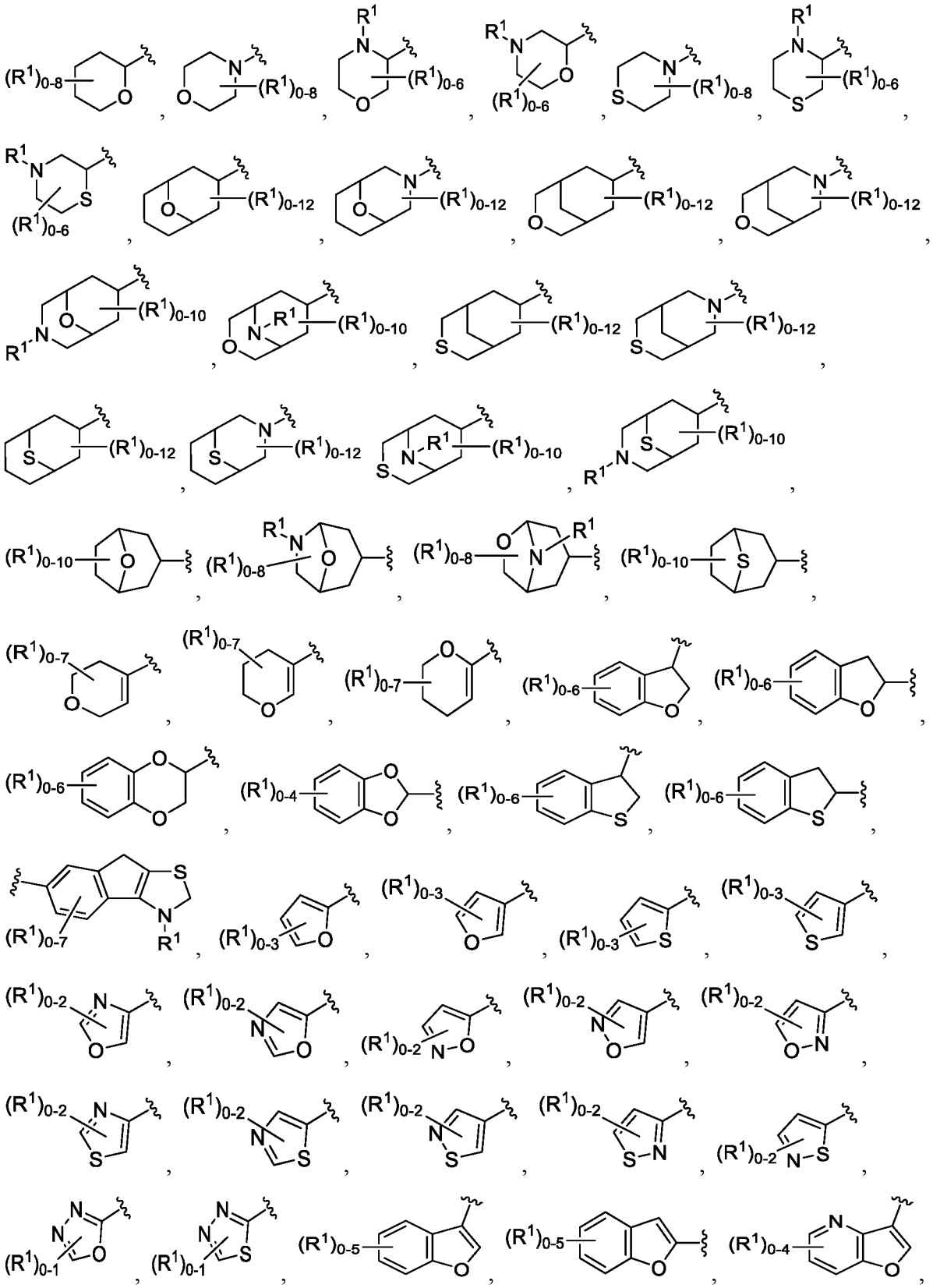


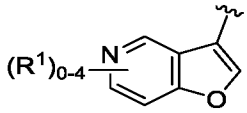
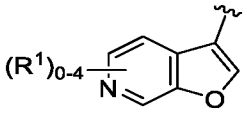
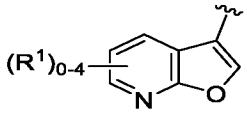
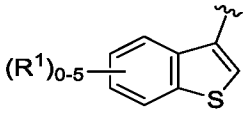
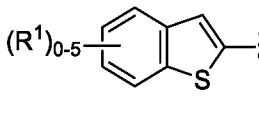
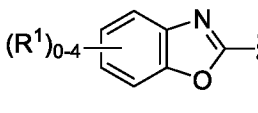
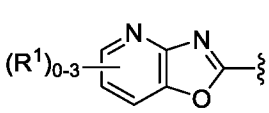
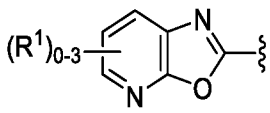
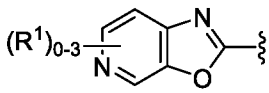
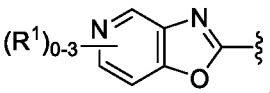
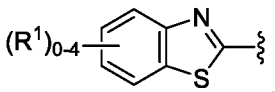
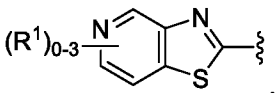
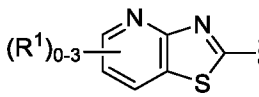
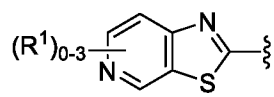
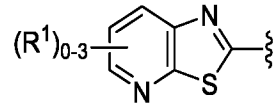
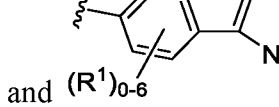
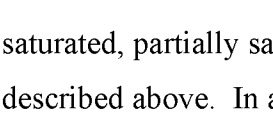
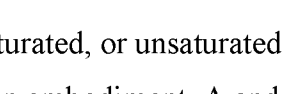
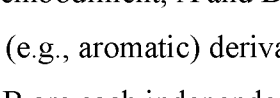


wherein each R^1 is as defined herein. In an embodiment, A and B are each independently a saturated, partially saturated, or unsaturated (e.g., aromatic) derivative of one of the rings described above. In an embodiment, A and B are each independently a stereoisomer of one of the rings described above.

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



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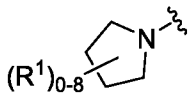
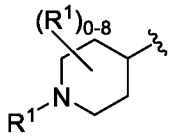
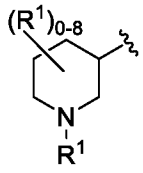
wherein each R^1 is as defined herein. In an embodiment, A and B are each independently a saturated, partially saturated, or unsaturated (e.g., aromatic) derivative of one of the rings described above. In an embodiment, A and B are each independently a stereoisomer of one of the rings described above.

In some embodiments, A is selected from 
, 
, 
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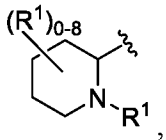
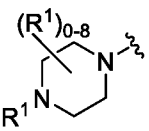
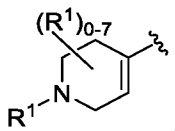
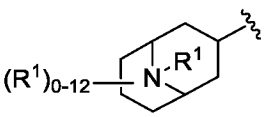
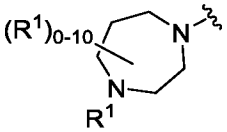

, 
, 
, 
, 
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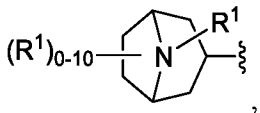
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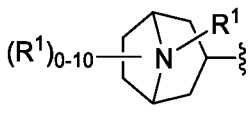
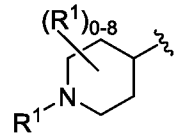
In some embodiments, A is selected from 
, 
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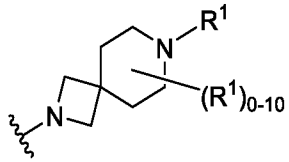
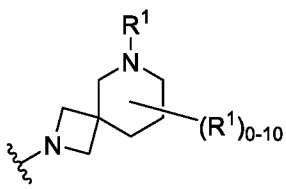
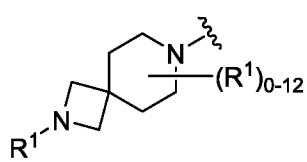
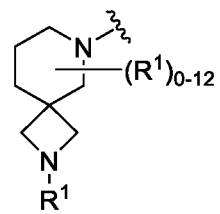

, 
, 
, 
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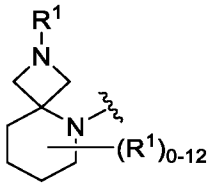
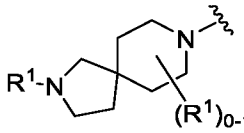
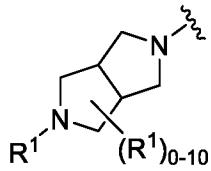
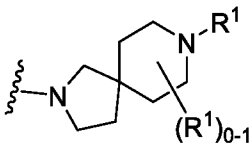
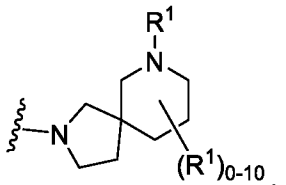
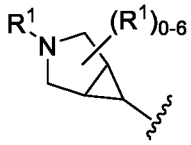
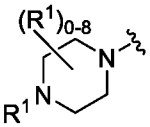
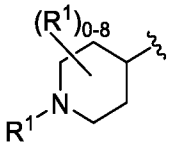
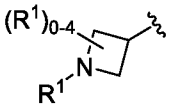
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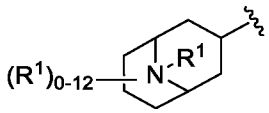
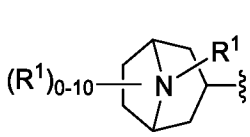
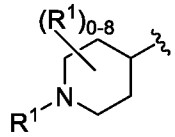

, wherein R^1 is as defined herein.

In some embodiments, A is selected from


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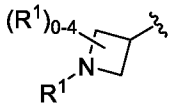
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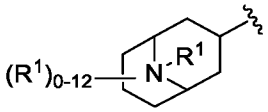
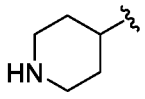
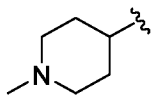
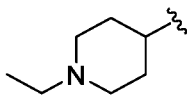
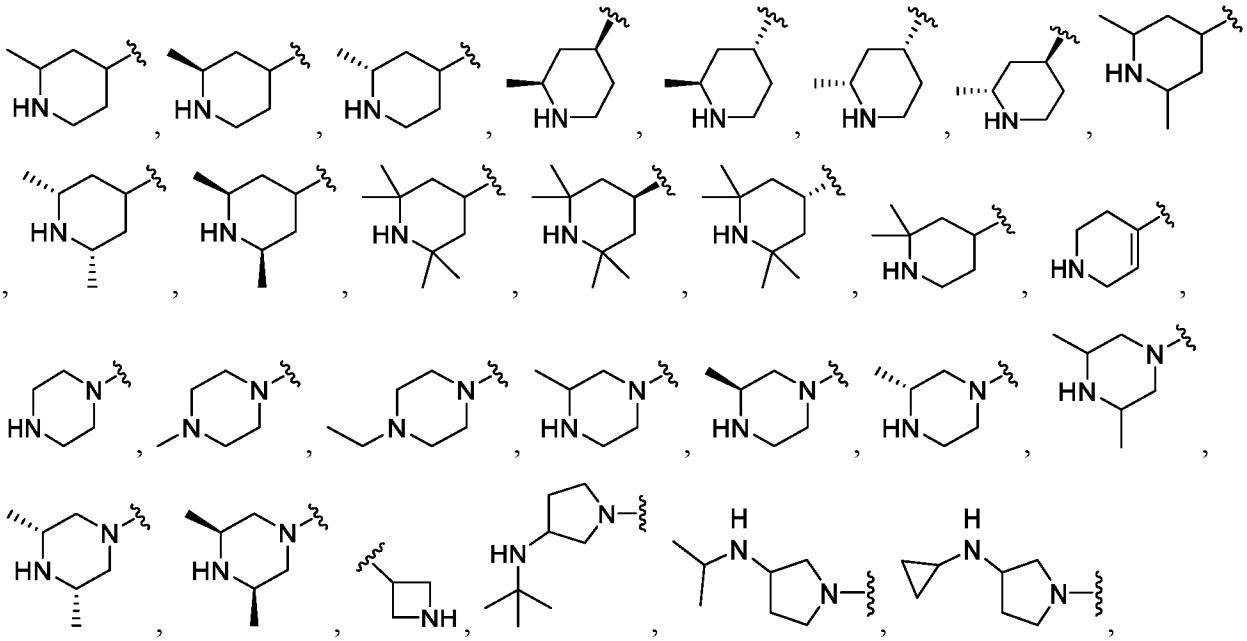
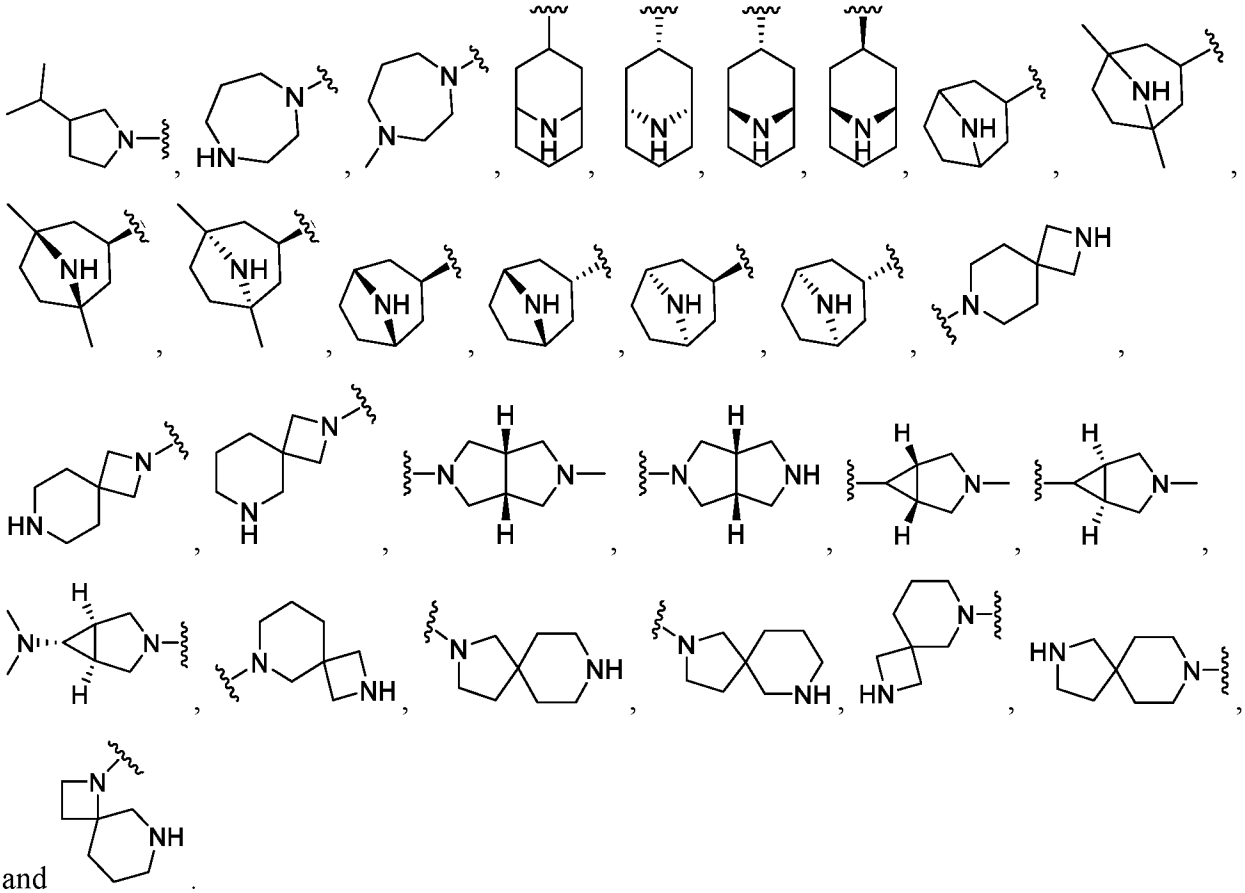
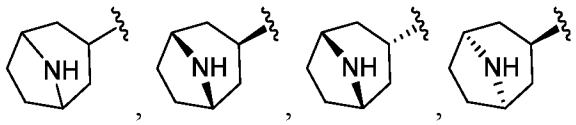
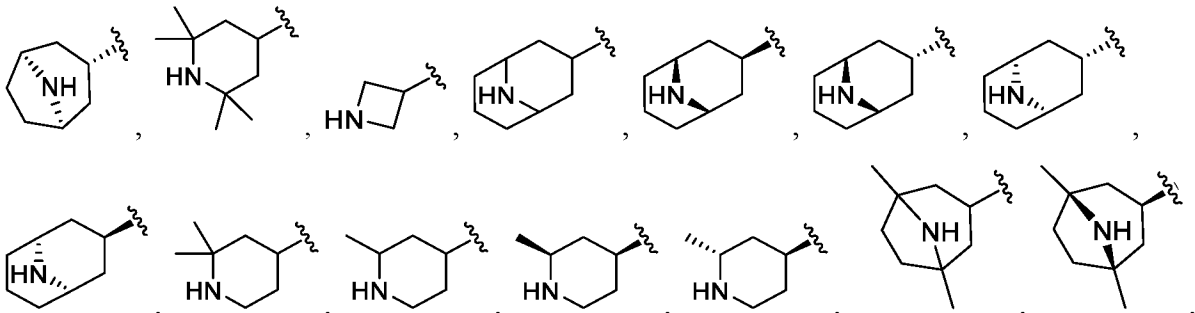

, wherein R^1 is as defined herein.

In some embodiments, A is selected from





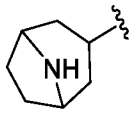
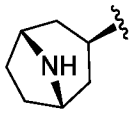
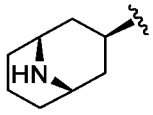
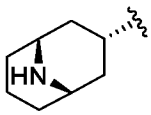
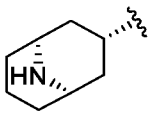
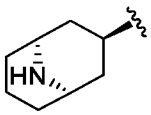
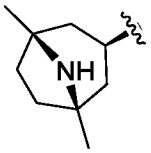


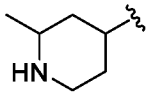
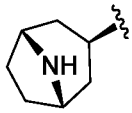
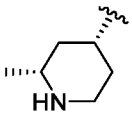
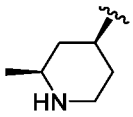
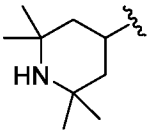
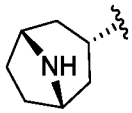
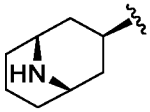
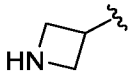
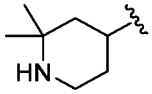
and .

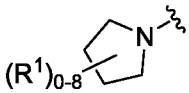
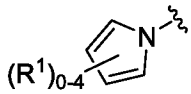
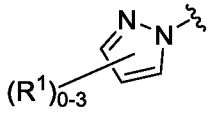
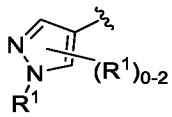
In some embodiments, A is selected from ,

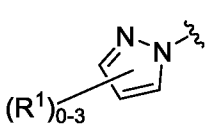
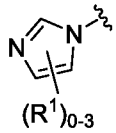
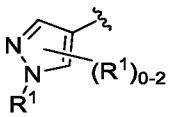
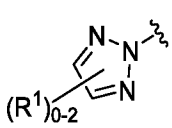
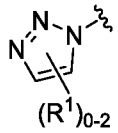
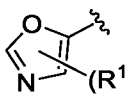
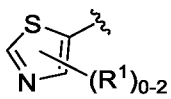
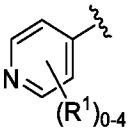
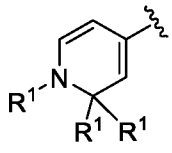
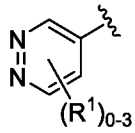
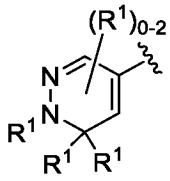
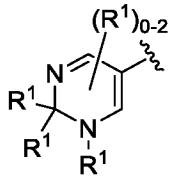
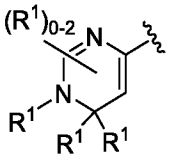


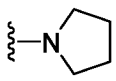
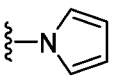
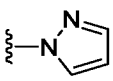
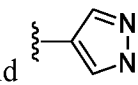
and .

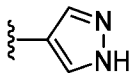
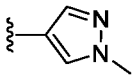
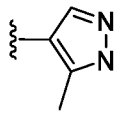
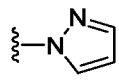
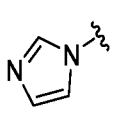
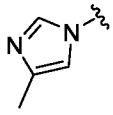
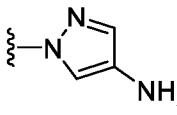
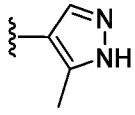
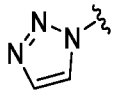
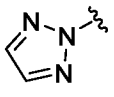
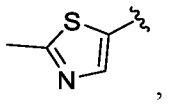
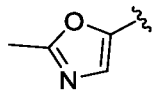
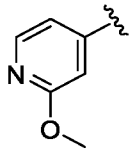
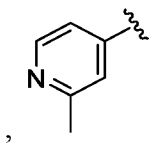
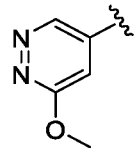
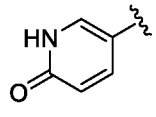
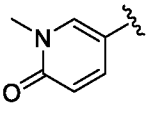
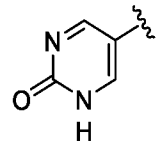
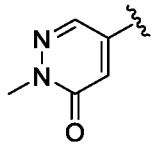
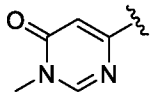
In some embodiments, A is selected from , , , , , , and .

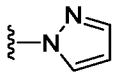
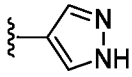
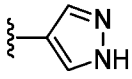
In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is .

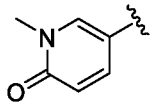
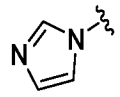
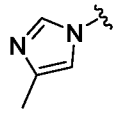
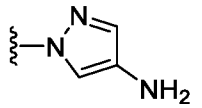
In some embodiments, B is selected from , , , and , wherein R^1 is as defined herein.

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

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

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

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

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

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

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

In some embodiments, L 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^5. In some embodiments, the heteroalkylene comprises 1 or more heteroatoms. In some embodiments, the heteroalkylene comprises one or more of oxygen, sulfur, nitrogen, boron, silicon, or phosphorus. In some embodiments, L is -N(R^4)C(O)-. In some embodiments, L is -C(O)N(R^4)-.

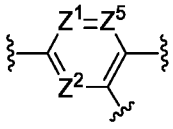
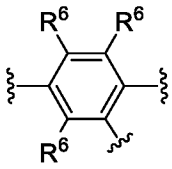
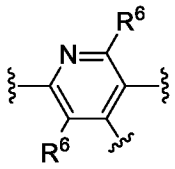
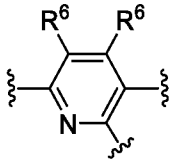
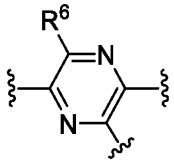
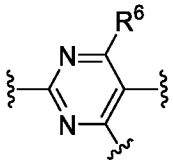
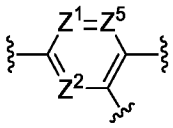
In some embodiments, L is oxygen. In some embodiments, L is nitrogen, which may be substituted with R^4. In some embodiments, L is nitrogen substituted with one R^4. In some embodiments, L is -N(R^4)-. In some embodiments, R^4 is hydrogen, C_1-C_6 alkyl (e.g., CH_3 or CD_3), or cycloalkyl (e.g., cyclopropyl). In some embodiments, R4 is C_1-C_6 alkyl (e.g., CH_3), or

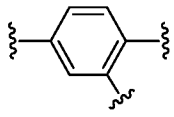
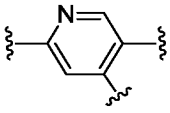
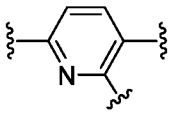
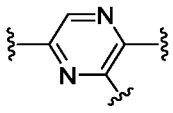
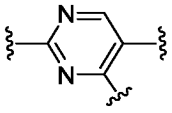
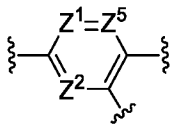
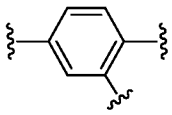
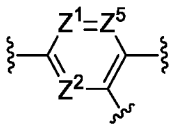
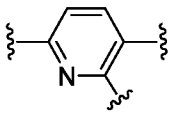
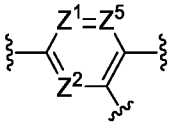
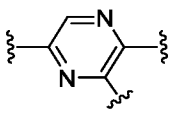
cycloalkyl (e.g., cyclopropyl) substituted with one or more R^{12} (e.g., deuterium). In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-. In some embodiments, L is -O-. In some embodiments, L is -S-.

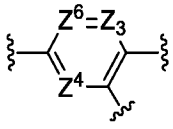
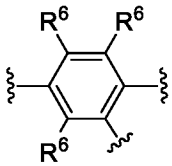
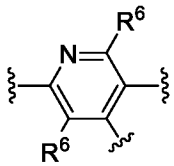
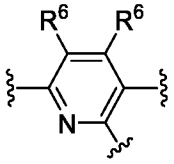
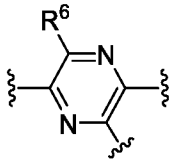
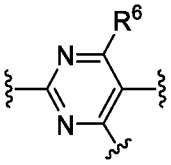
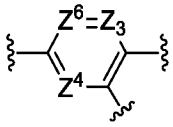
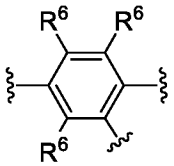
As generally described herein, Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) or N. In some embodiments, Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6). In some embodiments, R^6 is hydrogen. In some embodiments, one of Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 is independently N and the other of Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are independently C(R^6) (e.g., CH). In some embodiments, each of Z^1, Z^2, Z^3, and Z^4 independently refers to C(R^6) (e.g., CH) or N.

In some embodiments, Z^1 and Z^2 are each independently C(R^6), e.g., CH. In some embodiments, Z^3 and Z^4 are each independently C(R^6), e.g., CH. In some embodiments, one of Z^1 and Z^2 is C(R^6), and the other of Z^1 and Z^2 is N. In some embodiments, one of Z^3 and Z^4 is C(R^6), and the other of Z^3 and Z^4 is N. In some embodiments, Z^1 is C(R^6). In some embodiments, Z^1 is N. In some embodiments, Z^2 is C(R^6). In some embodiments, Z^2 is N. In some embodiments, Z^3 is C(R^6). In some embodiments, Z^3 is N. In some embodiments, Z^4 is C(R^6). In some embodiments, Z^4 is N. In some embodiments, Z^5 is C(R^6). In some embodiments, Z^5 is N. In some embodiments, Z^6 is C(R^6). In some embodiments, Z^6 is N.

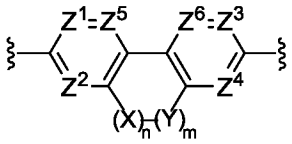
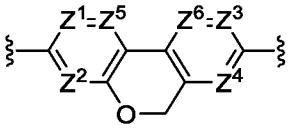
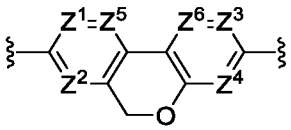
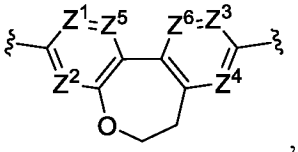
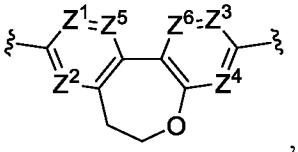
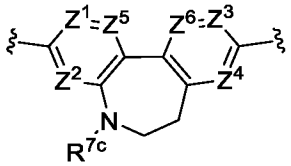
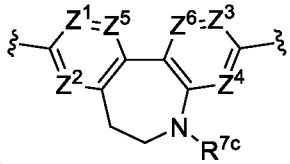
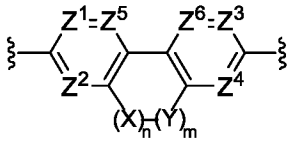
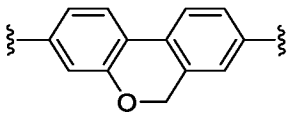
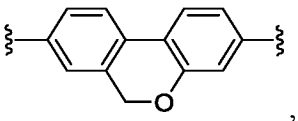
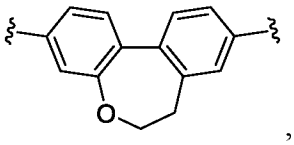
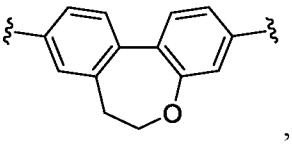
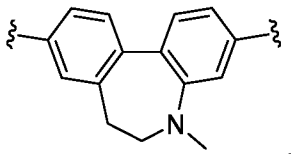
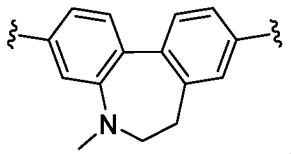
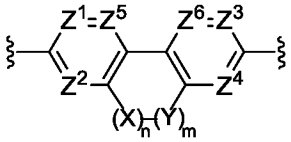
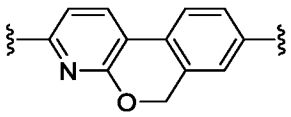
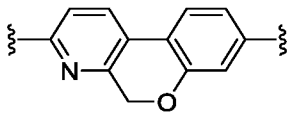
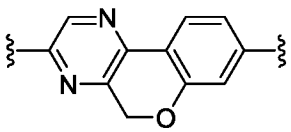
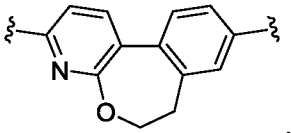
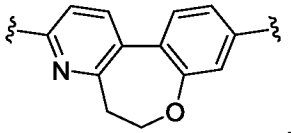
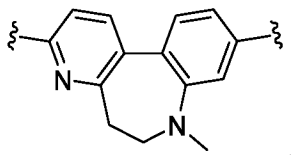
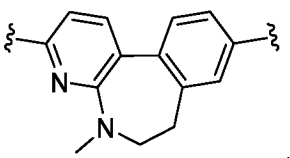
In some embodiments, Z^2 is N and each of Z^1, Z^3, Z^4, Z^5, and Z^6 is independently C(R^6). In some embodiments, each of Z^2 and Z^5 is independently N and each of Z^1, Z^3, Z^4, and Z^6 is independently C(R^6). In some embodiments, each of Z^2 is independently N and each of Z^1, Z^3, Z^4, Z^5, and Z^6 is independently C(R^6). In some embodiments, Z^1 is C(R^6) (e.g., CH) and Z^2 is N. In some embodiments, Z^1 is N and Z^2 is C(R^6) (e.g., CH). In some embodiments, each of Z^2 and Z^5 is independently N.

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

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

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

As generally described herein, each of X and Y independently refer to O, $C(R^{7a})(R^{7b})$, or $N(R^{7c})$. In some embodiments, one of X and Y is $C(R^{7a})(R^{7b})$, and the other of X and Y is O. In some embodiments, one of X and Y is $C(R^{7a})(R^{7b})$, and the other of X and Y is $N(R^{7c})$. In some embodiments, X is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$). In some embodiments, X is O. In some embodiments, X is $N(R^{7c})$. In some embodiments, Y is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$). In some embodiments, Y is O. In some embodiments, Y is $N(R^{7c})$. In some embodiments, X is O and Y is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$). In some embodiments, X is O and Y is $-CH_2-$. In some embodiments, X is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$) and Y is O. In some embodiments, X is $-CH_2-$ and Y is O. In some embodiments, X is $N(R^{7c})$ (e.g., $N(CH_3)$ and Y is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$). In some embodiments, X is $N(CH_3)$ and Y is $-CH_2-$. In some embodiments, Y is $N(R^{7c})$ (e.g., $N(CH_3)$ and X is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$). In some embodiments, Y is $N(CH_3)$ and X is $-CH_2-$.

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

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 (e.g., benzyl), unsubstituted C_1-C_6-alkenylene-aryl (e.g., benzyl), 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 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, each of R^{2a} and R^{2b} are independently hydrogen. In some embodiments, R^{2a} is hydrogen. In some embodiments, R^{2b} is hydrogen. In some embodiments, each of R^{2a} and R^{2b} are independently C_1-C_6-alkyl, C_2-C_6-alkenyl, or C_2-C_6-alkynyl. In some embodiments, R^{2a} is C_1-C_6-alkyl. In some embodiments, R^{2b} is C_1-C_6-alkyl. In some embodiments, R^{2a} is C_2-C_6-alkenyl. In some embodiments, R^{2b} is C_2-C_6-alkenyl. In some embodiments, R^{2a} is C_2-C_6-alkynyl. In some embodiments, R^{2b} is C_2-C_6-alkynyl. In some embodiments, R^{2a} is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^{2b} is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^{2a} is cyano. In some embodiments, R^{2b} is cyano. In some embodiments, R^{2a} is $-OR^A$ (e.g., –OH). In some embodiments, R^{2b} is $-OR^A$ (e.g., –OH).

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

In some embodiments, R^5 is C_1-C_6-alkyl. In some embodiments, R^5 is C_1-C_6-heteroalkyl. In some embodiments, R^5 is C_1-C_6-haloalkyl (e.g., $-CF_3$ or $-CHF_2$). In some embodiments, R^5 is cycloalkyl. In some embodiments, R^5 is halo (e.g., fluoro, chloro, bromo, or iodo). In some embodiments, R^5 is cyano. In some embodiments, R^5 is oxo. In some embodiments, R^5 is $-OR^A$ (e.g., –OH or –OMe). In some embodiments, R^5 is $-NR^BR^C$ (e.g., $-NH_2$ or $-NMe_2$). In some embodiments, R^5 is $-C(O)R^D$. In some embodiments, R^5 is $-C(O)OR^D$.

In some embodiments, R^6 is hydrogen. In some embodiments, R^6 is C_1-C_6 alkyl. In some embodiments, R^6 is C_2-C_6-alkenyl. In some embodiments, R^6 is C_2-C_6-alkynyl. In some embodiments, R^6 is halo (e.g., fluoro, bromo, chloro, or iodo). In some embodiments, R^6 is cyano. In some embodiments, R^6 is $-OR^A$ (e.g., –OH).

In some embodiments, R^{7a}, R^{7b}, and R^{7c} are each independently hydrogen or C_1-C_6-alkyl. In some embodiments, R^{7a} is hydrogen. In some embodiments, R^{7b} is hydrogen. In some embodiments, R^{7c} is hydrogen. In some embodiments, R^{7a} is C_1-C_6-alkyl. In some embodiments, R^{7b} is C_1-C_6-alkyl. In some embodiments, R^{7c} is C_1-C_6-alkyl. In some embodiments, R^{7c} is methyl. In some embodiments, R^{7a} and R^{7b}, together with the carbon atom to which they are attached to form an oxo group.

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 (e.g., $-CF_3$ or $-CHF_2$). 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 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^{10} is C_1-C_6-alkyl. In some embodiments, R^{10} 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 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}).

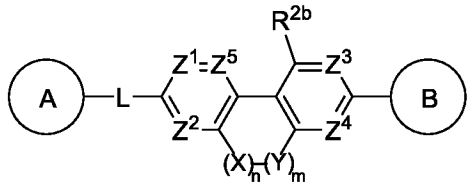
In some embodiments, R^D, R^E, or both are each independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl (e.g., benzyl), or C_1-C_6 alkylene-heteroaryl. In some embodiments, each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

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

In some embodiments, m is 1 or 2. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, n is 1 or 2. In some embodiments, n is 1. In some embodiments,

n is 2. In some embodiments, m and n are each 1. In some embodiments, n is 1 and m is 2. In some embodiments, n is 2 and m is 1. In some embodiments, x is an integer of 0, 1, or 2.

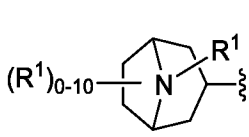
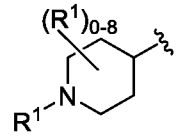
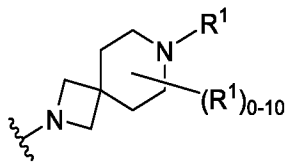
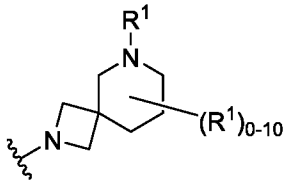
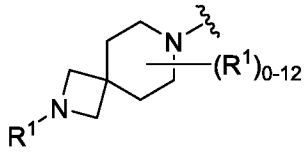
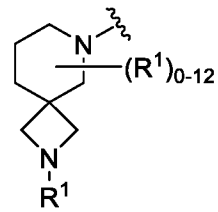
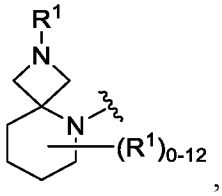
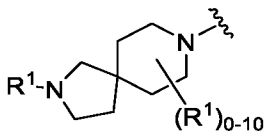
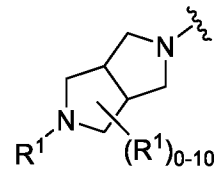
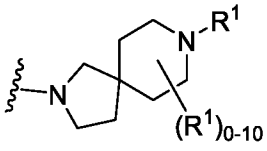
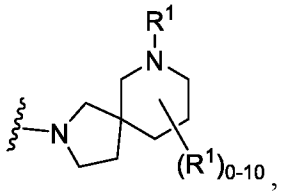
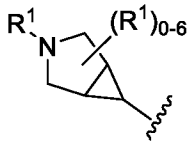
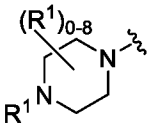
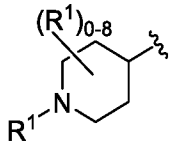
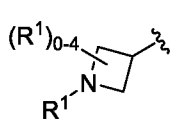
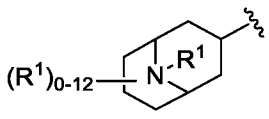
The present disclosure features a compound of Formula (I-a):

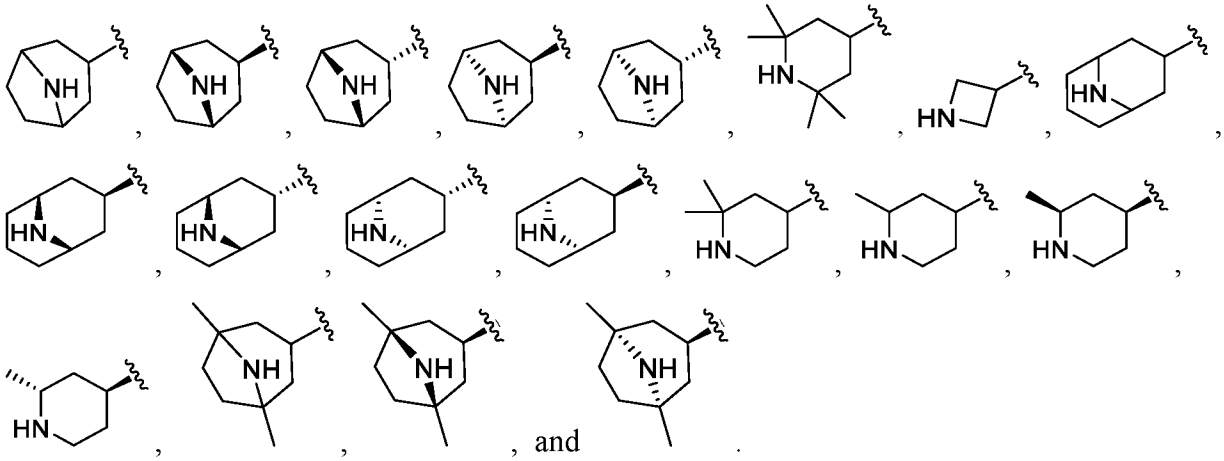


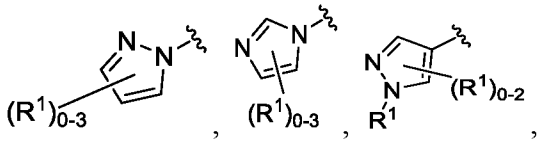
(I-a)

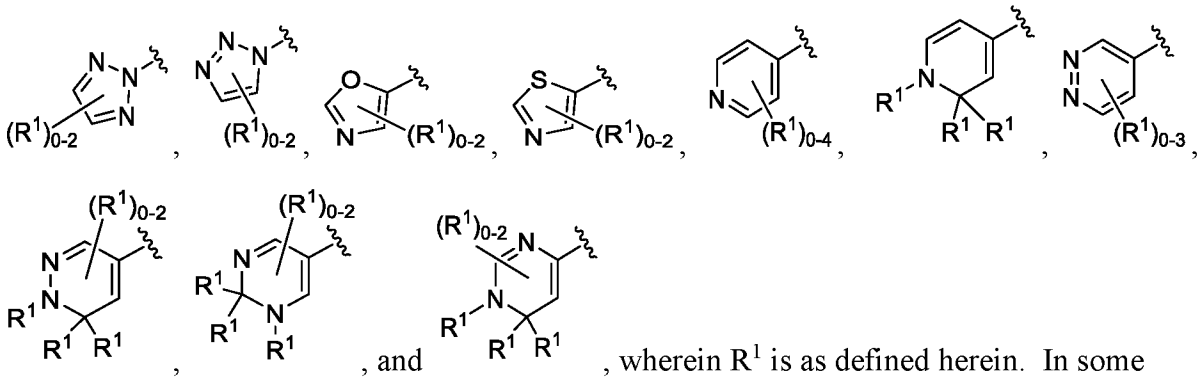
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; Z^1, Z^2, Z^3, Z^4, and Z^5 are each independently C(R^6) or N; X and Y are each independently O, C(R^{7a})(R^{7b}), or N(R^{7c}), wherein X and Y are not both O when n and m are both 1; R^{2b} is independently hydrogen, halo, cyano, 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, or –OR^A; each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –SR^E, or –$S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^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^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is independently 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^6 is hydrogen or C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or –OR^A; R^{7a}, R^{7b}, and R^{7c} are each independently hydrogen or C_1-C_6-alkyl; or R^{7a} and R^{7b}, together with the carbon atom to which they are attached, form an oxo group; each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –SR^E,

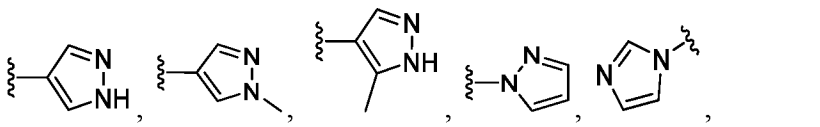
or $-S(O)_xR^D$, wherein each of alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11}; each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, 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 $-OR^A$; 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 C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{11} is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$; each R^{A1} is hydrogen or C_1-C_6-alkyl; each of m and n is independently 1 or 2; and x is 0, 1, or 2.

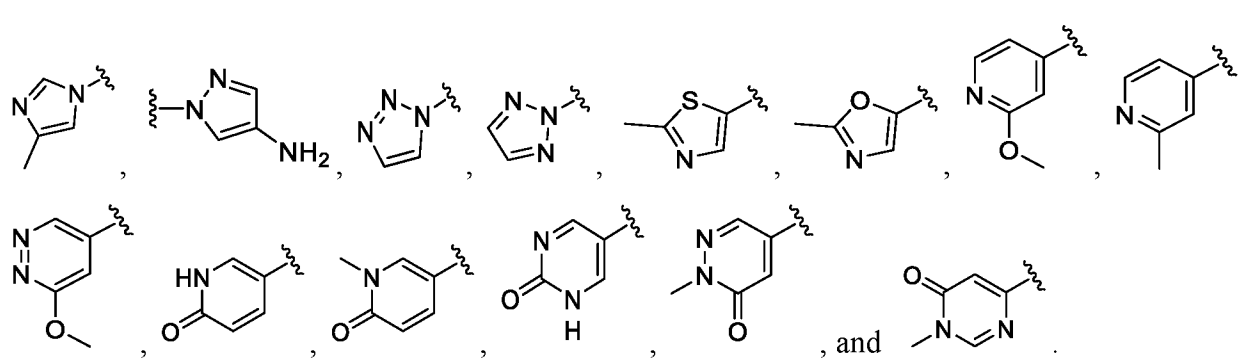
In some embodiments, A is selected from , , , , , , , , , , , , , , , and , wherein R^1 is as defined herein. In some embodiments, A is selected from



In some embodiments, B is selected from 



In some embodiments, B is selected from 



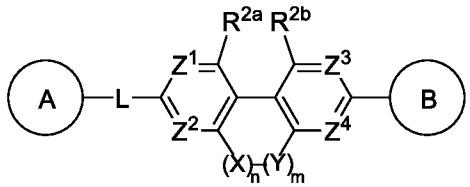
In some embodiments, L is -O-, -S-, or –N(R^4)-. In some embodiments, L is -O-. In some embodiments, L is -N(R^4)-. In some embodiments, R^4 is hydrogen, C_1-C_6 alkyl (e.g., CH_3

or CD_3), or cycloalkyl (e.g., cyclopropyl). In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-.

In some embodiments, each of Z^1, Z^2, Z^3, Z^4, and Z^5 independently refer to C(R^6) (e.g., CH) or N. In some embodiments, Z^1 and Z^2 are each independently C(R^6), e.g., CH. In some embodiments, Z^3 and Z^4 are each independently C(R^6), e.g., CH. In some embodiments, one of Z^1 and Z^2 is C(R^6), and the other of Z^1 and Z^2 is N. In some embodiments, one of Z^3 and Z^4 is C(R^6), and the other of Z^3 and Z^4 is N. In some embodiments, Z^1 is C(R^6). In some embodiments, Z^1 is N. In some embodiments, Z^2 is C(R^6). In some embodiments, Z^2 is N. In some embodiments, Z^3 is C(R^6). In some embodiments, Z^3 is N. In some embodiments, Z^4 is C(R^6). In some embodiments, Z^4 is N. In some embodiments, Z^5 is C(R^6). In some embodiments, Z^5 is N. In some embodiments, Z^1 is C(R^6) (e.g., CH) and Z^2 is N. In some embodiments, Z^1 is N and Z^2 is C(R^6) (e.g., CH). In some embodiments, Z^2 and Z^5 are each independently N.

In some embodiments, one of X and Y is C(R^{7a})(R^{7b}), and the other of X and Y is O. In some embodiments, one of X and Y is C(R^{7a})(R^{7b}), and the other of X and Y is N(R^{7c}). In some embodiments, X is C(R^{7a})(R^{7b}) (e.g., -CH_2-). In some embodiments, X is O. In some embodiments, X is N(R^{7c}). In some embodiments, Y is C(R^{7a})(R^{7b}) (e.g., -CH_2-). In some embodiments, Y is O. In some embodiments, Y is N(R^{7c}). In some embodiments, X is O and Y is C(R^{7a})(R^{7b}) (e.g., -CH_2-). In some embodiments, X is O and Y is -CH_2-. In some embodiments, X is C(R^{7a})(R^{7b}) (e.g., -CH_2-) and Y is O. In some embodiments, X is -CH_2- and Y is O.

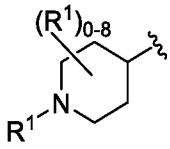
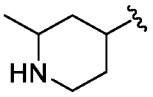
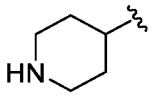
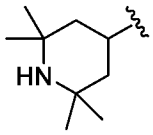
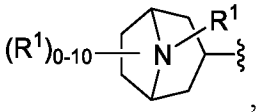
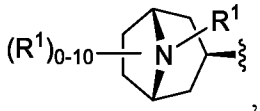
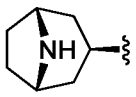
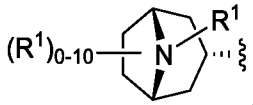
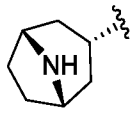
In some embodiments, a compound of Formula (I) is a compound of Formula (I-b):



(I-b)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; Z^1, Z^2, Z^3, and Z^4 are each

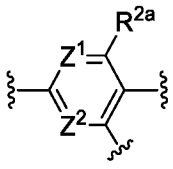
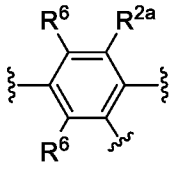
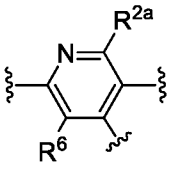
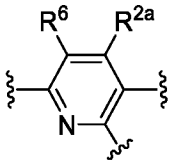
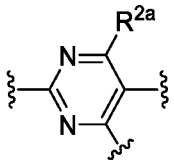
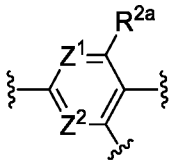
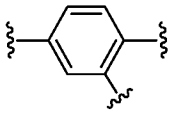
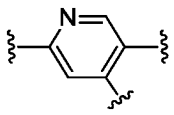
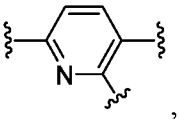
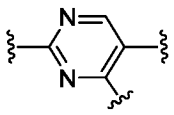
independently $C(R^6)$ or N; X and Y are each independently O, $C(R^{7a})(R^{7b})$, or $N(R^{7c})$, wherein X and Y are not both O when n and m are both 1; each of R^{2a} and R^{2b} is independently hydrogen, halo, cyano, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^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^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is independently 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^6 is hydrogen or C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$; R^{7a}, R^{7b}, and R^{7c} are each independently hydrogen or C_1-C_6-alkyl; or R^{7a} and R^{7b}, together with the carbon atom to which they are attached, form an oxo group; each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each 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 $-OR^A$; 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 C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{11} is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$; each R^{A1} is hydrogen or C_1-C_6-alkyl; each of m and n is independently 1 or 2; and x is 0, 1, or 2.

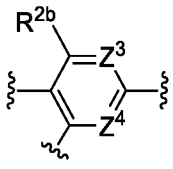
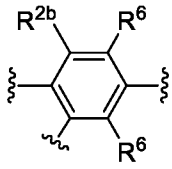
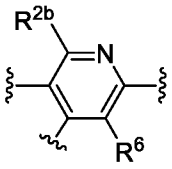
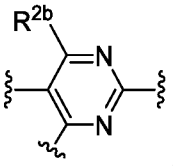
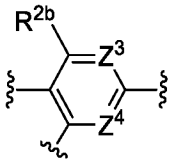
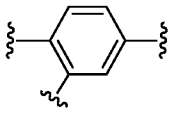
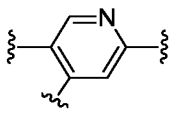
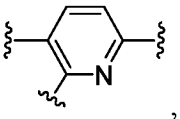
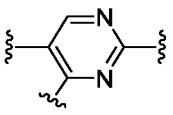
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl. In some embodiments, A is optionally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

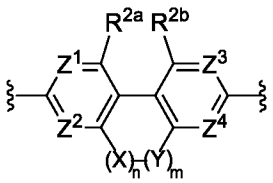
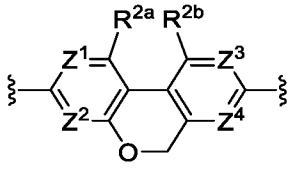
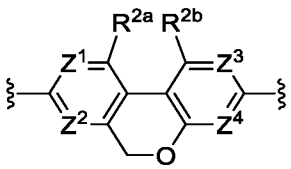
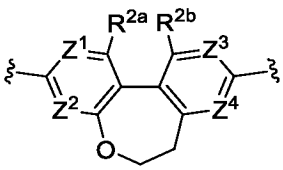
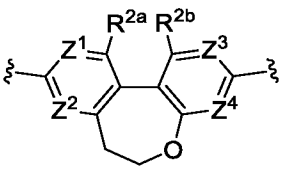
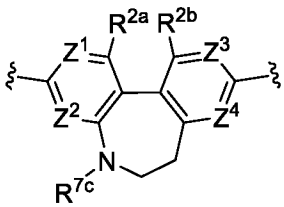
In some embodiments, L is oxygen. In some embodiments, L is nitrogen that is optionally substituted with R^4. In some embodiments, L is nitrogen substituted with one R^4. In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-.

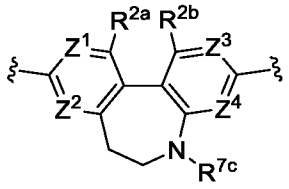
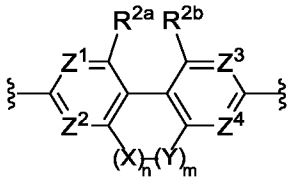
In some embodiments, each of Z^1, Z^2, Z^3, and Z^4 independently refer to C(R^6) (e.g., CH) or N. In some embodiments, Z^1 and Z^2 are each independently C(R^6), e.g., CH. In some embodiments, Z^3 and Z^4 are each independently C(R^6), e.g., CH. In some embodiments, one of Z^1 and Z^2 is C(R^6), and the other of Z^1 and Z^2 is N. In some embodiments, one of Z^3 and Z^4 is C(R^6), and the other of Z^3 and Z^4 is N. In some embodiments, Z^1 is C(R^6). In some embodiments, Z^1 is N. In some embodiments, Z^2 is C(R^6). In some embodiments, Z^2 is N. In

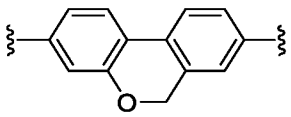
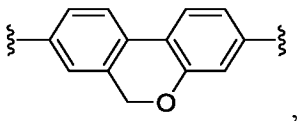
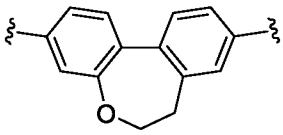
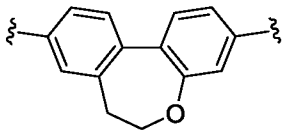
some embodiments, Z^3 is $C(R^6)$. In some embodiments, Z^3 is N. In some embodiments, Z^4 is $C(R^6)$. In some embodiments, Z^4 is N. In some embodiments, Z^1 is $C(R^6)$ (e.g., CH) and Z^2 is N. In some embodiments, Z^1 is N and Z^2 is $C(R^6)$ (e.g., CH).

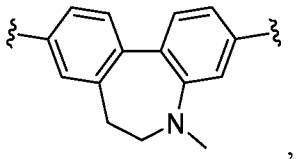
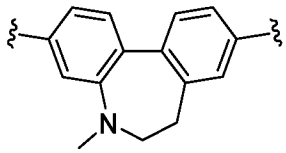
In some embodiments,  is selected from , , , , and . In some embodiments, is selected from , , , and .

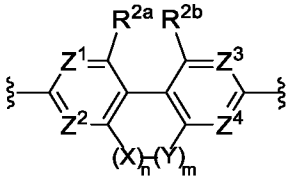
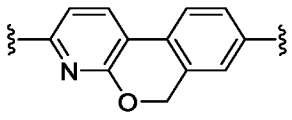
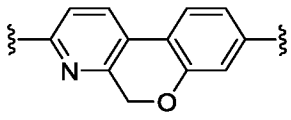
In some embodiments,  is selected from , , , , and . In some embodiments, is selected from , , , and .

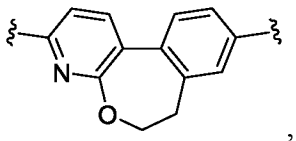
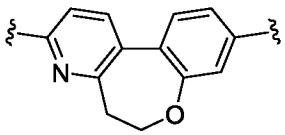
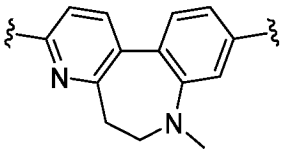
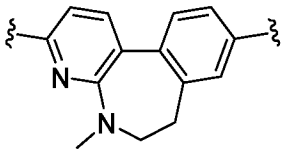
In some embodiments,  is selected from , , , , ,

and  . In some embodiments,  is selected from

, , , ,

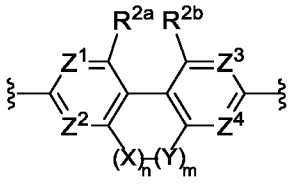
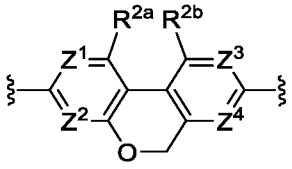
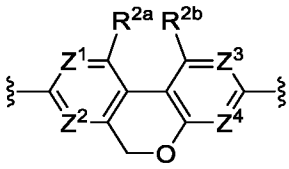
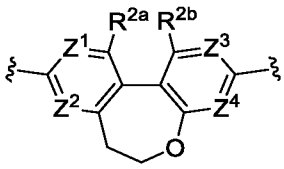
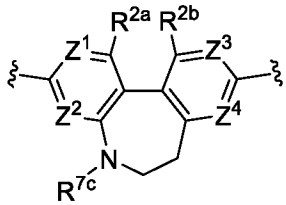
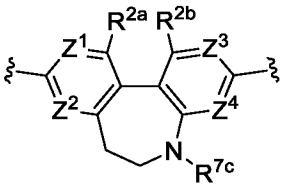
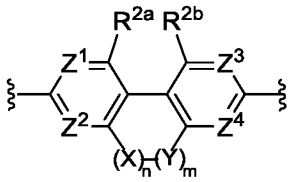
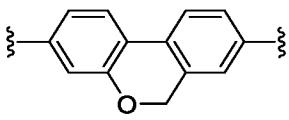
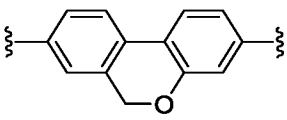
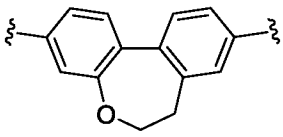
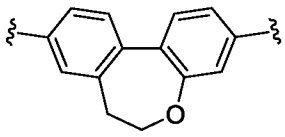
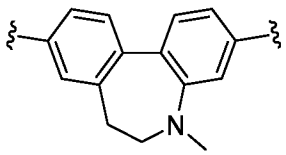
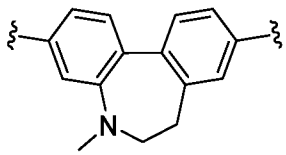
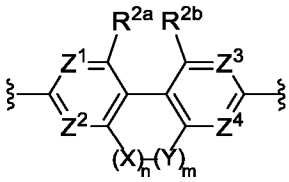
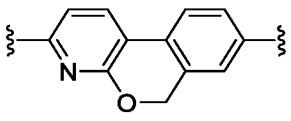
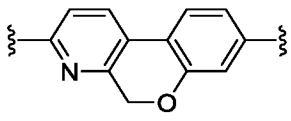
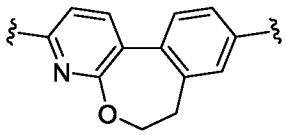
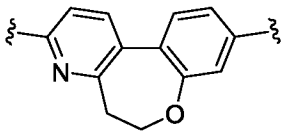
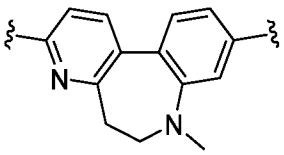
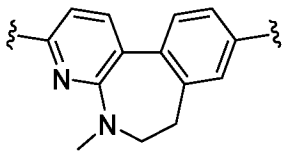
, and  . In some embodiments,

 is selected from , ,

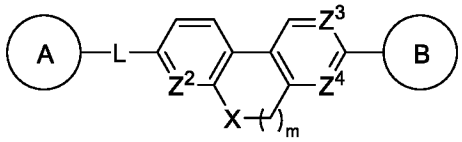
, , , and 

.

In some embodiments, one of X and Y is $C(R^{7a})(R^{7b})$, and the other of X and Y is O. In some embodiments, one of X and Y is $C(R^{7a})(R^{7b})$, and the other of X and Y is $N(R^{7c})$. In some embodiments, X is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$). In some embodiments, X is O. In some embodiments, X is $N(R^{7c})$. In some embodiments, Y is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$). In some embodiments, Y is O. In some embodiments, Y is $N(R^{7c})$. In some embodiments, X is O and Y is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$). In some embodiments, X is O and Y is $-CH_2-$. In some embodiments, X is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$) and Y is O. In some embodiments, X is $-CH_2-$ and Y is O. In some embodiments, X is $N(R^{7c})$ (e.g., $N(CH_3)$ and Y is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$). In some embodiments, X is $N(CH_3)$ and Y is $-CH_2-$. In some embodiments, Y is $N(R^{7c})$ (e.g., $N(CH_3)$ and X is $C(R^{7a})(R^{7b})$ (e.g., $-CH_2-$). In some embodiments, Y is $N(CH_3)$ and X is $-CH_2-$.

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

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

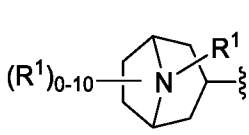
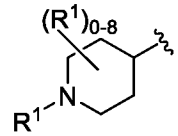
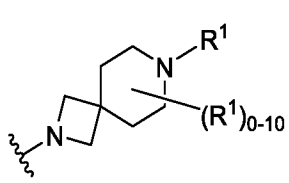
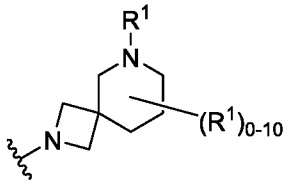
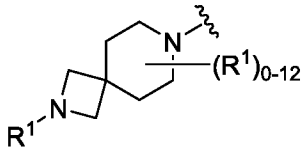
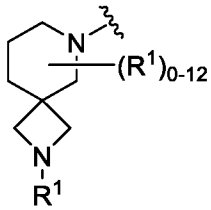
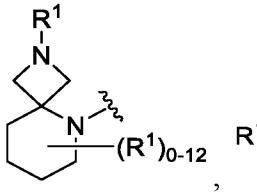
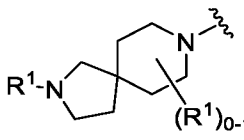
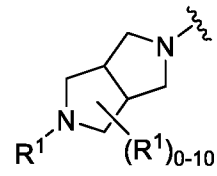
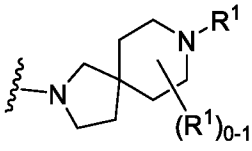
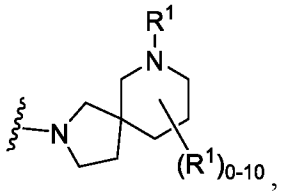
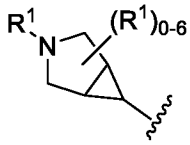
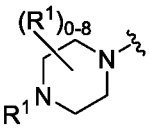
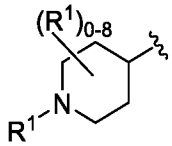
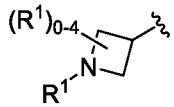
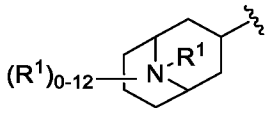
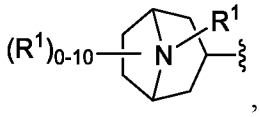
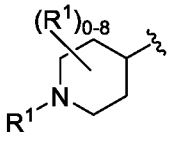
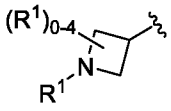
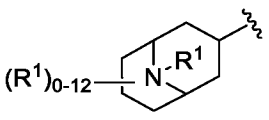
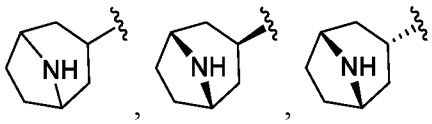


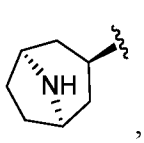
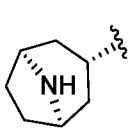
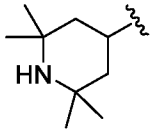
(I-c)

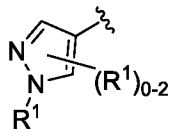
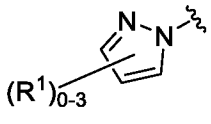
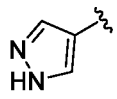
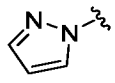
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; Z^2, Z^3, and Z^4 are each independently C(R^6) or N; X is O, C(R^{7a})(R^{7b}), or N(R^{7c}); each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –SR^E, or –$S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^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^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is independently 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^6 is hydrogen or C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or –OR^A; R^{7a}, R^{7b}, and R^{7c} are each independently hydrogen or C_1-C_6-alkyl; or R^{7a} and R^{7b}, together with the carbon atom to which they are attached, form an oxo group; each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –SR^E, or –$S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11}; each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, –$C(O)R^D$, or –$S(O)_xR^D$; each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or –OR^A; or R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^{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 C_1-C_6-alkyl, halo, cyano, oxo, or –OR^{A1}; each R^{11} is

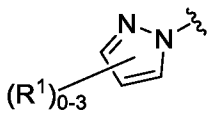
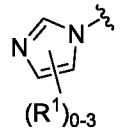
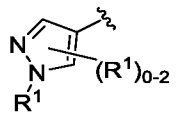
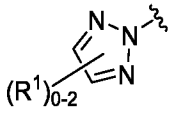
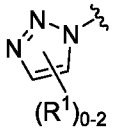
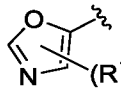
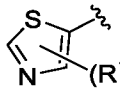
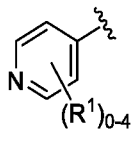
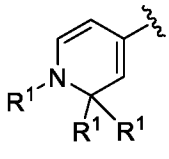
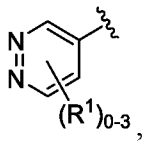
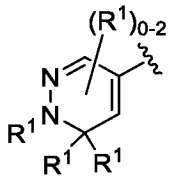
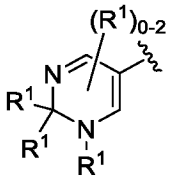
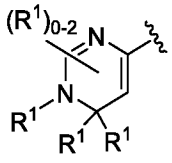
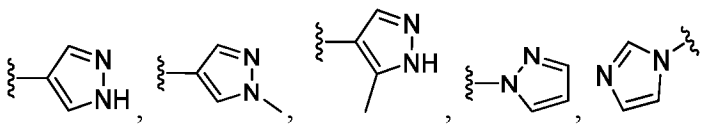
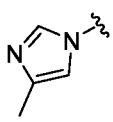
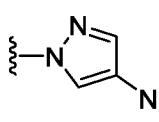
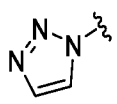
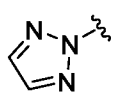
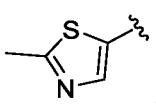
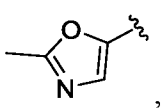
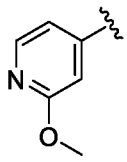
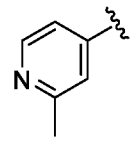
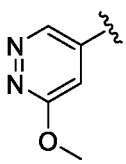
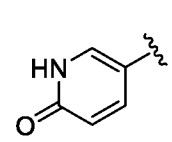
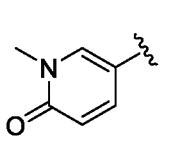
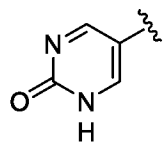
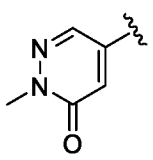
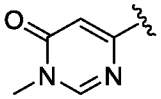
independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^{A}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m is 1 or 2; and x is 0, 1, or 2.

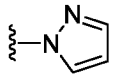
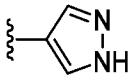
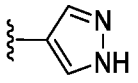
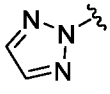
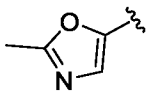
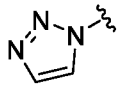
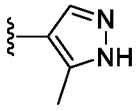
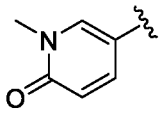
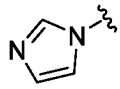
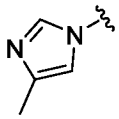
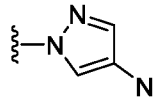
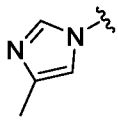
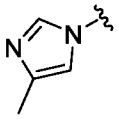
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl.

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

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 . In some embodiments, B 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

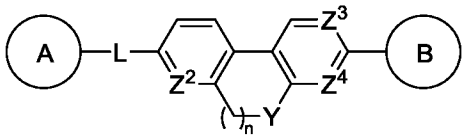
embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In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

In some embodiments, L is oxygen. In some embodiments, L is nitrogen that is optionally substituted with R^4. In some embodiments, L is nitrogen substituted with one R^4. In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-.

In some embodiments, each of Z^2, Z^3, and Z^4, are independently C(R^6). In some embodiments, Z^2 is C(R^6) or N. In some embodiments, Z^2 is C(R^6) (e.g., CH). In some embodiments, Z^2 is N. In some embodiments, Z^2 is CH. In some embodiments, X is O or C(R^{7a})(R^{7b}). In some embodiments, X is O. In some embodiments, X is O and m is 1. In some embodiments, X is O and m is 2. In some embodiments, X is C(R^{7a})(R^{7b}) (e.g., CH_2). In some embodiments, X is CH_2. In some embodiments, X is N(R^{7c}). In some embodiments, X is N(R^{7c}) and m is 2. In some embodiments, X is N(CH_3). In some embodiments, X is N(CH_3) and m is 2.

In some embodiments, R^1 is hydrogen. 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^4 is methyl. In some embodiments R^6 is hydrogen. In some embodiments, R^{7a} and R^{7b} are each hydrogen. In some embodiments, m is 1. In some embodiments, m is 2.

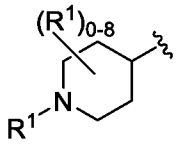
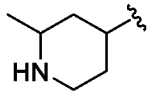
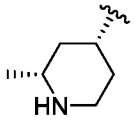
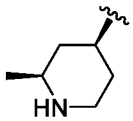
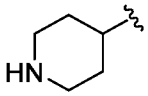
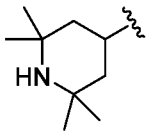
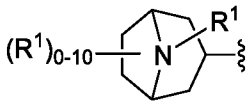
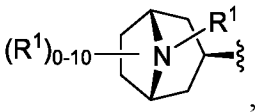
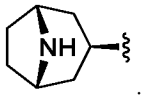
In some embodiments, the compound of Formula (I) is a compound of Formula (I-d):

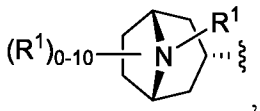
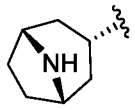


(I-d),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; Z^2, Z^3, and Z^4 are each independently C(R^6) or N; Y is O, C(R^{7a})(R^{7b}), or N(R^{7c}); each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –SR^E, or –$S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^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^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is independently 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^6 is hydrogen or C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or –OR^A; R^{7a}, R^{7b}, and R^{7c} are each independently hydrogen or C_1-C_6-alkyl; or R^{7a} and R^{7b}, together with the carbon atom to which they are attached, form an oxo group; each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –SR^E, or –$S(O)_xR^D$, wherein each 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 –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};

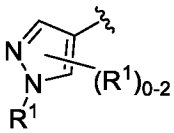
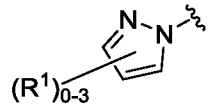
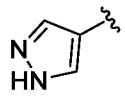
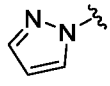
each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl; each R^{10} is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$; each R^{A1} is hydrogen or C_1-C_6-alkyl; n is 1 or 2; and x is 0, 1, or 2.

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

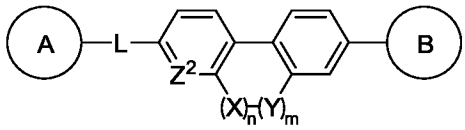
In some embodiments, L is oxygen. In some embodiments, L is nitrogen that is optionally substituted with R^4. In some embodiments, L is nitrogen substituted with one R^4. In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-.

In some embodiments, each of Z^2, Z^3, and Z^4, are independently C(R^6). In some embodiments, Z^2 is C(R^6) or N. In some embodiments, Z^2 is C(R^6) (e.g., CH). In some embodiments, Z^2 is N. In some embodiments, Z^2 is CH. In some embodiments, Y is O or C(R^{7a})(R^{7b}). In some embodiments, Y is O. In some embodiments, Y is O and n is 1. In some embodiments, Y is O and n is 2. In some embodiments, Y is C(R^{7a})(R^{7b}) (e.g., CH_2). In some embodiments, Y is CH_2. In some embodiments, Y is N(R^{7c}). In some embodiments, Y is N(R^{7c}) and n is 2. In some embodiments, Y is N(CH_3). In some embodiments, Y is N(CH_3) and n is 2.

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 . In some embodiments, B is .

In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_1-C_6-alkyl (e.g., methyl). In some embodiments R^6 is hydrogen. In some embodiments, R^{7a} and R^{7b} are each hydrogen. In some embodiments, n is 1. In some embodiments, n is 2.

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

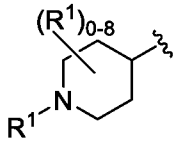


(I-e),

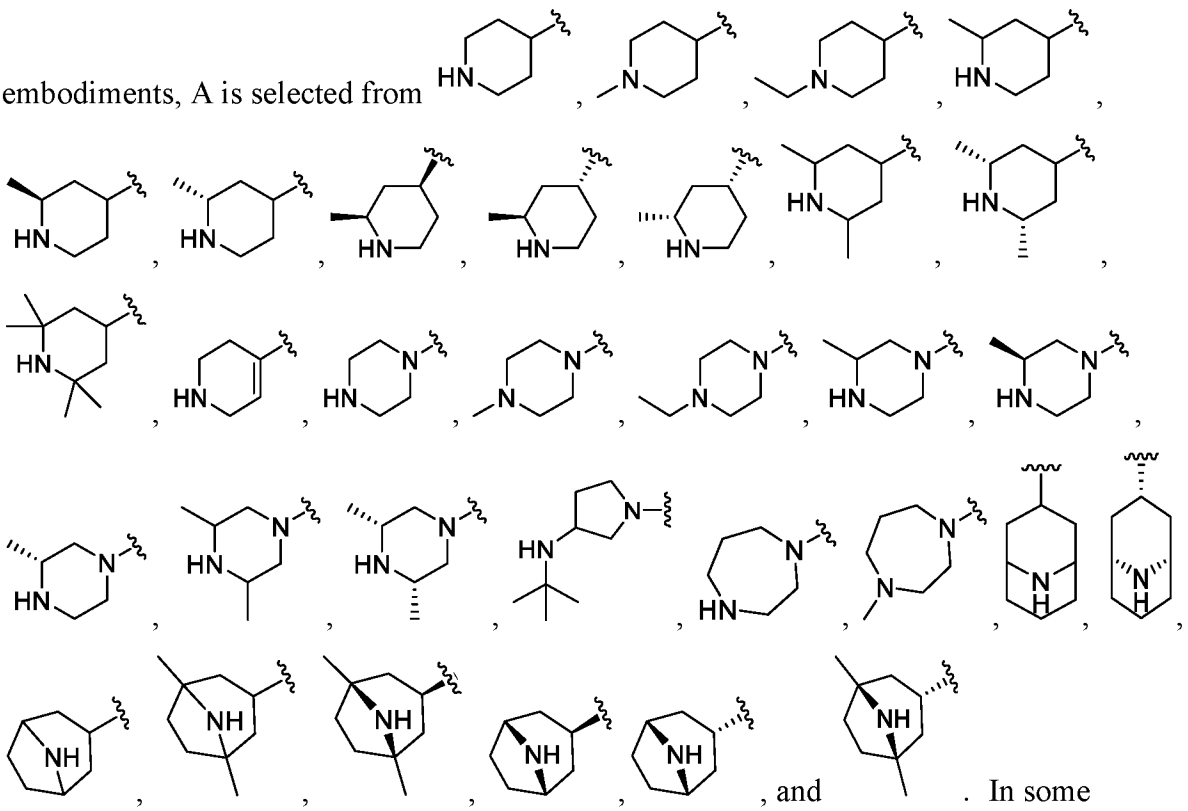
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; Z^2 is C(R^6) or N; X and Y are each independently O, C(R^{7a})(R^{7b}), or N(R^{7c}), wherein X and Y are not both O when n and m are both 1; each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –SR^E, or –$S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^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^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is independently 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^6 is hydrogen or C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or –OR^A; R^{7a}, R^{7b}, and R^{7c} are each independently hydrogen or C_1-C_6-alkyl; or R^{7a} and R^{7b}, together with the carbon atom to which they are attached, form an oxo group; each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –SR^E, or –$S(O)_xR^D$, wherein each 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 –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 C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$; each R^{A1} is hydrogen or C_1-C_6-alkyl; each of m and n is independently 1 or 2; and x is 0, 1, or 2.

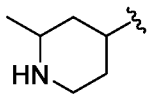
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl. In some embodiments, A is optionally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



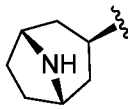
, wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is selected from



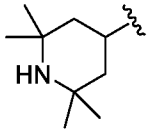
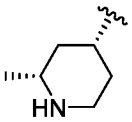
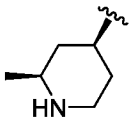
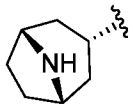
. In some embodiments, A is



. In some embodiments, A is

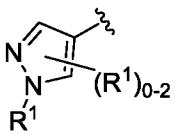


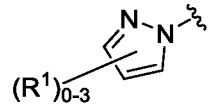
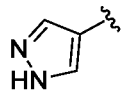
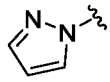
. In some embodiments,

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^4. In some embodiments, L is nitrogen substituted with one R^4. In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-.

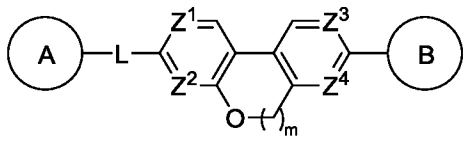
In some embodiments, Z^2 is C(R^6) or N. In some embodiments, Z^2 is C(R^6) (e.g., CH). In some embodiments, Z^2 is N. In some embodiments, Z^2 is CH. In some embodiments, X is O or C(R^{7a})(R^{7b}). In some embodiments, X is O. In some embodiments, X is O and m is 1. In some embodiments, X is O and m is 2. In some embodiments, X is C(R^{7a})(R^{7b}) (e.g., CH_2). In some embodiments, X is CH_2. In some embodiments, X is N(R^{7c}). In some embodiments, X is N(R^{7c}) and m is 2. In some embodiments, X is N(CH_3). In some embodiments, X is N(CH_3) and m is 2. In some embodiments, Y is O or C(R^{7a})(R^{7b}). In some embodiments, Y is O. In some embodiments, Y is O and n is 1. In some embodiments, Y is O and n is 2. In some embodiments, Y is C(R^{7a})(R^{7b}) (e.g., CH_2). In some embodiments, Y is CH_2. In some embodiments, Y is N(R^{7c}). In some embodiments, Y is N(R^{7c}) and n is 2. In some embodiments, Y is N(CH_3). In some embodiments, Y is N(CH_3) and n is 2. In some embodiments, X is O and Y is C(R^{7a})(R^{7b}) (e.g., CH_2). In some embodiments, Y is O and X is C(R^{7a})(R^{7b}) (e.g., CH_2). In some embodiments, X is O and Y is CH_2. In some embodiments, Y is O and X is CH_2. In some embodiments, X is N(R^{7c}) and Y is C(R^{7a})(R^{7b}) (e.g., CH_2). In some embodiments, Y is N(R^{7c}) and X is C(R^{7a})(R^{7b}) (e.g., CH_2). In some embodiments, X is N(CH_3) and Y is CH_2. In some embodiments, Y is N(CH_3) and X is CH_2.

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 . In some embodiments, B is .

In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_1-C_6-alkyl (e.g., methyl). In some embodiments R^6 is hydrogen. In some embodiments, R^{7a} and R^{7b} are each hydrogen. In some embodiments, n is 1. In some embodiments, n is 2.

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

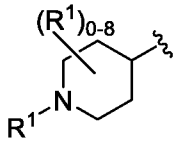


(I-f),

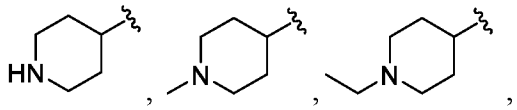
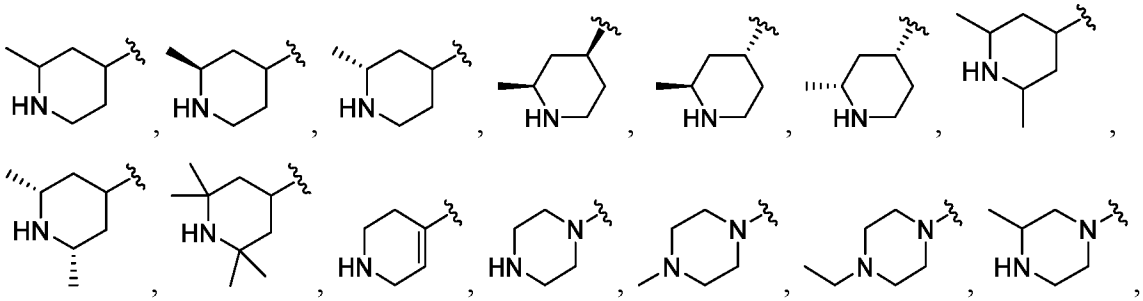
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; Z^1, Z^2, Z^3, and Z^4 are each independently C(R^6) or N; each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^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^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is independently 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^6 is hydrogen or C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $–OR^A$; each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, –

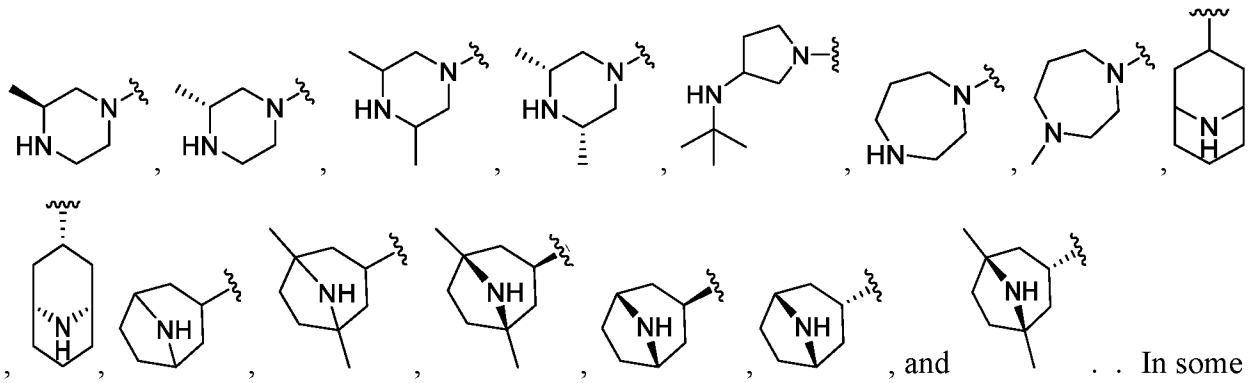
$C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each of alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11}; each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, 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 $-OR^A$; 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 C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m is 1 or 2; and x is 0, 1, or 2.

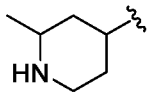
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl. In some embodiments, A is optionally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

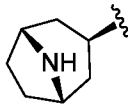


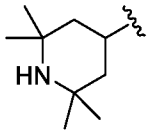
, wherein each R^1 is independently hydrogen or C_1-C_6-alkyl.

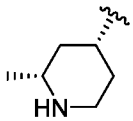
In some embodiments, A is selected from , 

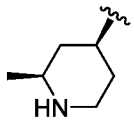


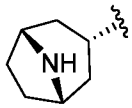
, and . . In some embodiments, A is 

. In some embodiments, A is 

. In some embodiments, A is 

. In some embodiments, A is 

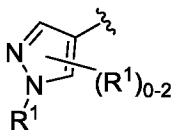
. In some embodiments, A is 

. In some embodiments, A is 

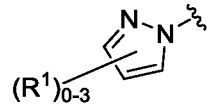
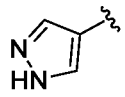
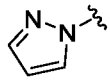
.

In some embodiments, L is oxygen. In some embodiments, L is nitrogen that is optionally substituted with R^4. In some embodiments, L is nitrogen substituted with one R^4. In some embodiments, L is $-N(CH_3)-$. In some embodiments, L is -NH-.

In some embodiments, Z^1 is $C(R^6)$ (e.g., CH). In some embodiments, Z^1 is N. In some embodiments, Z^1 is CH. In some embodiments, Z^2 is $C(R^6)$ (e.g., CH). In some embodiments, Z^2 is N. In some embodiments, Z^2 is CH. In some embodiments, Z^3 is $C(R^6)$ (e.g., CH). In some embodiments, Z^3 is N. In some embodiments, Z^3 is CH. In some embodiments, Z^4 is $C(R^6)$ (e.g., CH). In some embodiments, Z^4 is N. In some embodiments, Z^4 is CH.

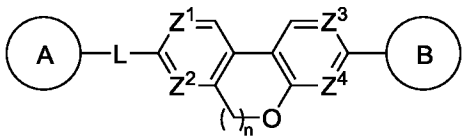
In some embodiments, B is heteroaryl optionally substituted with one or more R^1. In some embodiments, B is monocyclic heteroaryl. In some embodiments, B is monocyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is 

, 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 . In some embodiments, B is .

In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_1-C_6-alkyl (e.g., methyl). In some embodiments R^6 is hydrogen. In some embodiments, m is 1. In some embodiments, m is 2.

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

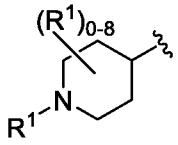


(I-g),

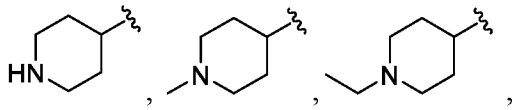
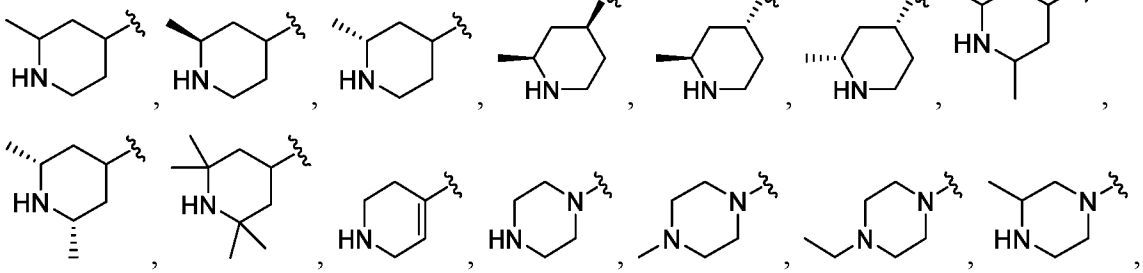
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; Z^1, Z^2, Z^3, and Z^4 are each independently C(R^6) or N; each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^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^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is independently 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^6 is hydrogen or C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $–OR^A$; each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, –

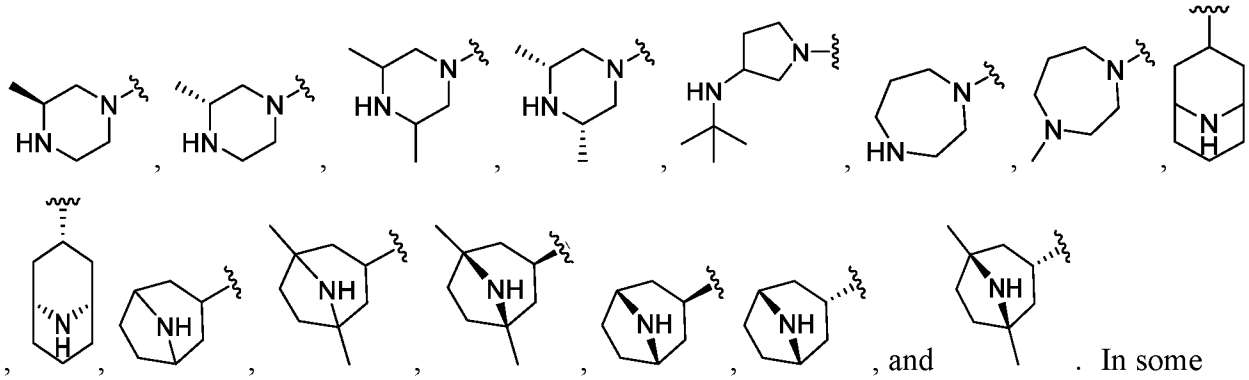
$C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each of alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11}; each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, 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 or 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 C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m is 1 or 2; and x is 0, 1, or 2.

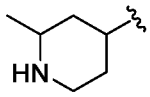
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl. In some embodiments, A is optionally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

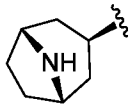


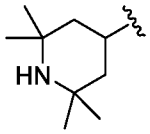
, wherein each R^1 is independently hydrogen or C_1-C_6-alkyl.

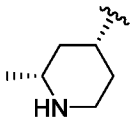
In some embodiments, A is selected from , 

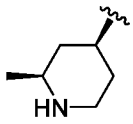


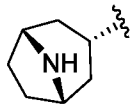
, and . In some embodiments, A is 

. In some embodiments, A is 

. In some embodiments, A is 

. In some embodiments, A is 

. In some embodiments, A is 

. In some embodiments, A is 

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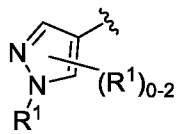
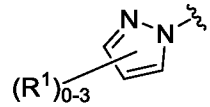
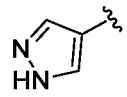
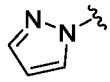
In some embodiments, L is oxygen. In some embodiments, L is nitrogen that is optionally substituted with R^4. In some embodiments, L is nitrogen substituted with one R^4. In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-.

In some embodiments, Z^1 is C(R^6) (e.g., CH). In some embodiments, Z^1 is N. In some embodiments, Z^1 is CH. In some embodiments, Z^2 is C(R^6) (e.g., CH). In some embodiments, Z^2 is N. In some embodiments, Z^2 is CH. In some embodiments, Z^3 is C(R^6) (e.g., CH). In some embodiments, Z^3 is N. In some embodiments, Z^3 is CH. In some embodiments, Z^4 is C(R^6) (e.g., CH). In some embodiments, Z^4 is N. In some embodiments, Z^4 is CH.

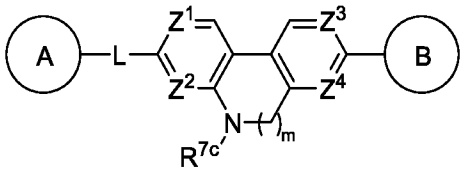
In some embodiments, B is heteroaryl optionally substituted with one or more R^1. In some embodiments, B is monocyclic heteroaryl. In some embodiments, B is monocyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is 

, 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 . In some embodiments, B is .

In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_1-C_6-alkyl (e.g., methyl). In some embodiments R^6 is hydrogen. In some embodiments, n is 1. In some embodiments, n is 2.

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

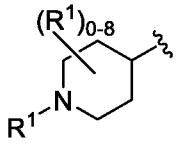


(I-h),

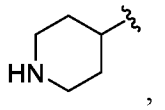
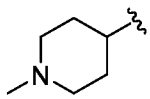
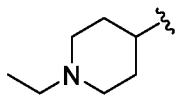
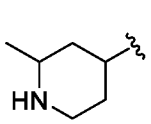
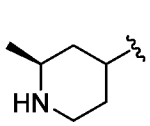
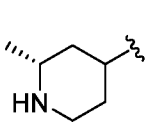
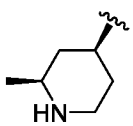
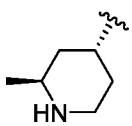
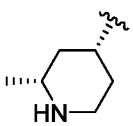
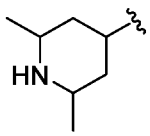
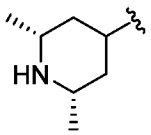
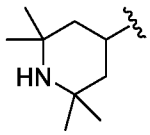
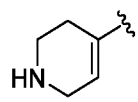
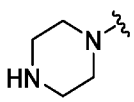
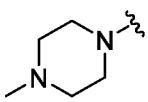
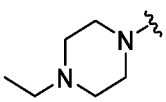
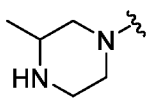
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; L is absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; Z^1, Z^2, Z^3, and Z^4 are each independently C(R^6) or N; each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^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^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is independently 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^6 is hydrogen or C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $–OR^A$; R^{7c} is hydrogen or C_1-C_6-alkyl; each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, –

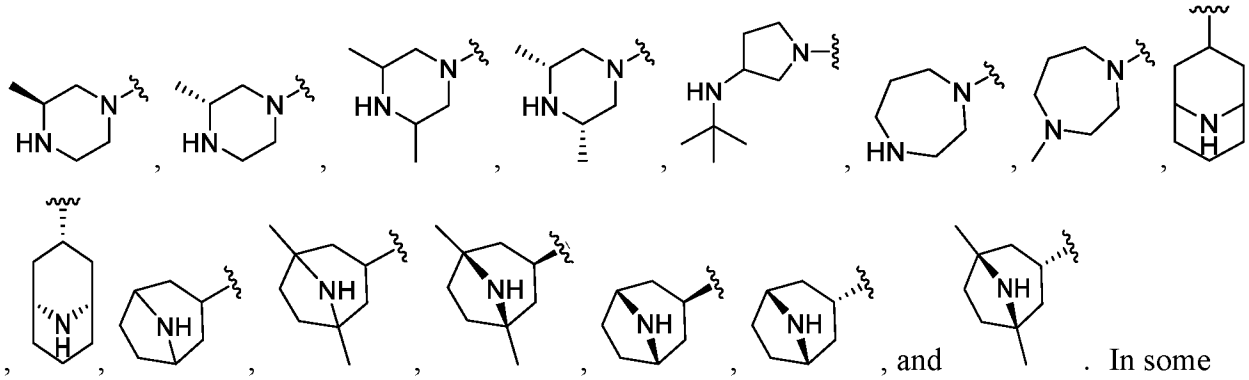
$NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each of alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11}; each R^A is independently hydrogen, C_1-C_6 alkyl, 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 or 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 C_1-C_6-alkyl, halo, cyano, oxo, or $–OR^{A1}$; each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $–OR^A$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m is 1 or 2; and x is 0, 1, or 2.

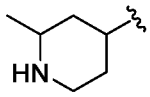
In some embodiments, A is heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is bicyclic heterocyclyl. In some embodiments, A is monocyclic nitrogen-containing heterocyclyl. In some embodiments, A is bicyclic nitrogen-containing heterocyclyl. In some embodiments, A is optionally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

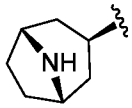


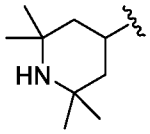
, wherein each R^1 is independently hydrogen or C_1-C_6-alkyl.

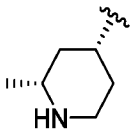
In some embodiments, A is selected from , , , , , , , , , , , , , , , , .

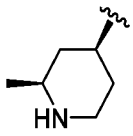


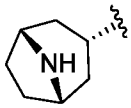
, and . In some embodiments, A is 

. In some embodiments, A is 

. In some embodiments, A is 

. In some embodiments, A is 

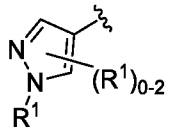
. In some embodiments, A is 

. In some embodiments, A is 

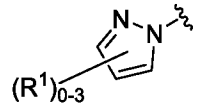
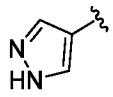
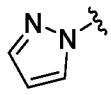
.

In some embodiments, L is oxygen. In some embodiments, L is nitrogen that is optionally substituted with R^4. In some embodiments, L is nitrogen substituted with one R^4. In some embodiments, L is $-N(CH_3)-$. In some embodiments, L is -NH-.

In some embodiments, Z^1 is $C(R^6)$ (e.g., CH). In some embodiments, Z^1 is N. In some embodiments, Z^1 is CH. In some embodiments, Z^2 is $C(R^6)$ (e.g., CH). In some embodiments, Z^2 is N. In some embodiments, Z^2 is CH. In some embodiments, Z^3 is $C(R^6)$ (e.g., CH). In some embodiments, Z^3 is N. In some embodiments, Z^3 is CH. In some embodiments, Z^4 is $C(R^6)$ (e.g., CH). In some embodiments, Z^4 is N. In some embodiments, Z^4 is CH.

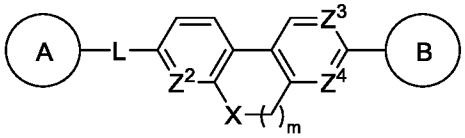
In some embodiments, B is heteroaryl optionally substituted with one or more R^1. In some embodiments, B is monocyclic heteroaryl. In some embodiments, B is monocyclic nitrogen-containing heteroaryl. In some embodiments, B is optionally substituted pyrazolyl. In some embodiments, B is 

, 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 . In some embodiments, B is .

In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_1-C_6-alkyl (e.g., methyl). In some embodiments R^6 is hydrogen. In some embodiments R^{7c} is hydrogen. In some embodiments R^{7c} is C_1-C_6-alkyl (e.g., methyl). In some embodiments R^{7c} is methyl. In some embodiments, m is 1. In some embodiments, m is 2.

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

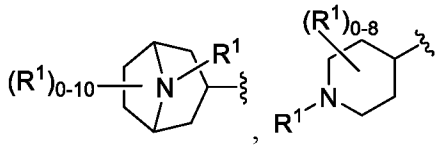
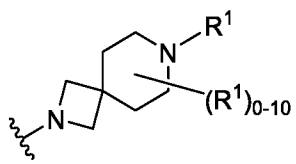
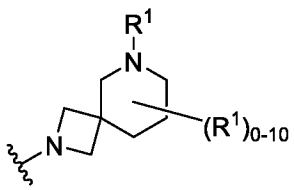
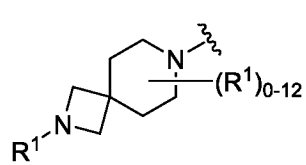
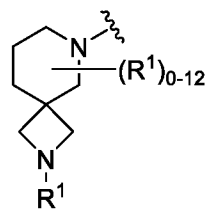


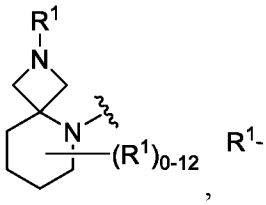
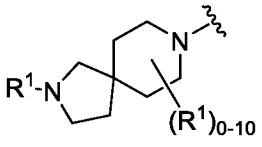
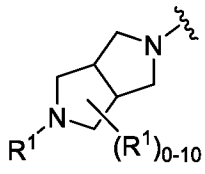
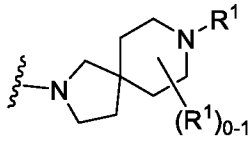
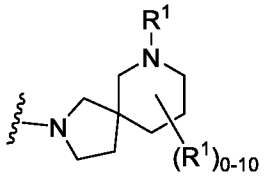
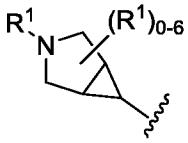
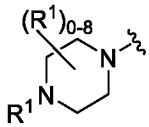
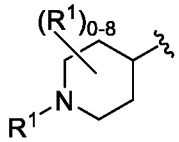
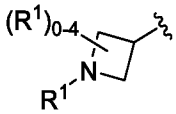
(I-i)

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-, -S-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; Z^2, Z^3, and Z^4 are each independently C(R^6) or N; X is O, C(R^{7a})(R^{7b}), or N(R^{7c}); 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, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, C_2-C_6 alkenylene-heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^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^4 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, or heterocyclyl, wherein each alkyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^{12}; each R^5 is independently 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^6 is hydrogen or C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$; R^{7a}, R^{7b}, and R^{7c} are each independently hydrogen or C_1-C_6-alkyl; or R^{7a} and R^{7b}, together with the carbon atom to which they are attached, form an oxo group; each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, $-SR^E$, or $-S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^{11}; each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, or $-S(O)_xR^D$; each of R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$; or R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^{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 C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{11} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $-OR^A$; each R^{12} is independently deuterium, halo, cyano, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-C(O)R^D$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m is 1 or 2; and x is 0, 1, or 2.

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

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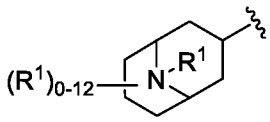
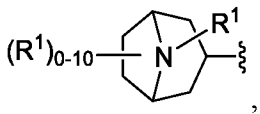
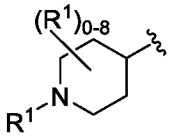
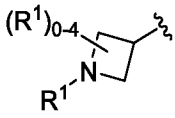

, wherein R^1 is as defined herein. In some embodiments, A is selected from



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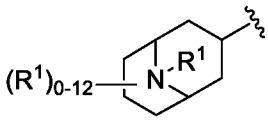
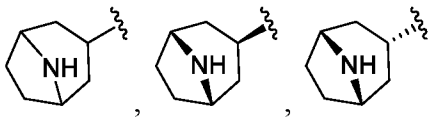

, wherein R^1 is as defined herein. In some embodiments, A is selected from

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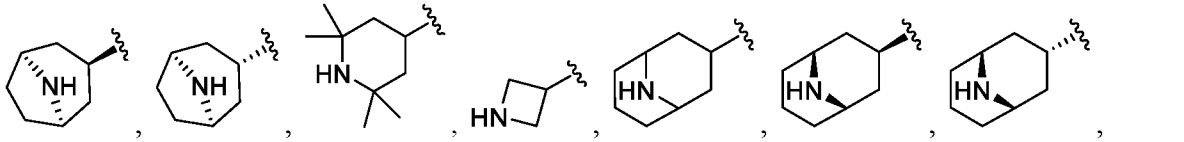
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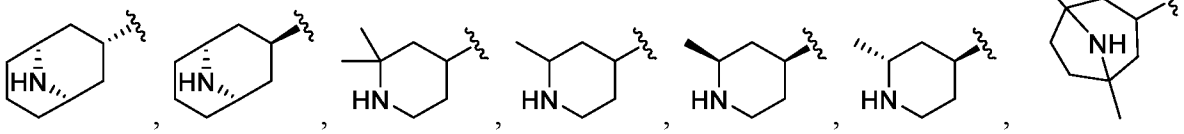
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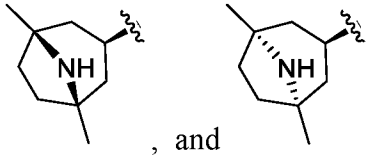
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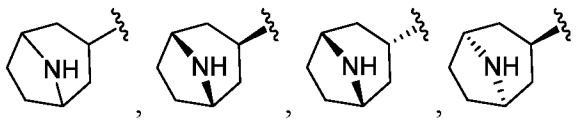
In some embodiments, A is selected from

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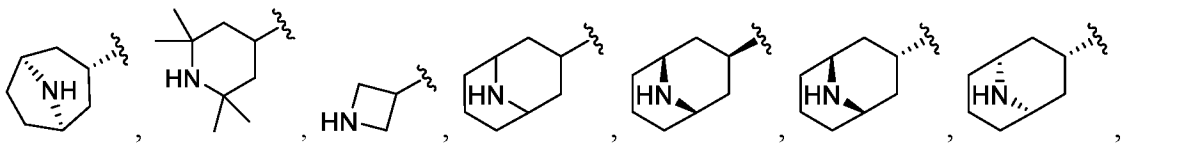
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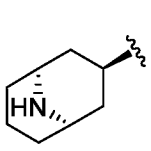
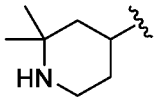
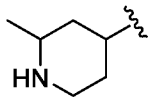
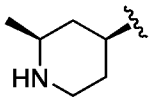
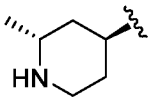
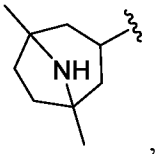
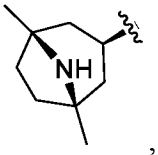
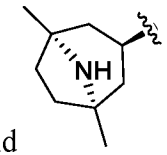
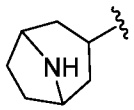
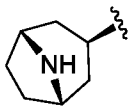
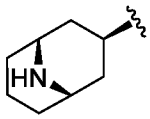
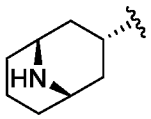
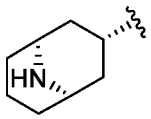
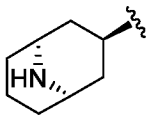
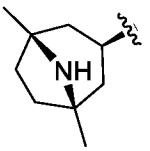
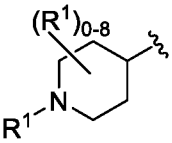
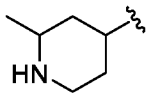
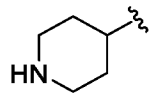
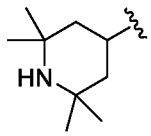
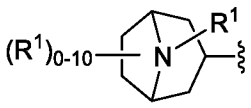
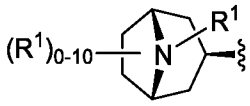
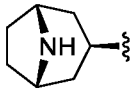
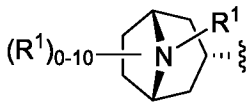
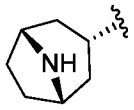









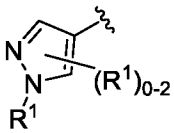
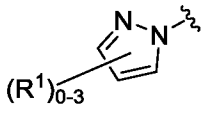
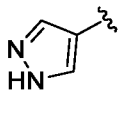
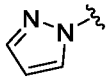
and .

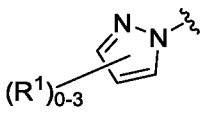
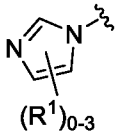
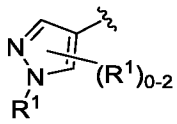
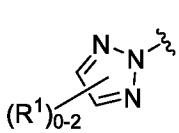
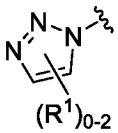
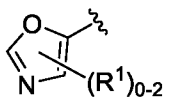
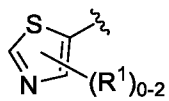
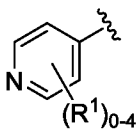
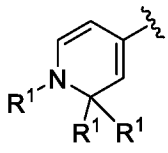
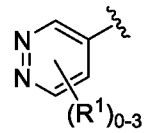
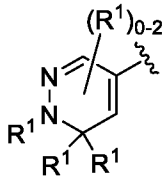
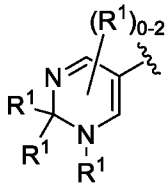
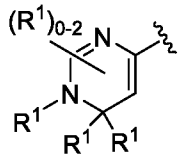
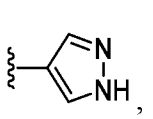
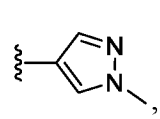
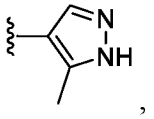
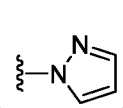
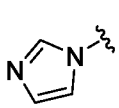
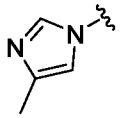
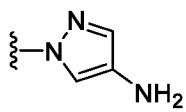
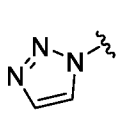
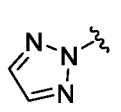
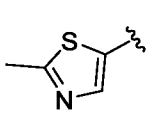
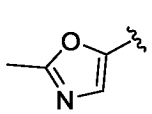
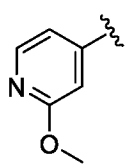
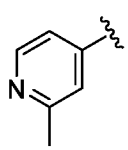
In some embodiments, A is selected from , , , , , , and .

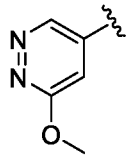
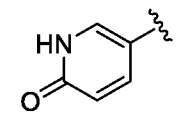
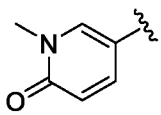
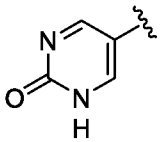
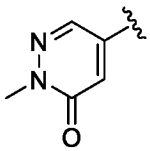
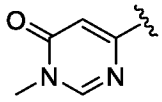
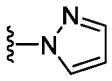
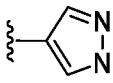
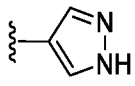
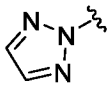
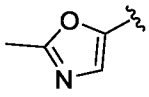
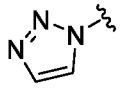
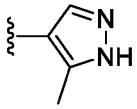
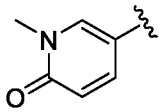
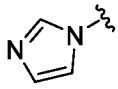
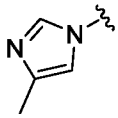
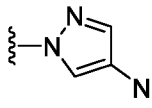
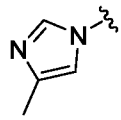
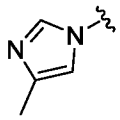
In some embodiments, A is optionally substituted piperidinyl. In some embodiments, A is optionally substituted azabicyclo[3.2.1]octanyl. In some embodiments, A is , wherein each R^1 is independently hydrogen or C_1-C_6-alkyl. In some embodiments, A is . In some embodiments, A is . In some embodiments,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

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


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

In some embodiments, 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 . In some embodiments, B 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 . 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, L is oxygen. In some embodiments, L is nitrogen that is optionally substituted with R^4. In some embodiments, L is nitrogen substituted with one R^4. In some embodiments, L is -N(CH_3)-. In some embodiments, L is -NH-.

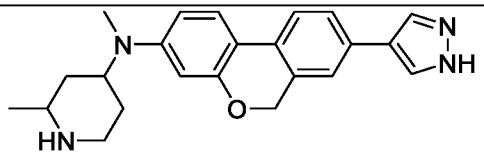
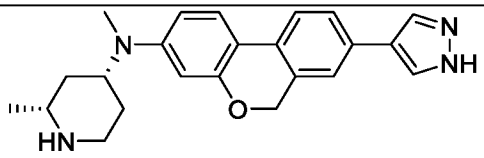
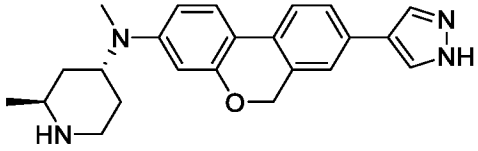
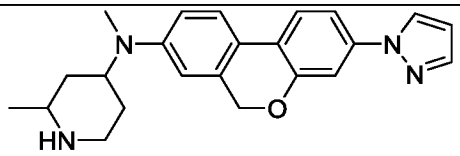
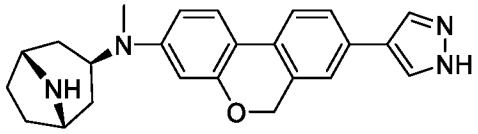
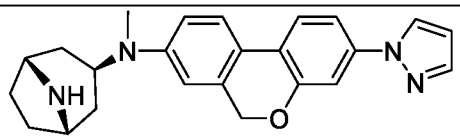
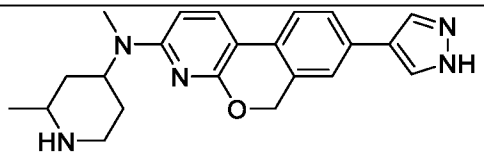
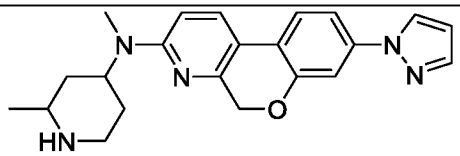
In some embodiments, each of Z^2, Z^3, and Z^4, are independently C(R^6). In some embodiments, Z^2 is C(R^6) or N. In some embodiments, Z^2 is C(R^6) (e.g., CH). In some embodiments, Z^2 is N. In some embodiments, Z^2 is CH. In some embodiments, X is O or C(R^{7a})(R^{7b}). In some embodiments, X is O. In some embodiments, X is O and m is 1. In some embodiments, X is O and m is 2. In some embodiments, X is C(R^{7a})(R^{7b}) (e.g., CH_2). In some embodiments, X is CH_2. In some embodiments, X is N(R^{7c}). In some embodiments, X is N(R^{7c}) and m is 2. In some embodiments, X is N(CH_3). In some embodiments, X is N(CH_3) and m is 2.

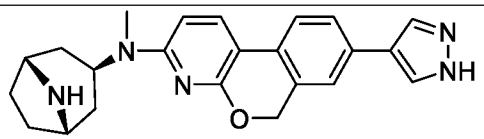
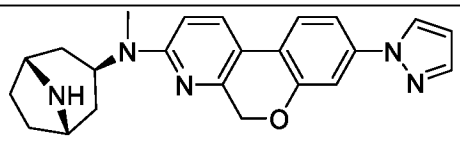
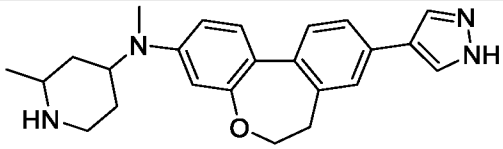
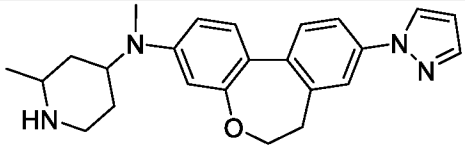
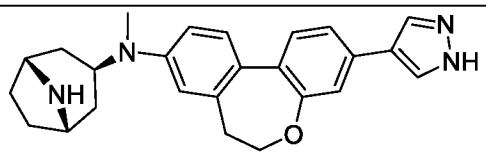
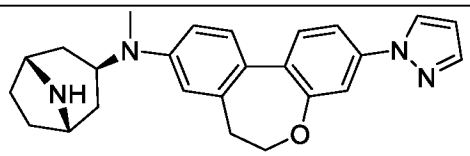
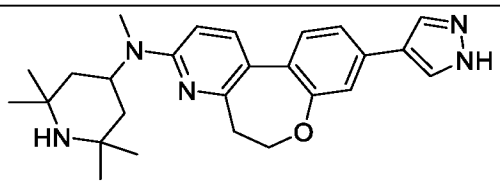
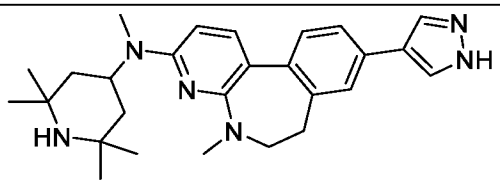
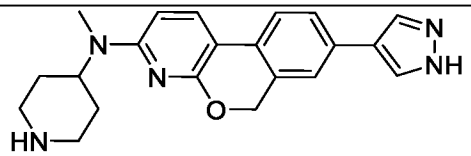
In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_1-C_6-alkyl (e.g., methyl). In some embodiments, R^1 is methyl. In some embodiments, R^4 is methyl. In some

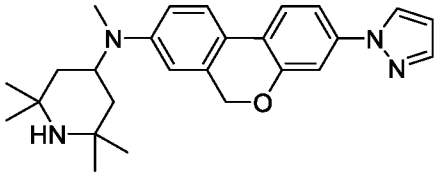
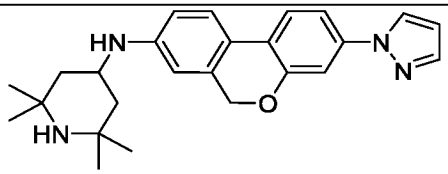
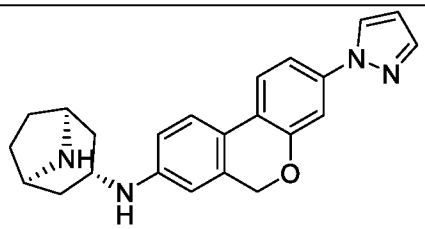
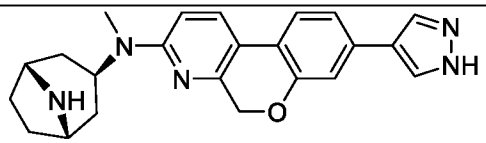
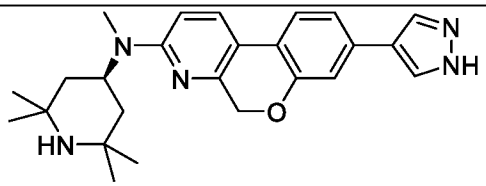
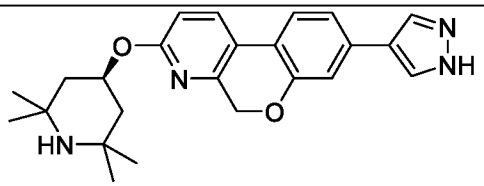
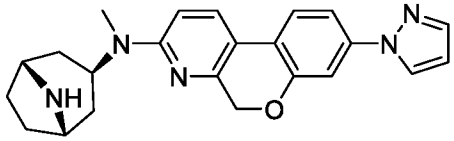
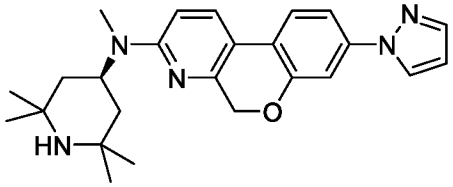
embodiments R^6 is hydrogen. In some embodiments, R^{7a} and R^{7b} are each hydrogen. In some embodiments, m is 1. In some embodiments, m is 2.

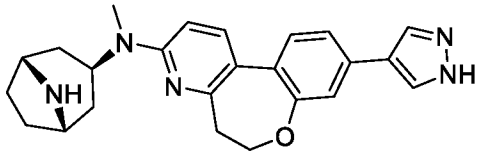
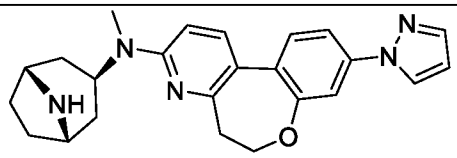
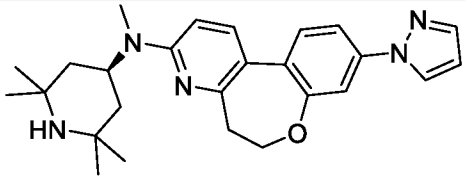
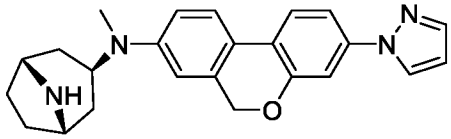
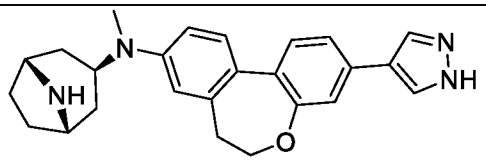
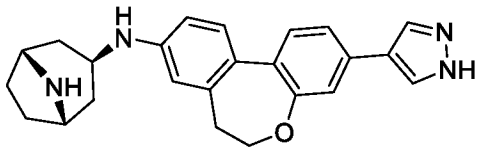
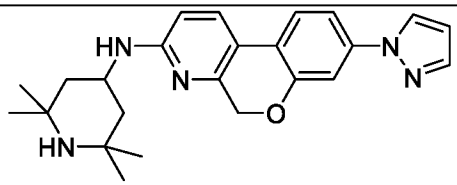
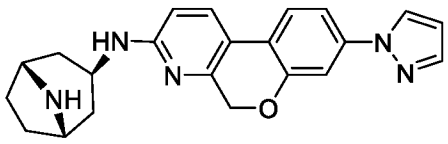
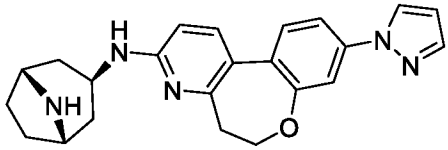
In some embodiments, the compound of Formula (I) is a compound selected from a compound in Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

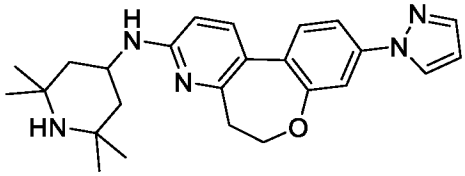
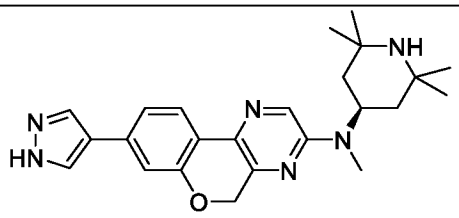
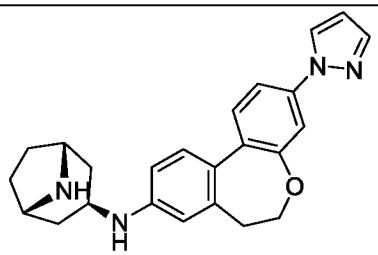
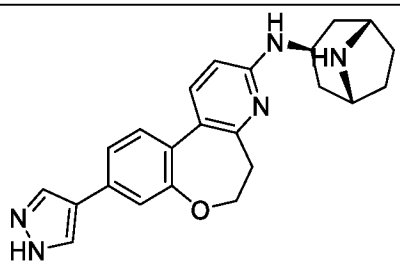
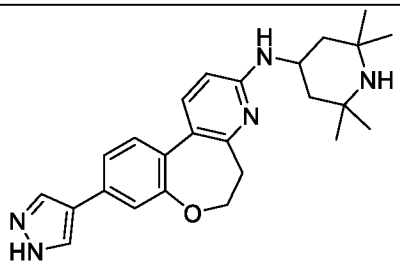
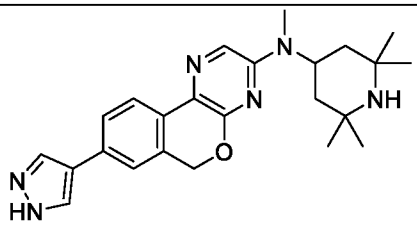
Table 1: Exemplary compounds

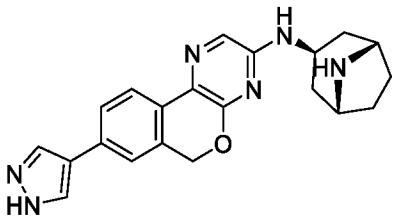
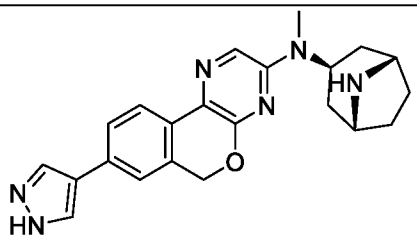
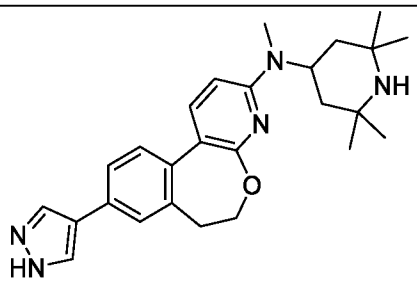
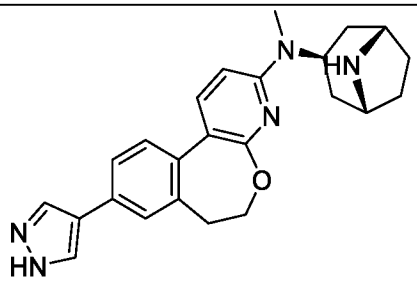
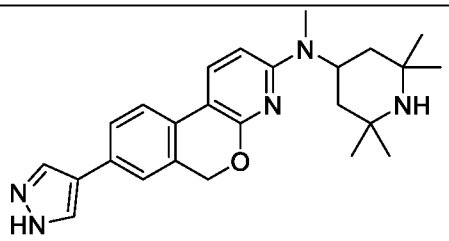
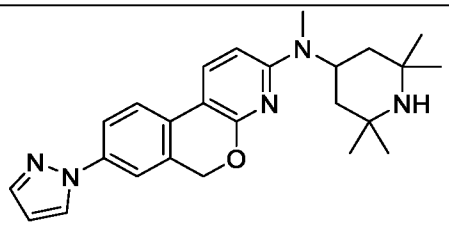
Compound No.	Structure
100	
101	
102	
103	
104	
105	
106	
107	

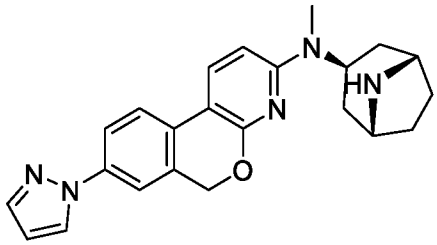
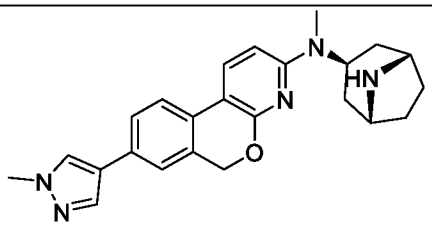
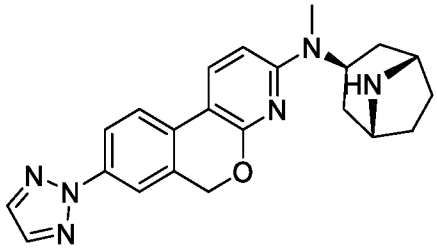
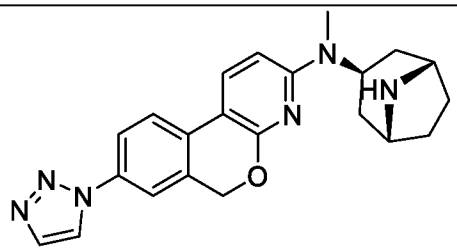
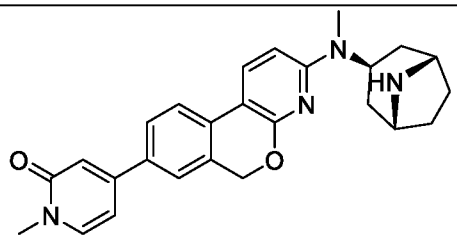
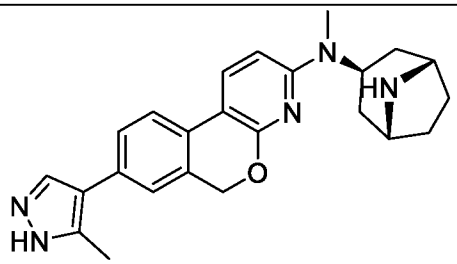
108	
109	
110	
111	
112	
113	
114	
115	
116	

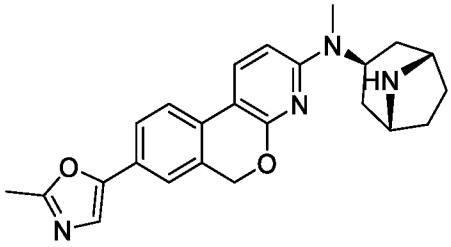
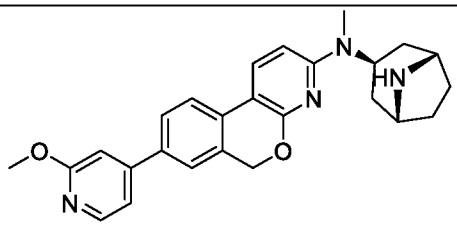
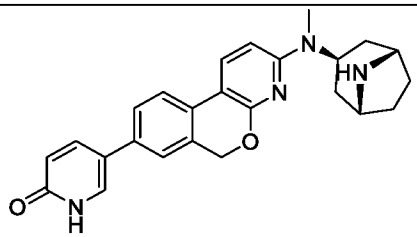
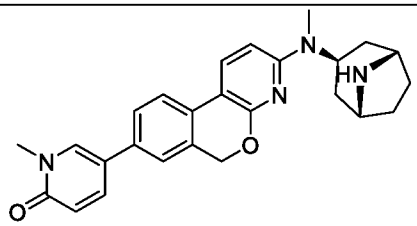
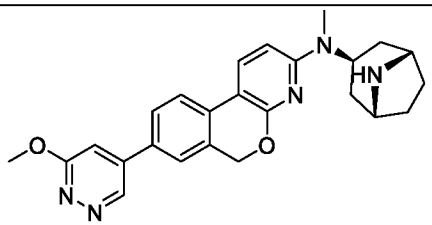
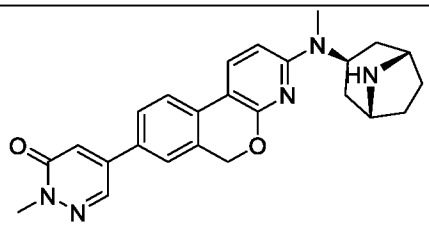
117	
118	
119	
121	
122	
123	
124	
125	

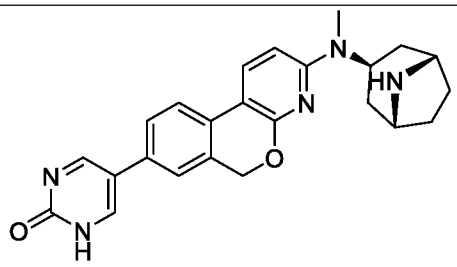
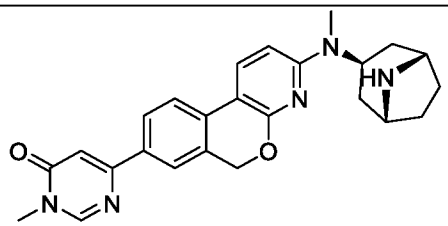
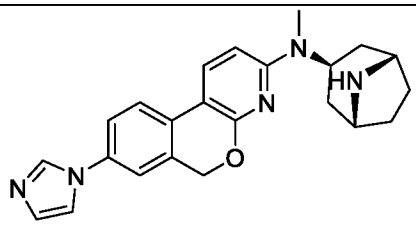
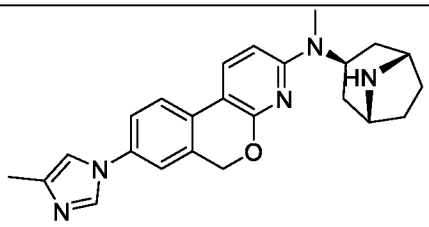
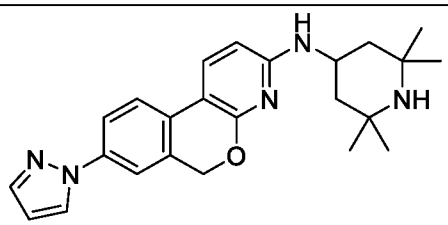
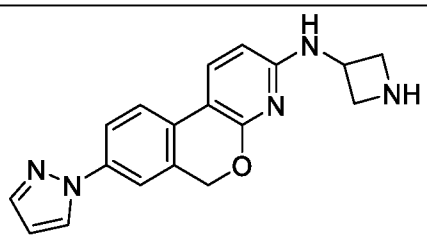
127	
128	
129	
130	
131	
132	
134	
135	
136	

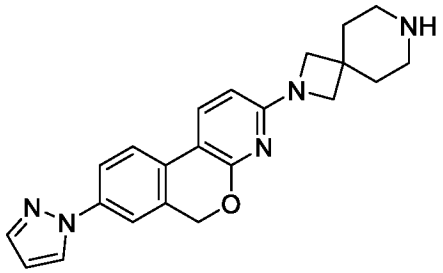
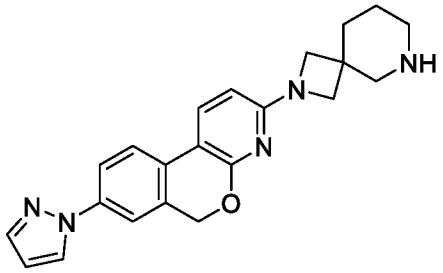
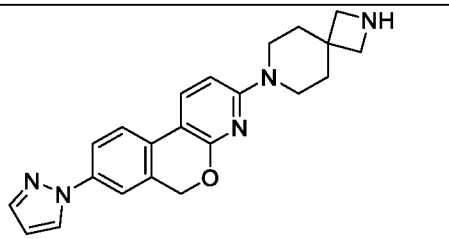
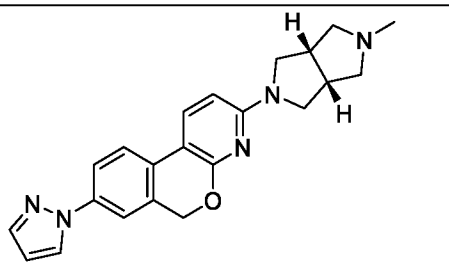
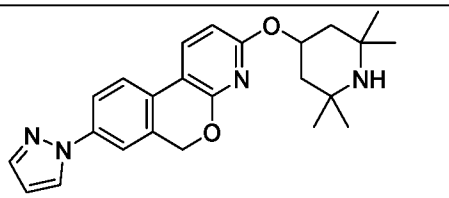
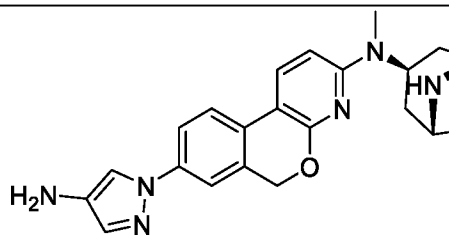
137	
138	
139	
140	
141	
142	

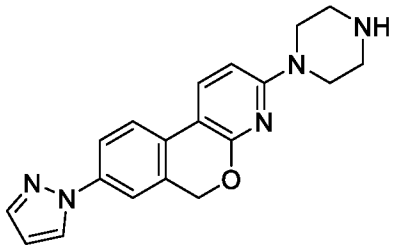
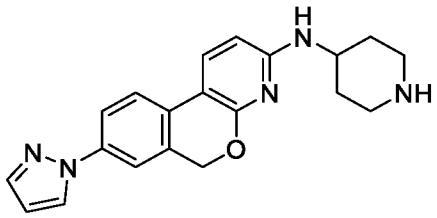
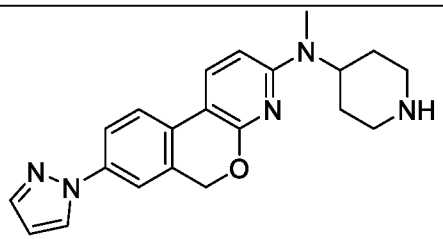
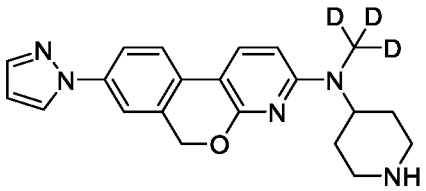
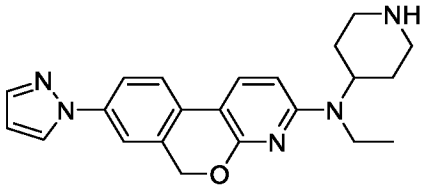
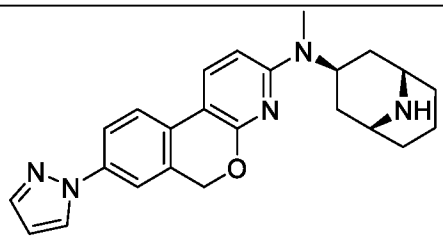
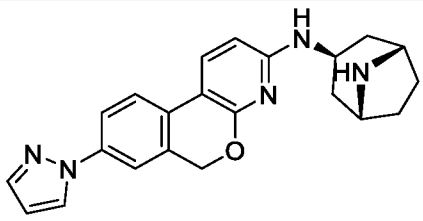
143	
144	
145	
146	
147	
148	

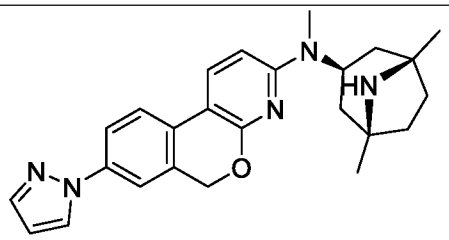
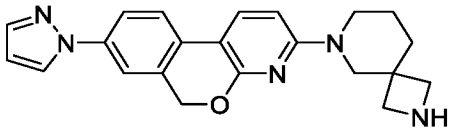
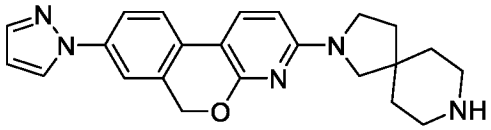
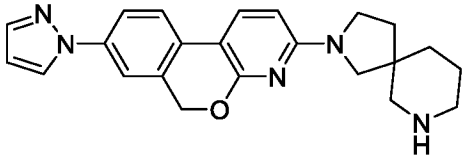
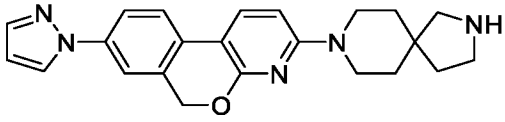
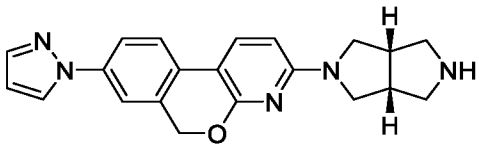
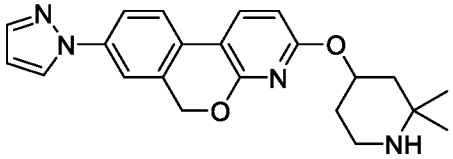
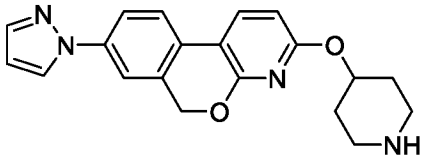
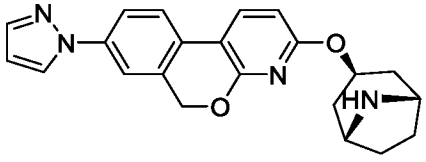
149	
150	
151	
152	
153	
154	

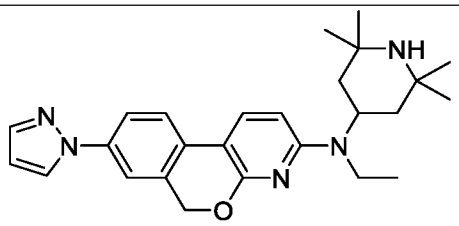
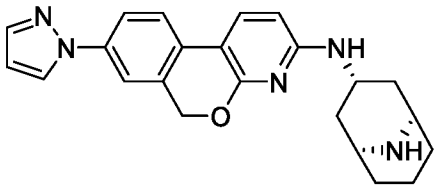
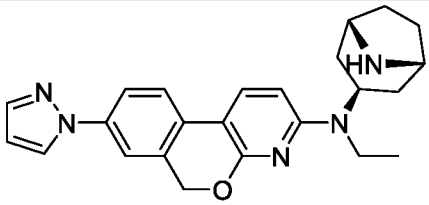
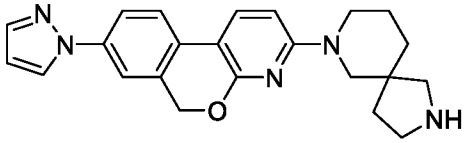
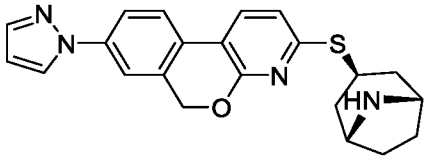
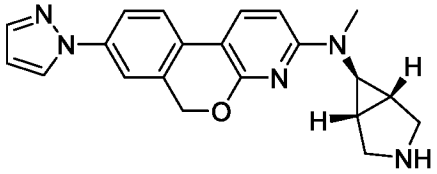
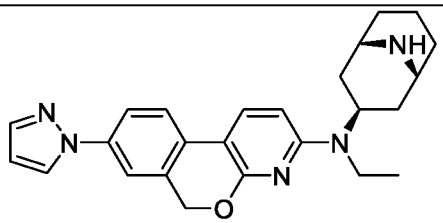
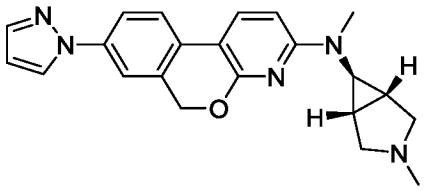
155	
156	
157	
158	
159	
160	

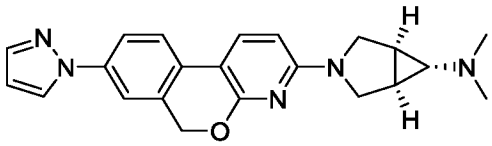
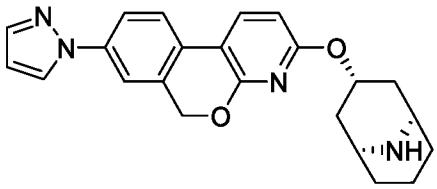
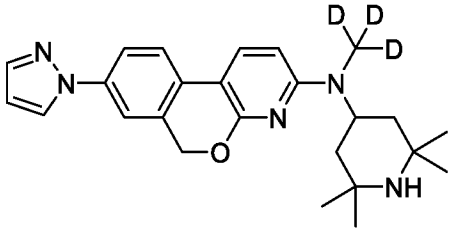
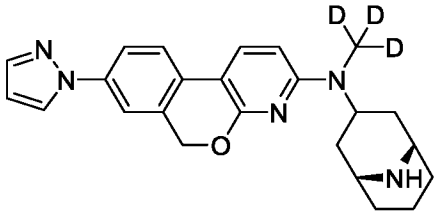
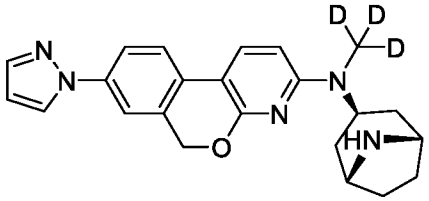
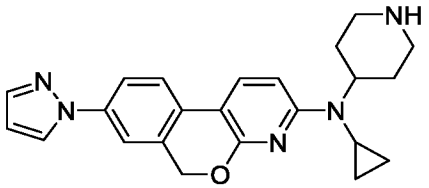
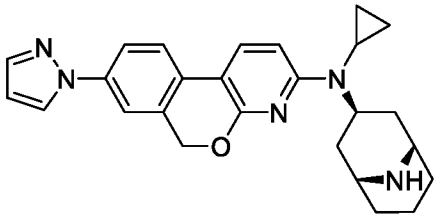
161	
162	
163	
164	
165	
166	

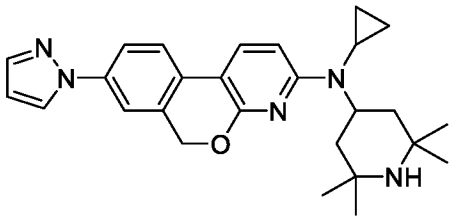
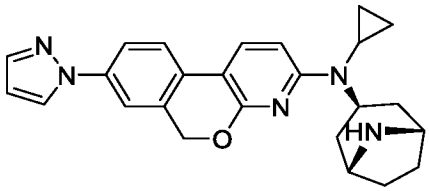
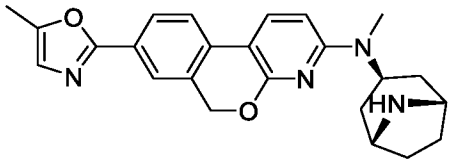
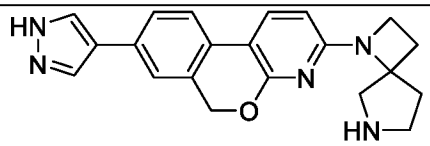
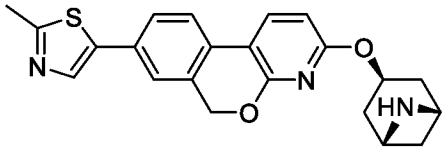
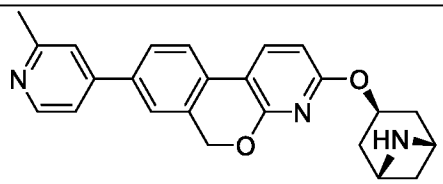
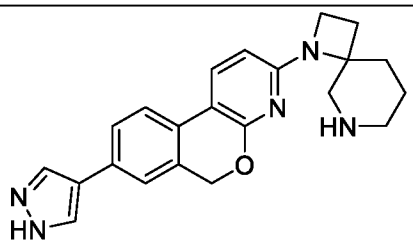
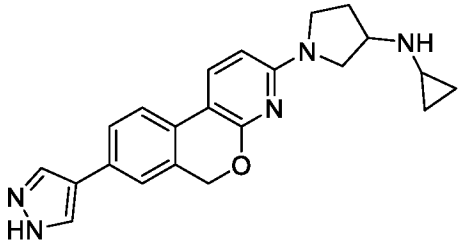
167	
168	
169	
170	
171	
172	

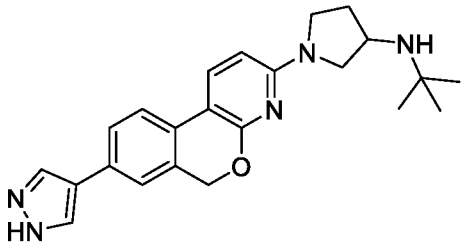
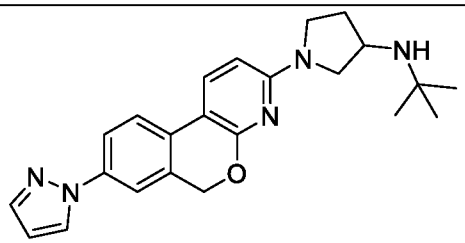
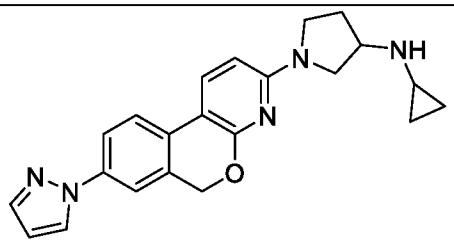
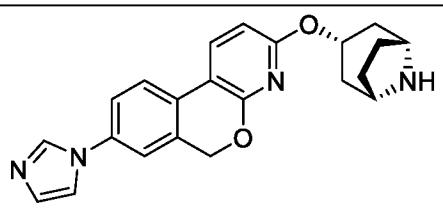
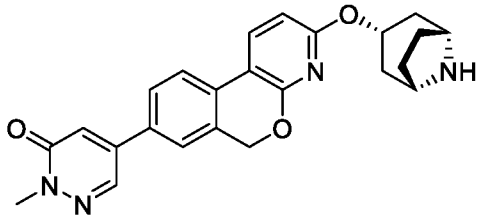
173	
174	
175	
176	
177	
178	
179	

180	
181	
182	
183	
184	
185	
186	
187	
188	

189	
190	
191	
192	
193	
194	
195	
196	

197	
198	
199	
200	
201	
202	
203	

204	
205	
206	
207	
208	
209	
210	
211	

212	
213	
214	
215	
216	

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., 2-methyl piperidinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^4)- (e.g., NMe); Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) (e.g., CH); X is O; Y is C(R^{7a})(R^{7b}) (e.g., CH_2); n and m are both 1; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-d) is Compound 100, 101, or 102, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., 2-methyl piperidinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^4)- (e.g., NMe); Z^1, Z^2, Z^3,

Z^4, Z^5, and Z^6 are each independently $C(R^6)$ (e.g., CH); X is $C(R^{7a})(R^{7b})$ (e.g., CH_2); Y is O; n and m are both 1; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-b), (I-c), and (I-e) is Compound 103, 117, 118, 119, 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 $-N(R^4)-$ (e.g., NMe); Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently $C(R^6)$ (e.g., CH); X is O; Y is $C(R^{7a})(R^{7b})$ (e.g., CH_2); n and m are both 1; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-d) is Compound 104, 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 $-N(R^4)-$ (e.g., NMe); Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently $C(R^6)$ (e.g., CH); X is $C(R^{7a})(R^{7b})$ (e.g., CH_2); Y is O; n and m are both 1; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-b), (I-c), and (I-e) is Compound 105, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., 2-methylpiperidinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is $-N(R^4)-$ (e.g., NMe); Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently $C(R^6)$ (e.g., CH); Z^2 is N; X is O; Y is $C(R^{7a})(R^{7b})$ (e.g., CH_2); n and m are both 1; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-d) is Compound 106, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., 2-methyl piperidinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is $-N(R^4)-$ (e.g., NMe); Z^1, Z^3, Z^4, Z^5, and Z^6 are each independently $C(R^6)$ (e.g., CH); Z^2 is N; X is $C(R^{7a})(R^{7b})$ (e.g., CH_2); Y is O; n and m are both 1; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-b), (I-c), and (I-e) is Compound 107, 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 $-N(R^4)-$ (e.g., NMe); Z^1, Z^3, and Z^4 are each independently $C(R^6)$ (e.g., CH); Z^2 is N; X is O; Y is $C(R^{7a})(R^{7b})$ (e.g.,

CH_2); n and m are both 1; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-d) is Compound 108, 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^4)- (e.g., NMe); Z^1, Z^3, Z^4, Z^5, and Z^6 are each are each independently C(R^6) (e.g., CH); Z^2 is N; X is C(R^{7a})(R^{7b}) (e.g., CH_2); Y is O; n and m are both 1; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-b), (I-c), and (I-e) is Compound 109, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., 2-methyl piperidinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^4)- (e.g., NMe); Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) (e.g., CH); X is O; Y is C(R^{7a})(R^{7b}) (e.g., CH_2); n is 1; m is 2; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-d) is Compound 110, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., 2-methyl piperidinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^4)- (e.g., NMe); Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) (e.g., CH); X is O; Y is C(R^{7a})(R^{7b}) (e.g., CH_2); n is 1; m is 2; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-d) is Compound 111, 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^4)- (e.g., NMe); Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) (e.g., CH); X is C(R^{7a})(R^{7b}) (e.g., CH_2); Y is O; n is 2; m is 1; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-b), (I-c), and (I-e) is Compound 112, 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^4)- (e.g., NMe); Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each are each independently C(R^6) (e.g., CH); X is C(R^{7a})(R^{7b}) (e.g., CH_2); Y is O; n is 2; m is 1; and R^{2a} and R^{2b} are each independently hydrogen. In some

embodiments, the compound of Formulas (I), (I-b), (I-c), and (I-e) is Compound 113, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., 2,2,6,6-tetramethylpiperidinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^4)- (e.g., NMe); Z^1, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) (e.g., CH); Z^2 is N; X is C(R^{7a})(R^{7b}) (e.g., CH_2); Y is O; n is 2; m is 1; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-b), (I-c), and (I-e) is Compound 114, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., 2,2,6,6-tetramethylpiperidinyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^4)- (e.g., NMe); Z^1, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) (e.g., CH); Z^2 is N; X is N(R^{7c}) (e.g., NMe); Y is C(R^{7a})(R^{7b}) (e.g., CH_2); n is 1; m is 2; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-a), (I-c), and (I-f) is Compound 115, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heterocyclyl (e.g., 2,2,6,6-tetramethylpiperidinyl or piperidinyl) or bicyclic heterocyclyl (e.g., azabicyclo[3.2.1]octanyl); B is monocyclic heteroaryl (e.g., pyrazolyl); L is -N(R^4)- (e.g., NMe or NH) or O; Z^1, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) (e.g., CH); Z^2 is N or C(R^6); one of X and Y is C(R^{7a})(R^{7b}) (e.g., CH_2), and the other of X and Y is O; n is 1 or 2; m is 1 or 2; and R^{2a} and R^{2b} are each independently hydrogen. In some embodiments, the compound of Formulas (I), (I-a), (I-d), and (I-e) and is Compound 116, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-b), (I-c), and (I-e) and is one of Compounds 117-119, 121-125, or 127-132, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, any one of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), and (I-i), A is monocyclic heterocyclyl (e.g., 2,2,6,6-tetramethylpiperidinyl or piperidinyl) or bicyclic heterocyclyl (e.g., azabicyclo[3.2.1]octanyl); B is monocyclic heteroaryl (e.g., pyrazolyl, imidazolyl, or methylimidazolyl) or monocyclic heterocyclyl; L is L is -N(R^4)- (e.g., N(CH_3) or N(CD_3)); X is O; Y is C(R^{7a})(R^{7b}) (e.g., CH_2); and Z^1, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) (e.g., CH); Z^2 is N. In some embodiments, the compound of any one of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), and (I-i) is a compound selected from

108, 116, 121, 143, 149, 150, 151, 153, 155, 158, 159, 160, 162, 163, 164, 169, 178, 180, 190, 200, and 201, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of any one of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), and (I-i) is a compound selected from Compound 108, 150, 151, 153, 155, 159, 160, 162, 163, 164, 178, 180, 190, and 200, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 108 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 150 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 151 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 153 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 155 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 159 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 160 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 162 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 163 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 164 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 178 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 180 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 190 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound is Compound 200 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

Pharmaceutical Compositions, Kits, and Administration

The present invention provides pharmaceutical compositions comprising a compound of

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

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

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

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

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

buffering agents, lubricating agents, and/or oils. Pharmaceutically acceptable excipients useful in the manufacture of the pharmaceutical compositions of the invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Methods of Use

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

snRNPs), or minor spliceosome members (U11, U12, U4atac, U6atac snRNPs) and their accessory splicing factors.

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

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

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

ARHGAP8, ARHGAP18, ARHGAP26, ARHGEF18, ARHGEF2, ARPC3, ARS2, ASH1L, ASH1L-IT1, ASNSD1, ASPM, ATAD5, ATF1, ATG4A, ATG16L2, ATM, ATN1, ATP11C, ATP6V1G3, ATP13A5, ATP7A, ATP7B, ATR, ATXN2, ATXN3, ATXN7, ATXN10, AXIN1, B2M, B4GALNT3, BBS4, BCL2, BCL2L1, BCL2-like 11 (BIM), BCL11B, BBOX1, BCS1L, BEAN1, BHLHE40, BMPR2, BMP2K, BPTF, BRAF, BRCA1, BRCA2, BRCC3, BRSK1, BRSK2, BTAF1, BTK, C2orf55, C4orf29, C6orf118, C9orf43, C9orf72, C10orf137, C11orf30, C11orf65, C11orf70, C11orf87, C12orf51, C13orf1, C13orf15, C14orf10l, C14orf118, C15orf29, C15orf42, C15orf60, C16orf33, C16orf38, C16orf48, C18orf8, C19orf42, C1orf107, C1orf114, C1orf130, C1orf149, C1orf27, C1orf71, C1orf94, C1R, C20orf74, C21orf70, C3orf23, C4orf18, C5orf34, C8B, C8orf33, C9orf114, C9orf86, C9orf98, C3, CA11, CAB39, CACHD1, CACNA1A, CACNA1B, CACNA1C, CACNA2D1, CACNA1G, CACNA1H, CALCA, CALCOCO2, CAMK1D, CAMKK1, CAPN3, CAPN9, CAPSL, CARD11, CARKD, CASZ1, CAT, CBLB, CBX1, CBX3, CCDC102B, CCDC11, CCDC15, CCDC18, CCDC5, CCDC81, CCDC131, CCDC146, CD4, CD274, CD1B, CDC14A, CDC16, CDC2L5, CDC42BPB, CDCA8, CDH10, CDH11, CDH24, CDH8, CDH9, CDK5RAP2, CDK6, CDK8, CDK11B, CD33, CD46, CDH1, CDH23, CDK6, CDK11B, CDK13, CEBPZ, CEL, CELSR3, CENPA, CENPI, CENPT, CENTB2, CENTG2, CEP110, CEP170, CEP192, CETP, CFB, CFTR, CFH, CGN, CGNL1, CHAF1A, CHD9, CHIC2, CHL1, CHN1, CHM, CLEC16A, CL1C2, CLCN1, CLINT1, CLK1, CLPB, CLPTM1, CMIP, CMYA5, CNGA3, CNOT1, CNOT7, CNTN6, COG3, COL11A1, COL11A2, COL12A1, COL14A1, COL15A1, COL17A1, COL19A1, COL1A1, COL1A2, COL2A1, COL3A1, COL4A1, COL4A2, COL4A5, COL4A6, COL5A2, COL6A1, COL7A1, COL9A1, COL9A2, COL22A1, COL24A1, COL25A1, COL29A1, COLQ, COMTD1, COPA, COPB2, COPS7B, COPZ2, CPSF2, CPXM2, CR1, CRBN, CRYZ, CREBBP, CRKRS, CSE1L, CSTB, CSTF3, CT45-6, CTNNB1, CUBN, CUL4B, CUL5, CXorf41, CXXC1, CYBB, CYFIP2, CYP3A4, CYP3A43, CYP3A5, CYP4F2, CYP4F3, CYP17, CYP19, CYP24A1, CYP27A1, DAB1, DAZ2, DCBLD1, DCC, DCTN3, DCUN1D4, DDA1, DDEF1, DDX1, DDX24, DDX4, DENND2D, DEPDC2, DES, DGAT2, DHFR, DHRS7, DHRS9, DHX8, DIP2A, DMD, DMTF1, DNAH3, DNAH8, DNAI1, DNAJA4, DNAJC13, DNAJC7, DNMT1, DNTTIP2, DOCK4, DOCK5, DOCK10, DOCK11, DOT1L, DPP3, DPP4, DPY19L2P2, DR1, DSCC1, DVL3, DUX4, DYNC1H1, DYSF, E2F1, E2F3, E2F8, E4F1, EBF1, EBF3, ECM2, EDEM3, EFCAB3, EFCAB4B, EFNA4, EFTUD2, EGFR, EIF3A, ELA1, ELA2A, ELF2, ELF3, ELF4, EMCN, EMD, EML5, ENO3, ENPP3,

EP300, EPAS1, EPB41L5, EPHA3, EPHA4, EPHB1, EPHB2, EPHB3, EPS15, ERBB4, ERCC1, ERCC8, ERGIC3, ERMN, ERMP1, ERN1, ERN2, ESR1, ESRRG, ETS2, ETV3, ETV4, ETV5, ETV6, EVC2, EWSR1, EXO1, EXOC4, F3, F11, F13A1, F5, F7, F8, FAH, FAM13A1, FAM13B1, FAM13C1, FAM134A, FAM161A, FAM176B, FAM184A, FAM19A1, FAM20A, FAM23B, FAM65C, FANCA, FANCC, FANCG, FANCM, FANK1, FAR2, FBN1, FBXO15, FBXO18, FBXO38, FCGBP, FECH, FEZ2, FGA, FGD6, FGFR2, FGFR1OP, FGFR1OP2, FGFR2, FGG, FGR, FIX, FKBP3, FLI1, FLJ35848, FLJ36070, FLNA, FN1, FNBP1L, FOLH1, FOSL1, FOSL2, FOXK1, FOXM1, FOXO1, FOXP4, FRAS1, FUT9, FXN, FZD3, FZD6, GAB1, GABPA, GALC, GALNT3, GAPDH, GART, GAS2L3, GATA3, GATAD2A, GBA, GBGT1, GCG, GCGR, GCK, GFI1, GFM1, GH1, GHR, GHV, GJA1, GLA, GLT8D1, GNA11, GNAQ, GNAS, GNB5, GOLGB1, GOLT1A, GOLT1B, GPATCH1, GPR158, GPR160, GPX4, GRAMD3, GRHL1, GRHL2, GRHPR, GRIA1, GRIA3, GRIA4, GRIN2B, GRM3, GRM4, GRN, GSDMB, GSTCD, GSTO2, GTF2I, GTPBP4, HADHA, HAND2, HBA2, HBB, HCK, HDAC3, HDAC5, HDX, HEPACAM2, HERC1, HES7, HEXA, HEXB, HHEX, HIPK3, HLA-DPB1, HLA-G, HLCS, HLTF, HMBS, HMGA1, HMGCL, HNF1A, HNF1B, HNF4A, HNF4G, HNRNPH1, HOXC10, HP1BP3, HPGD, HPRT1, HPRT2, HSF1, HSF4, HSF2BP, HSPA9, HSPG2, HTT, HXA, ICA1, IDH1, IDS, IFI44L, IKBKAP, IKZF1, IKZF3, IL1R2, IL5RA, IL7RA, IMMT, INPP5D, INSR, INTS3, INTU, IP04, IP08, IQGAP2, IRF2, IRF4, IRF8, IRX3, ISL1, ISL2, ITFG1, ITGA6, ITGAL, ITGB1, ITGB2, 1TGB3, ITGB4, ITIH1, ITPR2, IWS1, JAK1, JAK2, JAG1, JMJD1C, JPH3, KALRN, KAT6A, KATNAL2, KCNN2, KCNT2, KDM2A, KIAA0256, KIAA0528, KIAA0564, KIAA0586, KIAA1033, KIAA1166, KIAA1219, KIAA1409, KIAA1622, KIAA1787, KIF3B, KIF15, KIF16B, KIF5A, KIF5B, KIF9, KIN, KIR2DL5B, KIR3DL2, KIR3DL3, KIT, KLF3, KLF5, KLF7, KLF10, KLF12, KLF16, KLHL20, KLK12, KLKB1, KMT2A, KMT2B, KPNA5, KRAS, KREMEN1, KRIT1, KRT5, KRTCAP2, KYNU, L1CAM, L3MBTL, L3MBTL2, LACE1, LAMA1, LAMA2, LAMA3, LAMB1, LARP7, LDLR, LEF1, LENG1, LGALS3, LGMN, LHCGR, LHX3, LHX6, LIMCH1, LIMK2, LIN28B, LIN54, LMBRD1, LMBRD2, LMLN, LMNA, LMO2, LMO7, LOC389634, LOC390110, LPA, LPCAT2, LPL, LRP4, LRPPRC, LRRK2, LRRC19, LRRC42, LRWD1, LUM, LVRN, LYN, LYST, MADD, MAGI1, MAGT1, MALT1, MAP2K1, MAP4K4, MAPK8IP3, MAPK9, MAPT, MARC1, MARCH5, MATN2, MBD3, MCF2L2, MCM6, MDGA2, MDM4, ASXL1, FUS, SPR54, MECOM, MEF2C, MEF2D, MEGF10, MEGF11, MEMO1, MET, MGA, MGAM, MGAT4A, MGAT5, MGC16169,

MGC34774, MKKS, MIB1, MIER2, MITF, MKL2, MLANA, MLH1, MLL5, MLX, MME, MPDZ, MPI, MRAP2, MRPL11, MRPL39, MRPS28, MRPS35, MS4A13, MSH2, MSH3, MSMB, MST1R, 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, 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, AL358113.1,TJP2, AL441992.2, KYAT1, AL449266.1,CLCC1, AL590556.3, LINC00339, CDC42, ALAS1, ALB, ALDH16A1, ALDH1B1, ALDH3A1, ALDH3B2, ALDOA, ALKBH2, ALPL, AMD1, AMICA1, AMN1, AMOTL2, AMY1B, AMY2B, ANAPC10, ANAPC11, ANAPC15, ANG, RNASE4, AL163636.2, ANGEL2, ANGPTL1, ANKMY1, ANKRD11, ANKRD28, ANKRD46, ANKRD9, ANKS3, ANKS3,RP11-127I20.7, ANKS6, ANKZF1, ANPEP, ANXA11, ANXA2, ANXA8L2, AL603965.1, AOC3, AP000304.12, CRYZL1, AP000311.1, CRYZL1, AP000893.2,RAB30, AP001267.5, ATP5MG, AP002495.2, AP003175.1, OR2AT4, AP003419.1, CLCF1, AP005263.1, ANKRD12, AP006621.5, AP006621.1, AP1G1, AP3M1, AP3M2, APBA2, APBB1, APLP2, APOA2, APOL1, APOL3, APTX, ARAP1,STARD10, ARF4, ARFIP1, ARFIP2, ARFRP1, ARHGAP11A, ARHGAP33, ARHGAP4, ARHGEF10, ARHGEF3, ARHGEF35, OR2A1-AS1, ARHGEF35, OR2A1-AS1, ARHGEF34P, ARID1B, ARHGEF35, OR2A20P, OR2A1-AS1, ARHGEF9, ARL1, ARL13B, ARL16, ARL6, ARMC6, ARMC8, ARMCX2, ARMCX5, RP4-769N13.6, ARMCX5-GPRASP2, BHLHB9, ARMCX5-GPRASP2,GPRASP1, ARMCX5-GPRASP2,GPRASP2, ARMCX6, ARNT2, ARPP19, ARRB2, ARSA, ART3, ASB3,GPR75-ASB3, ASCC2, ASNS, ASNS, AC079781.5, ASPSCR1, ASS1, ASUN, ATE1, ATF1, ATF7IP2, ATG13, ATG4D, ATG7, ATG9A, ATM, ATOX1, ATP1B3, ATP2C1, ATP5F1A, ATP5G2, ATP5J, ATP5MD, ATP5PF, ATP6AP2, ATP6V0B, ATP6V1C1, ATP6V1D, ATP7B, ATXN1,

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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,

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Additional exemplary gene sequences and splice site sequences (e.g., 5' splice site sequences) include AAGgcaagau, AUGguaugug, GGGgugaggc, CAGguaggug, AAGgucagua,

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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,

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AUGguauguc, GUGgugugug, CUGgugaccu, AAUgugaaua, UAGgucucac, GAGguuauug, UGAguaggcu, CGGgcacgua, GCAguaaaua, CCGgugagag, UAAguugguc, CCGgugagcc, AAGguuguca, CUGguauuau, GGGguauggg, AAAgucagua, UUUguaugua, UAAguacugc, CAGguaccaa, GAAguucaga, AUGgugcggu, GUGgugaggu, UGAguaagcc, UAUguaaggg, GUGguggaaa, GAGgugauug, GGAguuugua, AAGgucacga, GUGguagagg, UAAguauauc, AAGgugucca, UAUgugguau, GAGguacaau, AAGgugggggg, GGAguaggug, and UAGgugacuu.

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

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

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

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

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

In some embodiments, a compound of Formula (I) described herein interacts with (*e.g.,* binds to) a splicing complex component (e.g., a nucleic acid (e.g., an RNA) or a protein). In

some embodiments, the splicing complex component is selected from 9G8, Al hnRNP, A2 hnRNP, ASD-1, ASD-2b, ASF, BRR2, B1 hnRNP, C1 hnRNP, C2 hnRNP, CBP20, CBP80, CELF, F hnRNP, FBP11, Fox-1, Fox-2, G hnRNP, H hnRNP, hnRNP 1, hnRNP 3, hnRNP C, hnRNP G, hnRNP K, hnRNP M, hnRNP U, Hu, HUR, I hnRNP, K hnRNP, KH-type splicing regulatory protein (KSRP), L hnRNP, LUC7L, M hnRNP, mBBP, muscle-blind like (MBNL), NF45, NFAR, Nova-1, Nova-2, nPTB, P54/SFRS11, polypyrimidine tract binding protein (PTB), a PRP protein (e.g., PRP8, PRP6, PRP31, PRP4, PRP3, PRP28, PRP5, PRP2, PRP19), PRP19 complex proteins, RBM42, R hnRNP, RNPC1, SAD1, SAM68, SC35, SF, SF1/BBP, SF2, SF3A complex, SF3B complex, SFRS10, an Sm protein (such as B, D1, D2, D3, F, E, G), SNU17, SNU66, SNU114, an SR protein, SRm300, SRp20, SRp30c, SRP35C, SRP36, SRP38, SRp40, SRp55, SRp75, SRSF, STAR, GSG, SUP-12, TASR-1, TASR-2, TIA, TIAR, TRA2, TRA2a/b, U hnRNP, Ul snRNP, U11 snRNP, U12 snRNP, U1-70K, U1-A, U1-C, U2 snRNP, U2AF1-RS2, U2AF35, U2AF65, U4 snRNP, U5 snRNP, U6 snRNP, Urp, and YB1.

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

In some embodiments, the splicing complex component comprises a protein, *e.g.,* a protein associated with an snRNA. In some embodiments, the protein comprises SC35, SRp55, SRp40, SRm300, SFRS10, TASR-1, TASR-2, SF2/ASF, 9G8, SRp75, SRp30c, SRp20 and P54/SFRS11. In some embodiments, the splicing complex component comprises a U2 snRNA auxiliary factor (e.g., U2AF65, U2AF35), Urp/U2AF1-RS2, SF1/BBP, CBP80, CBP 20, SF1 or PTB/hnRNP1. In some embodiments, the splicing complex component comprises a heterogenous ribonucleoprotein particle (hnRNP), e.g., an hnRNP protein. In some embodiments, the hnRNP protein comprises A1, A2/B1, L, M, K, U, F, H, G, R, I or C1/C2. Human genes encoding hnRNPs include *HNRNPA0*, *HNRNPA1*, *HNRNPA1L1*, *HNRNPA1L2*, *HNRNPA3*, *HNRNPA2B1*, *HNRNPAB*, *HNRNPB1*, *HNRNPC*, *HNRNPCL1*, *HNRNPD*, *HNRPDL*, *HNRNPF*, *HNRNPH1*, *HNRNPH2*, *HNRNPH3*, *HNRNPK*, *HNRNPL*, *HNRPLL*, *HNRNPM*, *HNRNPR*, *HNRNPU*, *HNRNPUL1*, *HNRNPUL2*, *HNRNPUL3*, and *FMR1*.

In one aspect, the compounds of Formula (I) and pharmaceutically acceptable salts,

solvates, hydrates, tautomers, stereoisomers, and compositions thereof, may modulate (e.g., increase or decrease) a splicing event of a target nucleic acid sequence (e.g., DNA, RNA, or a pre-mRNA), for example, a nucleic acid encoding a gene described herein, or a nucleic acid encoding a protein described herein, or a nucleic acid comprising a splice site described herein. In an embodiment, the splicing event is an alternative splicing event.

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

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

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

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

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

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

or transgenic pig.

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

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

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

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

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

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

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

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

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

In certain embodiments, the non-proliferative disease is an autoimmune disorder or an immunodeficiency disorder. In certain embodiments, the compound of Formula (I), or a

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

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

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

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

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

pulmonary disease (COPD), lung cancer, oxygen toxicity, emphysema, chronic bronchitis, and acute respiratory distress syndrome. All types of respiratory diseases, disorders, or conditions disclosed herein or known in the art are contemplated as being within the scope of the disclosure.

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

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

contemplated as being within the scope of the disclosure.

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

failure, dystonia, dopa-responsive, due to sepiapterin reductase deficiency, Beck-Fahrner syndrome, chromosome 2p12-p11.2 deletion syndrome, neuronopathy, spastic paraplegia, familial adult myoclonic, colorectal cancer, hypothyroidism, Culler-Jones syndrome, holoprosencephaly, myelokathexis, WHIM syndrome, Mowat-Wilson syndrome, mental retardation, an intellectual developmental disorder, autism spectrum disorder, epilepsy, epileptic encephalopathy, Dravet syndrome, migraines, a mental retardation disorder (e.g., a disorder caused by a SETD5 gene mutation, e.g., intellectual disability-facial dysmorphism syndrome, autism spectrum disorder), a disorder caused by a GATA2 mutation (e.g., GATA2 deficiency; GATA2 haploinsufficiency; Emberger syndrome; monocytopenia and mycobacterium avium complex/dendritic cell, monocyte, B and NK lymphocyte deficiency; familial myelodysplastic syndrome; acute myeloid leukemia; chronic myelomonocytic leukemia), and febrile seizures.

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

In certain embodiments, the disease, disorder, or condition is an autosomal dominant disease. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, or compositions comprising such compound or pharmaceutically acceptable salt thereof, is used to prevent or treat an autosomal dominant disease, disorder, or condition. An autosomal dominant disease may refer to a monogenic disease in which the mutated gene is a

dominant gene. These diseases may also be characterized by insufficient gene product activity (e.g., a level of gene product greater than 0%). In an embodiment, a compound of Formula (I) may increase the expression of a target (e.g., a gene) related to an autosomal dominant disease. Exemplary autosomal dominant diseases include Huntington's disease, achondroplasia, antithrombin III deficiency, Gilbert's disease, Ehlers-Danlos syndrome, hereditary hemorrhagic telangiectasia, intestinal polyposis, hereditary elliptosis, hereditary spherocytosis, marble bone disease, Marfan's syndrome, protein C deficiency, Treacher Collins syndrome, Von Willebrand's disease, tuberous sclerosis, osteogenesis imperfecta, polycystic kidney disease, neurofibromatosis, and idiopathic hypoparathyroidism.

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

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

In certain embodiments, the methods described herein comprise the additional step of administering one or more additional pharmaceutical agents in combination with the compound of Formula (I), a pharmaceutically acceptable salt thereof, or compositions comprising such

compound or pharmaceutically acceptable salt thereof. Such additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-diabetic agents, anti-inflammatory agents, immunosuppressant agents, and a pain-relieving agent. The additional pharmaceutical agent(s) may synergistically augment the modulation of splicing induced by the inventive compounds or compositions of this disclosure in the biological sample or subject. Thus, the combination of the inventive compounds or compositions and the additional pharmaceutical agent(s) may be useful in treating, for example, a cancer or other disease, disorder, or condition resistant to a treatment using the additional pharmaceutical agent(s) without the inventive compounds or compositions.

EXAMPLES

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

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

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

Reactions can be purified or analyzed according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear

magnetic resonance (NMR) spectroscopy (*e.g.*, ^{1}H or ^{13}C), infrared (IR) spectroscopy, spectrophotometry (*e.g.*, UV-visible), mass spectrometry (MS), or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

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

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

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

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

Condition 1: Column: Xselect CSH OBD Column 30 mm x 150 mm, 5um, n; 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: 30 B to 60 B in 8 min; Gradient 3: 3 B to 33 B in 8 min; Gradient 4: 15% B to 40% B in 8 min; Gradient 5: 3% B to 73% B in 8 min; Gradient 6: 25% B to 58% B in 8 min.

Condition 2: Column: XBridge Prep OBD C18 Column, 30 x 150mm, 5um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: acetonitrile; Flow rate:60 mL/min; Gradient 1:10% B to 50% B in 8 min; Gradient 2: 5% B to 50% B in 6 min; Gradient 3: 5% B to 35% B in 6 min; Gradient 4: 10% B to 35% B in 8 min; Gradient 5: 25% B to 57% B in 8 min; Gradient 6: 15% B to 55% B in 8 min; Gradient 7: 5% B to 45% B in 8 min; Gradient 8: 5% B to 40% B in 8 min; Gradient 9: 5% B to 35% B in 8 min; Gradient 10: 50% to 80% B in 7 min; Gradient 11: 30% to 60% B in 7 min; Gradient 12: 12% to 20% B in 7 min.

Condition 3: Column: Xselect CSH OBD Column 30 x 150mm 5um, n; Mobile Phase A:

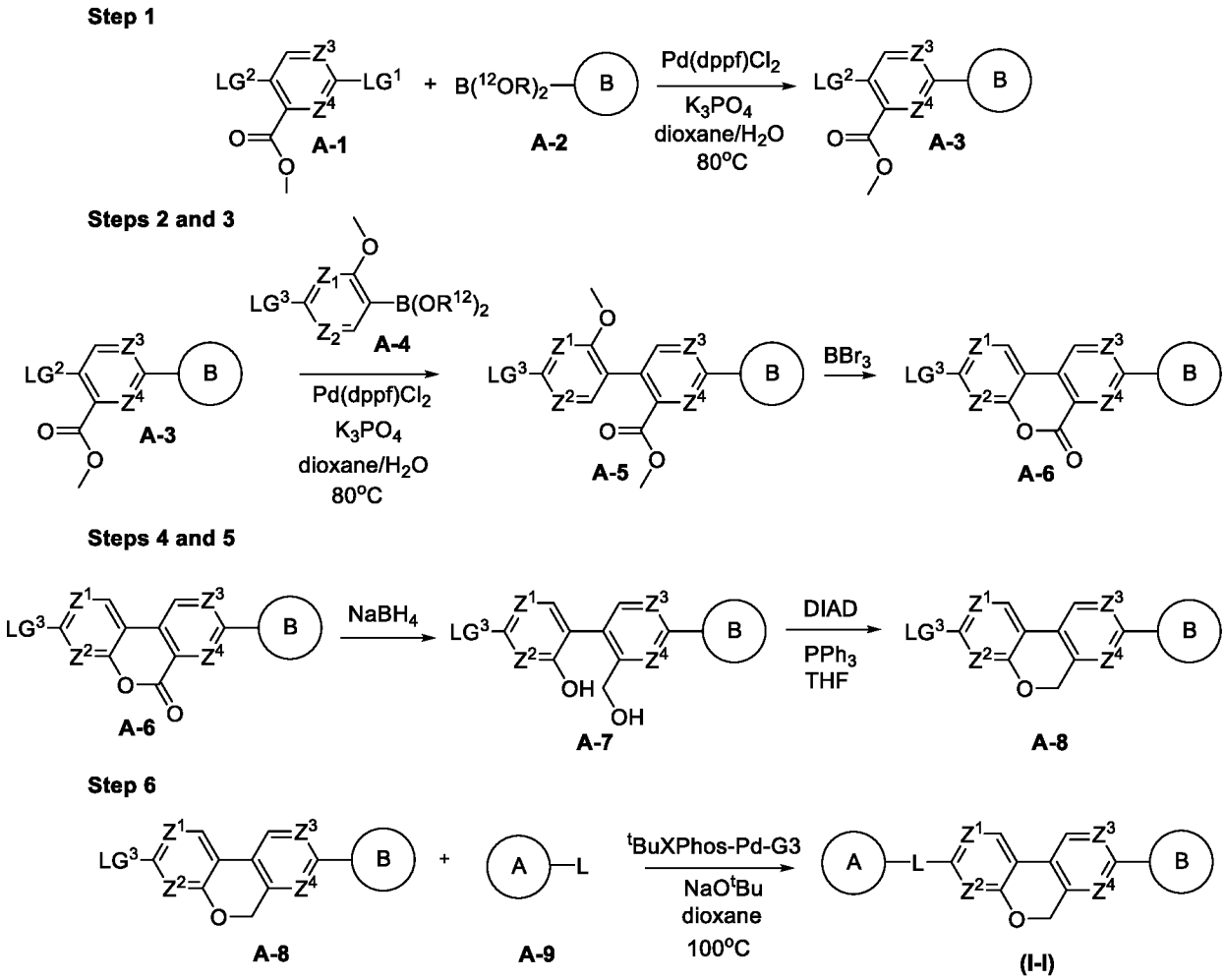
water (0.05% HCl); Mobile Phase B: acetonitrile; Flow rate: 60 mL/min; Gradient 1: 5 B to 35 B in 6 min; Gradient 2: 10 B to 29 B in 6 min.

Condition 4: Column YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: water; Mobile Phase B: 10 mmol/L NH_4HCO_3 in acetonitrile; Gradient: 10% B up to 70% 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 Schemes A-D below.



Scheme B. An exemplary method of preparing a compound of Formula (I); wherein A, B, L, Z^1, Z^2, Z^3, and Z^4 are as defined herein; LG^1, LG^2, and LG^3 are each independently a leaving group (e.g., halo); and–$B(OR^{12})_2$ is a boronic acid or ester (e.g., Bpin), wherein each R^{12} may be

hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, aryl, or heteroaryl; or two R^{12} groups, together with the atoms to which they are attached, form a heterocyclyl or heteroaryl.

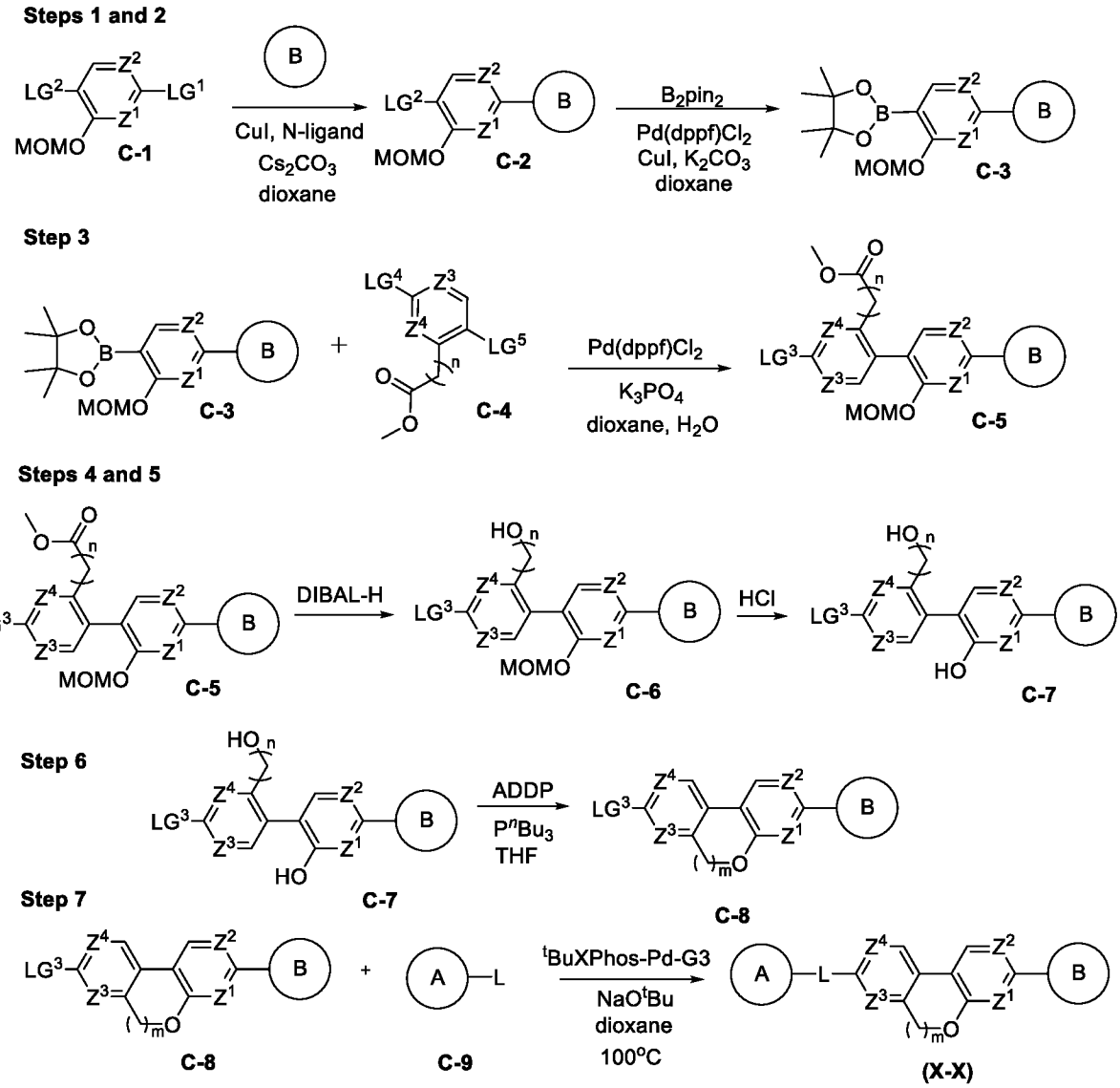
An exemplary method of preparing a compound described herein, such as a compound of Formula (I-I), is provided in Scheme A. In this scheme, A-3 is prepared in Step 1 by incubating A-1 with A-2 in the presence of 1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride ($Pd(dppf)Cl_2$) and tripotassium phosphate (K_3PO_4) or a similar reagent. Alternative catalysts to $Pd(dppf)Cl_2$ may also be used, such as a suitable palladium catalyst (e.g., a catalyst suitable for a Suzuki reaction). The coupling of A-1 and A-2 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-3.

In Step 2, A-5 is prepared by incubating A-3 with A-4 in the presence of 1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride ($Pd(dppf)Cl_2$) and tripotassium phosphate (K_3PO_4) or a suitable alternative, such as potassium acetate (KOAc). Alternative catalysts to $Pd(dppf)Cl_2$ might also be used, for example, tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$). The reaction can be carried out in dioxane, a mixture of dioxane and water, or a similar solvent or solvent mixture, at 80 °C or another temperature, for example, 60 °C or 100 °C, sufficient to provide A-5. In Step 3, A-5 is converted to A-6 by treatment with boron tribromide (BBr_3) or a suitable alternative (e.g., another Lewis acid).

In Step 4, A-6 is reduced to the diol A-7 using sodium borohydride ($NaBH_4$) or another suitable reductant. A-7 is then cyclized in Step 5 to provide A-8 by treatment of A-7 with diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (PPh_3) using tetrahydrofuran (THF) or any other suitable solvent. Step 5 may also be carried out with other reagents capable of cyclizing A-7 (e.g., reagents used for a Mitsunobu reaction). For example, alternatives to DIAD may include 1,1'-(azodicarbonyl)dipiperidine (ADDP) and di-tert-butyl azodicarboxylate (TBAD); alternatives to PPh_3 may include tributylphosphene ($P(^nBu)_3$).

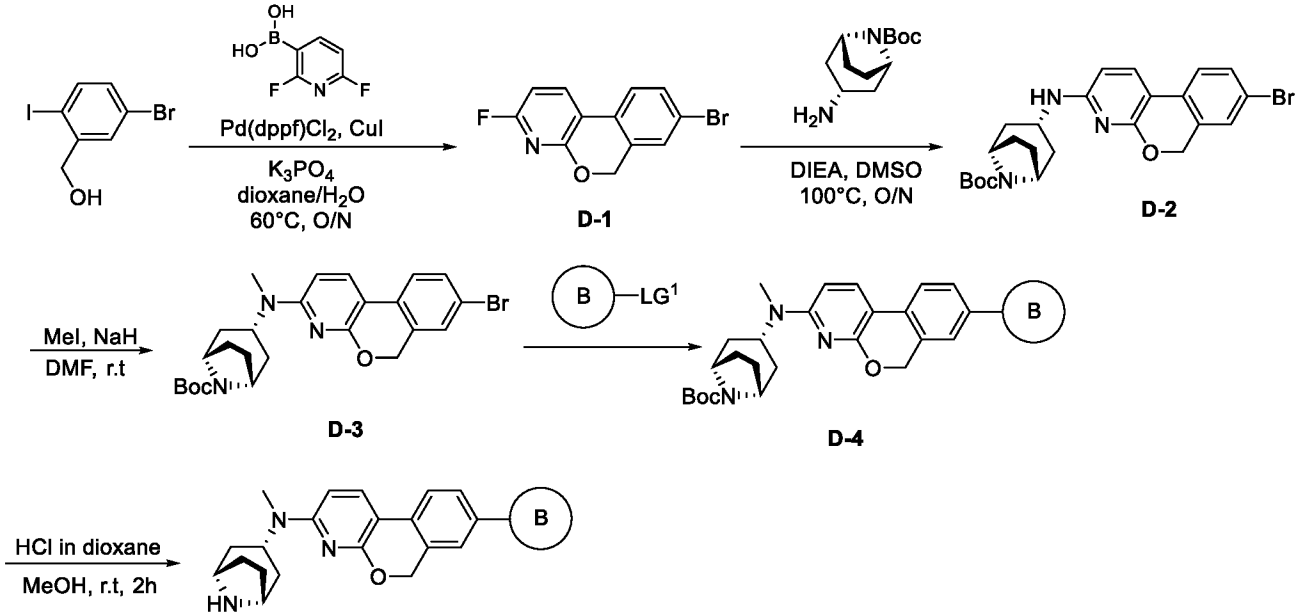
A-8 is then coupled with A-9 to provide the compound of Formula (I-I) in Step 6. This coupling reaction may be conducted in the presence of [(2-Di-*tert*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium(II) methanesulfonate (^{t}BuXPhos-Pd-G3) and NaO^tBu or a similar reagent. As in the previous steps, alternative catalysts to ^{t}BuXPhos-Pd-G3may be used, such as any suitable palladium catalyst, for example, $Pd(dppf)Cl_2$. Alternative salts to NaO^tBu may be used, such as K_3PO_4 or K_2CO_3. The reaction of

Step 6 is conducted in a mixture of dioxane and water, or other suitable solvents, and the mixture is heated to 80 °C or another temperature, for example, 100 °C, sufficient to provide the compound of Formula (I-I) or a precursor to a compound of Formula (I-I). A precursor to a compound of Formula (I-I) may be modified to arrive at a compound of Formula (I-I), for example, by removal of protecting groups and/or methylation. Each starting material and/or intermediate in Scheme A may be protected and deprotected using standard protecting group methods. In addition, purification and characterization of each intermediate as well as the final compound of Formula (I) may be afforded by any accepted procedure.

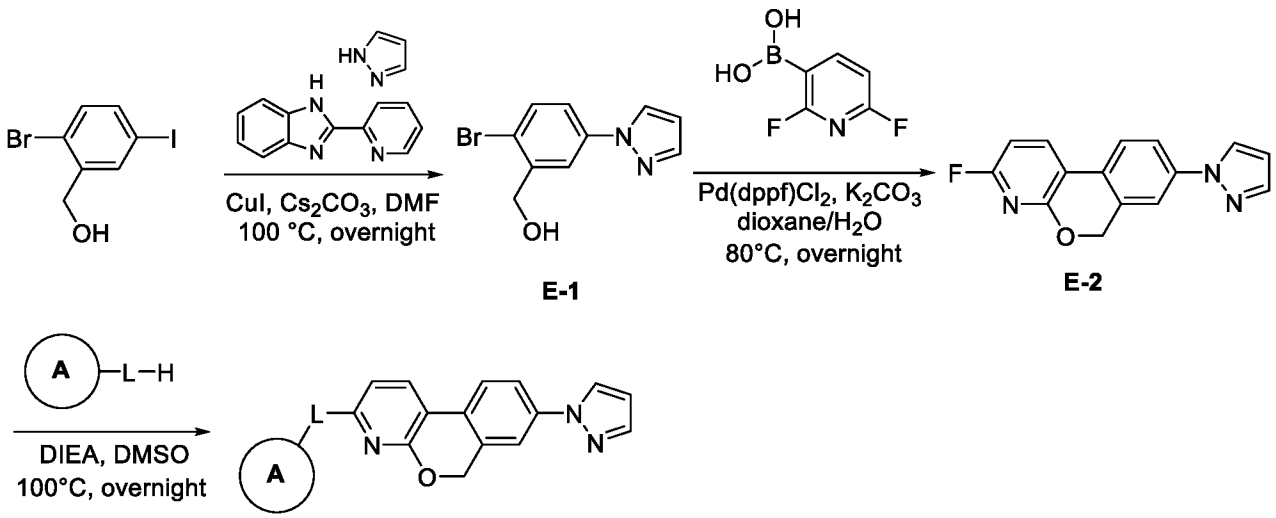


Scheme B. An exemplary method of preparing a compound of Formula (I); wherein A, B, L, Z^1, Z^2, Z^3, and Z^4 are as defined herein; n is 0 or 1; m is 1 or 2; LG^1, LG^2, and LG^3 are each independently a leaving group (e.g., halo); and–$B(OR^{12})_2$ is a boronic acid or ester (e.g., Bpin),

wherein each R^{12} may be hydrogen, C_1-C_6-alkyl, C_1-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.



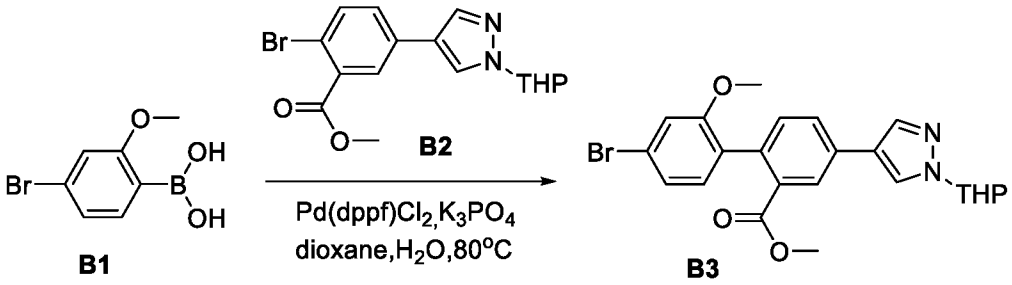
Scheme C. An exemplary method of preparing a compound of Formula (I) as outlined in Example 32, wherein B is as defined herein; LG^1 is a leaving group (e.g., halo, $-B(OR^{12})_2$) or hydrogen.



Scheme D. An exemplary method of preparing a compound of Formula (I) as outlined in Example 33; wherein A and L are defined herein.

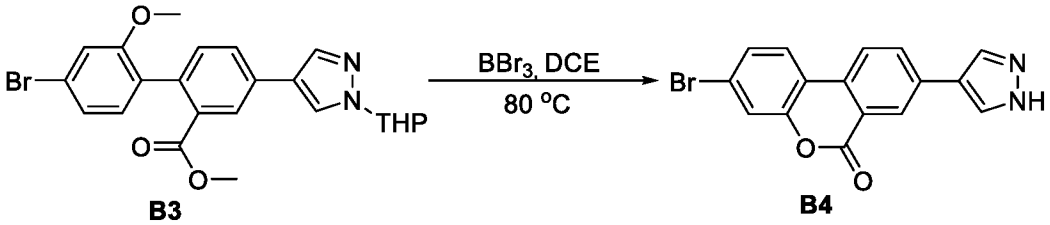
Example 1: Synthesis of Compound 101

Synthesis of Intermediate B3



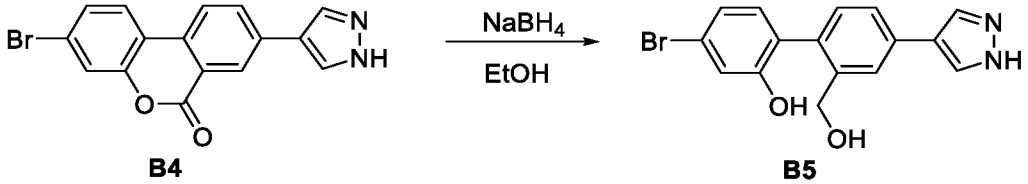
A 500-mL 3-necked round-bottom flask was purged and maintained under an atmosphere of nitrogen, and 4-bromo-2-methoxyphenylboronic acid (2.8 g, 12.13 mmol, 1 equiv), dioxane/H_2O (200 mL), methyl 2-bromo-5-[1-(oxan-2-yl) pyrazol-4-yl] benzoate (4.87 g, 0.013 mmol, 1.1 equiv), Pd(dppf)Cl_2-CH_2Cl_2 (0.5 g, 0.001 mmol, 0.05 equiv), and K_3PO_4 (7.72 g, 0.036 mmol, 3 equiv) were added to the flask. The resulting solution was stirred for 3h at 50 °C, then cooled to 0 °C with a water/ice bath. The solids were then removed by filtration, the filtrate was extracted with ethyl acetate (3 x 100 mL), and the combined organic layers were concentrated under vacuum. The crude product was purified with by CombiFlash on a C18 silica gel column, eluting with acetonitrile/H_2O (50:50, increasing to 80:20 within 40 min), to provide methyl 4'-bromo-2'-methoxy-4-[1-(oxan-2-yl) pyrazol-4-yl]-[1,1'-biphenyl]-2-carboxylate (B3; 2.2 g) as a foam. **LCMS** (ES, *m/z*): 471 $[M+H]^+$.

Synthesis of Intermediate B4



Methyl 4'-bromo-2'-methoxy-4-[1-(oxan-2-yl) pyrazol-4-yl]-[1,1'-biphenyl]-2-carboxylate (B3; 2.1 g, 4.455 mmol, 1 equiv), dichloroethane (220 mL), and boron tribromide (26 mL, 26.732 mmol, 6 equiv) were added to a 500-mL 3-necked round-bottom flask, and the resulting solution was stirred for 2h at 80 °C. The reaction mixture was cooled to room temperature with a water/ice bath, and then quenched by the addition of methanol (250 mL). The resulting mixture was concentrated under vacuum and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were concentrated under vacuum to provide 3-bromo-8-(1H-pyrazol-4-yl) benzo[c]chromen-6-one (B4; 0.9 g) as a solid. **LCMS** (ES, *m/z*): 341 $[M+H]^+$.

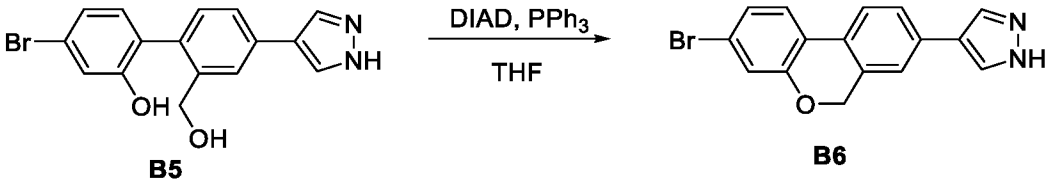
Synthesis of Intermediate B5



B4 B5

3-Bromo-8-(1H-pyrazol-4-yl)benzo[c]chromen-6-one (B4; 0.9 g, 2.638 mmol, 1 equiv), ethanol (100 mL), and $NaBH_4$ (199.61 mg, 5.276 mmol, 2 equiv) were added to a 250-mL 3-necked round-bottom flask, and the resulting solution was stirred for 3h at 25 °C. The reaction was then quenched by the addition of water (50 mL), and the resulting mixture was concentrated under vacuum, to provide 4-bromo-2'-(hydroxymethyl)-4'-(1H-pyrazol-4-yl)-[1,1'-biphenyl]-2-ol (B5; 800 mg) as a solid. **LCMS** (ES, *m/z*): 345 $[M+H]^+$.

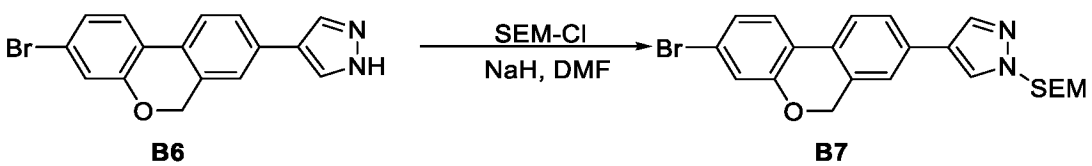
Synthesis of Intermediate B6



B5 B6

A 250-mL 2-necked round-bottom flask was purged and maintained under an atmosphere of nitrogen, and 4-bromo-2'-(hydroxymethyl)-4'-(1H-pyrazol-4-yl)-[1,1'-biphenyl]-2-ol (B5; 800 mg, 2.318 mmol, 1 equiv), tetrahydrofuran (80 mL), triphenylphosphine (911.8 mg, 3.476 mmol, 1.5 equiv), and diisopropyl azodicarboxylate (DIAD; 562.4 mg, 2.781 mmol, 1.2 equiv) were added to the flask. The resulting solution was stirred for 2h at 25 °C, and then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with saturated NaCl (100 mL) and dried over anhydrous sodium sulfate. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:2), to provide 4-[3-bromo-6H-benzo[c]chromen-8-yl]-1H-pyrazole (B6; 550 mg) as a solid. **LCMS** (ES, *m/z*): 327 $[M+H]^+$.

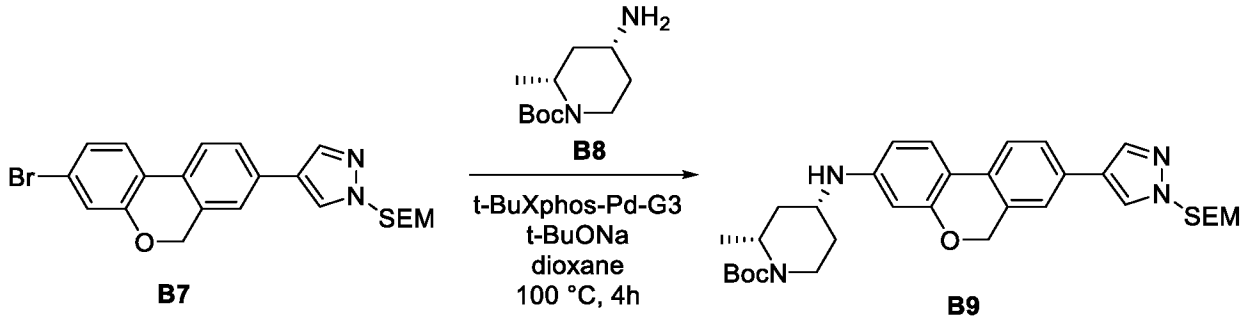
Synthesis of Intermediate B7



B6 B7

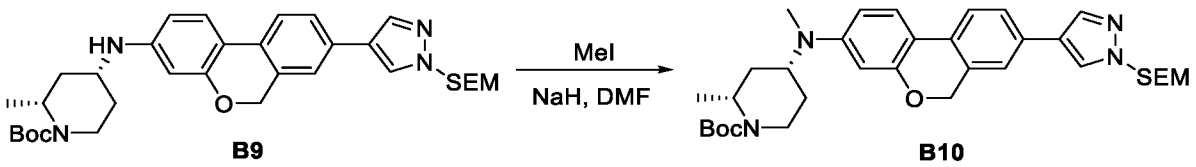
4-[3-Bromo-6H-benzo[c]chromen-8-yl]-1H-pyrazole (B6; 350 mg, 1.074 mmol, 1 equiv), dimethylformamide (15 mL), sodium hydride (38.7 mg, 1.61 mmol, 1.5 equiv), and [2-(chloromethoxy)ethyl] trimethylsilane (SEM-Cl; 268.7 mg, 1.61 mmol, 1.5 equiv) were added to a 20-mL vial, and the resulting solution was stirred for 2h at room temperature. The solution was then extracted with ethyl acetate (3 x 15 mL), and the combined organic layers were washed with saturated NaCl (15 mL), then dried over anhydrous sodium sulfate, and concentrated under vacuum to provide 4-[3-bromo-6H-benzo[c]chromen-8-yl]-1-[[2-(trimethylsilyl)ethoxy] methyl] pyrazole (B7; 215 mg) as an oil. **LCMS** (ES, *m/z*): 457 $[M+H]^+$.

Synthesis of Intermediate B9



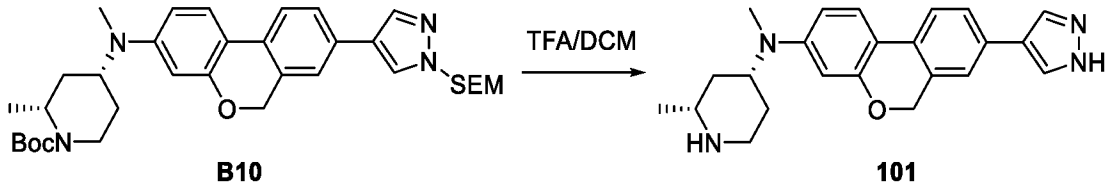
A 20-mL vial was purged and maintained under an atmosphere of nitrogen, and 4-[3-bromo-6H-benzo[c]chromen-8-yl]-1-[[2-(trimethylsilyl) ethoxy]methyl]pyrazole (B7; 215 mg, 0.470 mmol, 1 equiv), *tert*-butyl (2*R*,4*R*)-4-amino-2-methylpiperidine-1-carboxylate (B8; 151.09 mg, 0.705 mmol, 1.5 equiv), t-BuONa (135.51 mg, 1.410 mmol, 3 equiv), t-BuXPhos palladium(II) biphenyl-2-amine mesylate (18.67 mg, 0.024 mmol, 0.05 equiv), and dioxane (4 mL) were added to the vial. The resulting solution was stirred for 3.5h at 100 °C, and the reaction was quenched by the addition of water/ice (10 mL). The resulting solution was extracted with ethyl acetate (3 x 10 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/hexanes (1:1) to provide *tert*-butyl (2*R*,4*R*)-2-methyl-4-[[8-(1-[[2-(trimethylsilyl) ethoxy]methyl]pyrazol-4-yl)-6H-benzo[c]chromen-3-yl] amino] piperidine-1-carboxylate (B9; 100 mg) as a solid. **LCMS** (ES, *m/z*): 591 $[M+H]^+$.

Synthesis of Intermediate B10



A 25-mL 3-necked round-bottom flask was purged and maintained under an atmosphere of nitrogen, and *tert*-butyl(2*R*,4*R*)-2-methyl-4-[[8-(1-[[2-(trimethylsilyl) ethoxy] methyl] pyrazol-4-yl)-6H-benzo[c]chromen-3-yl]amino] piperidine-1-carboxylate (B9; 90 mg, 0.152 mmol, 1 equiv), dimethylformamide (5 mL), and sodium hydride (36.55 mg, 1.523 mmol, 10 equiv) were added to the flask. The resulting solution was stirred for 0.5h at 0 °C, then methyl iodide (216.21 mg, 1.523 mmol, 10 equiv) was added, and the resulting solution was stirred for 4h at 25 °C. The reaction was then quenched, and the resulting solution was extracted with ethyl acetate (3 x 10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum, and the residue purified by silica gel column chromatography eluting with ethyl acetate/hexanes (1:1) to provide *tert*-butyl (2*R*,4*R*)-2-methyl-4-[methyl[8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-benzo[c]chromen-3-yl]amino]piperidine-1-carboxylate (B10; 90 mg) as a solid. **LCMS** (ES, *m/z*): 605 $[M+H]^+$.

Synthesis of Compound 101

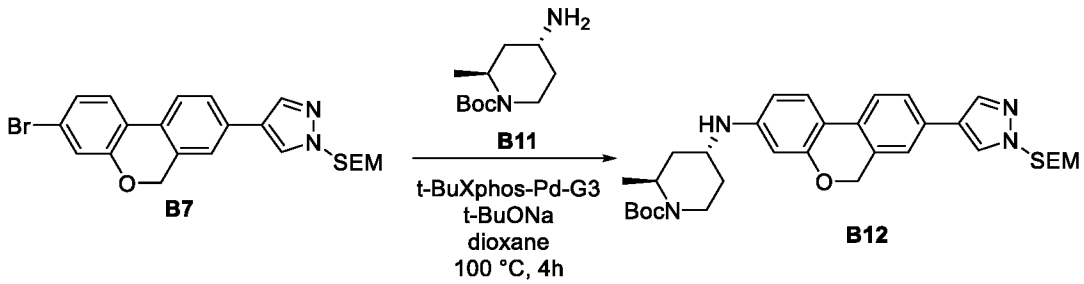


tert-Butyl (2*R*,4*R*)-2-methyl-4-[methyl[8-(1-[[2-(trimethylsilyl) ethoxy] methyl]pyrazol-4-yl)-6H-benzo[c]chromen-3-yl] amino] piperidine-1-carboxylate (B10; 90 mg), dichloromethane (2 mL), and trifluoroacetic acid (3 mL) were added to a 25-mL round-bottom flask, and the resulting solution was stirred for 2h at 25 °C. The solution was then concentrated under vacuum and dissolved in methanol (3 mL). The crude product was purified by preparative HPLC (Condition 1, Gradient 1), to provide (2*R*,4*R*)-N,2-dimethyl-N-[8-(1H-pyrazol-4-yl)-6H-benzo[c]chromen-3-yl] piperidin-4-amine (Compound 101; 21.4 mg) as a solid. **LCMS** (ES, *m/z*): 375 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d4) δ 7.98 (s, 2H), 7.61 (dd, *J* = 8.5, 2.1 Hz, 2H), 7.55 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.39 (d, *J* = 1.7 Hz, 1H), 6.60 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.41 (d, *J* = 2.5 Hz, 1H), 5.08 (s, 2H), 3.85 (td, *J* = 11.2, 5.4 Hz, 1H), 3.21 – 3.12 (m, 1H), 2.83 (s,

3H), 2.82 – 2.74 (m, 1H), 1.78 (d, J = 13.4 Hz, 1H), 1.71 (tt, J = 11.8, 5.4 Hz, 2H), 1.40 (q, J = 11.8 Hz, 1H), 1.17 (d, J = 6.3 Hz, 3H), 0.12 (d, J = 1.1 Hz, 1H).

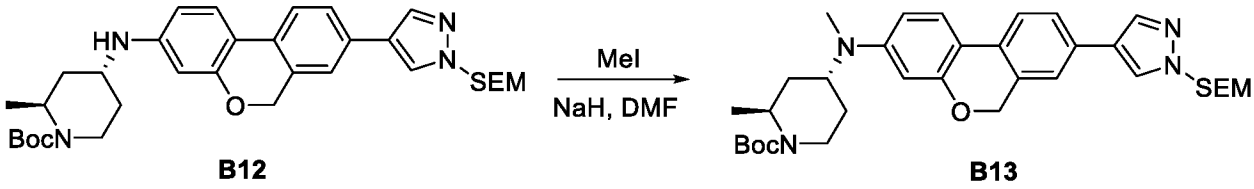
Example 2: Synthesis of Compound 102

Synthesis of Intermediate B11



A 20-mL vial was purged and maintained under an atmosphere of nitrogen, and 4-[3-bromo-6H-benzo[c]chromen-8-yl]-1-[[2-(trimethylsilyl) ethoxy] methyl]pyrazole (B7 from Example 1; 215 mg, 0.47 mmol, 1 equiv), *tert*-butyl (2*S*,4*R*)-4-amino-2-methylpiperidine-1-carboxylate (B11; 151.1 mg, 0.71 mmol, 1.5 equiv), t-BuONa (135.5 mg, 1.41 mmol, 3 equiv), t-BuXPhos palladium(II) biphenyl-2-amine mesylate (18.7 mg, 0.05 equiv), and dioxane (4 mL) were added to the vial. The resulting solution was stirred for 4h at 100 °C, and then quenched by the addition of water/ice (10 mL). The resulting solution was extracted with ethyl acetate (3 x 10 mL), and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/hexanes (1:1), to provide *tert*-butyl (2*S*,4*R*)-2-methyl-4-[[8-(1-[[2-(trimethylsilyl) ethoxy] methyl]pyrazol-4-yl)-6H-benzo[c]chromen-3-yl] amino] piperidine-1-carboxylate (B12; 210 mg) as a solid. **LCMS** (ES, *m/z*): 591 $[M+H]^+$.

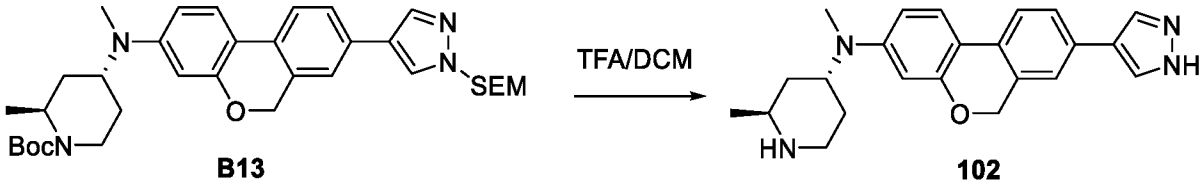
Synthesis of Intermediate B13



A 25-mL 3-necked round-bottom flask was purged and maintained under an atmosphere of nitrogen, and *tert*-butyl(2*S*,4*R*)-2-methyl-4-[[8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-benzo[c]chromen-3-yl]amino]piperidine-1-carboxylate (B12; 210 mg, 0.36 mmol, 1

equiv), dimethylformamide (5 mL), and sodium hydride (85.3 mg, 3.55 mmol, 10 equiv) were added to the flask. The resulting solution was stirred for 0.5h at 0 °C, then methyl iodide (504.5 mg, 3.55 mmol, 10 equiv) was added, and the mixture was stirred for 4h at 25 °C. The reaction was then quenched, and the resulting solution was extracted with ethyl acetate (3 x 10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum, to provide *tert*-butyl (2*S*,4*R*)-2-methyl-4-[methyl[8-(1-[[2-(trimethylsilyl) ethoxy] methyl]pyrazol-4-yl)-6H-benzo[c]chromen-3-yl] amino]piperidine-1-carboxylate (B13; 140 mg) as a solid. **LCMS** (ES, *m/z*): 605 $[M+H]^+$.

Synthesis of Compound 102

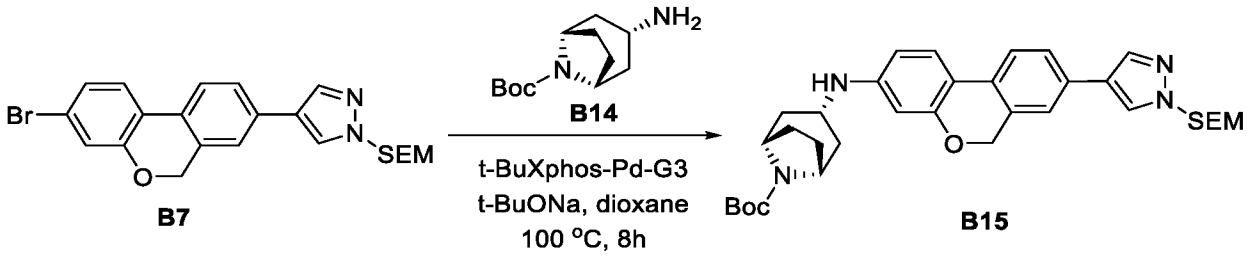


B13 102

tert-Butyl (2*S*,4*R*)-2-methyl-4-[methyl[8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-benzo[c]chromen-3-yl]amino]piperidine-1-carboxylate (B13; 140 mg), dichloromethane (2 mL), and trifluoroacetic acid (3 mL) were added to a 25-mL round-bottom flask, and the resulting solution was stirred for 2h at 25 °C. The solution was then concentrated under vacuum, and the residue was dissolved in methanol (3 mL). The crude product was purified by preparative HPLC (Condition 2, Gradient 1), to provide (2*S*,4*R*)-N,2-dimethyl-N-[8-(1H-pyrazol-4-yl)-6H-benzo[c]chromen-3-yl]piperidin-4-amine (Compound 102; 31.7 mg) as a solid. **LCMS** (ES, *m/z*): 375 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d4) δ 7.98 (s, 2H), 7.63 (dd, *J* = 8.4, 5.7 Hz, 2H), 7.56 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.40 (d, *J* = 1.8 Hz, 1H), 6.64 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 5.09 (s, 2H), 4.05 (dq, *J* = 9.9, 4.6, 4.1 Hz, 1H), 3.53 (td, J = 4.6, 2.5 Hz, 1H), 3.11 (dt, *J* = 9.7, 4.2 Hz, 1H), 3.03 (dt, *J* = 13.0, 4.1 Hz, 1H), 2.83 (s, 3H), 1.99 (ddd, *J* = 13.2, 11.1, 5.0 Hz, 1H), 1.83 (td, *J* = 9.6, 4.4 Hz, 2H), 1.70 – 1.60 (m, 1H), 1.37 (d, *J* = 7.0 Hz, 3H), 0.12 (s, 1H).

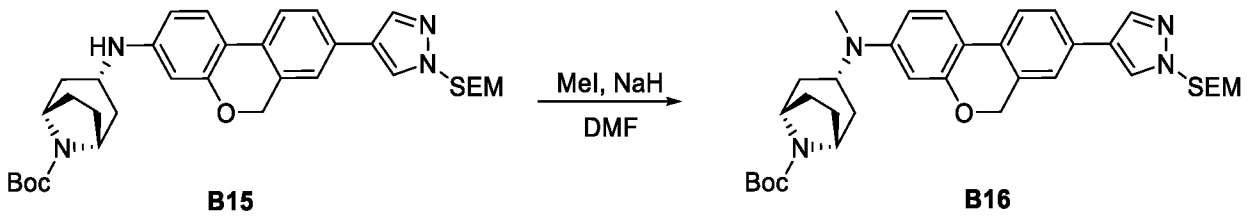
Example 3: Synthesis of Compound 104

Synthesis of Intermediate B15



A 20-mL sealed tube was purged and maintained under an atmosphere of nitrogen, and 4-[3-bromo-6H-benzo[c]chromen-8-yl]-1-[[2-(trimethylsilyl) ethoxy]methyl]pyrazole (B7 from Example 1; 105 mg, 0.23 mmol, 1 equiv), *tert*-butyl (1*R*,3*S*,5*S*)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (B14; 103.9 mg, 0.46 mmol, 2 equiv), t-BuONa (66.2 mg, 0.69 mmol, 3 equiv), dioxane (10 mL), and t-BuXPhos palladium(II) biphenyl-2-amine mesylate (9.1 mg, 0.01 mmol, 0.05 equiv) were added to the tube. The resulting solution was stirred for 8h at 100 °C, and then filtered and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated NaCl (10 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum, to provide *tert*-butyl (1*R*,3*S*,5*S*)-3-[[8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-benzo[c]chromen-3-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B15; 120.0 mg) as a solid. **LCMS** (ES, *m/z*): 603 $[M+H]^+$.

Synthesis of Intermediate B16



A 25-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-[[8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-benzo[c]chromen-3-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B15; 130 mg, 0.22 mmol, 1 equiv), dimethylformamide (5 mL), and sodium hydride (51.8 mg, 2.16 mmol, 10 equiv) were added to the flask, and the resulting solution was stirred for 0.5h at 0 °C. Methyl iodide (306.6 mg, 2.16 mmol, 10 equiv) was then added, and the solution was stirred for 4h at 25 °C. The reaction was then quenched and extracted with ethyl acetate (3x10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under vacuum to provide

tert-butyl (1*R*,3*S*,5*S*)-3-[methyl[8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-benzo[c]chromen-3-yl] amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B16; 120 mg) as a solid. **LCMS** (ES, *m/z*): 617 $[M+H]^+$.

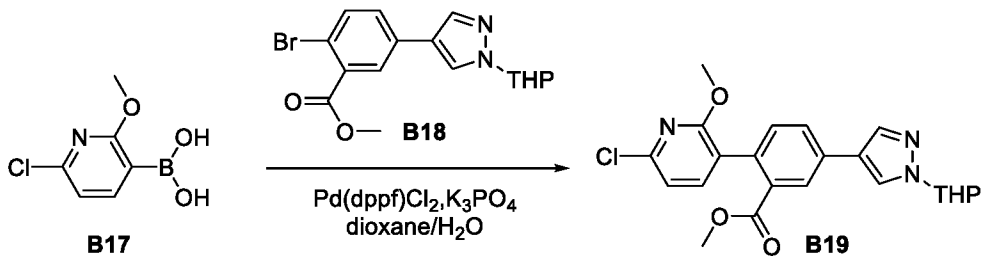
Synthesis of Compound 104



tert-Butyl (1*R*,3*S*,5*S*)-3-[methyl[8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-benzo[c]chromen-3-yl] amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B16; 110 mg), dichloromethane (3 mL), and trifluoroacetic acid (1 mL) were added to a 25-mL round-bottom flask, and the resulting solution was stirred for 2h at 25 °C. The resulting mixture was concentrated under vacuum, and purified by preparative HPLC (Condition 2, Gradient 1), to provide (1*R*,3*S*,5*S*)-N-Methyl-N-[8-(1H-pyrazol-4-yl)-6H-benzo[c]chromen-3-yl]-8-azabicyclo[3.2.1]octan-3-amine (Compound 104; 9.3 mg) as a solid. **LCMS** (ES, *m/z*): 387 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d4) δ 7.98 (s, 2H), 7.61 (dd, *J* = 8.4, 3.7 Hz, 2H), 7.55 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.39 (d, *J* = 1.7 Hz, 1H), 6.60 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.40 (d, *J* = 2.6 Hz, 1H), 5.08 (s, 2H), 4.16 (tt, *J* = 11.6, 5.5 Hz, 1H), 3.70 (s, 2H), 2.81 (s, 3H), 2.01 – 1.86 (m, 6H), 1.71 (dt, *J* = 12.9, 4.5 Hz, 2H), 0.12 (d, *J* = 1.0 Hz, 2H).

Example 4: Synthesis of Compound 108

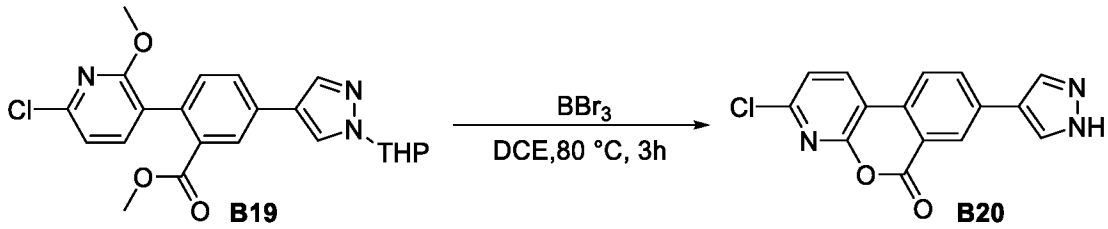
Synthesis of Intermediate B19



Potassium carbonate (6.64 g, 0.05 mmol) and $Pd(dppf)Cl_2CH_2Cl_2$ (1.31 g, 0.002 mmol) were added to a solution of 6-chloro-2-methoxypyridin-3-ylboronic acid (B17; 3g, 16 mmol) and methyl 2-bromo-5-[1-(oxan-2-yl) pyrazol-4-yl] benzoate (B18; 4.68 g, 0.013 mmol) in dioxane (80 mL) and H_2O (20 mL), and the resulting mixture was stirred for 2h at 80 °C. The mixture

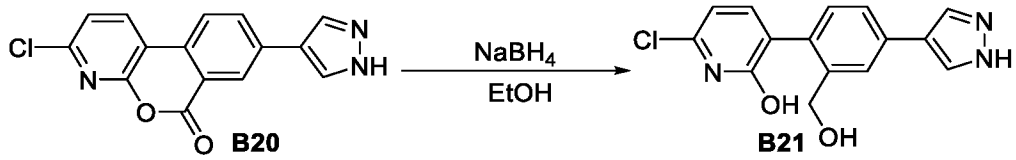
was then extracted with dichloromethane (3 x 50 mL), and the combined organic layers were washed with H_2O (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography using a C_{18} silica gel column, eluting with methanol in water (10% to 50% gradient in 10 min), to afford methyl 2-(6-chloro-2-methoxypyridin-3-yl)-5-[1-(oxan-2-yl) pyrazol-4-yl] benzoate (B19; 4.1 g) as an oil. **LCMS** (ES, *m/z*): 428 $[M+H]^+$.

Synthesis of Intermediate B20



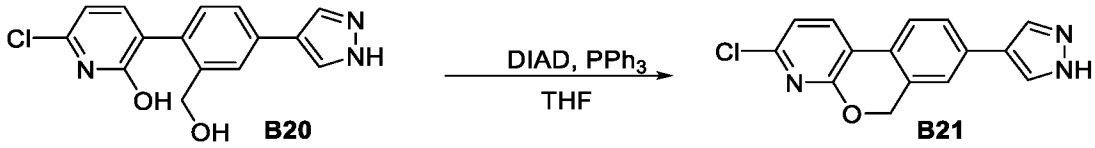
Boron tribromide (18.2 g, 72 mmol) was added to a solution of methyl 2-(6-chloro-2-methoxypyridin-3-yl)-5-[1-(oxan-2-yl) pyrazol-4-yl] benzoate (B19; 3.1 g, 7.25 mmol) in dichloroethane (300 mL) and the mixture was stirred for 10 min at 30 °C under an atmosphere of nitrogen, followed by heating at 80 °C for a further 2 h. The mixture was then concentrated, and the residue was purified by column chromatography eluting with ethyl acetate in hexanes (0-50% gradient) to afford 3-chloro-8-(1H-pyrazol-4-yl)isochromeno[3,4-b]pyridin-6-one (B20; 1.4 g) as an oil. **LCMS** (ES, m/z): 298 $[M+H]^+$.

Synthesis of Intermediate B21



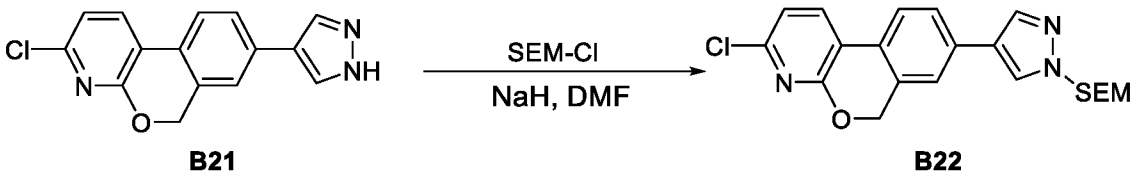
Sodium borohydride (0.54 g, 0.014 mmol) was added to a solution of 4-[3-chloro-6-methy lideneisochromeno[3,4-b]pyridin-8-yl]-1H-pyrazole (1.4 g, 0.005 mmol) in ethanol (60 mL), and the resulting mixture was stirred for 4 h at 25 °C, then concentrated to dryness. The residue was purified by reversed flash chromatography using a C_{18} silica gel column, eluting with methanol in water (10% to 50% gradient in 10 min), to afford 6-chloro-3-[2-(hydroxymethyl)-4-(1H-pyrazol-4-yl) phenyl] pyridin-2-ol (B21; 1.1 g) as an oil. **LCMS** (ES, *m/z*): 302 $[M+H]^+$.

Synthesis of Intermediate B21



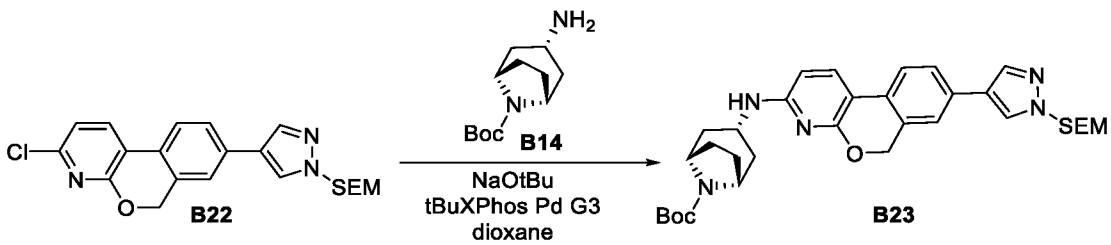
Triphenylphosphine (1.58 g, 6 mmol) and diisopropyl azodicarboxylate (1.13 g, 6.5 mmol) were added to a solution of 6-chloro-3-[2-(hydroxymethyl)-4-(1H-pyrazol-4-yl) phenyl]pyridin-2-ol (B20; 1.4 g, 4.64 mmol) in tetrahydrofuran (110 mL) and the mixture was stirred for 50 min at 0 °C, then concentrated. The residue was purified by column chromatography eluting with ethyl acetate in in hexanes (0-50% gradient) to provide 4-[3-chloro-6H-isochromeno[3,4-b] pyridin-8-yl]-1H-pyrazole (B21; 1.1 g) as a solid. **LCMS** (ES, *m/z*): 284 $[M+H]^+$.

Synthesis of Intermediate B22



Sodium hydride (0.17 g, 4 mmol) was added to a solution of 4-[3-chloro-6 H-isochromeno[3,4-b]pyridin-8-yl]-1H-pyrazole (1 g, 4 mmol) in dimethylformamide (20 mL), and the mixture was stirred for 30 min at 25 °C. Next, [2-(chloromethoxy)ethyl]trimethylsilane (0.59 g, 4 mmol) was added, and the mixture was stirred for 2h at 25 °C. The residue was purified by column chromatography eluting with ethyl acetate in hexanes (0-50%) to provide 4-[3-chloro-6H-isochromeno[3,4-b] pyridin-8-yl]-1-[[2-(trimethylsilyl) ethoxy] methyl] pyrazole (B22; 326 mg) as a solid. **LCMS** (ES, *m/z*):414 $[M+H]^+$.

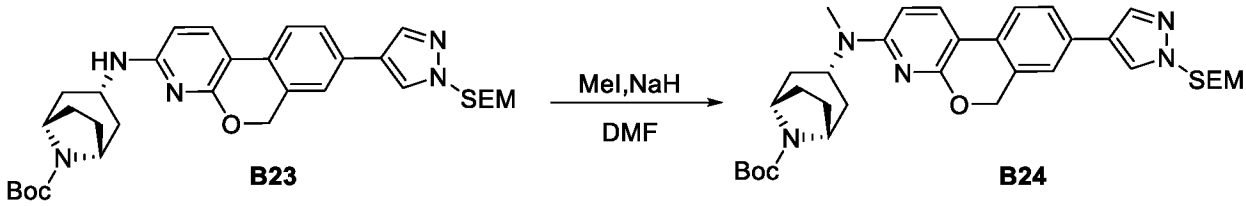
Synthesis of Intermediate B23



Sodium tert-butoxide (83.6 mg, 0.87 mmol), tert-butyl-3-amino-8-azabicyclo [3.2.1] octane-8-carboxylate (B14; 72.2 mg, 0.33 mmol), and t-BuXPhos palladium(II) biphenyl-2-amine mesylate (46.1 mg, 0.058 mmol) were added to a solution of 4-[3-chloro-6H-isochromeno[3,4-b] pyridin-8-yl]-1-[[2-(trimethylsilyl) ethoxy] methyl] pyrazine (B22; 120 mg, 0.29 mmol) in

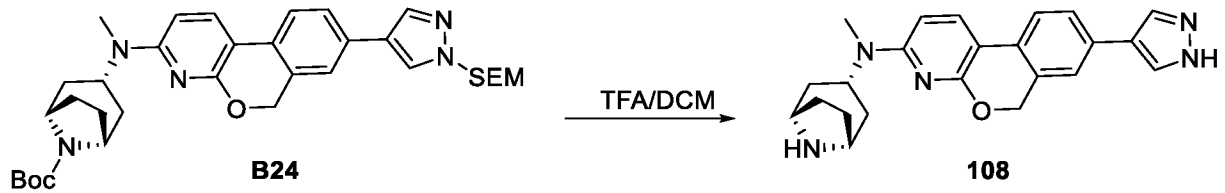
dioxane (12 mL), and the mixture was stirred for 3 h at 100 °C. The resulting mixture was extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were concentrated, and purified by column chromatograph eluting with ethyl acetate in hexanes (0-50% gradient), to afford tert-butyl-3-[[8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B23; 75 mg) as a solid. **LCMS** (ES, *m/z*): 604 $[M+H]^+$.

Synthesis of Intermediate B24



Sodium hydride (11.8 mg, 0.49 mmol) was added to a solution of 4-[[8-(1-[[2-(trimethylsilyl) ethoxy]methyl]pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]amino]piperidine-1-carboxylate (B23; 95 mg, 0.16 mmol) in dimethylformamide (15 mL), and the mixture was stirred for 30 min at 0 °C. Methyl iodide (35 mg, 0.25 mmol) was then added, and the mixture was stirred for 30 min at 0 °C. The reaction was quenched by the addition of water (20 mL) at 0 °C, and the aqueous layer was extracted with ethyl acetate (3 x 320 mL). The combined organic layers were concentrated under reduced pressure, to provide tert-butyl (1R,5S)-3-[methyl[8-(1-[[2-(trimethylsilyl) ethoxy]methyl]pyrazol-4-yl)-6H-isochromeno[3,4-b] pyridin-3-yl]amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (B24; 46 mg) as a solid. **LCMS** (ES, m/z): 618 $[M+H]^+$.

Synthesis of Compound 108

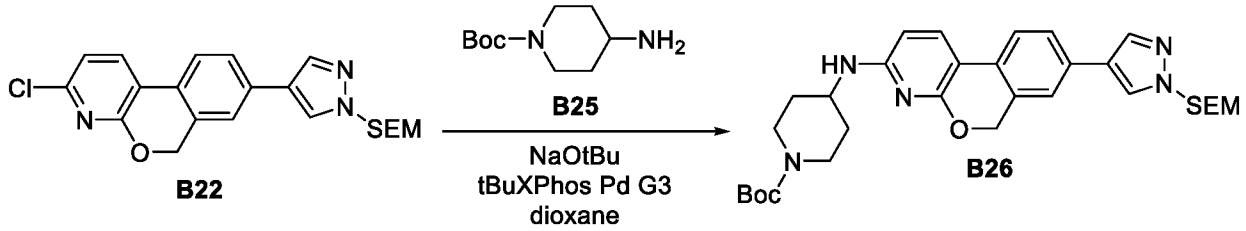


Trifluoroacetic acid (1 mL, 13.5 mmol) was added to a solution of tert-butyl (1R,5S)-3-[methyl [8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B24; 45 mg, 0.073 mmol) in dichloromethane (3 mL) and the mixture was stirred for 10 min at 25 °C, then dried and concentrated. The crude product was purified by preparative HPLC (Condition 2, Gradient 2) to afford (1R,5S)-N-Methyl-N-[8-(1H-pyrazol-4-yl)-6H-isochromeno[3,4-b] pyridin-3-yl]-8-

azabicyclo [3.2.1] octan-3-amine (Compound 108; 21.4 mg) as a solid. **LCMS** (ES, m/z): 387[M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 12.94 (s, 1H), 8.17 (s, 2H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.63 – 7.52 (m, 2H), 7.46 (d, *J* = 1.7 Hz, 1H), 6.34 (d, *J* = 8.6 Hz, 1H), 5.23 (s, 2H), 4.87 (s, 1H), 3.50 (s, 2H), 2.81 (s, 3H), 1.71 (q, *J* = 10.5, 7.5 Hz, 7H), 1.45 (d, *J* = 11.2 Hz, 2H).

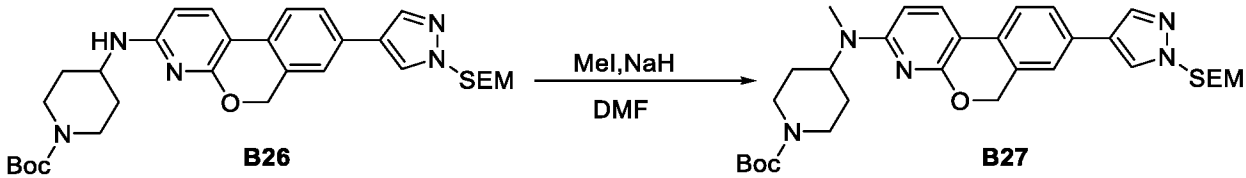
Example 5: Synthesis of Compound 116

Synthesis of Intermediate B26



Sodium tert-butoxide (76.6 mg, 0.8 mmol), tert-butyl 4-aminopiperidine-1-carboxylate (B25; 58.5 mg, 0.29 mmol) and t-BuXPhos palladium(II) biphenyl-2-amine mesylate (42.2 mg, 0.05 mmol) were added to a solution of 4-[3-chloro-6H-isochromeno[3,4-b]pyridin-8-yl]-1-[[2-(trimethylsilyl) ethoxy]methyl pyrazole (B22 from Example 4; 110 mg, 0.27 mmol) in dioxane (11 mL), and the resulting mixture was stirred for 3h at 100 °C under an atmosphere of nitrogen. The mixture was then extracted with ethyl acetate (3 x 50mL), and the combined organic layers were washed with water (3 x 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography using a C18 silica gel column, eluting with methanol in water (10% to 50% gradient in 10 min), to afford tert-butyl 4-[[8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl] amino] piperidine-1-carboxylate (B26; 80 mg) as a solid. **LCMS** (ES, *m/z*): 578 [M+H]$^+$.

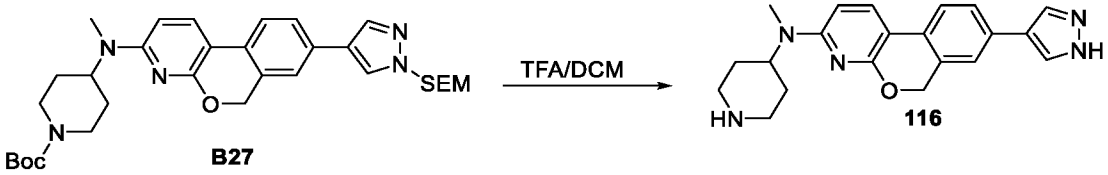
Synthesis of Intermediate B27



Sodium hydride (11.8 mg, 0.49 mmol) was added to a solution of tert-butyl 4-[[8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]amino]piperidine-1-carboxylate (95 mg, 0.164 mmol) in dimethylformamide (15 mL), and the mixture was stirred for 30 min at 0 °C. Methyl iodide (35 mg, 0.25 mmol) was then added, and

the resulting mixture was stirred for a further 30 min at 0 °C, then quenched by the addition of water (20 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organic layers were concentrated under reduced pressure to provide tert-butoxy(4-[methyl[8-(1-[[2-(trimethylsilyl) ethoxy] methyl] pyrazol-4-yl)-6H-isochromeno[3,4-b] pyridin-3-yl] amino] piperidin-1-yl) methanol (B27; 46 mg) as a solid. **LCMS** (ES, *m/z*): 592 $[M+H]^+$.

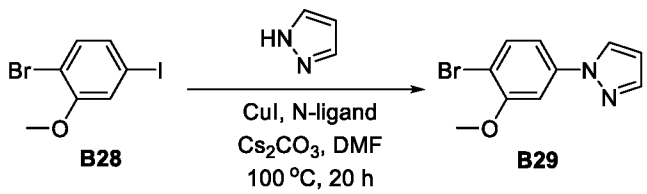
Synthesis of Compound 116



Trifluoroacetic acid (3 mL, 40 mmol) was added to a solution of tert-butoxy(4-[methyl[8-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]amino]piperidin-1-yl)methanol (B27; 55 mg, 0.093 mmol) in dichloromethane (9 mL), and the mixture was stirred for 2h at 25 °C, then dried and concentrated. The crude product was purified by preparative HPLC (Condition 2, Gradient 2) to provide N-Methyl-N-[8-(1H-pyrazol-4-yl)-6H-isochromeno[3,4-b] pyridin-3-yl]piperidin-4-amine (Compound 116; 8.3 mg) as a solid. **LCMS** (ES, *m/z*): 362 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 8.16 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.94 (s, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.56 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.46 (d, *J* = 1.7 Hz, 1H), 6.37 (d, *J* = 8.5 Hz, 1H), 5.21 (s, 2H), 4.44 (s, 1H), 3.02 (d, *J* = 12.1 Hz, 2H), 2.85 (s, 3H), 2.58 (d, *J* = 11.9 Hz, 1H), 1.66 – 1.54 (m, 2H), 1.50 (d, *J* = 11.7 Hz, 2H).

Example 6: Synthesis of Compound 118

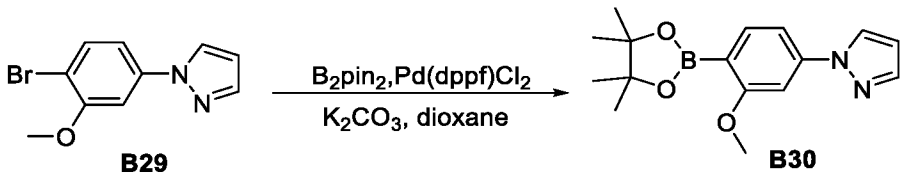
Synthesis of Intermediate B29



A mixture of 1-bromo-4-iodo-2-methoxybenzene (B28; 30 g, 96 mmol), pyrazole (9.1 g, 0.13 mol), 2-(pyridin-2-yl)-1H-1,3-benzodiazole (1.87 g, 10 mmol), copper iodide (1.8 g, 10 mmol), Cs_2CO_3 (94 g, 0.29 mol), in dimethylformamide (600 mL) was stirred for 20 h at 100 °C under an atmosphere of nitrogen. The mixture was then filtered, the filtrate was extracted with ethyl acetate (3 x 300 mL), and the combined organic layers were was washed with brine (3 x 300 mL), then dried over anhydrous sodium sulfate and concentrated under vacuum. The residue

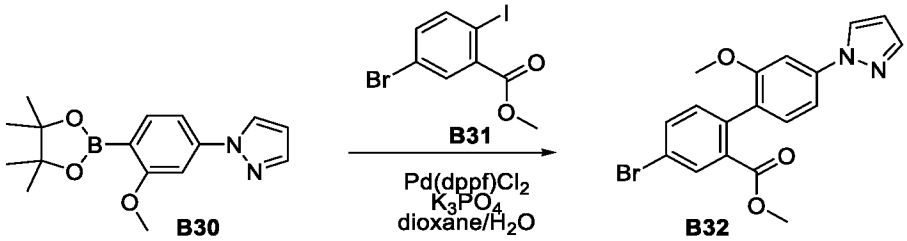
was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (9:50) to provide 1-(4-bromo-3-methoxyphenyl)pyrazole (B29; 18 g). **LCMS** (ES, *m/z*): 253 $[M+H]^+$.

Synthesis of Intermediate B30



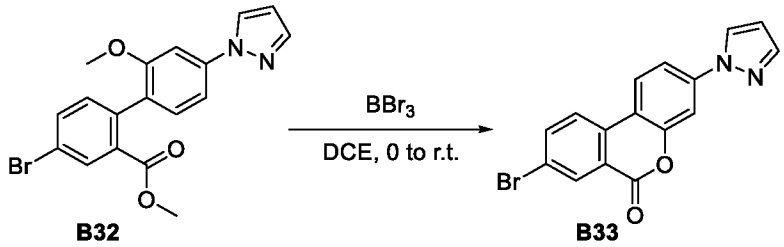
A mixture of 1-(4-bromo-3-methoxyphenyl)pyrazole (B29; 8 g, 31.6 mmol), K_2CO_3 (4.37 g, 31.6 mmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (2.58 g, 3.2 mmol), and B_2pin_2 (14.45 g, 56.9 mmol) in dioxane (15 mL) was stirred for 8 h at 80 °C under an atmosphere of nitrogen. The mixture was then filtered, the filtrate was extracted with ethyl acetate (3 x 100 mL), and the combined organic layers were washed with saturated NaCl (100 mL), then dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:5), to afford 1-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazole (B30; 6.7 g) as a solid. **LCMS** (ES, *m/z*): 301 $[M+H]^+$.

Synthesis of Intermediate B32



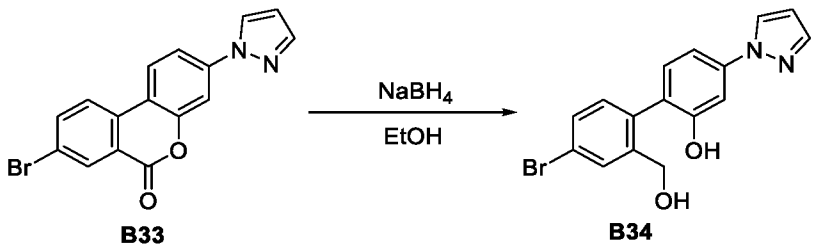
A mixture of 1-[3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazole (B30; 3.3 g, 11 mmol), methyl 5-bromo-2-iodobenzoate (B31; 3.37 g, 9.9 mmol), $Pd(dppf)Cl_2$ CH_2Cl_2 (0.9 g, 1.1 mmol), and K_3PO_4 (7 g, 33 mmol) in dioxane/H_2O (100 mL) was stirred for 3 h at 0 °C under an atmosphere of nitrogen. The mixture was then filtered, the filtrate was extracted with ethyl acetate (3 x 30 mL), and the combined organic layers were washed with saturated NaCl (30 mL). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum, and purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:5) to provide methyl 4-bromo-2'-methoxy-4'-(pyrazol-1-yl)-[1,1'-biphenyl]-2-carboxylate (B32, 1.8 g) as a solid. **LCMS** (ES, *m/z*):387 $[M+H]^+$.

Synthesis of Intermediate B33



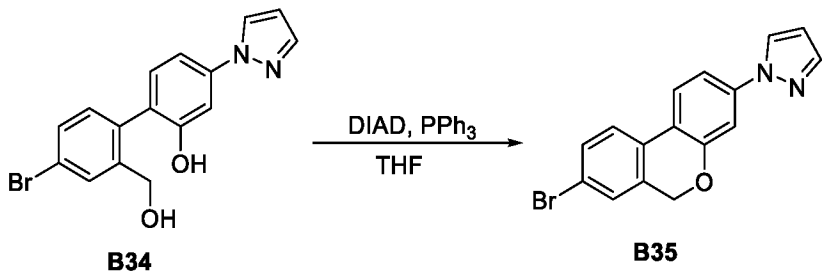
A mixture of methyl 4-bromo-2 (1.8 g, 4.77 mmol) and boron tribromide (17.9 g, 0.07 mol) in dichloromethane (500 mL) was stirred for 4 h at room temperature, and then concentrated under vacuum. The pH value of the solution was adjusted to 8 using $NaHCO_3$, and the resulting solution was extracted with ethyl acetate (10 mL). The combined organic layers were then filtered to provide 8-bromo-3-(1-methyl-2-methylidenehydrazin-1-yl)benzo[c]chromen-6-one (B33; 1.4 g) as a solid. **LCMS** (ES, *m/z*):341 $[M+H]^+$.

Synthesis of Intermediate B34



A mixture of 8-bromo-3-(pyrazol-1-yl) benzo[c]chromen-6-one (1.4 g, 4.1 mmol) and sodium borohydride (1.24 g, 0.03 mmol) in ethanol (120 mL) was stirred for 5 h at room temperature, then concentrated under vacuum, to provide crude 4'-bromo-2'-(hydroxymethyl)-4-(pyrazol-1-yl)-[1,1'-biphenyl]-2-ol (B34; 3 g) as a solid. **LCMS** (ES, *m/z*):345 $[M+H]^+$.

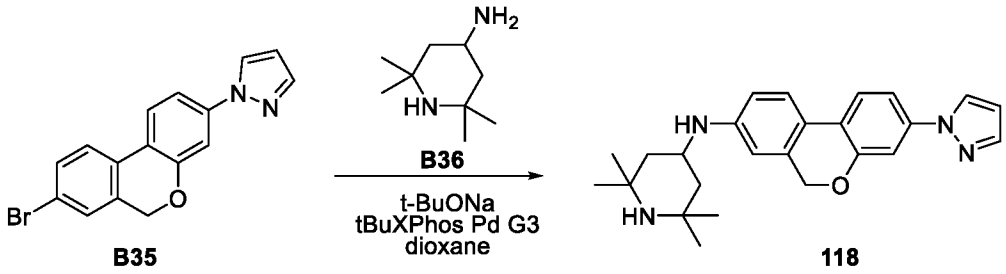
Synthesis of Intermediate B35



A mixture of 4'-bromo-2'-(hydroxymethyl)-4-(pyrazol-1-yl)-[1,1'-biphenyl]-2-ol (B34; 2.9 g crude), triphenylphosphine (3.31 g, 12.6 mmol), and diisopropyl azodicarboxylate (2.55 g, 12.6 mmol) in tetrahydrofuran (150 mL) was stirred for 4 h at 0 °C, then concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl

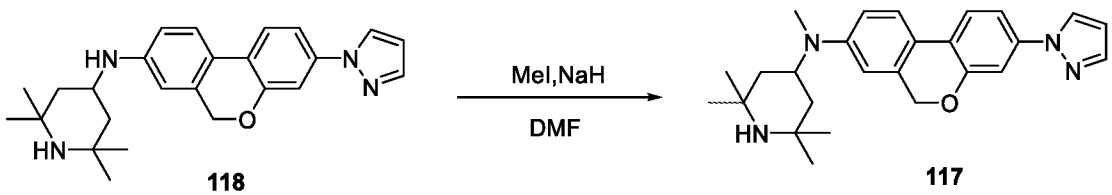
acetate/petroleum ether (7:50) to afford 1-[8-bromo-6H-benzo[c]chromen-3-yl]pyrazole (1.2 g as a solid. **LCMS** (ES, *m/z*): 327 $[M+H]^+$.

Synthesis of Compound 118



A mixture of 1-[8-bromo-6H-benzo[c]chromen-3-yl]pyrazole (B35; 200 mg, 0.61 mmol), 2,2,6,6-tetramethylpiperidin-4-amine (B36; 191 mg, 1.22 mmol), t-BuXPhos Phos palladium(II) biphenyl-2-amine mesylate (48.6 mg, 0.06 mmol), and t-BuONa (117 mg, 1.22 mmol) in dioxane was stirred for 8 h at 80 °C under an atmosphere of nitrogen. The resulting solution was extracted with ethyl acetate (3 x 10 mL), the combined organic layers were washed with saturated NaCl (10 mL), and then dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (4:5) to afford 2,2,6,6-tetramethyl-N-[3-(pyrazol-1-yl)-6H-benzo[c]chromen-8-yl]piperidin-4-amine (Compound 118; 146 mg) as a solid. A portion of the material was further purified by preparative HPLC (Condition 1, Gradient 2). **LCMS** (ES, *m/z*): 403 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$, *ppm*) δ 8.50 (d, *J* = 2.5 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.48 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.39 (d, *J* = 2.2 Hz, 1H), 6.64 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.57 – 6.50 (m, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 5.73 (d, *J* = 8.1 Hz, 1H), 5.06 (s, 2H), 3.71 (s, 1H), 1.84 (d, *J* = 12.1 Hz, 2H), 1.27 – 1.22 (m, 6H), 1.09 – 1.05 (m, 6H), 0.98 (s, 2H).

Example 7: Synthesis of Compound 117

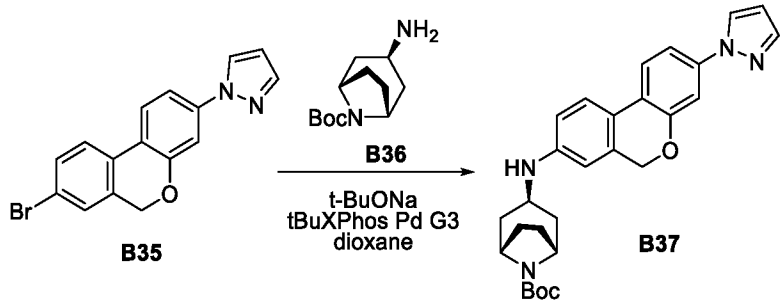


A mixture of 2,2,6,6-tetramethyl-N-[3-(pyrazol-1-yl)-6H-benzo[c]chromen-8-yl]piperidin-4-amine (Compound 118; 100 mg, 0.25 mmol), sodium hydride (59.6 mg, 2.5 mmol), and methyl iodide (176 mg, 1.2 mmol) in DMF (5 mL) was stirred for 5 h at 0 °C, and then extracted with

ethyl acetate (3 x 5 mL). The combined organic layers were washed with saturated NaCl (5 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by preparative HPLC (Condition 1, Gradient 2) to afford N,2,2,6,6-pentamethyl-N-[3-(pyrazol-1-yl)-6H-benzo[c]chromen-8-yl]piperidin-4-amine (Compound 117; 8.9 mg) as a solid. **LCMS** (ES, *m/z*):417 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6, *ppm*) δ 8.51 (d, *J* = 2.5 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 1.8 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.50 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 6.69 (s, 1H), 6.57 – 6.51 (m, 1H), 5.13 (s, 2H), 4.16 (d, *J* = 12.4 Hz, 1H), 2.76 (s, 3H), 1.53 (d, *J* = 11.8 Hz, 2H), 1.38 (s, 3H), 1.27 (s, 6H), 1.14 (d, *J* = 11.3 Hz, 1H), 1.10 (s, 6H).

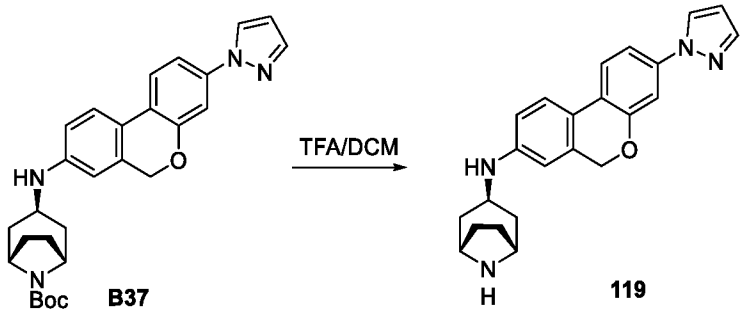
Example 8: Synthesis of Compound 119

Synthesis of Intermediate B37



A mixture of 1-[8-bromo-6H-benzo[c]chromen-3-yl]pyrazole (B35; 100 mg, 0.3 mmol), tert-butyl-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (69 mg, 0.3 mmol), tBuXPhos Pd G3 (24.28 mg, 0.03 mmol), and t-BuONa (58.7 mg, 0.61 mmol) in 1,4-dioxane (10 mL) was stirred for 8 h at 80 °C, and then filtered. The filtrate was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with saturated NaCl (10 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (4:25) to afford tert-butyl-3-[[3-(pyrazol-1-yl)-6H-benzo[c]chromen-8-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B37; 20 mg) as a solid. **LCMS** (ES, *m/z*):473 $[M+H]^+$.

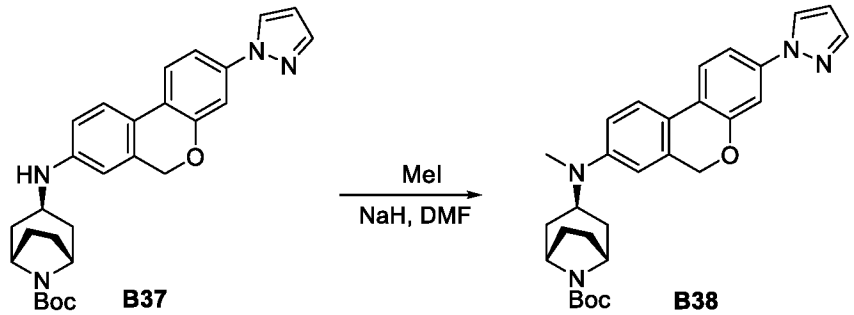
Synthesis of Compound 119



A mixture of tert-butyl-3-[methyl[3-(pyrazol-1-yl) -6H-benzo[c]chromen-8-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (20 mg, 1 equiv) and dichloromethane/trifluoroacetic acid (5:1, 10 mL) was stirred for 2 h at room temperature, and then concentrated under vacuum. The crude product was purified by preparative HPLC (Condition 1, Gradient 2) to provide N-methyl-N-[3-(pyrazol-1-yl)-6H-benzo[c]chromen-8-yl]-8-azabicyclo[3.2.1]octan-3-amine (Compound 119; 1.4 mg) as a solid. **LCMS**: (ES, *m/z*):373 $[M+H]^+$. **^{1}H NMR**: (400 MHz, DMSO-d_6, *ppm*) δ 8.49 (d, *J* = 2.6 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.47 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.38 (d, *J* = 2.2 Hz, 1H), 6.64 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.56 – 6.50 (m, 1H), 6.47 (d, *J* = 2.3 Hz, 1H), 5.71 (d, *J* = 8.2 Hz, 1H), 5.06 (s, 2H), 3.53 (s, 2H), 1.92 (d, *J* = 12.8 Hz, 2H), 1.83 – 1.72 (m, 4H), 1.37 (t, *J* = 11.8 Hz, 2H), 0.08 (s, 1H).

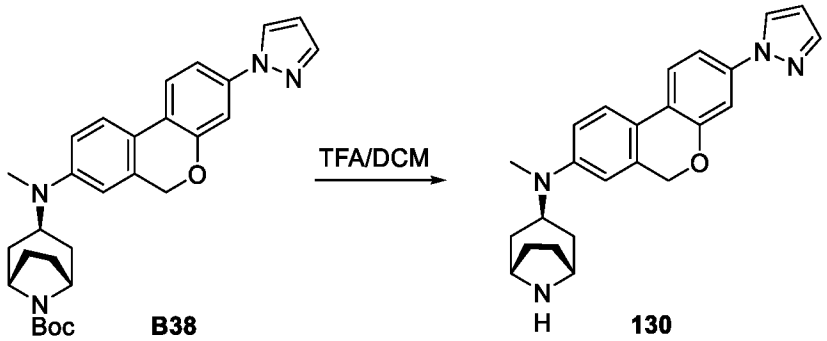
Example 9: Synthesis of Compound 130

Synthesis of Intermediate B38



A mixture of tert-butyl-3-[[3-(pyrazol-1-yl)-6H-benzo[c] chromen-8-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B37; 220 mg, 0.47 mmol), sodium hydride (16.8 mg, 0.7 mmol), and methyl iodide (264 mg, 1.86 mmol) in dimethylformamide (2 mL) was stirred for 5 h at 0 °C. The resulting solution was extracted with ethyl acetate (3 x 10 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum, to afford tert-butyl-3-[methyl[3-(pyrazol-1-yl)-6H-benzo[c]chromen-8-yl] amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B38; 200 mg) as a solid. **LCMS** (ES, *m/z*):487 $[M+H]^+$.

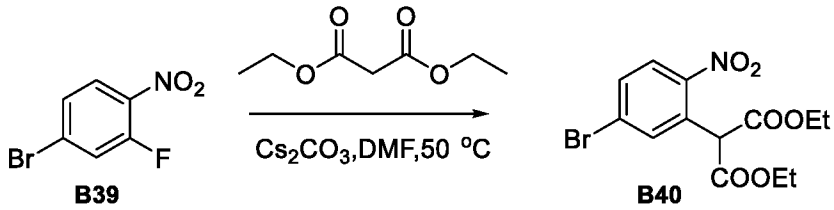
Synthesis of Compound 130



A mixture of tert-butyl-3-[methyl[3-(pyrazol-1-yl)-6H-benzo[c]chromen-8-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (200 mg) and DCM/TFA (5:1 10 mL) was stirred for 2 h at room temperature, and then concentrated under vacuum. The crude product was purified by preparative HPLC (Condition 1, Gradient 2) to afford N-methyl-N-[3-(pyrazol-1-yl)-6H-benzo[c]chromen-8-yl]-8-azabicyclo[3.2.1] octan-3-amine (Compound 130; 34.7 mg) as a solid. **LCMS** (ES, *m/z*):387 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6, *ppm*) δ 8.50 (d, *J* = 2.5 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 1.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.49 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.40 (d, *J* = 2.3 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.67 (d, *J* = 2.6 Hz, 1H), 6.54 (t, *J* = 2.1 Hz, 1H), 5.12 (s, 2H), 4.07 (dt, *J* = 11.7, 5.9 Hz, 1H), 3.49 (s, 2H), 2.75 (s, 3H), 1.73 (d, *J* = 11.5 Hz, 5H), 1.52 (d, *J* = 11.4 Hz, 2H).

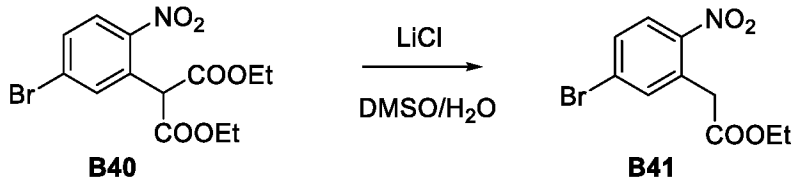
Example 10: Synthesis of Compound 131

Synthesis of Intermediate B40



A mixture of 4-bromo-2-fluoro-1-nitrobenzene (B39; 65.3 g, 297 mmol), diethyl malonate (52 g, 327 mmol), and Cs_2CO_3 (116 g, 356 mmol) in dimethylformamide (650 mL) was stirred for 12 h at 50 °C under an atmosphere of nitrogen. The reaction was then quenched by the addition of water/ice (1.5 L), and the resulting solution was extracted with ethyl acetate (3 x 1 L), 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 (1:5) to afford 1,3-diethyl 2-(5-bromo-2-nitrophenyl) propanedioate (B40; 92 g) as a solid.

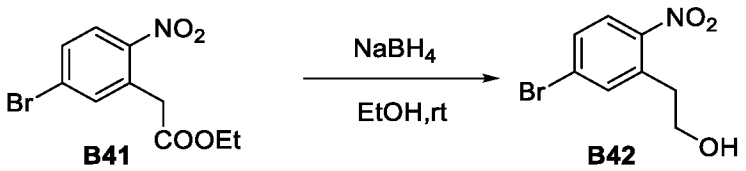
Synthesis of Intermediate B41



B40 B41

A mixture of 1,3-diethyl 2-(5-bromo-2-nitrophenyl) propanedioate (B40; 89.7 g, 249 mmol) and lithium chloride (15.8 g, 374 mmol) in DMSO/H_2O (10:1, 1.1 L) was stirred for 12 h at 100 °C under an atmosphere of nitrogen. The reaction was then quenched by the addition of water/ice (1.5 L), extracted with ethyl acetate (3 x 1 L), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting mixture was washed with n-hexane (3 x 150 mL), and the solids were collected by filtration to provide ethyl 2-(5-bromo-2-nitrophenyl) acetate (B41; 57 g) as a solid.

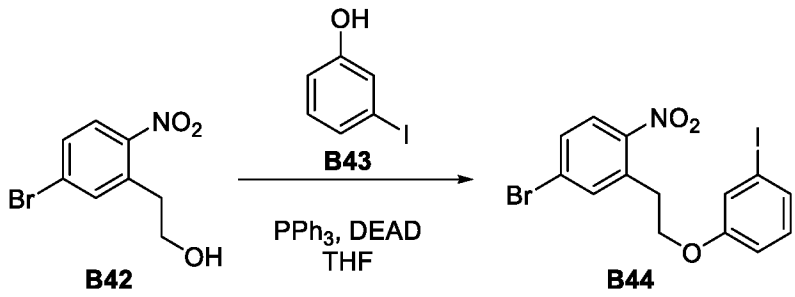
Synthesis of Intermediate B42



B41 B42

A mixture of ethyl 2-(5-bromo-2-nitrophenyl) acetate (B41; 53.2 g, 185 mmol) and sodium borohydride (27.94 g, 739 mmol) in ethanol (600 mL) was stirred for 4 h at 25 °C under an atmosphere of nitrogen. The reaction was then quenched by the addition of acetone (100 mL), extracted with dichloromethane (3 x 500 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 (1:5) to afford 2-(5-bromo-2-nitrophenyl) ethanol (B42; 36 g) as an oil.

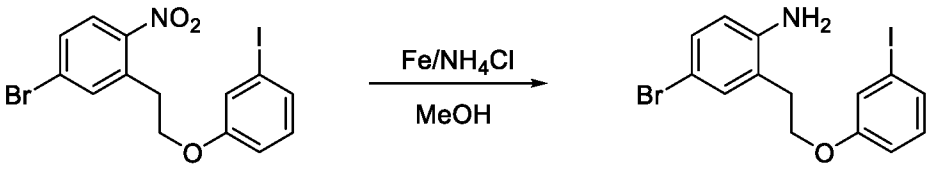
Synthesis of Intermediate B44



B42 B44

A mixture of 2-(5-bromo-2-nitrophenyl) ethanol (B42; 18 g, 73.1 mmol) and 3-iodophenol (B43; 319 g, 87.8 mmol) in tetrahydrofuran (200 mL) was stirred for 10 min at 0 °C under an atmosphere of nitrogen. Triphenylphosphine (38.37 g, 146 mmol) and diethyl azodicarboxylate (25.5 g, 146 mmol) were then added, and the resulting solution was stirred for 2 h at 25 °C. The reaction was quenched by the addition of water/ice (300 mL), extracted with ethyl acetate (3 x 200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum, to provide crude 4-bromo-2-[2-(3-iodophenoxy) ethyl]-1-nitrobenzene (B44; 65) as a solid.

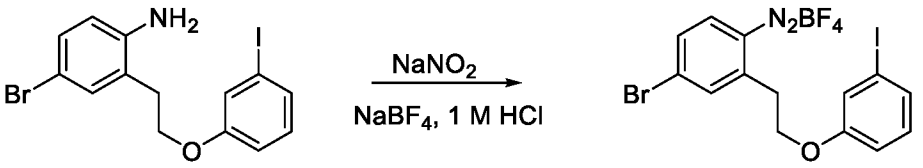
Synthesis of Intermediate B45



B44 **B45**

A mixture of 4-bromo-2-[2-(3-iodophenoxy) ethyl]-1-nitrobenzene (B44; 65 g, 145 mmol), ammonium chloride (77.6 g, 1.45 mol), and iron (81 g, 1.45 mol) in methanol (650 mL) was stirred for 3 h at 65 °C under an atmosphere of nitrogen. The mixture was then filtered and concentrated under vacuum, and the reaction was quenched by the addition of water (300 mL). The resulting solution was extracted with ethyl acetate (3 x 200 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 (1:4) to afford 4-bromo-2-[2-(3-iodophenoxy) ethyl] aniline (B45; 15 g) as an oil. **LCMS** (ES, *m/z*): 418 $[M+H]^+$.

Synthesis of Intermediate B46

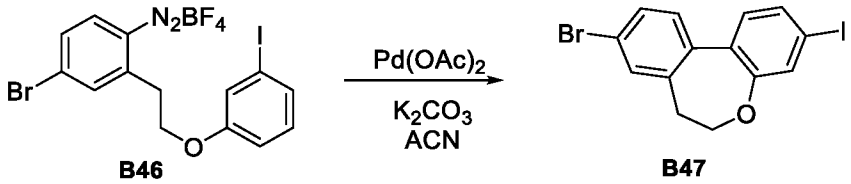


B45 **B46**

A mixture of 4-bromo-2-[2-(3-iodophenoxy) ethyl] aniline (B45; 8.5 g, 20 mmol), HCl (1M, 85 mL) and sodium nitrite (1.68 g, 24 mmol) was stirred for 2 h at 0 °C under an atmosphere of nitrogen. Sodium tetrafluoroborate (4.47 g, 40.7 mmol) was then added, and the resulting solution was stirred for 0.5 h at 0 °C. The mixture was extracted with ethyl acetate (3 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting mixture was washed with methyl tert-butyl ether (3 x 40 mL), and the solids were

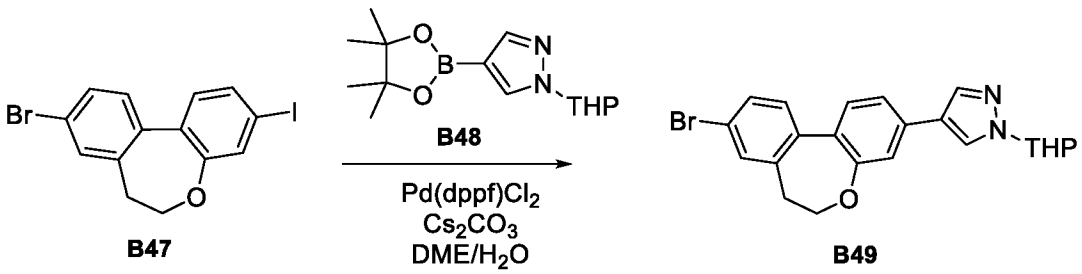
collected by filtration to provide (E)-[4-bromo-2-[2-(3-iodophenoxy)ethyl] phenyl] (tetrafluoro-λ5-boranyl) diazene (B46; 6.4 g) as a solid. **LCMS** (ES, *m/z*): 429 $[M+H]^+$.

Synthesis of Intermediate B47



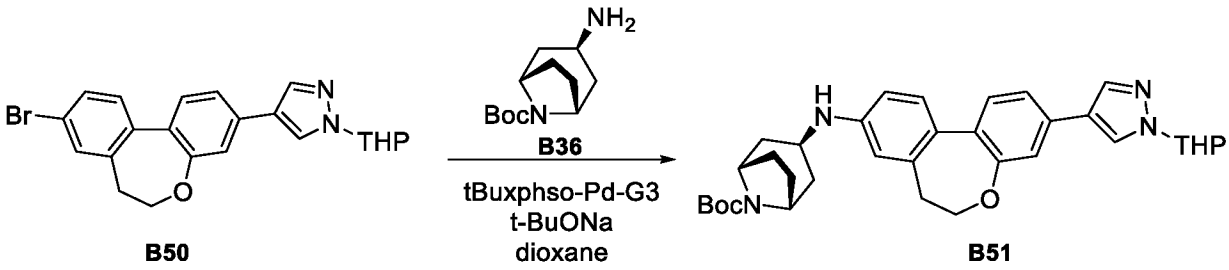
A mixture of (E)-[4-bromo-2-[2-(3-iodophenoxy) ethyl] phenyl] (tetrafluoro- λ5-boranyl) diazene (4 g, 7.74 mmol), K_2CO_3 (2.14 g, 15.5 mmol), and acetyl(oxo)palladium (0.17 g, 0.77 mmol) in acetonitrile (150 mL) was stirred for 2 h at 80 °C under an atmosphere of nitrogen. The reaction was then quenched by the addition of water (100 mL) and extracted with ethyl acetate (3 x 100 mL), and the combined organic layers were 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 (1:20) to afford 13-bromo-5-iodo-8-oxatricyclo [9.4.0.0^ [2,7]] pentadeca-1(15),2(7),3,5,11,13-hexaene (B47; 145 mg) as a solid.

Synthesis of Intermediate B49



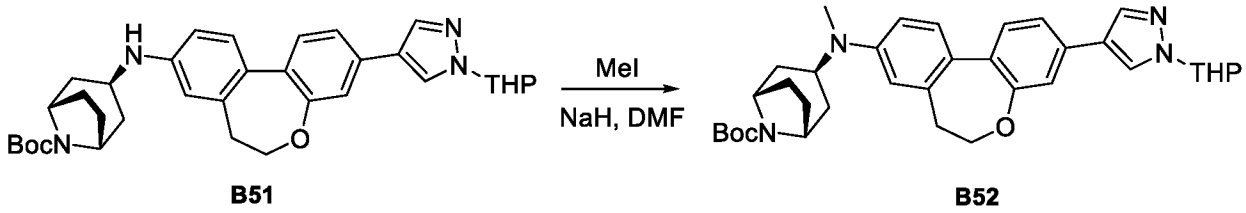
A mixture of 13-bromo-5-iodo-8-oxatricyclo [9.4.0.0^ [2,7]] pentadeca-1(15),2(7),3,5,11,13-hexaene (B47; 145 mg, 0.362 mmol), 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyrazole (B48; 120.7 mg, 0.43 mmol), Cs_2CO_3 (236 mg, 0.72 mmol), and $Pd(dppf)Cl_2$-CH_2Cl_2 (29.5 mg, 0.036 mmol, 0.1 equiv) in DME/H_2O (5:1; 5 mL) was stirred for 4 h at 80 °C under an atmosphere of nitrogen. The resulting mixture was concentrated under vacuum, and purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:10) to afford 4-[13-bromo-8-oxatricyclo [9.4.0.0^ [2,7]] pentadeca-1(11),2(7),3,5,12,14-hexaen-5-yl]-1-(oxan-2-yl) pyrazole (B49; 110 mg) as a semi-solid. **LCMS** (ES, *m/z*): 425 $[M+H]^+$.

Synthesis of Intermediate B50



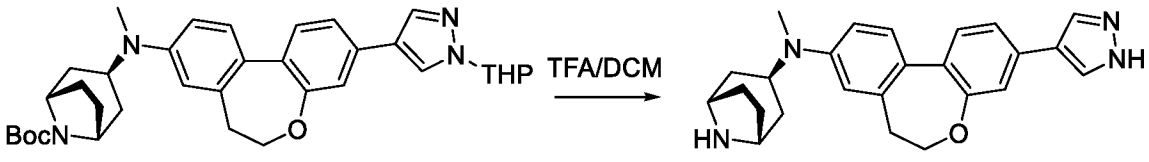
A mixture of 4- [13-bromo-8-oxatricyclo [9.4.0.0^ [2,7]] pentadeca-1(11),2(7),3,5,12,14-hexaen-5-yl]-1-(oxan-2-yl) pyrazole (B50; 110 mg, 0.26 mmol), tert-butyl-3-amino-8-azabicyclo [3.2.1] octane-8-carboxylate (117 mg, 0.52 mmol), t-BuONa (49.7 mg, 0.52 mmol), and t-BuXPhos-Pd-G3 (20.5 mg, 0.026 mmol, 0.1 equiv) in dioxane (5 mL) was stirred for 4 h at 80 °C under an atmosphere of nitrogen. The resulting mixture was concentrated under vacuum and purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:20), to provide tert-butyl-3-([5-[1-(oxan-2-yl) pyrazol-4-yl]-8-oxatricyclo [9.4.0.0^ [2,7]] pentadeca-1(11),2(7),3,5,12,14-hexaen-13-yl] amino)-8-azabicyclo [3.2.1] octane-8-carboxylate (B51; 109 mg) as a solid. **LCMS** (ES, *m/z*): 571 $[M+H]^+$.

Synthesis of Intermediate B52



A mixture of tert-butyl-3-([5-[1-(oxan-2-yl)pyrazol-4-yl]-8-oxatricyclo[9.4.0.0^[2,7]]pentadeca-1 (11),2(7),3,5,12,14-hexaen-13-yl]amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (B51; 65 mg, 0.114 mmol) and sodium hydride (13.7 mg, 0.57 mmol) in dimethylformamide (3 mL) was stirred for 0.5 h at 0 °C under an atmosphere of nitrogen. Methyl iodide (162 mg, 1.14 mmol) was then added, and the resulting solution was stirred for 12 h at 25 °C. The reaction was quenched by the addition of water/ice (10 mL), extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were dried in an oven under reduced pressure, the solids were filtered out, and the resulting mixture was concentrated under vacuum, to provide crude tert-butyl-3-[methyl([5-[1-(oxan-2-yl)pyrazol-4-yl]-8-oxatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-13-yl])amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (B52; 70 mg) as an oil. **LCMS** (ES, *m/z*): 585 $[M+H]^+$.

Synthesis of Compound 131



B52 131

A mixture of tert-butyl-3-[methyl([5-[1-(oxan-2-yl) pyrazol-4-yl]-8-oxatricyclo [9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-13-yl]) amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (B52; 65 mg), dichloromethane (2 mL), and trifluoroacetic acid (0.5 mL) was stirred for 2 h at 25 °C, and then concentrated under vacuum. The residue was dissolved in methanol (3 mL) and purified by preparative HPLC (Condition 3, Gradient 1) to provide N-methyl-N-[5-(1H-pyrazol-4-yl)-8-oxatricyclo [9.4.0.0^ [2,7]] pentadeca-1(11),2(7),3,5,12,14-hexaen-13-yl]-8-azabicyclo [3.2.1] octan-3-amine (Compound 131; 1.7 mg) as a solid. **LCMS** (ES, *m/z*): 401 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4, *ppm*) δ 8.37 (s, 2H), 7.82 – 7.76 (m, 2H), 7.75 – 7.68 (m, 1H), 7.61 (dd, J = 8.0, 1.8 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 1.8 Hz, 1H), 4.63 (t, J = 6.3 Hz, 2H), 4.34 (tt, J = 11.4, 6.1 Hz, 1H), 4.23 (d, J = 3.6 Hz, 2H), 3.37 (s, 3H), 2.96 (t, J = 6.3 Hz, 2H), 2.27 (d, J = 12.0 Hz, 2H), 2.14 (dq, J = 13.0, 8.8, 6.4 Hz, 3H), 2.05 (s, 1H), 0.12 (s, 1H).

Example 11: Synthesis of Compound 132



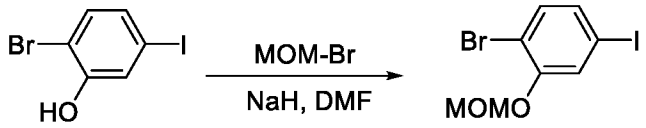
B51 132

A mixture of tert-butyl-3-([5-[1-(oxan-2-yl)pyrazol-4-yl]-8-oxatricyclo[9.4.0.0^[2,7]]pentadeca-(11), (7),3,5,12,14-hexaen-13-yl] amino)-8-azabicyclo [3.2.1] octane-8-carboxylate (B51; 39 mg), dichloromethane (2 mL), and trifluoroacetic acid (0.5 mL) was stirred for 2 h at 25 °C under an atmosphere of nitrogen. The resulting mixture was concentrated under vacuum, dissolved in methanol (3 mL), and purified by preparative HPLC (Condition 3, Gradient 1) to provide N-[5-(1H-pyrazol-4-yl)-8-oxatricyclo[9.4.0.0^[2,7]] pentadeca-1(11),2(7),3,5,12,14-hexaen-13-yl]-8-azabicyclo [3.2.1] octan-3-amine (Compound 132; 4.4 mg) as a solid. **LCMS** (ES, *m/z*): 387 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4, *ppm*) δ 8.45 (s, 1H), 7.69 – 7.58 (m, 1H), 7.58 – 7.46 (m, 2H), 4.63 (t, J = 6.2 Hz, 1H), 4.24 (d, J = 4.5 Hz, 1H), 4.11 (q, J = 8.2 Hz,

0H), 2.93 (t, J = 6.2 Hz, 1H), 2.28 – 2.22 (m, 2H), 2.17 (dd, J = 10.4, 5.8 Hz, 1H), 2.14 – 2.07 (m, 1H).

Example 12: Synthesis of Compound 134

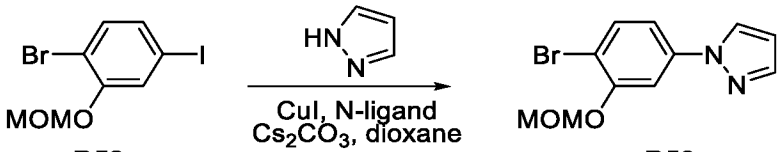
Synthesis of Intermediate B58



B57 **B58**

A mixture of 2-bromo-5-iodophenol (25 g, 83.6 mmol), sodium hydride (4 g, 167 mmol), and methyl bromomethyl ether (15.7 g, 125 mmol) in dimethylformamide (200 mL) was stirred for 4h at 0 °C. The reaction was then quenched by the addition of water (100 mL), and the resulting solution was extracted with ethyl acetate (3x200 mL), and the combined organic layers were washed with saturated NaCl solution (3 x200 mL). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (9:50) to afford 1-bromo-4-iodo-2-(methoxymethoxy)benzene (B58; 28g) as an oil. **LCMS** (ES, *m/z*):343 $[M+H]^+$.

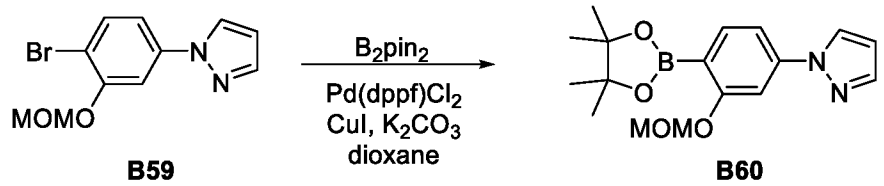
Synthesis of Intermediate B59



B58 **B59**

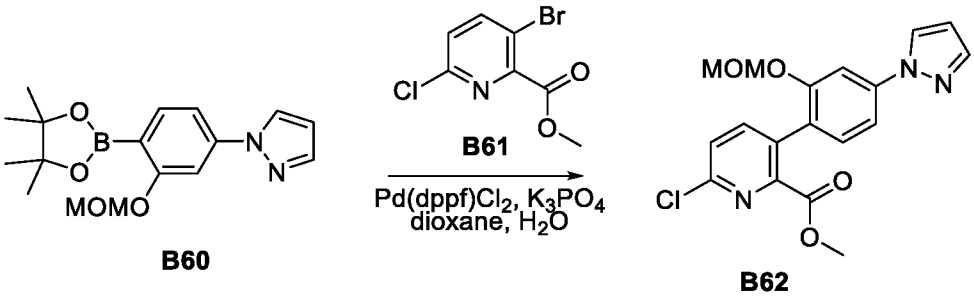
A mixture of copper iodide (1.11 g, 5.83 mmol), Cs_2CO_3 (22.8 g, 70 mmol), and N-ligand (1.14 g, 5.83 mmol) in dimethylformamide (200 mL) was stirred for 1 h at 60 °C. Pyrazole (5.56 g, 81.7 mmol) and 1-bromo-4-iodo-2-(methoxymethoxy)benzene (B58; 20 g, 58.3 mmol) were then added, and the resulting solution was stirred for 4 h at 100 °C. The mixture was then filtered, the filtrate was extracted with ethyl acetate (3 x200 mL), and the combined organic layers were washed with saturated NaCl solution (200 mL). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum, and purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:4) to afford 1-[4-bromo-3-(methoxymethoxy)phenyl]pyrazole (B59; 9.7) as an oil. **LCMS** (ES, *m/z*):283 $[M+H]^+$.

Synthesis of Intermediate B60



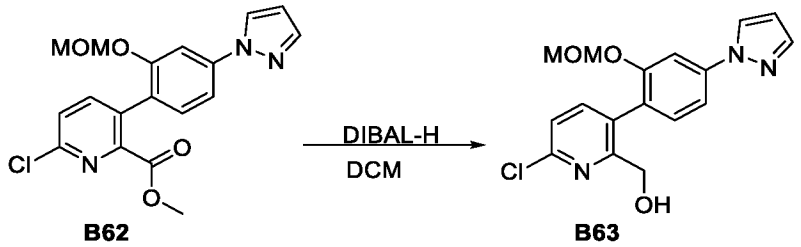
A mixture of 1-[4-bromo-3-(methoxymethoxy)phenyl]pyrazole (B59; 8 g, 28.3 mmol), B_2pin_2 (14.4 g, 56.5 mmol), K_2CO_3 (3.9 g, 28.3 mmol), Pd(dppf)Cl_2-CH_2Cl_2 (2.3 g, 2.83 mmol), and copper iodide (0.54 g, 2.8 mmol) in dioxane (80 mL) was stirred for 8 h at 80 °C. The mixture was then filtered, the filtrate was extracted with ethyl acetate (3x100 mL), and the combined organic layers were washed with saturated NaCl solution (100 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (3:50) to afford 1-[3-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl]pyrazole (B60; 7 g) as an oil. **LCMS** (ES, *m/z*):331 $[M+H]^+$.

Synthesis of Intermediate B62



A mixture of methyl 3-bromo-6-chloropyridine-2-carboxylate (B61; 4 g, 16 mmol), 1-[3-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazole (B60; 4.75 g, 14.4 mmol), Pd(dppf)Cl_2 (1.17 g, 1.6 mmol), and K_3PO_4 (10.2 g, 47.9 mmol) in dioxane/H_2O (40 mL) was stirred for 8 h at 80 °C under a nitrogen atmosphere, and then filtered. The filtrate was extracted with ethyl acetate (3x10 mL) and the combined organic layers were washed with saturated NaCl solution (10 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:10), to afford methyl 6-chloro-3-[2-(methoxymethoxy)-4-(pyrazol-1-yl)phenyl]pyridine-2-carboxylate (B62; 2.1 g) as an oil. **LCMS** (ES, *m/z*):374 $[M+H]^+$.

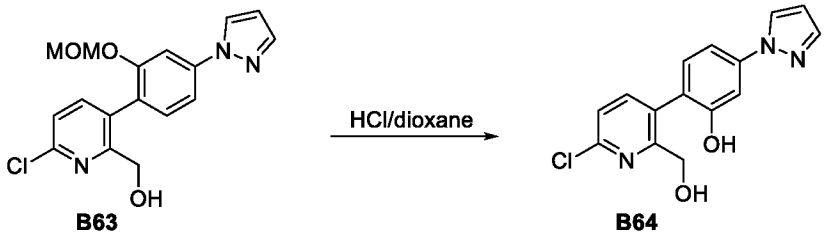
Synthesis of Intermediate B63



B62 B63

A mixture of methyl 6-chloro-3-[2-(methoxymethoxy)-4-(pyrazol-1-yl) phenyl]pyridine -2-carboxylate (B62; 1.9 g, 5.1 mmol), and DIBAL-H (27 mL, 133 mmol) in dichloromethane (80 mL) was stirred for 2 h at -30 °C under an atmosphere of nitrogen. The reaction mixture was cooled with a water/ice bath and quenched by the addition of 20 mL of water. The resulting solution was extracted with dichloromethane (3x40 mL), and the combined organic layers were washed with saturated NaCl solution (40 mL), then dried over anhydrous sodium sulfate and concentrated under vacuum, to afford crude [6-chloro-3-[2-(methoxymethoxy)-4-(pyrazol-1-yl)phenyl]pyridin-2-yl]methanol (B63; 1.3 g) as a solid. **LCMS** (ES, *m/z*):346 $[M+H]^+$.

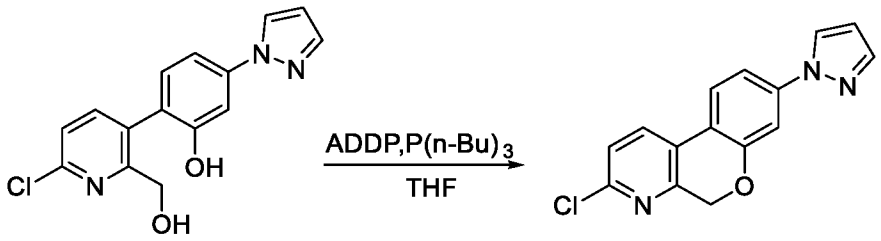
Synthesis of Intermediate B64



B63 B64

A mixture of [6-chloro-3-[2-(methoxymethoxy)-4-(pyrazol-1-yl)phenyl]pyridin-2-yl]methanol (B63; 1.3 g, 3.76 mmol) and HCl in dioxane (20 mL) was stirred for 2 h at room temperature, and then concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with dichloromethane/methanol (50:3), to afford 2-[6-chloro-2-(hydroxymethyl)pyridin-3-yl]-5-(pyrazol-1-yl)phenol (B64; 760 mg) as a solid. **LCMS** (ES, *m/z*):302 $[M+H]^+$.

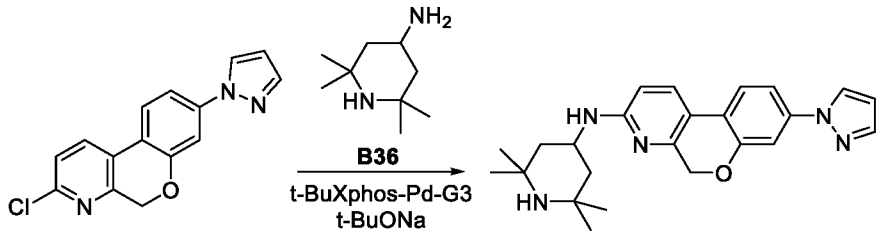
Synthesis of Intermediate B65



B64 B65

A mixture of 2-[6-chloro-2-(hydroxymethyl)pyridin-3-yl]-5-(pyrazol-1-yl)phenol (B64; 800 mg, 2.65 mmol), $P(t\text{-}Bu)_3$ (1.61 g, 7.95 mmol), and 1,1′-(azodicarbonyl)dipiperidine (2 g, 7.95 mmol) in tetrahydrofuran (100 mL) was stirred for 6 h at 0 °C under an atmosphere of nitrogen. The resulting solution was then extracted with ethyl acetate (3x50 mL), and the combined organic layers were washed with a saturated solution of NaCl (50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:4) to afford 1-[3-chloro-5H-chromeno[3,4-b]pyridin-8-yl]pyrazole (B65; 400 mg) as a solid. **LCMS** (ES, *m/z*):284 $[M+H]^+$.

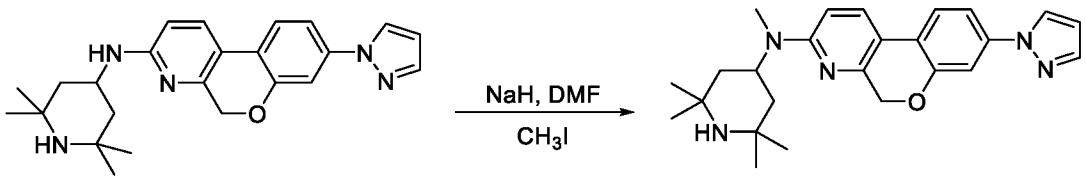
Synthesis of Compound 134



B65 134

A mixture of 1-[3-chloro-5H-chromeno[3,4-b]pyridin-8-yl]pyrazole (B65; 200 mg, 0.71 mmol), 2,2,6,6-tetramethylpiperidin-4-amine (B36; 220 mg, 1.41 mmol), tBuXPhos Pd G3 (56 mg, 0.07 mmol), and t-BuONa (135 mg, 1.41 mmol) in dioxane (5 mL) was stirred for 8 h at 80 °C in a sealed tube under an atmosphere of nitrogen. The resulting mixture was then filtered, the filtrate was extracted with ethyl acetate (3x10 mL), and the combined organic layers were washed with saturated NaCl solution (10 mL), then dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with dichloromethane/methanol (10:1) to afford 2,2,6,6-tetramethyl-N-[8-(pyrazol-1-yl)-5H-chromeno [3,4-b]pyridin-3-yl]piperidin-4-amine (Compound 134; 260 mg) as a foam. **LCMS** (ES, *m/z*):404 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6, *ppm*) δ 8.51 (d, J = 2.5 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.76 – 7.68 (m, 2H), 7.50 (dd, J = 8.5, 2.2 Hz, 1H), 7.41 (d, J = 2.2 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.56 – 6.47 (m, 2H), 5.02 (s, 2H), 4.21 – 4.14 (m, 1H), 1.81 (dd, J = 12.3, 3.6 Hz, 2H), 1.21 (s, 6H), 1.03 (d, J = 20.4 Hz, 8H).

Example 13: Synthesis of Compound 125

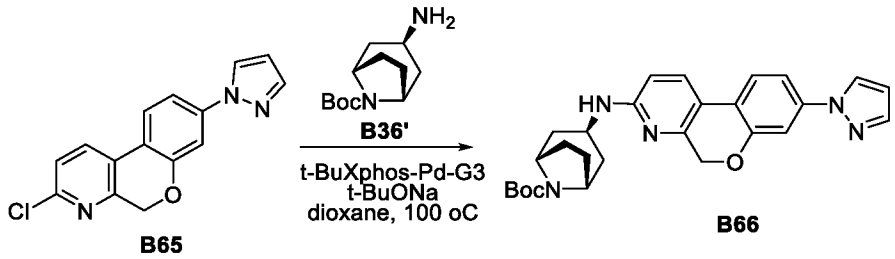


134 125

A mixture of 2,2,6,6-tetramethyl-N-[8-(pyrazol-1-yl)-5H-chromeno [3,4-b]pyridin-3-yl]piperidin-4-amine (Compound 134 from Example 12; 60 mg, 0.15 mmol), sodium hydride (17.8 mg, 0.75 mmol), and methyl iodide (42.2 mg, 0.3 mmol) was stirred for 8 h at room temperature in a sealed tube. The reaction was then quenched by the addition of 5 mL of water/ice, and the resulting solution was extracted with ethyl acetate (3x5 mL), and the combined organic layers were washed with 5 mL of saturated NaCl solution. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum, and the crude product was purified by preparative HPLC (Condition 1, Gradient 2) to afford N,2,2,6,6-pentamethyl-N-[8-(pyrazol-1-yl) -5H-chromeno[3,4-b]pyridin-3-yl]piperidin-4-amine (Compound 125; 11.8 mg) as a solid. **LCMS** (ES, *m/z*):418 $[M+H]^+$. **^{1}HNMR** (400 MHz, Methanol-d_4, *ppm*) δ 8.21 (dd, *J* = 2.5, 0.6 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.75 – 7.65 (m, 2H), 7.39 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.32 (d, *J* = 2.2 Hz, 1H), 6.57 – 6.51 (m, 2H), 5.05 (s, 2H), 4.27 (s, 1H), 2.41 (s, 3H), 2.01 (d, *J* = 12.5 Hz, 2H), 1.44 (t, *J* = 12.3 Hz, 2H), 1.27 (d, *J* = 3.5 Hz, 12H), 0.12 (d, *J* = 1.0 Hz, 1H).

Example 14: Synthesis of Compound 124

Synthesis of Intermediate B66

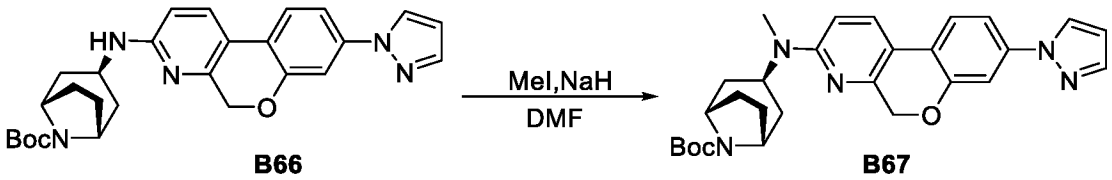


B65 B66

A mixture of 1-[3-chloro-5H-chromeno[3,4-b]pyridin-8-yl]pyrazole (B65; 200 mg, 0.71 mmol), tert-butyl (1R,3S,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (B36'; 319 mg, 1.41 mmol), tBuXPhos Pd G3 (56 mg, 0.07 mmol), and t-BuONa (135 mg, 1.41 mmol) in dioxane (10 mL) was stirred for 8 h at 80 °C in a sealed tube under an atmosphere of nitrogen. The mixture was then filtered, the filtrate was extracted with ethyl acetate (3 x10 mL), and the combined organic extracts were washed with saturated NaCl (10 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography

eluting with ethyl acetate/petroleum ether (1:4) to afford tert-butyl (1R,3S,5S)-3-[[8-(pyrazol-1-yl)-5H-chromeno[3,4-b]pyridin-3-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B66; 270 mg) as a foam. **LCMS** (ES, *m/z*):474 $[M+H]^+$.

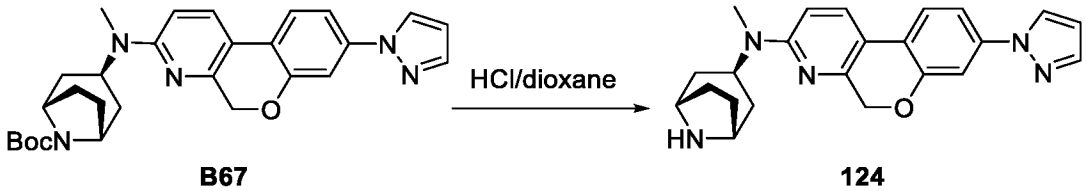
Synthesis of Intermediate B67



B66 **B67**

A mixture of tert-butyl (1R,3S,5S)-3-[[8-(pyrazol-1-yl)-5H-chromeno[3,4-b]pyridin-3-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B66; 150 mg, 0.32 mmol, sodium hydride (76mg, 3.17 mmol), and methyl iodide (450 mg, 3.17 mmol) in dimethylformamide (10 mL) was stirred for 2 h at 0 °C in a sealed tube under a nitrogen atmosphere, and the reaction was then quenched by the addition of water. The resulting solution was extracted with ethyl acetate (3 x10 mL), and the combined organic layers were washed with saturated NaCl solution (10 mL), then dried over anhydrous sodium sulfate and concentrated under vacuum, to afford crude tert-butyl (1R,3S,5S)-3-[methyl[8-(pyrazol-1-yl)-5H-chromeno [3,4-b]pyridin-3-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B67; 140 mg) as a solid. **LCMS** (ES, *m/z*):488 $[M+H]^+$.

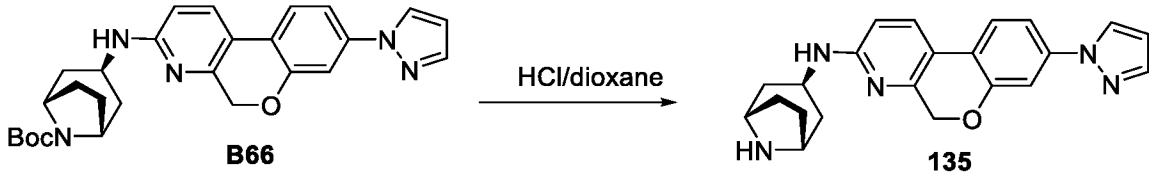
Synthesis of Compound 124



B67 **124**

A mixture of tert-butyl (1R,3S,5S)-3-[methyl[8-(pyrazol-1-yl)-5H-chromeno[3,4-b]pyridin-3-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B67; 150 mg), and HCl in dioxane (10 mL) was stirred for 2 h at room temperature, and then concentrated under vacuum. The resulting crude product was purified by preparative HPLC (Condition 1, Gradient 2) to afford (1R,3S,5S)-N-methyl-N-[8-(pyrazol-1-yl)-5H-chromeno [3,4-b]pyridin-3-yl]-8-azabicyclo[3.2.1]octan-3-amine (Compound 124; 20.3 mg) as a solid. **LCMS** (ES, *m/z*):387 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.52 (d, J = 2.5 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.96 (s, 3H), 7.79 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 1.7 Hz, 1H), 7.52 (dd, J = 8.5, 2.3 Hz, 1H), 7.44 (d, J = 2.2 Hz, 1H), 6.74 (d, J = 8.9 Hz, 1H), 6.57 – 6.52 (m, 1H), 5.09 (s, 2H), 3.96 (s, 2H), 2.89 (s, 3H), 2.04 (t, J = 13.0 Hz, 2H), 1.96 (s, 5H), 1.65 (d, J = 13.0 Hz, 2H).

Example 15: Synthesis of Compound 135

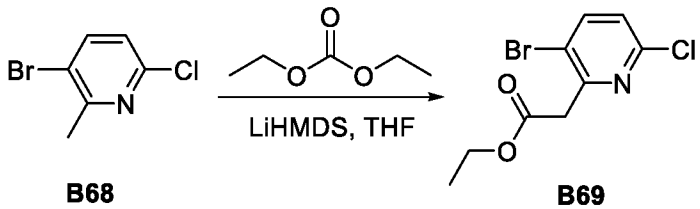


B66 135

A mixture of tert-butyl (1R,3S,5S)-3-[[8-(pyrazol-1-yl)-5H-chromeno[3,4-b]pyridin-3-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B66; 80 mg, 0.17 mmol) and HCl in dioxane (10 mL) was stirred for 2 h at room temperature, and the resulting mixture was concentrated under vacuum. The crude product was purified by preparative HPLC (Condition 1, Gradient 2) to afford (1R,3S,5S)-N-[8-(pyrazol-1-yl)-5H-chromeno[3,4-b]pyridin-3-yl]-8-azabicyclo[3.2.1]octan-3-amine (Compound 135; 18.3 mg) as a solid. **LCMS** (ES, *m/z*):373 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.51 (d, *J* = 2.5 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.76 – 7.68 (m, 2H), 7.49 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.56 – 6.47 (m, 2H), 5.03 (s, 2H), 4.11 (s, 1H), 3.56 (s, 2H), 1.97 – 1.87 (m, 2H), 1.77 – 1.72 (m, 4H), 1.48 – 1.38 (m, 2H).

Example 16: Synthesis of Compound 128

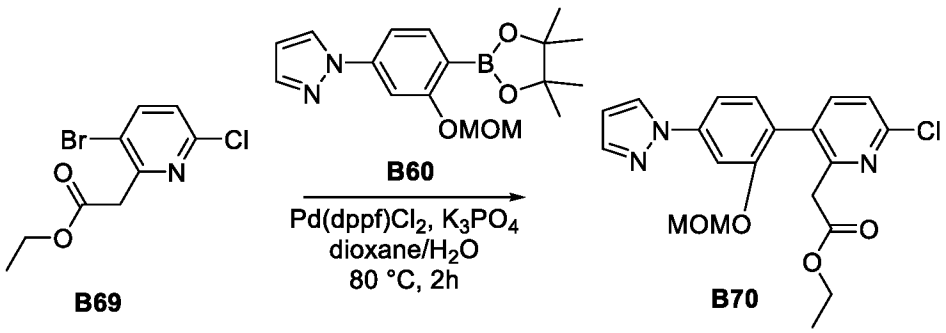
Synthesis of Intermediate B69



B68 B69

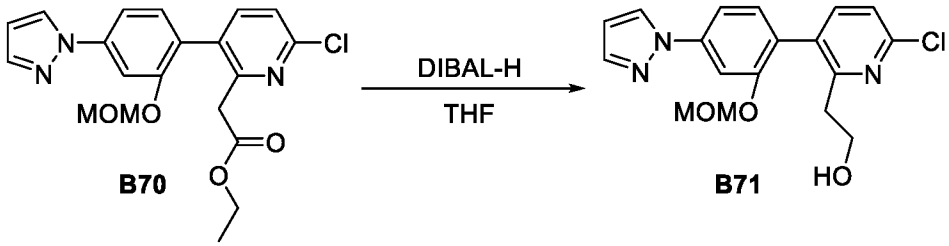
Lithium bis(trimethylsilyl)amide (5 g, 30 mmol) was added in portions to a solution of 3-bromo-6-chloro-2-methylpyridine (B68; 2.1 g, 10 mmol) in tetrahydrofuran (60 mL) at room temperature under a nitrogen atmosphere, the mixture was stirred for an additional 0.5 h. Diethyl carbonate (1.89 g, 16 mmol) was then added, and the resulting mixture was stirred for 1 h. The reaction mixture was then quenched with water and diluted with ethyl acetate. The aqueous phase was separated, and further extracted with ethyl acetate (2 x 100 mL). The combined organic layers were then washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (9:1), to afford ethyl 2-(3-bromo-6-chloropyridin-2-yl)acetate (B69; 2.3g) as an oil. **LCMS** (ES, m/z): 278 $[M+H]^+$.

Synthesis of Intermediate B70



Tripotassium phosphase (1.14 g, 5.4 mmol) and $Pd(dppf)Cl_2$-CH_2Cl_2 (146 mg, 0.18 mmol) were added to a mixture of 1-[3-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazole (B60 from Example 12; 593 mg, 1.8 mmol) and ethyl 2-(3-bromo-6-chloropyridin-2-yl)acetate (B69; 500 mg, 1.8 mmol) in dioxane (10 mL) and H_2O (2 mL), and the resulting mixture was stirred for 1 h at 80 °C under an atmosphere of nitrogen. The mixture was then concentrated under reduced pressure, and purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (5:1), to afford ethyl 2-[6-chloro-3-[2-(methoxymethoxy)-4-(pyrazol-1-yl)phenyl]pyridin-2-yl]acetate (B70; 300 mg) as an oil. **LCMS** (ES, m/z): 402 $[M+H]^+$.

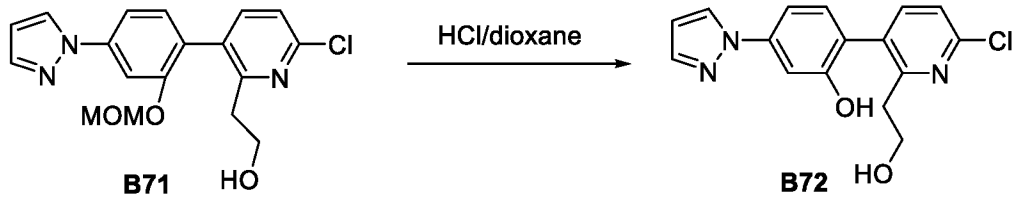
Synthesis of Intermediate B71



DIBAL-H (531 mg, 3.74 mmol) was added in portions to a solution of ethyl 2-[6-chloro-3-[2-(methoxymethoxy)-4-(pyrazol-1-yl)phenyl]pyridin-2-yl]acetate (B70; 300 mg, 0.75 mmol) in dichloromethane (5 mL) at -40 °C under a nitrogen atmosphere, and the resulting mixture was stirred for 1 h at -40 ° C. The reaction mixture was quenched with water, and basified to pH 10 with saturated NaOH (aq.). The aqueous phase was then separated and extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate

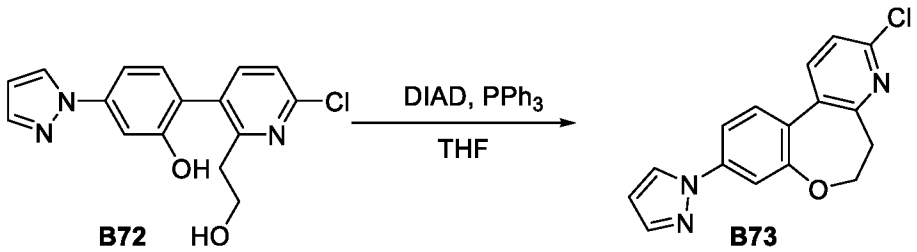
(1:1) to afford 2-[6-chloro-3-[2-(methoxymethoxy)-4-(pyrazol-1-yl)phenyl]pyridin-2-yl]ethanol (B71; 170 mg) as a solid. **LCMS** (ES, m/z): 360 $[M+H]^+$.

Synthesis of Intermediate B72



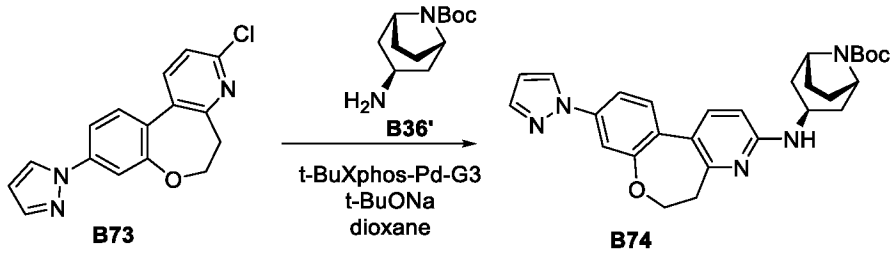
A mixture of 2-[6-chloro-3-[2-(methoxymethoxy)-4-(pyrazol-1-yl)phenyl]pyridin-2-yl]ethanol (B71; 200 mg, 0.56 mmol), HCl in 1,4-dioxane (2 mL, 35 mmol), and methanol (1 ml) was stirred for 1 h at room temperature, and then concentrated. Methanol and triethylamine were then added to neutralize the pH, and the solvent was evaporated. The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (1:1) to afford 2-[6-chloro-2-(2-hydroxyethyl)pyridin-3-yl]-5-(pyrazol-1-yl)phenol (B72; 102 mg) as a solid. **LCMS** (ES, m/z): 316 $[M+H]^+$.

Synthesis of Intermediate B73



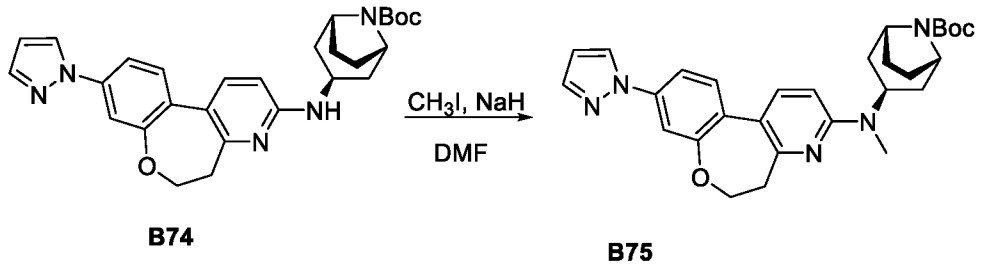
Diisopropyl azodicarboxylate (141 mg, 0.7 mmol) was added dropwise at to a solution of 2-[6-chloro-2-(2-hydroxyethyl)pyridin-3-yl]-5-(pyrazol-1-yl)phenol (B72; 110 mg, 0.35 mmol) and triphenylphosphine (183 mg, 0.7 mmol) in tetrahydrofuran (2 mL) at 0 °C, and the mixture was stirred for 2 h at room temperature. The mixture was then concentrated, and the residue was purified by preparative TLC eluting with petroleum ether/ethyl acetate (3:1), to afford 5-chloro-13-(pyrazol-1-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaene (B73; 49 mg) as a solid. **LCMS** (ES, m/z): 298 $[M+H]^+$.

Synthesis of Intermediate B74



Sodium tert-butoxide (41.6 mg, 0.43 mmol) and t-BuXPhos palladium(II) biphenyl-2-amine mesylate (11.5 mg, 0.014 mmol) were added to a mixture of 5-chloro-13-(pyrazol-1-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaene (B73; 43 mg, 0.14 mmol) and tert-butyl (1R,3S,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (B36'; 49 mg, 0.22 mmol) in dioxane (3 mL), and the resulting mixture was stirred overnight at 100 ° C under a nitrogen atmosphere, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (5:1) to afford tert-butyl (1R,3S,5S)-3-[[13-(pyrazol-1-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B74; 42 mg) as a solid. **LCMS** (ES, m/z): 488 $[M+H]^+$.

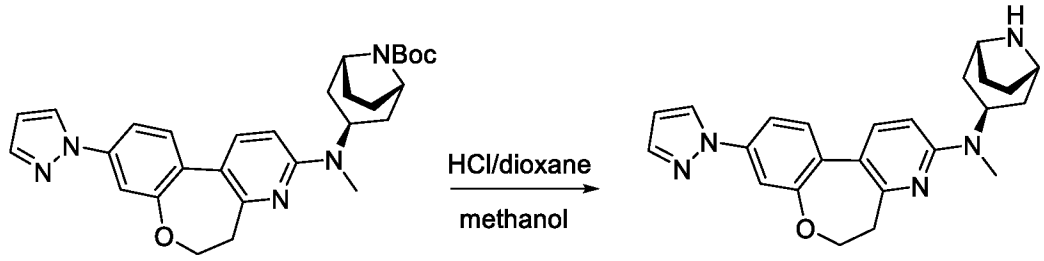
Synthesis of Intermediate B75



Sodium hydride (4.1 mg, 0.17 mmol) was added to a mixture of tert-butyl (1R,3S,5S)-3-[[13-(pyrazol-1-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B74; 42 mg, 0.09 mmol) in dimethylformamide (2 mL), and the mixture was stirred for 0.5 h at 0 °C. Methyl iodide (24.5 mg, 0.17 mmol) was then added, and the resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (10 mL) at 0 °C, and extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with brine (3x15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, to afford crude tert-butyl (1R,3S,5S)-3-[methyl[13-(pyrazol-1-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-

1(11),2(7),3,5,12,14-hexaen-5-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B75; 21 mg) which was used directly in the next step. **LCMS** (ES, m/z): 502 $[M+H]^+$.

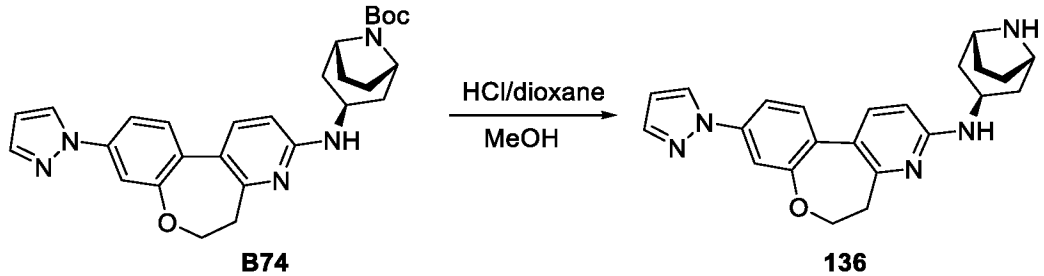
Synthesis of Compound 128



B75 **128**

A mixture of tert-butyl (1R,3S,5S)-3-[methyl[13-(pyrazol-1-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B75; 27 mg, 0.054 mmol), 4 M HCl in dioxane (1 mL), and methanol (1 mL) was stirred for 0.5 h at room temperature. The solvent was evaporated and the resulting residue was purified by preparative HPLC (Condition 2, Gradient 1) to afford N-[(1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl]-N-methyl-13-(pyrazol-1-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (Compound 128; 6.1 mg) as a solid. **LCMS** (ES, m/z): 402 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d4) δ 8.26 (d, J = 2.5 Hz, 1H), 7.75 (d, J = 1.8 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.60 (dd, J = 8.4, 2.4 Hz, 1H), 7.52 – 7.46 (m, 2H), 6.66 (d, J = 8.7 Hz, 1H), 6.56 (t, J = 2.2 Hz, 1H), 5.37 – 5.24 (m, 1H), 4.69 (t, J = 6.3 Hz, 2H), 3.74 (s, 2H), 2.99 – 2.90 (m, 5H), 2.03 – 1.90 (m, 6H), 1.75 – 1.65 (m, 2H).

Example 17: Synthesis of Compound 136

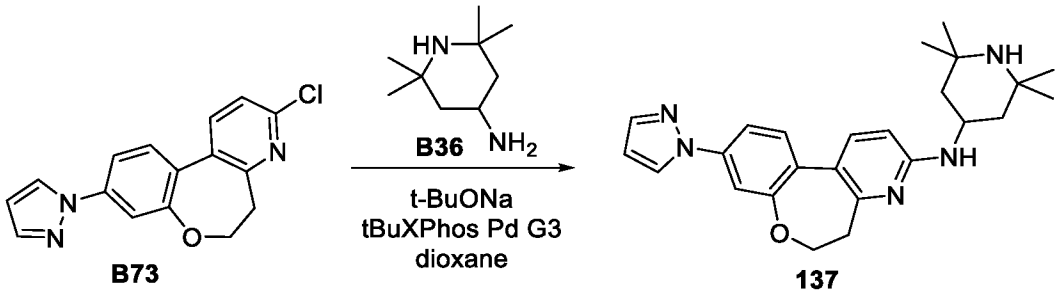


B74 **136**

A mixture of tert-butyl(1R,3S,5S)-3-[[13-(pyrazol-1-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]] pentadeca-1 (11),2(7),3,5,12,14-hexaen-5-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B74 from Example 16; 30 mg, 0.062 mmol), 4M HCl in dioxane (1 mL) and methanol (1 mL) was stirred for 0.5 h at room temperature. The solvent was then evaporated and the residue was purified by preparative HPLC (Condition 2, Gradient 1) to afford N-[(1R,3S,5S)-8-

azabicyclo[3.2.1]octan-3-yl]-13-(pyrazol-1-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (Compound 136; 6.2 mg) as a solid. **LCMS** (ES, m/z): 388 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-*d_4, ppm*) δ 8.26 (d, J = 2.5 Hz, 1H), 7.75 (d, J = 1.9 Hz, 1H), 7.60 (dd, J = 8.4, 2.3 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.51 (d, J = 2.3 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 6.59 – 6.54 (m, 2H), 4.69 (t, J = 6.3 Hz, 2H), 4.35 – 4.23 (m, 1H), 3.69 (s, 2H), 2.91 (t, J = 6.3 Hz, 2H), 2.17 – 2.06 (m, 2H), 2.02 – 1.93 (m, 4H), 1.61 – 1.48 (m, 2H).

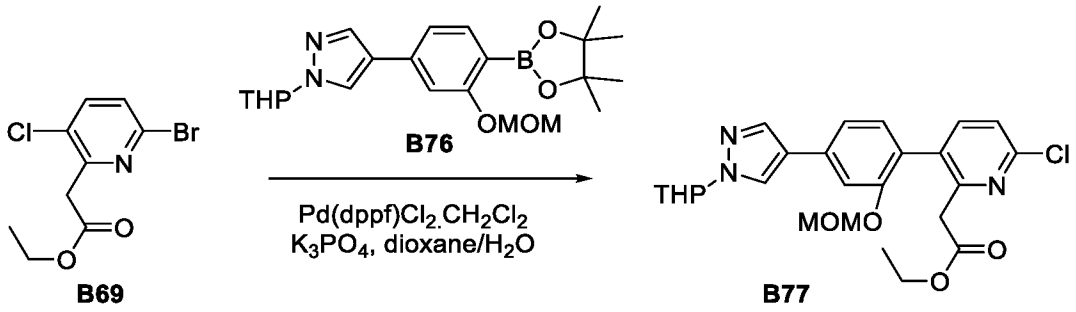
Example 18: Synthesis of Compound 137



Sodium tert-butoxide (145 mg, 1.5 mmol) and t-BuXPhos Phos palladium(II) biphenyl-2-amine mesylate (40 mg, 0.05 mmol) were added to a mixture of 5-chloro-13-(pyrazol-1-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3, 5,12,14-hexaene (B73 from Example 16; 150 mg, 0.5 mmol) and 2,2,6,6-tetramethylpiperidin-4-amine (B36; 118 mg, 0.76 mmol) in dioxane (2 mL), and the mixture was stirred overnight at 100 °C under a nitrogen atmosphere, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with dichloromethane/methanol, followed by preparative HPLC (Condition 2, Gradient 1) to afford 13-(pyrazol-1-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-10-oxa-6-azatricyclo [9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (Compound 137; 23.3 mg) as a solid. **LCMS** (ES, m/z): 418 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d4) δ 8.26 (d, J = 2.6 Hz, 1H), 7.75 (d, J = 1.8 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.54 – 7.45 (m, 2H), 6.60 – 6.53 (m, 2H), 4.69 (t, J = 6.3 Hz, 2H), 4.42 – 4.28 (m, 1H), 2.91 (t, J = 6.3 Hz, 2H), 2.10 (d, J = 13.1 Hz, 2H), 1.48 – 1.38 (m, 7H), 1.31 – 1.25 (m, 7H).

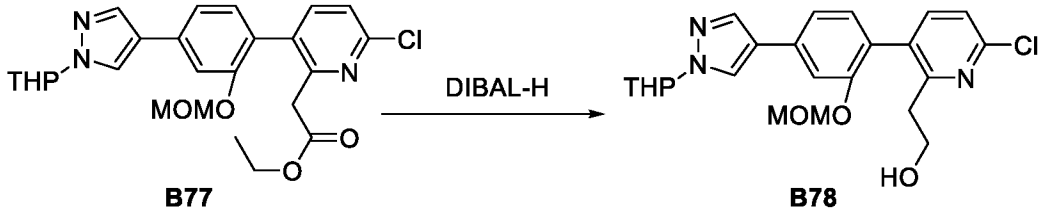
Example 19: Synthesis of Compound 127

Synthesis of Intermediate B77



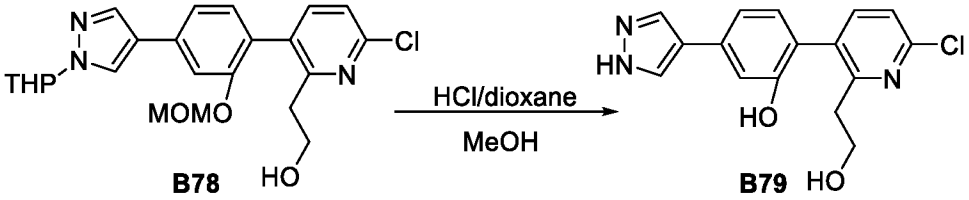
Tripotassium phosphate (4.57 g, 21.5 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (585 mg, 0.72 mmol) were added to a solution of 4-[3-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-(oxan-2-yl)pyrazole (B76; 2.97 g, 7.18 mmol) and ethyl 2-(3-bromo-6-chloropyridin-2-yl)acetate (B69 from Example 16; 2 g, 7.18 mmol) in dioxane (50 mL) and H_2O (10 mL), and the mixture was stirred for 1 h at 80 ° C under a nitrogen atmosphere, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (5:1), to afford ethyl 2-[6-chloro-3-[2-(methoxymethoxy)-4-[1-(oxan-2-yl)pyrazol-4-yl]phenyl]pyridin-2-yl]acetate (B77; 1.71 g) as an oil. **LCMS** (ES, m/z): 486 $[M+H]^+$.

Synthesis of Intermediate B78



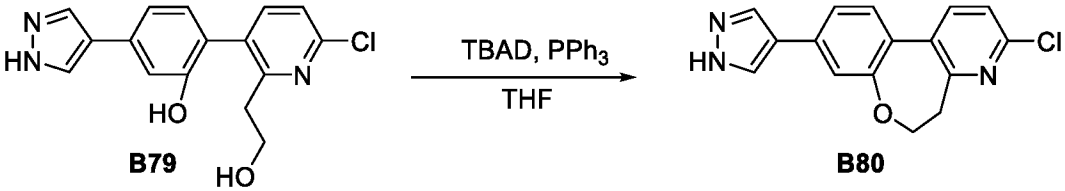
A mixture of DIBAL-H (5 g, 35 mmol) in toluene (35 mL) was added dropwise to a solution of ethyl 2-[6-chloro-3-[2-(methoxymethoxy)-4-[1-(oxan-2-yl)pyrazol-4-yl]phenyl] pyridin-2-yl]acetate (B77; 1.71 g, 3.52 mmol) in toluene (5 mL) at -78 °C under a nitrogen atmosphere. The resulting mixture was then stirred for 1 h at -50 ° C, then H_2O (1.5 mL) was added and the mixture was stirred for 15 min, followed by the addition of 15% aqueous sodium hydroxide (1.5 mL) with stirring for 15 min. Next, water (3.5 mL) was added, and the mixture was dried with anhydrous sodium sulfate. The resulting mixture was filtered, the filter cake was washed with ethyl acetate (3x30 mL), and the filtrate was concentrated under reduced pressure, to afford crude 2-[6-chloro-3-[2-(methoxymethoxy)-4-[1-(oxan-2-yl)pyrazol-4-yl]phenyl]pyridin-2-yl]ethanol (B78; 235 mg) as an oil, that was used directly in the next step. **LCMS** (ES, m/z): 444 $[M+H]^+$.

Synthesis of Intermediate B79



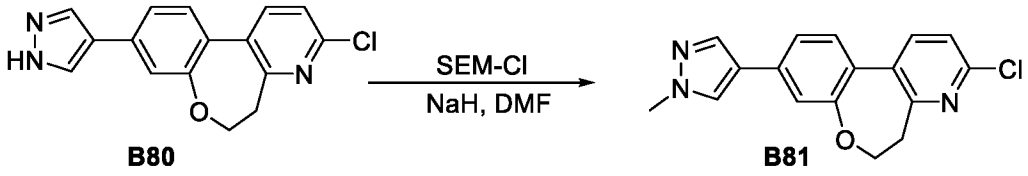
A solution of 2-[6-chloro-3-[2-(methoxymethoxy)-4-[1-(oxan-2-yl)pyrazol-4-yl]phenyl]pyridin-2-yl]ethanol (B78; 253 mg, 0.57 mmol), and HCl in 1,4-dioxane (2 mL), in methanol (2 mL) was stirred for 1 h at room temperature. The solvent was then evaporated, and the residue was dissolved in methanol (2 mL) and basified with triethylamine. After the solvent was evaporated, the residue was purified by silica gel column chromatography, eluting with dichloromethane/methanol (12:1), to afford crude 2-[6-chloro-2-(2-hydroxyethyl)pyridin-3-yl]-5-(1H-pyrazol-4-yl)phenol (B79; 203 mg) as a solid. **LCMS** (ES, m/z): 416 $[M+H]^+$.

Synthesis of Intermediate B80



A mixture of di-tert-butyl azodicarboxylate (265 mg, 1.15 mmol) in tetrahydrofuran (4 mL) was added dropwise to a solution of 2-[6-chloro-2-(2-hydroxyethyl)pyridin-3-yl]-5-(1H-pyrazol-4-yl)phenol (B79; 121 mg, 0.38 mmol) and triphenylphosphine (201 mg, 0.77 mmol) in tetrahydrofuran (6 mL) at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature, then the solvent was evaporated, and the residue was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (1:1), to afford crude 5-chloro-13-(1H-pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaene (B80; 130 mg) as a solid. **LCMS** (ES, m/z): 298 $[M+H]^+$.

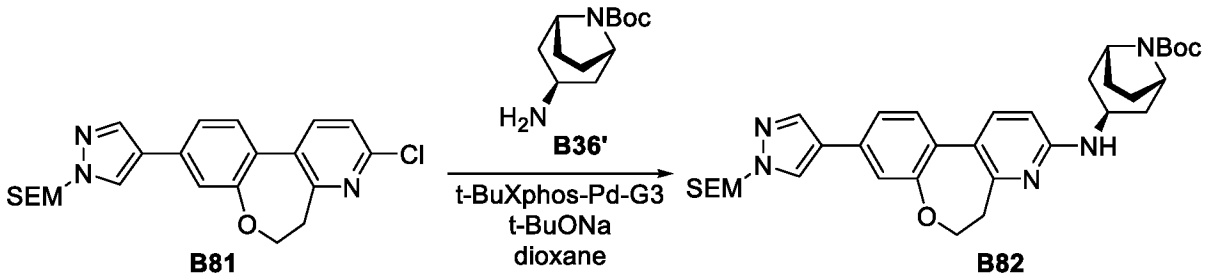
Synthesis of Intermediate B81



Sodium hydride (19.5 mg, 0.81 mmol) was added in portions to a solution of 5-chloro-13-(1H-pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]] pentadeca-1(11),2(7),3,5,12,14-hexaene (121

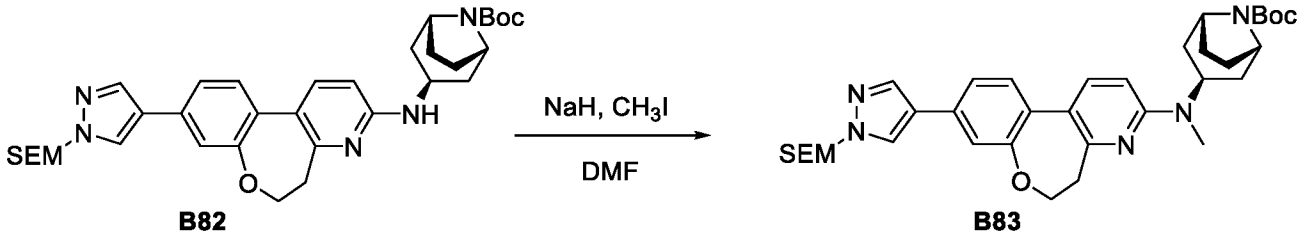
mg, 0.406 mmol) in dimethylformamide (3 mL) at 0 °C under a nitrogen atmosphere. After stirring for 30 min, SEMCl (203 mg, 1.22 mmol) was added dropwise, and the resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with water (5 mL) at 0 °C and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (5:1), to afford 5-chloro-13-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaene (B81; 131 mg) as a solid. **LCMS** (ES, m/z): 428 $[M+H]^+$.

Synthesis of Intermediate B82



Sodium tert-butoxide (47 mg, 0.49 mmol) and t-BuXPhos Phos palladium(II) biphenyl-2-amine mesylate (13 mg, 0.016 mmol) were added to a solution of 5-chloro-13-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaene (B81; 70 mg, 0.16 mmol) and tert-butyl (1R,3S,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (B36'; 74 mg, 0.33 mmol) in dioxane (3 mL), and the mixture was stirred for 3 h at 100 °C under a nitrogen atmosphere, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with petroleum ether/ethyl acetate (5:1), to afford tert-butyl (1R,3S,5S)-3-[[13-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B82; 41 mg) as a solid. **LCMS** (ES, m/z): 618 $[M+H]^+$.

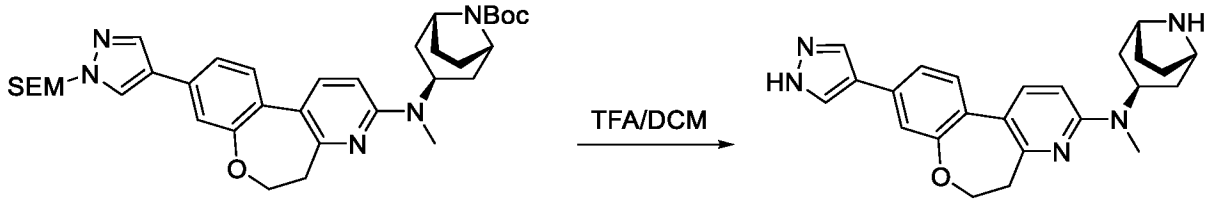
Synthesis of Intermediate B83



B82 B83

Sodium hydride (6.4 mg, 0.27 mmol) was added in portions to a solution of tert-butyl (1R,3S,5S)-3-[[13-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B82; 41 mg, 0.066 mmol) in dimethylformamide (2 mL) at 0 °C under a nitrogen atmosphere, and the mixture was stirred for 30 min. Methyl iodide (28.3 mg, 0.2 mmol) was then added, and the resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (5 mL) at 0 °C and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, to afford crude tert-butyl (1R,3S,5S)-3-[methyl[13-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B83; 32 mg) as a solid, which was used directly in the next step. **LCMS** (ES, m/z): 632 $[M+H]^+$.

Synthesis of Compound 127



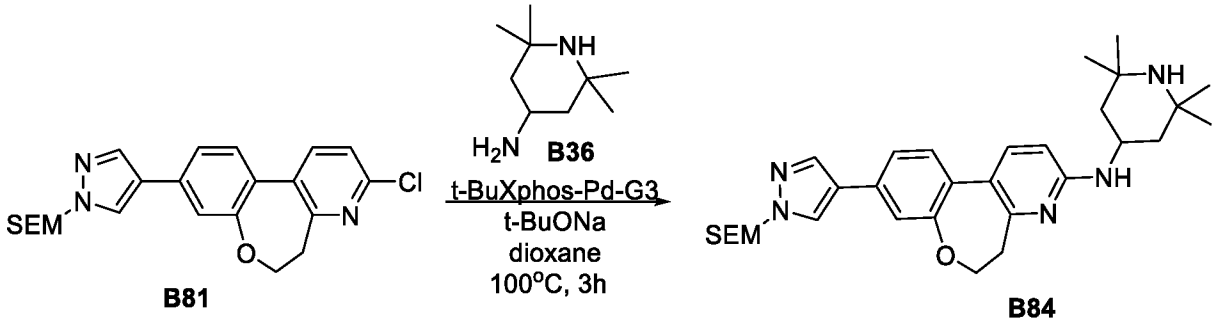
B83 127

A mixture of tert-butyl (1R,3S,5S)-3-[methyl[13-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B83; 12 mg, 0.019 mmol) and trifluoroacetic acid (1 mL) in dichloromethane (1 mL) was stirred for 1 h at room temperature. The solvent was then evaporated, and the resulting residue was purified by preparative HPLC (Condition 2, Gradient 4), to afford N-[(1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl]-N-methyl-13-(1H-pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (Compound

127; 3.1 mg) as a solid. **LCMS** (ES, m/z): 402 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.99 (s, 2H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 7.9, 1.8 Hz, 1H), 7.39 – 7.32 (m, 2H), 6.65 (d, *J* = 8.7 Hz, 1H), 5.37 – 5.21 (m, 1H), 4.66 (t, *J* = 6.4 Hz, 2H), 3.77 (s, 2H), 2.97 – 2.88 (m, 5H), 2.01 – 1.92 (m, 6H), 1.77 – 1.66 (m, 2H).

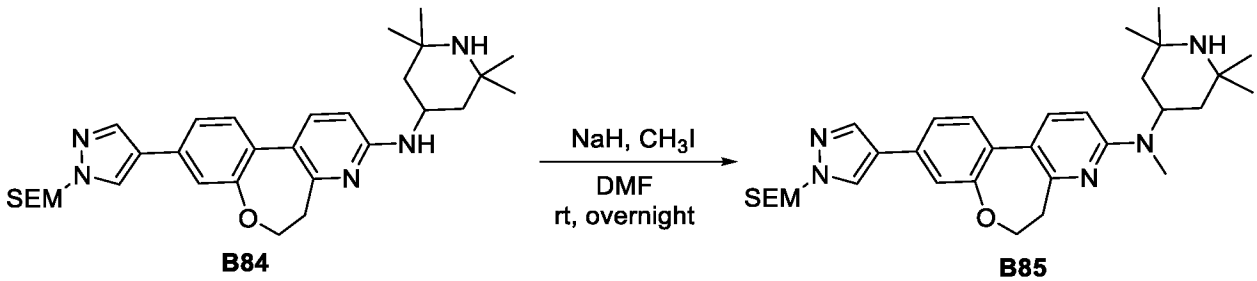
Example 20: Synthesis of Compound 114

Synthesis of Intermediate B84



Sodium tert-butoxide (59 mg, 0.62 mmol) and tBuXPhos Pd G3 (16 mg, 0.02 mmol) were added to a solution of 5-chloro-13-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-10-oxa-6-azatricyclo [9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaene (B81 from Example 21; 88 mg, 0.22 mmol) and 2,2,6,6-tetramethylpiperidin-4-amine (B36; 64 mg, 0.41 mmol) in dioxane (3 mL), and the mixture was stirred for 3 h at 100 °C under a nitrogen atmosphere. The mixture was then concentrated under reduced pressure, and purified by silica gel column chromatography eluting with dichloromethane/methanol (10:1), to afford N-(2,2,6,6-tetramethylpiperidin-4-yl)-13-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (B84; 51 mg) as a solid. **LCMS** (ES, m/z): 548 $[M+H]^+$.

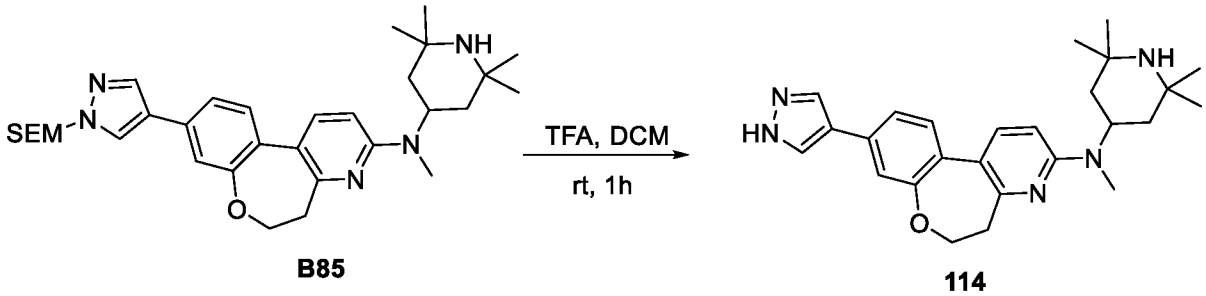
Synthesis of Intermediate B85



Sodium hydride (4.5 mg, 0.19 mmol) was added in portions to a solution of N-(2,2,6,6-tetramethylpiperidin-4-yl)-13-(1-[[2-(trimethylsilyl) ethoxy]methyl]pyrazol-4-yl)-10-oxa-6-

azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (B84; 51 mg, 0.093 mmol) in dimethylformamide (2 mL) at 0 °C under a nitrogen atmosphere, and the mixture was stirred for 30 min. Methyl iodide (39.6 mg, 0.28 mmol) was then added, and the resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (0.5 mL) at 0 °C, and purified by reverse flash chromatography on a C18 column, eluting with acetonitrile (10% to 50% over 10 min) in water, to afford N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-13-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-10-oxa-6-azatricyclo [9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (B85; 21 mg) as an oil. **LCMS** (ES, m/z): 562 $[M+H]^+$.

Synthesis of Compound 114

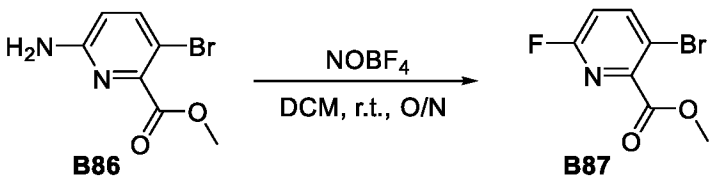


B85 114

A mixture of N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-13-(1-[[2-(trimethylsilyl)ethoxy]methyl] pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (B85; 6 mg, 0.011 mmol) and trifluoroacetic acid (1 mL) in dichloromethane (1 mL) was stirred for 1 h at room temperature. The solvent was then evaporated and the resulting residue was purified by preparative HPLC (Condition 2, Gradient 4), to afford N-methyl-13-(1H-pyrazol-4-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (Compound 114; 0.6 mg) as a solid. **LCMS** (ES, m/z): 432 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.99 (s, 2H), 7.56 (d, J = 8.5 Hz, 1H), 7.45 (dd, J = 7.9, 1.8 Hz, 1H), 7.38 – 7.32 (m, 2H), 6.57 (d, J = 8.5 Hz, 1H), 4.65 (t, 2H), 4.59 (s, 1H), 2.89 (t, J = 6.3 Hz, 2H), 2.57 (s, 3H), 2.25 – 2.08 (m, 2H), 1.62 – 1.54 (m, 2H), 1.46 – 1.34 (m, 12H).

Example 21: Synthesis of Compound 121

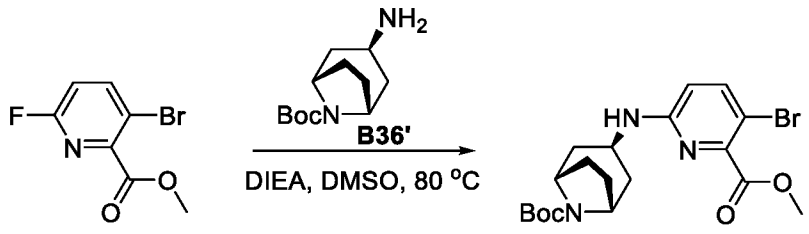
Synthesis of Intermediate B87



B86 B87

A mixture of methyl 6-amino-3-bromopyridine-2-carboxylate (B86; 4.5 g, 19.5 mmol) and nitrosonium tetrafluoroborate (2.96 g, 0.03 mmol) in dichloromethane (30 mL) was stirred for 36 h at 0 °C. The reaction was then quenched with water (50 mL), and the residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (3:25). The resulting mixture was washed with sat. NaCl (50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum, to afford methyl 3-bromo-6-fluoropyridine-2-carboxylate (B87; 3.2 g) as an oil. **LCMS** (ES, *m/z*): 234 $[M+H]^+$.

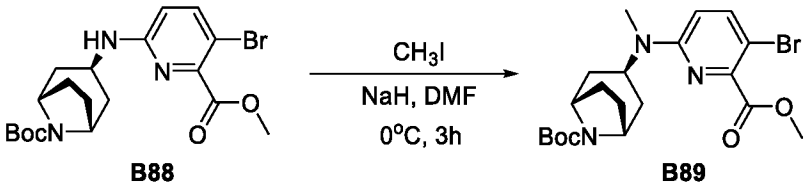
Synthesis of Intermediate B88



B87 B88

A mixture of methyl 3-bromo-6-fluoropyridine-2-carboxylate (B87; 1.6 g, 6.84 mmol), tert-butyl (1R,3S,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (B36'; 3.09 g, 13.7 mmol), and diisopropylethylamine (2.65 g, 20.5 mmol), in dimethyl sulfoxide (30 mL) was stirred for 5 min at 80 °C in a sealed tube. The resulting solution was then extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with sat. NaCl (20 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (3:10), to afford tert-butyl (1R,3S,5S)-3-[[5-bromo-6-(methoxycarbonyl)pyridin-2-yl]amino]-8-azabicyclo [3.2.1]octane-8-carboxylate (B88; 2 g) as a solid. **LCMS** (ES, *m/z*): 440 $[M+H]^+$.

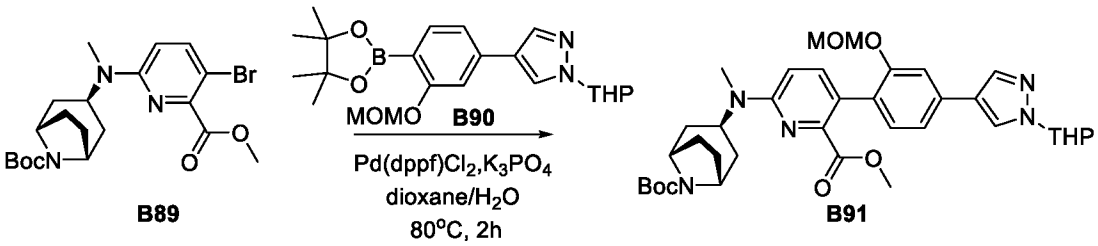
Synthesis of Intermediate B89



B88 B89

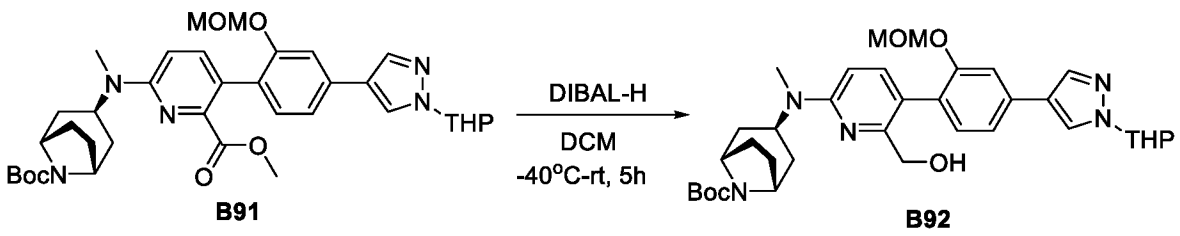
A mixture of tert-butyl (1R,3S,5S)-3-[[5-bromo-6-(methoxycarbonyl)pyridin-2-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B88; 1 g, 2.27 mmol), sodium hydride (0.27 g, 11.4 mmol), and methyl iodide (0.64 g, 4.5 mmol), in dimethylformamide (10 mL) was stirred for 3 h at 0 °C, and was then quenched by the addition of ice water (10 mL). The resulting solution was extracted with ethyl acetate (3x10 mL) and the combined organic layers were washed with sat. NaCl (10 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum, to afford tert-butyl (1R,3S,5S)-3-[[5-bromo-6-(methoxycarbonyl)pyridin-2-yl](methyl)amino] -8-azabicyclo[3.2.1]octane-8-carboxylate (B89; 0.9 g) as an oil. **LCMS** (ES, *m/z*): 454 $[M+H]^+$.

Synthesis of Intermediate B91



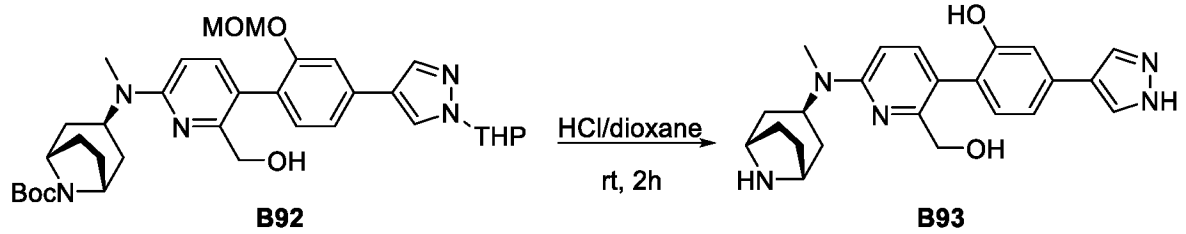
A mixture of tert-butyl (1R,3S,5S)-3-[[5-bromo-6-(methoxycarbonyl)pyridin-2-yl](methyl)amino]-8-azabicyclo [3.2.1]octane-8-carboxylate (B89; 900 mg, 1.98 mmol), K_3PO_4 (1.26 g, 5.94 mmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (161 mg, 0.2 mmol), 4-[(3E)-4-(methoxymethoxy)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,3-dien-2-yl]-1-(oxan-2-yl)pyrazole (B90; 801 mg, 1.98 mmol) in dioxane (20 mL) was stirred for 2 h at 80 °C in a 40-mL sealed tube under an atmosphere of nitrogen. The mixture was then filtered and extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with sat. NaCl (20 mL), and the mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/hexane (3:10), to afford tert-butyl (1R,3S,5S)-3-[[6-(methoxycarbonyl)-5-[2-(methoxymethoxy)-4-[1-(oxan-2-yl)pyrazol-4-yl]phenyl]pyridin-2-yl](methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B91; 1 g) as an oil. **LCMS** (ES, *m/z*): 663 $[M+H]^+$.

Synthesis of Intermediate B92



A mixture of tert-butyl (1R,3S,5S)-3-[[6-(methoxycarbonyl)-5-[2-(methoxymethoxy)-4-[1-(oxan-2-yl)pyrazol-4-yl]phenyl]pyridin-2-yl](methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B91; 1 g, 1.51 mmol), DIBAL-H (6 mL, 6 mmol), and toluene (20 mL) was stirred for 5 h, initially at a temperature of -40 °C that was gradually warmed to room temperature. The reaction mixture was then cooled to 0 °C and quenched with water (0.3 mL) and stirred for 30 min. A 15% solution of aqueous sodium hydroxide (0.3 mL) was then added and the mixture was stirred for 30 min. Next, water (0.1 mL) was added, and the mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with sat. NaCl (50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum, to afford tert-butyl (1R,3S,5S)-3-[[6-(hydroxymethyl)-5-[2-(methoxymethoxy)-4-[1-(oxan-2-yl)pyrazol-4-yl] phenyl]pyridin-2-yl](methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B92; 0.8 g) as a solid. **LCMS** (ES, *m/z*): 634 $[M+H]^+$.

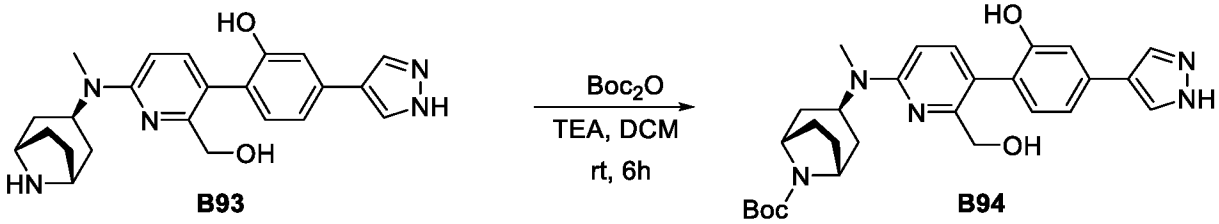
Synthesis of Intermediate B93



B92 **B93**

A mixture of tert-butyl (1R,3S,5S)-3-[[6-(hydroxymethyl)-5-[2-(methoxymethoxy)-4-[1-(oxan-2-yl)pyrazol-4-yl]phenyl]pyridin-2-yl](methyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B92; 700 mg, 1.1 mmol) and HCl in dioxane (2M, 10 mL) was stirred for 2 h at room temperature, then concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (2:5), to afford 2-[6-[(1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl(methyl)amino]-2-(hydroxymethyl)pyridin-3-yl]-5-(1H-pyrazol-4-yl)phenol (B93; 400 mg) as a solid. **LCMS** (ES, *m/z*): 406 $[M+H]^+$.

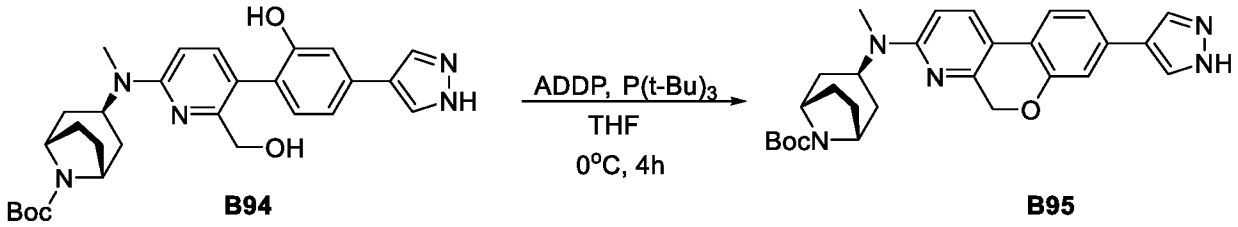
Synthesis of Intermediate B94



B93 **B94**

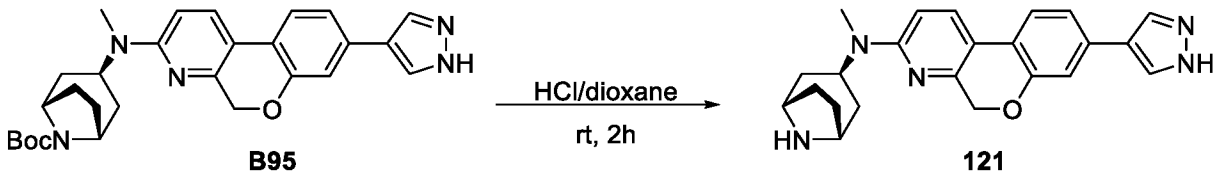
A mixture of 2-[6-[(1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl(methyl)amino]-2-(hydroxymethyl)pyridin-3-yl]-5-(1H-pyrazol-4-yl)phenol (B93; 400 mg, 0.99 mmol), di-tert-butyl dicarbonate (215 mg, 0.99 mmol), and trifluoroacetic acid (337 mg, 2.96 mmol) in dichloromethane (10 mL) was stirred for 6 h at room temperature. The resulting solution was extracted with ethyl acetate (3x10 mL) and the combined organic layers were washed with sat. NaCl (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum, to afford tert-butyl (1R,3S,5S)-3-([5-[2-hydroxy-4-(1H-pyrazol-4-yl)phenyl]-6-(hydroxymethyl)pyridin-2-yl](methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (B94; 380 mg) as a solid. **LCMS** (ES, *m/z*): 506 $[M+H]^+$.

Synthesis of Intermediate B95



A mixture of tert-butyl(1R,3S,5S)-3-([5-[2-hydroxy-4-(1H-pyrazol-4-yl)phenyl]-6-(hydroxymethyl)pyridin -2-yl](methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (B94; 380 mg, 0.75 mmol), $P(t\text{-}Bu)_3$ (760 mg, 3.76 mmol), and 1,1'-(azodicarbonyl)dipiperidine (941 mg, 3.76 mmol) in tetrahydrofuran (30 mL) was stirred for 4 h at 0 °C under an atmosphere of nitrogen. The resulting solution was extracted with ethyl acetate (3 x 15 mL), and the combined organic layers were washed with sat. NaCl (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum, to afford tert-butyl (1R,3S,5S)-3-[methyl[8-(1H-pyrazol-4-yl)-5H-chromeno[3,4-b]pyridin-3-yl] amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B95; 170 mg) as a solid. **LCMS** (ES, *m/z*): 488 $[M+H]^+$.

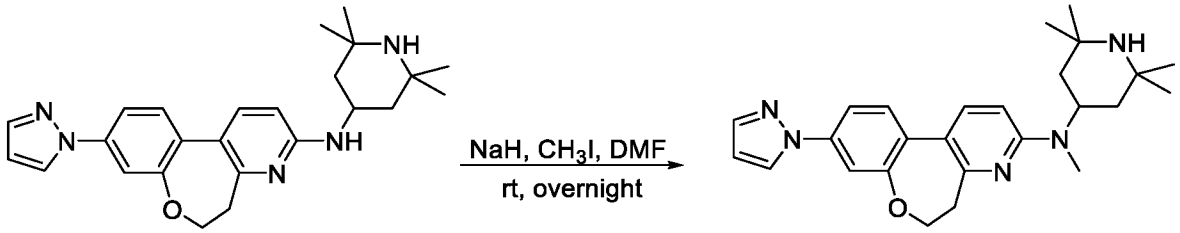
Synthesis of Compound 121



A mixture of tert-butyl (1R,3S,5S)-3-[methyl[8-(1H-pyrazol-4-yl)-5H-chromeno[3,4-b]pyridin-3-yl]amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (B95; 70 mg, 0.14 mmol) and HCl in dioxane (10 mL) was stirred for 2 h at room temperature, then concentrated. The residue was

dissolved in methanol (2 mL) and filtered. The crude product was purified by preparative HPLC (Condition 1; Gradient 3), to afford (1R,3S,5S)-N-methyl-N-[8-(1H-pyrazol-4-yl)-5H-chromeno[3,4-b] pyridin-3-yl]-8-azabicyclo[3.2.1]octan-3-amine (Compound 121; 15 mg) as a solid. **LCMS** (ES, *m/z*): 388 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$, *ppm*) δ 12.93 (s, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.27 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.19 (d, *J* = 1.7 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 5.01 (s, 2H), 3.50 (d, *J* = 12.3 Hz, 4H), 2.86 (d, *J* = 12.6 Hz, 4H), 1.74 (s, 9H), 1.49 (s, 3H).

Example 22: Synthesis of Compound 129

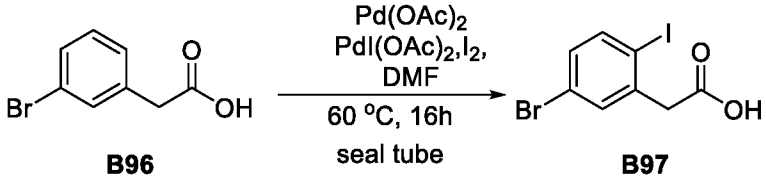


137 **129**

Sodium hydride (1.7 mg, 0.072 mmol) was added to a solution of 13-(pyrazol-1-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (Compound 137 from Example 19; 15 mg, 0.036 mmol) in dimethylformamide (1 mL), and the mixture was stirred for 30 min at 0 °C. Methyl iodide (10.2 mg, 0.072 mmol) was then added, and the resulting mixture was stirred overnight at room temperature. The reaction was quenched with methanol (1 mL) at 0 °C, and purified by preparative HPLC (Condition 2, Gradient 5), to afford N-methyl-13-(pyrazol-1-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (Compound 129; 4.9 mg) as a solid. **LCMS** (ES, m/z): 432 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d$_4$) δ 8.26 (dd, *J* = 2.5, 0.6 Hz, 1H), 7.75 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.53 – 7.46 (m, 2H), 6.58 – 6.54 (m, 2H), 4.69 (t, *J* = 6.3 Hz, 2H), 4.29 – 4.19 (m, 1H), 2.90 (t, *J* = 6.3 Hz, 2H), 2.41 (s, 3H), 2.12 – 1.95 (m, 2H), 1.52 – 1.40 (m, 2H), 1.36 – 1.15 (m, 12H).

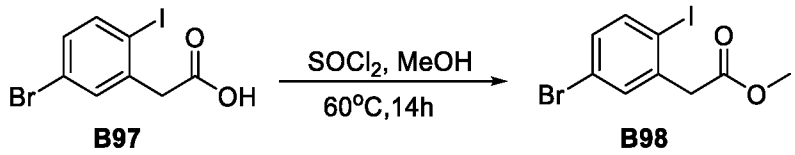
Example 23: Synthesis of Compound 138

Synthesis of Intermediate B97



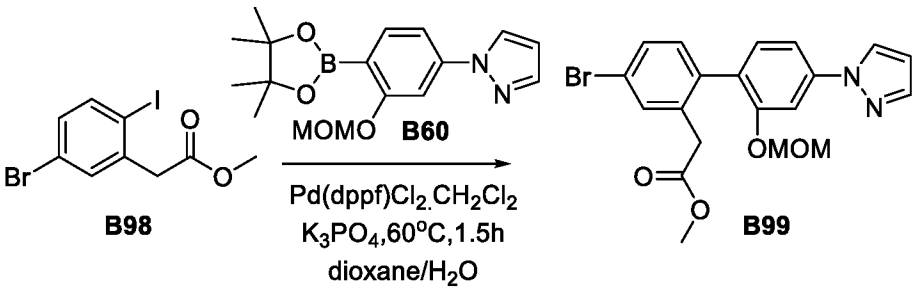
A mixture of meta-bromophenylacetic acid (B96; 10 g, 46.5 mmol), (diacetoxyiodo)benzene (11.2 g, 34.9 mmol), iodine (8.85 g, 34.9 mmol), and $Pd(OAc)_2$ (1.04 g, 4.65 mmol) in dimethylformamide (120 mL) was stirred for 16 h at 60 °C in a 250-mL sealed tube. The reaction was then quenched with water (150 mL), and the resulting solution was extracted with ethyl acetate (3x150 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluting with ethyl acetate/hexane (1:3), to afford (5-bromo-2-iodophenyl) acetic acid (B97; 10.7 g) as a solid. **LCMS** (ES, *m/z*): 341 $[M+H]^+$.

Synthesis of Intermediate B98



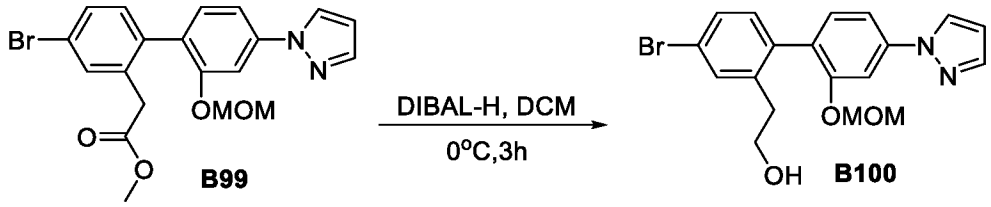
A mixture of (5-bromo-2-iodophenyl) acetic acid (B97; 10.7 g, 31.3 mmol) in methanol (150 mL) was treated with thionyl chloride (7.47 g, 62. 8 mmol) at 0 °C, and the resulting solution was then stirred for 14 h at 60 °C. The reaction was quenched with water (200 mL) and extracted with ethyl acetate (3x200 mL). The combined organic layers were then dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting mixture was washed with petroleum ether (2 x30 mL), and filtered, to afford methyl 2-(5-bromo-2-iodophenyl) acetate (B98; 6.4 g) as a solid. **LCMS** (ES, *m/z*): 355 $[M+H]^+$.

Synthesis of Intermediate B99



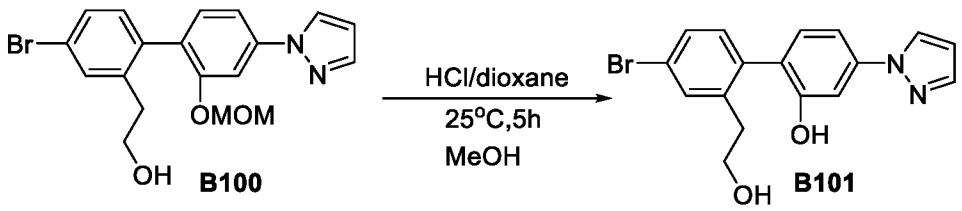
A mixture of methyl 2-(5-bromo-2-iodophenyl) acetate (B98; 500 mg, 5.63 mmol), 1-[3-(methoxymethoxy)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl] pyrazole (B60; 2.23 g, 6.76 mmol), K_3PO_4 (3.59 g, 16.9 mmol), and $Pd(dppf)Cl_2.CH_2Cl_2$ (0.23 g, 0.28 mmol), in dioxane/H_2O (4:1; 50 mL) was irradiated with microwave for 1.5 h at 60 °C. The resulting solution was then extracted with ethyl acetate (3x50 mL) and the combined organic layers were 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 (1:3), to afford methyl 2-[4-bromo-2'-(methoxymethoxy)-4'-(pyrazol-1-yl)-[1,1'-biphenyl]-2-yl] acetate (B99; 900 mg) as an oil. LCMS (ES, *m/z*): 431 $[M+H]^+$.

Synthesis of Intermediate B100



DIBAL-H (4 mL, 19.7 mmol) was added to a mixture of methyl 2-[4-bromo-2'-(methoxymethoxy)-4'-(pyrazol-1-yl)-[1,1'-biphenyl]-2-yl] acetate (B99; 850 mg, 1.97 mmol) in dichloromethane (35 mL) at -40 °C under an atmosphere of nitrogen, and the resulting solution was stirred for 3 h at 0 °C. The reaction was then quenched by the addition of water (30 mL), filtered, and extracted with dichloromethane (3x35 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum, to afford 2-[4-bromo-2'-(methoxymethoxy)-4'-(pyrazol-1-yl)-[1,1'-biphenyl]-2-yl] ethanol (B100; 830 mg) as an oil. **LCMS** (ES, *m/z*): 403 $[M+H]^+$.

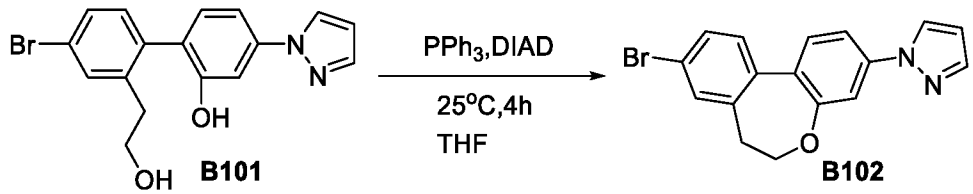
Synthesis of Intermediate B101



A mixture of 2-[4-bromo-2 (B100; 870 mg, 2.16 mmol), methanol (10 mL), and HCl in 1,4-dioxane (3 mL) was stirred for 5 h at 25 °C under an atmosphere of nitrogen. The resulting mixture was concentrated under vacuum, and the residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:5), to afford 4'-bromo-2'-(2-

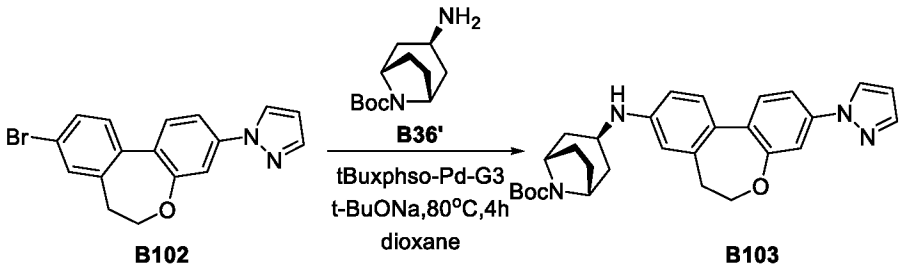
hydroxyethyl)-4-(pyrazol-1-yl)-[1,1'-biphenyl]-2-ol (B101; 310 mg) as a solid. **LCMS** (ES, *m/z*): 359 $[M+H]^+$.

Synthesis of Intermediate B102



A mixture of 4'-bromo-2'-(2-hydroxyethyl)-4-(pyrazol-1-yl)-[1,1'-biphenyl]-2-ol (B101; 250 mg, 0.7 mmol) and triphenylphosphine (365 mg, 1.4 mmol) in tetrahydrofuran (15 mL) was treated with diisopropylazodicarboxylate (281 mg, 1.39 mmol) at 0 °C, and the resulting solution was stirred for 4 h at 25 °C under an atmosphere of nitrogen. The reaction was then quenched ice water (30 mL), and extracted with dichloromethane (3x30 mL). The combined organic layers were 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 (1:5), to afford 1- [13-bromo-8-oxatricyclo [9.4.0.0^ [2,7]] pentadeca-1(15),2(7),3,5,11,13-hexaen-5-yl] pyrazole (B102; 150 mg) as a solid. **LCMS** (ES, *m/z*): 341 $[M+H]^+$.

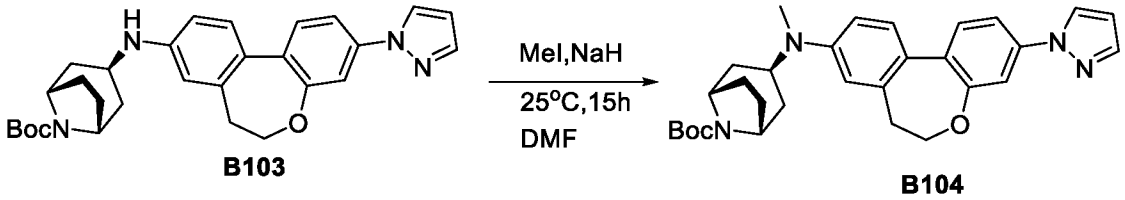
Synthesis of Intermediate B103



A mixture of 1-[13-bromo-8-oxatricyclo[9.4.0.0^[2,7]]pentadeca-1(15),2(7),3,5,11,13-hexaen-5-yl]pyrazole (B102; 140 mg, 0.41 mmol), tert-butyl (1R,3S,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (B36'; 186 mg), sodium tert-butoxide (79 mg, 0.82 mmol), and t-BuXPhos Phos palladium(II) biphenyl-2-amine mesylate (16.3 mg, 0.021 mmol) in dioxane (5 mL) was stirred for 4 h at 80 °C under an atmosphere of nitrogen. The reaction was then quenched with 15 mL of water, and extracted with ethyl acetate (3x15 mL). The combined organic layers were 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 (1:2), to afford tert-butyl (1R,3S,5S)-3-[[5-(pyrazol-1-yl)-8-

oxatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-13-yl]amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (B103; 145 mg) as a solid. **LCMS** (ES, *m/z*): 487 $[M+H]^+$.

Synthesis of Intermediate B104



A mixture of tert-butyl(1R,3S,5S)-3-[[5-(pyrazol-1-yl)-8-oxatricyclo[9.4.0.0^[2,7]] pentadeca-1(11),2(7),3,5,12,14-hexaen-13-yl] amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (B103; 100 mg, 0.21 mmol) in dimethylformamide (5 mL) was treated with sodium hydride (24.7 mg, 1.03 mmol) at 0 °C, and the resulting solution was stirred for 0.5 h under an atmosphere of nitrogen. Methyl iodide (292 mg, 2.06 mmol) was then added over 1 min, and the resulting solution was stirred for 12 h at 25 °C. The reaction was quenched by the addition of 15 mL of water/ice, and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum, to afford tert-butyl (1R,3S,5S)-3-[methyl[5-(pyrazol-1-yl)-8-oxatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-13-yl]amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (B104; 100 mg) as an oil. LCMS (ES, *m/z*): 501 $[M+H]^+$.

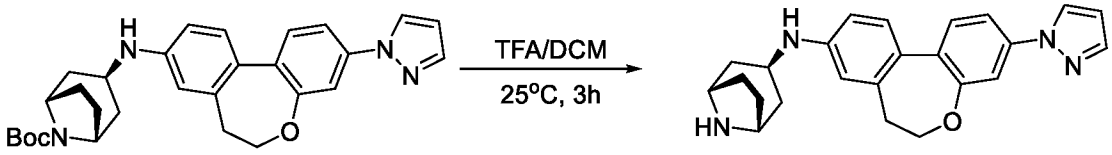
Synthesis of Compound 138



A mixture of tert-butyl(1R,3S,5S)-3-[methyl[5-(pyrazol-1-yl)-8-oxatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7), 3,5,12,14-hexaen-13-yl] amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (B104; 90 mg, 0.18 mmol) and trifluoroacetic acid (1 mL) in dichloromethane (3 mL) was stirred for 3 h at 25 °C, then concentrated under vacuum. The residue was dissolved in methanol (3 mL) and purified by preparative HPLC (Condition 2, Gradient 6), to afford (1R,3S,5S)-N-methyl-N-[5-(pyrazol-1-yl)-8-oxatricyclo[9.4.0.0^[2,7]] pentadeca-1(11),2(7), 3,5,12,14-hexaen-13-yl]-8-azabicyclo [3.2.1] octan-3-amine (Compound 138; 26.4 mg) as a solid. **LCMS** (ES, *m/z*): 401 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ

8.53 (d, *J* = 2.5 Hz, 1H), 7.75 (d, *J* = 1.7 Hz, 1H), 7.68 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 6.84 – 6.75 (m, 2H), 6.58 – 6.52 (m, 1H), 4.53 (t, *J* = 6.2 Hz, 2H), 4.08 (tt, *J* = 11.1, 5.3 Hz, 1H), 3.50 (s, 2H), 2.76 (d, *J* = 5.8 Hz, 5H), 1.81 – 1.69 (m, 6H), 1.54 (dt, *J* = 12.9, 4.0 Hz, 2H).

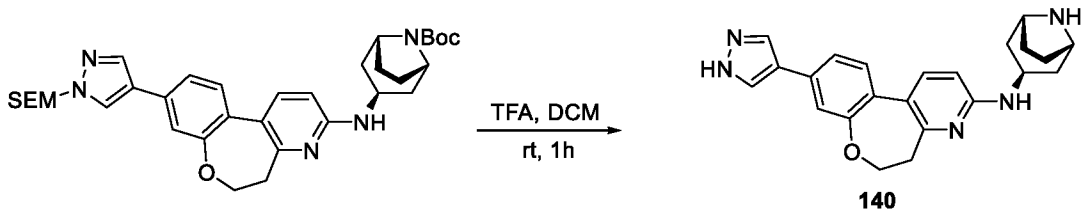
Example 24: Synthesis of Compound 139



B103 **139**

A mixture of tert-butyl (1R,3S,5S)-3-[[5-(pyrazol-1-yl)-8-oxatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen -13-yl]amino]-8-azabicyclo [3.2.1] octane-8-carboxylate (B103 from Example 25; 50 mg, 0.1 mmol) and trifluoroacetic acid (1 mL) in dichloromethane (3 mL) was stirred for 3 h at 25 °C. The resulting mixture was concentrated under vacuum, and the residue was dissolved in methanol (3 mL) and purified by preparative HPLC (Condition 2, Gradient 6) to afford (1R,3S,5S)-N-[5-(pyrazol-1-yl)-8-oxatricyclo [9.4.0.0^ [2,7]] pentadeca-1(11),2(7),3,5,12,14-hexaen-13-yl]-8-azabicyclo [3.2.1] octan-3-amine (Compound 139; 13.1 mg) as a solid. **LCMS** (ES, *m/z*): 387 $[M+H]^+$. **^{1}HNMR** (400 MHz, DMSO-d_6) δ 8.52 (d, *J* = 2.5 Hz, 1H), 7.74 (d, *J* = 1.7 Hz, 1H), 7.66 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.54 (d, *J* = 2.3 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 6.64 – 6.52 (m, 3H), 5.49 (d, *J* = 8.4 Hz, 1H), 4.51 (t, *J* = 6.2 Hz, 2H), 3.61 (s, 1H), 3.49 – 3.42 (m, 2H), 2.69 (t, *J* = 6.2 Hz, 2H), 1.96 – 1.86 (m, 2H), 1.72 (tq, *J* = 9.2, 5.4 Hz, 4H), 1.40 – 1.29 (m, 2H).

Example 25: Synthesis of Compound 140

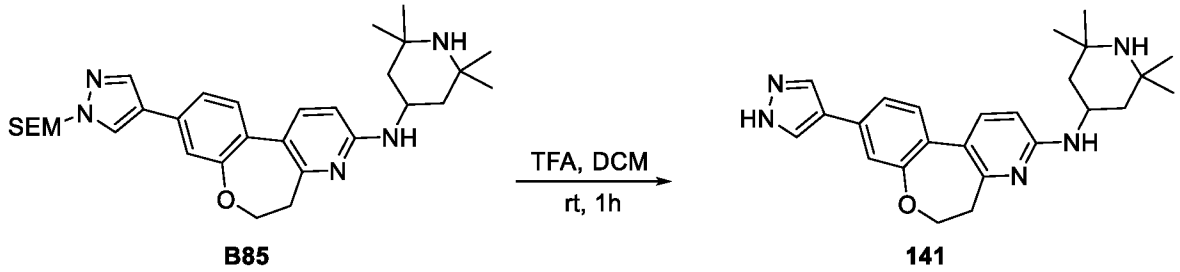


B83 **140**

A mixture of tert-butyl (1R,3S,5S)-3-[[13-(1-[[2-(trimethylsilyl)ethoxy]methyl]pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-yl]amino]-8-azabicyclo[3.2.1] octane-8-carboxylate (34 mg, 0.055 mmol) and trifluoracetic acid (1 mL) in dichloromethane (1 mL) was stirred for 1 h at room temperature. The solvent was then

evaporated and the resulting residue was purified by preparative HPLC (Condition 2, Gradient 4) to afford N-[(1R,3S,5S)-8-azabicyclo[3.2.1]octan-3-yl]-13-(1H-pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (Compound 140; 11 mg) as a solid. **LCMS** (ES, m/z): 388 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.99 (s, 2H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.45 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.37 – 7.32 (m, 2H), 6.56 (d, *J* = 8.6 Hz, 1H), 4.65 (t, *J* = 6.3 Hz, 2H), 4.32 – 4.22 (m, 1H), 3.72 (s, 2H), 2.88 (t, *J* = 6.4 Hz, 2H), 2.19 – 2.09 (m, 2H), 2.01 – 1.94 (m, 4H), 1.62 – 1.51 (m, 2H).

Example 26: Synthesis of Compound 141

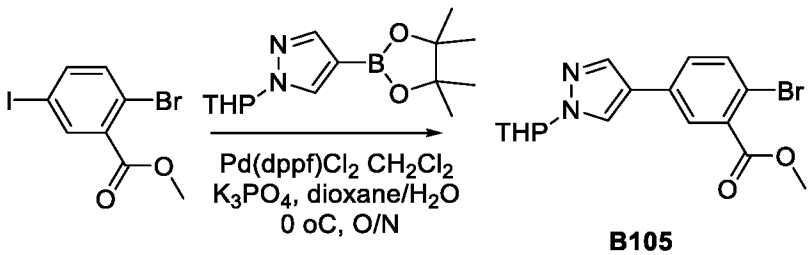


B85 **141**

A mixture of N-(2,2,6,6-tetramethylpiperidin-4-yl)-13-(1-[[2-(trimethylsilyl)ethoxy]methyl] pyrazol-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (B84 from Example 20; 10 mg, 0.018 mmol) and trifluoroacetic acid (1 mL) in dichloromethane (1 mL) was stirred for 1 h at room temperature. The solvent was then evaporated and the residue was purified by preparative HPLC (Condition 2, Gradient 4), to afford 13-(1H-pyrazol-4-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)-10-oxa-6-azatricyclo[9.4.0.0^[2,7]]pentadeca-1(11),2(7),3,5,12,14-hexaen-5-amine (Compound 141; 1.5 mg) as a solid. **LCMS** (ES, m/z): 418 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.00 (s, 2H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.46 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.38 – 7.31 (m, 2H), 6.58 (d, *J* = 8.5 Hz, 1H), 4.65 (t, *J* = 6.4 Hz, 2H), 4.47 – 4.38 (m, 1H), 2.89 (t, *J* = 6.3 Hz, 2H), 2.19 (d, *J* = 13.0 Hz, 2H), 1.52 (s, 6H), 1.38 (s, 6H), 1.36 – 1.32 (m, 2H).

Example 27: Synthesis of Compound 142

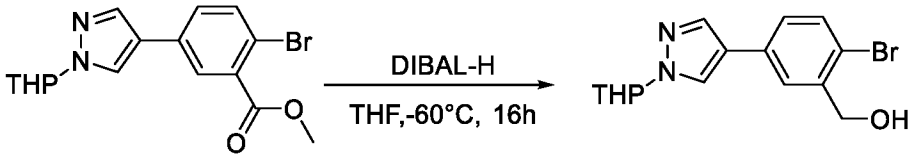
Synthesis of Intermediate B105



B105

To a solution of methyl 2-bromo-5-iodobenzoate (5.00 g, 14.665 mmol), 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (4895.14 mg, 17.598 mmol) and K_3PO_4 (7.78 g, 36.662 mmol) in dioxane (40 mL) and H_2O (10 mL) was added Pd(dppf)Cl_2 (536.53 mg, 0.733 mmol) under a N_2 atmosphere. The reaction mixture was stirred for 18 h at 0°C, diluted with EtOAc (60 mL) and water (70 mL), followed by extraction of the aqueous layer with EtOAc (2 x 60 mL). The organic layers were combined and washed with saturated brine (120 mL), dried over anhydrous sodium sulfate and concentrated to give a residue. The residue was purified by flash column chromatography (80g silica gel column, 37% EA in PE) to afford methyl 2-bromo-5-[1-(oxan-2-yl)pyrazol-4-yl]benzoate (4.2 g, 78.41%) as an oil. **LCMS** (ESI, *m/z*): 336.90 [M+H]. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$, *ppm*) δ 8.38 (s, 1H), 7.94 (s, 1H), 7.77 (d, *J* = 2.3 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.46 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.50 – 5.37 (m, 2H), 4.54 (d, *J* = 5.6 Hz, 2H), 3.95 (dq, *J* = 11.6, 3.3, 2.6 Hz, 1H), 3.65 (ddd, *J* = 11.5, 8.1, 5.8 Hz, 1H), 2.14 (tdd, *J* = 12.5, 10.2, 4.4 Hz, 1H), 1.98 – 1.89 (m, 2H), 1.70 (ddt, *J* = 17.5, 15.0, 6.2 Hz, 1H), 1.55 (tq, *J* = 7.6, 3.8 Hz, 2H).

Synthesis of Intermediate B106

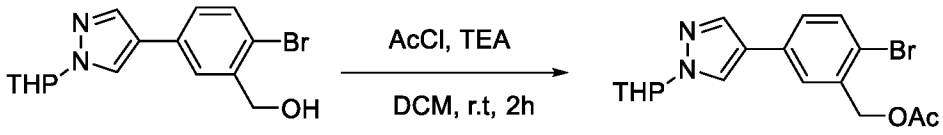


B105 **B106**

To a solution of methyl 2-bromo-5-[1-(oxan-2-yl)pyrazol-4-yl]benzoate (4.2 g, 11.5 mmol) in THF (50 mL) was added DIBAL (57.5 mL, 0.055 mmol) at -70 °C under a N_2 atmosphere. The reaction mixture was stirred at -60 °C for 16 h, then quenched with water (20 mL) at -60 °C. The resulting mixture was filtered and the filter cake washed with ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford [2-bromo-5-[1-(oxan-2-yl)pyrazol-4-yl] phenyl]methanol (3.2 g, 82.52%) as an oil. **LCMS** (ESI, *m/z*): 336.90 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$, *ppm*) δ 8.38 (s, 1H), 7.94 (s, 1H), 7.77 (d, *J* = 2.3 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.46 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.50 – 5.37 (m, 2H), 4.54 (d, *J* = 5.6 Hz, 2H), 3.95 (dq, *J* = 11.6, 3.3, 2.6 Hz, 1H), 3.65 (ddd, *J* =

11.5, 8.1, 5.8 Hz, 1H), 2.14 (tdd, *J* = 12.5, 10.2, 4.4 Hz, 1H), 1.98 – 1.89 (m, 2H), 1.70 (ddt, *J* = 17.5, 15.0, 6.2 Hz, 1H), 1.55 (tq, *J* = 7.6, 3.8 Hz, 2H).

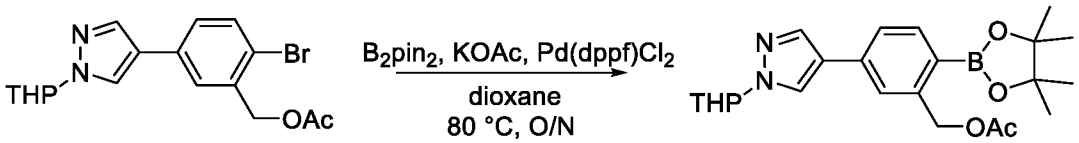
Synthesis of Intermediate B107



B106 **B107**

To a solution of [2-bromo-5-[1-(oxan-2-yl)pyrazol-4-yl]phenyl]methanol (1.00 g, 2.965 mmol) and TEA (1.03 mL, 7.412 mmol) in DCM (10 mL) was added AcCl (0.25 mL, 3.558 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2 h, then concentrated *in vacuo* to afford a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (3:1) to afford [2-bromo-5-[1-(oxan-2-yl)pyrazol-4-yl]phenyl]methyl acetate (950 mg, 84.47%) as an oil. **LCMS** (ESI, *m/z*): 378.95 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6, ppm) δ 8.44 (d, *J* = 0.8 Hz, 1H), 8.00 (d, *J* = 0.8 Hz, 1H), 7.75 (d, *J* = 2.2 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.57 (dd, *J* = 8.3, 2.2 Hz, 1H), 5.42 (dd, *J* = 10.0, 2.3 Hz, 1H), 5.12 (s, 2H), 4.00 – 3.91 (m, 1H), 3.70 – 3.61 (m, 1H), 2.13 (s, 4H), 1.99 – 1.88 (m, 2H), 1.76 – 1.63 (m, 1H), 1.56 (dq, *J* = 10.5, 6.5, 5.0 Hz, 2H).

Synthesis of Intermediate B108

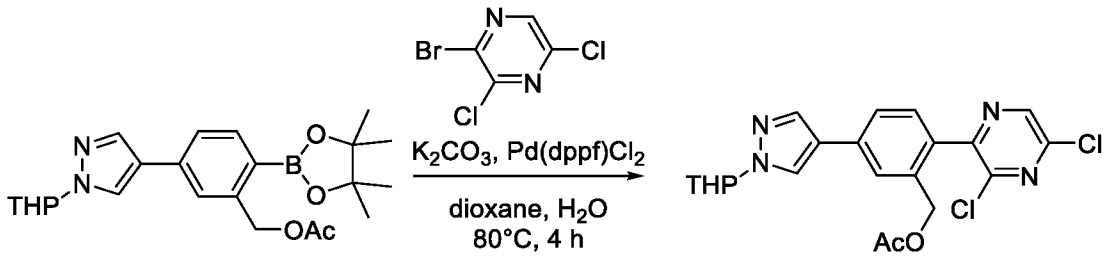


B107 **B108**

To a mixture of [2-bromo-5-[1-(oxan-2-yl)pyrazol-4-yl]phenyl]methyl acetate (950 mg, 2.505 mmol), bis(pinacolato)diboron (1.272 g, 5.010 mmol, 2.00 equiv), and KOAc (737.52 mg, 7.515 mmol) in dioxane (10 mL) was added $Pd(dppf)Cl_2$ (183.28 mg, 0.250 mmol). After stirring for overnight at 100°C under a nitrogen atmosphere, the reaction mixture was concentrated *in vacuo* and partitioned between ethyl acetate (20 mL) and water (15 mL). The aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with saturated brine (45 mL), dried over anhydrous sodium sulfate and concentrated to give [5-[1-

(oxan-2-yl)pyrazol-4-yl]-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl acetate (2 g) as an oil. **LCMS** (ESI, *m/z*): 427.05 $[M+H]^+$.

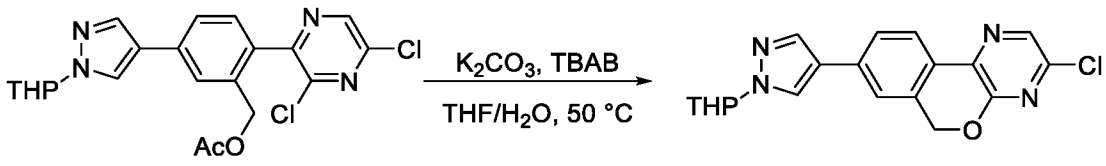
Synthesis of Intermediate B109



B108 **B109**

To a solution of 2-bromo-3,5-dichloropyrazine (1.00 g, 4.388 mmol), [5-[1-(oxan-2-yl)pyrazol-4-yl]-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl acetate (1.87 g, 4.388 mmol), and K_2CO_3 (1.82 g, 13.165 mmol) in dioxane (16 mL) and H_2O (4 mL) was added $Pd(dppf)Cl_2$ (160.55 mg, 0.219 mmol). The reaction mixture was stirred at 80 °C for 4 h, then partitioned between ethyl acetate (30 mL) and water (45 mL). The aqueous layer was extracted with ethyl acetate (2 x 30 mL). The organic layers were combined and washed with saturated brine (80mL), dried over anhydrous sodium sulfate, and concentrated to give a residue. The residue was purified by flash column chromatography (40g silica gel column, 35% EA in PE) to afford [2-(3,5-dichloropyrazin-2-yl)-5-[1-(oxan-2-yl)pyrazol-4-yl]phenyl]methyl acetate (990 mg, 50.43%) as oil. **LCMS** (ESI, *m/z*): 447.00 $[M+H]^+$.

Synthesis of Intermediate B110

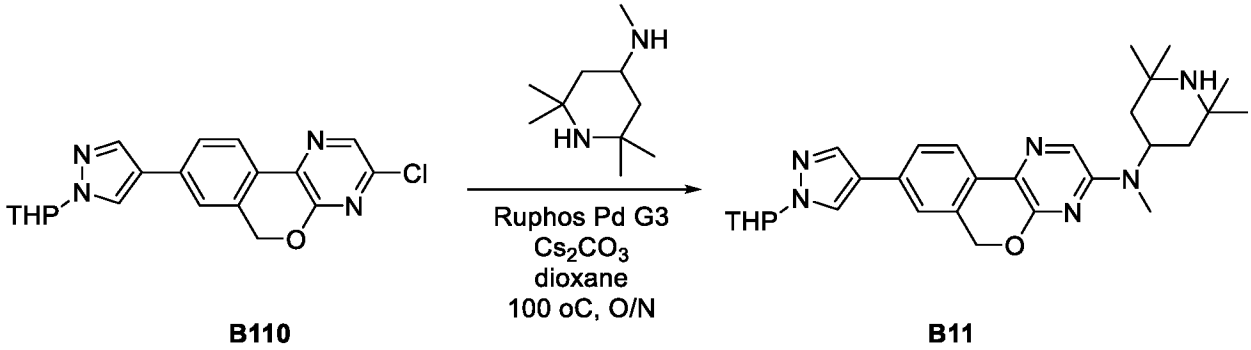


B109 **B110**

To a solution of [2-(3,5-dichloropyrazin-2-yl)-5-[1-(oxan-2-yl)pyrazol-4-yl]phenyl]methyl acetate (750 mg, 1.677 mmol) in THF (20 mL) and H_2O (20 mL) was added K_2CO_3 (2250.03 mg, 16.280 mmol) and TBAB (54.05 mg, 0.168 mmol). The reaction mixture was stirred at 50 °C for 3 days, then partitioned between ethyl acetate (25 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (2x25 mL). The organic layers were combined and washed

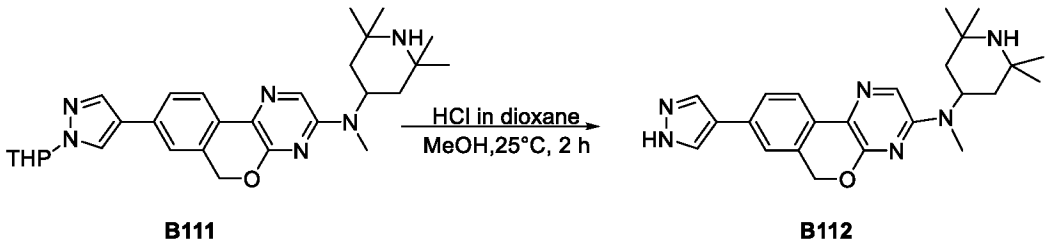
with brine (40 mL), dried with Na_2SO_4, and concentrated *in vacuo* to afford 4-[3-chloro-6H-isochromeno[3,4-b]pyrazin-8-yl]-1-(oxan-2-yl)pyrazole (400 mg, 64.68%) as a brown solid. **LCMS** (ESI, *m/z*): 369.00 $[M+H]^+$.

Synthesis of Intermediate B111



To a solution of 4-[3-chloro-6H-isochromeno[3,4-b]pyrazin-8-yl]-1-(oxan-2-yl)pyrazole (100 mg, 0.271 mmol), N,2,2,6,6-pentamethylpiperidin-4-amine (92.35 mg, 0.542 mmol), and Cs_2CO_3 (265.02 mg, 0.813 mmol) in dioxane (1 mL) was added RuPhos Palladacycle Gen.3 (22.68 mg, 0.027 mmol) under a N_2 atmosphere. The reaction mixture was stirred at 100 °C for 16 h, then partitioned between ethyl acetate (5 mL) and water (5 mL). The aqueous layer was extracted with ethyl acetate (2x5 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo to give crude product. The crude product was purified by Prep-TLC (PE/EA=1:1) to afford N,2,2,6,6-pentamethyl-N- [8-[1-(oxan-2-yl)pyrazol-4-yl]-6H-isochromeno [3,4-b]pyrazin-3-yl]piperidin-4-amine (20 mg, 14.67%) as a solid. **LCMS** (ESI, *m/z*):503.15 $[M+H]^+$.

Synthesis of Intermediate B112

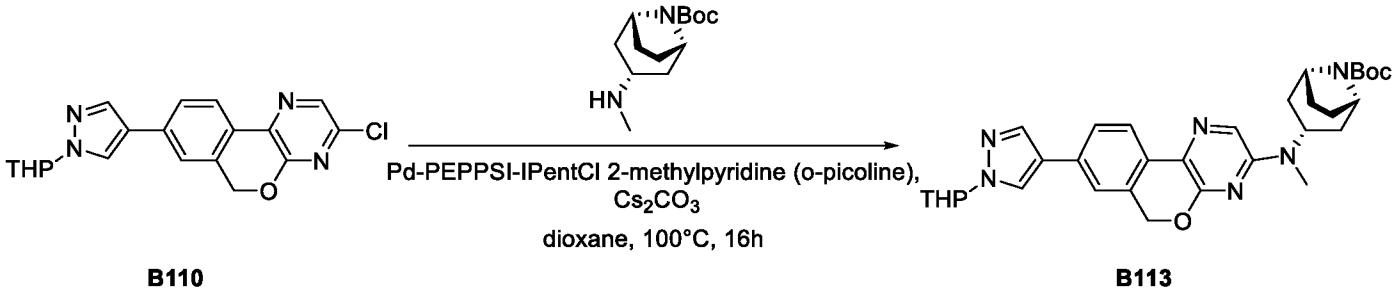


To a solution of N,2,2,6,6-pentamethyl-N-[8-[1-(oxan-2-yl)pyrazol-4-yl]-6H-isochromeno[3,4-b] pyrazin-3-yl]piperidin-4-amine (20 mg, 0.040 mmol) in methanol (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL). The reaction mixture was stirred at 25 °C for 2 h, then concentrated *in vacuo* to afford a residue. The residue was purified by Prep-HPLC (Condition 2, Gradient 7) to afford N,2,2,6,6-pentamethyl-N-[8-(1H-pyrazol-4-yl) -6H-isochromeno[3,4-b]pyrazin-3-yl]piperidin-4-

amine (6.9 mg, 41.43%) as a solid. **LCMS** (ESI, *m/z*): 419.15[M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$, *ppm*) δ 12.97 (s, 1H), 8.19-7.95 (m, 2H), 7.86 – 7.78 (m, 2H), 7.63 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.49 (d, *J* = 1.7 Hz, 1H), 5.39 (s, 2H), 4.84 (s, 1H), 2.91 (s, 3H), 1.49 (t, *J* = 6.6 Hz, 2H), 1.42 (t, *J* = 12.1 Hz, 2H), 1.26 (s, 6H), 1.11 (s, 6H).

Example 28: Synthesis of Compound 144

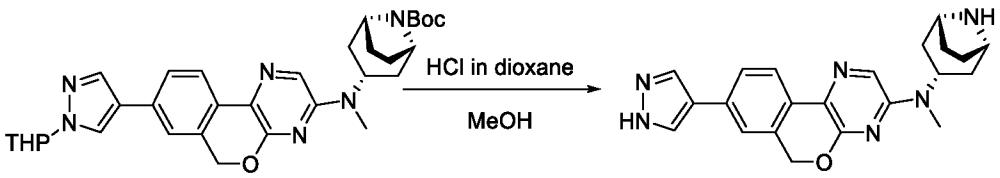
Synthesis of Intermediate B113



B110 **B113**

To a solution of 4-[3-chloro-6H-isochromeno[3,4-b]pyrazin-8-yl]-1-(oxan-2-yl)pyrazole (100 mg, 0.271 mmol), tert-butyl(exo)-3-(methylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate (130.33 mg, 0.542 mmol), and Cs_2CO_3 (265.02 mg, 0.813 mmol) in dioxane (1 mL) was added Pd-PEPPSI-IPentCl 2-methylpyridine(o-picoline) (22.81 mg, 0.027 mmol). The reaction mixture was stirred at 100 °C for 16 h under a N_2 atmosphere, then partitioned between ethyl acetate (10 ml) and water (10 ml). The aqueous layer was extracted with ethyl acetate (2x10 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, evaporated under reduced pressure, and the residue was purified by Prep-TLC(PE/EA=1:1) to afford tert-butyl (exo)-3-[methyl([8-[1-(oxan-2-yl)pyrazol-4-yl]-6H-isochromeno[3,4-b]pyrazin-3-yl])amino]-8-azabicyclo[3.2.1]octane-8-carboxylate(40 mg, 25.76%) as a solid. **LCMS** (ESI, m/z): 573.20[M+H]$^+$.

Synthesis of Compound 144



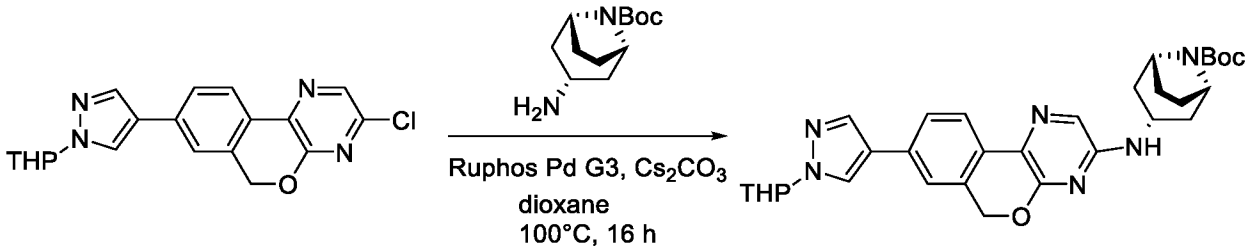
B113 **144**

To a solution of tert-butyl (exo)-3-[methyl([8-[1-(oxan-2-yl)pyrazol-4-yl]-6H-isochromeno [3,4-b]pyrazin-3-yl])amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (35 mg, 0.061 mmol) in methanol (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL). The reaction mixture was stirred at

25 °C for 2 h. The crude product was purified by Prep-HPLC (Condition 2, Gradient 8) to afford (exo)-N-methyl-N-[8-(1H-pyrazol-4-yl)-6H-isochromeno[3,4-b]pyrazin-3-yl] -8-azabicyclo[3.2.1]octan-3-amine (6.2 mg, 24.23%) as a solid. **LCMS** (ESI, *m/z*): 389.10 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.07 (s, 2H), 7.84 -7.77 (m, 2H), 7.62 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.49 (d, *J* = 1.7 Hz, 1H), 5.39 (s, 2H), 4.78 (dt, *J* = 12.2, 6.2 Hz, 1H), 3.51 (s, 2H), 2.89 (s, 3H), 1.74 (td, *J* = 15.1, 10.0 Hz, 6H), 1.48 (d, *J* = 10.2 Hz, 2H).

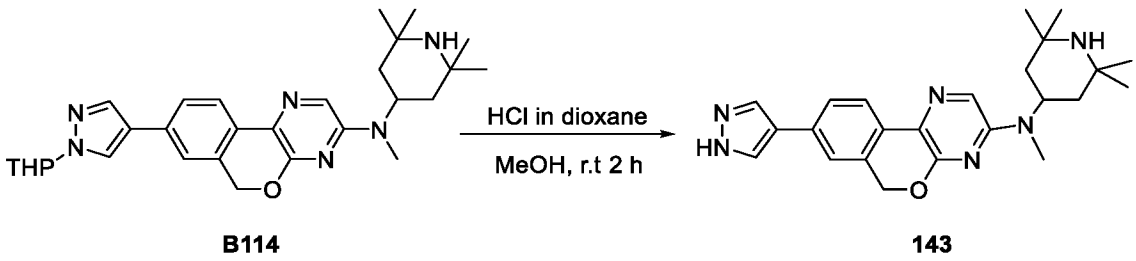
Example 29: Synthesis of Compound 143

Synthesis of Intermediate B114



To a solution of 4-[3-chloro-6H-isochromeno[3,4-b]pyrazin-8-yl]-1-(oxan-2-yl)pyrazole (100 mg, 0.271 mmol), tert-butyl (exo)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (122.73 mg, 0.542 mmol), and Cs_2CO_3 (265.02 mg, 0.813 mmol) in dioxane (1 mL) was added RuPhos Palladacycle Gen.3 (22.68 mg, 0.027 mmol). The reaction mixture was stirred at 100 °C for 16 h under a N_2 atmosphere, then partitioned between ethyl acetate (10 ml) and water (10 ml). The aqueous layer was extracted with ethyl acetate (2x10 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, evaporated under reduced pressure, and the residue was purified by Prep-TLC(PE/EA=1:1) to afford tert-butyl (exo)-3-([8-[1-(oxan-2-yl) pyrazol-4-yl]-6H-isochromeno[3,4-b] pyrazin-3-yl]amino)-8-azabicyclo[3.2.1]octane-8-carboxylate(40 mg, 26.41%) as a solid. **LCMS** (ESI, *m/z*): 559.25 $[M+H]^+$.

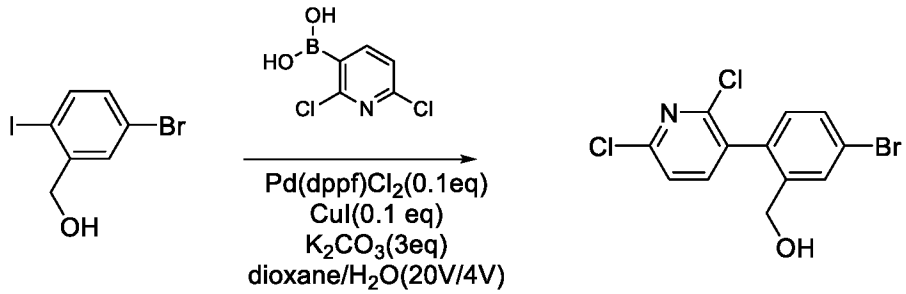
Synthesis of Compound 143



To a solution of tert-butyl (exo)-3-([8-[1-(oxan-2-yl)pyrazol-4-yl]-6H-isochromeno[3,4-b]pyrazin-3-yl] amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (35 mg, 0.063 mmol) in methanol (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL). The reaction mixture was stirred at 25 °C for 2 h, then concentrated *in vacuo* to a residue. The residue was purified by Prep-HPLC (Condition 2, Gradient 9) to afford (exo)-N-[8-(1H-pyrazol-4-yl)-6H-isochromeno[3,4-b]pyrazin-3-yl] -8-azabicyclo[3.2.1]octan-3-amine (4.7 mg, 19.12%) as a solid. **LCMS** (ESI, *m/z*): 375.00 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.96 (s, 1H), 8.06 (s, 2H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.63 (s, 1H), 7.60 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.47 (d, *J* = 1.7 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 5.34 (s, 2H), 4.05 (s, 1H), 3.60 (s, 2H), 1.90 (d, *J* = 12.0 Hz, 2H), 1.81–1.70 (m, 4H), 1.47 (t, *J* = 11.9 Hz, 2H).

Example 30: Synthesis of Compound 147

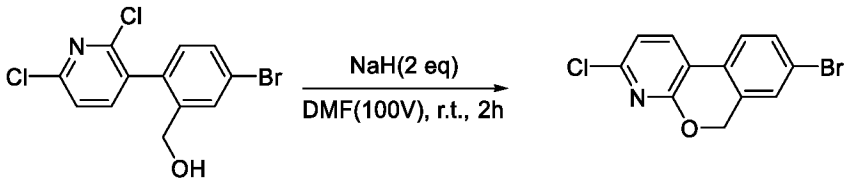
Synthesis of Intermediate B115



B115

To a solution of (5-bromo-2-iodophenyl)methanol (1 g, 3.196 mmol), 2,6-dichloropyridin-3-ylboronic acid (1.23 g, 6.391 mmol), and K_2CO_3 (1.32 g, 9.587 mmol) in dioxane (8 mL) and H_2O (2 mL) was added CuI (60.86 mg, 0.320 mmol) and $Pd(dppf)Cl_2$ (233.82 mg, 0.320 mmol). The reaction mixture was stirred at 60 °C for 16 h, then partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined and washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated to give a residue. The residue was purified by flash column chromatography (40g silica gel column) to afford [5-bromo-2-(2,6-dichloropyridin-3-yl)phenyl]methanol (780 mg, 73.30%) as a solid. **LCMS** (ESI, *m/z*):331.75$[M+H]^+$.

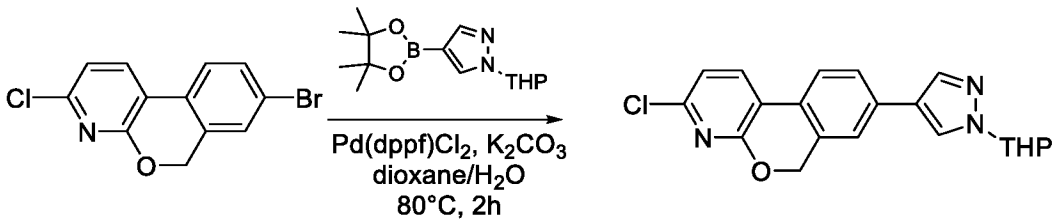
Synthesis of Intermediate B116



B115 **B116**

To a solution of [5-bromo-2-(2,6-dichloropyridin-3-yl)phenyl]methanol (700 mg, 2.102 mmol) in DMF (70 mL, 904.523 mmol) was added NaH (168.15 mg, 4.204 mmol, 60%) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, then partitioned between ethyl acetate (100 mL) and water (100 mL) at 0°C. The aqueous layer was extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with brine (200 mL), dried with Na_2SO_4, evaporated under reduced pressure to give a residue. The residue was purified by flash column chromatography (40g silica gel column, 30% EA in PE) to afford 8-bromo-3-chloro-6H-isochromeno[3,4-b]pyridine (440 mg, 70.59%) as a solid. **LCMS** (ESI, *m/z*):295.8[M+H]$^+$.

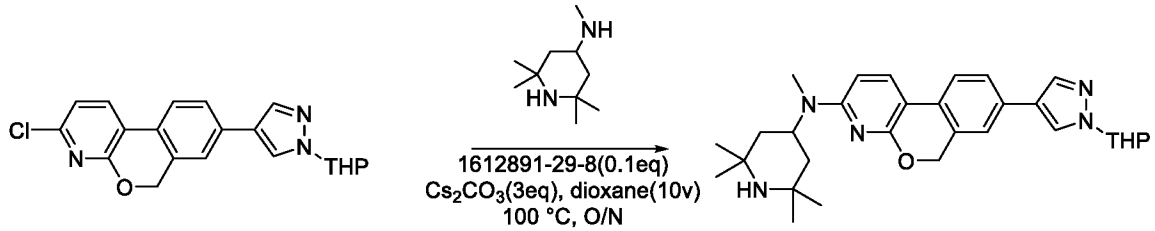
Synthesis of Intermediate B117



B116 **B117**

To a solution of 8-bromo-3-chloro-6H-isochromeno[3,4-b]pyridine (200 mg, 0.674 mmol) and 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (225.12 mg) in dioxane (1.6 mL) and H_2O (0.4 mL) was added Pd(dppf)Cl_2 (49.35 mg, 0.067 mmol). The reaction mixture was stirred at 80 °C for 2 h, then partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL). The organic layers were combined and washed with saturated brine (20 mL), dried over anhydrous sodium sulfate, and concentrated to give a residue. The residue was purified by flash column chromatography (40g silica gel column, 30% EA in PE) to afford 4-[3-chloro-6H-isochromeno[3,4-b]pyridin-8-yl]-1-(oxan-2-yl)pyrazole (160 mg, 64.50%) as a solid. **LCMS** (ESI, *m/z*): 368.10[M+H]$^+$.

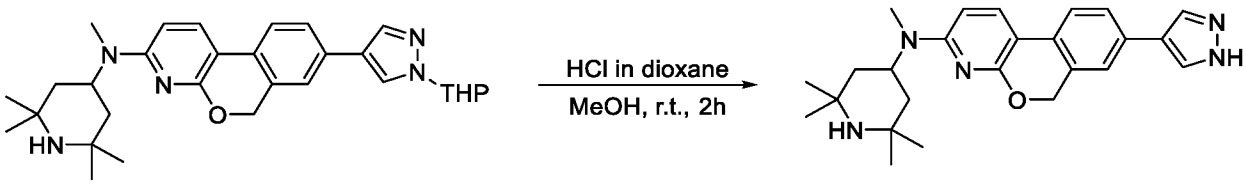
Synthesis of Intermediate B118



B117 B118

To a solution of 4-[3-chloro-6H-isochromeno[3,4-b]pyridin-8-yl]-1-(oxan-2-yl)pyrazole (140 mg, 0.381 mmol), N,2,2,6,6-pentamethylpiperidin-4-amine (129.64 mg, 0.761 mmol), and Cs_2CO_3 (372.03 mg, 1.142 mmol) in dioxane (2 mL) was added Pd-PEPPSI-IPentCl 2-methylpyridine (o-picoline) (31.98 mg, 0.038 mmol). The reaction mixture was stirred at 100 °C for 16 h, then partitioned between ethyl acetate (10 ml) and water (10 ml). The aqueous layer was washed with EtOAc (2x10 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, evaporated under reduced pressure, and the residue was purified by Prep-TLC(PE/EA=1:1) to afford N,2,2,6,6-pentamethyl-N-[8-[1-(oxan-2-yl)pyrazol-4-yl]-6H -isochromeno[3,4-b]pyridin-3-yl]piperidin-4-amine (55 mg, 28.8%) as a solid. **LCMS** (ESI, *m/z*):502.35 $[M+H]^+$.

Synthesis of Compound 147

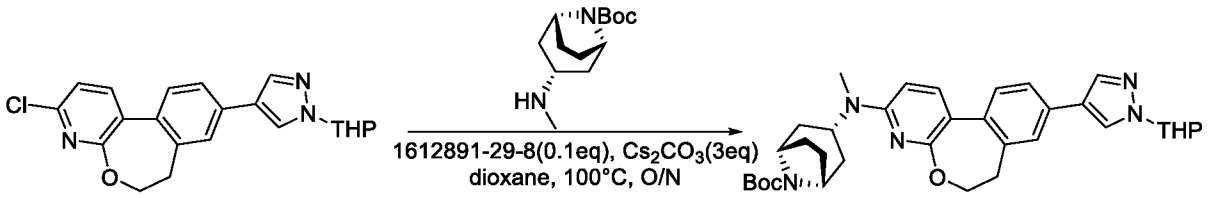


B118 147

To a solution of N,2,2,6,6-pentamethyl-N-[8-[1-(oxan-2-yl)pyrazol-4-yl]-6H-isochromeno [3,4-b]pyridin-3-yl]piperidin-4-amine (50 mg, 0.100 mmol) in methanol (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL). The reaction mixture was stirred at 25 °C for 2 h, then concentrated *in vacuo* to give a residue. The residue was purified by Prep-HPLC (Condition 1, Gradient 4) to afford N,2,2,6,6-pentamethyl-N-[8-(1H-pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]piperidin-4-amine (21.8 mg, 52.38%) as a solid. **LCMS** (ESI, *m/z*): 418.6 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 8.02 – 8.00 (m, *J* = 8.6 Hz, 3H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.56 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.46 (d, *J* = 1.7 Hz, 1H), 6.38 (d, *J* = 8.6 Hz, 1H), 5.24 (s, 2H), 4.93 (s, 1H), 2.84 (s, 3H), 1.55 – 1.40 (m, 4H), 1.30 (s, 6H), 1.16 (s, 6H).

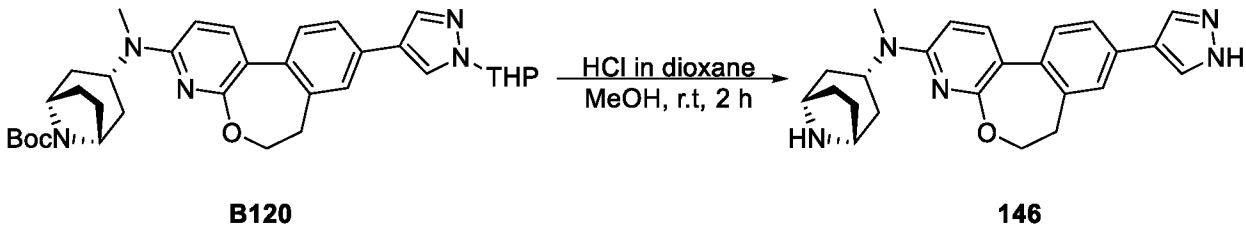
Example 31: Synthesis of Compound 146

Synthesis of Intermediate B120



To a solution of 3-chloro-9-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6,7-dihydrobenzo[4,5] oxepino[2,3-b]pyridine (20 mg, 0.052 mmol), tert-butyl (exo)-3-(methylamino)-8-azabicyclo[3.2.1]octane-8-carboxylate (25.18 mg, 0.105 mmol), and Cs_2CO_3 (51.19 mg, 0.157 mmol) in dioxane (1 mL) was added Pd-PEPPSI-IPentCl 2-methylpyridine (4.40 mg, 0.005 mmol). The reaction mixture was stirred at 100 °C for 16 h, then partitioned between ethyl acetate (10 ml) and water (10 ml). The aqueous layer was extracted with ethyl acetate (2x10 mL). The organic layers were combined, washed with brine (20 mL), dried with Na_2SO_4, evaporated under reduced pressure to a residue, and the residue was purified by Prep-TLC(PE/EA=1:1) to afford tert-butyl (exo)-3-(methyl(9-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6,7-dihydrobenzo[4,5]oxepino[2,3-b]pyridin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (110 mg,71.71%) as a solid. **LCMS** (ESI, *m/z*): 586.10 $[M+H]^+$.

Synthesis of Compound 146

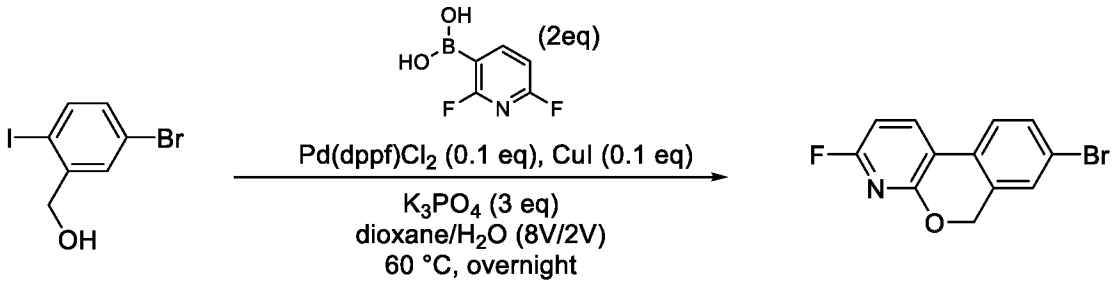


To a solution of tert-butyl (exo)-3-(methyl(9-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6,7- dihydrobenzo[4,5]oxepino[2,3-b]pyridin-3-yl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.171 mmol) in methanol (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL). The reaction mixture was stirred at 25 °C for 2 h, then concentrated *in vacuo* to give a residue. The residue was purified by Prep-HPLC (Condition 1, Gradient 5) to afford N-((exo)-8-azabicyclo[3.2.1]octan-3-yl)-N-methyl -9-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6,7-dihydrobenzo[4,5]oxepino[2,3-b]pyridin-3-amine (39.8mg, 48%) as a solid. **LCMS** (ESI, *m/z*):

402.10 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 8.05 (s, 2H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.54 (s, 2H), 7.32 (d, *J* = 7.7 Hz, 1H), 6.51 (d, *J* = 8.5 Hz, 1H), 4.76 (s, 1H), 4.55 (t, *J* = 5.9 Hz, 2H), 3.48 (s, 2H), 2.84 (d, *J* = 15.3 Hz, 5H), 1.73 (t, *J* = 10.6 Hz, 6H), 1.48 (d, *J* = 11.8 Hz, 2H).

Example 32: Synthesis of Compound 149

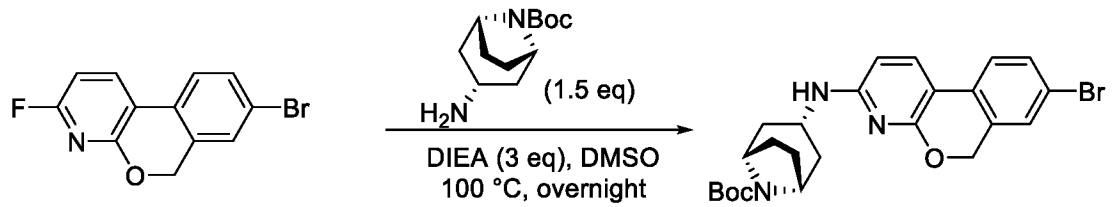
Synthesis of Intermediate B121



B121

To a solution of (5-bromo-2-iodophenyl)methanol (10 g, 32.0 mmol), 2,6-difluoropyridin-3-ylboronic acid (10.16 g, 63.9 mmol), and K_3PO_4 (5.04 g, 23.7 mmol) in a mixture of water (20 mL) and dioxane (80 mL) was added $Pd(dppf)Cl_2$ (2.60 g, 3.2 mmol) and CuI (0.61 g, 3.2 mmol). The reaction mixture was stirred at 60 °C for overnight, partitioned between ethyl acetate (150 mL) and water (150 mL), and the aqueous layer was extracted with ethyl acetate (2 x 150 mL). The organic layers were combined, washed with saturated brine (400 mL), dried over anhydrous sodium sulfate, and concentrated to give a residue. The residue was purified by flash column chromatography (30% EA in PE) to afford 8-bromo-3-fluoro-6H-isochromeno[3,4-b]pyridine (2.5 g, 27.93%) as a solid. **LCMS** (ESI, *m/z*): 279.90 $[M+H]^+$.

Synthesis of Intermediate B122

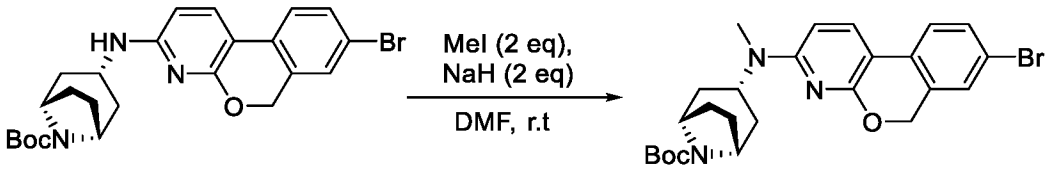


B121 **B122**

To a solution of 8-bromo-3-fluoro-6H-isochromeno[3,4-b]pyridine (2.2 g, 7.9 mmol) in DMSO (25 mL, 352 mmol) was added tert-butyl (1R,3R,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (2.67 g, 11.8 mmol) and DIEA (4.10 mL, 23.6 mmol). The reaction mixture was

stirred at 120 °C for overnight, partitioned between ethyl acetate (50 mL) and water (50 mL), the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The organic layers were combined and washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, then concentrated to give a residue. The residue was purified by flash column chromatography (30% EA in PE) to afford tert-butyl (exo)-3-({8-bromo-6H-isochromeno[3,4-b]pyridin-3-yl}amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (2.6 g, 68.05%) as a soild. **LCMS** (ESI, *m/z*): 486.15 [M+H].

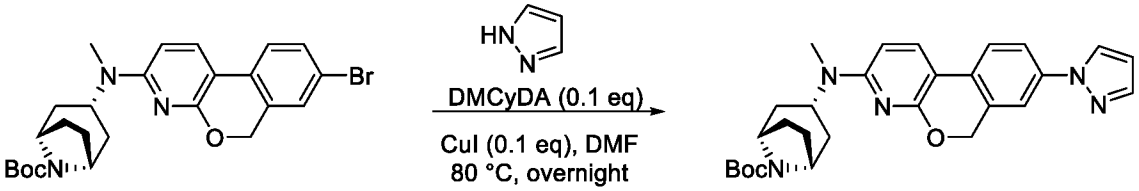
Synthesis of Intermediate B123



B122 **B123**

To a solution of tert-butyl (exo)-3-({8-bromo-6H-isochromeno[3,4-b]pyridin-3-yl}amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (4.6 g, 9.5 mmol) in DMF (50 mL) was added NaH (0.45 g, 18.9 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Then MeI (2.68 g, 18.9 mmol) was added, the reaction mixture was stirred for another 2 h at room temperature. The reaction mixture was quenched by the addition of water (100 mL) at 0°C, and the aqueous layer was extracted with ethyl acetate (3 x 80 mL). The organic layers were combined and washed with saturated brine (150 mL), dried over anhydrous sodium sulfate, and concentrated to give a residue. The residue was purified by flash column chromatography (30% EA in PE) to afford tert-butyl (exo)-3-({8-bromo-6H-isochromeno[3,4-b]pyridin-3-yl}(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (3.7 g, 78.18%) as a solid. **LCMS** (ESI, *m/z*): 500.00 [M+H].

Synthesis of Intermediate B124

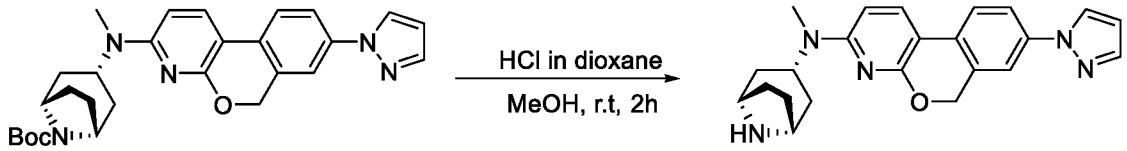


B123 **B124**

To a solution of tert-butyl (exo)-3-({8-bromo-6H-isochromeno[3,4-b]pyridin-3-yl}(methyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (90 mg, 0.180 mmol), pyrazole (24.49 mg, 0.360 mmol) and Cs_2CO_3 (175.79 mg, 0.540 mmol) in DMF (2 mL, 25.844 mmol,

143.70 equiv) was added CuI (3.43 mg, 0.018 mmol) and (1R,2R)-1-N,2-N-dimethylcyclohexane-1,2-diamine (2.56 mg, 0.018 mmol). The reaction mixture was stirred at 120 °C for 16 h, then partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous layer was washed with ethyl acetate (2 x 10 mL), the extract was washed with brine (20 mL), dried with Na_2SO_4, and evaporated under reduced pressure to give a residue. The residue was purified by Prep-TLC (PE/EA=1:1) to afford tert-butyl (exo)-3-{methyl[8-(pyrazol-1-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]amino}-8-azabicyclo[3.2.1] octane-8-carboxylate (50 mg) as a solid. **LCMS** (ESI, *m/z*): 487.75 [M+H].

Synthesis of Compound 149

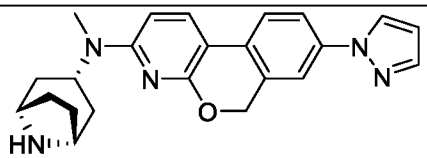


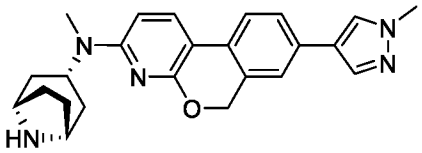
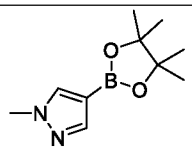
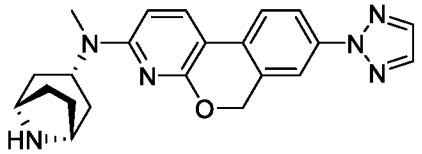
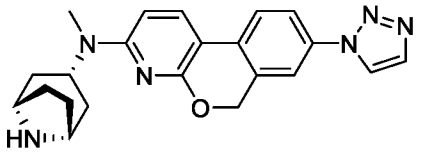
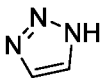
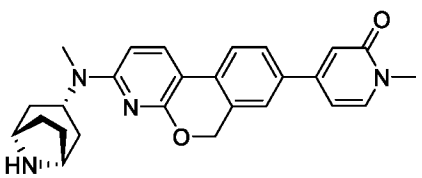
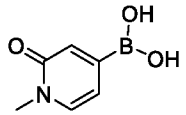
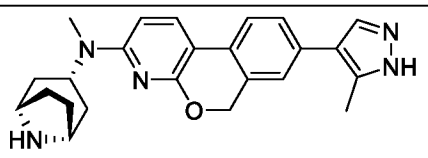
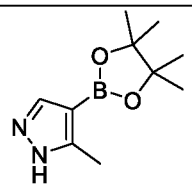
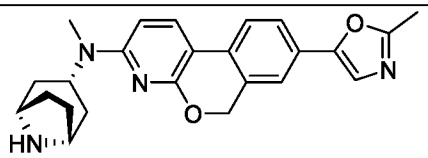
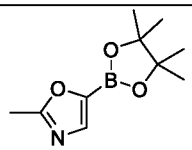
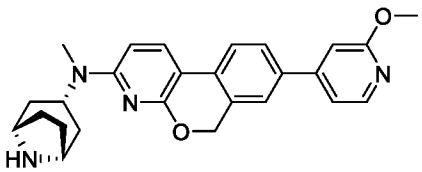
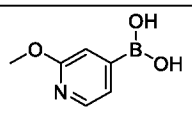
B124 **149**

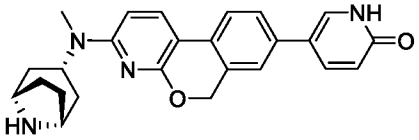
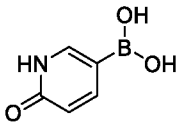
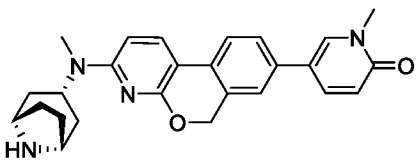
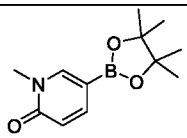
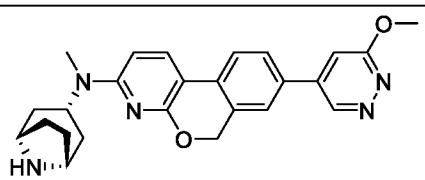
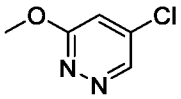
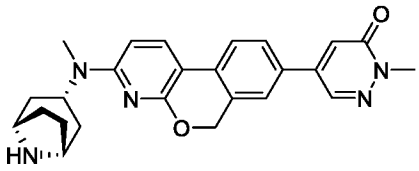
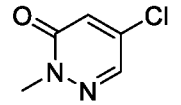
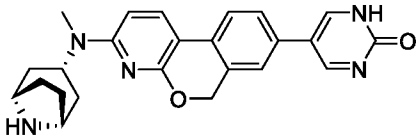
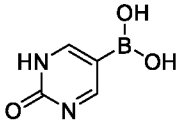
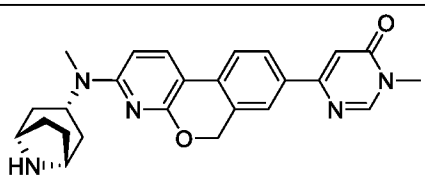
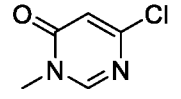
To a solution of tert-butyl (exo)-3-{methyl[8-(pyrazol-1-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]amino}-8-azabicyclo[3.2.1]octane-8-carboxylate (45 mg) in MeOH (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL). The reaction mixture was stirred at room temperature for 2 h, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 4) to afford (exo)-N-methyl-N-[8-(pyrazol-1-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]-8-azabicyclo[3.2.1]octan-3-amine (18.9 mg, 52.27%) as a solid.

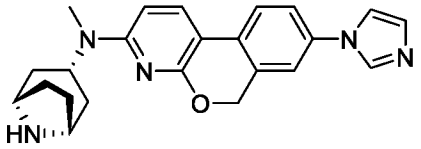
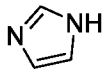
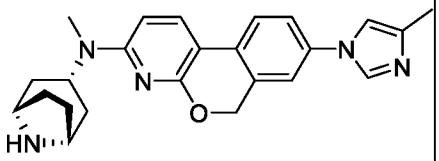
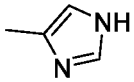
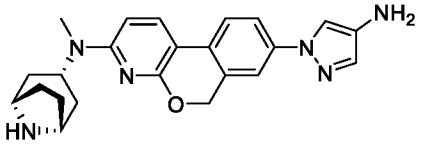
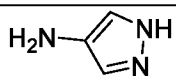
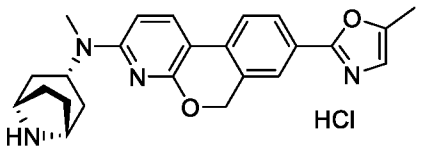
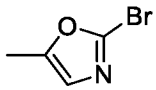
Compounds 150-164, 172, and 206 were prepared according to the same procedure outlined in this Example 32 and generalized by Scheme C. Table 2 below provides intermediates used in these procedures and final compound characterization data.

Table 2: Intermediates and characterization data for compounds prepared according to Example 32 protocol and general Scheme C

Compound No. and Structure	**B-LG[1] of Scheme C**	**LCMS (ESI, *m/z*) $[M+H]^+$**	**^{1}H NMR (400 MHz, DMSO-d_6) δ**
 **149**		388.15	8.47 (d, *J* = 2.5 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.81 - 7.68 (m, 4H), 6.58 - 6.52 (m, 1H), 6.37 (d, *J* = 8.6 Hz, 1H), 5.28 (s, 2H), 4.84 (s, 1H), 3.48 (t, *J* = 3.2 Hz, 2H), 2.82 (s, 3H), 1.71 (tdt, *J* = 13.4, 9.6, 4.5 Hz, 6H), 1.45 (ddd, *J* = 12.4, 6.0, 2.8 Hz, 2H)

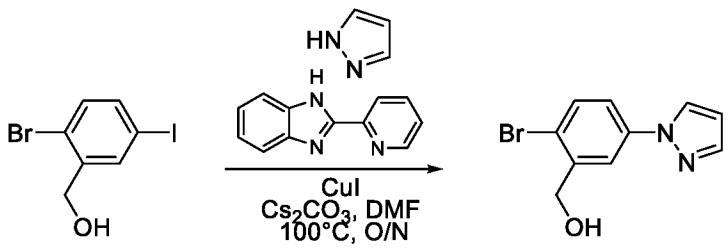
 **150**		402.00	8.12 (s, 1H), 7.98 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 0.8 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.41 (d, *J* = 1.8 Hz, 1H), 6.34 (d, *J* = 8.5 Hz, 1H), 5.22 (s, 2H), 3.87 (s, 3H), 3.46 (s, 2H), 2.80 (s, 3H), 1.70 (q, *J* = 9.7, 7.4 Hz, 6H), 1.44 (q, *J* = 5.6, 5.1 Hz, 2H)
 **151**		389.20	8.12 (s, 2H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.96 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.90 (d, *J* = 2.2 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 6.38 (d, *J* = 8.6 Hz, 1H), 5.33 (s, 2H), 4.86 (s, 1H), 3.47 (s, 2H), 2.82 (s, 3H), 1.70 (dt, *J* = 11.8, 8.5 Hz, 6H), 1.50 – 1.40 (m, 2H)
 **152**		389.10	8.80 (d, *J* = 1.2 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.98 (d, *J* = 1.1 Hz, 1H), 7.88 – 7.78 (m, 3H), 6.39 (d, *J* = 8.6 Hz, 1H), 5.32 (s, 2H), 4.87 (s, 1H), 3.47 (s, 2H), 2.83 (s, 3H), 1.71 (ddd, *J* = 20.8, 11.3, 5.2 Hz, 6H), 1.45 (ddd, *J* = 12.4, 5.6, 2.6 Hz, 2H)
 **153**		429.20	8.04 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 7.1 Hz, 1H), 7.69 (d, *J* = 2.3 Hz, 2H), 7.62 (d, *J* = 1.6 Hz, 1H), 6.71 (d, *J* = 2.1 Hz, 1H), 6.61 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.38 (d, *J* = 8.6 Hz, 1H), 5.28 (s, 2H), 4.86 (s, 1H), 3.46 (d, *J* = 7.1 Hz, 5H), 2.82 (s, 3H), 1.77 – 1.62 (m, 6H), 1.49 – 1.40 (m, 2H)
 **154**		401.75	7.98 (d, *J* = 8.6 Hz, 1H), 7.78 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.40 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.30 (d, *J* = 1.8 Hz, 1H), 6.35 (d, *J* = 8.6 Hz, 1H), 5.24 (s, 2H), 4.85 (s, 1H), 3.47 (s, 2H), 2.81 (s, 3H), 2.39 (s, 3H), 1.71 (s, 6H), 1.46 (s, 2H)
 **155**		402.90	8.01 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.60 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.54 – 7.46 (m, 2H), 6.36 (d, *J* = 8.6 Hz, 1H), 5.26 (s, 2H), 4.86 (s, 1H), 3.50 – 3.45 (m, 2H), 2.82 (s, 3H), 2.48 (s, 3H), 1.76 – 1.63 (m, 6H), 1.49 – 1.40 (m, 2H)
 **156**		429.25	8.22 (d, *J* = 5.4 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.34 (dd, *J* = 5.4, 1.6 Hz, 1H), 7.13 (d, *J* = 1.6 Hz, 1H), 6.38 (d, *J* = 8.6 Hz, 1H), 5.29 (s, 2H), 4.86 (s, 1H), 3.90 (s, 3H), 3.47 (s, 2H), 2.83 (s, 3H), 1.77 – 1.65 (m, 6H), 1.49 – 1.42 (m, 2H)

 **157**		415.1	(400 MHz, DMSO-d_6) δ 7.99 (d, *J* = 8.6 Hz, 1H), 7.85 (dd, *J* = 9.5, 2.8 Hz, 1H), 7.73 (d, *J* = 2.8 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.51 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 6.44 (d, *J* = 9.5 Hz, 1H), 6.35 (d, *J* = 8.6 Hz, 1H), 5.24 (s, 2H), 4.86-4.83 (s, 1H), 3.49 – 3.43 (m, 2H), 2.81 (s, 3H), 1.76 – 1.62 (m, 6H), 1.44 (ddd, *J* = 12.5, 5.4, 2.6 Hz, 2H)
 **158**		428.85	8.15 (d, *J* = 2.7 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.85 (dd, *J* = 9.5, 2.7 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.53 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.44 (d, *J* = 1.9 Hz, 1H), 6.49 (d, *J* = 9.4 Hz, 1H), 6.35 (d, *J* = 8.6 Hz, 1H), 5.25 (s, 2H), 4.86 (t, *J* = 6.8 Hz, 1H), 3.52 (s, 3H), 3.46 (t, *J* = 3.3 Hz, 2H), 2.81 (s, 3H), 1.70 (dtt, *J* = 15.6, 7.9, 2.9 Hz, 6H), 1.44 (ddd, *J* = 12.6, 5.8, 2.6 Hz, 2H)
 **159**		430.15	9.37 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.90-7.88 (m, 1H), 7.77 - 7.75 (m, 1H), 7.82 7.82 (m, 1H) 7.50 (s, 1H), 6.38 (d, *J* = 8.8 Hz, 1H), 5.29 (s, 2H), 4.87 (s, 1H), 3.69 (s, 3H), 3.47 (s, 2H), 2.83 (s, 3H) 1.74 1.46 (m, 6H), 1.47 - 1.45 (m, 2H)
 **160**		430.25	8.37 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.82 - 7.80 (m, 1H), 7.75 7.31(m, 2H), 7.22 (2, 1H), 6.38 (d, *J* = 8.8 Hz, 1H), 5.28 (s, 2H), 4.87 (s, 1H), 3.69 (s, 3H), 3.47 (s, 2H), 2.82 (s, 3H), 1.74 1.67 (m, 6H), 1.47 - 1.45 (m, 2H)
 **161**		416.15	8.63 (s, 2H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.58 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 6.36 (d, *J* = 8.6 Hz, 1H), 5.24 (s, 2H), 4.90 – 4.82 (m, 1H), 3.47 (m, 2H), 2.82 (s, 3H), 1.71 (qd, *J* = 13.3, 12.4, 4.6 Hz, 6H), 1.46 (dd, *J* = 12.1, 5.2 Hz, 2H)
 **162**		430.15	8.54 (s, 1H), 8.08 - 7.98 (m, 2H), 7.94 (d, *J* = 1.8 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 0.8 Hz, 1H), 6.38 (d, *J* = 8.6 Hz, 1H), 5.29 (s, 2H), 4.86 (s, 1H), 3.48 (d, *J* = 5.1 Hz, 2H), 3.44 (s, 3H), 2.83 (s, 3H), 1.77 - 1.65 (m, 6H), 1.45 (dt, *J* = 12.7, 3.6 Hz, 2H)

 **163**		388.15	8.24 (t, *J* = 1.2 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.78 – 7.71 (m, 2H), 7.59 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.54 (d, *J* = 2.3 Hz, 1H), 7.11 (t, *J* = 1.1 Hz, 1H), 6.37 (d, *J* = 8.6 Hz, 1H), 5.27 (s, 2H), 4.86 (s, 1H), 3.47 (s, 2H), 2.82 (s, 3H), 1.77 – 1.64 (m, 6H), 1.50 – 1.40 (m, 2H)
 **164**		402	8.11 (d, *J* = 1.4 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.54 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.43 (s, 1H), 6.36 (d, *J* = 8.6 Hz, 1H), 5.25 (s, 2H), 4.85 (s, 1H), 3.48 (t, *J* = 3.4 Hz, 2H), 2.81 (s, 3H), 2.17 (s, 3H), 1.78 – 1.62 (m, 6H), 1.44 (ddd, *J* = 12.7, 5.7, 2.7 Hz, 2H)
 **172**		403	7.98 (d, *J* = 8.5 Hz, 1H), 7.70 – 7.58 (m, 3H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.26 (s, 1H), 6.35 (d, *J* = 8.5 Hz, 1H), 5.25 (s, 2H), 4.86 (s, 1H), 4.20 (s, 2H), 3.50 (s, 2H), 2.80 (s, 3H), 1.72 (q, *J* = 10.0, 8.5 Hz, 6H), 1.50 – 1.42 (m, 2H)
 **206**		439	9.30 (d, *J* = 10.2 Hz, 1H), 8.93 (s, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.81 – 7.64 (m, 2H), 6.99 (d, *J* = 1.5 Hz, 1H), 6.46 (d, *J* = 8.6 Hz, 1H), 5.31 (s, 2H), 5.0 (s, 1H), 4.07 (s, 2H), 2.90 (s, 3H), 2.39 (d, *J* = 1.2 Hz, 3H), 2.25 – 2.13 (m, 2H), 2.04 (q, *J* = 7.5, 6.0 Hz, 2H), 2.00 – 1.94 (m, 2H), 1.72 – 1.62 (m, 2H)

Example 33: Synthesis of Compound 148

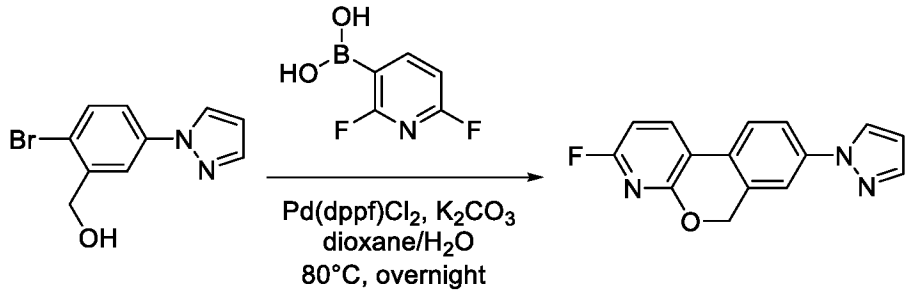
Synthesis of Intermediate B125



B125

To a solution of (2-bromo-5-iodophenyl)methanol (1 g, 3.196 mmol), pyrazole (0.33 g, 4.794 mmol), and Cs_2CO_3 (2.08 g, 6.392 mmol) in DMF (10 mL, 129 mmol) was added 2-(pyridin-2-yl)-1H-1,3-benzodiazole (0.06 g, 0.320 mmol) and CuI (0.06 g, 0.320 mmol) under N_2. The reaction mixture was stirred at 100 °C overnight, then partitioned between ethyl acetate (40 mL) and water (40 mL). The aqueous layer was washed with ethyl acetate (2 x 40 mL). The extract was washed with brine (100 mL), dried with Na_2SO_4, and evaporated under reduced pressure to give a residue. The residue was purified by flash column chromatography (20% EA in PE) to afford [2-bromo-5-(pyrazol-1-yl)phenyl]methanol (600 mg) as a solid. **LCMS** (ESI, *m/z*): 252.90 [M+H].

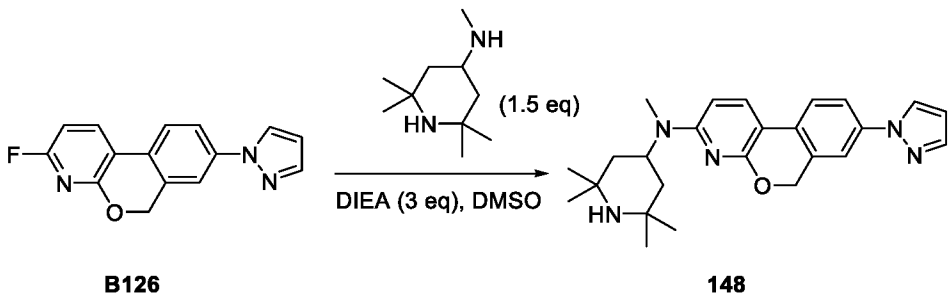
Synthesis of Intermediate B126



B125 **B126**

To a solution of [2-bromo-5-(pyrazol-1-yl)phenyl]methanol (300 mg, 1.185 mmol) and K_2CO_3 (491.45 mg, 3.555 mmol) in a mixture of water and dioxane was added $Pd(dppf)Cl_2$ (96.56 mg, 0.119 mmol) under N_2. The reaction mixture was stirred at 80 °C overnight, then partitioned between ethyl acetate (50 mL) and water (50 mL), and the aqueous layer extracted with ethyl acetate (2 x 50 mL). The organic layers were combined and washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a residue. The residue was purified by flash column chromatography (30% EA in PE) to afford 1-{3-fluoro-6H-isochromeno[3,4-b]pyridin-8-yl}pyrazole (180 mg) as a solid. **LCMS** (ESI, *m/z*): 268.00 [M+H].

Synthesis of Compound 148

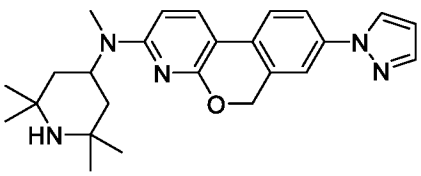
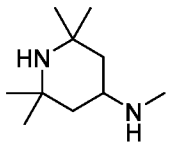
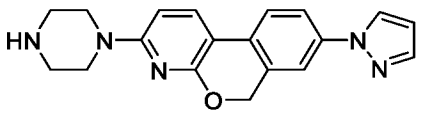
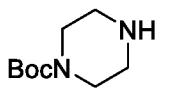
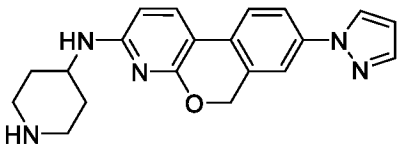
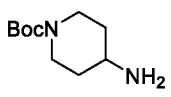


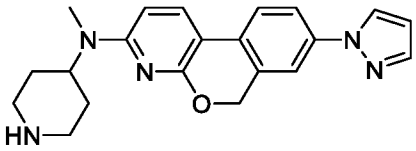
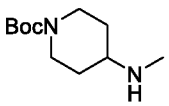
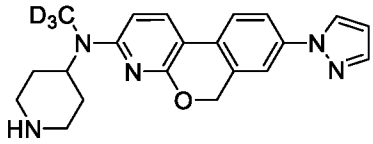
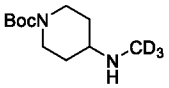
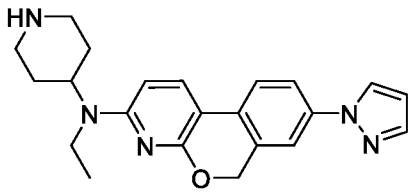
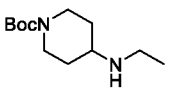
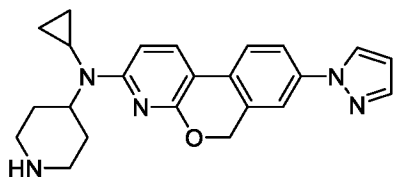
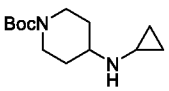
B126 **148**

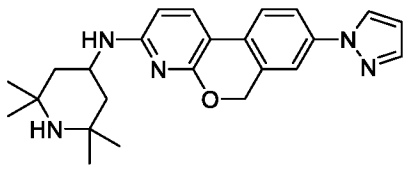
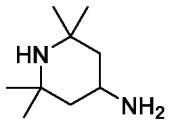
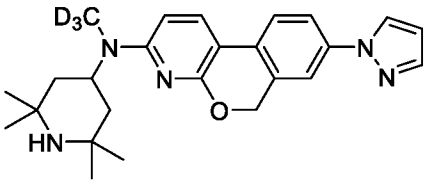
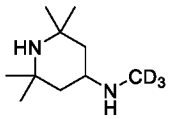
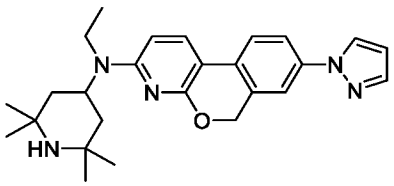
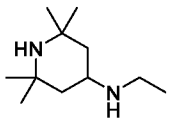
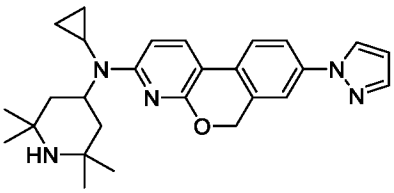
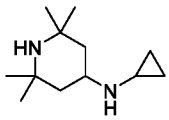
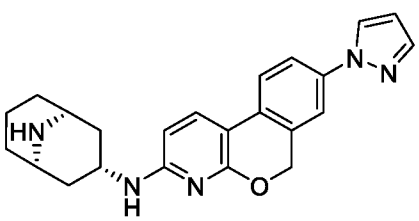
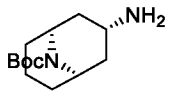
To a solution of 1-[3-fluoro-6H-isochromeno[3,4-b]pyridin-8-yl]pyrazole (160.00 mg, 0.599 mmol) in DMSO (20 mL) was added DIEA (0.31 mL, 1.797 mmol) and N,2,2,6,6-pentamethylpiperidin-4-amine (152.93 mg, 0.898 mmol). The reaction mixture was stirred at 120 °C overnight, then concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Condition 1, Gradient 6) to afford N,2,2,6,6-pentamethyl-N-[8-(pyrazol-1-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]piperidin-4-amine (22.8 mg) as a solid.

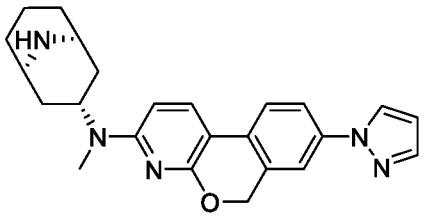
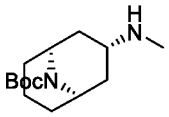
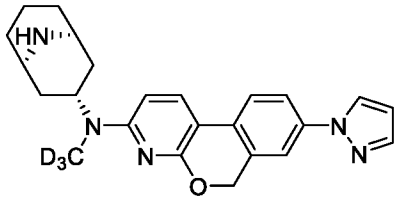
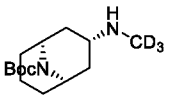
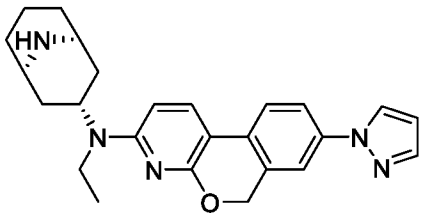
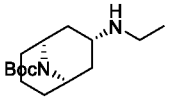
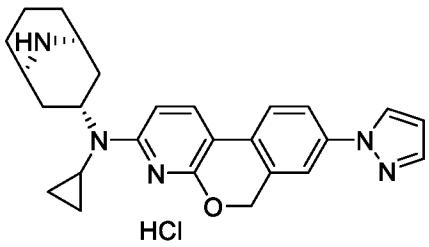
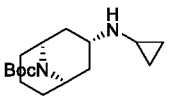
Compounds 165-171 and 173-205 were prepared according to the same procedure outlined in this Example 33 and generalized by Scheme D. Table 3 below provides intermediates used in these procedures and final compound characterization data.

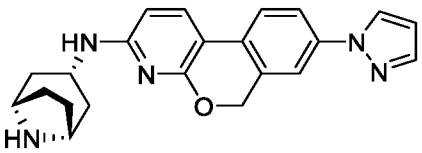
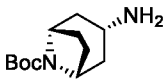
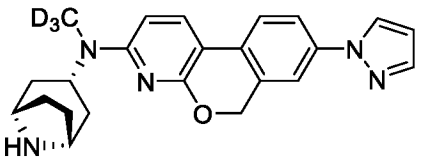
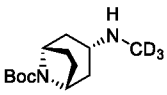
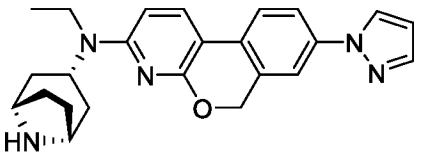
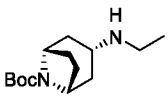
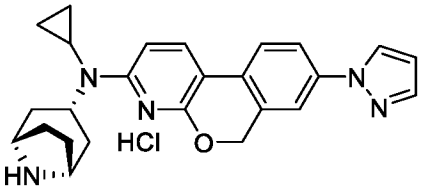
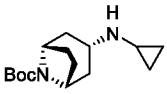
Table 3: Intermediates and characterization data for compounds prepared according to Example 33 protocol and general Scheme D

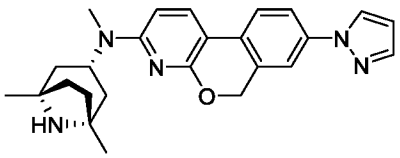
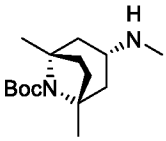
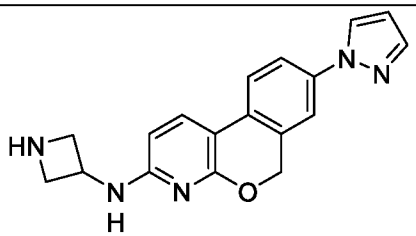
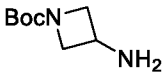
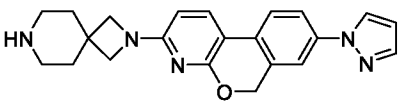
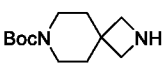
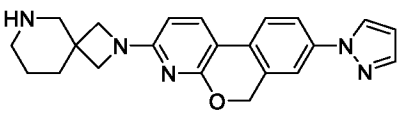
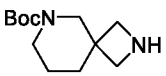
Compound No. and Structure	**A-L-H of Scheme D**	**LCMS (ESI, *m/z*) $[M+H]^+$**	**^{1}H NMR (400 MHz, DMSO-d_6) δ**
 **148**		418.15	(400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.76 (ddd, *J* = 20.9, 8.7, 2.2 Hz, 4H), 6.55 (t, *J* = 2.1 Hz, 1H), 6.39 (d, *J* = 8.6 Hz, 1H), 5.29 (s, 2H), 4.90 (s, 1H), 2.84 (s, 3H), 1.45 (dd, *J* = 12.0, 3.5 Hz, 2H), 1.36 (t, *J* = 12.1 Hz, 2H), 1.24 (s, 6H), 1.08 (s, 6H)
 **173**		334	(400 MHz, DMSO-*d*$_6$) δ 8.49 (d, *J* = 2.5 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 7.83 – 7.71 (m, 4H), 6.55 (dd, *J* = 5.1, 3.0 Hz, 2H), 5.28 (s, 2H), 3.47 – 3.40 (m, 4H), 2.80 – 2.73 (m, 4H)
 **174**		348	(400 MHz, DMSO-*d*$_6$) δ 8.47 (d, *J* = 2.5 Hz, 1H), 8.36 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.73 – 7.65 (m, 2H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.55 (t, *J* = 2.1 Hz, 1H), 6.27 (d, *J* = 8.4 Hz, 1H), 5.25 (s, 2H), 3.84 (td, *J* = 10.5, 9.1, 5.3 Hz, 1H), 3.15 (dt, *J* = 13.0, 4.0 Hz, 2H), 2.80 (td, *J* = 12.1, 2.8 Hz, 2H), 1.96 (dd, *J* = 13.4, 3.6

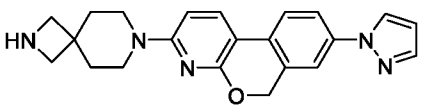
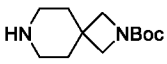
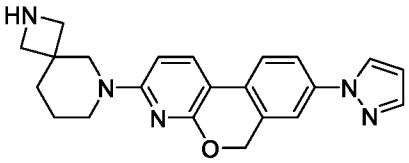
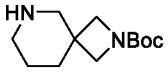
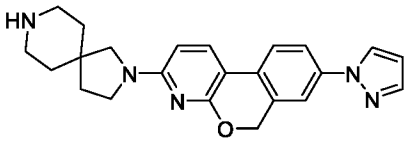
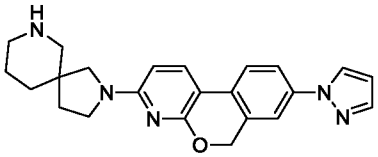
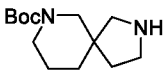
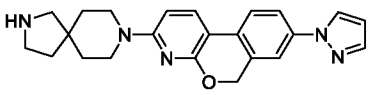
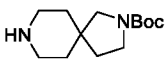
			Hz, 2H), 1.51 (dd, *J* = 10.9, 3.7 Hz, 2H)
 **175**		362	(400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.79 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.74 (dd, *J* = 8.6, 1.7 Hz, 3H), 6.58 – 6.53 (m, 1H), 6.40 (d, *J* = 8.6 Hz, 1H), 5.27 (s, 2H), 4.45 (s, 1H), 3.03 (d, *J* = 12.1 Hz, 2H), 2.86 (s, 3H), 2.59 (t, *J* = 11.7 Hz, 2H), 1.68 – 1.47 (m, 4H)
 **176**		409	(400 MHz, DMSO-d_6) δ 8.46 (d, *J* = 2.5 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.82 – 7.69 (m, 4H), 6.59 – 6.52 (m, 1H), 6.40 (d, *J* = 8.5 Hz, 1H), 5.28 (s, 2H), 4.48 – 4.38 (m, 1H), 3.02 (d, *J* = 12.1 Hz, 2H), 2.57 (td, *J* = 12.1, 2.6 Hz, 2H), 1.60 (qd, *J* = 11.8, 4.1 Hz, 2H), 1.55 – 1.47 (m, 2H)
 **177**		347	(400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.82 – 7.69 (m, 4H), 6.55 (t, *J* = 2.1 Hz, 1H), 6.38 (d, *J* = 8.6 Hz, 1H), 5.27 (s, 2H), 4.40 (s, 1H), 3.40 (q, *J* = 6.8 Hz, 2H), 3.01 (d, *J* = 12.1 Hz, 2H), 2.61 – 2.53 (m, 2H), 1.56 (dd, *J* = 8.2, 3.3 Hz, 4H), 1.13 (t, *J* = 6.9 Hz, 3H)
 **202**		361	(400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.84 – 7.71 (m, 4H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.56 (t, *J* = 2.1 Hz, 1H), 5.29 (s, 2H), 4.27 (ddt, *J* = 12.1, 8.3, 3.8 Hz, 1H), 3.00 (d, *J* = 11.8 Hz, 2H), 2.68 (p, *J* = 1.9 Hz, 1H), 2.52 (s, 2H), 2.49 – 2.41 (m, 2H), 1.66 (d, *J* = 11.3 Hz, 2H), 1.00 – 0.91 (m, 2H), 0.62 (dt, *J* = 7.1, 3.5 Hz, 2H)

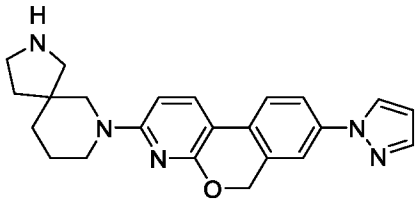
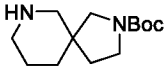
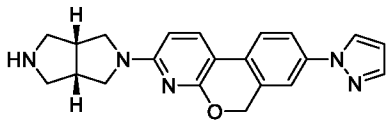
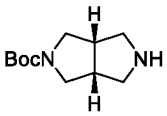
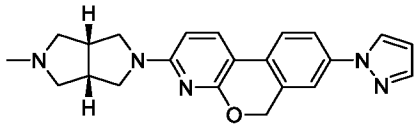
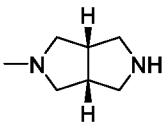
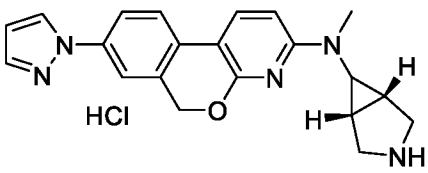
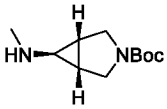
 **165**		404	(400 MHz, DMSO-d_6) δ 8.47 (d, J = 2.4 Hz, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.72 – 7.64 (m, 2H), 6.67 (d, J = 7.9 Hz, 1H), 6.55 (dd, J = 2.5, 1.8 Hz, 1H), 6.23 (d, J = 8.4 Hz, 1H), 5.25 (s, 2H), 4.12 (d, J = 10.5 Hz, 1H), 1.78 (dd, J = 12.2, 3.6 Hz, 2H), 1.20 (s, 6H), 1.04 (s, 6H), 0.99 (t, J = 12.0 Hz, 2H)
 **199**		421	(400 MHz, DMSO-d_6) δ 8.47 (d, J = 2.5 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.72 – 7.64 (m, 2H), 6.67 (d, J = 7.9 Hz, 1H), 6.57 – 6.52 (m, 1H), 6.23 (d, J = 8.4 Hz, 1H), 5.26 (s, 2H), 4.04 (s, 1H), 1.82 – 1.74 (m, 2H), 1.26 (t, J = 12.1 Hz, 2H), 1.07 (d, J = 9.6 Hz, 12H)
 **189**		432	(400 MHz, DMSO-d_6) δ 8.48 (d, J = 2.5 Hz, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.82 – 7.69 (m, 4H), 6.58 – 6.52 (m, 1H), 6.36 (d, J = 8.6 Hz, 1H), 5.28 (s, 2H), 4.86 (s, 1H), 3.38 (q, J = 7.1 Hz, 2H), 1.51 (d, J = 10.4 Hz, 2H), 1.34 (t, J = 12.2 Hz, 2H), 1.23 (s, 6H), 1.12 (t, J = 6.9 Hz, 3H), 1.07 (s, 6H)
 **204**		444	(400 MHz, DMSO-d_6) δ 8.50 (d, J = 2.5 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.84 – 7.72 (m, 4H), 6.77 (d, J = 8.5 Hz, 1H), 6.56 (q, J = 2.2 Hz, 1H), 5.30 (s, 2H), 4.87 (s, 1H), 2.09 (s, 1H), 1.60 (s, 4H), 1.22 (d, J = 15.2 Hz, 6H), 1.07 (s, 6H), 0.94 (d, J = 6.3 Hz, 2H), 0.60 (s, 2H)
		388	(400 MHz, DMSO-d_6) δ 8.47 (d, J = 2.5 Hz, 1H), 7.89 (dd, J = 9.1, 4.4 Hz, 1H), 7.80 – 7.63 (m, 4H), 6.64 (d, J = 8.1 Hz, 1H), 6.55 (t, J = 2.1 Hz, 1H), 6.22 (t, J = 7.9 Hz, 1H), 5.25 (s, 2H), 4.62 (s, 1H), 4.23 (s, 1H), 3.10 (s, 1H), 1.97 (dd,

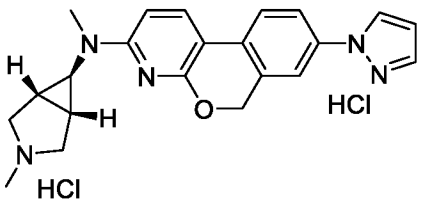
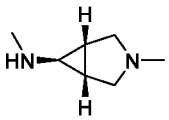
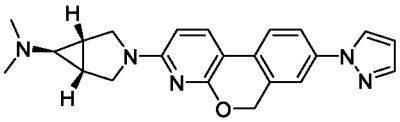
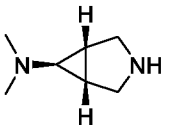
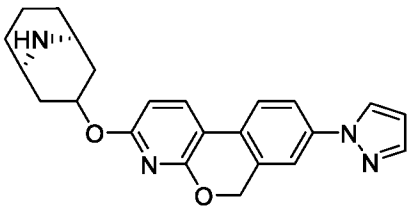
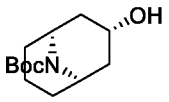
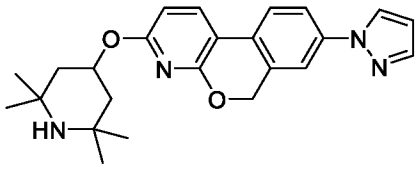
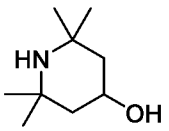
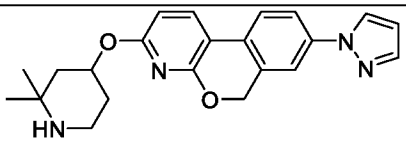
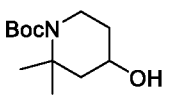
190			J = 12.5, 5.9 Hz, 4H), 1.83 – 1.71 (m, 1H), 1.64 (t, J = 17.0 Hz, 3H), 1.56 (td, J = 12.2, 4.8 Hz, 2H)
 **178**		401	(400 MHz, DMSO-d_6) δ 8.48 (d, J = 2.5 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.76 (ddd, J = 20.9, 8.6, 2.4 Hz, 4H), 6.55 (t, J = 2.1 Hz, 1H), 6.34 (d, J = 8.6 Hz, 1H), 5.6 (m, 1H), 5.29 (s, 2H), 3.20 (d, J = 5.4 Hz, 2H), 2.82 (s, 3H), 2.07 – 1.93 (m, 3H), 1.91 (dd, J = 12.7, 5.3 Hz, 2H), 1.87 –1.66 (m, J = 13.9, 5.6 Hz, 3H), 1.57 (dd, J = 12.6, 6.0 Hz, 2H)
 **200**		405	(400 MHz, DMSO-d_6) δ 8.48 (d, J = 2.5 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.82 – 7.70 (m, 5H), 6.55 (t, J = 2.1 Hz, 1H), 6.34 (d, J = 8.5 Hz, 1H), 5.59 (s, 1H), 5.29 (s, 2H), 3.18 (s, 2H), 2.1-1.91 (m, 3H), 1.91 (ttd, J = 34.9, 12.7, 6.9 Hz, 3H), 1.75 – 1.61 (m, 2H), 1.64 – 1.52 (m, 2H)
 **195**		416	(400 MHz, DMSO-d6) δ 8.57 (s, 1H), 8.24 (d, J = 2.5 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.77 – 7.68 (m, 3H), 7.61 (d, J = 1.8 Hz, 1H), 6.56 (t, J = 2.2 Hz, 1H), 6.44 (d, J = 8.6 Hz, 1H), 5.75 (tt, J = 12.4, 5.9 Hz, 1H), 5.34 (s, 2H), 3.76 (s, 2H), 3.43 (q, J = 7.0 Hz, 3H), 2.1-2.0 (dt, J = 13.6, 7.0 Hz, 2H), 2.00 – 1.98 (m, 2H), 1.92 – 1.83 (m, 5H), 1.26 (t, J = 7.0 Hz, 3H)
 **203**		428	(400 MHz, DMSO-d6) δ 8.83 (s, 1H), 8.70 (d, J = 12.2 Hz, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.13 (d, J = 8.6 Hz, 1H), 7.86 – 7.73 (m, 4H), 6.80 (d, J = 8.5 Hz, 1H), 6.56 (t, J = 2.1 Hz, 1H), 5.39 (dt, J = 12.9, 7.2 Hz, 1H), 5.32 (s, 2H), 3.72 (s, 2H), 2.48 – 2.36 (m, 2H), 2.00 (dt, J = 19.3, 6.4 Hz, 5H), 1.86 (d, J = 9.3 Hz, 2H), 1.75 (d, J

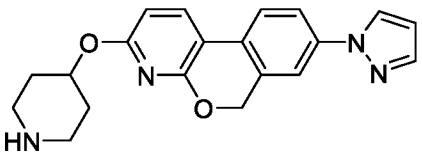
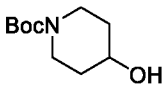
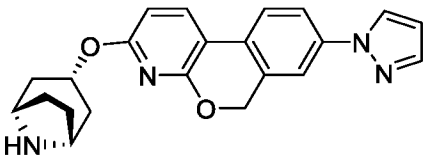
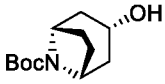
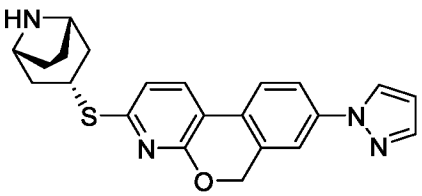
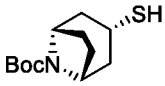
			= 6.5 Hz, 1H), 0.97 (dd, *J* = 7.1, 5.1 Hz, 2H), 0.70 (q, *J* = 4.0, 3.6 Hz, 2H)
 **179**		373	(400 MHz, DMSO-d6) δ 8.47 (d, *J* = 2.5 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.71 (d, *J* = 2.2 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.55 (t, *J* = 2.1 Hz, 1H), 6.22 (d, *J* = 8.4 Hz, 1H), 5.24 (s, 2H), 4.04 (s, 1H), 3.4 (m, 2H), 1.82 (dt, *J* = 12.4, 4.1 Hz, 2H), 1.72 – 1.62 (m, 4H), 1.35 (t, *J* = 11.3 Hz, 2H)
 **201**		391	(400 MHz, DMSO-d6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.78 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.77 – 7.69 (m, 3H), 6.55 (t, *J* = 2.2 Hz, 1H), 6.36 (d, *J* = 8.5 Hz, 1H), 5.28 (s, 2H), 4.89 – 4.82 (m, 1H), 3.49 (d, *J* = 4.4 Hz, 2H), 1.72 (ddd, *J* = 14.5, 10.2, 5.2 Hz, 6H), 1.50 – 1.41 (m, 2H)
 **191**		402	(400 MHz, DMSO-d6) δ 8.47 (d, *J* = 2.5 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.82 – 7.72 (m, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 6.55 (t, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 8.6 Hz, 1H), 5.28 (s, 2H), 4.78 (s, 1H), 3.48 (s, 2H), 3.34 (d, *J* = 7.3 Hz, 2H), 1.68 (t, *J* = 12.8 Hz, 6H), 1.52 (t, *J* = 8.5 Hz, 2H), 1.11 (t, *J* = 6.9 Hz, 3H)
 **205**		414	(400 MHz, DMSO-d_6) δ 8.75 (s, 2H), 8.53 (dd, *J* = 20.3, 2.5 Hz, 1H), 8.19 – 8.09 (m, 2H), 7.86 (d, *J* = 25.7 Hz, 2H), 7.85 – 7.73 (m, 2H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.61 – 6.54 (m, 1H), 5.31 (s, 2H), 4.72 (dt, *J* = 12.0, 6.3 Hz, 1H), 4.06 (d, *J* = 14.9 Hz, 3H), 2.43 – 2.36 (m, 1H), 2.24 (t, *J* = 12.8 Hz, 2H), 2.05-1.79 (m, 8H), 0.95 (dd, *J* =

			6.9, 5.1 Hz, 2H), 0.66 (q, *J* = 5.0, 4.0 Hz, 2H)
 **180**		416	(400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.79 (dd, *J* = 8.5, 2.2 Hz, 4H), 6.55 (t, *J* = 2.2 Hz, 1H), 6.37 (d, *J* = 8.5 Hz, 1H), 5.28 (s, 2H), 4.88 (s, 1H), 2.82 (s, 3H), 1.75 (t, *J* = 6.7 Hz, 2H), 1.53 – 1.42 (m, 6H), 1.17 (s, 6H)
 **166**		320	(400 MHz, DMSO-d6) δ 8.47 (d, *J* = 2.6 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.72 (m, 2H), 7.74 – 7.67 (m, 2H), 7.45 (s, 1H), 6.55 (t, *J* = 2.2 Hz, 1H), 6.25 (d, *J* = 8.3 Hz, 1H), 5.26 (s, 2H), 4.57 (m, 1H), 4.12 (m, 1H), 3.96 (m, 3H)
 **167**		374	(400 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 2.5 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 7.62 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 2.2 Hz, 1H), 6.48 (t, *J* = 2.1 Hz, 1H), 6.03 (d, *J* = 8.3 Hz, 1H), 5.32 (s, 2H), 3.9 (s, 4H), 2.97 (t, *J* = 5.5 Hz, 4H), 1.93 (t, *J* = 5.6 Hz, 4H)
 **168**		374	(400 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 2.5 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 1.8 Hz, 1H), 7.62 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 2.2 Hz, 1H), 6.49 (dd, *J* = 2.5, 1.8 Hz, 1H), 6.07 (d, *J* = 8.3 Hz, 1H), 5.33 (s, 2H), 3.92 (d, *J* = 8.3 Hz, 2H), 3.80 (d, *J* = 8.4 Hz, 2H), 3.12 (s, 2H), 2.93 (s, 2H), 1.86 (d, *J* = 6.2 Hz, 2H), 1.72 (s, 2H)

 **169**		374	(400 MHz, DMSO-d6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.83 – 7.71 (m, 4H), 6.60 (d, *J* = 7.5 Hz, 1H), 6.56 (t, *J* = 2.1 Hz, 1H), 5.28 (s, 2H), 3.59 (s, 1H), 3.50 (s, 5H), 3.29 (s, 2H), 1.71 (t, *J* = 5.3 Hz, 4H)
 **181**		374	(400 MHz, DMSO-d6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.83 – 7.71 (m, 4H), 6.65 (d, *J* = 8.6 Hz, 1H), 6.56 (t, *J* = 2.1 Hz, 1H), 5.29 (s, 2H), 3.67 (s, 2H), 3.48 (dt, *J* = 23.5, 6.8 Hz, 4H), 3.2 (m, 2H), 1.78 – 1.71 (m, 2H), 1.52 (s, 2H)
 **182**		388	(400 MHz, DMSO-d_6) δ 8.47 (d, *J* = 2.5 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.70 (m, 4H), 6.55 (d, *J* = 2.2 Hz, 1H), 6.23 (d, *J* = 8.5 Hz, 1H), 5.26 (s, 2H), 3.45 (t, *J* = 7.2 Hz, 4H), 2.82 – 2.60 (m, 4H), 1.82 (t, *J* = 7.1 Hz, 2H), 1.45 (d, *J* = 5.3 Hz, 4H)
 **183**		388	(400 MHz, DMSO-d_6) δ 8.47 (d, *J* = 2.5 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.75 (td, *J* = 9.4, 2.1 Hz, 4H), 6.55 (t, *J* = 2.1 Hz, 1H), 6.21 (d, *J* = 8.5 Hz, 1H), 5.26 (s, 2H), 3.54 – 3.38 (m, 3H), 3.11 (d, *J* = 10.8 Hz, 1H), 2.69 (s, 1H), 2.58 (d, *J* = 12.0 Hz, 2H), 2.48 (s, 1H), 1.90 (s, 1H), 1.70 (dt, *J* = 12.4, 8.3 Hz, 1H), 1.60 – 1.53 (m, 1H), 1.53 – 1.36 (m, 3H)
 **184**		388	(400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.05 (dd, *J* = 8.6, 4.4 Hz, 1H), 7.83 – 7.73 (m, 4H), 7.73 (d, *J* = 2.0 Hz, 1H), 6.60 (dd, *J* = 8.6, 3.3 Hz, 1H), 6.56 (t, *J* = 2.1 Hz, 1H), 5.28 (s, 2H), 3.56 (dtt, *J* = 31.5, 13.1, 6.8 Hz, 4H), 3.32 (d, *J* = 7.0 Hz, 1H), 3.17 (s, 1H), 2.83 (t, *J* = 7.1 Hz, 1H), 2.61 (s,

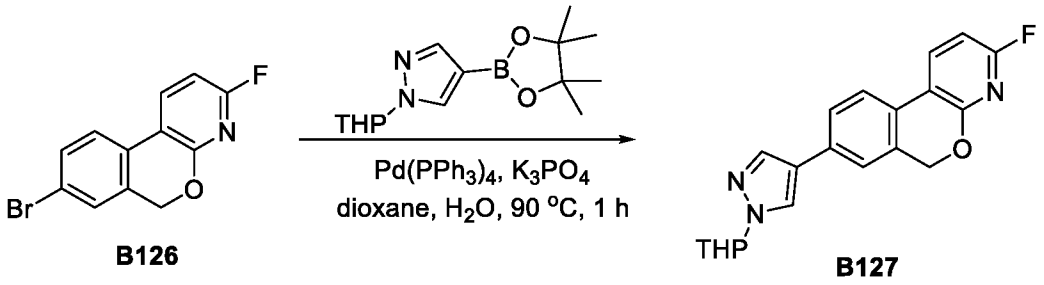
			1H), 1.76 (t, *J* = 7.1 Hz, 1H), 1.52 (dt, *J* = 15.3, 6.4 Hz, 5H)
 **192**		388	(400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.03 (dd, *J* = 8.7, 3.7 Hz, 1H), 7.82 – 7.70 (m, 4H), 6.60 (dd, *J* = 8.6, 4.4 Hz, 1H), 6.56 (t, *J* = 2.1 Hz, 1H), 5.28 (s, 2H), 3.62 (d, *J* = 13.1 Hz, 1H), 3.48 (t, *J* = 13.4 Hz, 3H), 3.37 (q, *J* = 14.1, 10.6 Hz, 1H), 3.24 – 3.15 (m, 1H), 2.96 (d, *J* = 10.7 Hz, 1H), 1.57 (s, 6H), 1.39 (d, *J* = 2.8 Hz, 1H)
 **185**		361	(400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.04 (t, *J* = 7.8 Hz, 1H), 7.75 (ddd, *J* = 12.0, 7.7, 2.3 Hz, 4H), 6.55 (t, *J* = 2.2 Hz, 1H), 6.25 (dd, *J* = 8.5, 6.0 Hz, 1H), 5.27 (d, *J* = 2.3 Hz, 2H), 3.58 (ddd, *J* = 23.6, 10.7, 7.1 Hz, 3H), 3.21 (ddd, *J* = 20.6, 10.9, 3.6 Hz, 3H), 3.01 – 2.89 (m, 2H), 2.82 (d, *J* = 7.4 Hz, 1H), 2.63 (dd, *J* = 10.8, 2.9 Hz, 1H)
 **170**		374	(400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 2.5 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.82 – 7.72 (m, 4H), 6.56 (t, *J* = 2.1 Hz, 1H), 6.27 (d, *J* = 8.5 Hz, 1H), 5.27 (s, 2H), 3.59 (dd, *J* = 10.7, 8.0 Hz, 2H), 3.30 (dd, *J* = 11.0, 3.1 Hz, 3H), 2.90 (s, 2H), 2.45 (dd, *J* = 9.1, 2.8 Hz, 3H), 2.22 (s, 3H)
 **194**		460	(400 MHz, DMSO-d6) δ 9.52 (s, 1H), 9.17 (s, 1H), 8.49 (d, *J* = 2.5 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.85 – 7.73 (m, 4H), 6.60 – 6.53 (m, 2H), 5.30 (s, 2H), 3.54 (dd, *J* = 11.8, 6.0 Hz, 2H), 3.40 (d, *J* = 9.5 Hz, 2H), 3.02 (s, 3H), 2.71 (t, *J* = 2.5 Hz, 1H), 2.12 (s, 2H)

 **196**		373	(400 MHz, DMSO-d6) δ 9.06 (s, 1H), 8.79 (d, *J* = 3.0 Hz, 2H), 8.56 (s, 1H), 8.22 (d, *J* = 8.6 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.73 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.64 (d, *J* = 2.2 Hz, 1H), 7.13 (t, *J* = 2.9 Hz, 1H), 6.61 (d, *J* = 8.5 Hz, 1H), 5.32 (s, 2H), 3.96 (s, 3H), 3.54 (d, *J* = 6.0 Hz, 2H), 3.50 (m, 2H), 3.05 (s, 3H), 2.62 (t, *J* = 2.5 Hz, 1H), 2.16 (d, *J* = 3.0 Hz, 2H)
 **197**		374	(400 MHz, DMSO-*d*6) δ 8.48 (d, *J* = 2.4 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.82 – 7.70 (m, 4H), 6.55 (t, *J* = 2.1 Hz, 1H), 6.20 (d, *J* = 8.4 Hz, 1H), 5.26 (s, 2H), 3.59 (d, *J* = 10.6 Hz, 2H), 3.43 – 3.35 (m, 2H), 2.25 (s, 6H), 1.72 (s, 1H), 1.72 (d, *J* = 5.8 Hz, 1H), 1.35 (t, *J* = 2.2 Hz, 1H)
 **198**		388	(400 MHz, DMSO-*d*6) δ 8.53 (d, *J* = 2.5 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.90 – 7.75 (m, 4H), 6.60 – 6.55 (m, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 5.78 (tt, *J* = 11.4, 6.3 Hz, 1H), 5.39 (s, 2H), 3.18 (d, *J* = 4.4 Hz, 2H), 2.11 (dd, *J* = 12.4, 6.4 Hz, 2H), 1.73 (dq, *J* = 12.0, 8.1, 5.4 Hz, 6H), 1.59 (d, *J* = 8.6 Hz, 2H)
 **171**		405	(400 MHz, Chloroform-*d*) δ 7.96 – 7.90 (m, 2H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.68 – 7.57 (m, 2H), 7.54 (d, *J* = 1.9 Hz, 1H), 6.52 – 6.43 (m, 2H), 5.50 (tt, *J* = 11.0, 4.2 Hz, 1H), 5.37 (s, 2H), 2.11 (dd, *J* = 12.6, 4.1 Hz, 2H), 1.35 (s, 8H), 1.25 (s, 6H)
 **186**		376	(400 MHz, DMSO-d6) δ 8.52 (d, *J* = 2.5 Hz, 1H), 8.24 (d, *J* = 8.3 Hz, 1H), 7.90 – 7.81 (m, 2H), 7.78 (dd, *J* = 7.9, 1.8 Hz, 2H), 6.57 (t, *J* = 2.1 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 1H), 5.38 (s, 2H), 5.14 (tt, *J* =

			10.6, 4.4 Hz, 1H), 2.84 (ddd, *J* = 13.2, 4.9, 3.3 Hz, 1H), 2.76 (td, *J* = 13.3, 12.4, 2.9 Hz, 1H), 2.01 – 1.92 (m, 1H), 1.86 (ddd, *J* = 12.0, 4.4, 1.7 Hz, 1H), 1.65 (s, 1H), 1.39 – 1.21 (m, 2H), 1.09 (d, *J* = 4.3 Hz, 6H)
 **187**		348	(400 MHz, DMSO-d6) δ 8.52 (d, *J* = 2.5 Hz, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 7.90 – 7.81 (m, 2H), 7.78 (dd, *J* = 8.5, 1.9 Hz, 2H), 6.60 – 6.51 (m, 2H), 5.37 (s, 2H), 4.97 (s, 1H), 3.74 (s, 1H), 3.16 (s, 1H), 2.96 (d, *J* = 12.4 Hz, 1H), 2.58 (t, *J* = 11.4 Hz, 1H), 1.99 – 1.89 (m, 2H), 1.48 (d, *J* = 11.2 Hz, 2H)
 **188**		375	(400 MHz, DMSO-d6) δ 8.52 (d, *J* = 2.6 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 7.90 – 7.81 (m, 2H), 7.78 (dd, *J* = 8.6, 1.9 Hz, 2H), 6.57 (t, *J* = 2.2 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 1H), 5.38 (s, 2H), 5.24 – 5.17 (m, 1H), 3.48 (s, 2H), 2.02 (d, *J* = 9.3 Hz, 2H), 1.72 – 1.62 (m, 4H), 1.51 (t, *J* = 10.9 Hz, 2H)
 **193**		391	(400 MHz, DMSO-d_6) δ 8.54 (d, *J* = 2.5 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.87 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.80 (dd, *J* = 13.1, 2.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.58 (dd, *J* = 2.5, 1.7 Hz, 1H), 5.40 (s, 2H), 4.22 (t, *J* = 7.3 Hz, 1H), 3.40 (s, 2H), 2.29 (ddd, *J* = 14.5, 7.6, 4.0 Hz, 2H), 1.97 (t, *J* = 7.0 Hz, 2H), 1.77 – 1.66 (m, 4H)

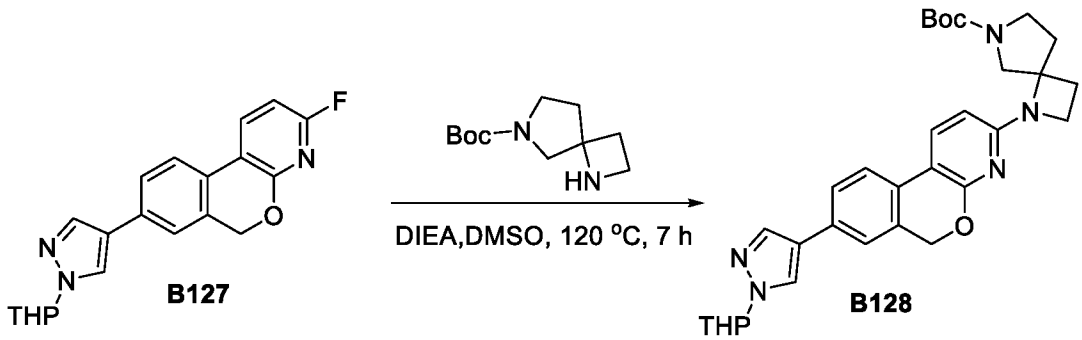
Example 34: Synthesis of Compound 207

Synthesis of Intermediate B127



To a stirred mixture of 8-bromo-3-fluoro-6H-isochromeno[3,4-b]pyridine (B126, 1.50 g, 5.355 mmol, 1.0 equiv) and 1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (1.49 g, 5.355 mmol, 1.0 equiv) in dioxane (20 mL)/H_2O (2 mL) were added K_3PO_4 (1.71 g, 8.033 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (0.62 g, 0.536 mmol, 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 filtered, and the filtrated was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and the product was eluted with PE / EA (5:1) to afford 3-fluoro-8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6H- isochromeno[3,4-b]pyridine (1.9 g, 83.80%) as a an oil. **LCMS** (ES, m/z): 352 $[M+H]^+$

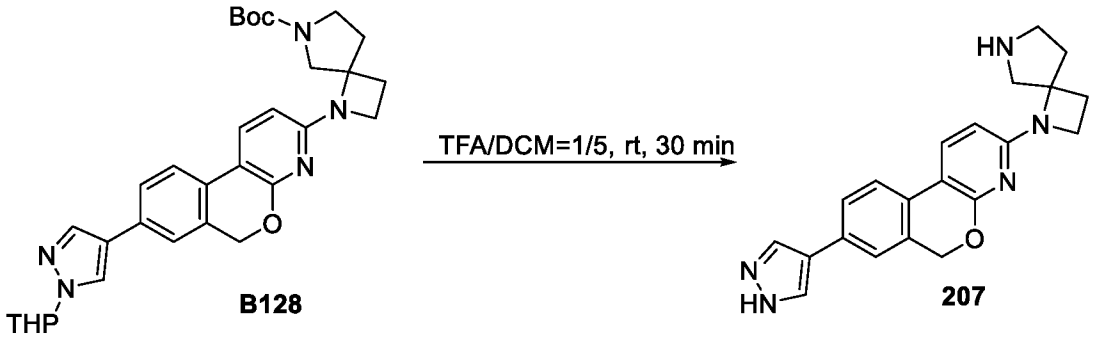
Synthesis of Intermediate B128



To a stirred mixture of 3-fluoro-8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6H-isochromeno [3,4-b]pyridine (B127, 100.0 mg, 0.285 mmol, 1.0 equiv) and tert-butyl 1,6-diazaspiro[3.4]octane-6-carboxylate (90.6 mg, 0.427 mmol, 1.5 equiv) in DMSO (1 mL) was added DIEA (110.3 mg, 0.855 mmol, 3.0 equiv) at room temperature. The resulting mixture was stirred for 7 h at 120 °C. The resulting mixture was diluted water and extracted with EA, and the combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and eluted with PE / EA (1:1) to afford tert-butyl 1-(8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl)-1,6-

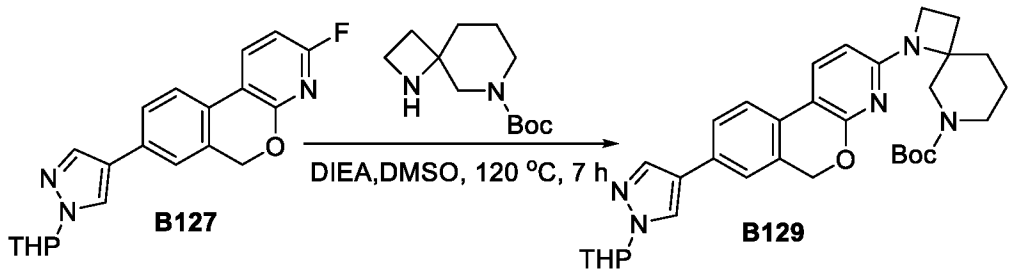
diazaspiro[3.4]octane-6-carboxylate (B128, 110 mg, 68.96%) as a solid. **LCMS** (ES, m/z): 544 $[M+H]^+$

Synthesis of Compound 207



To a stirred mixture of tert-butyl 1-(8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6H- isochromeno[3,4-b]pyridin-3-yl)-1,6-diazaspiro[3.4]octane-6-carboxylate (B128, 70.0 mg, 0.129 mmol, 1.0 equiv) in DCM (0.70 mL) was added TFA (0.14 mL) dropwise at room temperature. The resulting mixture was stirred for 30 min at room temperature, then concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Condition 2, Gradient 5) to afford 8-(1H-pyrazol-4-yl)-3-(1,6-diazaspiro[3.4]octan-1-yl)-6H-isochromeno[3,4-b]pyridine (Compound 207, 13 mg, 28.09%) as a solid. **LCMS** (ES, m/z): 360 $[M+H]^+$ **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.05 (s, 2H), 7.99 (dd, J = 12.0, 8.2 Hz, 1H), 7.64-7.51 (m, 2H), 7.45 (s, 1H), 6.09 (dd, J = 19.4, 8.2 Hz, 1H), 5.21 (s, 2H), 3.80 (s, 2H), 3.29 (d, J = 11.3 Hz, 1H), 3.08 (d, J = 7.5 Hz, 1H), 2.82-2.65 (m, 2H), 2.35 (dd, J = 8.3, 5.0 Hz, 3H), 1.87 (s, 1H).

Example 35: Synthesis of Compound 210



To a stirred mixture of 4-{3-fluoro-6H-isochromeno[3,4-b]pyridin-8-yl}-1-(oxan-2-yl)pyrazole (B127, 200.0 mg, 0.569 mmol, 1.00 equiv) and tert-butyl 1,6-diazaspiro[3.5]nonane-6-carboxylate (128.8 mg, 0.569 mmol, 1 equiv) in DMSO (2 mL, 28.157 mmol, 49.47 equiv) was added DIEA (220.7 mg, 1.707 mmol, 3 equiv) at room temperature .The resulting mixture was stirred for 7 h at 120 degrees C. The resulting mixture was diluted with water and extracted

with EtOAc, and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl 1-{8-[1-(oxan-2-yl)pyrazol-4-yl]-6H-isochromeno[3,4-b]pyridin-3-yl}-1,6-diazaspiro[3.5]nonane-6-carboxylate (B129, 115 mg) as an oil. **LCMS** (ES, m/z): 558 $[M+H]^+$

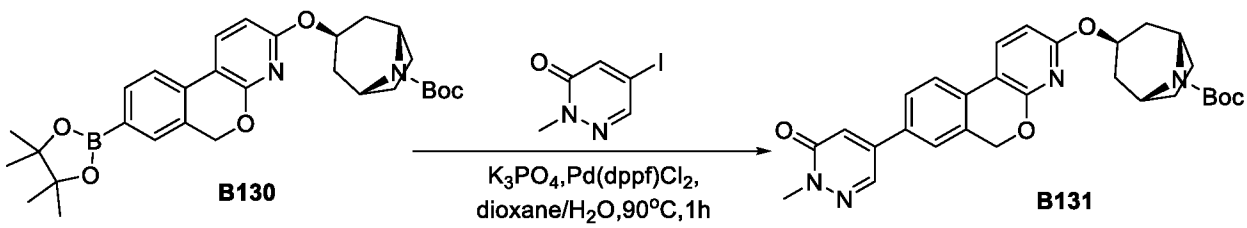
Synthesis of Compound 210



To a stirred mixture of tert-butyl 1-{8-[1-(oxan-2-yl)pyrazol-4-yl]-6H-isochromeno[3,4-b]pyridin-3- yl}-1,6-diazaspiro[3.5]nonane-6-carboxylate (B129, 105 mg, 0.188 mmol, 1.0 equiv) in DCM (2.0 mL) was added TFA (1.0 mL) dropwise at room temperature. The resulting mixture was stirred for 3 h at room temperature, then concentrated under reduced pressure. The crude product was purified by Prep-HPLC with the following conditions (Condition 2, Gradient 10) to afford 8-(1H-pyrazol-4-yl)-3-(1,6-diazaspiro[3.5]nonan-1-yl)-6H-isochromeno[3,4-b]pyridine (Compound 210, 50 mg) as a solid. **LCMS** (ES, m/z): 374 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.93-12.92 (m, 1H), 8.31-7.86 (m, 3H), 7.61-7.51 (m, 2H), 7.45 (s, 1H), 6.04 (d, J = 8.3 Hz, 1H), 5.20 (s, 2H), 3.77 (t, J = 7.5 Hz, 2H), 3.18 (d, J = 11.7 Hz, 1H), 2.88-2.73 (m, 2H), 2.45-2.14 (m, 3H), 2.12-2.01 (m, 1H), 1.80 (d, J = 12.4 Hz, 1H), 1.59 (d, J = 13.4 Hz, 1H), 1.39 (d, J = 13.3 Hz, 1H).

Example 36: Synthesis of Compound 216

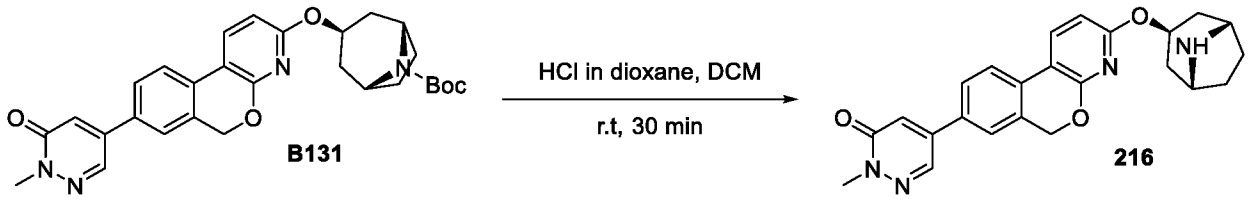
Synthesis of Intermediate B131



To a stirred mixture of tert-butyl (1R,3s,5S)-3-((8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6H- isochromeno[3,4-b] pyridin-3-yl) oxy)-8-azabicyclo [3.2.1]octane-8-

carboxylate (B130, 70.0 mg, 0.131 mmol, 1.0 equiv) and 5-iodo-2-methylpyridazin-3-one (30.9 mg, 0.131 mmol, 1.0 equiv) in dioxane /H_2O (10:1, 0.7 mL) were added K_3PO_4 (55.6 mg, 0.262 mmol, 2.0 equiv) and Pd(dppf)Cl_2 (9.6 mg, 0.013 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, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl (1R,3s,5S)-3-((8- (1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl)oxy)-8-azabicyclo[3.2.1] octane-8-carboxylate (B131, 56.6 mg) as a solid. **LCMS** (ES, *m/z*): 517 $[M+H]^+$.

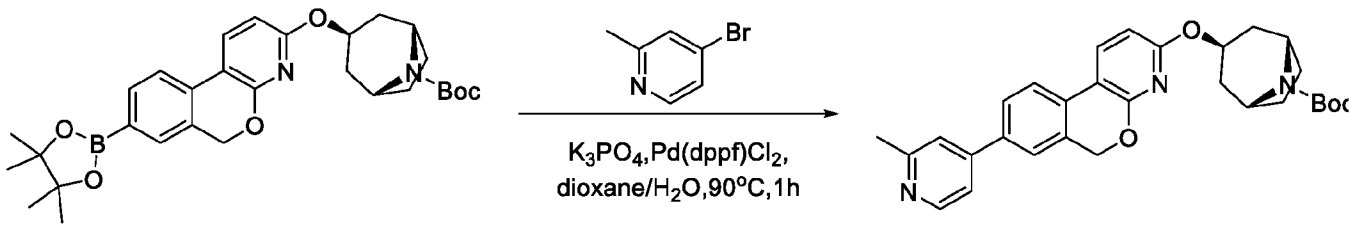
Synthesis of Compound 216



To a stirred solution of tert-butyl (1R,3s,5S)-3-((8-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)-6H- isochromeno[3,4-b]pyridin-3-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (B131, 56.6 mg, 0.136 mmol, 1.0 equiv) in DCM (0.74 mL) was added dropwise 4 M HCl(gas) in 1,4-dioxane (0.17 mL) at room temperature. The resulting mixture was stirred for 30 min at room temperature, then the mixture was neutralized to pH 7 with saturated Na_2CO_3 (aq.). The crude product was purified by Prep-HPLC with the following conditions (Condition 2, Gradient 5) to afford 5-(3-(((1R,3s,5S)-8-azabicyclo [3.2.1] octan-3-yl) oxy)-6H-isochromeno-[3,4-b]-pyridin-8-yl)-2-methylpyridazin-3(2H)-one (Compound 216, 14.5 mg) as a solid. **LCMS** (ES, *m/z*): 417 $[M+H]^+$ **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 2.3 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.63-7.54 (m, 1H), 7.37 (s, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 1H), 5.40 (s, 3H), 3.86 (s, 3H), 3.74 (s, 2H), 2.25 (d, *J* = 13.2 Hz, 2H), 1.98-1.85 (m, 4H), 1.73 (t, *J* = 11.8 Hz, 2H).

Example 37: Synthesis of Compound 209

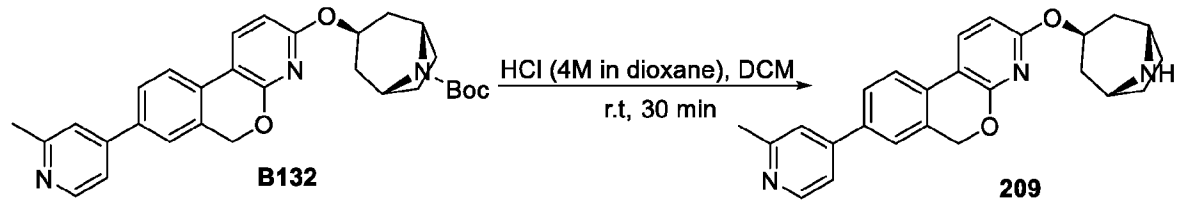
Synthesis of Intermediate B132



B130 B132

To a stirred mixture of tert-butyl (1R,3s,5S)-3-((8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6H- isochromeno[3,4-b]pyridin-3-yl) oxy)-8-azabicyclo [3.2.1] octane-8-carboxylate (B130, 80.0 mg, 0.150 mmol, 1.0 equiv) and 4-bromo-2-methylpyridine (25.8 mg, 0.150 mmol, 1.0 equiv) in dioxane/H_2O (1 mL /0.1 mL) were added K_3PO_4 (63.6 mg, 0.300 mmol, 2.0 equiv) and $Pd(dppf)Cl_2$ (11.0 mg, 0.015 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. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford tert-butyl (1R,3s,5S)-3-((8-(2-methylpyridin-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (58.7 mg) as a solid. **LCMS** (ES, *m/z*): 500 $[M+H]^+$

Synthesis of Compound 209



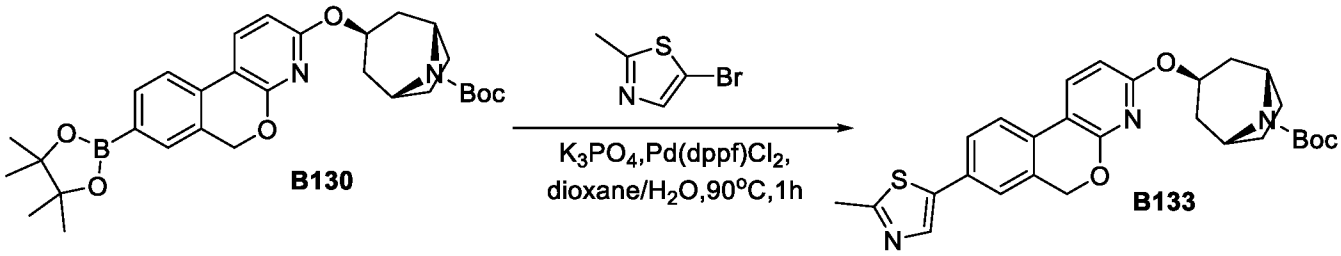
B132 209

To a stirred solution of tert-butyl (1R,3s,5S)-3-((8-(2-methylpyridin-4-yl)-6H-isochromeno[3,4-b] pyridin-3-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (B132, 58.7 mg, 0.147mmol, 1.0 equiv) in DCM (0.8 mL) was added 4 M HCl(gas)in 1,4-dioxane (0.2 mL) at room temperature. The resulting mixture was stirred for 30 min at room temperature, then neutralized to pH 7 with saturated Na_2CO_3 (aq.). The crude product was purified by Prep-HPLC using Condition 2, Gradient 11 to afford 3-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-8-(2-methylpyridin-4-yl)- 6H-isochromeno [3,4-b] pyridine (Compound 209, 24.7 mg) as a solid. **LCMS** (ES, *m/z*): 400 $[M+H]^+$ **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.51 (d, J = 5.3 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 7.92-7.72 (m, 3H), 7.63 (s, 1H), 7.54 (d, J = 5.3 Hz, 1H), 6.51 (d, J = 8.3 Hz, 1H), 5.40 (s,

2H), 5.30-5.09 (m, 1H), 3.47 (s, 2H), 2.54 (s, 3H), 2.09-1.98 (m, 2H), 1.77-1.60 (m, 4H), 1.56-1.45 (m, 2H).

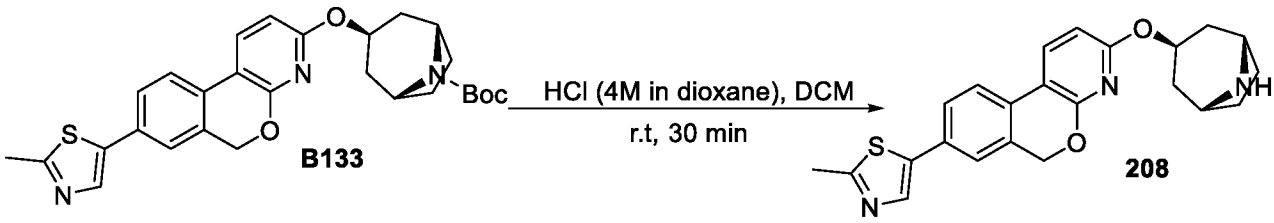
Example 38: Synthesis of Compound 208

Synthesis of Intermediate B133



To a stirred mixture of tert-butyl (1R,3s,5S)-3-((8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6H-isochromeno [3,4-b] pyridin-3-yl) oxy)-8-azabicyclo [3.2.1] octane-8-carboxylate (B130, 80 mg, 0.150 mmol, 1.0 equiv) and 5-bromo-2-methyl-1,3-thiazole (26.65 mg, 0.150 mmol, 1.0 equiv) in dioxane /H_2O (1 mL /0.1 mL) were added K_3PO_4 (63.55 mg, 0.300 mmol, 2.0 equiv) and Pd(dppf)Cl_2 (10.95 mg, 0.015 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, then concentrated under reduced pressure and purified by silica gel column chromatography, eluting with PE / EA (1:1) to afford tert-butyl (1R,3s,5S)-3-((8-(2-methylthiazol-5-yl)-6H-isochromeno[3,4-b]pyridin-3-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (80 mg, 99.36%) as a solid. **LCMS** (ES, *m/z*): 506 $[M+H]^+$

Synthesis of Compound 208

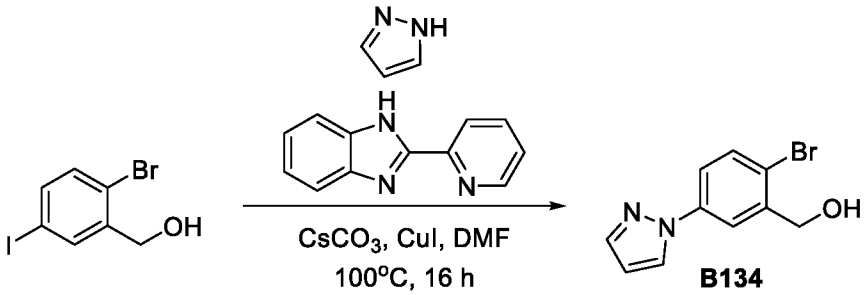


To a stirred solution of tert-butyl (1R,3s,5S)-3-((8-(2-methylthiazol-5-yl)-6H-isochromeno[3,4-b] pyridin-3-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (72 mg, 0.143 mmol, 1.0 equiv) in DCM (1.0 mL) was added 4 M HCl(gas)in 1,4-dioxane (0.2 mL) at room temperature. The resulting mixture was stirred for 30 min at room temperature. The mixture was neutralized to pH 7 with saturated Na_2CO_3 (aq.), and the crude product was purified by Prep-HPLC using Condition 2, Gradient 11 to afford 3-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)oxy)-8-(2-methylthiazol-5-yl)- 6H-isochromeno[3,4-b]pyridine (Compound 208, 32.1 mg) as

a solid. **LCMS** (ES, *m/z*): 406 [M+H] $^+$ **^{1}H NMR** (300 MHz, DMSO-*d6*) δ 8.22 (d, *J* = 8.4 Hz, 1H), 8.06 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.62 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 1H), 5.35 (s, 2H), 5.20 (dt, *J* = 10.5, 5.3 Hz, 1H), 3.47 (s, 2H), 2.69 (s, 3H), 2.11-1.97 (m, 2H), 1.72-1.60 (m, 4H), 1.51 (t, *J* = 11.3 Hz, 2H).

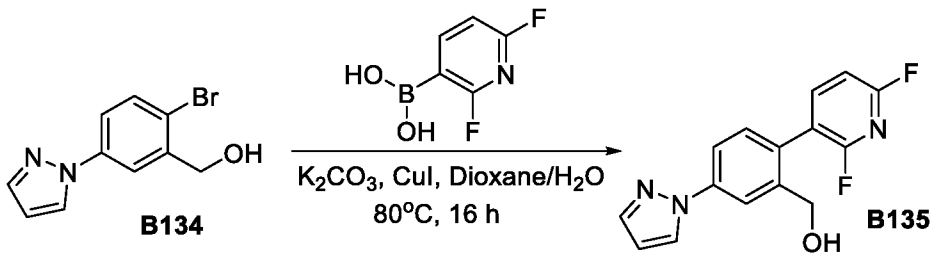
Example 39: Synthesis of Compound 214

Synthesis of Intermediate B134



To a stirred solution of (2-bromo-5-iodophenyl) methanol (5.00 g, 15.978 mmol, 1.0 equiv) and 2-(pyridin-2-yl)-1H-1,3-benzodiazole (0.31 g, 1.598 mmol, 0.1 equiv) and pyrazole (1.60 g, 23.967 mmol, 1.5 equiv) in DMF was added Cs_2CO_3 (10.40 g, 31.956 mmol, 2.0 equiv) and CuI (0.30 g, 1.598 mmol, 0.1 equiv) at room temperature under N_2 atmosphere . The resulting mixture was stirred for 16 h at 100 degrees C under N_2 atmosphere, then diluted with water and extracted with EA. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and purified by silica gel column chromatography, eluting with PE/EA (2/1) to afford (2-bromo-5-(1H-pyrazol-1-yl)phenyl)methanol (1.32 g, 32.64%) as a solid. **LCMS** (ES, *m/z*): 253 [M+H] $^+$

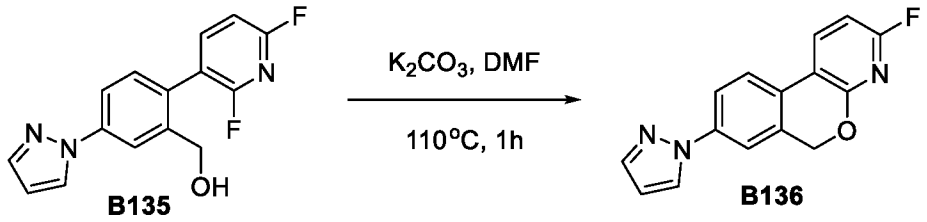
Synthesis of Intermediate B135



To a stirred mixture of [2-bromo-5-(pyrazol-1-yl)phenyl]methanol (1.30 g, 5.136 mmol, 1.0 equiv) and 2,6-difluoropyridin-3-ylboronic acid (1.63 g, 10.272 mmol, 2.0 equiv) and K_2CO_3 (2.13 g, 15.408 mmol, 3.0 equiv) in dioxane/H_2O (10/1, 13 mL) were added CuI (0.10 g, 0.514

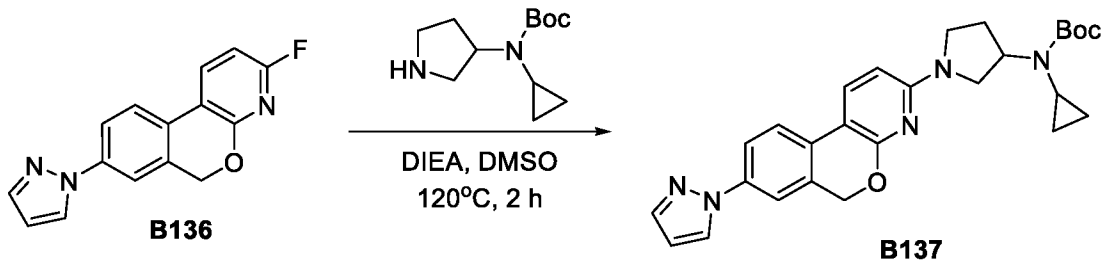
mmol, 0.1 equiv) and $Pd(dppf)Cl_2CH_2Cl_2$ (0.38 g, 0.514 mmol, 0.1 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred at 100 degrees C under N_2 atmosphere, then concentrated under vacuum and purified by silica gel column chromatography, eluting with PE/EA (2/1) to afford (2-(2,6-difluoropyridin-3-yl)-5-(1H-pyrazol-1-yl)phenyl)methanol (940 mg) as a solid. **LCMS** (ES, *m/z*): 288 $[M+H]^+$

Synthesis of Intermediate B136



To a stirred solution of [2-(2,6-difluoropyridin-3-yl)-5-(pyrazol-1-yl)phenyl]methanol (940 mg, 3.272 mmol, 1.0 equiv) in DMF (8.9 mL) was added K_2CO_3 (1357 mg, 9.816 mmol, 3.0 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 1 h at 110 degrees C. The reaction solution was diluted with water and extracted with EA. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (2/1) to afford1-{3-fluoro-6H-isochromeno[3,4-b]pyridin-8-yl}pyrazole (450 mg, 51.46%) as a solid. **LCMS** (ES, *m/z*): 268 $[M+H]^+$

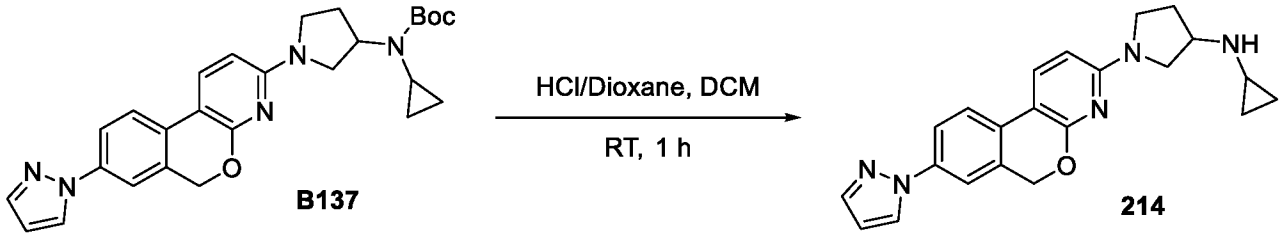
Synthesis of Intermediate B137



To a stirred mixture of 1-{3-fluoro-6H-isochromeno[3,4-b]pyridin-8-yl}pyrazole (60.0 mg, 0.224 mmol, 1.0 equiv) and tert-butyl N-cyclopropyl-N-(pyrrolidin-3-yl)carbamate (101.6 mg, 0.448 mmol, 2.0 equiv) in DMSO (0.6 mL) was added DIEA (87.0 mg, 0.672 mmol, 3.0 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 2 h at 120

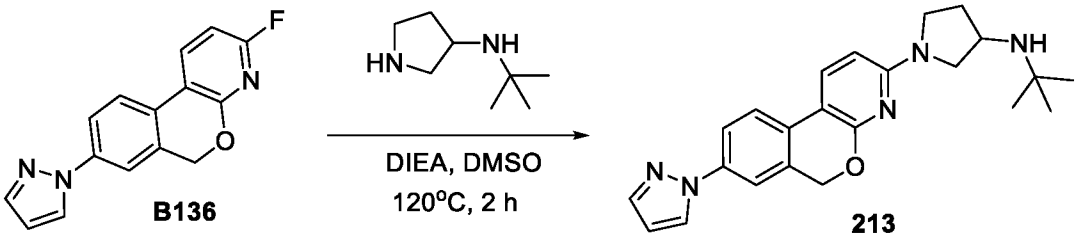
degrees C under N_2 atmosphere. The reaction solution was diluted with water and extracted with EA. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford tert-butyl N-cyclopropyl-N-{1-[8-(pyrazol-1-yl)-6H-isochromeno[3,4-b]pyridin-3-yl] pyrrolidin-3-yl}carbamate (140 mg, 99.68%) as a solid. **LCMS** (ES, *m/z*): 474 $[M+H]^+$

Synthesis of Compound 214



To a stirred mixture of tert-butyl N-cyclopropyl-N-{1-[8-(pyrazol-1-yl)-6H-isochromeno[3,4-b] pyridin-3-yl]pyrrolidin-3-yl}carbamate (140 mg, 0.224 mmol, 1.0 equiv) in DCM (1.4 mL) was added 4 M HCl/Dioxane (1.4 mL). The mixture was stirred for 1 h at room temperature under N_2 atmosphere. The resulting mixture was concentrated under vacuum, then the crude product was purified by Prep-HPLC using Condition 2, Gradient 12 to afford N-cyclopropyl-1-[8-(pyrazol-1-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]pyrrolidin-3-amine (Compound 214, 13 mg) as a solid. **LCMS** (ES, *m/z*): 374 $[M+H]^+$ **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.47 (d, J = 2.5 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.79-7.71 (m, 4H), 6.55 (t, J = 2.1 Hz, 1H), 6.20 (d, J = 8.5 Hz, 1H), 5.26 (s, 2H), 3.58 (dd, J = 10.6, 6.1 Hz, 1H), 3.48 (ddd, J = 15.0, 10.8, 6.6 Hz, 2H), 3.42-3.34 (m, 1H), 3.22 (dd, J = 10.6, 4.9 Hz, 1H), 2.10 (ddt, J = 13.7, 11.1, 4.9 Hz, 2H), 1.86 (dq, J = 13.0, 6.7 Hz, 1H), 0.41 (d, J = 6.7 Hz, 2H), 0.24 (dd, J = 6.8, 3.4 Hz, 2H).

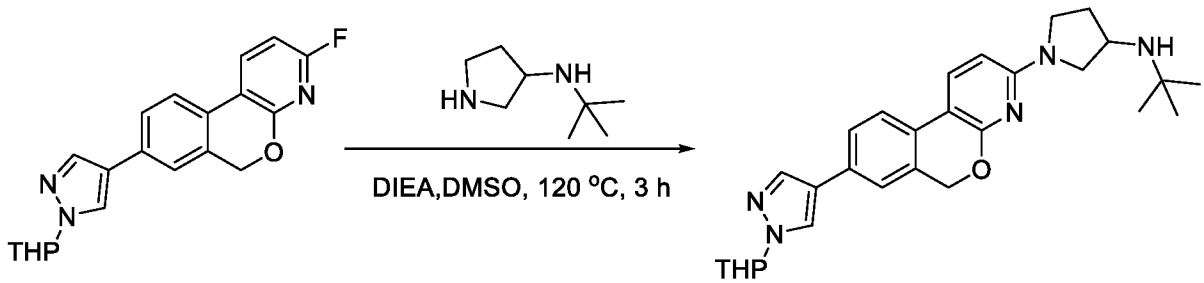
Example 40: Synthesis of Compound 213



To a stirred mixture of 1-{3-fluoro-6H-isochromeno[3,4-b]pyridin-8-yl}pyrazole (40.0 mg, 0.150 mmol, 1.00 equiv) in DMSO (10 mL) was added DIEA (58.0 mg, 0.450 mmol, 3.0 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 2 h at 120 degrees C under N_2 atmosphere. The crude product was purified by Prep-HPLC using Condition 2, Gradient 5 to afford N-tert-butyl-1-[8-(pyrazol-1-yl)-6H-isochromeno[3,4-b]pyridin-3-yl]pyrrolidin-3-amine (Compound 213, 21.1 mg) as a solid. **LCMS** (ES, *m/z*): 390 $[M+H]^+$ **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.47 (d, *J* = 2.6 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.91-7.58 (m, 4H), 6.58-6.52 (m, 1H), 6.19 (d, *J* = 8.5 Hz, 1H), 5.26 (s, 2H), 3.71-3.62 (m, 1H), 3.54-3.44 (m, 2H), 3.30-3.25 (m, 1H), 2.96 (dd, *J* = 10.3, 7.3 Hz, 1H), 2.13 (ddd, *J* = 12.6, 8.3, 4.7 Hz, 1H), 1.77-1.63 (m, 2H), 1.08 (s, 9H).

Example 41: Synthesis of Compound 212

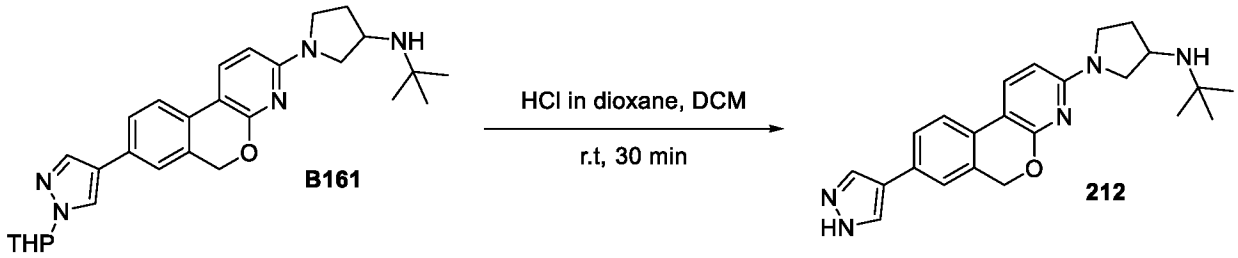
Synthesis of Intermediate B161



B160 **B161**

To a stirred mixture of 3-fluoro-8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6H-isochromeno [3,4-b] pyridine (80 mg, 0.228 mmol, 1.0 equiv) and N-tert-butylpyrrolidin-3-amine (64.8 mg, 0.456 mmol, 2.0 equiv) in DMSO (0.8 mL) was added DIEA (88.3 mg, 0.684 mmol, 3.0 equiv) at room temperature. The resulting mixture was stirred for 3 h at 120 °C. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressureto give N-(tert-butyl)-1-(8-(1-(tetrahydro-2H-pyran-2-yl)-1H- pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl)pyrrolidin-3-amine (107 mg, crude). It was used in the next step directly without further purification. **LCMS** (ES, *m/z*): 474 $[M+H]^+$

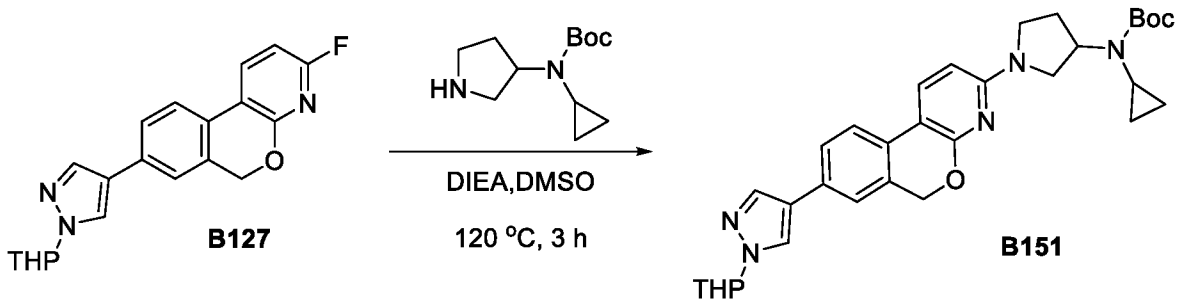
Synthesis of Compound 212



To a stirred solution of N-(tert-butyl)-1-(8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl)pyrrolidin-3-amine (107mg, 0.226mmol, 1.0 equiv) in DCM (1.1 mL) was added 4 M HCl(gas)in 1,4-dioxane (1.1 mL) at room temperature. The resulting mixture was stirred for 30 min at room temperature .The mixture was neutralized to pH 7 with saturated Na_2CO_3 (aq.). The crude product was purified by Prep-HPLC to afford 1-(8-(1H-pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl)- N-(tert-butyl)pyrrolidin-3-amine (Compound 212, 43.3 mg) as a solid. **LCMS** (ES, *m/z*): 390 $[M+H]^+$ **^{1}H NMR** (300 MHz, DMSO-*d6*) δ 9.44 (s, 2H), 8.22 (s, 2H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.70-7.55 (m, 2H), 7.51 (d, *J* = 1.7 Hz, 1H), 6.28 (d, *J* = 8.4 Hz, 1H), 5.25 (s, 2H), 4.04 (s, 1H), 3.88 (dd, *J* = 11.1, 7.1 Hz, 1H), 3.65 (dq, *J* = 15.0, 5.3, 4.3 Hz, 2H), 3.38 (dt, *J* = 10.2, 7.6 Hz, 1H), 2.49-2.29 (m, 2H), 1.39 (s, 9H).

Example 42: Synthesis of Compound 211

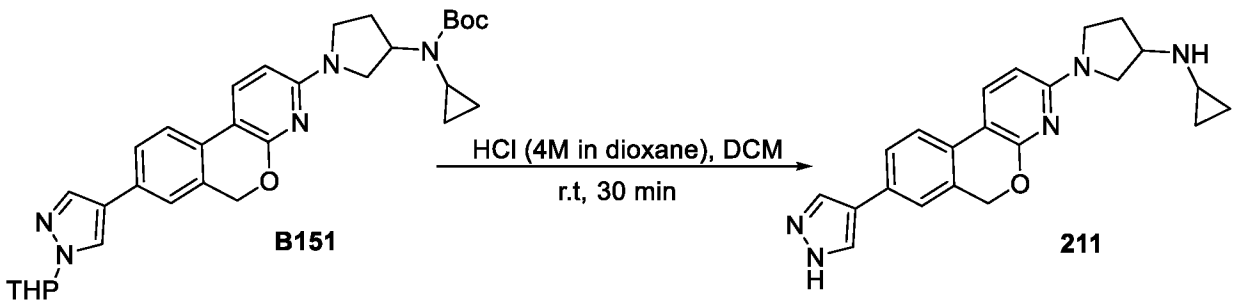
Synthesis of Intermediate B151



To a stirred mixture of 3-fluoro-8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6H-isochromeno [3,4-b]pyridine (80 mg, 0.228 mmol, 1.0 equiv) and tert-butyl cyclopropyl(pyrrolidin-3-yl) carbamate (103 mg, 0.456 mmol, 2.0 equiv) in DMSO (0.8 mL) was added DIEA (88 mg, 0.684 mmol, 3.0 equiv) at room temperature. The resulting mixture was stirred for 3 h at 120 °C. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give tert-butyl cyclopropyl(1-(8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl)pyrrolidin-3-

yl)carbamate (126 mg, crude). It was used in the next step directly without further purification. **LCMS** (ES, *m/z*): 558 [M+H] $^+$

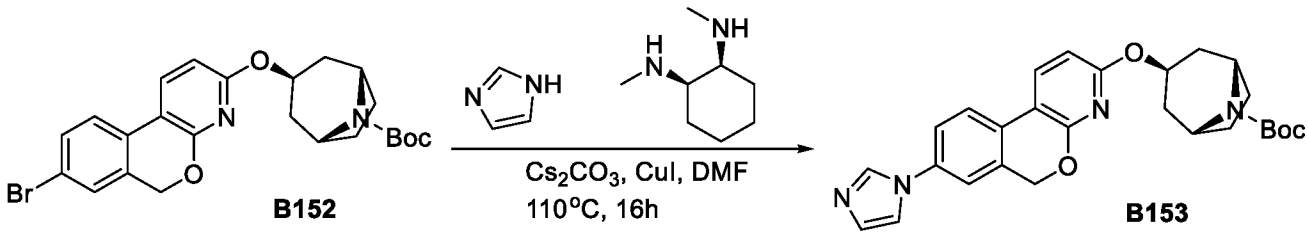
Synthesis of Compound 211



To a stirred solution of tert-butyl cyclopropyl(1-(8-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl)pyrrolidin-3-yl)carbamate (126 mg, crude) in DCM (1.25 mL) was added 4 M HCl(gas)in 1,4-dioxane (1.25 mL) at room temperature. The resulting mixture was stirred for 30 min at room temperature, then neutralized to pH 7 with saturated Na_2CO_3 (aq.). The crude product was purified by Prep-HPLC using Condition 2, Gradient 5 to afford 1-(8-(1H-pyrazol-4-yl)-6H-isochromeno[3,4-b]pyridin-3-yl)-N-cyclopropylpyrrolidin-3-amine (Compound 211, 26.6 mg) as a solid. **LCMS** (ES, *m/z*): 374 [M+H] $^+$ **^{1}H NMR** (300 MHz, DMSO-*d6*) δ 12.94 (s, 1H), 8.17 (s, 1H), 7.98-7.92 (m, 2H), 7.65-7.51 (m, 2H), 7.45 (s, 1H), 6.18 (d, *J* = 8.4 Hz, 1H), 5.20 (s, 2H), 3.60-3.52 (m, 1H), 3.51-3.40 (m, 3H), 3.25-3.16 (m, 1H), 2.13-2.03 (m, 2H), 1.91-1.79 (m, 1H), 0.40 (dd, *J* = 6.6, 1.7 Hz, 2H), 0.24 (dd, *J* = 4.1, 2.1 Hz, 2H).

Example 43: Synthesis of Compound 215

Synthesis of Intermediate B152



To a stirred mixture of tert-butyl (1R,3s,5S)-3-((8-bromo-6H-isochromeno[3,4-b]pyridin-3-yl)oxy)-8- azabicyclo[3.2.1]octane-8-carboxylate (70.0 mg, 0.144 mmol, 1.0 equiv) and imidazole (19.6 mg, 0.288 mmol, 2.0 equiv) in DMF (1.4 mL) were added Cs_2CO_3 (140.4 mg, 0.432 mmol, 3.0 equiv), CuI (2.7 mg, 0.014 mmol, 0.1 equiv) and (1R,2S)-N1,N2-

dimethylcyclohexane-1,2-diamine (2.0 mg, 0.014 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 19 h at 110 °C under nitrogen atmosphere, then extracted with EtOAc (3 x 3mL). The combined organic layers were washed with water (3x5 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with CH_2Cl_2/MeOH (20:1) to afford tert-butyl (1R,3s,5S)-3-((8-(1H-imidazol-1-yl)-6H-isochromeno[3,4-b]pyridin-3-yl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (50 mg, 66.76%) as a yellow oil. **LCMS** (ES, *m/z*): 475 $[M+H]^+$

Synthesis of Compound 215



B153 215

To a stirred solution of tert-butyl (1R,3s,5S)-3-((8-(1H-imidazol-1-yl)-6H-isochromeno[3,4-b] pyridin- 3-yl)oxy)-8-azabicyclo [3.2.1]octane-8-carboxylate (50 mg, 0.105 mmol, 1.0 equiv) in DCM (0.5 mL) was added TFA (0.1 mL) at room temperature. The resulting mixture was stirred for 30 min at room temperature . The mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC using Condition 2, Gradient 5 to afford 3-(((1R,3s,5S)-8-azabicyclo [3.2.1] octan-3-yl) oxy)-8-(1H-imidazol-1-yl)-6H-isochromeno[3,4-b]pyridine (13.3 mg) as a solid. **LCMS** (ES, *m/z*): 375 $[M+H]^+$ **^{1}H NMR** (300 MHz, DMSO-*d6*) δ 8.32-8.22 (m, 2H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.78 (s, 1H), 7.71-7.59 (m, 2H), 7.13 (s, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 5.36 (s, 2H), 5.26-5.16(m, 1H), 3.51-3.43 (m, 2H), 2.08-1.97 (m, 2H), 1.72-1.60 (m, 4H), 1.51 (t, *J* = 11.4 Hz, 2H).

Example 44: Exemplary splicing assay for monitoring expression levels of splice variants

Compounds described herein were used to modulate RNA transcript abundance in cells. The expression of a target mRNA was measured by detecting the formation of an exon-exon junction in the canonical transcript (CJ). A compound mediated exon-inclusion event was detected by observing an increase in formation of a new junction with an alternative exon (AJ). Real-time qPCR assays were used to detect these splicing switches and interrogate the potency of various compounds towards different target genes. A high-throughput real time quantitative PCR (RT-

qPCR) assay was developed to measure these two isoforms of the mRNA (CJ and AJ) for an exemplary gene, HTT, together with a control housekeeping gene, GAPDH or GUSB or PPIA, used for normalization. Briefly, the A673 or K562 cell line was treated with various compounds described herein (e.g., compounds of Formula (I)). After treatment, the levels of the HTT mRNA targets were determined from each sample of cell lysate by cDNA synthesis followed by qPCR.

Materials:

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

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

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

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

Probe/primer sequences

Canonical junction (CJ)

HTT Primer 1: TCCTCCTGAGAAAGAGAAGGAC

HTT Primer 2: GCCTGGAGATCCAGACTCA

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

Alternative junction (AJ)

HTT Primer 1: TCCTGAGAAAGAGAAGGACATTG

HTT Primer 2: CTGTGGGCTCCTGTAGAAATC

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

Description

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

The K562 cell line was cultured in IMDM with 10% FBS. For K562, cells were diluted with full growth media and plated in either a 96-well plate (50,000 cells in 50uL media per well) or a 384-well plate (8,000-40,000 cells in 45uL media per well). An 11-point 3-fold serial dilution of the compounds were made in DMSO then diluted in media in an intermediate plate. Compound was transferred from the intermediate plate to the cell plate with the top dose at a final concentration of 10uM in the well. Final DMSO concentration was kept at or below 0.25%. Final volume was 100uL for 96-well plate and 50uL for 384-well plate. The cell plate was then placed in an incubator at 37°C with 5% CO2 for 24 hours.

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

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

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

Component	**1X**
Taqman 1-step RT-qPCR mix (4X)	2.5
20X AJ Primers+Probe (FAM)	0.5
20X CJ Primers+Probe (CY5)	0.5
20X PPIA Control (VIC)	0.5

Cell lysate (1X)	1-2
H_2O	4-5
Total volume	**10**

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

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

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

A summary of these results is illustrated in Table 4, 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 4: Modulation of RNA Splicing by Exemplary Compounds

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ IC_{50} (nM)
101	D	-
102	D	D
104	D	D
105	D	D
108	A	A
109	B	B
113	D	D
114	A	B
116	C	B
117	D	D
118	D	D
119	D	D
121	B	B
124	C	C
125	D	D
127	D	D
128	D	D
129	D	D
132	D	D
134	C	C
135	C	C
136	D	D
137	C	C
138	C	C
139	D	D
140	D	D
141	D	D
142	B	B
143	B	B
144	B	B
145	D	D
146	C	C
147	B	B
148	C	C
149	A	B
150	A	A
151	A	A

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ IC_{50} (nM)
152	A	B
153	A	A
154	B	B
155	A	A
156	A	A
157	C	C
158	B	B
159	A	A
160	A	A
161	D	D
162	A	A
163	A	A
164	A	A
165	B	B
166	D	D
167	D	D
168	D	D
169	B	B
170	C	C
171	C	C
172	B	B
173	D	D
174	D	D
175	C	D
176	C	C
177	D	D
178	A	A
179	B	B
180	A	A
181	D	D
182	D	D
183	D	D
184	C	C
185	D	D
186	C	C
187	D	C
188	B	B

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ IC_{50} (nM)
189	C	D
190	B	A
191	C	B
192	D	D
193	D	D
194	C	C
196	D	D
197	D	C
198	B	B

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ IC_{50} (nM)
199	C	C
200	A	A
201	B	B
202	D	C
203	C	C
204	D	C
205	B	C
206	B	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 5, 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 5: Modulation of RNA Splicing by Exemplary Compounds

Compound No.	HTT	SMN2	Target C
101	-	-	D
102	D	-	D
104	D	-	D
105	D	D	-
108	A	A	A
112	-	-	D

Compound No.	HTT	SMN2	Target C
113	D	D	D
114	B	-	A
116	B	B	B
117	D	D	-
118	D	D	-
119	D	-	C

Compound No.	HTT	SMN2	Target C
121	B	B	B
124	C	C	C
125	D	D	D
127	D	D	-
128	D	-	D
129	D	D	D
132	D	-	D
134	C	C	A
135	C	C	C
136	D	D	D
137	D	D	C
138	C	-	C
139	D	D	D
140	D	D	-
141	D	-	C
142	B	B	C
143	B	B	B
144	B	D	B
145	D	C	C
146	C	D	D
147	B	D	B
148	C	B	C
149	B	B	B
150	A	D	B
151	A	A	B
152	B	A	B
153	A	A	A
154	B	B	B
155	A	A	B
156	A	B	B
157	C	B	C
158	B	B	B
159	A	A	A
160	A	A	A
161	D	D	D
162	A	A	A
163	A	A	B
164	A	A	B

Compound No.	HTT	SMN2	Target C
165	B	A	B
166	D	C	D
167	D	D	D
168	D	D	D
169	B	B	B
170	C	C	D
171	C	B	C
172	B	A	B
173	D	C	D
174	D	C	D
175	D	C	D
176	C	C	D
177	D	D	D
178	A	A	B
179	B	B	B
180	A	A	B
181	D	D	D
182	D	D	D
183	D	B	D
184	C	C	C
185	D	C	D
186	C	B	D
187	C	C	D
188	B	B	C
189	D	C	D
190	A	A	B
191	B	B	C
192	D	D	D
193	C	D	D
194	D	D	D
195	B	B	C
196	D	D	D
197	C	D	D
198	B	B	C
199	C	C	D
200	A	A	B
201	B	A	B
202	C	D	D

EQUIVALENTS AND SCOPE

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

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

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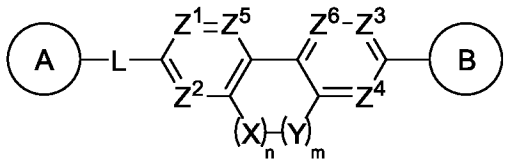
CLAIMS

1. A compound of Formula (I):



(I)

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

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

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

Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently C(R^6) or N;

X and Y are each independently O, C(R^{7a})(R^{7b}), or N(R^{7c}), wherein X and Y are not both O;

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, heteroaryl, C_1-C_6 alkylene-aryl, C_2-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, C_2-C_6 alkenylene-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^4 is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, or heterocyclyl, wherein each alkyl, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^{12};

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

R^6 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, aryl, heteroaryl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

R^{7a}, R^{7b}, and R^{7c} are each independently hydrogen, C_1-C_6-alkyl, or halo; or

R^{7a} and R^{7b}, together with the carbon atom to which they are attached, form an oxo group;

each R^8 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each 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-cycloalkyl, C_1-C_6 alkylene-heterocyclyl, 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, aryl, heteroaryl, C_1-C_6 alkylene-cycloalkyl, C_1-C_6 alkylene-heterocyclyl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, or $–OR^A$; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl or heteroaryl 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-cycloalkyl, C_1-C_6 alkylene-heterocyclyl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

each R^{10} is C_1-C_6-alkyl, halo, cyano, oxo, or $–OR^{A1}$;

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

each R^{12} is independently deuterium, halo, cyano, $-OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, or $–C(O)R^D$;

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

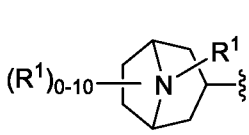
each of m and n is independently 1 or 2; and

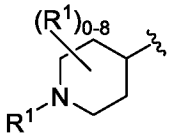
x is 0, 1, or 2.

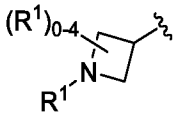
2. The compound of claim 1, wherein A is a monocyclic or bicyclic heterocyclyl.

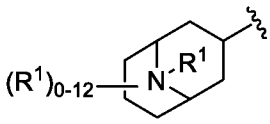
3. The compound of any one of the preceding claims, wherein A is a nitrogen-containing heterocyclyl.

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



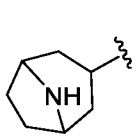
, 

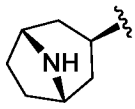
, 

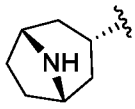
, and 

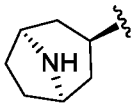
, wherein R^1 is as described in claim 1.

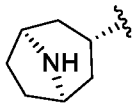
5. The compound of any one of the preceding claims, wherein A is selected from:

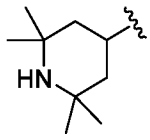


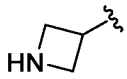
, 

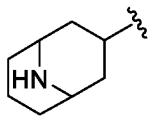
, 

, 

, 

, 

, 

, 

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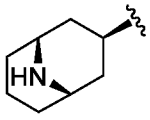
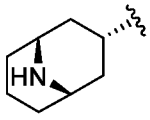
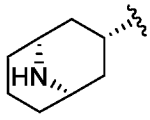
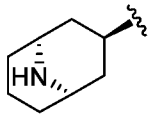
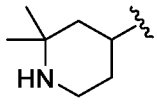
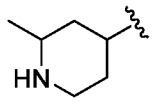


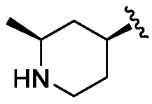
, 

, 

, 

, 

, 

, 

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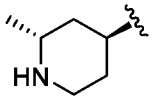
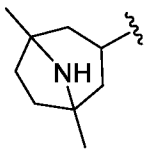
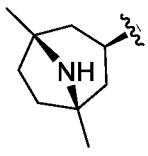
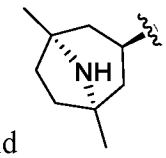


, 

, 

, and 

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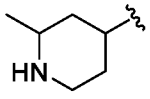
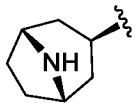
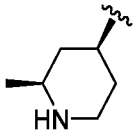
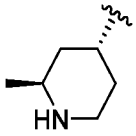
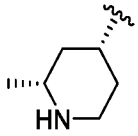
6. The compound of any one of the preceding claims, wherein A is selected from

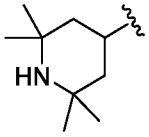


, 

, 

, 

, 

, and 

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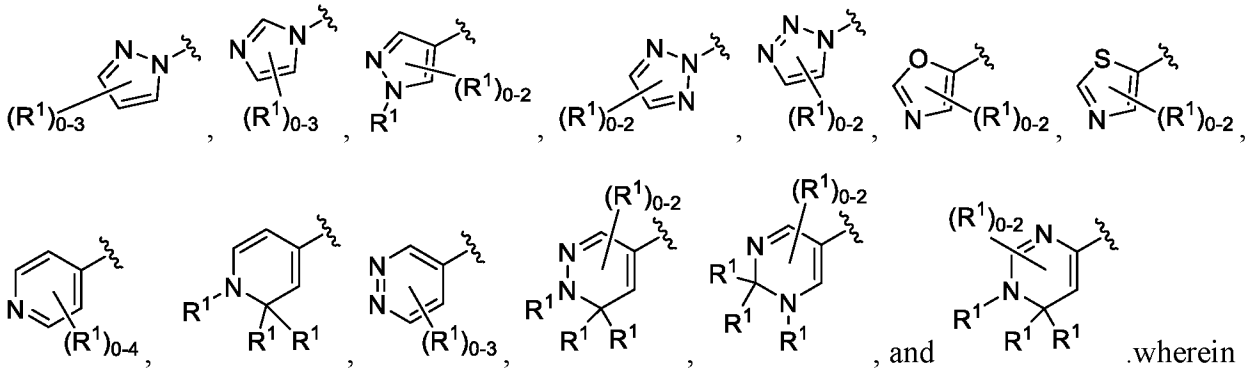
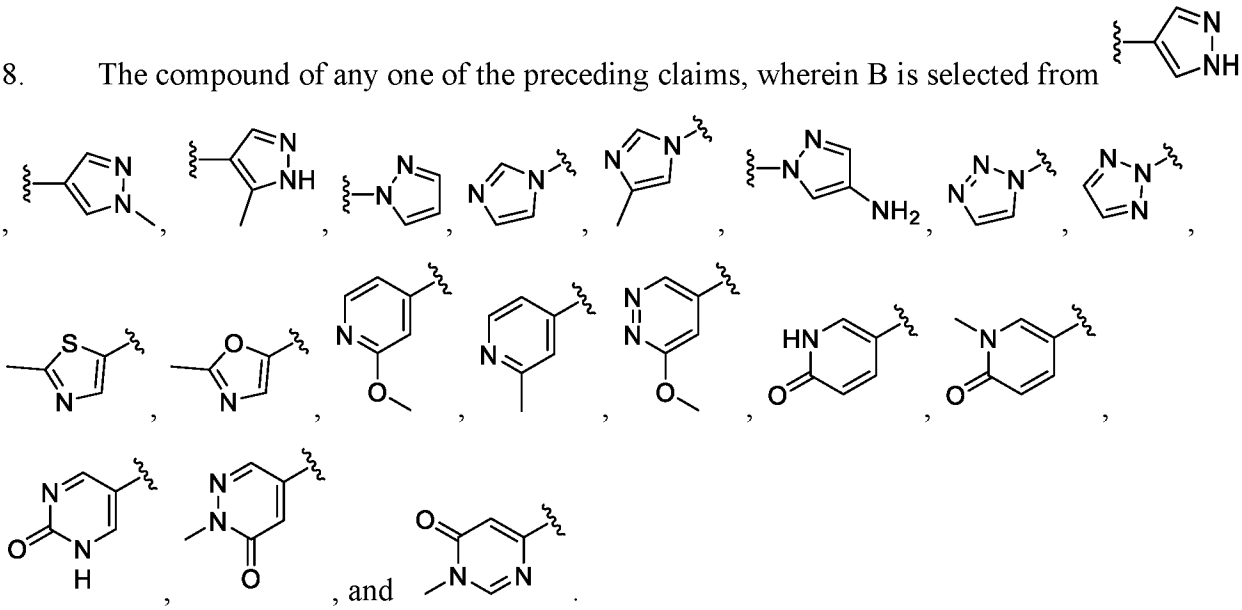
7. The compound of any one of the preceding claims, wherein B is selected from



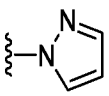
, and .wherein R^1 is as described in claim 1 .

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

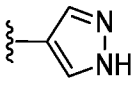


, and .

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



and



.

10. The compound of any one of the preceding claims, wherein L is -N(R^4)-, wherein R^4 is selected from hydrogen, C_1-C_6 alkyl, and cycloalkyl.

11. The compound of any one of the preceding claims, wherein L is -N(CH_3)-.

12. The compound of any one of the preceding claims, wherein four of Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are independently $C(R^6)$ (e.g., CH).

13. The compound of any one of the preceding claims, wherein Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 are each independently $C(R^6)$ (e.g., CH).

14. The compound of any one of claims 1-12, wherein one of Z^1, Z^2, Z^3, Z^4, Z^5, and Z^6 is independently $C(R^6)$.

15. The compound of any one of the preceding claims, wherein one of Z^2 and Z^5 is each independently N.

16. The compound of any one of the preceding claims, wherein Z^2 and Z^5 are each independently N.

17. The compound of any one of the preceding claims, wherein one of X and Y is $C(R^{7a})(R^{7b})$, and the other of X and Y is O.

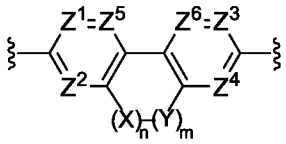
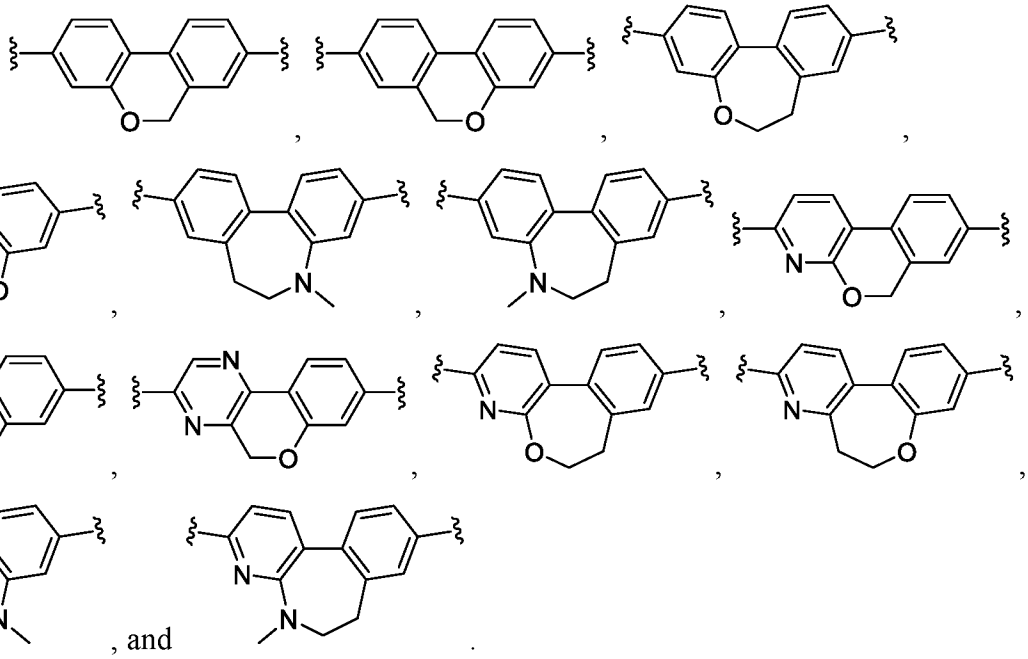
18. The compound of any one of the preceding claims, wherein X is O and Y is CH_2.

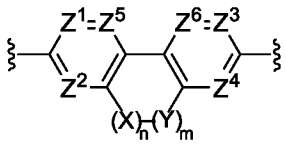
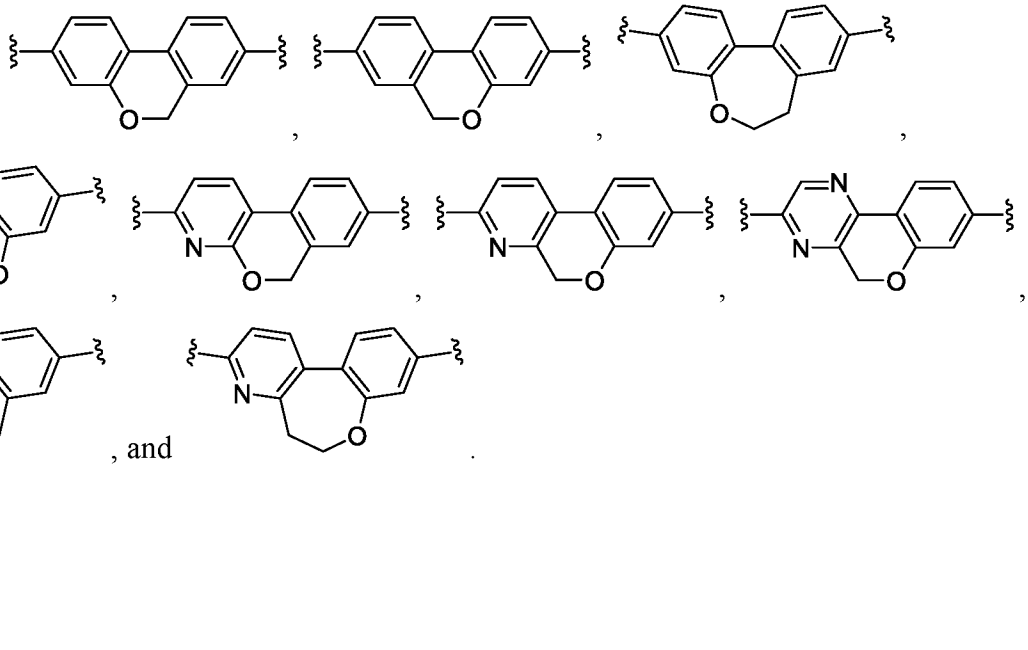
19. The compound of any one of claims 1-17, wherein X is CH_2 and Y is O.

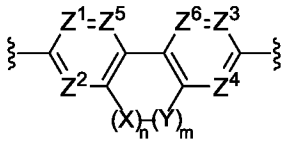
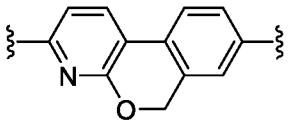
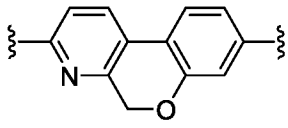
20. The compound of any one of the preceding claims, wherein n and m are both 1.

21. The compound of any one of claims 1-19, wherein n is 1 and m is 2.

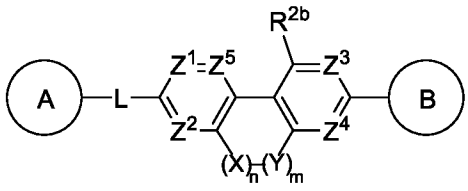
22. The compound of any one of claims 1-19, wherein n is 2 and m is 1.

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

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

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

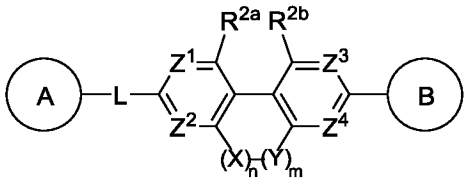
26. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-a):



(I-a)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L, Z^1, Z^2, Z^3, Z^4, Z^5, X, Y, R^{2b}, m, n, and subvariables thereof are as defined in claim 1.

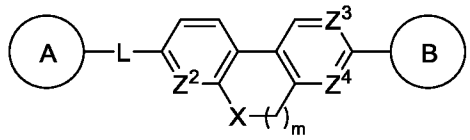
27. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-b):



(I-b)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L, Z^1, Z^2, Z^3, Z^4, X, Y, R^{2a}, R^{2b}, m, n, and subvariables thereof are as defined in claim 1.

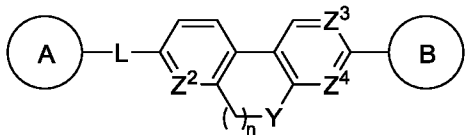
28. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-c):



(I-c)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L, Z^2, Z^3, Z^4, X, m, and subvariables thereof are as defined in claim 1.

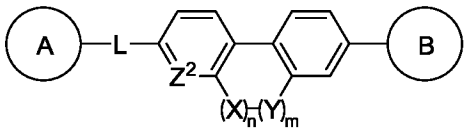
29. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-d):



(I-d),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L, Z^2, Z^3, Z^4, Y, m, and subvariables thereof are as defined in claim 1.

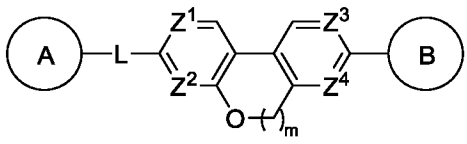
30. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-e):



(I-e),

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

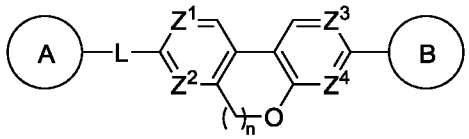
31. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-f):



(I-f),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L, Z^1, Z^2, Z^3, Z^4, m, and subvariables thereof are as defined in claim 1.

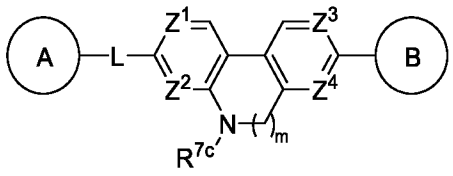
32. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-g):



(I-g),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L, Z^1, Z^2, Z^3, Z^4, n, and subvariables thereof are as defined in claim 1.

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



(I-h),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L, Z^1, Z^2, Z^3, Z^4, R^{7c}, m, and subvariables thereof are as defined in claim 1.

34. 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.

35. A pharmaceutical composition comprising a compound of any one of claims 1-34 and a pharmaceutically acceptable excipient.

36. The compound of any one of claims 1-35 or the pharmaceutical composition of claim 36, wherein the compound alters a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

37. The compound of any one of claims 1-35 or the pharmaceutical composition of claim 36, wherein the compound binds to a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

38. The compound of any one of claims 1-35 or the pharmaceutical composition of claim 36, wherein the compound stabilizes a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

39. The compound of any one of claims 1-35 or the pharmaceutical composition of claim 36, 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.

40. The compound of any one of claims 1-35 or the pharmaceutical composition of claim 36, 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 %.

41. A method of modulating splicing of a nucleic acid (e.g., DNA, RNA, e.g., a pre-mRNA) comprising contacting the nucleic acid with a compound of Formula (I) as described in any one of claims 1-35.

42. The method of claim 41, 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.

43. The method of claim 41, 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.

44. 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), comprising contacting the nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA) with a compound of Formula (I) as described in any one of claims 1-35.

45. The method of claim 44, wherein the component of a spliceosome is recruited to the nucleic acid in the presence of the compound of Formula (I).

46. 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) as described in any one of claims 1-35.

47. The method of claim 46, wherein the altering comprises forming a bulge in the nucleic acid.

48. The method of claim 46, wherein the altering comprises stabilizing a bulge in the nucleic acid.

49. The method of claim 46, wherein the altering comprises reducing a bulge in the nucleic acid.

50. The method of any one of claims 46-49, wherein the nucleic acid comprises a splice site.

51. 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 1-35 or the pharmaceutical composition of claim 36.

52. The composition for use of claim 51, wherein the disease or disorder comprises a proliferative disease (e.g., cancer, a benign neoplasm, or angiogenesis).

53. The composition for use of claim 51, 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.

54. The composition for use of claim 51, wherein the disease or disorder comprises neurological disease or disorder.

55. The composition for use of claim 51, wherein the disease or disorder comprises Huntington's disease.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/020157

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P9/00 A61K31/352 A61K31/517 A61P25/00 A61P31/00
A61P35/00 A61P37/00 C07D403/12 C07D405/12 C07D451/04
C07D451/06 C07D491/06

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2017/100726 A1 (PTC THERAPEUTICS INC [US]) 15 June 2017 (2017-06-15) page 7, line 7 - page 12, line 27, "Formula (Ia)"; page 13, "Formula (Ia15)"; page 22, "Formula (Ia11); page 35, "Formulas (Ia16) and (Ia17)"; examples, e.g. Example 2 and Table 3; claims -----	1-55
Y	WO 2016/128343 A1 (F HOFFMANN-LA ROCHE AG [CH]; HOFFMANN-LA ROCHE INC [US]) 18 August 2016 (2016-08-18) page 14, line 17 - page 17, line 19; examples, e.g. Example 1 and the Table at pages 80-81; claims -----	1-55

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2021	03/05/2021

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

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2019/028440 A1 (SKYHAWK THERAPEUTICS INC [US]) 7 February 2019 (2019-02-07) [0006]; [0047]; [0296]-[0298]; [0325]-[0329]; [0461]; [0491]; [0541], "Table 1A: Exemplary SMSM compounds"; examples, e.g. Example 13, Example 14 and [01104], Example 15 and [01118]; Example 22; claims; Figure 15/31	1-55
Y	WO 2019/060917 A2 (SKYHAWK THERAPEUTICS INC [US]) 28 March 2019 (2019-03-28) [0041]; [0055]; [0062]; [00139], e.g. compounds 26-32; examples, e.g. Example 10 and paragraphs [00154], [00158]-[00161]; Example 11; claims	1-55
A	US 2016/152628 A1 (QUAN MIMI L [US] ET AL) 2 June 2016 (2016-06-02) [0010]; [0025]-[0048]; [0552]-[0554]; claims, e.g. Claims 1, 16 and 17	1-55

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/020157

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